PATIENT-CONTROLLED ANALGESIA

IN THE POSTOPERATIVE PERIOD

SUBMITTED BY

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ABSTRACT

Patient-controlled delivery systems deliver drugs at a rate which is controlled by the patient in order to achieve plasma concentrations consistent with acceptable efficacy and minimal side-effects. They can be used therapeutically to provide pain relief after surgery and as a research tool to measure the efficacy of other analgesic techniques.

Patient-controlled analgesia (PCA) was investigated in the postoperative period. Comparative studies of PCA devices revealed little difference in terms of clinician and patient satisfaction. As a research tool, PCA proved useful in evaluating alternative methods of providing postoperative analgesia.

Ambulatory PCA devices were more portable ($p=0.01$) on the first postoperative day with less nausea ($p=0.02$) on the second. Mean (SEM) postoperative morphine requirements were 82.9 (9.8) mg and 120.6 (17.5) mg for the ambulatory and bedside PCAS respectively ($p=0.06$). Mean (SEM) postoperative morphine consumption between the electronic 35.1 (8.5) mg and nonelectronic devices 35.7 (6.6) mg were similar ($p=0.77$).

In evaluating other methods of analgesia, there was no significant difference between active and placebo TCENS. Mean (SEM) postoperative opioid requirements were 35.6 (5.3) mg and 31.6 (3.5) mg for the active and placebo groups respectively ($p=0.5$). Subcutaneous wound infiltration with bupivacaine 0.5% also failed to decrease mean (SEM) opioid requirements for the first postoperative day, which were 56.7 (6.1) mg and 67.3 (6.4) mg for the bupivacaine and saline groups respectively ($p=0.89$).

When diamorphine and morphine were compared for dose and effect, the postoperative mean (SEM) requirements were 20.2 (2.4) mg and 44 (6.8) mg respectively ($p=0.004$). No significant differences were found in side-effects.

After PCA and i.m. morphine no differences were detected in mean (SEM) postoperative consumption - 34.8 (5.0) mg and 30.2 (6.7) mg in the PCA and i.m. groups respectively ($p=0.17$). Overall requirements for antiemetics were not significant ($p=0.69$). In the PCA group, 53% patients did not vomit, were not nauseated and did not require antiemetics compared with 27% patients in the i.m. group ($p=0.14$).

CONTENTS

CONTENTS (cont'd)

List of Abbreviations

<	less than
>	more than
5HT	5-hydroxytryptamine
AMH	A-fibre mechano-heat (nociceptors)
ATP	adenosine triphosphate
CGRP	calcitonin gene-related peptide
CMH	C-fibre mechano-heat (nociceptors)
CNS	central nervous system
CO_2	carbon dioxide
CSF	cerebro-spinal fluid
CTZ	chemoreceptor trigger zone
FIO_2	faction inspired oxygen
h	hour
Hz	Hertz
i.m.	intramuscular
i.m.i.	intermittent intramuscular injection
I.U.	international units
i.v.	intravenous
i.v.i.	intravenous infusion
LCD	liquid crystal display
LNTU	Leicester neuroelectric therapy unit
M3G	morphine 3-glucuronide
M6G	morphine 6-glucuronide
mcg	microgram
MEAC	minimum effective analgesic concentration
mg	milligram
ml	millilitre

List of Abbreviations (cont'd)

MST	proprietary name for morphine modified release tablets
NMDA	N-methyl-D-aspartate-acid
NSAID	nonsteroidal anti-inflammatory drug
PCA	patient-controlled analgesia
PCAS	patient-controlled analgesia system
prn	*pro re nata* (when required)
SaO_2	oxygen saturation
SP	substance P
SSR	surgical stress response
TCENS	transcranial electrical nerve stimulation
TENS	transcutaneous electrical nerve stimulation
VAS	visual analogue scale
VRS	verbal rating scale

List of Tables

List of tables (cont'd)

List of Figures

List of figures (cont'd)

PATIENT-CONTROLLED ANALGESIA IN THE POSTOPERATIVE PERIOD

Introduction

Patient-controlled delivery systems deliver drugs at a rate which is controlled by the patient. The theoretical basis of this technique is that the patient will titrate the rate of delivery in order to achieve plasma concentrations consistent with acceptable efficacy and minimal side-effects.

Whilst patient-controlled analgesia (PCA) has been in use for over 20 years as a research tool, it has only very recently become an accepted method of delivering analgesia for the relief of postoperative pain. During the last decade, in Britain, PCA has gradually been introduced into District General Hospitals to provide postoperative analgesia, with very favourable results (Nottcutt and Morgan, 1990; Wheatley et al., 1991). During this time I was a research nurse in the Department of Anaesthesia, in Leicester, and I performed several studies investigating PCA. This thesis, therefore, is a culmination of these studies.

The technique of PCA was investigated by comparisons of an electronic bedside device with electronic and nonelectronic ambulatory devices, two opioids (morphine and diamorphine) and by using PCA as a research tool to evaluate other methods of providing postoperative analgesia. The problem of postoperative nausea and vomiting with PCA was also addressed.

I have set out the work in two sections. The first section is concerned with the background of PCA in order to put it into context and it reviews the literature regarding: the pathophysiology of pain (Chapter 1); the incidence and management of postoperative pain (Chapters 2 and 3); the history, theory and application of PCA

(Chapter 4) and the methods of assessing patients' subjective responses to pain (Chapter 5). The second section is devoted to the studies upon which this thesis is based (Chapters 6-12).

Initially, and in preparation for later studies, I carried out a pilot study (Chapter 6) using the Graseby patient-controlled analgesia system (PCAS). At the time there were few alternatives to this new computerized model and the facility to attach a printer gave this device obvious research advantages.

The patients in this pilot (undergoing total hip or total knee replacement) proved suitable because the procedure necessitated their admission to hospital 48 hours prior to operation and therefore in plenty of time to instruct them in the use of the PCA. In addition, the operation required opioid postoperative analgesia for a minimum of 24 hours (generally) which provided a realistic time span to evaluate PCA.

Once familiarity was established with the Graseby PCAS its capabilities were compared with two other (portable) devices. This would lay the groundwork for research into alternative methods of providing postoperative analgesia. It was necessary to consider any differences in the performance of these devices in alleviating postoperative pain and assessing patient and clinician satisfaction.

The first study compared the mains-operated Graseby PCAS with a small portable battery operated device, the Bionica MDS 110 (Chapter 7). In the second study the Graseby was compared with an extremely portable, nonelectronic, non-battery operated, disposable device, the Baxter Watch (Chapter 8).

Amongst other reasons, the lack of recording facilities precluded the use of the ambulatory devices as research tools (Chapters 7 and 8) so the Graseby PCAS was adopted for the next three studies. The first two evaluated alternative methods of

providing postoperative analgesia; transcranial electrical nerve stimulation (TCENS - Chapter 9) and wound infiltration with a local anaesthetic (Chapter 10). The third study evaluated the dose and effect of diamophine, for postoperative analgesia, when compared with morphine.

Whilst undertaking the above studies a clinical impression was gained that some patients became very nauseated with PCA. Nausea and vomiting are unwanted but accepted side-effects of opioid analgesia. The final study, therefore, assessed the emetic sequelae of PCA when compared with conventional (although 4 hourly) intramuscular (i.m.) therapy.

The analgesic used in all of the studies was morphine because it is the most widely used opioid analgesic for moderate to severe pain (Pasternak, 1993) and the gold standard against which other opioid analgesics are compared.

The studies were carried out in Leicester at Glenfield General Hospital and Leicester Royal Infirmary. All patients participating in the studies were ASA grades 1-2 as set out by the American Society of Anesthesiologists' (Appendix 1). Patients receiving opioids preoperatively or those with a history of psychiatric illness were excluded. All patients gave written informed consent to the relevant study which was approved by the local Ethics Committee.

CHAPTER 1

The Physiology of Acute Pain

1.1 Background

Pain is one of the commonest symptoms in medicine and the reason for a third of all first consultations with the G.P. (Bowsher, 1987b). The International Association for the Study of Pain (IASP subcommittee on taxonomy, 1979) defined pain as:

> "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Note: Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life.... It is unquestionably a sensation in a part or parts of the body but it is also always unpleasant and therefore also an emotional experience. ....."

Pain, like all conscious sensations, is the culmination of complex sensory processing within the highest levels of the nervous system. In order to understand the pathogenesis of pain it is necessary to identify the nature of the signals that trigger the perception of the sensation of pain, but not of the other sensory experiences. An understanding of the physiology of acute pain will help to explain the pain that is experienced following surgery and also how drugs, notably opioids, can control postoperative pain.

Woolf defines two types of pain; physiological pain, a normal sensation and pathological pain, the result of an abnormal state (Woolf, 1989). He further subdivides pathological pain into inflammatory (or clinical) and neuropathic pain (Woolf, 1987). Inflammatory and neuropathic pain both have common features which differ from those of physiological pain.

At the beginning of the 20th century Charles Sherrington devised the term 'noxious' to describe the transient sensations (pain) that we experience in response to stimuli which damage, or threaten to damage, tissues (Sherrington, 1906). This is physiological pain. The stimuli activate high threshold sensory receptors, nociceptors, in the skin and therefore physiological pain can be considered to constitute a nociceptor-mediated pain (Woolf, 1991a).

Pathological pain results from a low intensity or an innocuous stimulus following tissue or nerve damage and is characterized by a disruption of normal sensory mechanisms (Woolf, 1991a). Pain may occur in response to previously non-painful stimuli, or in response to intense noxious stimuli, as a result of tissue damage or the inflammatory response that accompanies tissue injury (i.e. postoperatively). In both cases the pain is nociceptor-mediated and may be described as clinical pain (Woolf, 1991b). If, however, there is the sensation of pain in the absence of an obvious stimulus, this is a consequence of damage to the nervous system and the pain is neuropathic (Woolf, 1987).

In spite of their differences, neuropathic and clinical pain share the same features which are quite different from those of physiological pain. Woolf (1991b) describes them thus: a reduction in the threshold necessary to elicit pain (allodynia); an increase in the response to noxious stimuli (hyperalgesia); a prolongation in the response to a transient stimulus (persistent pain) and a spatial spread of the pain to uninjured tissue (referred pain).

Neuropathic pain is important clinically as it is responsible for a large number of intractable painful conditions; for example, postherpetic neuralgia following an attack of shingles (Watson et al., 1988), causalgia following partial damage to a major nerve (Roberts, 1986) or central pain following a thalamic infarct (Bogousslavsky et al., 1988).

The mechanism causing neuropathic pain is little understood (Bennet, 1994) and is therefore difficult to treat (Fields, 1994). Some drugs have a limited effect but complete pain control is rarely achieved and whilst it is widely believed that neuropathic pain is almost totally resistant to opioid analgesics (Arner and Meyerson, 1988; Hanks, 1991), some studies have suggested otherwise (Rowbotham et al., 1991; Jadad et al., 1992).

The fact that physiological and clinical pain are nearly always responsive to opioid analgesia, and neuropathic pain is usually not, suggests that the mechanism of neuropathic pain must be quite different from that of nociceptor-mediated pain (Bowsher, 1987a). For the purposes of this thesis, however, because I am only concerned with postoperative pain, I will concentrate on the pathophysiology of nociceptor-mediated pain.

1.2 Physiological Pain

Physiological pain (Sherrington's noxious stimulus) arises from the excitation of small-diameter sensory nerve fibres (nociceptors) in the periphery caused by mechanical, thermal or chemical stimuli. In this instance the stimuli may, or may not cause tissue damage or an excessive inflammatory response (Woolf, 1989).

Physiological pain is localized and if no tissue is damaged, the result of a pinch, for example, then the sensation is transient. The function of this sensation is important as it informs the body of potential danger (Woolf, 1989). It is this pain, which we perceive in response to firm pressure (mechanical), extreme heat or cold (thermal) and chemical irritants, that correlates with the flexion withdrawal response (Willer, 1977). For example, withdrawing the hand from a hot surface.

Once tissue is damaged, as a result of surgery for instance, a chain of events leads to enhanced pain response to innocuous stimuli. This is termed hyperalgesia (Meyer and Campbell, 1981). In addition to this, there is a corresponding increase in the responsiveness of nociceptors, known as sensitization (Meyer and Campbell, 1981; LaMotte et al., 1982). These two characteristics will be discussed later in this chapter.

Nociceptors

There are two main groups of nociceptor afferents, small myelinated A-delta fibres and larger unmyelinated C fibres. The C nociceptors are the largest group. These are abundant polymodal nociceptors, C-fibre mechano-heat receptors (CMHs), that respond to all three types of noxious stimuli; thermal, mechanical and chemical (Burgess and Perl, 1967; Bessou and Perl, 1969; Van Hees and Gybels, 1981).

The second group of nociceptors are the fine myelinated fibres known as A-mechano-heat (AMH) fibres. Two types of these fibres have been identified: Type I AMH and Type II AMH (Campbell and Meyer, 1986) and as the name suggests they respond mainly to mechanical and thermal noxious stimulation[1]. They do respond to chemical stimuli, such as bradykinin (Dray and Perkins, 1993) and, to a lesser degree, capsaicin (Bevan and Szolcsanyi, 1990).

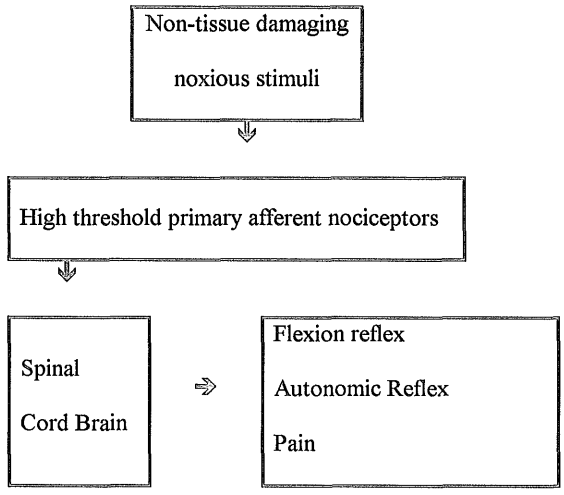
Whilst C fibres are found in almost all tissues, except the central nervous system itself, A-delta fibres are found almost entirely in the skin (Bowsher, 1987b). This explains why it is only on the body surface that a pinprick can be felt. Interestingly, morphine, when given in a dose adequate to suppress clinical pain, does not interfere with pinprick sensation. This can be observed in patients as they usually feel their next intramuscular, or intravenous, injection.

[1] In most studies of nociceptors only heat and mechanical stimuli have been used hence the terms: C-fibre mechano-heat (CMH); A-fibre mechano-heat (AMH) (Meyer et al., 1994).

It is possible to stimulate single A-delta and C nociceptor fibres by the technique known as microneurography (Van Hees and Gybels, 1972; Torebjork and Hallin, 1974; Schady et al., 1983). This technique has provided valuable information for the role of CMHs in the coding for pain. If, for example, the C-fibre in the median nerve (in the hand) is stimulated a dull aching pain occurs (Schady et al., 1983). The pain is dull, poorly localized, and arises slowly after injury (Chapman and Bonica, 1983).
In contrast, stimulation of single A-delta fibres gives rise to sharp pricking or stinging sensations on a small number of points on the skin (Campbell et al., 1979). Stepped heat stimuli evokes a double sensation of pain. First there is a pricking sensation and secondly a burning feeling. It would appear that A-delta fibres must signal the first sensation of pain as it is too quick to be carried by the slowly conducting C-fibres (Campbell and LaMotte, 1983). As the threshold of heat is substantially lower in Type II AMHs than Type I AMHs it has been suggested that Type II AMHs must be responsible for this first pain (Treede et al., 1991). These two sensations of pain correspond roughly to the first (rapid) and second (slow) pains of classical physiology (Lewis and Pochin, 1937).

With high intensity noxious stimuli (i.e. surgical intervention), A-delta fibre and C-fibre nociceptors are activated and once their threshold is exceeded, these afferents relay the message of pain to the spinal cord (Woolf, 1991a). Three different efferent responses are produced: activation of flexor motor neurones producing the flexion withdrawal reflex, activation of sympathetic preganglionic neurones producing a general autonomic response; heart rate, blood pressure, a segmental response; piloerection, sweating, changes in local blood flow and the generation of the sensation of pain; facial distortion, vocalisation, etc. (Fig.1.1).

Figure 1.1 Nociceptor mediated pain - I. After Woolf (1991a).



Pain Thresholds

Bowsher (1985) describes nociceptor-mediated pain as having two types of pain threshold. The first, the pain perception threshold is defined as "the least stimulus intensity at which a subject perceives pain" (IASP, 1979). Studies have shown that this threshold is relatively constant, both in the same individual and in different subjects, at approximately 44-45°C when applied to the glabrous skin of the human hand (Gybels et al., 1979; Meyer and Campbell, 1981; Van Hees and Gybels, 1981; Torebjork et al., 1984).

In contrast to the pain perception threshold is the pain tolerance threshold. Increases in intensity of stimulus produce a stimulus-response relationship until the pain exceeds a certain tolerance level. It has been demonstrated in trained subjects that there are well defined thresholds for when the sensations, triggered by the above stimuli, cease becoming those of pressure, heat or cold and become those of pain (LaMotte and Campbell, 1978; LaMotte and Thalhammer, 1982; LaMotte et al., 1982, 1983;). This is

defined as "the greatest stimulus intensity causing pain that a subject is prepared to tolerate" (IASP, 1979). When the pain becomes intolerable it is often then that the patient seeks medical advice.

In clinical medicine this is important as the pain threshold varies from individual to individual and, also, within the same person at different times and under different circumstances (Koltzenburg and Handwerker, 1993). This is very obvious in the clinical situation by the varying amounts of opioid that different patients require. Anecdotally, I have observed the differences in opioid requirements in patients who have had one hip replacement, returned at a later date to have the other hip replaced, with the same surgeon and anaesthetist performing the same operation. There are, however, important psychological factors involved (Chapter 2) and these of course cannot be discounted.

1.3 Clinical Pain

Once peripheral tissue has been damaged the threshold of stimuli required to produce pain falls to a level where innocuous inputs begin to generate pain (Woolf, 1991b). This can be seen postoperatively. For example, what would normally be a subthreshold stimulus, i.e. mild pressure, when applied to the site of a wound begins to produce pain. In addition, the duration of the pain can outlast the duration of the stimulus and the response to the stimulus can be grossly exaggerated (to a corresponding stimulus, i.e. mild pressure, in undamaged tissue). This pathological state can be produced by A-delta and C nociceptors, but also, unlike physiological pain, by large myelinated A-beta fibres. This is known as A-fibre mediated pain (Woolf, 1991a).

A-beta afferents are low threshold afferents activated by low intensity stimuli and do not usually produce pain (Torebjork et al., 1984, 1987). This implies that clinical pain

involves a transformation from a situation where only nociceptors can produce pain to one where A-beta afferents can.

Hyperalgesia and sensitization of nociceptors

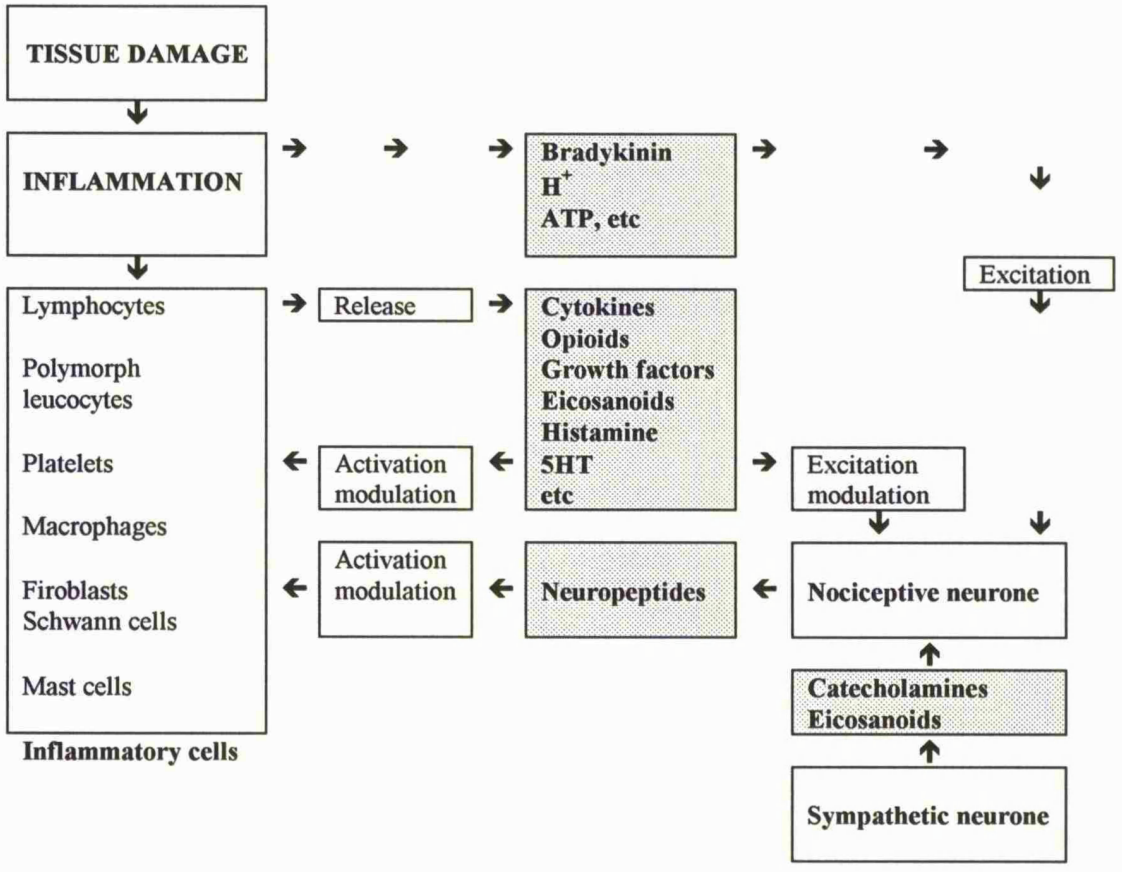
Hyperalgesia, an increased state of sensitivity to noxious stimulation (IASP, 1979), is a consistent feature of tissue injury and inflammation (Meyer et al., 1994). Lewis (1935) identified two types of hyperalgesia: primary and secondary hyperalgesia. The mechanism of primary hyperalgesia occurs at the site of injured tissue (i.e. postoperatively) and causes: a decreased pain threshold, increased pain to suprathreshold stimuli and sometimes spontaneous pain (Raja et al., 1988). This is quite distinct from that of secondary hyperalgesia which involves a lowered pain threshold in areas beyond the site of injury and may be of greater functional importance. (Lewis, 1935, 1942; Bessou and Perl, 1969). Secondary hyperalgesia occurs primarily through changes in central synaptic transmission rather than in peripheral sensory nerve terminals (see later in this chapter).

The neural mechanisms for primary and secondary hyperalgesia differ and are dependent on the form of injury (i.e. thermal or mechanical stimuli) and the type of tissue involved (Raja et al., 1984). However, it would seem that secondary hyperalgesia is mediated through adaptive changes in both the peripheral and central nervous systems (Raja et al., 1988).

In clinical, or postoperative, pain A-delta and C nociceptors have an important characteristic, namely plasticity. One aspect of this plasticity is the capacity to modify their sensitivity, a process known as peripheral sensitization (Bessou and Perl, 1969; Campbell et al., 1979). This is possible by the complex interactions between the neuronal and non-neuronal cells that occur with inflammation, along with the production of a variety of chemical mediators (Rang et al., 1991) (Fig. 1.2).

The various mediators include: bradykinin, prostaglandins, leukotrienes, serotonin, 5-Hydroxytryptamine (5HT), histamine, substance P (SP), thromboxanes, platelet activating factor, protons, free radicals and have direct and indirect actions. Some directly open membrane channels of the neurone, which when opened depolarizes and activates the neurone, while others involve the generation and activation of other messengers. These second messengers, for example: prostaglandins, thromboxanes and leukotrienes, are a group of arachidonic acid metabolites known as eicosanoids. They, in turn, can lead either to activation or to sensitization of nociceptors to natural stimuli and other endogenous chemicals (Ferreira et al., 1974).

Figure 1.2 Various mediators produced by injury and inflammation.
After Rang, Bevan and Dray (1991).

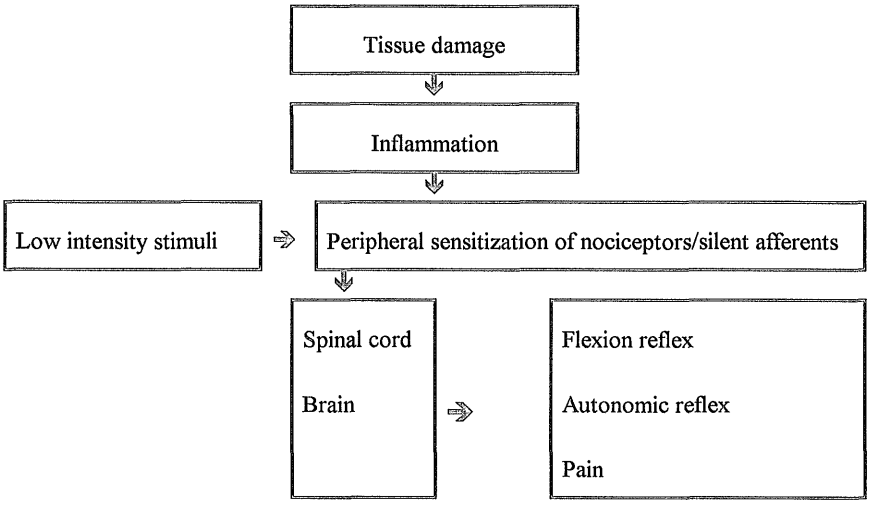


The A-delta and C afferents, in addition to transferring electrical signals to the CNS, also have a motor function. They release neurotransmitters in the form of peptides, such as SP and CGRP (calcitonin gene-related peptide), that act on inflammatory cells, smooth muscle cells and endothelial cells. These substances (and other tachykinins) have the ability to induce many of the signs of acute inflammation such as vasodilation and the extravasation of plasma proteins (Brain and Williams, 1985). This accounts for the red (axon reflex) flare that appears in inflammation and may be seen around the site of a wound, postoperatively. The vasodilation may be an indirect effect related to histamine release from mast cells (Ebertz et al., 1897). CGRP also has vasodilator properties and may play a role in long-term vascular responses to injury (Pedersen-Bjergaard et al., 1991).

To complicate matters further it would appear that the mechanisms underlying the sensitization of the nociceptors to mechanical (i.e. surgery) and thermal stimuli, differ to those from chemical stimuli (Martin et al., 1987; Davis et al., 1993). However, the net consequence of these intracellular activities is that the transduction properties of some high threshold nociceptors are altered (Lang, 1990). Therefore, nociceptors which are not normally activated by low intensity stimuli now become active (sensitized) and pain results (Fig.1.3).

The fact that the peripheral termini of primary afferent nociceptors can become sensitized is important, clinically, in acute pain states. It may be the exclusive cause of pathological pain in rare conditions (Ochoa, 1986) but in cutaneous injury there are few reports of this happening (Bessou and Perl, 1969). Instead, most examples of cutaneous peripheral sensitization are in response to thermal stimuli (Campbell et al., 1979). One easily demonstrable example of thermal peripheral sensitization is that of sunburn (Campbell et al., 1989).

Figure 1.3 Nociceptor mediated pain - II. After Woolf (1991a).



Raja and colleagues (1984), demonstrated that with cutaneous injury there is considerable mechanosensitivity in the zone of secondary hyperalgesia. As the nociceptors do not appear to change it would seem that there is an abnormal central response due to the altered sensitivity, that of central sensitization. Torebjork and colleagues (1992) found that when rapidly conducting A fibres with receptive fields are stimulated (in normal skin) they produce innocous sensations. However, when these afferents have receptive fields in a zone of secondary hyperalgesia their activation begins to produce painful sensations.

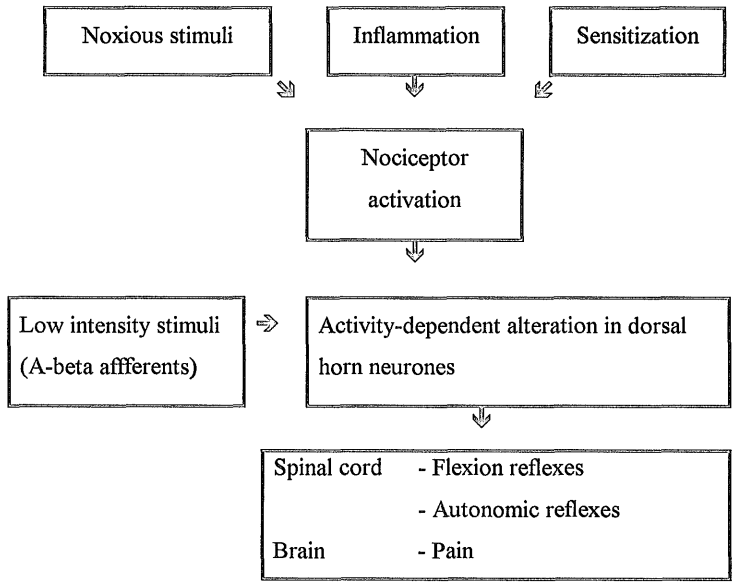
The pathology behind this lies in the capacity of neurones in the dorsal horn of the spinal cord to undergo prolonged alterations in their response properties (Levine et al., 1993). This state of central sensitization agrees well with the features of clinical (postoperative) pain (allodynia, hyperalgesia, spread of sensitization, persistent pain).

The nociceptors are activated by noxious stimuli, or following sensitization by low-intensity stimuli, in such a way that they produce activity-dependent alterations in dorsal horn neurones and they begin to respond in an abnormal (exaggerated) way to A-beta afferent inputs. These afferents transfer electrical signals to the central nervous system (LaMotte et al., 1983; Raja et al., 1988) where they now evoke flexion withdrawal reflexes, autonomic responses and pain sensations (Woolf, 1989). The reason for this is the ability of the small diameter afferents of the A-delta and C afferents to produce slow synaptic potentials in spinal neurones (Thompson et al., 1990).

Two mechanisms operate to facilitate these long lasting depolarizations. The first is the release by nociceptor afferents of neuropeptides, such as SP, CGRP and neurokinin (large myelinated fibres, for example A-beta fibres, do not contain these neuropeptides), which have long lasting effects. The second is that the dorsal horn neurones possess a form of excitatory amino acid receptor, the N-methyl-D-aspartate acid (NMDA) receptor, that acts to prolong the duration of synaptic potentials. When stimulated repeatedly, by identical stimuli, C-fibre afferents send volleys to the spinal cord neurones which, in turn, respond with increasingly greater discharges, producing larger and larger responses. This is known as wind-up (Mendell, 1984). The NMDA receptor has a key role in the induction and maintenance of central sensitization (Woolf and Thompson, 1991).

This series of events shows how a noxious stimulus, by activating nociceptors, can change the excitability of dorsal horn neurones resulting in long lasting changes in the CNS (Woolf, 1991b). The A-beta afferents then begin to produce pain because the receptive field properties of dorsal horn neurones are altered (Woolf and King, 1989). (Fig. 1.4). Now, an increase in synaptic activity, resulting from a brief nociceptive afferent input, will produce an increase in response to standard stimuli, an expansion of the size of receptive fields and a reduction in pain threshold (Woolf and King, 1990).

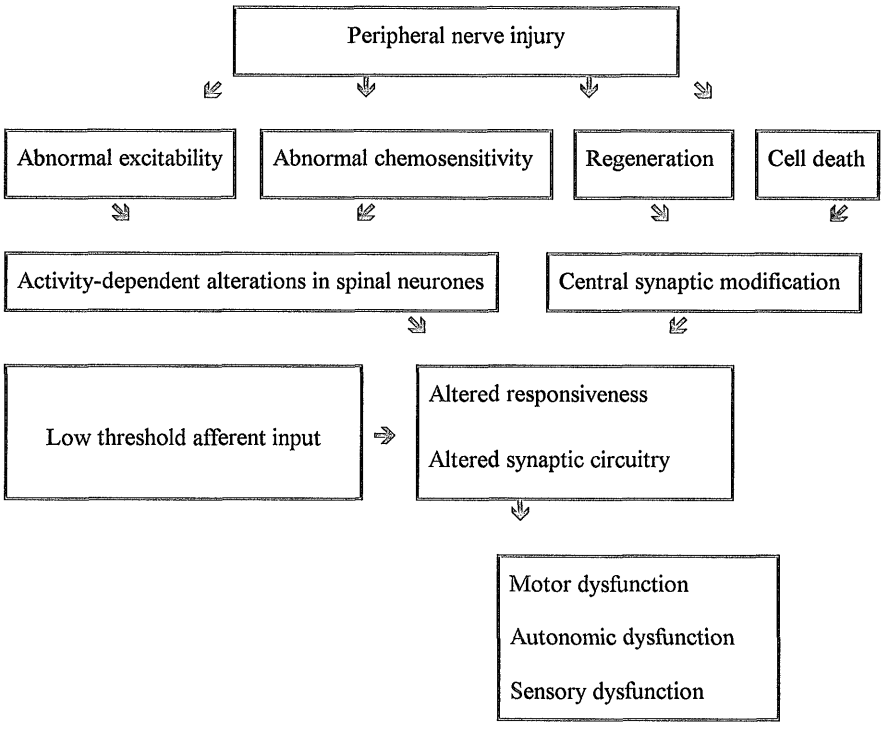
Figure 1.4 A-fibre mediated pain - I. After Woolf (1991a).



The same sort of changes will occur following peripheral nerve injury (Fig. 1.5). Here the pain will have an A-fibre mediated component that is the result of activity dependent changes in spinal neurones and of an altered synaptic circuitry dependent on degenerative and regenerative changes produced by the nerve injury.

Clinically the ability of nociceptive afferents to induce a state of central sensitization is important in the management of all pain states, including postoperative pain. Central sensitization should be prevented if possible. If it has been produced then there is no point in directing treatment at preventing nociceptor activation in the periphery because whilst the nervous system is in an abnormal state it will be driven by low threshold afferents.

Figure 1.5 A-fibre mediated pain - II. After Woolf (1991a).



CHAPTER 2

Postoperative Pain

2.1 Background

Postoperative pain comprises the largest group of patients suffering acute pain yet the treatment of it has been inadequate for many years (Woolf, 1991b). The pain is likely to be short-lived and despite the availability of a variety of opiate and non-opiate analgesics, there has been a complacency in the treatment of postoperative pain. This was in complete contrast to chronic pain, into which much research has been conducted and pain clinics have been an integral part of anaesthetic departments for many years. Acute (postoperative) pain may have fallen behind in research because of its transitory nature, although this very fact should render it more amenable to treatment (Ogilvy and Smith, 1992).

It is impossible to accurately predict how much pain a patient will suffer after an operation or how much analgesic will be required to provide adequate pain relief. For a long time it was assumed that the quality of analgesia was insufficient but after numerous studies investigating various analgesic agents and modes of administration it became apparent that the problem was with the method of administration rather than the analgesic agent (Austin et al., 1980a).

In a review of the literature over the last three decades Tamsen (1985) reported that between one-quarter and three-quarters of patients prescibed traditional treatment received inadequate pain relief after surgery. Donovan and colleagues (1987) found that 75% of medical and surgical patients experienced unrelieved pain. From a later study, Ferrante and Covino (1990) estimated that at least 50% of patients experience uncontrolled postoperative pain. This was confirmed by Owen and colleagues (1990b)

in a survey carried out at a teaching hospital in Adelaide, Australia, where they looked at patients' expectations and their experiences of postoperative pain and found that more than half of patients had pain for all or most of the time.

Until 2-3 years ago there had been no apparent improvement in the management of acute pain in Great Britain since the first world war. In some centres it is still routine practice to treat postoperative pain with an intramuscular (i.m.) injection of a fixed dose of opioid, on a fixed, or pro re nata (prn), basis, regardless of the knowledge that it provides poor pain relief.

Historically, effective anaesthesia evolved in the middle of the 19th century and this led to recognition of postoperative pain which required immediate attention (Raj, 1993). In the early 1900s, the surgeon George Crile suggested that the control of postoperative pain could favourably influence the results of surgery (Crile and Lower, 1914) but not until the late 1940s were postanaesthesia recovery units well established (Brown, 1989).

It was in 1952 when the first study was carried out to evaluate the efficacy of various analgesics (Papper et al., 1952). Since then numerous studies have been conducted, all with similar results. For example, Donovan and colleagues found that after conventional i.m. treatment 58% of patients suffered excruciating pain (Donovan et al., 1987). Owen and colleagues' research, also after i.m. therapy, revealed that 37% of patients considered their pain to be severe or unbearable after 24 hours and 26% suffered severe pain after 72 hours (Owen et al., 1990b).

Marks and Sachar (1973) were probably the next notable authors to renew interest in the management of pain. In their survey of 37 medical patients requiring opioid analgesia, 32% continued to suffer severe distressing pain and 41% moderate pain. The authors concluded that the results were due to poor analgesic usage and fear of

addiction. Admittedly this was not a survey conducted with surgical patients but other authors who have studied surgical patients concur with these findings (Cohen, 1980; Donovan, 1983; Weis et al., 1983; Seers, 1987, 1989).

Investigations involving children have generally corroborated the extent of undertreatment of postoperative pain. Mather and Mackie (1983) analysed the incidence of postoperative pain in 170 children in two teaching hospitals. They found that 25% were pain-free on the day of surgery whilst 13% experienced severe pain and 53% were pain-free on the first postoperative day compared with 17% who were in severe pain. Overall 48% of medicated patients reported moderate or severe pain at one time or another.

In the early 1990s the main criticisms of contemporary practice of providing postoperative analgesia were against the administration of an i.m. injection. This method does have its advantages. For instance, it is familiar practice for doctors and nurses, special equipment is not necessary nor is there any need for additional experienced personnel to operate it. Additionally, the gradual onset of analgesia allows time for monitoring of side-effects (Mitchell and Smith, 1989).

However, i.m. therapy does have some drawbacks, which often result in poor pain control, thus rendering it an unsatisfactory method of providing postoperative pain relief. One of these is that postoperative pain management is often delegated to junior staff with limited experience. Another is the fear of drug addiction and/or side-effects (especially respiratory depression) which has led nursing staff to withold medication (Weis et al., 1983; Seers 1989; Smith, 1989a). Cohen (1980) and Sriwatanakul and colleagues (1983b) demonstrated that when nurses were allowed to choose from a range of drug doses, the lowest dose was chosen repeatedly regardless of the patient's response. Ten years later, Kuhn and colleagues (1990) confirmed that medical and nursing staff still failed to prescribe and administer analgesics with reference to

individual response. During the past five years, fortunately there has been some progress and the practice of administering postoperative analgesia has improved with the advent of acute pain teams (Justins and Richardson, 1991) and increasing use of PCA (Chapter 4).

Judging pain is difficult and so is measuring it (Chapter 5) as the experience is purely subjective. Adjusting the dose of analgesic to achieve a measured effect is also difficult because of interpatient variability (Osborne et al., 1990). It is necessary to find the optimal balance between pain relief and side-effects. Patient-controlled analgesia is one form of therapy that appears to have found this balance (Hill and Mather, 1993). The variability of individual analgesic requirements and fluctuation in blood levels leads to over and under prescribing resulting in inadequate analgesia and sedation. In addition, pain is enhanced by the delay between a patient's request and administration of the drug (Hug, 1980).

Patients' perceptions account for another reason towards unsatisfactory pain relief. Their expectation of good pain relief is low (Kuhn et al., 1990; Owen et al., 1990b; Lavies et al., 1992). In one study Owen and colleagues demonstrated that preoperatively 42% of patients expected moderate pain and 13% severe pain. Postoperatively only 27% expected complete relief from pain after analgesics and 65% were prepared to only ask for analgesics when the pain became severe. Just 6% of patients asked for analgesics regardless of how much pain they were in.

There is also some evidence of diurnal variation in patients' experience of postoperative pain (Burns et al., 1989; Park and Fulton, 1991). Burns and colleagues found that patients demanded more analgesics at 0900h and 2000h when presumably the activity of morning toiletry and evening visiting took its toll, whereas Park and Fulton found postoperative pain to be more severe in the afternoon rather than the morning.

2.2 The Incidence of Postoperative Pain

Rawal (1992) describes the factors leading to the incidence of postoperative pain. These include: the physiological and psychological make-up of the patient; patient's preparation for surgery (pharmacological and psychological); the site of operation; the nature and duration of surgery; the occurrence of postoperative complications; the anaesthetic management and postoperative care.

Parkhouse and colleagues (1961) investigated the incidence of postoperative pain in 1,000 general surgery patients. The interval between the return from the operating room and the administration of the first injection for pain and the total number of injections received in the first 48 hours was assessed. The authors found that the site of operation was the single most important factor affecting the severity of postoperative pain and that operations on the upper abdomen were the most painful. This finding was also corroborated by Yeager (1989).

Age, sex, race, cultural background, individual personality and other psychological variables also affect the experience of postoperative pain irrespective of the method used for its relief (Hashish et al., 1988; Burns et al., 1989; Thomas et al., 1990; Thomas and Rose, 1991).

There is some dispute as to the effect of age on the severity of postoperative pain. Miller and Shuter (1984), for example, found that patients over 40 years of age reported more pain than younger ones. Yet, Kuhn and colleagues (1990) found no differences between age and severity of postoperative pain and neither did Mather and Mackie (1983) in their studies with children.

Kaiko (1980), in a study of 946 surgical patients ranging from 18 to 89 years of age, found that 50% of the oldest patients experienced an average of 5 hours of pain relief

compared with 3 hours for the youngest. He concluded that the duration of analgesia, rather than its peak effect, is responsible for age-related differences. This could be due to a decline in the function of organs responsible for drug breakdown and elimination. Kaiko's findings, however, have been supported elsewhere (Bellville et al., 1971; Berkowitz et al., 1975; Taenzer et al., 1986; McQuay et al., 1990).

There is also conflicting evidence of the influence of gender on postoperative pain. Pain scores in some studies have shown that women generally exhibit more pain than men (Nayman, 1979; Miller and Shuter, 1984). Kuhn and colleagues (1990), however, found no differences between the sexes. This may be due to a difference in expression of pain. Conversely, with respect to analgesic consumption, Burns and colleagues (1989) and Nayman (1979) found that males consumed more medication than females. Streltzer and Wade (1981) could find no significant differences between males and females in the postoperative consumption of analgesics and studies using patient-controlled analgesia have also demonstrated that there is no sex difference in demand for analgesics (Dahlstrom et al., 1982; Tamsen et al., 1982b, 1982c).

It is becoming increasingly obvious that psychological factors influence the experience of pain and may account for much of the variation in response to surgery and to opioid analgesics (Chapman, 1985; Craig, 1989; Heath and Thomas, 1993a).

Chapman (1985) divides psychological factors into two types: predisposing and situational factors. The predisposing factors consist of personality type; intelligence level; social class; family history. With regard to personality, the most frequently documented psychological consequence of acute pain appears to be anxiety and it has been shown that patients with low pain tolerance demonstrate high scores on anxiety and neuroticism personality scales (Austin et al., 1980b).

Various studies of preoperative state anxiety[2] and its relation to postoperative pain and analgesic requirements have consistently demonstrated significant correlations (Lim et al., 1983; Scott et al., 1983; Thomas et al., 1990).

In addition to this, other studies have shown that there is a correlation between preoperative neuroticism scores and impairment of postoperative vital capacity and a consequential increased incidence of postoperative chest infection (Parbrook et al., 1973; Boyle and Parbrook, 1977).

The situational factors involved in the psychological response to surgery include the attitudes of the nursing and medical staff and the response of other patients to pain and the ward environment itself (Chapman, 1985). Thirty years ago, Egbert and colleagues demonstrated that analgesic requirements could be cut by half when anaesthetists, preoperatively, took the time to explain about pain and how to reduce its severity by protecting and relaxing abdominal musculature (Egbert et al., 1964). Other studies have also shown that oral and written information can reduce postoperative pain and anxiety (Leigh et al., 1977).

2.3 The Mismanagement of Postoperative Pain

Uncontrolled postoperative pain has a potential for many side-effects (Brown, 1989; Yeager, 1989). These include: nausea and vomiting (Andersen and Krohg, 1976); slow recovery from surgery; increased morbidity in the postoperative period; reduced or delayed normal pulmonary function; decreased mobility (leading to the postoperative complications of thrombosis and embolus) and an increased catecholamine response causing cardiac arrythmias, hypertension and myocardial ischaemia (Rawal, 1992).

[2] "State anxiety" is a transitory emotional condition that varies in intensity and is associated with particular circumstances. This is in opposition to "trait anxiety" which is a personality disposition that predisposes people to become anxious.

To give an indication of how many people could suffer from mismanaged postoperative pain Raj (1993) quotes from a study conducted in the USA which surveyed 25.6 million patients undergoing surgery in short stay hospitals. Of these patients, 655,000 had hysterectomies, 536,000 had cholecystectomies and 308,000 had gastrectomies. The operations cited above would certainly produce postoperative pain (Parkhouse et al., 1961).

Therefore the search for new drugs and exotic ways to deliver them may well have obscured some of the basic principles which should guide the management of acute pain. The failure of standard regimens is often due to the unpredictable variability of pain intensity, patient characteristics and pharmacological responses. Unrelieved acute pain produces psychological, physiological and socioeconomic consequences.

The above echoes the findings of the Working Party on Pain after Surgery (Royal College of Surgeons and Anaesthetists, 1990) and concurs with Justins and Richardson (1991) when they state that ideally overall management of postoperative pain should be delegated to an acute pain service team. This team would be wholly dedicated to the control of acute postoperative pain. These teams are well established in the USA (Ready et al., 1988), and are appearing in parts of Australia (MacIntyre et al., 1990) and the UK (Wheatley et al., 1991), many of which include PCA (Notcutt and Morgan, 1990; Wheatley et al., 1991). In the Trent Regional Health Authority 90% of acute hospitals have them but they need to to be a standard feature in all hospitals where patients may expect to experience pain.

CHAPTER 3

The Management of Postoperative Pain

3.1 Background

> "The aims of management in acute pain are to minimize discomfort, facilitate recovery and avoid treatment side-effects. Any method must be effective, safe, feasible and cost effective and should balance analgesia and side-effects on the one hand against pain and the patient's wishes on the other."
>
> (Justins and Richardson, 1991).

As with all other types of pain, acute postoperative pain is a highly complex sensation and in the past the traditional treatment of it has failed to recognize this (Chapters 1 and 2). To recap, acute pain may be seen as an integration of three components: afferent nociceptive stimulation, interpretation of these signals by higher centres (involving memory and experiences of painful situations) and an emotive (affective) component which generally comprises anxiety and, for example, depression.

The adequate treatment of pain in the postoperative period is important not only from a humanitarian point of view but also from a physiological aspect. Physiologically pain, especially uncontrolled pain, has many detrimental effects on the cardiovascular system (Yeager et al., 1987), respiratory system (Jones et al., 1990; Wheatley et al., 1990) and on gastrointestinal function (Thoren and Wattwil, 1988; Wattwil, 1988). Pain may also mediate the surgical stress response (Kehlet, 1989).

The endocrine, metabolic and inflammatory responses to surgical injury and infection are the combination of physiological changes called the surgical stress response (SSR). Kehlet defines postoperative pain as a neural stimulus and subsequent release

mechanism for the SSR. He argues that effective postoperative analgesia does not necessarily decrease SSR because of incomplete afferent neural blockade of several fast conducting pathways, instead, he feels that it is highly dependent on the technique used to provide postoperative pain relief.

Yeager, on the other hand, is of the view that pain affects global organ function because the stress response to surgery manifests itself in various metabolic effects. These effects may lead to organ dysfunction and possibly disease. Therefore, as pain is an important stimulus for neuroendocrine activation, controlling pain will control the surgical stress response (Yeager, 1989).

Good pain relief not only reduces the risks of postoperative complications, but also aids early mobilization and decreases the time spent in hospital (Finley et al., 1984; Heath and Thomas, 1993f). It has also been suggested that it may help to decrease morbidity and even mortality (Kehlet, 1988; Scott and Kehlet, 1988; Cousins, 1989).

The biggest problem in acute pain management is the variability of pain (incidence, intensity and time course), of patient characteristics and of pharmacological factors. Opioids along with local anaesthetics and nonsteroidal anti-inflammatory drugs (NSAIDs), form the cornerstone of effective pharmacological management of postoperative pain. Although they have been administered by every conceivable route, the effect of changing route with the same drug may be greater than that of changing the drug within the same route (McQuay, 1991).

In recent years there have been two predominant topics of interest to enable postoperative pain to be managed more effectively. One, is in attempting to optimize the systemic administration of opioids by PCA, the other is in looking to improve on systemic opioid administration by applying opioids more or less directly to the spinal cord, whereby analgesia is administered by the intrathecal or epidural route.

This chapter deals with the action of opioids, routes of administration in current practice, and the alternatives to opioid analgesia.

3.2 Opioids

The terminology for describing morphine and its analogues can be quite confusing. Morphine is the major active constituent of opium which has been used for the relief of pain for over 2,000 years (Tainter, 1948). Opium is extracted from the juice of the unripe seed capsules of the poppy plant. Raw opium is the dried powdered mixture of at least 20 alkaloids, several of which have analgesic properties, for instance morphine and codeine. The name opium is derived from the Greek word opion (meaning poppy juice). All of these naturally-occurring substances are known as opiates.

Pure morphine was extracted from opium by the German chemist, Serturner, in 1806 as Principium Somniferum (he renamed it morphine in 1817). Its chemical structure was proposed by Gulland and Robinson in the 1920s, but its total synthesis was only completed fully (by Gates and Tschudi) in 1952 (Encyclopaedia Britannica, 1993).

It is now possible to synthesize morphine-like drugs which are not derived from the natural constituents of opium. The term opioid is given to all naturally-occurring opiates (endogenous) and also the newer totally synthetic (exogenous) substances that possess morphine-like properties. While opioid and opiate are commonly used interchangeably, opioid is the term that has been adopted to designate the receptor for these substances and is the preferred term for the agents that interact with these receptors (Mather, 1993).

In the past, narcotic has been used to describe morphine-like drugs which, depending on the dose, also have the properties to induce sleep (narcotic is from the Greek prefix narco meaning to numb or deaden and Morphine is from Morpheus, the Greek god of

dreams). Today, the term narcotic tends to be associated with American drug enforcement agencies who also include a variety of controlled substances (e.g. CNS depressants and stimulants) as being drugs of dependence.

Opioid Receptors

Opioid drugs, such as morphine, affect the perception of pain, consciousness, motor control and autonomic function by interacting with specific receptors now known as opioid binding sites. These sites were first demonstrated by Pert and Snyder (1973) more than 20 years ago and they exist throughout the central and peripheral nervous system. The endogenous ligands of the opioid receptors comprise a family of opioid peptides. The first of these peptides were discovered by Hughes and colleagues (1975) in extracts of pig brain. They called these compounds enkephalins. Soon after this, two more opioid peptides; endorphin[3] (Bradbury et al., 1976) and dynorphin (Goldstein et al., 1979) were described and since then at least six more opioid peptides have been isolated.

Morphine, and other opioids, mimic the actions of these naturally occurring peptides. Morphine remains the most widely used analgesic for moderate to severe pain (Pasternak, 1993) and, unlike local anaesthetics, it does not change sensory thresholds but instead eliminates the subjective feeling of pain. Anecdotally, patients receiving morphine often report that the pain remains but it does not bother them. This is particularly true with PCA whereby patients can titrate their analgesic requirements against unwanted side-effects, and frequently opt for some algesia.

In the 1960s it had been assumed that there must be multiple opioid receptors in order to explain the agonistic-antagonistic effect of nalorphine (n-allynormorphine, a derivative of morphine) which had been observed clinically (Akil et al., 1976). Martin

[3] Endorphins are larger peptides and these contain sequences of aminoacids that can be split off as enkephalins.

(1979) proposed the concept of receptor dualism (one receptor for morphine and one for nalorphine) and that nalorphine was an antagonist at the morphine site and an agonist at the nalorphine site (Table 3.1).

Table 3.1 Alternative Classification of Opioids. From Twycross (1994).

Class	Definition	Example
Agonist	A drug which, when bound to the receptor, stimulates the receptor to the maximum level; by definition, the intrinsic activity of a full agonist is unity.	Morphine
Antagonist	A drug which, when bound to the receptor, fails completely to produce any stimulation of that receptor; by definition, the intrinsic activity of a pure antagonist is zero.	Naloxone
Partial agonist	A drug which, when bound to the receptor, stimulates the receptor to a level below the maximum level; by definition, the intrinsic activity of a partial agonist lies between zero and unity.	Buprenorphine (partial mu agonist)
Mixed agonist-antagonist	A drug which acts simultaneously on different subtypes, with the potential for agonist action on one or more subtypes and antagonist action on one or more subtypes.	Pentazocine (partial mu agonist, kappa agonist, delta antagonist)

Martin and colleagues (1976) subsequently extended the classification of opioid receptor subtypes, naming them after the drugs used in their studies; mu (morphine), kappa (ketocyclazine) and sigma (SKF 10047, N-allylnormetazocine). A year later

Lord and colleagues (1977) discovered a binding site in the isolated mouse vas deferens which they named the delta (deferens) receptor.

Only mu, delta and kappa receptors are currently recognized as opioid receptors and all three mediate analgesia (Atcheson and Lambert, 1994). The sigma receptor was originally thought to be an opioid receptor but recent work has disproved this (Walker et al., 1990). Walker and colleagues demonstrated that sigma receptor-mediated effects are not reversed by high concentrations of opioid antagonists, such as naloxone. In addition, whereas opioid receptors are enantioselective for negative isomers of opioid receptor agonists and antagonists, sigma receptors are enantioselective for the corresponding positive isomers.

The understanding of this, and indeed opioid receptors per se, relates to the importance of the stereochemistry of opioids. Usually only one enantiomer[4] of an enantiomer pair is effective as an opioid agonist or antagonist (Beckett, 1959), therefore it is to be expected that only the effective enantiomer will bind to any relevant receptor and produce the relevant effect. This is in contrast to non-specific binding to recognition sites, sites that recognize and accept the general chemistry of the molecule (Laduron, 1984).

No endogenous opioid is specific for any one receptor. The dynorphin-related peptides and the enkephalins appear to be the endogenous ligands for kappa and delta receptors respectively. It is not clear whether beta-endorphin or morphine itself is the endogenous ligand for the mu receptor (Kosterlitz, 1987). Table 3.2 lists the current state of knowledge of the characteristics of these three opioid receptors (Atcheson and Lambert, 1994).

[4] Enantiomers (enantiomorphs/optical isomers) may be defined as stereoisomers in which the atoms or groups comprising the compound are arranged in two different ways to form two molecular species which differ from one another only as an object differs from its mirror image (i.e. the structure is not superimposable on its mirror image).

Table 3.2 Characteristics of mu, delta and kappa opioid receptors.[5,6]

	Receptor		
	Mu	Delta	Kappa
Endogenous Ligand	Beta-endorphin?	Enkephalin	Dynorphin
Exogenous agonist	Morphine, fentanyl, DAMGO	DPDPE, DSLET	Enadoline, U50,488H, U69,593
Antagonist	CTOP, naloxonazine	Naltrindole	NorBNI
Cloned	Yes	Yes	Yes
Subtypes	$mu_{1,2}$	$delta_{1,2}$	$kappa_{1,2,3}$
Adenylate cyclase	Inhibits	Inhibits	Inhibits
Voltage-dependent calcium channels	Inactivates	Inactivates	Inactivates
Potassium channel conductance	Increases	Increases	
Function	Analgesia, respiratory depression, constipation	Analgesia, respiratory depression ?	Analgesia, respiratory depression ? diuresis, dysphoria

[5] Apart from morphine, fentanyl, naloxone and enadoline (currently undergoing clinical trials), the agonists and antagonists illustrated are restricted to the laboratory. They are important because their introduction helped considerably the characterization of the various receptor subtypes. Naloxone is active at mu, delta and kappa receptors. DPDPE = [D-Pen^2, D-Pen^5] enkephalin, DAMGO = [D-Ala^2, MePhe^4, Gly(ol)^5] enkephalin, DSLET = [D-Ser^2, Leu^5, Thr^6] enkephalin, NorBNI = norbinaltorphimine, CTOP = D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH_2

[6] From Atcheson and Lambert (1994), with permission.

Opioid receptors belong to a family of G protein-coupled receptors. G proteins are essential intermediaries in cell communication; they underlie hormonal control of metabolism and are key elements in normal brain function (Yost, 1993). During the past decade the understanding of basic cellular processes has increased markedly. This has permitted exploration of the molecular mechanisms of the cellular effects of drugs, such as opioids, which act through G proteins. In addition, molecular biology techniques have enabled the cloning of opioid receptors (mu, delta, kappa and their subtypes), and their amino-acid sequence has been defined (Evans et al., 1992; Chen et al., 1993; Yasuda et al., 1993). This is of immense importance for clinical use as it should now be possible to develop highly selective (i.e. subtype specific) receptor agonists and antagonists (Atcheson and Lambert, 1994).

There are significant pharmacological and functional differences between the receptor subtypes. For instance morphine produces analgesia via mu_1 (supraspinal) and mu_2 (spinal) receptors and respiratory depression via mu_2 (brainstem) receptors. Understandably the distinction between mu_1 and mu_2 systems are important with regard to the (increasing) use of epidural and intrathecal morphine, and other opioids (Pasternak, 1993).

Activation of opioid receptors directly decreases neurotransmission by presynaptic inhibition of neurotransmitter release or postsynaptic inhibition of activity (Mulder and Schoffelmeer, 1993). The reduction in neurotransmitter release is due to increased potassium conductance (leading to hyper-polarization), calcium channel inactivation, or both (North, 1993).

The nervous system displays considerable functional plasticity. In contrast to the general inhibitory effects of opioids, excitatory effects have also been observed. In an arthritic rat model very low doses of morphine have been shown to produce hyperalgesia, and increased doses, analgesia (Kayser et al., 1987). In addition,

electrophysical studies have shown that low doses of opioids can prolong the action potential by either decreasing potassium or increasing calcium conductance (Crain and Schen, 1990). The reasons for these excitatory effects are unclear but it has been suggested that they may represent an early warning system of noxious stimuli at certain critical sensory neurones, or account for some of the side-effects of opioid analgesics, such as pruritus and euphoria (Atcheson and Lambert, 1994).

Further electrophysical studies have shown that following peripheral inflammation functional changes develop in both spinal transmission and modulatory systems. This resulted in alterations in the potency of opioid agonists, particularly the mu agonist morphine, which showed a 30 fold increase in potency (Stanfa et al., 1992).

Traditionally, opioid analgesia has been associated with the activation of opioid receptors in the CNS exclusively (Stein, 1993). However, there is increasing clinical evidence to suggest that exogenous and endogenous opioid agonists also evoke peripheral analgesic effects. In one study, morphine administered intra-articularly, following arthroscopic knee surgery, elicited a profound analgesic effect without evidence of significant systemic absorption (Stein et al., 1991).

The majority of clinically used opioids are preferentially, but by no means specifically, mu receptor agonists. No mu agonist is totally mu specific. Morphine, for example, is principally a mu receptor agonist (97.5%) although it does have some activity at the delta (1.9%) and kappa (0.6%) receptors (Kosterlitz and Paterson, 1990).

3.2 Pharmacodynamic and Pharmacokinetic Factors Influencing the Administration of Opioids

Pharmacodynamics is concerned with the action of drugs on the body. There is a relationship between the plasma opioid concentration and the degree of analgesia and its severity of side-effects. Increased concentrations are associated with greater analgesia but increased side-effects. The lowest opioid concentration which will produce analgesia with minimal side-effects has been described as the minimum effective analgesic concentration (MEAC) (Austin et al., 1980b). However between patients there is a 2-5 fold variability in blood drug concentrations required to relieve pain (Austin et al., 1980a; Gourlay et al., 1988; Lehmann et al., 1988) and the validity of the MEAC has been challenged (Owen et al., 1990a).

The study of pharmacokinetics is concerned with how the body handles a drug; how it is absorbed, distributed, metabolized and excreted. There are great variations in plasma opioid concentrations after an i.m. injection, for example. Studies of multiple injections of pethidine (administered in the gluteal muscle) have shown that maximum blood concentration may occur from 10 minutes to 90 minutes, accompanied by a four-fold variability in the maximum blood concentrations attained (Mather et al., 1975a; Austin et al., 1980a). Similar four-fold differences have been found after intravenous (Mather et al., 1975b; Austin et al., 1981) and oral (Mather and Tucker, 1976) administration.

The pharmacokinetic properties of opioids can be affected by the extremes of age, pathophysiology and the actions of other drugs. To take pethidine for an example, the mean total body clearance tends to be reduced and the half-life tends to be increased in both very young and elderly people (Mather, 1986). Liver disease reduces the hepatic metabolic clearance of pethidine and prolongs its half-life without altering the distribution (this does not follow with morphine probably because metabolism in the kidneys can compensate). Anaesthesia with halothane, propofol or thiopentone can

reduce the clearance of pethidine by decreasing the hepatic blood flow whilst at the same time decreasing hepatic extraction (Mather et al., 1986, 1990).

It is also necessary to understand the specific metabolism of each opioid. Morphine, for example, produces metabolites each having a lower clearance than morphine itself and which are eliminated by the kidneys. The principal metabolites of morphine in man are morphine 3-glucuronide (M3G) and morphine 6-glucuronide (M6G). M3G is inactive although on continued dosing of morphine the blood concentrations of M3G may be many times more than those of morphine (Glare and Walsh, 1991). Some investigators have suggested that M3G is antagonistic to morphine and M6G (Smith et al., 1990; Gong et al., 1992). M6G, which can be found in similar blood concentrations (but is many times more potent) to morphine, is active as an analgesic agent in its own right and in both single and repeated doses may contribute substantially to the analgesic effect of morphine (Osborne et al., 1992; Portenoy et al., 1992). Prolonged respiratory depression has been reported in patients with impaired renal function in association with negligable plasma concentrations of morphine but with very high concentrations of M6G (Osborne et al., 1986). Conversely, a study with healthy volunteers revealed less respiratory depression with M6G than with morphine sulphate (Peat et al., 1991).

Pharmacokinetic and pharmacodynamic factors are not predictable in most people and the variability between patients in the dose-blood concentration relationship has been shown to be one important cause of the variability in effect of opioid analgesia (Austin et al., 1980a). Standard regimens cannot cater for this variability and to be effective analgesic administration needs to be tailored for each individual. Recognition of these points has provided a basis for the development of rate-controlled delivery of opioid analgesia. The ideal is that a steady plasma concentration will be reached, such that analgesia will be maintained without causing toxicity.

Traditionally it is clinical practice to calculate opioid requirements on a body-weight basis (mg/kg). Austin and colleagues (1980a), however, found no evidence in adults to suggest there is any reason to do this and clinical observation would bear this out. Many, so-called, "thin" people require the same amount (or more) of analgesic agent as their "fatter" counterparts.

3.3 Side-effects of Opioid Drugs

The side-effects of opioid drugs occur largely because the stimulation of opioid receptors produces many effects other than that of analgesia. The majority of clinically used opioids are mu receptor agonists which produce analgesia along with the (unwanted) side-effects. Unfortunately these side-effects often become unacceptable to patients before adequate analgesia is achieved. Although the side-effects differ in quality and quantity, they most commonly include: nausea, vomiting, constipation and drowsiness. In larger doses respiratory depression and even death may occur. It is this risk that often leads to over-cautious prescribing by medical staff (Mather, 1993).

Another reason for medical and nursing staff being over-frugal with their administration of analgesics is the fear of dependence (Marks and Sachar 1973; Cohen, 1980; Seers, 1989). In fact postoperatively this is extremely rare. In 1980 the Boston Collaborative Drug Surveillance Programme examined the files of 11,882 inpatients who had received therapeutic opioids. They found only four clear cases of dependence in individuals with no previous history of addiction (Porter and Jick, 1980). This puts the incidence at 1:3,000 and it has been suggested that those who administer opioids are at more risk of addiction than those who receive them! It is generally recognized that physical and psychological dependence is rare in patients treated for postoperative pain if medication is discontinued within three weeks (Brown, 1989).

There is a high concentration of mu receptors in the medullary respiratory centre (in the brainstem) which is why opioids are such powerful respiratory depressants. Depression of these neurones results in decreased respiratory rate, tidal volume and minute ventilation, and a right shift in the CO_2 response curve (Borison 1977; Daykin et al., 1986). There is no comparative evidence to suggest that equi-analgesic doses of the various agonist opioids differ in their potential for respiratory depression and so there is no clinical advantage in one mu-agonist over another (McQuay, 1991). Morphine remains the gold standard against which any new drug must be compared (Mitchell and Smith, 1989).

Sedation may be induced with the use of morphine. Mild sedation can be beneficial but over sedation leads to decreased ability on behalf of the patient to co-operate. Over sedation is also a sign of potential respiratory failure. Pulse oximetry is the usual way to monitor opioid (and other) induced ventilatory disturbances. Whilst this is routine procedure in the operating theatre, and sometimes in the recovery ward, it is not always continued once the patient is transferred to the ward. Although the warning is given from the pulse oximeter after arterial oxygen desaturation has occurred it is better than no warning at all. There is evidence for linking desaturations to clinical morbidity and mortality (Chapter 9) in that they are often accompanied by the type of cardiac arrythmias which may signal disaster in certain individuals (Pateman and Hanning, 1989).

Opioids also suppress the cough reflex (this is why morphine and codeine are found in small amounts in some cough preparations). This is an undesirable effect after surgery as an active cough reflex will reduce the risk of chest infection.

All mu-agonists delay gastric emptying (Nimmo, 1981) and decrease gastrointestinal motility (Wattwil, 1988) which may result in constipation. Nausea and vomiting are triggered by stimulation (for example, by opioids) of the chemoreceptor trigger zone

(CTZ) which is in the medulla. There is the risk, therefore, of inhalation of gastric contents and aspiration pneumonia. Morphine also causes spasm of the bowel wall and there is some evidence that its use in the postoperative period is associated with anastomotic dehiscence (Aitkenhead and Robinson, 1989).

All mu-agonists can also cause spasm of the sphincter of Oddi and subsequent biliary tract hypertension, resulting in biliary colic. This spasm can be antagonized by naloxone.

Urinary retention may also occur. It is characterized by an increased urgency and urinary sphincter pressure is increased. For some time this side-effect was attributed to the administration of epidural opioids but it does also occur after intravenous and intramuscular injections of opioids. Tolerance to this effect occurs rapidly and is also reversed by naloxone (Mather, 1993).

Opioids may cause arterial and venous dilation due to either direct activity or histamine release (Levy et al., 1989). The propensity for each depends on the opioid. For instance morphine and pethidine may cause both venous dilation and histamine release, but fentanyl (a cogener of pethidine) is believed to cause neither (Ferrante, 1993a). In high doses opioids cause some direct myocardial depression but this effect is not noticeable in the normal therapeutic range (Ferrante, 1993a).

Tolerance may also be seen as a side-effect (McQuay et al., 1981). This is the need for a bigger dose (or higher plasma concentration) to achieve the same pharmacological effect. Addicts develop tolerance but the distinction here is that they use opiates in the absence of pain. Acute tolerance to opiates (McQuay, 1991) has been demonstrated in animal studies and also in man (McQuay et al., 1981; Marshall et al., 1985) but clinically it is somewhat of an enigma. When drugs are used in appropriate doses to treat pain which is opiate sensitive, tolerance (like respiratory depression) is not a

problem. When opiates are used in the absence of an opiate sensitive pain, or in inappropriately high doses when the pain is sensitive, then tolerance (like respiratory depression) can occur.

Opiate insensitive pain may be defined as pain which does not respond progressively to an increasing opiate dose. This is more likely to be demonstrated in chronic pain states as not all chronic pains are relieved by opiates. The most common causes of opiate insensitive pain are nerve compression and nerve destruction (Arner and Meyerson, 1988; McQuay, 1988). There are some types of acute pain that are opioid sensitive and others that are less so (McQuay, 1988). Clinically, it is well accepted that some patients are more responsive to one type of opioid than another but there needs to be more research in this area (Mather, 1993).

All opioids cause dysphoria, some less than others. For example, there is a greater than 20% incidence with pentazocine and nalbuphine compared with a 3% incidence seen with other opioids (McQuay, 1991). There is little sense, therefore, in using an agent which causes a high incidence of dysphoria unless it has other compensating advantages.

In recent years some work has been carried out on the use of kappa receptor agonists as mediators of analgesia as they do not exhibit the side-effects characteristic of mu-agonists, for example respiratory depression and constipation. Unfortunately they are associated with other side-effects such as sedation, dysphoria and diuresis. They also provide weaker analgesia. Pentazocine is one example of an agent found to have kappa-agonist activity. Like most opioids it is not receptor specific, sometimes having mu-agonist or antagonist activity (Millan, 1990). Further work is being carried out on several kappa agonists (e.g. enadoline - Hunter et al., 1990) in an attempt to find the ultimate analgesic agent (i.e. without the side-effects).

New methods of opioid administration, especially PCA (Hill and Mather, 1993), have decreased the problems of interpatient variability by achieving optimal analgesia with minimum side-effects. Whilst there are still relatively large pharmacokinetic and pharmacocologic differences between drugs and pharmacokinetic and pharmacodynamic differences between patients, preselection of the ideal prescription for each patient is extremely difficult. Whatever route is used, treatment of pain by opioids is best served by regular evaluation with a view to dose revision (Mather, 1993).

3.4 Routes of Administration for Opioids

There are two routes which enable the administration of opioids to reach their receptors in the brain and spinal cord (Mather, 1991). There are those in which the drug has direct access to receptors by diffusion, and/or bulk flow (epidural, intrathecal and intracerebroventricular) and those where it has indirect, or blood-borne, access (intravenous and virtually all absorption routes).

The direct routes of administration of opioid analgesics offer the possibility of regionally selective effects and allow minimal doses to be used. This is because of the proximity of delivery to the required region. The indirect routes, however, lead to the drug being dispersed in the general circulation. Regional selectivity is, therefore, highly unlikely as all regions of the body receive distribution of the drug in proportion to their share of cardiac output.

Intramuscular Route

Simplicity and economy would appear to be the only advantages with the i.m. method of administering opioids. The injections are painful and, as discussed, there is a wide variation in absorption, onset, peak, duration and toxicity. As peak concentration rises with successive injections there is an increased risk of respiratory depression (Wheatley

et al., 1990). Adequate, regular administration of opioids can produce high quality analgesia but sadly this rarely occurs in a ward environment. Patient-controlled administration has been used (Davenport and Wright, 1980), but requires a larger dose than intravenously because of the unpredictable uptake of opioid from the muscle.

Subcutaneous Route

This method is generally used for controlling chronic pain. It is simple and often effective, particularly when used as an infusion where it may be combined with PCA (White, 1990; Walsh et al., 1992). Unfortunately, as with the i.m. route, the method is prone to wide variability because of unpredictable uptake from the subcutaneous tissue.

Oral Route

The oral route is not ideal for acute pain control because first-pass metabolism by the liver results in variable bioavailability (Sawe et al., 1981) which leads to unpredictable results. Using intravenous morphine it has been shown that the oral-to-intravenous potency ratio is 1:3; i.e. a 10 mg dose of intravenous morphine is equivalent to a 30 mg oral dose (Kalso and Vainio, 1990). Postoperative gastric stasis, vomiting and inability to swallow also limit the usefulness of this route. Controlled release preparations of morphine (MST) (Kaiko, 1989) have compared favourably with traditional techniques (Derbyshire et al., 1985) but due to the delay in intestinal absorption, in the first 24 hours following surgery, it is not a satisfactory formulation to use in the postoperative period (Pinnock et al., 1986).

Buccal and sublingual Route

The kinetic logic behind this route is that the opioid is absorbed systemically (analogous to an intramuscular dose) avoiding any first-pass metabolism and so increasing relative systemic bioavailability. Clinically this is important as any given dose

should be more predictable than an oral dose because it is the variability of first-pass metabolism which makes short-term use of oral opiates difficult.

Sublingual buprenorphine is the best example of the kinetic gain in availability. Postoperatively 0.4 mg sublingually is equivalent to 0.3 mg intramuscularly (McQuay et al., 1986a). Buprenorphine has been used successfully as the sole analgesic for major abdominal surgery but the major disadvantages are a relatively high degree of sedation and nausea (Ellis et al., 1982).

Opioids with a high oral bioavailability, such as morphine, do not demonstrate a significant kinetic gain (McQuay et al., 1986b). Claims for kinetic advantage with buccal morphine (Bell et al., 1985) have not been substantiated (Weinberg et al., 1988). In a study carried out by Manara and colleagues (1990) buccal morphine did not significantly reduce postoperative pethidine consumption when compared with placebo.

However, sublingual preparations are particularly useful when strong opioids are necessary but cannot be taken by mouth, or injections are contra-indicated (in haemophiliacs) or if they are problematical (i.e. in children or in the community).

Inhaled Route

In recent years some work has been carried out to investigate the potential of administering opioids via the mucous membranes of the upper respiratory tract. The human respiratory system offers a large area for absorption and as patients receive oxygen postoperatively it would be quite feasible to add opioids to the solution together with a nebulizer connected to the oxygen. A pilot study with inhaled fentanyl has suggested that this is an effective method of administering analgesia and one that merits further investigation (Worsley et al., 1990).

Chrubasik and colleagues (1993a) carried out several studies using a morphine aerosol for the treatment of postoperative pain after cardiac and abdominal surgery. They found that whilst after cardiac surgery the quality of analgesia was comparable to that provided by continuous intravenous morphine therapy, this was not the case after abdominal surgery. The low relative bioavailability in humans during inhalation revealed a large wastage of the drug (65-91%) and accounted for the lack of reliability of the method. However, continuous inhalation of morphine (when compared with continuous intravenous morphine therapy) was associated with far lower serum morphine concentrations and, therefore, less sedation and a lower incidence of side-effects.

Rectal Route

Morphine sulphate suppositories are sustained release preparations that offer an alternative method of administration (Kaiko et al., 1989). Plasma morphine concentration after oral and rectal routes suggests that oral and rectal doses for morphine sulphate are the same (Hanning et al., 1985). This mode of administration may overcome problems of variable absorption and uneven control (Hanning et al., 1988; Hanning, 1990). The route is used for patients who are unable to swallow tablets (Kaiko et al., 1989) and it is useful for children.

Transdermal Route

Topically applied opioids can be absorbed transdermally into the systemic circulation to provide analgesia. This method of administration is simple, has minimal staff demands and is economical. However, as the opioid uptake and distribution is slow, precise control of postoperative pain is difficult.

The rate of absorption is dependent on the degree of lipid solubility of individual drugs and on skin perfusion. The use of fentanyl patches has been shown to produce equivalent plasma concentrations to that of an intravenous infusion delivering the same

dose (Duthie et al., 1988). In their study, Duthie and colleagues demonstrated that in order to achieve an intial high plasma concentration (sufficient to maintain acceptable analgesia) an intravenous loading dose of opioid was required.

Fentanyl patches (100 mcg/h) do not provide adequate analgesia for upper abdominal surgery, but they do reduce opioid requirements administered by other routes (Rowbotham et al., 1989b). Drug absorption is also decreased if skin perfusion is reduced due to hypovolaemia, hypotension or hypothermia. Morphine has been administered by this route but it has a slower absorption rate because of its lower lipid solubility (Ogilvy and Smith, 1992).

Intravenous Route

This route offers the advantage of immediate, reliable uptake of opioid by the systemic circulation, producing rapid onset so that the dose can be titrated for each patient. The main disadvantage is the narrow safety margin between adequate analgesia and serious side-effects. Most intravenous techniques demand a high level of supervision and special equipment, such as syringe pumps.

There are various methods of administering opioids via the intravenous route. An intermittent bolus has the advantage of a rapid, predictable onset allowing titration of dose against pain. This method is labour intensive and toxicity is common. The duration of analgesia is brief and so this method is best suited for acute perioperative administration. Regular intermittent administration of opioids forms the basis of the technique of PCA (Chapter 4).

Continuous infusion of opioids avoids the peaks and troughs of intermittent administration but the pharmacokinetics are complicated and need to be addressed to ensure smoother pain control (Stapleton et al., 1979). Most authors suggest an initial

bolus dose prior to infusion but this dose bears little relationship to the maintenance dose required to control the pain thereafter (Justins and Richardson, 1991).

There are several problems associated with this technique. The most important problem is the potential for overdosage, and therefore respiratory depression (Catling et al., 1980), particularly if the initial assessment of opioid requirement did not take into account the slow onset of some drugs. Continuous infusion techniques should only be used in high dependency areas where the inherent problems of respiratory depression can be diagnosed and treated.

Spinal Route

The clinical use of spinal opioids (Green, 1992) is contentious. It has been suggested that this mode of delivery has a potential for greater morbidity than conventional routes (McQuay, 1991) and some claim that there is no evidence to suggest that spinal opioids produce analgesia superior to that produced by other routes of administration (Morgan, 1989). On the other hand, some authors claim superior analgesia (Cullen et al., 1985; Loper et al., 1989) with spinal routes and reduced morbidity and mortality than with other routes of administration (Yeager et al., 1987). Stenkamp and colleagues (1989), in a retrospective study, found that the length of hospital stay was decreased with the use of spinal opioids, compared with i.m. opioids, in patients following Caesarean section.

The presence of opioid receptors in the dorsal horn of the spinal cord (Pert and Snyder, 1973) is a logical basis for spinal opioid use (Sabbe and Yaksh, 1990), by the epidural and intrathecal routes, although this has been disputed (McQuay, 1991). Compared with conventional routes, epidural and intrathecal administration carry a potentially higher morbidity. Therefore, the use of spinal opioids can only be justified if it results in pain relief of a greater quality and duration than by more conventional routes (Twycross, 1994).

Duration of analgesic effect after spinal opioids is considerably longer than after i.m. injection (Mathews and Abrams, 1980; Kalso, 1983; Paterson et al., 1984). It would appear that epidural administration is associated with a potentially lower morbidity than intrathecally, notably headache and infection (Twycross, 1994). On the other hand spinal opioid availability is less certain with the intrathecal route. Only 10-20% of an epidural dose of morphine (low lipid-solubility) crosses the dura into the CSF. This is reflected in the higher doses used by this method. Extradural morphine, 5 mg twice daily, has been found to be equivalent to 1 mg of intrathecal morphine once a day (Watson et al., 1984). Doses used with infusions have been as low as 0.3 mg/h (Cullen et al., 1985).

Because of the potentially serious complications associated with spinal opioid administration many clinicians feel that patients should be nursed on high dependency or intensive care units. Others suggest that patients are nursed on normal postoperative wards with adequate monitoring techniques, regularly assessed by nursing staff who are following strict protocols (Morgan, 1989).

3.4 Non-opioids

Non-opioid analgesics, such as aspirin and the nonsteroidal anti-inflammatory drugs (NSAIDs) have their main pharmacological action in the periphery where the pain originates, although they do have some activity in the CNS (Malmberg and Yaksh, 1992). They are distinct from the opioid analgesics in that they do not bind to the opioid receptor sites. Non-opioid analgesics are used alone, or in conjuction with opioids to produce an enhanced effect. As a group these drugs are commonly administered orally but can also be administered parentally, topically and rectally.

Unlike opioids, tolerance and physical dependence does not develop with this group of drugs. Non-opioids have a ceiling effect in that increasing the dose beyond a certain

level does not produce additional analgesic effects, although it may increase the duration of the effect. Since many of the peripherally acting analgesics act as potent prostaglandin synthetase inhibitors, they possess analgesic, antipyretic, antiplatelet (i.e. causing the unwanted side-effects of prolonged bleeding) and anti-inflammatory properties.

NSAIDs

NSAIDs have become increasingly popular in recent years for the treatment of postoperative pain. This is largely due to an increased understanding of the role of inflammatory mechanisms in tissue injury and their effects on nociception. They are particularly advantageous as they lack the side-effects of opioids, namely respiratory depression, sedation and dependence.

NSAIDs decrease pain by a peripheral action by inhibiting cyclo-oxygenase, thereby reducing prostaglandin-mediated inflammation at the site of injury. They may also stabilize phagocytic polymorphneutrophils and reduce their release of proteolytic enzymes and reactive oxygen species, thus decreasing tissue inflammation (Ogilvy and Smith, 1992). NSAIDs are also now known to exert an effect within the CNS where administration directly into the spinal intrathecal space diminishes pain (Malmberg and Yaksh, 1992).

Of the several different classes of NSAIDs, those that are proving more useful for postoperative pain are those which can either be given via the i.m. or i.v. routes; such as diclofenac (Campbell et al., 1990), ketorolac (Power et al., 1990) and indomethacin (Maunuksela et al., 1988); or those that can be administered per rectum; such as diclofenac (Colquhoun and Fell, 1989). These routes allow analgesic administration when oral routes are contra-indicated.

It has been reported that NSAIDs provide good analgesia after minor operations when given as the sole analgesic agent (McLoughlin et al., 1990). After major surgery they can provide a useful supplement to other analgesics and have been shown to reduce opioid requirements (Hodsman et al., 1987; Maunuksela et al., 1988; Kinsella et al., 1992) and to be more effective than papaveretum following total hip replacement (Buchanan et al., 1988). Improved and more consistent analgesia may be obtained if NSAIDs are given as intravenous infusions rather than as intermittent i.m. injections (Ogilvy and Smith, 1992).

However, there are well-known side-effects associated with prolonged use of NSAIDs and these include gastric ulceration, decreased renal function and an increased bleeding tendency. Despite claims that short term treatment (< 1 week) with NSAIDs has no effect on morbidity, further studies are required in patients potentially at risk (Dahl and Kehlet, 1991).

3.5 Regional Analgesia

Regional analgesic techniques aim to interrupt nociceptive transmission in the peripheral nervous system, with local anaesthetic, thus blocking the conduction between the peripheral and central processes. There is documentary evidence for local anaesthetic techniques being performed over 100 years ago when Koller (1884) used cocaine to anaesthetize the eye. They are capable of producing complete pain relief without any central depressant effect on consciousness or respiration (Wildsmith, 1989). In addition, it has been reported that reduced muscle tone and sympathetic block may enhance healing; central blocks may suppress the stress response and improve respiration and neural blockade may actually suppress the spinal cord changes which potentiate pain and predispose to painful sequelae (Justins and Richardson, 1991).

There are disadvantages as well. Acute pains may involve both the somatic and visceral pathways which represent a wide spread of spinal segments that may not easily be blocked. Performing blocks requires skill on the part of the anaesthetist and it is time consuming. Failures sometimes occur. Misplacement of needles, drug dose, volume, spread and vascularity may all influence the outcome. Also, as drugs only act for a limited time, repeated administration may be impractical.
As with any method of delivering analgesia there are side-effects. With regional analgesia these may include: immediate complications, such as needle trauma; neural damage, if the needle traumatizes the nerve of an anaesthetized patient; local anaesthetic toxicity, if the dose limits of the local anaesthetic are exceeded. Delayed effects may also occur, resulting from motor or autonomic blockade.

Nerve Blocks

Nerve blocks performed on digits, wrists, ankles, groins and penises, for example, are relatively simple techniques and have been put to good use in outpatient departments and on paediatric units. Intercostal blocks produce very effective analgesia following unilateral abdominal incisions, but whilst they reduce the incidence of postoperative pulmonary complications, the risk of pneumothorax is a major disadvantage (Sabanathan and Mearns, 1990).

Plexus block

With this block, a catheter can be inserted near the brachial (Sarma, 1990) or lumbar (Anker-Moller et al., 1990) plexus and an infusion of local anaesthetic is used to provide continuous analgesia following limb surgery.

Intrapleural block

In this block a local anaesthetic solution is infused via a catheter and inserted into the intrapleural space. This method produces very effective analgesia following thoracotomy and unilateral abdominal operations (Lee et al., 1990). The major

disadvantages of this method are the potential side-effects of pneumothorax and local anaesthetic toxicity due to rapid absorption from the interpleural space (Stromskag et al., 1990).

Paravertebral blocks

This technique is a useful alternative to multiple intercostal blocks because it requires only a single injection of 15 ml of bupivacaine to block up to four intercostal nerves. However, the spread of local anaesthetic solution into the extradural space is possible with subsequent extradural block, and there is also a significant risk of pneumothorax.

Epidural analgesia

Epidural analgesia has all the advantages and disadvantages of regional analgesia for postoperative pain control. These blocks can provide complete pain relief; improve respiratory function; suppress the endocrine-metabolic response; reduce the incidence of thromboembolic episodes; improve gastrointestinal function and speed recovery. The disadvantages are a high incidence of side-effects, such as hypotension, urinary retention and muscular weakness (Chrubasik et al., 1993b).

Most commonly used are the lumber and thoracic routes, but caudal injections can provide excellent pain relief both in children and adults following urological, pelvic and perineal surgery. Epidurals are particularly effective for the pain of childbirth (Harrison et al., 1988; Stenkamp et al., 1989; Cohen et al., 1991).

The most effective techniques use either intermittent top-ups, or a continuous infusion of either local anaesthetic alone, or a mixture of dilute local anaesthetic and a low dose of opioid (Scott et al., 1989). It is the mixture of local anaesthetic and opioid which produces the more superior analgesia.

Cryoanalgesia

Cryoanalgesia as been used to produce very prolonged analgesia, usually after thoracotomy (Maiwand et al., 1986). A cryoprobe (used as an alternative to local anaesthetics) is applied to the readily accessible intercostal nerves at the time of surgery, freezing them, thereby forming an intercostal block. This technique produces excellent somatic analgesia but as it does not block visceral pain, opioid supplements are frequently necessary in the early postoperative period. Depending on the duration of freezing, numbness can be produced for a period of 30-200 days after application and this prolonged numbness can be worrying for the patient. Other side-effects include the development of hyperaesthesia in the dermatomal distribution of the nerve treated. Gough and colleagues (1988) found cryoanalgesia to be inferior when they compared it to epidural fentanyl infusions following thoracotomy.

Wound infiltration

The technique of injecting local anaesthetic solution into the edges of a surgical incision was described in 1935, but recently there has been a renewed interest in the technique (Chapter 10). It is a worthwhile technique when a nerve block is not feasible and especially useful for day-case surgery analgesia (Reid et al., 1987). The technique abolishes only somatic pain and has little effect on visceral pain. However, conflicting results have been claimed for this technique following abdominal surgery. Whereas some authors have not found a reduction in postoperative requirements for opioids (Maier et al., 1994), others have (Partridge and Stabile, 1990) and were able to demonstrate the beneficial effects for at least 24 hours postoperatively.

Topical analgesia

Regional techniques are not always complex and topical application of local anaesthetic is very simple and often very effective: for example, lignocaine prior to venepuncture and catheterization (Maunuksela and Korpela, 1986; McCafferty et al., 1989) or for pain relief on skin graft donor sites (Owen and Dye, 1990). Wound

perfusion after surgery can also be a beneficial method of providing analgesia, such as intra-articular infusion following menisectomy (Lyons et al., 1995).

3.6 TENS

Transcutaneous electrical nerve stimulation (TENS) and acupuncture are both methods of providing analgesia which appear to act by stimulating the non-pain afferent fibres. A variation of TENS, transcranial electrical nerve stimulation (TCENS) was the technique used in one of the studies in this thesis (Chapter 9) and therefore I will describe TENS in more detail.

For postoperative pain control, TENS is used frequently in the form of two electrodes placed either side of a surgical incision. Alternatively, electrodes may be placed over the dermatome where pain is perceived. It has been suggested that the more effective sites for TENS electrodes correspond to established acupuncture points (Ogilvy and Smith, 1992).

Studies of the efficacy of TENS producing analgesia in the postoperative period have revealed conflicting results. As many fail to meet the essential criteria for meaningful analgesic studies, few firm conclusions regarding the efficacy of TENS for postoperative pain relief, can be drawn from the published literature.

TENS has not been shown to be universally effective in producing satisfactory postoperative analgesia (McCallum et al., 1988), but it may produce a modest reduction in the overall requirements for systemic opioids (Sodipo et al., 1980; Ali et al., 1981). Its main advantages are that it is non-invasive and it is drug-free.

Hymes and colleagues (1973) were the first investigators to report successful use of TENS for the management of acute postoperative pain following thoracotomy incision.

The majority of studies on postoperative pain following non-thoracic surgery, however, suggest that TENS is beneficial but do not exclude the possibility of a placebo effect (Tyler et al., 1982). Significantly lower pain scores, decreased hospital stay, improved tolerance to chest therapy (Warfield et al., 1985) and lower requirements for antiemetics following thoracotomy (Stubbing and Jellicoe, 1988) have been demonstrated with TENS and supplemental opioids as opposed to opioid analgesia. Hymes and colleagues went on to compare patients, after abdominal surgery, to historic controls and found that the majority of patients reported an 80% reduction in pain with TENS (Hymes et al., 1974). In contrast to this, a large prospective study on the use of TENS following abdominal surgery, in which placebo TENS was utilized as a control, failed to reveal any significant effect (Cuschieri et al., 1985).

In general a TENS unit comprises of an electrical pulse generator (usually battery operated) with dials to adjust various electrical stimulation parameters. The pulse generator is connected by wires to two or more electrodes which are placed on the skin. For the treatment of postoperative pain they are usually placed adjacent to the surgical wound. To date no studies have compared TENS parameters or electrode placements and therefore optimal settings are unclear.

Various electrical parameters have been utilized and an output of 10-20 milliamps (mA) is generally appropriate, delivered by a constant current generator with a waveform that may be biphasic, symmetrical or asymmetrical and modulated at frequencies between 5 and 200 Hz. Asymmetric waveforms are thought to be more comfortable for the patient, causing less muscle contraction during low frequency stimulation (Tyler et al., 1982). However, some patients may respond to one waveform and not another, and therefore units should have the availability of different waveform settings.

The pulse duration (Tyler et al., 1982) describes the relation between the durations of various applied electrical stimuli and the amplitude of current needed to activate nerve or muscle fibres. There are minimum thresholds for current strength and pulse duration below which the fibres will not be activated. Both thresholds are higher for muscle than for nerve.

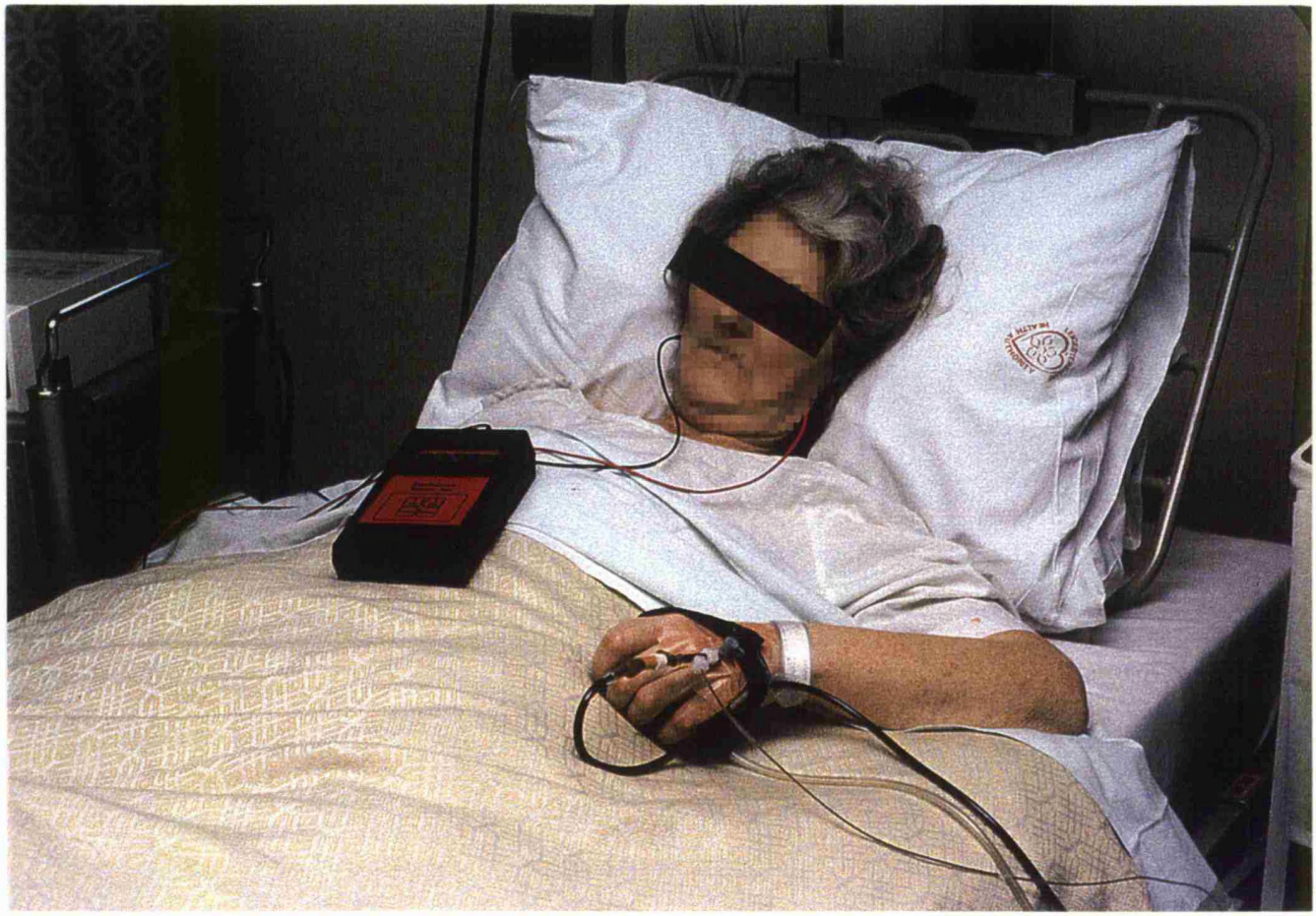
TENS may be administered by two variations in technique, dependent on the frequency of stimulation. Conventional TENS uses continuous stimulation at a constant high frequency (usually 50-100 Hz). The ideal frequency is unknown but most investigators use 80-100 Hz. Acupuncture-like TENS uses bursts of 100 Hz pulses delivered at a low frequency of 1-4 Hz. The aim of conventional TENS is to produce a strong but comfortable paraesthesia in the area of application whilst acupuncture-like TENS attempts to evoke local muscle contraction. Onset of analgesia with this method may be slow and the muscle contractions uncomfortable. The majority of studies for postoperative analgesia has been with conventional TENS.

The mechanism of TENS is uncertain (Katz, 1993) but it would appear that whilst the low frequencies (i.e. 5-10 Hz) stimulate endorphin output it is the higher frequencies of around 200 Hz that operate the pain gate (Melzack and Wall, 1965). Melzack and Wall proposed that afferent activity from large myelinated (A) fibres blocked central transmission of nociceptive impulses from small myelinated A-delta and unmyelinated C fibres, thus closing the gate to transmission of pain impulses. This theory gave new impetus to the study of nerve stimulation for analgesia and soon a variety of patients were being treated for chronic pain problems (Burton, 1972; Shealy, 1972; Long, 1974).

Burst, or on/off, modulation delivered at a low frequency is thought to be more beneficial in stimulating endogenous opioid production (Pinnock, 1985). This may also account for the relative successes of TENS in chronic pain.

The Leicester Neuroelectric Therapy Unit (LNTU) is a purpose built device, designed in the Academic Department of Anaesthesia and built by the Medical Physics Department at the Leicester Royal Infirmary (Fig. 3.1). It was intended for use for postoperative pain, although it does have versatility in providing appropriate stimulatory parameters for both acute and chronic pain states. It is a battery powered compact stimulator, which comprises an internal microprocessor chip, two output terminals, a liquid crystal display and a flat key pad. It produces an asymmetrical biphasic waveform of similar shape to the nerve action potential which may be varied in the following manner: peak current 10-50 mA in 10 mA steps; pulse duration 50-500 microsecs in 50 microsecs steps; frequency 5-995 millisecs in 5 millisecs steps and burst modulation 5-995 millisecs in 5 millisecs steps.

Figure 3.1 The Leicester Neuroelectric Therapy Unit.



The LNTU is designed to be used with mastoid electrodes which enable the electrical signal to penetrate the brain stem, in the region of the fourth ventricle, and to trigger the release of endogenous opioids (most notably beta-endorphin). Enkephalins and dynorphins are thought to be involved at spinal cord level where they may modulate the release of Substance P, thus altering transmission of centrally directed pain stimuli (the basis for the pain gate theory) (Pinnock, 1985).The output of the LNTU does not produce any detectable sensory sensation thus enabling its use in a double-blind study.

Acupuncture

There have been few studies of the use of acupuncture in the treatment of postoperative pain in Western Europe and its use is confined mainly to chronic pain.

3.7 Psychological Methods

A variety of psychological methods have been described in the management of acute pain and these are associated with patients' improvement in the postoperative period (Chapman, 1985). Sadly, many of these methods should not have to be spelled out as all doctors and nurses should be courteous towards their patients and take the time to explain the method of treatment relevant to them. Anxiety, as already discussed, is a well accepted high factor contributing to the experience of postoperative pain (Chapter 2).

However, the overall description of what constitutes good medical practice has been divided (Chapman, 1985) into the following components:

1. *Cognitive methods* — The provision of adequate explanations and coaching of the patient.

2. *Behavioural methods*	The use of distraction, suggestion, relaxation and other skills (e.g. electromyographic biofeedback) which may be beneficial in reducing analgesic requirements.
3. *Social modelling*	By direct social observation or introducing patients to others who have coped successfully with the same problem.

3.8 Hypnosis

This technique is claimed to reduce analgesic requirements, although at present there is little corroboratory evidence as the technique has not been used extensively.

Despite the sophistication of some invasive methods of pain relief in highly specialized units, Ferrante (1993a) is quite correct when he states that the practitioner of postoperative pain management must be a complete expert. He points out that postoperative pain management continues well beyond the cessation of these sophisticated and invasive techniques.

CHAPTER 4

Patient-Controlled Analgesia

4.1 The History of PCA

Patient-controlled analgesia was developed simultaneously in the U.K. and the U.S.A. in the 1960s. The concept was initially designed as a research tool to evaluate methods of administering opioids. It was Roe who found that by giving small doses of opioid intravenously the patient derived more benefit than by receiving conventional i.m. injections and that the overall dose requirements were lower (Roe, 1963). However, there were two major disadvantages with this method. The duration of analgesia was relatively short-lived because blood levels declined rapidly as a result of drug uptake by storage tissues and elimination from the body. The second disadvantage was that if larger boluses were used, to achieve a sustained analgesic effect, the method was associated with a higher incidence of side-effects.

Sechzer followed this up with his objective measurement of pain technique using true on-demand administration of medication (Sechzer, 1968). Postoperatively he instructed patients to press a button when they felt pain. He then had nurses administer i.v. boluses of 1 ml of pethidine- or morphine-containing solution and record the effect this had on the patient. Sechzer found that the postoperative analgesic requirement was cyclical and although needs varied considerably between subjects, they were consistent within each subject. He concluded that "the analgesic demand system is excellent for treatment of postoperative pain". Unfortunately there was still one drawback, the nurse:patient ratio necessary to administer analgesia in this fashion was not practicable. Thus, the first devices for self-administration of analgesia were developed.

4.2 The History of PCA Devices

The original PCA device that Sechzer (1971) used consisted of an electronically controlled infusion pump connected to two electro-mechanical timing devices. The device had a thumb button attached to a cord, which when the patients experienced pain they triggered the device by pressing this button. This enabled a small amount of opioid to be delivered into the patient's intravenous cannula. The timer was important in that it rendered the machine incapable of delivering further analgesia until a given time had elapsed (the lockout period). This allowed the first dose of medication to reach its peak pharmacological effect before delivery of the second dose. Consequently it was found to be a safer and more effective method of administering analgesia than the conventional intermittent i.m. injection.

Meanwhile, in the U.K., James Scott was also experimenting with PCA, with patients suffering from pain whilst "in labour". In 1969 he presented his findings to an American audience of obstetricians and gynaecologists. He described a hand-held, spring-loaded clamp which controlled the rate of infusion of a 500 ml bottle of 5% glucose to which was added pethidine 300 mg. As with Sechzers's device, the patient was instructed to press the clamp (to open it) until pain relief was achieved. The fail-safe component of this device was that if the patient fell asleep then the clamp would close automatically. He described this sytem as "patient controlled meperidine[7] administration" (Scott, 1970).

More sophisticated devices soon followed these early reports. Forrest described a pilot study using the Demand Dropmaster (Forrest et al., 1970). This device, which could automatically switch between up to four chambers containing different analgesic agents, administered analgesia when the patient pressed the button on the handset. In a pilot study involving 30 patients, the investigators reported that both patient and

[7] Pethidine is known as meperidine in the U.S.A.

physician acceptance was good and that the fail-safe features of the system were reliable.

Other authors also confirmed the advantages of PCA. For example, Keeri-Szanto using a device called the Demanalg (Keeri-Szanto, 1971), which was based on a syringe-driver, reported that this method decreased the incidence of substantial postoperative pain from 20-40% to less than 5%. When the demand analgesia group returned to conventional i.m. therapy, the incidence of incomplete analgesia increased to 30% even though many of these patients received a larger amount of analgesic medication (Keeri-Szanto and Heaman, 1972).

With the technical knowledge gained from earlier devices the first commercially produced patient-controlled analgesia device, the Cardiff palliator, was marketed. The Cardiff palliator (Graseby Dynamics Ltd, Watford, England) was developed by investigators at the School of Medicine, Cardiff, Wales (Evans et al., 1976). It too was a syringe pump which could be programmed to deliver the desired dose, the flow rate and time between doses of opioid. The parameters were adjustable to accomodate a wide variety of drugs and dosage regimens. The patient had a handset with which to operate the device. The button on the handset required two presses, within one second, in order to activate it. A tone sounded with a successful demand and a yellow indicator lamp remained on during the lockout interval. There were thumbwheel switches to control the incremental dose, dilution control, interval time and delivery rate.

With the aid of the Cardiff palliator, Evans and colleagues (1976) assessed the efficacy of two new opioids, buprenorphine and meptazinol. Buprenorphine was then a new agonist-antagonist and they compared it with pethidine (Chakravarty et al., 1979) and pentazocine (Harmer et al., 1983). It was found to be almost 600 times more potent as an analgesic than pethidine and more than 200 times more potent than pentazocine, but was unfortunately associated with a similar incidence of side-effects. Meptazinol, when

compared with pethidine (Slattery et al., 1981), was found to be a less potent analgesic and associated with a higher incidence of nausea.

Although the Cardiff palliator was generally well accepted by patients and hospital staff, the device had some disadvantages. For example: it only accommodated 20 ml syringes; it was mains operated with no battery back-up (which therefore precluded portability if a patient needed to go to the X-Ray department for example); it was heavy, relatively large and needed a separate trolley to accommodate it; the patients frequently had difficulty in pressing the button on the handset twice (within the required one second) when they were drowsy in the immediate postoperative period. In addition, the thumbwheel switches were not tamper proof and this was, in retrospect, potentially quite dangerous.

In the mid 1970s Hull and colleagues developed a highly sophisticated self-administering analgesia computer. It was a microprocessor-controlled interactive demand apparatus (Hull et al., 1979; Hull and Sibbald, 1981). The device had four cassette tape recorders and was able to communicate orally with the patient. Every five minutes, regular prompts were made to the patient to request analgesia and there was feedback to the patient when a demand was positive. It was believed that this system was useful in helping the patients to remember to push the button twice. However, it was not totally reliable and some patients did not like the repetitive messages (Hull, 1985). Hull included a concurrent background infusion, as he was using fentanyl (a short-acting opioid which required patients to make frequent demands) and the rate was adjusted according to the number of demands made. This prototype also included a respiratory monitor which suspended delivery of the opioid should the respiratory rate fall below a pre-set value.

This on demand analgesic computer became known as the ODAC and was successfully marketed by Janssen Scientific Instruments (Beerse, Belgium). Using this device other

investigators reported that postoperative analgesia was comparable with that produced by epidural bupivacaine (White et al., 1979), and that PCA using the ODAC was judged superior by 84% of patients when compared with their previous experiences of i.m. postoperative analgesia (Lehmann et al., 1985).

By the early 1980s Tamsen and colleagues had performed a number of studies looking at the pharmacokinetics and pharmacodynamics of PCA (Tamsen et al., 1979, 1982a, 1982d, 1982e; Dahlstrom et al., 1982). They used a microprocessor- controlled, programmable drug injector called the Prominject (Pharmacia, Priscataway, New Jersey). The authors of these studies found that neither age, sex, body weight, nor the rate of drug elimination appeared to be related to the resulting therapeutic (analgesic) concentrations. Both the analgesic requirement and the resultant therapeutic concentrations were highly variable (fourfold to sixfold) but patients maintained relatively constant plasma concentrations when allowed to self-administer pethidine or morphine during the early postoperative period.

The late 1980s witnessed a renewed interest in postoperative pain with the development of acute pain services (Ready et al., 1988) and PCA underwent a renaissance. With the advances in microchip technology the competition between the various manufacturers led to the development of a wide variety of PCA devices for commercial use. Some devices have become more sophisticated and compact, even miniaturized (O'Keefe et al., 1994), while others are simple and disposable.

Of the numerous devices currently available, two types of electronic PCA device have developed from the earlier models; the bedside drug delivery systems and those for ambulatory use. For postoperative pain the mains operated bedside devices have become popular whilst the ambulatory devices have been put to good use for chronic pain states. There is no particular reason for this. In fact it could be argued that postoperative patients would derive greater benefit from a device that does not

necessitate being unplugged every time they leave their beds. The bedside machines tend to be more complex with facilities for detailed printouts (a necessity for research purposes) whilst the Baxter disposable PCA system, for example (Chapter 8), relies on a spring-loaded clamping mechanism similar to that described by Scott in 1970 (albeit in a miniature and disposable form). The cycle of development with the advent of the Baxter device has now turned full circle (Rowbotham, 1992).

The Graseby patient-controlled analgesia system (Graseby PCAS) succeeded the Cardiff palliator. It is an example of microchip technology and is described at the end of this chapter. The Baxter and Graseby devices have been compared in children after major surgery (Irwin et al., 1992) and in women after major gynaecological surgery (Chapter 8). In each, pain and sedation scores and morphine consumption were found to be very similar in all patients. The Baxter device has its limitations as, once primed, the variables cannot be changed (see later in this chapter) but it does perform well for the majority of patients postoperatively (Chapter 8). An additional (and excellent) use was found for these devices when they were issued to soldiers in the Gulf War (Kent, 1991).

Currently, there is a wide variety of PCA devices to choose from (Heath and Thomas, 1993b). These are designed to satisfy various needs, such as research and chronic pain, and some have specially adapted handsets to enable use by patients with disabilities or who are unable (temporarily) to activate the device.

4.3 The Theory of PCA

The first meeting held for PCA was in 1984 where it was decided that "patient-controlled analgesia" was the appropriate terminology to use to describe the technique

(Norman, 1985). However, other phrases such as "self-administered analgesia", "on-demand analgesia" [8] and "patient-activated analgesia" remain in use.

The clinical use of PCA in the U.K. has become popular and widespread only in the past five years when it has made the transition from that of research tool to one of clinical acceptability. An understanding of the importance of pharmacokinetic and pharmacodynamic variability in the management of acute pain has led to the introduction of improved delivery systems, including those for PCA (White, 1989). Patient-controlled analgesia allows the patient to determine, within limits, the dose of analgesic administered, and it avoids the delay between perception of pain and the administration of analgesic drugs. PCA reduces narcotic and antiemetic use (Bennet et al., 1982) and patient anxiety resulting from delays in receiving pain-relieving medication (Scott et al., 1983; Pierce, 1988). PCA also saves time in drug preparation, distribution and documentation, which increases the nursing time available and results in improved quality of nursing care (Defede et al., 1988; Panfilli et al., 1988; Smith and Rennie, 1991).

In considering ways of improving the drug treatment of acute pain, Norman (1985) suggested that these questions should be asked about the system to be used to deliver analgesia:

1. Who selects the drug to be used?
2. Who decides the dose?
3. Who decides when the drug shall be given?
4. Who decides when more drug is necessary?
5. Who assesses the efficacy of the treatment?
6. Who assesses the dangers?

[8] "on-demand analgesia" is often used when referring to the conventional method of administering i.m. analgesia.

Norman concluded that the logical person to be in control of the drug delivery system should be the patient, after all the patient is best able to answer questions 3-5.

The theoretical basis of PCA is that patients will titrate the delivery of opioid to achieve plasma concentrations consistent with good analgesia and minimal side-effects (Graves et al., 1983; White, 1988). Possibly the greatest advantage of PCA over other techniques of opioid analgesia is the minute-to-minute control of drug administration that it affords (Owen et al., 1988).

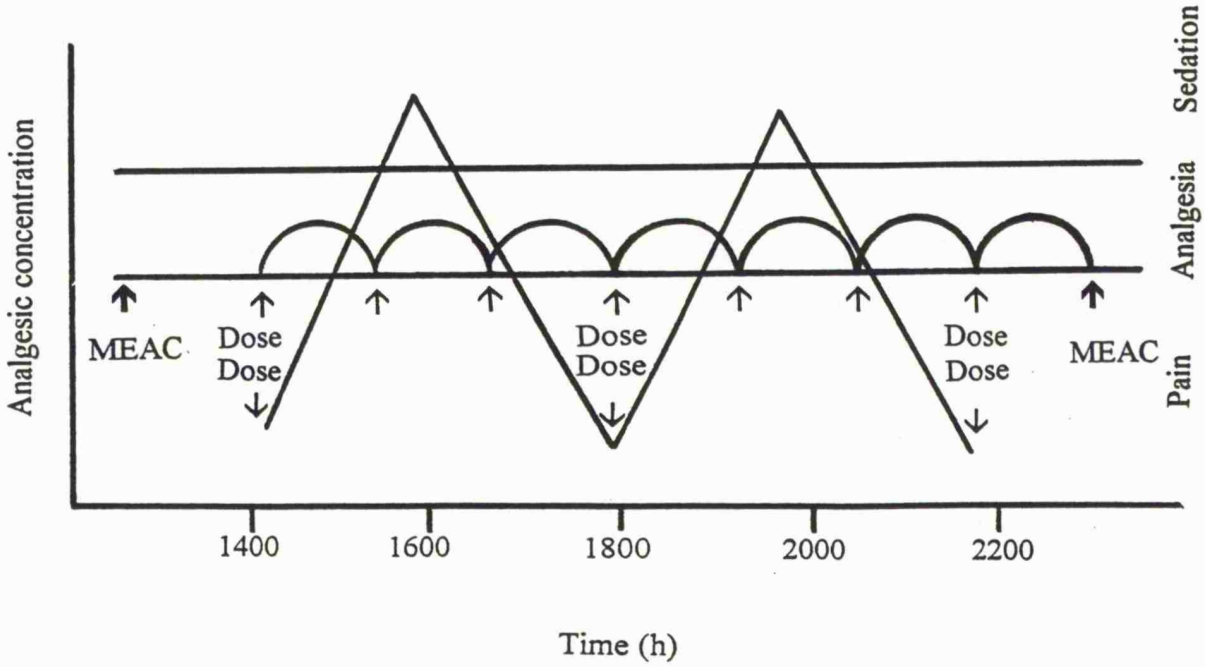
Attempts have been made to improve opioid dosage regimens based on the pharmacokinetic and pharmacodynamic characteristics of the drugs (Mather, 1983; 1987; Nimmo and Duthie, 1987; Stanski, 1987; Owen et al., 1988). As discussed in the previous chapter it has been proposed that there is a continuous relationship between opioid agonist blood concentrations and response, that there is a minimum blood drug concentration associated with effective analgesia (MEAC) and that pharmacokinetic techniques can be applied to design dosage regimens to achieve the target blood drug concentrations (Nimmo and Duthie, 1987; Stanski, 1987).

The acceptance of PCA is attributable to the increased awareness that consistent analgesic blood levels cannot always be obtained with repetitive doses of opioid intramuscularly. I.m. injections may result in erratic absorption with peak concentrations between 10 and 100 minutes after injection (Tamsen, 1985) and a possible ineffective blood concentration for 65% of the dosing interval (Owen et al., 1988). Analgesia is achieved when the plasma opioid concentration reaches a particular level, dependent on the individual patient. For small increases in plasma concentration, a rapid decrease in pain is perceived. Complete pain relief defines the MEAC. For increases in plasma concentration of opioid above MEAC, there is no increased analgesic effect. For small decreases in plasma concentration below MEAC, pain is rapidly appreciated. MEAC exhibits marked interpatient variability, and this may

explain the large variability in analgesic requirements among patients (Ferrante, 1993b).

The relationship between opioid concentration, analgesia and dosing intervals defines the therapeutic efficacy of a particular method of opioid administration. The plasma concentrations for i.m. injection are characteristically unpredictable. Within each individual, peak concentration of opioid (C_{max}) can vary twofold with repetitive injections. Time to peak concentration (T_{max}) can vary threefold with repetitive i.m. injections (Austin et al., 1980a). There can be a fivefold variation in C_{max} in any given patient population, whereas T_{max} can vary sevenfold (Austin et al., 1980a). At the same time, plasma concentrations will fluctuate in phase with the dosing interval. It has been calculated that opioid concentrations are in excess of MEAC only 35% of the time during any 4-hour dosing interval (Ferrante, 1993b).

Figure 4.1 The relationship between plasma opioid concentration, dosing interval and analgesic effect. After Ferrante, 1993.



PCA avoids these variable absorption phenomena by allowing repetitive small doses of opioid (Fig. 4.1). When the patient's plasma concentration falls below MEAC, the patient rapidly appreciates pain. Thus, PCA is flexible because patients titrate their plasma concentration of opioid around MEAC. PCA provides more constant plasma levels of opioid (Dahlstrom et al., 1982; Tamsen et al., 1982b, 1982c) and more consistent analgesia (Ferrante et al., 1988).

4.4 The Variables of PCA

There are four basic variables of PCA: the drug choice, the bolus dose (incremental dose per demand), the maximum dose (or dose rate) and the lockout interval between demands (Owen et al., 1988). The bolus dose is the dose delivered by the device when the patient presses the button. The lockout time is the period, after a dose has been given, during which any further demands by the patient will be ignored by the device. This enables the opioid bolus to have an effect before another is given. A maximum dose facility is available on most current systems which prevents the device from delivering more than the maximum preset dose over a period of time.

Most devices enable a background infusion of opioid to be delivered independent of patient demand. The aim of a continuous infusion with current PCA is to reduce the need for patients to make demands and therefore reduce the dosage of the drug. The use of a concurrent infusion is not, strictly speaking, PCA and there has been some debate regarding the safety of a concurrent infusion (Owen et al., 1989b). This is discussed later in this chapter.

4.5 The Efficacy of PCA

PCA may be administered by any route, including orally, if the patient is actually controlling the administration. The common routes, however, are the i.v. and epidural

routes. In recent years there has been some interest in subcutaneous PCA, (White, 1990) although this is more suited to chronically ill patients because i.v. siting of cannulae is unlikely to occur outside of the hospital.

PCA v I.M. Therapy

There have been numerous studies during the past 15 years to compare the efficacy of PCA against well established and alternative methods of administering analgesia for postoperative pain. Of the many studies comparing PCA with intermittent intramuscular injection (i.m.i.), using the same opioids, the majority have demonstrated that PCA was associated with lower pain scores, although there was no significant difference in total dose of morphine administered (Rowbotham and Smith, 1993). Most investigators have compared morphine; only one has described pethidine (Cohen et al., 1991).

The use of PCA (versus i.m.i.) has been evaluated in a wide variety of surgical procedures including Caesarean section (Perez-Woods et al., 1991), upper abdominal surgery (Kenady et al., 1992), orthopaedic surgery (Berde et al., 1991) and a variety of major elective surgeries (Egbert et al., 1990). Most data relate to the average surgical population but Berde and colleagues' study was conducted in children (1991) and that of Egbert and colleagues was in frail, elderly men (1990).

Many of the studies undertaken are open to criticism because of the way in which they were conducted. For example, Dahl and colleagues (1987) did not find PCA to be superior to i.m. analgesia but on closer examination the control group was supplemented with i.v. boluses of morphine when requested by the patient. This clearly was not a well controlled study. Most studies have been open studies and have therefore been observer and patient biased (Slattery et al., 1983), some studies have used different opioids for i.m. and PCA administration (Welchew, 1983) and others have used morphine equivalents (Ferrante et al., 1988).

Albert and Talbott (1988) studied 62 patients undergoing colonic surgery and found that the group using PCA, with a 1 mg bolus dose of morphine and lockout time of 10 minutes, had the same pain scores as the i.m. group receiving morphine 5-12 mg, 3-4 hourly. After 72 hours patients had received a mean (range) total dose of morphine 69.6 (3-133) mg in the PCA group compared with 92.2 (35-204) mg in the i.m. group. It is possible that the patients in the PCA group (who, not surprisingly, were significantly less well sedated) may have had lower pain scores if the lockout time for the PCA had been less.

All the studies showing greater efficacy of PCA, (than i.m. therapy), utilized lockout periods of 10 minutes or less. There is of course a relationship between the bolus dose and lockout interval (which requires further research) but it has been suggested that the optimal bolus size of morphine is 1 mg (Owen et al., 1989a). This is in order to achieve a balance between pain relief and fewer side-effects. Most investigators have individual preferences for opioids and regimens. For example, Notcutt favours diamorphine (which has a high lipid solubility) 1 mg with a 5 minute lockout period (Notcutt and Morgan, 1990), Heath and Thomas (1993d) use papaveretum 2 mg with a 6 minute lockout interval whilst Wheatley and colleagues (1991) use morphine 1 mg with a 5 minute lockout period.

Despite the inadequacies of these studies, several investigators have commented on the patients' preference for PCA over i.m. therapy. For instance, in one study patients who had undergone a repeat Caesarean section in which i.m. postoperative analgesia had been utilized previously, 90% of those receiving PCA on the second occasion said that they much preferred PCA (Eisenach et al., 1988). In another study, McGrath and colleagues (1989) found that of the 88 patients who had undergone cholecystectomy (in which those receiving PCA had similar or inferior pain scores to those receiving i.m.), 86% of those receiving PCA would recommend the technique to a friend whereas only 31% of the i.m. group would recommend their technique.

Epidural PCA

Eisenach and colleagues (1988) used epidural PCA in their study and it is only in recent years that studies have been undertaken to review this relatively new technique. At present there is no evidence to suggest that opioid epidural PCA is more advantageous than opioid i.v. PCA. No significant differences have been demonstrated in pain, sedation or nausea scores after abdominal surgery (Welchew and Breen, 1991) and pain scores and pulmonary function tests after thoracotomy (Grant et al., 1991).

Patient-controlled administration of local anaesthetic into the epidural space during labour has been compared with more conventional techniques but the analgesia is only comparable, and not better, than midwife controlled top-ups (Gambling et al., 1990) and continuous infusions of local anaesthetics (Gambling et al., 1988).

PCA v Epidural Opioids

There have been several claims that intermittent opioid epidural analgesia is superior to PCA (Loper et al., 1989; Cohen et al., 1991; Kilbride et al., 1992) but these studies are flawed because of their methodology. In Loper and colleagues' and Kilbride and colleagues' studies the patients in the PCA groups underwent general anaesthesia only, whilst the epidural groups had combined general and morphine and, local and morphine epidural anaesthesia, respectively. Cohen and colleagues' claim for superior epidural analgesia was equally difficult to assess because the PCA was with pethidine and the epidural analgesia with morphine.

There have been some well controlled studies, although no significant differences were demonstrated in pain scores in lower abdominal surgery between epidural diamorphine and PCA diamorphine (Madej et al., 1992); nor after hip or knee replacements with epidural morphine and PCA morphine (Weller et al., 1991). However as yet there are no consistent data to suggest that intermittent opioid epidural analgesia provides better

pain relief than i.v. PCA or, conversely, that the efficacy of PCA is superior to that of epidural opioid analgesia.

Despite the claims that epidural analgesia provides improved pain relief, there is evidence to suggest that patients prefer PCA. For example, after repeat Caesarean section in patients previously treated with intramuscular analgesia, only 65% of those receiving epidural analgesia preferred the method compared with 90% in the PCA group (Eisenach et al., 1988). In a similar study where patients underwent repeat Caesarean sections, two patients said they would not wish a similar epidural procedure for pain relief whereas all patients in the PCA group stated they would prefer to repeat the technique (Harrison et al., 1988).

PCA v Epidural Local Anaesthesia

It is widely accepted that the degree of analgesia obtained with local anaesthetic solutions in the epidural space is optimum and a well managed regimen is almost bound to produce superior analgesia compared with intravenous opioid PCA (Rowbotham and Smith, 1993). However, to date this has not been confirmed by controlled investigation.

PCA v Epidural Opioid/Local Anaesthetic Mixtures

The analgesic effects of a mixture of opioid and local anaesthetic in the epidural space has been compared with opioid PCA (Weller et al., 1991; Madej et al., 1992). After lower abdominal surgery pain scores were found to be considerably lower with epidural analgesia. Madej and colleagues also reported on their first year's experience of an acute pain team in which 510 patients were treated with PCA and 150 with mixed epidural infusion analgesia (Wheatley et al., 1991). Pain scores were low with PCA but they were significantly lower in the epidural group. This would suggest that a mixture of local anaesthetic and opioids produce superior analgesia to PCA but the optimum doses have yet to be determined. This area is likely to be the subject of

considerable research in the next few years and part of that research should comprise comparison with PCA regimens.

PCA v Constant Rate Intravenous Opioid Infusion

At the time of writing this thesis, no direct comparison of PCA and constant rate intravenous opioid infusion has been reported although there have been comparisons of this technique with PCA using a background infusion. There is some dispute as to whether a background infusion may improve the efficacy of PCA and whereas some investigators have shown that it improves analgesia, albeit at the expense of excessive nausea (McCoy et al., 1993), others have shown that it increases dosage without improving pain relief (Marshall et al., 1985; Rosen, 1986; Vickers et al., 1987; Owen et al., 1989b).

In a study of patients after major gynaecological surgery, Owen and colleagues (1989b) demonstrated that patients with a continuous infusion used twice as much morphine as the patients using PCA alone. The pain scores in this study were found to be similar in both groups, as were those in other studies using morphine: after major abdominal surgery (Zacharias et al., 1990); after hysterectomy (Parker et al., 1991); Caesarean section (Sinatra et al., 1989); in children after major surgery (Berde et al., 1991).

One of the reasons for investigators advocating a background infusion with PCA is that it allows patients to sleep more easily. However this was not confirmed by Parker and colleagues who demonstrated that a night-time infusion, supplementing PCA after hysterectomy, did not improve patients' ability to sleep at night (Parker et al., 1992).

The relative safety of PCA relies on the patient being the only factor in controlling the rate of opioid administration. Constant rate intravenous infusions are associated with a relatively high incidence of respiratory depression (Catley et al., 1985) and it has been

demonstrated that respiratory depression is more likely to occur with PCA when there is the addition of an i.v. infusion (Owen et al., 1989b; McCoy et al., 1993).

PCA v Intermittent Nurse-Controlled Intravenous Administration

Choiniere and colleagues compared the efficacy of nurse-administered intravenous morphine boluses and morphine PCA in 24 patients suffering from burns (Choiniere et al., 1992). In this study there was a tendency for the pain and anxiety scores to be lower in the PCA group, although this was not statistically significant, but the overall efficacy ratings as judged by the nurses were significantly better in the PCA group. The total amount of morphine administered was the same in both groups. As mentioned previously, intermittent nurse controlled intravenous administration of opioid is as efficacious as i.v. PCA, but the nurse:patient ratio needs to be high and this rarely exists on most general surgical wards.

4.6 Problems with Patient-Controlled Analgesia

In order to assess patients' views on PCA, Kluger and Owen (1990b) asked 80 healthy patients to list the advantages and disadvantages of PCA. The advantages cited most frequently included: not bothering the nurses; the rapid onset of analgesia and being in control of their pain relief. 45% of patients did not feel that there were any disadvantages to PCA but approximately 10% were worried about loss of nurse contact and the possibility of overdose. 6% were worried about machine malfunction whilst 4% were worried about addiction.

There is no doubt that in many situations PCA provides improved pain relief after surgery but, unfortunately, there are some complications specific to the technique of PCA. With all electronic devices it is possible to make serious errors during programming (Ball et al., 1992; Farmer and Harper, 1992; Nimmo, 1992; Parker et al., 1992) or whilst changing syringes (White, 1987). In addition, patients (or their

relatives) may tamper with the machine for nocuous or innocuous reasons (Jones and Reeder, 1990; Stevens et al., 1991; Farmer and Harper, 1992; O'Connor et al., 1992).

When connecting a PCA device to a patient it must be connected to other intravenous lines by a non-return (antireflux) valve (Kluger and Owen, 1990a). If this valve is omitted, or connected incorrectly, a dangerous bolus could be inadvertently delivered, especially if the concentration of opioid is high. There is also a need for an antisyphon valve (Notcutt and Morgan, 1990) because if the cassette or syringe develops a crack and the machine is above the intravenous insertion of the device, the entire contents may be emptied into the patient with serious consequences (Thomas and Owen, 1988).

There have been instances of machine malfunction and the contents of the syringe being emptied into the patient in a very short time (Hanning et al., 1989; Grover and Heath, 1992; Notcutt et al., 1992). The manufacturers continue to make fail-safe claims but the devices are clearly not foolproof at present.

The side-effects of opioids, particularly respiratory depression and nausea and vomiting, are associated with all techniques of opioid administration and PCA is no exception.

There have been several reports of significant respiratory depression whilst using PCA (Notcutt and Morgan, 1990; Stack and Massey, 1990; Wheatley et al., 1990, 1991; VanDercar et al., 1991; Etches, 1994) but these reports need to be put into perspective when compared with other analgesic techniques. For instance, Notcutt and Morgan found respiratory problems (respiratory rate < 8/min) occurred in 7 of the 1000 patients using PCA, which they studied, whilst Etches found respiratory depression in 8 of 1600 patients, (3 of whom were associated with a concurrent background infusion).

Several authors have compared respiratory rates in patients receiving i.m. analgesia against those using PCA and have found no consistent evidence of any significant difference between the two methods. There have been comparisons in children (Berde et al., 1991), in adults (Eisenach et al., 1988; Wasylak et al., 1990; Wheatley et al., 1990) and in frail, elderly men (Egbert et al., 1990). Wasylak and colleagues found that minute ventilation returned to normal significantly earlier in patients receiving PCA whilst Brose and Cohen (1989) found that 63% of patients receiving i.m. analgesia had episodes of severe respiratory depression ($SaO_2 < 85\%$) compared with 30% of patients using PCA. This was also statistically significant.

Of the many groups that have investigated the incidence of hypoxaemia in epidural opioids compared with PCA opioids, only Weller and colleagues (1991) have demonstrated a significant decrease with epidural opioids. With the evidence available it is not possible to ascertain whether epidural opioid analgesia given on demand, rather than by constant infusion, is more likely to cause significant hypoxaemia and further work is required in this area.

Many clinicians feel that nausea and vomiting are more common with PCA than with i.m. analgesia (Wheatley et al., 1991; Sharma and Davies, 1993). The study outlined in Chapter 12 set out to investigate this view. There were no significant differences in the incidence of nausea and vomiting between the two groups although an impression was gained that patients using PCA required fewer i.m. injections of antiemetic than those receiving i.m. analgesia. This is discussed further in Chapter 12.

Most investigators have reported no significant differences in the incidence of nausea and vomiting between epidural opioid analgesia and PCA. However, Madej and colleagues (1992) did find an increased incidence in a PCA group.

PCA has been associated with less sedation than with i.m. analgesia (Albert and Talbott, 1988; Berde et al., 1991; Kenady et al., 1992), although in studies in which sedation scores were not significantly different, it was found that PCA produced superior analgesia (Hecker and Albert, 1988; Egbert et al., 1990).

In epidural opioid analgesia, there is little data to compare the technique with PCA but Weller and colleagues (1991) did not find any significant differences between the two groups after orthopaedic surgery.

In the studies in which this was measured, no significant differences were found for pruritus between PCA and i.m. analgesic therapy (Eisenach et al., 1988; Harrison et al., 1988; Wheatley et al., 1990). In epidural opioid analgesia, however, it is possible that pruritus occurs more frequently than with PCA (Eisenach et al., 1988; Harrison et al., 1988; Loper et al., 1989; Weller et al., 1991) although some authors have not found significant differences (Loper and Ready, 1989; Wheatley et al., 1990; Madej et al., 1992).

Urinary retention was not found to be statistically significant in either group when i.m. analgesia was compared with PCA (Hecker and Albert, 1988; Egbert et al., 1990; Wheatley et al., 1990; Berde et al., 1991) and there is no clear evidence from the literature to suggest that opioid epidural analgesia is more likely to lead to urinary retention than PCA.

It has been mentioned that local epidural analgesia should be superior to i.v. opioid PCA. Unfortunately there is little data to confirm this observation, probably because a knowledge of the physiological effects of epidural anaesthesia implies that these studies are not necessary. The same applies to complications of local epidural analgesia, namely hypotension, which is a major concern and more likely to occur with this technique. Wheatley and colleagues concurred with this view in their review of the

activity of their pain service in patients receiving an opioid/bupivacaine epidural infusion (Wheatley et al., 1991).

4.7 Positive Effects of PCA

It has been suggested that it is better to be in pain than to be killed by the analgesic, so to be of clinical use PCA must be an improvement on conventional therapy, yet be at least as safe (Rosen, 1984).

There can be little doubt that PCA produces superior analgesia compared with conventional i.m. analgesia. Some authors have demonstrated that hospital stay is reduced with PCA (Wasylak et al., 1990; Heath and Thomas, 1993f). Others, however, have disputed this (Egbert et al., 1990; Kenady et al., 1992), although it is a difficult variable to study given the many factors which govern the time of patients' discharge from surgical wards.

Egbert and colleagues (1990) found that significantly fewer elderly male patients became confused with PCA than with i.m. analgesia and significantly fewer had pulmonary complications. Wasylak and colleagues (1990) also comparing i.m. therapy with i.v. PCA, found that PCA was associated with significant improvements in the ambulatory rate of patients, less antibiotics were administered and solid food was tolerated earlier. The same authors observed less pyrexia in the PCA group, a finding also noted by Kenady and colleagues (1992).

Whilst the level of analgesia is important to the patient, acceptability of the method is equally if not more important. PCA by the i.v. route is accepted well by many patients (Ferrante, 1993b) and is more popular than intramuscular (Eisenach et al., 1988) and probably also epidural analgesia (Harrison et al., 1988). Some patients, content with the pain relief regimen, do not necessarily attempt to self-administer greater quantities

of opioid in order to achieve very low or zero pain scores but instead titrate their opioid requirements against acceptable side-effects, namely less sedation and less nausea.

PCA is relatively safe only if errors, either staff- or machine-induced, are avoided (Chapter 4.6). In addition, there is tentative evidence to suggest that PCA may improve postoperative outcome (Wasylak et al., 1990; Heath and Thomas, 1993f) but considerably more work needs to be carried out in this area.

4.8 A Review of the PCA Devices Used in this Thesis

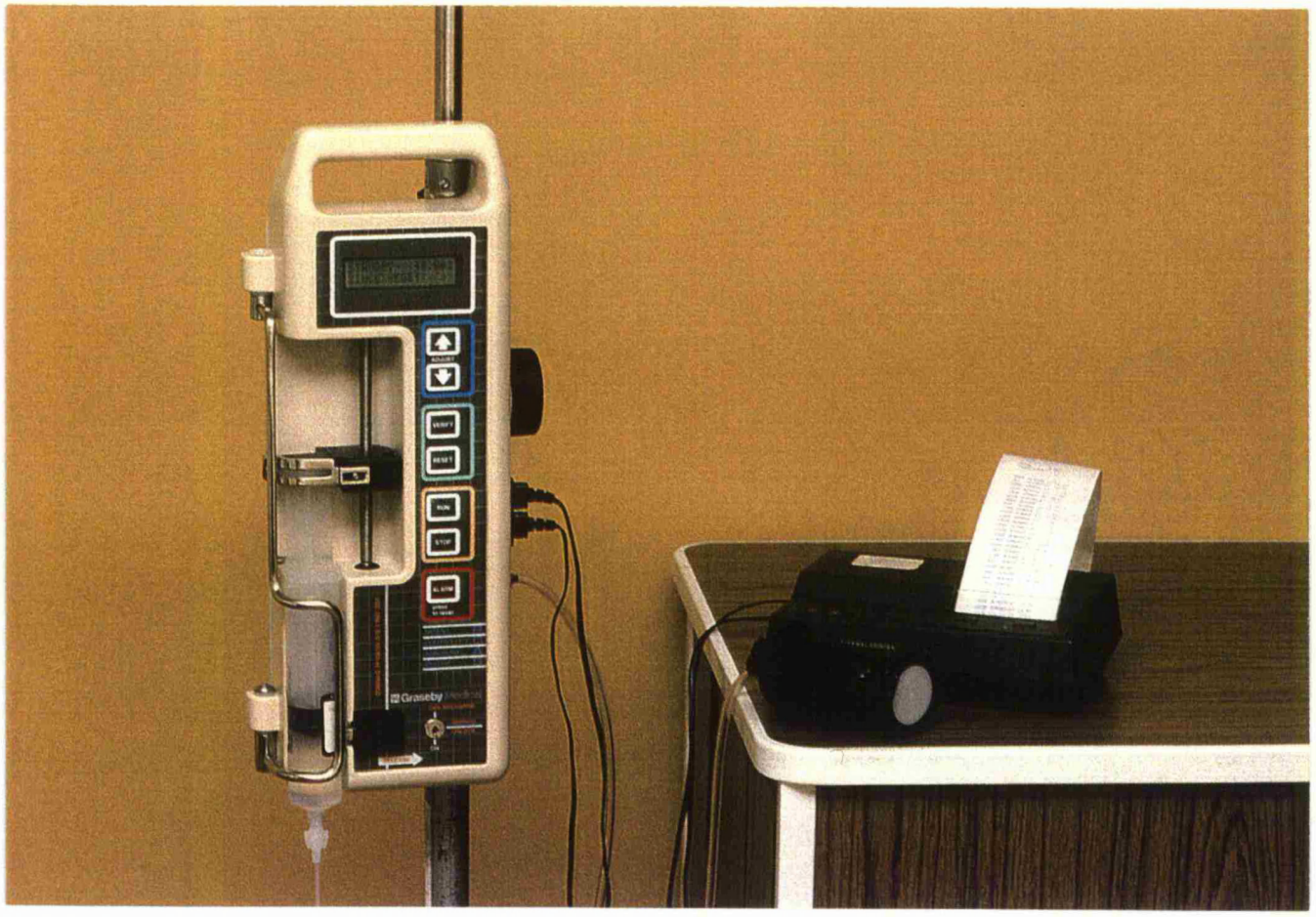
Graseby PCAS

The Graseby (Graseby Medical Ltd., England) patient-controlled analgesia system (PCAS) is a fully computerized syringe pump with a liquid crystal display (LCD) which records the amount of drug delivered and the number of demands the patient has made (Fig. 4.2). It is mains or battery (with a back-up life of approximately 8 hours) operated and the illuminated alpha numeric message facilitates the setting up and operation of the pump. It has wide parameters for different drugs and regimens and also has a facility for attachment to a printer (Hewlett Packard thermal printer). This enables the time, bolus dose, dose duration, lockout duration, concentration of drug (per ml of dilution fluid), a background infusion (if any) and the total amount of the drug administered. It also records the time of the patient's demand and whether the demand was successful or not.

The patient has a handset, which is pneumatically operated by a button which is depressed once in order to receive a dose of opioid. The button is flush with the casing but requires a conscious effort in order to depress it fully for a successful demand. On receiving the opiate the patient is rewarded by a bleep. A green light illuminates the

corner of the run button and flashes on and off whilst the drug is infused. The green light remains off during the following, pre-programmed, lockout period.

Figure 4.2 The Graseby PCAS.



The PCAS is programmed, and subsequently activated, with a key. This key also locks the syringe into place. Before the advent of this key there had been some problems in the U.S.A. with syringes being stolen. After this refinement the thieves then took the whole device!

The Graseby PCAS will only take a 50/60 ml luer-lock syringe. This is adequate for most opioid dilutions and will often last for a 24 hour period.

This device has a series of alarm functions that notify all concerned if:

- there is an occlusion
- the syringe is nearly empty
- the infusion is at an end
- there is AC failure
- the battery is low
- the loading dose is too small
- the loading dose is too large
- the bolus is too small
- the bolus is too large
- the pump has stopped (eg. the operation is suspended for more than a minute due to a syringe/nightgown change)
- the PCAS is not running (key in the wrong position)
- the pump has an internal fault

The Graseby PCAS performed well. After experience with the Cardiff palliator, it was compact, easy to transport, relatively easy to programme and the facility for the printer was invaluable for research purposes. The only disadvantage was that occasionally the fail-safe device was activated for no apparent reason. Subsequent research into this phenomena has revealed that power surges may have been the cause, or static electricity from the patients and hospital staff (Notcutt et al., 1992).

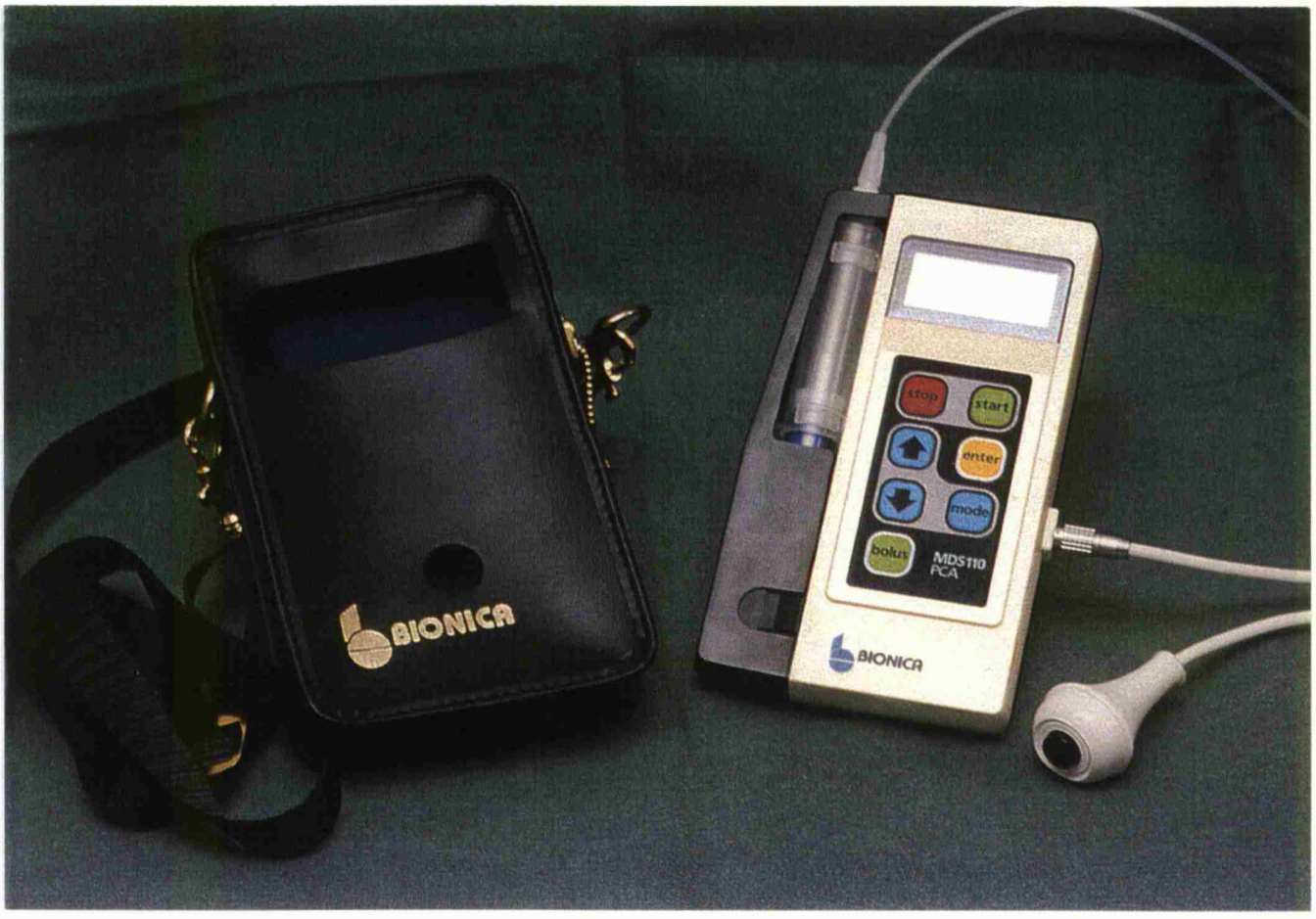
Bionica MDS 110 [9]

The Bionica MDS 110 [International Medication Systems (U.K.) Ltd] was a micro-computer-controlled drug infusion pump designed to provide patient-controlled

[9] The Bionica was withdrawn from the market during clinical trials.

analgesia (Fig. 4.3). Like the Graseby PCAS, it had an LCD and the pump could be programmed, using scroll buttons, for basal delivery (i.e. background infusion), bolus delivery or both. The pump provided the patient with the facility to command an additional analgesic bolus delivery (within pre-programmed limits) to overcome intermittent periods of pain not controlled by the basal delivery. The MDS 110 PCA used 10 ml glass, empty or pre-filled (morphine), syringes manufactured by International Medication Systems (IMS).

Figure 4.3 The Bionica MDS 110 PCA device.



The pump could be stopped and started with stop and start buttons. It also facilitated the use of a password entry to the keyboard (the use of this was optional) to prevent the dosage being tampered with. The locking feature also secured the syringe and its contents.

The Bionica also had a handset. This differed from the Graseby in that it had an electrically operated button which lay proud from the casing and it was necessary to depress the button for one second in order to receive a bolus. It too made a bleep with a successful demand. The device had a set of alarms similar to those of the Graseby, but obviously minus those related to AC power.

There were several disadvantages with the Bionica MDS 110. The concentration of drug allowed in solution (10 mg/ml-100 mg/ml) was a major disadvantage when using morphine and also potentially dangerous (Grover and Heath, 1992). Experience has shown that accuracy and precision of repetitive doses are best served when the bolus is contained in a relatively large volume (> 0.5 ml). This will also minimize errors caused by drip occlusion (Heath and Thomas, 1993b). Given the size of the syringe (10 ml), it was clearly impractical to put morphine in a solution of 0.5 ml. This would only have allowed 20 mg morphine per syringe and would have been costly and time-consuming.

Another disadvantage was the glass syringe. It is not ideal to use glass syringes because the weight and ease of movement of the plungers make syphoning more likely to occur should other conditions favour it (Thomas and Owen 1988; Grover and Heath, 1992). In addition, glass syringes are more easily broken than plastic ones.

A third problem was the length of time it took for the bolus dose of opioid to be infused. Whereas the Graseby could be programmed to infuse stat (100 ml/h infusion rate), or up to 15 minutes in steps of 1 minute, it took the Bionica 8.5 minutes to

deliver the bolus dose. This, in effect, lengthened the lockout period (10-200 minutes) which only commenced once the drug was delivered.

The handset presented another problem. Often, patients still sleepy from the anaesthetic found it difficult to depress the button for a full second in order to activate the device and consequently did not always receive satisfactory analgesia.

Whilst the device was extremely portable and therefore convenient for the patients to use, it was unnecessarily complex to programme and despite the locking feature for the syringe, an impression was formed that it would not take too much effort to force the syringe casing away from the syringe.

Shortly after the study (Chapter 7) was completed, the Bionica MDS 110 was withdrawn from the market. An incident had occurred, in a London hospital, whereby the glass syringe had disengaged from the drive mechanism resulting in a massive overdose of papaveretum (Grover and Heath, 1992). In this case the patient was successfully resuscitated and went on to make an uneventful recovery.

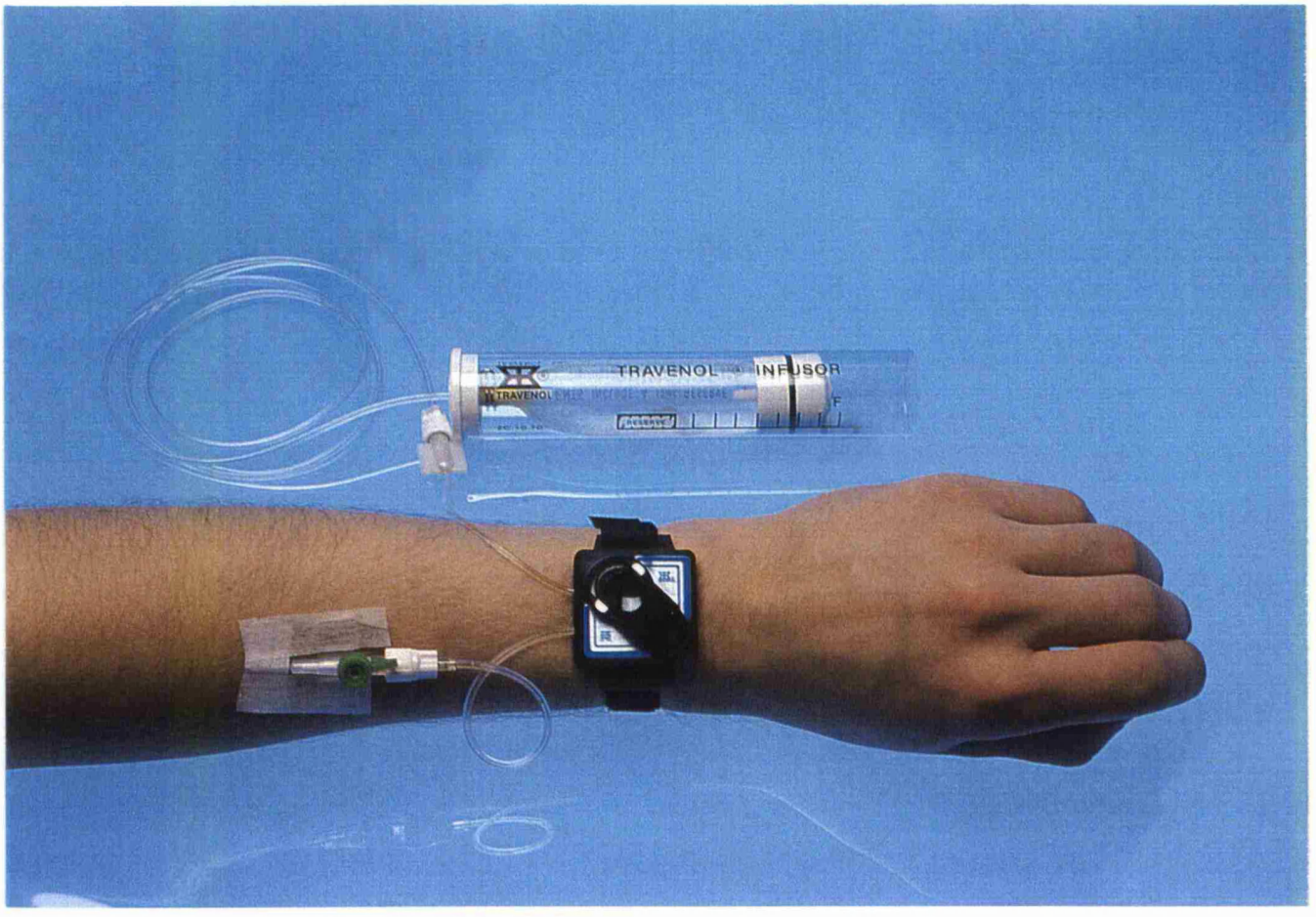
The Baxter PCA Infusor

The Baxter PCA Infusor (Baxter Healthcare Ltd., England) is a small nonelectric device that is completely disposable. It consists of two components; a plastic cylindrical container, in which there is an elastic balloon containing the medication, and a patient control module, which is worn on the wrist like a watch. Indeed, it is often referred to as the Baxter watch (Fig. 4.4). The two components are connected with microbore tubing and an additional microbore tube connects to the dedicated i.v. site at the patient's wrist.

This device is not programmable as the drug chamber holds a volume of 60 ml, and the amount of drug delivered is dependent upon the opioid concentration in that chamber.

The patient-control module contains a small bladder with a capacity of 0.5 ml. The bladder fills in 6 minutes because the infusor used delivers solution at the rate of 5 ml/hr as the balloon reservoir slowly deflates. The patient pushes a button, on the face of the module, in order to release the bolus of opioid. The button is recessed into the surround of the device to reduce the chance of inadvertent activation. The button, when pressed, releases a clamp and the contents of the bladder are delivered to the patient.

Figure 4.4 The Baxter disposable PCA system.



There is no provision for the use of a background infusion with this system and the simple design removes the need for failsafe features and alarms.

There is no doubt that this device is less flexible than the electronic (programmable) ones. In addition, it is not possible to record accurately the number of boluses or the total dose administered to the patient, although an approximate measurement can be made from the markings on the side of the infusor or with adhesive labels which are provided for this purpose. However, laboratory evaluation of these devices have concluded that any departures from nominal delivery are not considered to be of clinical significance (Mackey et al., 1993).

The Baxter PCA device functioned well overall and it was well accepted by the patients (Chapter 8.4). One reason for this may have been the simplicity of the design. Not all patients appreciate sophisticated high tech devices and, as mentioned previously, there is a fear amongst some of machine malfunction (Kluger and Owen, 1990b).

CHAPTER 5

Measurement of Subjects' Responses

5.1 Background

In the studies which follow, (Chapters 6-12) it was important to use the most effective method of assessing patient responses to certain variables. Various methods have been used by clinicians which are designed to assess the response from a patient to a certain stimulus. This stimulus is often pain but other stimuli such as nausea and sedation can also be assessed.

The measurement of pain is still in its infancy and until recently the methods used treated pain as though it were a single unique quality that varies only in intensity (Beecher, 1959). There is still no uniform basis for pain measurement, but two principal models have emerged. One is a medical model, in which pain represents pathology or a threat of injury, and the other is a behavioural model, in which pain is a perception that is influenced by cognition, behaviour and predisposing personality factors (Jamison, 1993). The medical model is more traditional and relies on objective findings of pathology whilst the behavioural model encompasses subjective factors such as past experiences and learned behaviours. These two fundamental differences in perspective typify some of the difficulties inherent in assessing pain accurately.

Pain is a subjective experience, everyone has different perceptions of it and of how they quantify it. For example, some individuals would never say that their pain was "10" on a scale from 0-10 whereas other individuals report their pain as a constant "10", despite looking calm and relaxed. Also, all the numeric scales that are used to measure pain have floor and ceiling effects. If pain is described to be a "10" on a 0-10 scale, there is no way to describe any increase in intensity of pain.

There are a number of factors which make comparisons of pain measurement difficult. These include site (Yeager, 1989), duration, pattern of pain and the demographic factors of gender (Miller and Shuter, 1984), age (Kaiko, 1980) and ethnic background (Melzack and Wall, 1988). In addition, past experiences of pain (Peck, 1986; Thomas and Rose, 1991; Craig, 1994) may influence the patients' perceptions, as may medication (Gracely, 1994), sleep disturbance (Parker et al., 1992) and affect (Craig, 1994). Patients who are clinically depressed and/or anxious tend to report increased pain intensity (Taenzer et al., 1986; Thomas et al., 1990; Egan et al., 1992).

Frequent pain measurement does require a level of compliance on the patient's part however, which may prove to be a problem over a long period of time. Furthermore, the awareness of pain that coincides with frequent monitoring may contribute to increased anxiety, especially when the pain ratings are constantly high or there is an increase in intensity (Jamison and Brown, 1991). This may lead to imprecise measurement or exaggeration of pain.

On the other hand, it has also been suggested that patients monitoring their pain may experience an increased sense of control over it which actually reduces their perception of pain (Jamison, 1993).

Despite the limitations in the assessment of pain (and other stimuli) there are a number of acceptable methods that are in use, some of which are discussed below. The most common way to quantify pain is through self-report measures, where patients may use words, numbers, or mark intensity levels on a line to indicate their pain. Although some scales include more than one form of measurement, most scales are unidimensional.

5.2 Numeric Rating Scales

Numeric rating scales are used to determine the intensity of pain experienced. Pain intensity ratings were developed by Budzynski and colleagues (1973) and Melzack (1975). Patients would be asked to rate their pain from 0, or no pain, to some number representing pain as intense as it could be. These scales allow for increased sensitivity (rather than a yes or a no), are easy to administer and reliable when compared with other methods (Kerns et al., 1988). Patients also find them easy to use, especially if the numbers are accompanied by recognizable descriptions of pain.

Numeric rating scales are frequently used in the clinical setting and are particularly valuable when treating numerous patients, for instance, as with a postoperative pain service.

5.3 Visual Analogue Scales (VAS)

This is a simple approach to rating responses and the ease of administration and scoring has contributed to the popularity of this method (Gracely, 1994). The VAS is most usually a 10 cm unmarked line, labelled at the anchor points with no pain and worst possible pain, or similar (Fig. 5.1). The line can be either horizontal (Huskisson, 1983) or vertical (Sriwatanakul et al., 1983a). The patients indicate the pain they are currently experiencing, by placing a mark on the line. The distance in millimetres or centimetres from no pain to the patient's mark is used as a numerical index of the severity of pain.

Figure 5.1 Visual analogue scale used to measure pain intensity.

A variation of VAS is the graphic rating scale (Karoly and Jensen, 1987). To assist in describing the intensity of the pain, words are placed along the scale. However, patients tend to place their responses around these descriptive words and for this reason use of graphic rating scales has become less popular.

In the past, studies have demonstrated good correlation between VAS and other numerical and verbal measures of pain intensity (Ohnhaus and Adler, 1975; Downie et al., 1978; Kremer et al., 1981; Ekblom and Hansson, 1988).

The VAS has a number of advantages: it is reliable (Revill et al., 1976; Seymour, 1982); it is easy and brief to administer and score (Joyce et al., 1975; Jensen et al., 1986); patients find this measure easy to understand (Chapman et al., 1985), particularly children (Scott et al., 1977); there is an even distribution of ratings using the VAS (Huskisson, 1983); the measure is reproducible over time (Revill et al., 1976); there is adequate sensitivity for assessment of treatment effects (Joyce et al., 1975; Turner, 1982).

The VAS may not be easily administered to patients who have impaired eyesight or those who are elderly, because of problems perceiving the line and coordinating their marks (Jensen et al., 1986).

5.4 Verbal Rating Scales

A verbal rating scale uses a list of words with which patients may describe the intensity of their pain. There are a number of different verbal rating scales, including four-point scales (Joyce et al., 1975; Seymour, 1982), five-point scales (Kremer et al., 1981; Frank et al., 1982), six-point scales (Melzack, 1975), twelve-point scales (Tursky et al., 1982) and fifteen-point scales (Gracely et al., 1978a). The words are usually ranked

according to severity and numbered sequentially from least intense to most intense (Table 5.1).

Table 5.1 Examples of verbal rating scales of pain intensity.

Four-point:	Six-point:
1. No pain	1. No pain
2. Mild	2. Mild
3. Moderate	3. Discomforting
4. Severe	4. Distressing
	5. Horrible
	6. Excruciating

The advantages of verbal rating scales, like VAS, are that they are easy to administer, simple to score and demonstrate adequate reliability and validity (Harms-Ringdahl et al., 1986; Jensen et al., 1986). Jensen and colleagues demonstrated that verbal scales are highly correlated with measures of pain intensity, whereas Rybstein-Blinchik (1979) found that they correlated poorly with personality factors influencing pain. As pain is such a personal experience, verbal rating scales are better able to reflect the multi-dimensional nature of pain which is why, to date, verbal pain rating scales have been the most popular means of measuring pain sensation (Jamison, 1993).

Unfortunately, verbal rating scales also possess a number of weaknesses. One weakness is that they may be distorted. Clinical studies have shown that changes in sensory and affective ratings of pain can occur after neurological procedures and medication regimens (Gracely et al., 1978b).

Another weakness is that differences in diagnosis can alter scoring of verbal scales. For example, patients with malignant pain tend to report low levels of pain intensity

compared with patients with benign pain (Kremer et al., 1982). In addition, conflicting evidence exists as to how accurately verbal reports of pain correlate with medical diagnosis. Fordyce (1976), for example, suggested that pain language is influenced by a number of factors apart from the pathology of pain.

Some VRS use multiple descriptors to assist in accurate diagnosis (Table 5.2) and chronic pain patients, using more than one word to describe their pain, have been shown to experience more emotional distress and to be at a greater risk for treatment failure (Jamison et al., 1987).

Table 5.2 Example of a list of verbal pain descriptors.

1. Piercing	4. Burning	7. Aching	10. Numbing
2. Stabbing	5. Throbbing	8. Stinging	11. Itching
3. Shooting	6. Cramping	9. Squeezing	12. Tingling
			13. None

5.5 The McGill Pain Questionnaire

In 1971, Melzack and Torgerson classified a list of words describing pain qualities into three major classes: sensory, affective and evaluative words. From this list evolved the McGill pain questionnaire (MPQ). The MPQ consists of 20 subclasses of descriptors as well as a pain intensity score ranging from 0 (no pain) to 5 (excruciating pain). It is a multi-dimensional measurement of pain containing three types of measures: a pain intensity index; the number of words chosen; an overall pain intensity score. A short form of the MPQ (Melzack, 1987) has also been developed for use in specific research settings, when the time available to obtain information is limited and where more information is required than can be provided by other measures, such as the VAS.

The MPQ has been demonstrated to be valid, reliable, consistent and useful in research and chronic pain states (Van Buren and Kleinknecht, 1979; Melzack, 1983; Chapman et al., 1985; Reading 1989; Wilkie et al., 1990), but there are a number of limitations in its use. Multi-dimensional methods are complex and time consuming. It is too cumbersome for repeated evaluations of acute pain states as it takes at least five minutes to complete (Melzack and Katz, 1994). It also contains pain descriptors that may not be easily understood, for example, lancinating and rasping, which need additional time for explanation. A simpler method of introducing further dimensions into acute pain scoring is to use VAS ratings for anxiety to tranquility in addition to no pain to severe pain (Mitchell and Smith, 1989).

The fact that the three scales correlate highly with one another has been criticized because they may only be measuring one dimension and not multi-dimensional factors (Turk et al., 1985). In addition there has been some question about the stability and internal consistency of the sensory and evaluative subscales (Karoly and Jensen, 1987). However, despite these limitations the MPQ has been used frequently in clinical practice over the years for the subjective measurement of pain.

5.6 Dermatomal Pain Drawing

Pain drawings are simple, easy to use and to score (Margolis et al., 1986). Patients are asked to indicate the location and distribution of their pain by shading areas of a dermatomal chart. The chart usually portrays front and back views of the human body and the patient is asked to fill in the areas of the chart that correspond to the location of the pain they have. Some clinicians use colours to represent different sensations of pain (e.g. red for pain; blue for numbness).

Pain drawings are a popular assessment tool (Jamison, 1993) but there are some drawbacks to this method. Patients may fabricate the drawings (Margoles, 1983), some

patients do not find them easy to use, particularly elderly patients and those whose physical condition prohibits them from filling in the charts successfully. It has been suggested that there is a weak correlation between abnormal pain drawings and psychopathology (Schwartz and DeGood, 1984). For this reason it has been recommended that the drawings should not be used to assess psychopathology but rather be incorporated as a descriptive assessment of the patient's pain (Karoly and Jensen, 1987).

VAS and VRS are the scales used most frequently for the quantification of clinical pain (Royal College of Surgeons and Anaesthetists. Report on the working party on pain after surgery, 1990). The uni-dimensional method of the VRS has a good correlation with the more complex VAS and an acceptable degree of variation between individuals (Mitchell and Smith, 1989). There is some evidence to suggest that VAS are more sensitive to treatment effects than VRS (von Graffenried and Nuesch, 1990; Wallenstein, 1991; Price et al., 1994) but whilst the VAS is most effective for monitoring the progress of an individual patient, the VRS has advantages in inter-individual assessment (Owen et al., 1990b).

As both are reliable, patients like them (they are not too intrusive) and they are easy to administer and score for repetitive evaluation, VRS and VAS were the methods employed in the studies described in this thesis.

CHAPTER 6

A Pilot Study at Glenfield General Hospital, Leicester

6.1 Background

PCA was a relatively new concept to the hospitals in Leicester when I became involved in research relating to it. This study was undertaken to familiarize the ward staff (nurses, doctors, physiotherapists, pharmacists and any other ancillary workers) with the technique of PCA and to ensure that the investigator (myself) had established adequate procedures to support the planned studies. This proved a valuable exercise because it also raised problems that were circumvented, in the subsequent studies. As a result this improved the quality of the data and prevented unnecessary waste of time and resources.

The University Department of Anaesthesia, in Leicester, had already been using the Cardiff palliator for some clinical trials. Graseby Medical had recently replaced the Cardiff palliator with the Graseby PCAS and the company were willing to loan the equipment. Of the models available at the time very few were suitable for research purposes but the Graseby PCAS was a new computerized model that had yet to be put through its paces in a practical environment. It was also a vast improvement on the Cardiff palliator. The Graseby, therefore, was the device used for this study.

The use of PCA on one ward (orthopaedic) initially, allowed anaesthetists, nurses and ancillary staff to develop familiarity with the system in a contained environment (Notcutt, 1988).

In addition to the stated aims of gaining expertise with the technique of PCA and the Graseby PCAS, the study would provide valuable first hand experience of opioid

requirements with PCA, how long the patients would need opioid analgesia postoperatively (clinical experience suggested a 24 hour period to be adequate) and to determine any problems with the regimen.

6.2 Methods

Fifty-three patients, undergoing knee or hip replacement surgery, gave verbal consent for inclusion in this preliminary study. In the knee group there were six males (aged 59-80 years) compared with eight females (aged 63-78 years), whilst in the hip group there were nine males (aged 57-81 years) compared with twenty-six females (aged 22-81 years).

At a preoperative interview, the informal nature of the study was explained to the patients and at the same time they were instructed in the use of a Graseby PCAS .

As this was a familiarization study there was no need to standardize the anaesthetic technique. Morphine, for postoperative analgesia, was given in recovery at the anaesthetist's discretion, until the patient was comfortable.

On return to the ward the patients were re-familiarized with the mode of activation of the PCAS. A recent study in Leicester (Colquhoun and Fell, 1989) had used parameters which were deemed adequate for the majority of patients and this was the regimen adopted for use. The PCAS was set to deliver a 2 mg bolus of morphine, with a lockout interval of 10 minutes. Initially morphine 50 mg syringes were allocated to patients over 60 years and 100mg syringes to patients under 60 years as it was expected that this amount of morphine would be adequate for the 24 hour postoperative period. Operation of the PCAS - dose regimen, total dose of opioid, time and success (or otherwise) of a demand - was recorded by a Hewlett Packard thermal printer.

To ensure that patients received adequate analgesia, additional prescriptions of morphine 5-10 mg were available as escape analgesia. An antiemetic was also prescibed.

The ward nurses were reminded that postoperative observations were to be the same as for other postoperative patients; hourly blood pressure, pulse and respiratory rate for four hours and then four hourly. If the respiratory rate dropped below 10 breaths per minute the anaesthetist was to be informed. If the rate dropped below 8 then PCA should be stopped and the anaesthetist informed.

At the end of the 24 hour postoperative period the patients were invited to comment on the method of administering analgesia.

6.3 Results

Four patients discontinued use of PCA before the 24 hour period had expired. Two patients were unhappy with the PCAS, one of whom was elderly and had become disorientated after surgery, and reverted to i.m. therapy. The other two were discontinued for reasons of safety, due to the ward nurses' inexperience with the PCAS. On both occasions the PCAS had registered "fault" because the mains lead had become disconnected.

Both operations had similar requirements for opioids, the mean (SEM) amount of morphine administered by PCA, for the 24 hour observation period, was 39.6 mg (4.1) in the knee group and 34.8 mg (3.3) in the hip group (Table 6.1). At the extremes, one patient used 4 mg whilst two others used 76 mg.

Two patients required escape analgesia but continued to use the PCAS until the completion of 24 hours whilst a further two patients required one dose of i.m.

morphine after the 24 hour observation period. Seven patients administered the maximum amount of morphine available but did not require further i.m. doses.

Table 6.1 Mean, SEM and range of doses of morphine given during surgery, in the recovery room and with PCA.

	Group 1 Knee group (n=14)			Group 2 Hip group (n=35)		
	Mean	SEM	Range	Mean	SEM	Range
Intraoperative	11.3	1.0	7-20	9.9	0.7	0-20
Recovery	2.2	1.1	0-7.5	5.1	0.9	0-17.5
Postoperative	39.6	4.1	4-66	34.8	3.3	10-76

Table 6.2 shows the number of doses of antiemetic administered per patient in the intraoperative period and for the 24 hour postoperative period. Approximately 20% of patients from each group did not require antiemetics, the remainder required doses ranging from 1-3, with one other patient receiving a total of 7 doses.

Table 6.2 Number of doses (%) of antiemetic administered intramuscularly.

Doses	Group 1 Knee group (n=14)		Group 2 Hip group (n=35)	
	(n)	(%)	(n)	(%)
0	3	21	8	22
1	9	65	16	46
2	1	7	9	26
3	1	7	1	3
>3	0	0	1	3

6.4 Discussion

This study proved to be valuable in highlighting a number of problems. In clinical trials there is always a percentage of patients who are excluded from results for one reason or another. Of the 53 patients in this study, four were excluded because they discontinued use of PCA before the 24 hour study period had elapsed. Of these four, two were not coping well with the PCAS (a factor impossible to forsee) and two as a result of night staff being unfamiliar with the device and rightly discontinuing use of the PCAS for safety reasons. A positive effort had been made to instruct the night staff in the technique but because of the rapid turnover and shortage of staff working the night shift this did not always produce the required results.

Two patients who completed the 24 hour period required escape morphine. One was an extremely anxious 24 year old. Despite using 76 mgs, in addition to the 5 mg morphine escape dose, she was never totally pain-free. This experience concurs with others that anxiety is related to increased analgesic consumption (Thomas et al., 1990). The other patient was a 76 year old lady who, in retrospect, was probably not a very good candidate. At the preoperative interview she had seemed quite bright and alert but postoperatively it soon became apparent that she was unable to use the PCAS effectively. This highlighted the risks inherent in randomized recruitment for future studies.

Two patients required further analgesia after the 24 hour period. They were two females in the hip replacement group and required 5 mg and 10 mg morphine (at 2315h and 2320h respectively) both five hours after PCA had been discontinued. Despite this, it suggested that for the majority a 24 hour period was adequate to administer PCA for hip and knee replacement surgery.

Although for both operations patients had similar requirements for opioids (Table 6.1), the results show quite clearly the diversity of inter-patient variability (Ferrante,1993) with extremes of 4 mg and 76 mg.

The two patients who administered the largest amount of morphine (76 mg) were aged 22 and 24 years. The patient who administered the least amount (4 mg) was aged 68 years. This concurs with the findings of several authors who noted that elderly patients tend to experience pain relief for longer periods (and therefore require less analgesics) than younger patients (Bellville et al., 1971; Berkowitz et al., 1975; Kaiko, 1980; Taenzer et al., 1986; McQuay et al., 1990).

Seven patients, six of them in the knee group, self-administered the entire contents of the 50 mg syringe within a time-scale ranging from 2-9 hours. As these patients were uncomplaining, they were judged to be pain-free by the nursing staff and the syringes were not replaced! Although these patients did not require further opioid analgesia, and they were satisfied with the method of administration, this highlighted a problem in that PCA should be patient- and not nurse-controlled (Notcutt and Morgan, 1990; Rowbotham, 1992; Heath and Thomas, 1993c).

From the research viewpoint it was also important to note that failure to replace used syringes would jeopardize the results of later studies - not to mention compromising the patients' well-being.

Interference from well-meaning relatives had to be a consideration for future studies because on several occasions I found they had "....pressed the button because the patient could not". However, one cannot eliminate the rogue element. One elderly gentleman was extremely pleased with his PCAS and was eager to demonstrate it to his relatives and fellow patients whenever he could, painfree or not!

There was a tendency amongst staff to blame the new technique of PCA for a wide variety of routine postoperative complications (Notcutt and Morgan, 1990). The most important risk from intravenous opiates is respiratory depression (VanDercar et al., 1991) but there was no experience of the respiratory rate falling, with PCA, in this preliminary study.

A common, but unwanted side-effect of morphine is nausea and vomiting (Heath and Thomas, 1993e). There did not appear to be any correlation between the amount of morphine self-administered and nausea and vomiting in this pilot study. The patient who required seven doses of antiemetic only self-administered 18 mg morphine. Against this, the patient who self-administered 76 mg morphine did not receive any antiemetic. Only one patient complained of feeling nauseated and two patients complained of a bitter/dry taste immediately following activation of the PCAS. In this study, there were no problems with side-effects other than can be expected with i.m. opioid therapy (Chapter 3.3).

The comments which the patients made at the end of the 24 hour observation period indicated that in general they were satisfied with the technique of PCA. This was particularly apparent in those patients who had previous experience of i.m. analgesic therapy.

This preliminary study highlighted several areas that would need consideration for the proposed future studies (Chapters 7-12). Sufficient patient numbers would be necessary to provide accurate analyses and to accomodate the inevitable percentage of patient exclusions. When approaching patients for inclusion in the studies some patients, particularly the elderly, although at an initial meeting may appear to be good candidates, they may not always turn out to be suitable.

The consideration of physical disabilities also needs to be addressed. For instance, many patients requiring orthopaedic surgery have severe osteo or rheumatoid arthritis which may prevent them from activating the PCA device. Education of the ward staff is also of paramount importance. They need to become familiar with the devices, unafraid of them and need to understand the importance of the technique being patient-controlled and not nurse/relative-controlled.

When selecting the regimen, account must be taken of inter-patient variability. In addition, an adequate supply of opioid syringes, and someone well-versed in the technique to replace them, is necessary - especially at night. Finally the patients must be adequately observed for side-effects and not forgotten because "a machine is looking after them".

Despite all the potential pitfalls PCA had been successfully introduced onto the wards and clinical research into PCA therapy could begin.

CHAPTER 7

A Comparison of the Bionica MDS 110 with the Graseby PCAS

7.1 Background

The pilot study with the Graseby PCAS had suggested it to be an effective, reliable device for administering PCA, but as PCA was gaining in popularity, there was an upsurge in the production of PCA devices and manufacturers were competing to capture the market. At this time, there were few small, portable devices available and those that were tended to be continuous infusion devices for use in chronic pain (Heath and Thomas, 1993b). The Leicester micropalliator (Burt et al., 1985) was the prototype for an ambulatory PCA device and it had been developed a few years earlier in an attempt to improve on existing PCA devices. This device combined a background infusion with PCA, but when Vickers and colleagues assessed its efficacy for pain relief against the Cardiff palliator (Vickers et al., 1987), they found little improvement. Thus it was never available commercially.

A few years later, International Medication Systems (U.K.) Ltd introduced the Bionica MDS 110 (Chapter 4.8). This was a lightweight, relatively inexpensive device (when compared with the bedside, mains-operated devices), battery powered and easily carried in a shoulder holster. In terms of size it had only one rival in the U.K., the Pharmacia Deltec CADD-PCA (Ferrante, 1993b), but this device was nearly as expensive as the some of the bedside electronic models.

The object of this study was to compare the Graseby PCAS, a bedside electronic device, with the battery operated, ambulatory device (Bionica MDS 110), in terms of quality of analgesia and frequency of side-effects. Also, to assess whether the

portability of the MDS 110 offered practical advantages in the management of pain in the postoperative period.

7.2 Methods

This study was carried out at the Leicester Royal Infirmary where the staff already had some experience of PCA. Thirty female patients undergoing elective hysterectomy participated in this study. In each group, patients were assigned randomly to receive postoperative analgesia with either the Bionica MDS 110 or the Graseby PCAS.

For the purpose of this study, both the Bionica and Graseby were preset to deliver a 2 mg bolus dose of morphine with a lockout interval of 10 minutes. The Bionica used an IMS 10 ml syringe containing 100 mg of morphine in 10 ml of normal saline and the Graseby a 50 ml syringe containing 100 mg of morphine in 50 ml of normal saline.

At the preoperative interview, the appropriate device was explained to the patient as was the VAS scoring method for pain, nausea and sedation. The extremes of the VAS were: no pain, worst possible pain; no nausea, worst possible nausea; wide awake, unable to stay awake.

The ward nurses were also instructed preoperatively in the use of VAS to assess the portability of the two devices. Again each VAS was a 10 cm unmarked line with extremes of: a great nuisance, no nuisance at all. These were measured: whilst in bed; whilst sitting in a chair; whilst mobile. For continuity, one nurse was allocated to each patient

All patients received a standard anaesthetic technique consisting of diazepam 10 mg orally as premedication, thiopentone 3-4 mg/kg, neuromuscular blockade and 67% nitrous oxide with 33% oxygen. A small concentration of a volatile agent was

administered to maintain anaesthesia. Anaesthesia was supplemented with morphine 0.1-0.2 mg/kg.

In the recovery room the patients were given their allocated device and reminded of how to activate it. I.m. morphine 10-15 mg was available as escape analgesia. Prochlorperazine 12.5 mg intramuscularly was available for antiemesis as required. Visual analogue scores for pain, nausea and sedation were measured by the investigator at two hourly intervals (during the day) on the first and second postoperative days. VAS for performance of the devices were assessed by the ward nurses at 24 and 48 hours postoperatively. At the end of the 48 hour study period, patients' pain relief and acceptability of method was assessed by a three-point verbal rating scale. Patients were asked if the pain relief and the method of pain relief was: good, adequate or poor and if, given the opportunity, would they use PCA in the future.

Data were analysed by unpaired Student's t-test, Wilcoxon rank sum test and Chi-squared test with Yates' correction as appropriate. MANOVA for repeated measures was used for VAS scores.

7.3 Results

Two patients from the Graseby group were excluded from the study because of protocol violations and therefore data was available for analysis from 28 patients who were well matched for age, height and weight. There was a significant difference found in the duration of surgery ($p=0.02$), but no significant differences were found between the groups in mean (SEM) doses of morphine administered in the operating theatre; 10.3 (1.2) mg in the Bionica group and 10.8 (0.9) mg in the Graseby group ($p=0.76$), or in the 48 hour postoperative period; 82.9 (9.8) mg in the Bionica group and 120.6 (17.5) mg in the Graseby group ($p=0.06$; Table 7.1).

Table 7.1 Patient data, intra and postoperative dose of morphine (mg).

*** $p < 0.05$.**

	Group 1 Bionica (n=15)			Group 2 Graseby (n=13)		
	Mean	SEM	Range	Mean	SEM	Range
Age (yr)	46.1	2.5	34-70	42.9	2.3	28-60
Weight (kg)	66.5	2.6	49-94	63.0	2.0	49.4-74
Height (cm)	163.0	1.8	150-175	158.7	1.3	152-168
Duration of surgery (min)	56.7	2.8	45-80	71.9	5.4	45-120*
Intraoperative	10.3	1.2	0-20	10.8	0.9	7.5-20
Postoperative	82.9	9.8	14-180	120.6	17.5	52-276

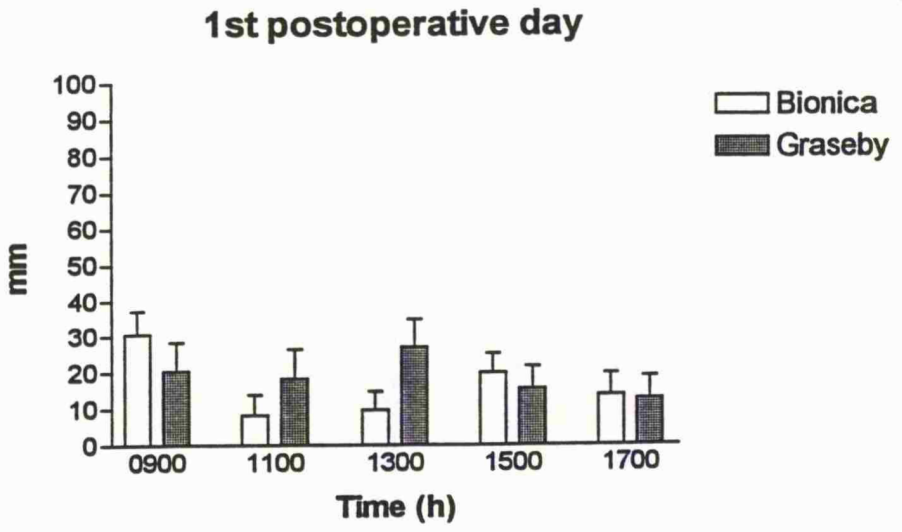
A significant difference between the groups was found in the VAS for nausea at 1300h on the first postoperative day (Fig. 7.2). There were no differences in requirements for prochlorperazine ($p=0.9$; Table 7.2) or in the VAS scores for pain (Fig. 7.1) and sedation (Fig. 7.3).

Table 7.2 Number (%) of prochlorperazine doses administered intramuscularly. No significant differences.

Doses	Group 1 Bionica (n=15)		Group 2 Graseby (n=13)	
n	(n)	(%)	(n)	(%)
0	7	47	5	39
1	3	20	4	31
2	3	20	3	23
3	2	13	1	7

The nurses' VAS scores showed a significant difference in their perception of patients' mobility with the devices, on the second postoperative day whilst in bed (Fig. 7.4). The patients' VRS did not reveal any differences in their experiences of pain, method of pain relief, activation and portability of the devices (Table 7.3).

Figure 7.1 Mean (SEM) visual analogue scores for Pain.



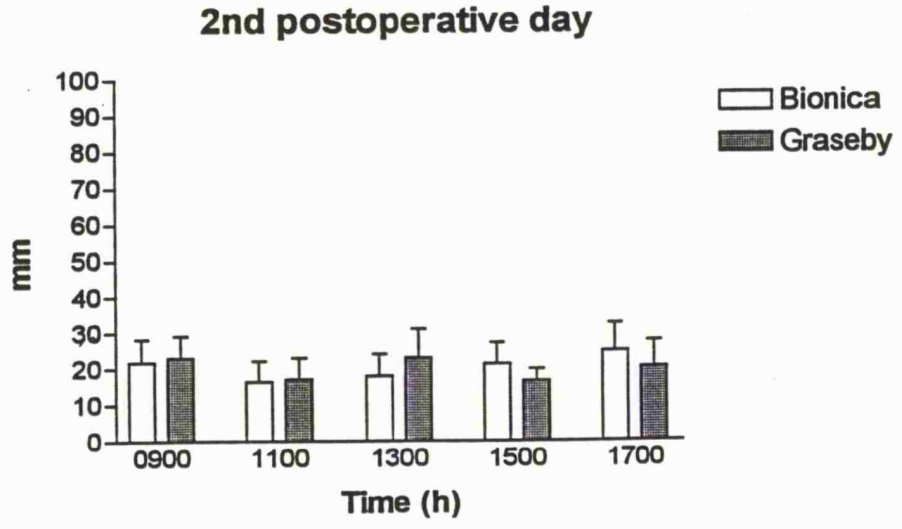


Figure 7.2 Mean (SEM) visual analogue scores for Nausea.

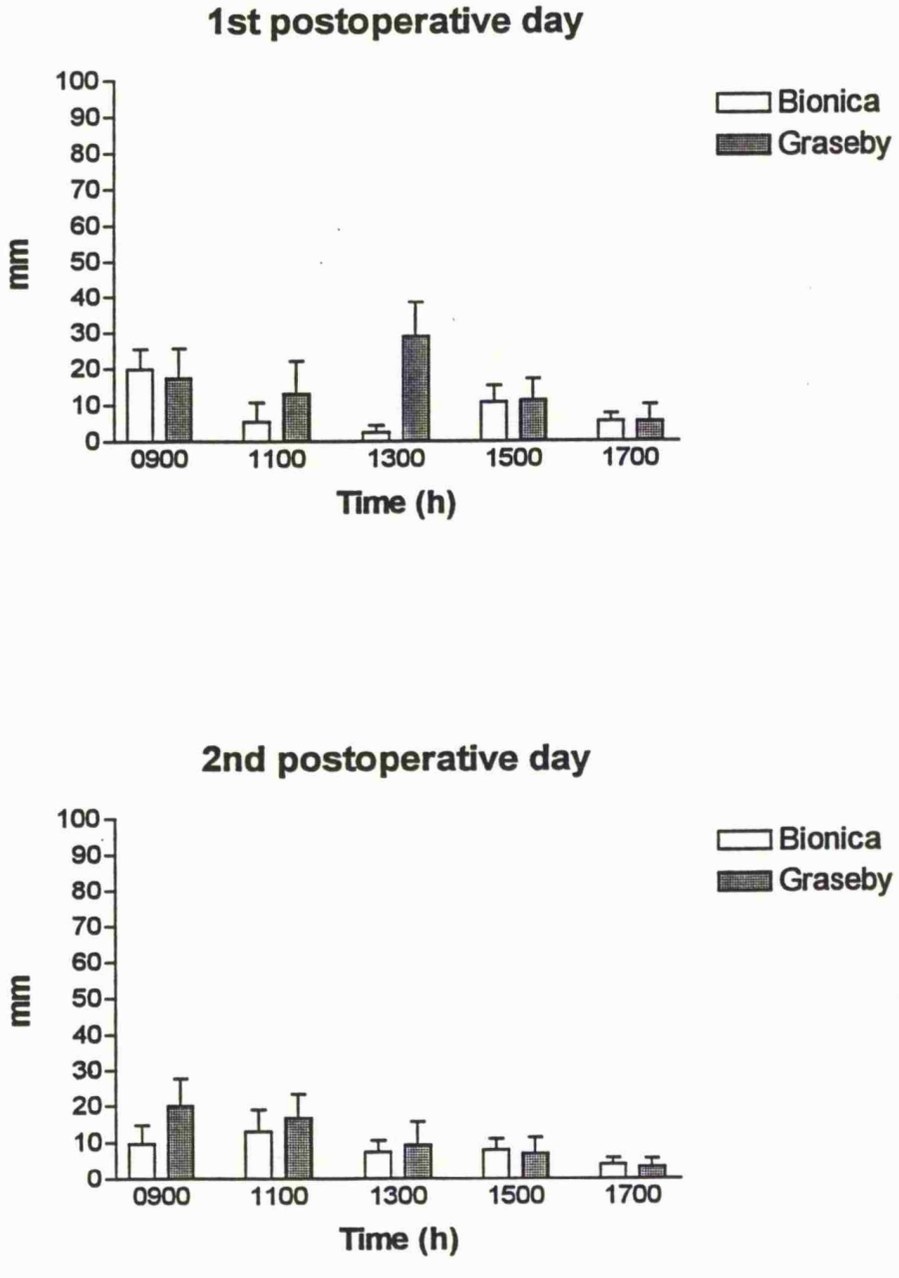
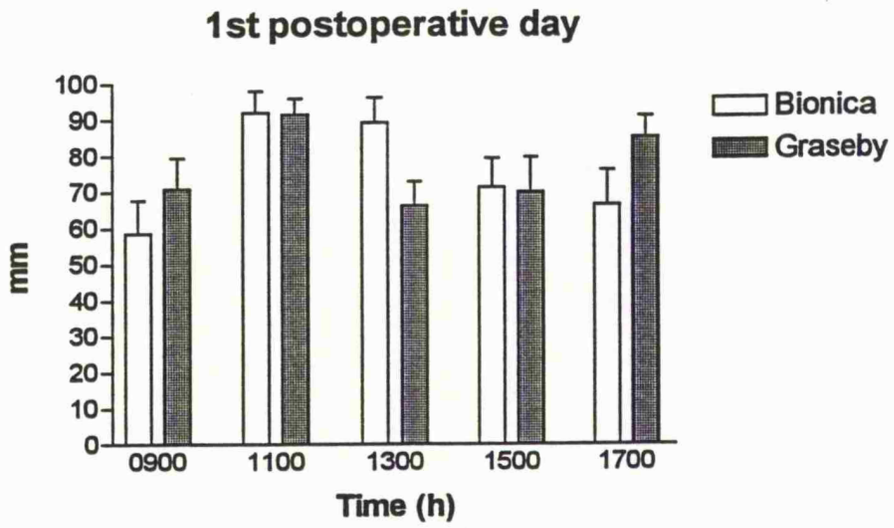


Figure 7.3 Mean (SEM) visual analogue scores for Sedation.



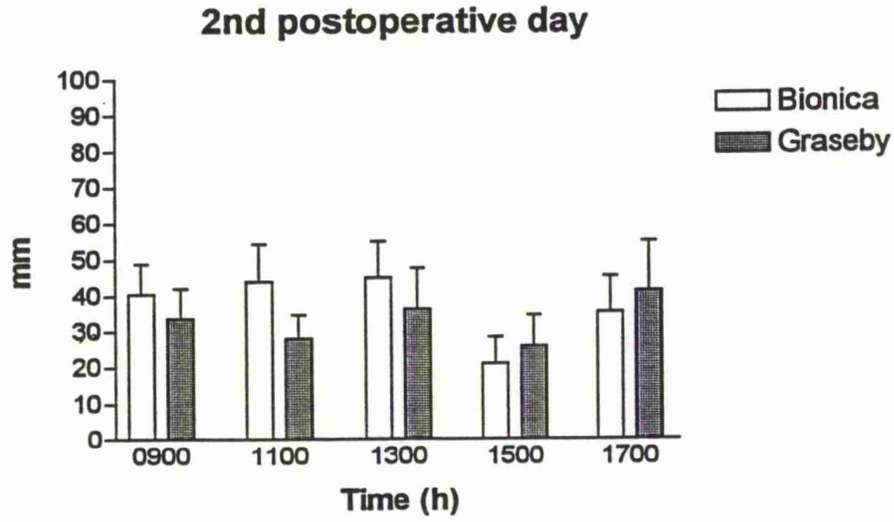
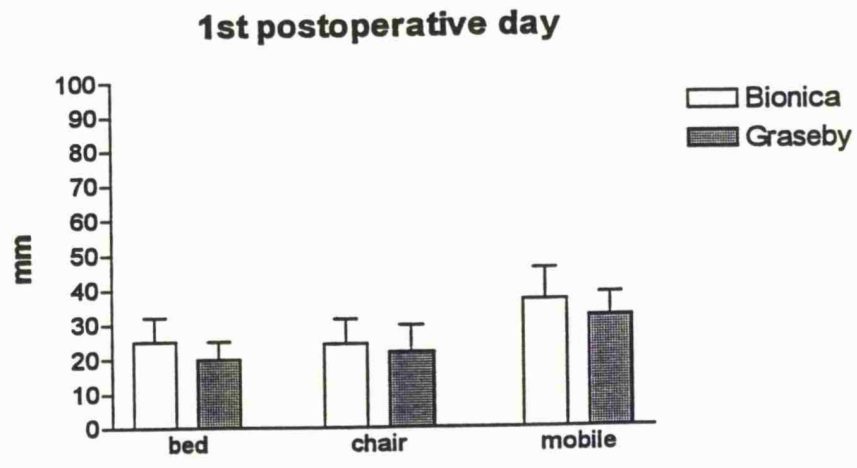


Figure 7.4 Mean (SEM) visual analogue scores for Nurses' assessment for performance of device.



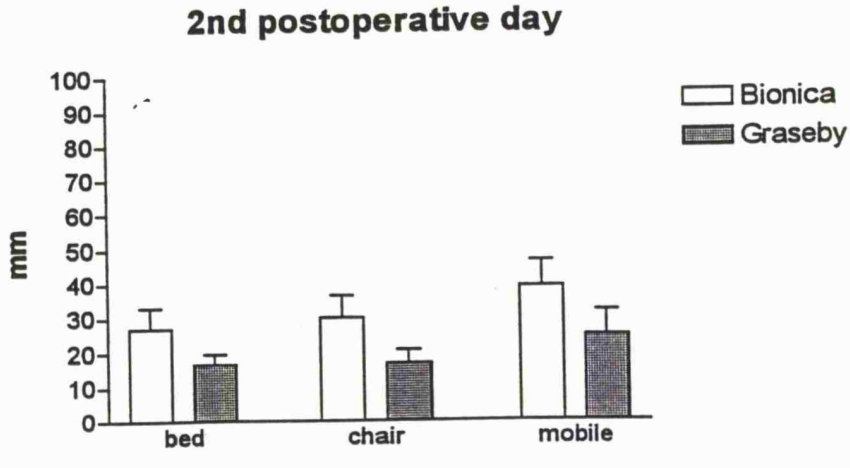


Table 7.3 Three-point VRS for overall analgesia, satisfaction with method and willingness to repeat technique. No significant differences.

	Group 1 Bionica (n=15)		Group 2 Graseby (n=13),	
	(n)	(%)	(n)	(%)
Pain relief				
1. Good	10	67	9	69
2. Adequate	5	33	4	31
3. Poor	0	0	0	0
Method				
1. Good	11	73	11	85
2. Adequate	4	27	2	15
3. Poor	0	0	0	0
Future use				
1. Yes	12	80	11	85
2. Perhaps	2	13	2	15
3. No	1	7	0	0

7.4 Discussion

The results of this study show that comparable analgesia and side-effects were achieved with the Bionica MDS 110 and the Graseby PCAS when used to provide postoperative analgesia after hysterectomy.

There was a statistically significant difference in the duration of operation (p=0.02). However, this difference is unlikely to have affected the overall findings of the study as

the amount of morphine administered intraoperatively was not statistically significant (Table 7.1).

Patients in the Graseby group self-administered 50% more morphine than those in the Bionica group (Table 7.1). This may be accounted for by the length of time it took the Bionica to deliver the bolus dose. Once the bolus button is depressed the dose of medication is injected over 8.5 minutes before the lockout period commences and it is not possible to receive further medication for 10 minutes (Chapter 4.8). In effect this allowed the patient to receive 6.49 mg morphine in one hour compared with 12 mg per hour using a Graseby, whose bolus delivered in 36 seconds.

Despite this, there were no statistically significant differences ($p=0.06$) in morphine requirements, although it is possible that this may have become significant if more patients had been studied. The results were skewed by one patient in the Graseby group receiving 276 mg, the rest of the patients in the two groups administered between 14-194 mg.

There was a significant difference found in the VAS nausea score at 1300h on the first postoperative day ($p=0.02$), the Graseby group demonstrating a higher score (Fig. 7.2). This score may have corresponded to the amount of morphine administered at this time as the pain score for 1300h on the first postoperative day was also at its highest. However, the overall requirement for antiemetics between the groups was not significant and all the nausea scores were quite low.

There were no significant differences demonstrated between the devices in pain scores. On the first postoperative day, although the scores at 1100h and 1300h for the Graseby group looked as though they may have been statistically significant (Fig. 7.1), t-tests disproved this. No differences were found in the scores of VAS for sedation.

On the second postoperative day, a significant difference was found in the efficacy and portability of the two devices whilst in bed ($p=0.01$), as assessed by the nurses' VAS (Fig. 7.4). The nurses were in favour of the Bionica. This may have been because this smaller device was easier to manipulate when bathing and changing nightwear. The VAS for the second postoperative day, whilst in the chair, was also borderline ($p=0.057$). This was not surprising as patients are obviously more mobile on the second postoperative day and it is inconvenient to push an i.v.i. stand around, especially if the i.v. infusion has been discontinued! In this instance the Bionica would be more attractive. Again, it is possible that greater patient numbers may have shown a statistical significance.

In the Graseby group two patients found the device to be a hindrance whilst mobilizing but none had problems with activating it. Compared with the Bionica it is substantially heavier if carried and slightly cumbersome when pushed around on an i.v.i. stand, as it tends to upset the balance. These patients also found the Graseby a problem when changing nightwear. The syringe needs to be removed from the device for this procedure, which requires nursing assistance. The Bionica, however, was small enough to pass through most items of clothing.

One patient in the Bionica group found the device difficult to activate. The problem was in operating the bolus button as it was required to be depressed for one second in order for it to function. In theory this does not sound too difficult but in practice, when patients were drowsy postoperatively, it did cause problems occasionally.

All patients in the Graseby group said that they would use the method in the future and one patient in the Bionica group would not want it again.

Although it was not possible to blind this study, which theoretically subjected it to a certain amount of bias, none of the patients had previous experience of PCA and were,

therefore, completely objective to the devices assigned to them. This study has demonstrated a significant difference between the Graseby electronic PCAS and the Bionica MDS 110 portable PCA device with respect to nurse acceptability (in favour of the Bionica) on the second postoperative day. There did not appear to be any advantages of the Bionica MDS 110 with respect to performance and patient acceptability, after major gynaecological surgery, however greater patient numbers may have altered these findings. Unfortunately, this was not possible as the Bionica was withdrawn towards the end of the study due to the issuing of the hazard warning (Grover and Heath, 1992) discussed in Chapter 4.8.

CHAPTER 8

A Comparison of the Baxter Disposable PCA Device with the Graseby PCAS

8.1 Background

The previous study (Chapter 7) compared an ambulatory, electronic device with an electronic bedside one. Unfortunately the portable device was withdrawn before a full evaluation of its capabilitites could be achieved. Although there are several reliable electronic patient-controlled analgesia systems available, they are expensive and considerable capital investment is required if they are to be made available to all patients after surgery.

Baxter Healthcare Corporation have developed a lightweight, nonelectronic PCA device. This is a disposable PCAS (Chapter 4.8) which has already been shown to provide satisfactory analgesia (Rowbotham et al., 1989a). However, at the time of conducting the clinical work for this thesis, a direct comparison of this device with an electronic device had not been made. This study, therefore, compared the performance of the Baxter disposable PCA device with the Graseby Dynamics electronic PCA syringe pump, in patients after surgery.

8.2 Methods

This study was carried out at the Leicester Royal Infirmary with female patients, aged 26-59 years, undergoing major gynaecological surgery.

At a preoperative interview, patients were allocated randomly to receive postoperative analgesia with either the Baxter or Graseby device. They were instructed in the use of the device and in the VAS method for assessment of pain and sedation. Each linear

analogue comprised a 10 cm unmarked line, the ends of which denoted the extremes of the variables in question, i.e. no pain, worst possible pain; wide awake, unable to stay awake.

All patients were premedicated with temazepam 20 mg given orally 1 hour before surgery. Anaesthesia was induced with thiopentone 3-4 mg/kg and tracheal intubation was facilitated by vecuronium 0.1 mg/kg. The lungs were ventilated with 66% nitrous oxide and enflurane in oxygen and morphine 0.2 mg/kg was given to supplement anaesthesia.

In the recovery room the patients were given their allocated devices. The Graseby was set to deliver a dose of morphine 1 mg with a lockout time of 6 minutes. A solution of morphine 2 mg/kg was prepared and attached to the Baxter device which gave a bolus dose of 1 mg with an effective lockout time of 6 minutes. Prochlorperazine 12.5 mg intramuscularly was given for nausea as required.

VAS for pain and sedation were measured at 6, 24 and 30 hours after commencement of PCA. At the end of the 30 hour study period, pain relief and acceptability of the method was assessed by a verbal three-point scoring system: good, adequate and poor for pain relief and method of delivery; yes, perhaps and no for willingness to use again.

At the end of the study, solution was aspirated from the Baxter disposable device and the volume administered to the patient was calculated. This was compared with the value given by the volume indicator on the device.

Data were analysed by unpaired Student's t-test, Wilcoxon rank sum test and Chi-squared test with Yates' correction as appropriate. MANOVA for repeated measures was used for visual analogue scores.

8.3 Results

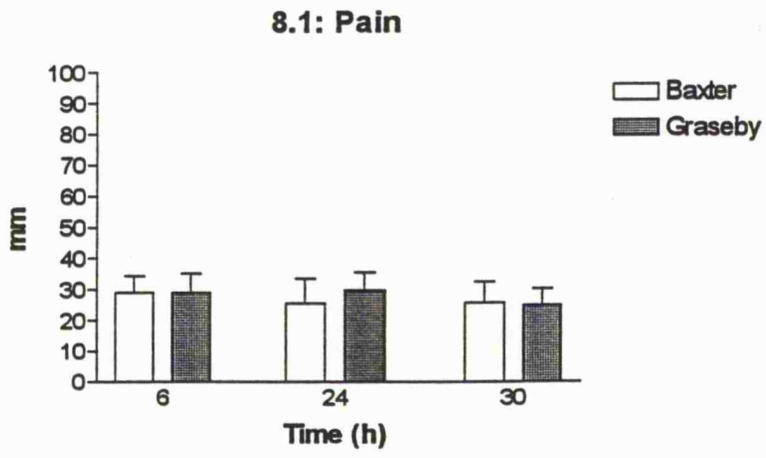
A total of 32 patients were studied. The results of one patient in each group were excluded from analysis because of protocol violations. Patients were well matched for age, height and weight and there were no significant differences between the groups with respect to mean doses of morphine administered in the operating theatre; 13.2 (1.9) mg in the Baxter group and 10.2 (0.4) mg in the Graseby group (p=0.21), or in the 30 hour postoperative period; 35.1 (8.5) mg in the Baxter group and 35.7 (6.6) mg in the Graseby group (p=0.77; Table 8.1).

There were no differences between the groups in the requirements for prochlorperazine (p=0.06; Table 8.2) or in the VAS scores for pain (Fig. 8.1) and sedation (Fig. 8.2).

Table 8.1 Patient data, intra and postoperative dose of morphine (mg). No significant differences.

	Group 1 Baxter (n=15)			Group 2 Graseby (n=15)		
	Mean	SEM	Range	Mean	SEM	Range
Age (yr)	42.0	3.1	23-73	41.7	1.9	26-53
Weight (kg)	62.3	3.1	44-88	64.8	3.2	44-100
Height (cm)	162.0	1.9	150-173	160.1	1.6	150-170
Duration of surgery (min)	66.0	5.6	30-105	80.1	5.9	50-110
Intraoperative	13.2	1.9	7.5-35	10.2	0.4	7.5-15
Postoperative	35.1	8.5	2-112	35.7	6.6	1-90

Figure 8 Mean (SEM) visual analogue scores.



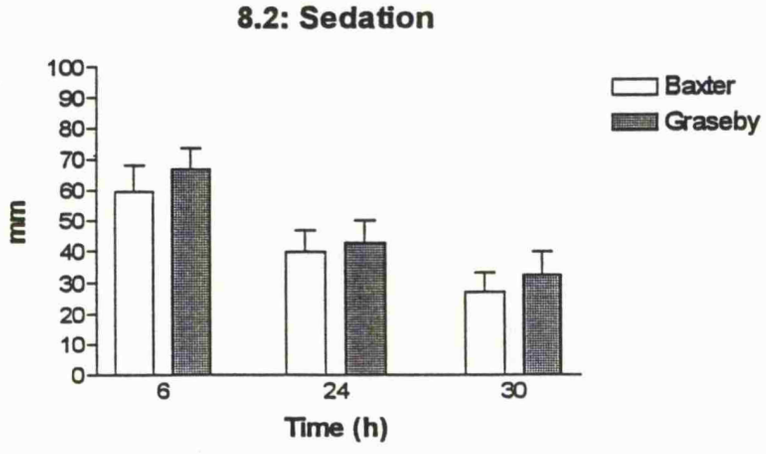


Table 8.2 Number (%) of prochlorperazine doses administered intramuscularly. No significant differences.

Doses	Group 1 Baxter (n=15)		Group 2 Graseby (n=15)	
(n)	(n)	(%)	(n)	(%)
0	9	60	5	33
1	0	0	4	27
2	4	27	4	27
3	2	13	0	0
>3	0	0	2	13

The verbal three-point scoring system for pain relief and method of delivery are shown in Table 8.3. Two patients in the Graseby group rated the method and quality of pain relief as poor and three stated they would not want to use the technique in future. This was not found in the Baxter group but the differences were not significant.

The Baxter device tended to underestimate the volume of morphine administered. The mean difference between the measured volume and the value given by the device was 2.6 ml. The range was an underestimate of 7.3 ml to an overestimate of 2.7 ml.

Table 8.3 Three-point VRS for overall analgesia, satisfaction with method and willingness to repeat technique. No significant differences.

	Group 1 Baxter (n=15)		Group 2 Graseby (n=15)	
	(n)	(%)	(n)	(%)
Pain relief				
1. Good	12	80	11	74
2. Adequate	3	20	2	13
3. Poor	0	0	2	13
Method				
1. Good	13	87	13	87
2. Adequate	2	13	0	0
3. Poor	0	0	2	13
Future use				
1. Yes	14	93	12	80
2. Perhaps	1	7	0	0
3. No	0	0	3	20

8.4 Discussion

In this study there were no significant differences between the Graseby electronic PCAS and the Baxter disposable PCA device with respect to performance (postoperative PCA consumption of morphine demonstrated almost identical means) and acceptability in patients after major gynaecological surgery.

The lack of flexibility resulting from the fixed infusion rate (Nimmo and Todd, 1986) and bolus size can be a disadvantage with the disposable system. For example, if a

larger bolus is required, a new infusion device with a greater concentration of morphine must be prepared. However, Nimmo, when using electronic PCA systems, noted that the same dose and lockout settings could be used for almost all adults undergoing general surgery (Nimmo, 1992). The majority of patients received satisfactory analgesia and it was not found necessary to adjust the regimen for future studies.

It is not possible with the Baxter device to monitor the precise amount of morphine administered to the patient. The adhesive scale which attaches to the infusion device gives only an approximate indication. It was found that this may underestimate by 7.3 ml or overestimate by 2.7 ml. However, in clinical use where patients control their own administration and regular observations are taken by the nursing staff, this is not likely to be a significant problem.

More recently, laboratory examination of the device has demonstrated that the lockout interval and reservoir exhaustion characteristics showed some departure from nominal performance (Mackey et al., 1993). Davidson and colleagues, also evaluating the device in a laboratory, found that the maximum hourly dose of drug is affected both by changes in the ambient temperature of the dextrose solution and by the volume of fluid in the reservoir (Davidson et al., 1993). However, as the Baxter disposable PCA devices performed in a reliable and reproducible fashion, the authors of these studies did not consider their findings to be of clinical significance.

The most attractive feature of the disposable system is its simplicity and convenience. There have been a number of reports detailing both the effectiveness of the system and good patient acceptability (Gallion et al., 1987; Wermeling et al., 1987). Every patient in this study found the device acceptable whilst two patients described the Graseby PCAS technique as poor, but these differences were not statistically significant. The Baxter disposable device obviously has a much less high tech appearance than the

electronic pumps, which some patients prefer (Heath and Thomas, 1993b). Anecdotally, the nursing staff were also impressed - not least because it requires little maintenance from a nursing point of view.

The disposable device is also less prone to user error, as the regimen cannot be changed once commenced, and the device allows better mobility for the patient without interruption of the pump function. In addition, it is not subject to the electronic and software problems that have been reported with the electronic devices (White, 1987; Grover and Heath, 1992; Notcutt et al., 1992).

In summary, the Baxter disposable PCAS performed as well as the Graseby electronic PCAS in patients after major gynaecological surgery. For patient acceptability there was a trend towards the Baxter disposable PCA system and it is possible that for the majority of cases the technical complexity of electronic PCA machines add little to the effectiveness of this device.

CHAPTER 9

An Evaluation of Transcranial Electrical Nerve Stimulation

9.1 Background

Previous studies examining the efficacy of TENS have invariably studied postoperative opioid requirements by comparing opioid consumption administered by intermittent intramuscular injection (Chapter 9.4). This is relatively insensitive and a more accurate estimate of opioid requirements may be obtained by using PCA (Smith, 1989b). There are two main advantages of PCA: one, it is not ethical to have a group with no pain relief and two, morphine requirements (and therefore efficacy) are more accurate with PCA. This study, therefore, assessed the usefulness of transcranial electrical nerve stimulation (TCENS), using the LNTU (Chapter 3.6), for analgesia following total hip replacement. The technique used was similar to one that has previously been shown to decrease opioid requirement during surgery (Stanley et al., 1982).

It has been suggested that postoperative analgesia using intermittent intramuscular injections of opioid may be accompanied by periods of apnoea and relative arterial oxygen desaturation (Catling et al., 1980). Since the population of patients undergoing total hip replacement is a relatively elderly one, and therefore at a greater risk from desaturation, continuous assessment of arterial oxygen saturation was monitored using a non-invasive technique. This also provided the opportunity to observe the effects, if any, of oxygen desaturation whilst using PCA.

9.2 Methods

This study was carried out at Glenfield General Hospital, Leicester. Thirty-four patients undergoing total hip replacement were studied. All patients with a history of skin disease were excluded from participating as skin hypersensitivity occurs with an incidence of 10% (Katz, 1993). Other theoretic contra-indications (and not universally accepted) to the use of TENS, are patients with cardiac pacemakers, placement of electrodes on the neck (to avoid vagal stimulation), placement on the head in epileptics, placement on the chest in patients with cardiac arrythmias and in pregnancy (because of possible uterine contractions) in the third trimester.

At a preoperative interview, patients were instructed in the use of a Graseby PCAS and the VAS method for assessment of pain, nausea and sedation.

Premedication comprised oral diazepam 10 mg given 1-2 hours before surgery. A standardized anaesthetic technique was used in which morphine was the sole opioid for intraoperative anaesthesia. In the recovery room intravenous morphine was administered in 2 mg increments at the discretion of the anaesthetist.

On return to the ward patients received either an active LNTU (stimulation) or a placebo LNTU (non-stimulation). The unit was rendered active or inactive by the use of the appropriate leads connecting the unit to the electrodes. In the active group stimulation utilized the following variables: peak current 20 milliamps; frequency of stimulation 5 millisecs at 200 Hz; pulse duration 50 microsecs and burst modulation 85 millisecs.

The PCAS was programmed to deliver 2 mg boluses of morphine with a 10 minute lockout interval. Operation of the PCAS was monitored by a Hewlett Packard thermal printer. In addition, the patients were prescribed intramuscular morphine 5-10 mg for

escape analgesia and intramuscular prochlorperazine 12.5 mg, as required, for control of emesis.

Arterial saturation was monitored continuously in the 24 hour postoperative period by a Nelcor 100 pulse oximeter and the output was charted by a pen recorder.

The patients' subjective assessments of pain, nausea and sedation were recorded with VAS at 18 and 24 hours postoperatively. At the end of the 24 hour study period, the severity of pain (mild, moderate or severe) and the method of pain relief (good, adequate or poor) was assessed by a three-point VRS.

Data were analysed by unpaired Student's t-test, Wilcoxon rank sum test and Chi-squared test with Yates' correction as appropriate.

9.3 Results

Two patients were excluded from the study. One, because in the recovery room naloxone was required to reverse the opiate, and the second because of technical problems with the recording equipment. Data was therefore available from 32 patients, 10 males and 5 females in the active group and 5 males and 12 females in the placebo group, who were well matched for age and weight (Table 9.1). There were no significant differences in the mean (SEM) quantities of morphine used intraoperatively; 20.2 (5.0) mg in the active group and 12.7 (1.4) mg in the placebo group ($p=0.16$), or by PCA; 35.6 (5.3) mg in the active group and 31.6 (3.5) mg in the placebo group ($p=0.5$; Table 9.1). One patient required additional i.m. morphine. This patient was in the active group and escape analgesia was needed at 24 hours. There was a significant difference found in duration of surgery ($p=0.009$).

Table 9.1 Patient data, intra and postoperative dose of morphine (mg).

*** p=<0.05**

	Group 1 Active TCENS (n=15)			Group 2 Placebo TCENS (n=17)		
	Mean	SEM	Range	Mean	SEM	Range
Age (yr)	61.1	4.1	24-77	66.4	2.6	49-80
Weight (kg)	71.9	2.9	54-95	72.2	3.7	50-106
Height (cm)	171.8	1.9	155-185	167.6	2.4	152-193
Duration of surgery (min)	154.0	14.0	90-270	109.4	6.8	75-180*
Intraoperative	20.2	5.0	8-20	12.7	1.4	7.5-30
Postoperative	35.6	5.3	6-64	31.6	3.5	0-66

The number of doses of antiemetic used by each group ranged from 0-3 in both groups. This was not statistically significant (p=0.69; Table 9.2). VAS for pain (Fig. 9.1), nausea (Fig. 9.2) and sedation (Fig. 9.3) were similar for both groups. There were no significant differences between the two groups in patients' perception of pain and the method of administration of pain relief, as assessed by three-point VRS (Table 9.3).

Figure 9 Mean (SEM) visual analogue scores.

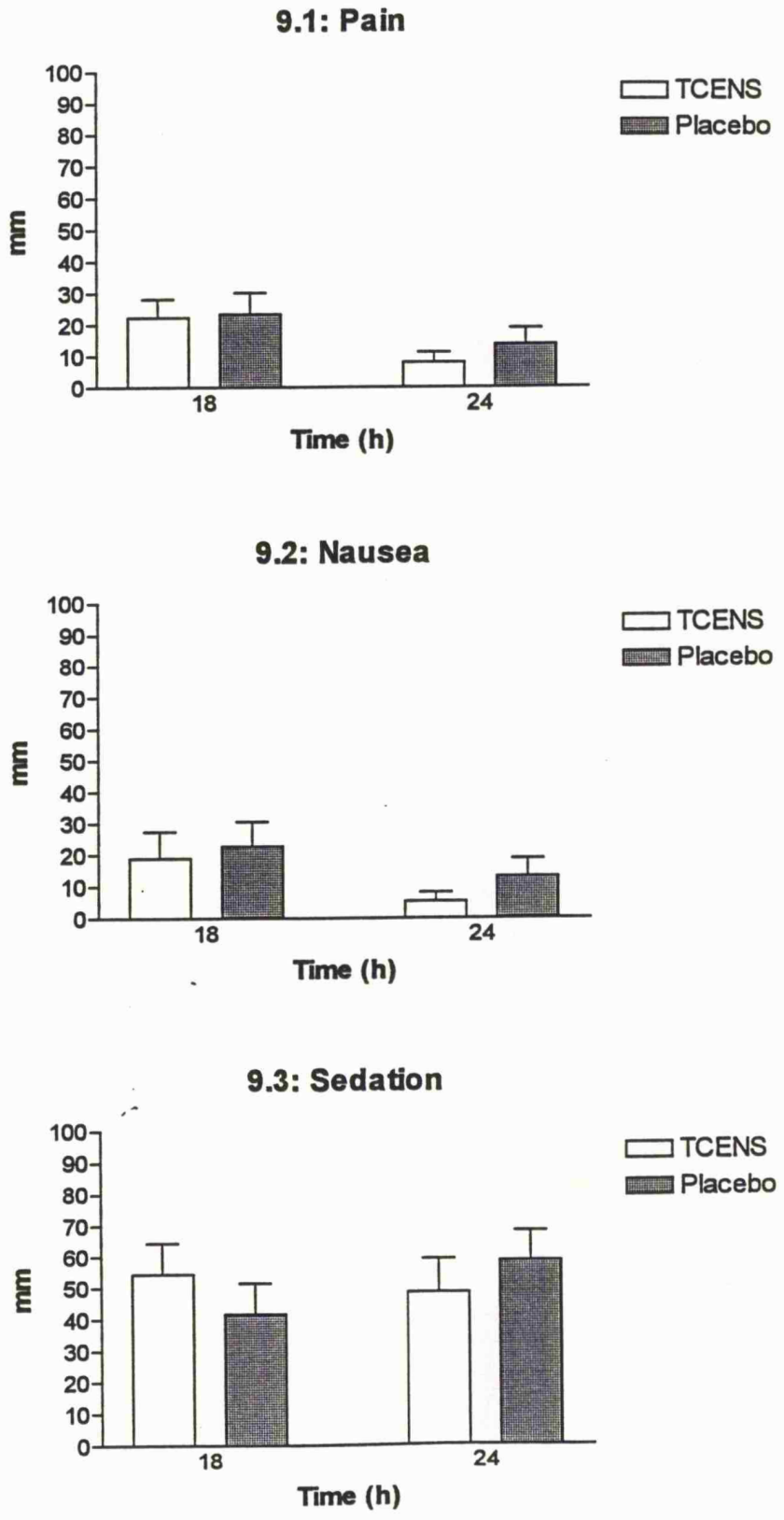


Table 9.2 Number (%) of prochlorperazine doses administered intramuscularly. No significant differences.

Doses	Group 1 Active TCENS (n=15)		Group 2 Placebo TCENS (n=17)	
(n)	(n)	(%)	(n)	(%)
0	3	20	6	35
1	8	53	7	41
2	3	20	2	12
3	1	7	2	12

Table 9.3 Three-point VRS for severity of pain and method of pain relief. No significant differences.

	Group 1 Active TCENS (n=15)		Group 2 Placebo TCENS (n=17)	
	(n)	(%)	(n)	(%)
Pain				
1. Mild	9	60	10	59
2. Moderate	3	20	4	23
3. Severe	3	20	3	18
Method of pain relief				
1. Good	13	87	15	88
2. Adequate	2	13	1	6
3. Poor	0	0	1	6

There were frequent episodes of arterial oxygen desaturation in both groups of patients. (Arterial desaturation being regarded as less than 85% oxygen for more than 30 seconds). 13 of the 15 patients receiving active TCENS exhibited desaturation whilst all of the patients in the placebo group had such episodes (Fig. 9.4). The lowest saturation observed was 53% in a patient in the active group whilst the lowest in the placebo group was 60% (Fig. 9.5).

Figure 9.4 Number of episodes of arterial oxygen desaturation (< 85% > 30 secs).

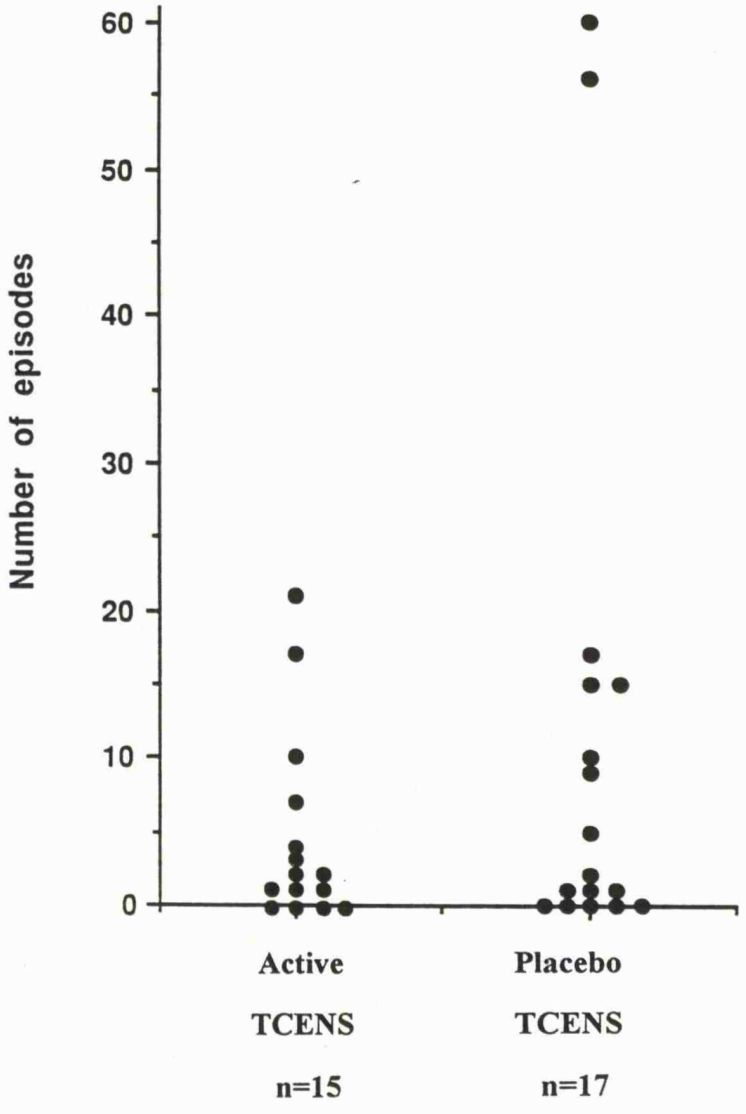
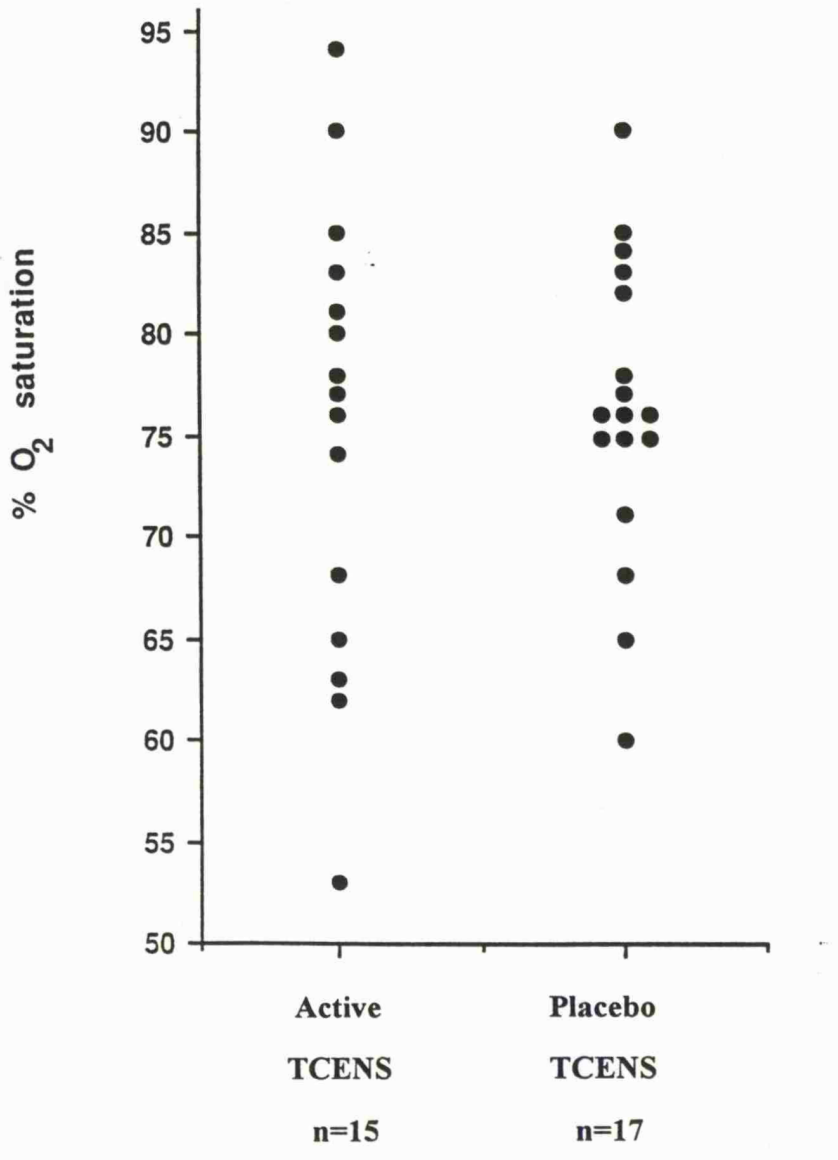


Figure 9.5 Lowest arterial SaO_2 (%).



9.4 Discussion

This study failed to demonstrate any significant effect of active TCENS compared with placebo TCENS, in terms of morphine consumption, or postoperative pain scores, following total hip replacement. There was a significant difference in duration of surgery (p=0.009) but as the intraoperative doses of morphine were not significantly different, this is unlikely to affect the overall results of this study.

Although several other studies have demonstrated that TENS reduced the amount of opioid required following hip replacement (Pike, 1978) and obstetric and gynaecological surgery (Evron et al., 1981), relatively insensitive methods of assessment of opioid requirements were used. In the present study, similar amounts of morphine were administered in each group (31.6 mg in the placebo group and 35.6 mg in the active group) which suggests that there was no obvious placebo effect produced by the inactive TCENS apparatus.

Although extremely low mean pain scores (less than 2.4 cm) were recorded (VAS) by patients (Fig. 9.1), the VRS (Table 9.3) revealed that 40% of patients from each group experienced moderate to severe pain at some time. However, 87% of the patients in Group 1 and 88% from Group 2, assessed the method of pain relief as "Good".

The majority of previous studies utilizing TENS, for postoperative analgesia, have employed electrodes placed on each side of the wound incision with the stimulation parameter adjusted to cause a sensation of tingling. This study utilized cranial electrical stimulation parameters set on a high frequency of 200 Hz with a burst (slow and fast) modulation of 2 Hz. This was in order to stimulate production of both endorphin and serotonin as low frequency techniques are thought to be opioid mediated and high frequency methods may be serotonin mediated (Pinnock, 1985). Similar parameters have been shown to produce a decrease in opioid requirements during and after surgery (Stanley et al., 1982). Although no sensation of tingling was produced in this study, Stanley and colleagues described how 40% of volunteers reported a warm and tingling sensation all over their bodies after one hour of cranial TENS, with similar parameters of stimulation to those described in this study.

Perhaps the most notable feature of this study was the extent and degree of episodic hypoxaemia, confirming previous studies that such episodes are frequent in patients receiving opioids for postoperative analgesia (Frater et al., 1989). None of the patients

received supplemental oxygen on return to the ward postoperatively and perhaps this practice should be queried (Rosenberg et al., 1989). Rosenberg and colleagues demonstrated how episodic arterial oxygen desaturation occurred in the late postoperative period and that these episodes correlated with episodes of tachycardia with a potential for myocardial ischaemia (Pateman and Hanning, 1989).

In this study episodic desaturation was observed in the late postoperative period but there was no apparent correlation to opioid administration as assessed by opioid demand recorded by the printer. Indeed, severe arterial oxygen desaturation (< 85% > 30 seconds) has been demonstrated to occur less frequently with PCA (pethidine) than with epidural (morphine) and conventional intermittent intramuscular therapy (pethidine) (Brose and Cohen, 1989).

CHAPTER 10

An Evaluation of Wound Infiltration with Local Anaesthetic

10.1 Background

Infiltration of a dilute solution of long-acting local anaesthetic (e.g. 0.5% bupivacaine) in the region of the surgical incision will produce effective relief of postoperative pain for up to 16 hours and results in a decrease in the total dosage of opioid required. This has been demonstrated following Keller's arthroplasty (Porter and Davies, 1985), herniotomy in children (Fell et al., 1988) and after excision of benign breast lumps (Owen et al., 1985). However, the beneficial effects are less clear after upper abdominal surgery. A reduction in opioid requirement after cholecystectomy has been demonstrated after infiltration of the peritoneum, muscle and subcutaneous tissues, but not after subcutaneous infiltration alone (Patel et al., 1983; Moss et al., 1986).

The opioid-sparing effect of subcutaneous wound infiltration with local anaesthetic agents has not been assessed previously after lower abdominal surgery in adults, with the exception of herniorraphy (Hashemi and Middleton, 1983). Patients undergoing Caesarian section mobilize early and would benefit from a technique which reduces opioid requirements and the incidence of related side-effects, and improves analgesia. Lower segment Caesarean section is performed routinely through a Pfannenstiel incision and is suitable, therefore, for the investigation of supplementary local anaesthetic techniques.

Previous studies (Patel et al., 1983; Moss et al., 1986) have measured the reduction in opioid requirement by the number of doses of opioid administered by intermittent intramuscular injection. Therefore, PCA was used as a research tool in this study to

assess the analgesic requirements and evaluate the potential of subcutaneous wound edge infiltration with bupivacaine after elective Caesarean section.

10.2 Methods

This study was carried out at the Leicester Royal Infirmary Maternity Unit where twenty-eight patients, aged 19-40 years, were scheduled for elective Caesarean section under general anaesthesia. Each patient was visited preoperatively and familiarized with the use of the Graseby PCAS. Patients were not studied if they gave a history of sensitivity to local anaesthetics or had severe pre-eclampsia or severe hypertension of pregnancy.

Premedication comprised ranitidine 150 mg orally administered on the evening before and on the morning of surgery and 30 ml sodium citrate 0.3 molar given orally immediately before induction of anaesthesia. Intravenous access was established and anaesthesia induced with a sleep dose of methohexitone followed by suxamethonium 1-1.5 mg/kg to facilitate tracheal intubation. Anaesthesia was maintained with 50% nitrous oxide in oxygen and supplemented with enflurane 1%. Muscle relaxation was accomplished with atracurium 0.5 mg/kg. The FIO_2 at delivery was reduced to 0.3, and morphine 5-10 mg and syntocinon 10 IU were given. Atropine 1.2 mg and neostigmine 2.5 mg were administered at the conclusion of surgery to antagonize residual neuromuscular blockade.

Patients were randomly allocated between two groups to receive either 20 ml of bupivacaine 0.5% or a control group receiving 20 ml of normal saline. The solutions were supplied by the hospital pharmacy in numbered vials in order to maintain blinding. After closure of the peritoneum the subcutaneous tissues were infiltrated with the trial solution by the surgeon, subject to a maximum of 0.4 ml/kg (2 mg/kg).

The PCAS was programmed to deliver morphine in 2 mg increments with a lockout time of 10 minutes. The number and timing of requests was recorded by the Hewlett Packard thermal printer. Prochlorperazine 12.5 mg intramuscularly was given on request for nausea. Escape analgesia (i.m. morphine) was available to each patient.

Patients returned to the ward after a short stay in the recovery area where they were reminded of the correct usage of the PCAS.

Pain, nausea and sedation were assessed by the patient at 2, 4, 6 and 24 hours, utilizing 10cm VAS. Overall efficacy of analgesia was rated at the end of the 24 hour period using a four-point VRS comprising: very good, good, moderate, or bad.

Data were analysed by unpaired Student's t-test, Wilcoxon rank sum test and Chi-squared test with Yates' correction as appropriate. MANOVA for repeated measures was used for visual analogue scores.

10.3 Results

Fourteen patients received wound infiltration with bupivacaine and 14 received normal saline. There were no significant differences between the two groups with respect to age, height and weight (Table 10.1).

There were no significant differences between the groups in mean (SEM) intraoperative consumption of morphine; 9.92 (0.85) mg in the bupivacaine group and 9.03 (0.45) mg in the saline group, or in the 24 hour postoperative period; 56.7 (6.05) mg in the bupivacaine group and 67.3 (6.44) mg in the saline group ($p=0.89$; Table 10.1). VAS for pain (Fig. 10.1), nausea (Fig. 10.2) and sedation (Fig. 10.3) revealed no significant differences between the groups.

Table 10.1 Patient data, intra and postoperative dose of morphine (mg). No significant differences.

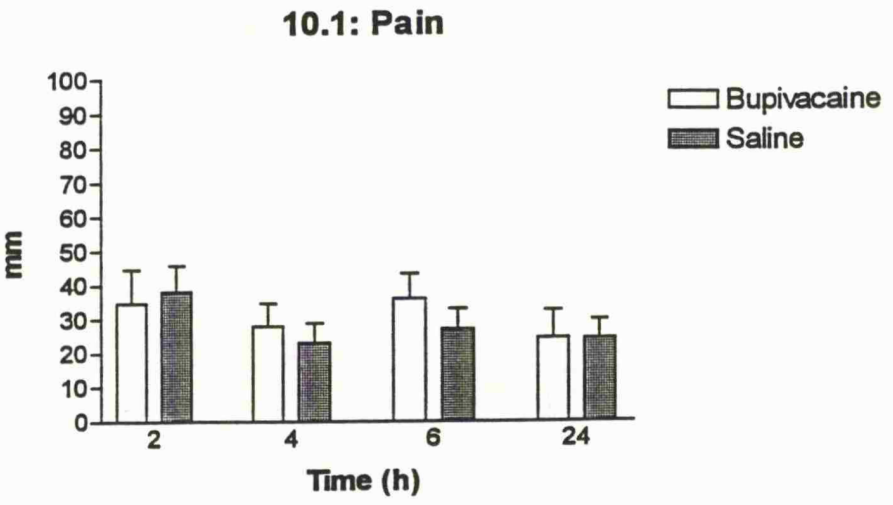
	Group 1 Bupivacaine (n=14)			Group 2 Saline (n=14)		
	Mean	SEM	Range	Mean	SEM	Range
Age (yr)	33.1	1.4	21-40	27.2	1.2	19-35
Height (cm)	157.6	1.9	152-173	158.7	1.8	152-170
Weight (kg)	80.7	3.7	61.5-109	68.5	3.6	50-99
Intraoperative	9.9	0.9	5-10	9.0	0.5	5-10
Postoperative	56.7	6.1	34-104	67.3	6.4	36-110

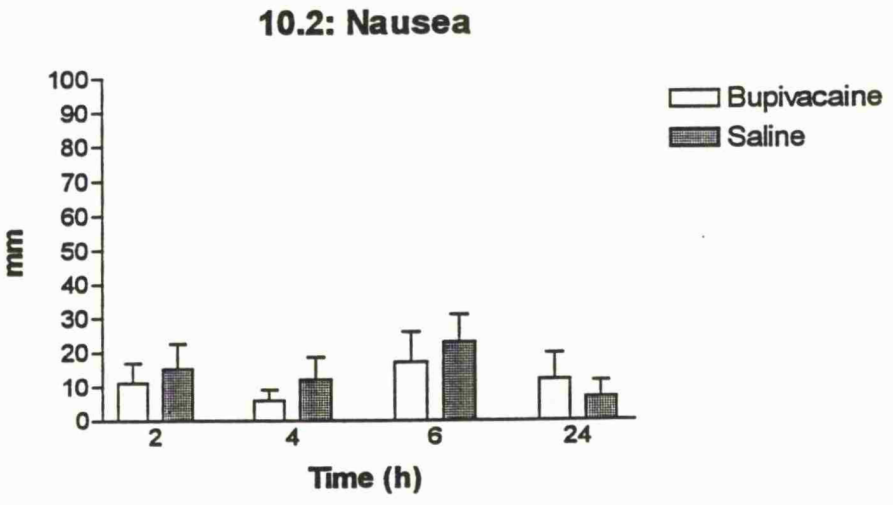
Both groups expressed a high degree of satisfaction with the quality of analgesia provided; the VRS assessment of quality of analgesia showed no difference between the groups (Table 10.2).

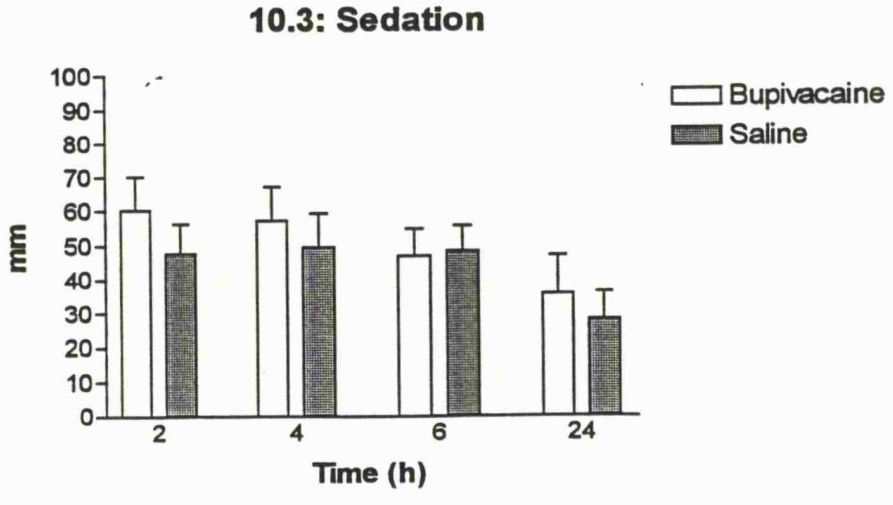
Table 10.2 Four-point VRS for assessment of quality of analgesia. No significant differences.

	Group 1 Bupivacaine (n=14)		Group 2 Saline (n=14)	
	(n)	(%)	(n)	(%)
1. Bad	0	0	0	0
2. Moderate	1	7	1	7
3. Good	5	36	5	36
4. Very good	8	57	8	57

Figure 10 Mean (SEM) visual analogue scores. No significant differences.







10.4 Discussion

This study demonstrated that subcutaneous wound infiltration with bupivacaine 0.5% did not decrease morphine requirements on the first postoperative day following Caesarean section.

The results of this study reaffirm the value of patient-controlled analgesia after Caesarean section, demonstrated elsewhere (Eisenach et al., 1988; Rayburn et al., 1988). In these studies PCA provided better analgesia and patient satisfaction when compared with intramuscular injections of opioids. In this study, PCA also provided a very high degree of patient satisfaction, with over 90% of patients describing their pain relief as either good or very good. This may have therapeutic implications.

Previous studies (Owen et al., 1985; Fell et al., 1988) have usually relied for assessment upon differences in intramuscular opioid given on request and differences in pain scores. However, numerous factors influence this regimen including inappropriate dosage, delays in drug administration and fear amongst staff of drug addiction (Sriwatanakul et al., 1983b). It is not possible, therefore, to assess accurately the opioid-sparing potential of an analgesic technique and comparison between studies is difficult. PCA overcomes these problems and provides a more ideal way of assessing the need for postoperative analgesia since patients titrate themselves to an acceptable level of comfort with minimal side-effects (Tamsen et al., 1979).

Previous studies investigating postoperative opioid requirements with wound infiltration have been after cholecystectomy where 40-50 ml of 0.5% bupivacaine (Moss et al., 1986) and 50 ml of 0.25% bupivacaine (Patel et al., 1983) demonstrated significant reductions in opioid requirements.

To date, there are no similar studies on wound infiltration after lower abdominal surgery using PCA with which to compare the results of this study.

Wound infiltration has been shown to provide equivalent postoperative analgesia to ilioinguinal nerve block in children after herniotomy (Reid et al., 1987). Bilateral ilioinguinal nerve blockade (Bunting and McConachie, 1988) using 20 ml of 0.5% bupivacaine (10 ml to each side) has been shown to reduce opioid requirements (intramuscular on demand) and pain scores after lower segment Caesarean section. Bilateral ilioinguinal nerve block may be a more appropriate technique in this situation since wound infiltration with a similar dose of bupivacaine was ineffective in reducing opioid requirements.

CHAPTER 11

Diamorphine and Morphine with PCA:

A comparison of dose requirements and effect

11.1 Background

It is frequently stated that diamorphine causes less nausea, vomiting and sedation and more euphoria than morphine (Scott, 1988), although it is difficult to find convincing data to support this contention. It has been reported also that diamorphine is twice as potent as morphine (Foldes et al., 1964; Jacobson et al., 1983).

Morphine has been accepted as the standard potent analgesic for many years whereas diamorphine achieved popularity in medical practice only during the first half of this century. Diamorphine is often preferred to morphine because of its greater potency and more rapid onset of action. Increasing illegal use led to its total ban for medicinal use in the U.S.A. in 1924. Diamorphine is often more popular than morphine where it is still available, in the U.K. for example, particularly in the relief of terminal pain and coronary care.

PCA is again used as a research tool in this study, which was designed to compare the relative potency and side-effects of morphine and diamorphine when administered for pain relief after total hip replacement.

11.2 Methods

This study was carried out at Glenfield General Hospital, Leicester. Thirty-six patients (14 males and 22 females) undergoing total hip replacement were studied. Patients

who were receiving opioid, sedative or antidepressant therapy and patients undergoing repeat surgery were not studied.

Patients were instructed in the use of a Graseby PCAS at an interview prior to surgery. VAS was the method used for assessment of sedation, nausea and well-being and this was also explained at this time. Each linear analogue comprised a 10 cm unmarked line, the ends of which denoted the extremes of the variables in question, i.e. wide awake, unable to stay awake; no nausea, worst possible nausea; very unhappy, delighted with everything.

All the patients were premedicated with temazepam 10-20 mg orally 1 hour before surgery. Anaesthesia was induced with thiopentone 3-4 mg/kg and tracheal intubation was facilitated by the use of a non-depolarizing muscle relaxant. The lungs were ventilated with 66% nitrous oxide and a small concentration of a volatile agent in oxygen for maintenance of anaesthesia. Anaesthesia was supplemented with morphine 0.1-0.2 mg/kg. Morphine was administered intravenously in 2 mg increments in the recovery room until pain control was judged to be satisfactory by the anaesthetist.

Patients were allocated randomly on return to the ward to receive morphine or diamorphine by PCAS, which was programmed to deliver morphine 2 mg or diamorphine 1 mg on demand with a lockout interval of 10 minutes for both groups. Operation of the PCAS was recorded by a Hewlett Packard thermal printer which registered the time and success of a patient demand. Intramuscular metoclopramide 10 mg was given for nausea at the discretion of the nursing staff.

VAS for sedation, nausea and well-being were made at 4, 8, 16, 20 and 24 hours after PCA was started. Pain, nausea and well-being were assessed by verbal three-point rating scales at the end of the 24 hour study period: severe, moderate and slight or none at all, for pain and nausea; miserable, average and happy for well-being.

Data were analysed by unpaired Student's t-test, Wilcoxon rank sum test and Chi-squared test with Yates' correction as appropriate. MANOVA for repeated measures was used for visual analogue scores.

11.3 Results

Four patients in the morphine group were excluded from analysis because of protocol violations, otherwise patients were well matched for age, sex and weight (Table 11.1).

Table 11.1 Patient data and intraoperative dose of morphine (mg).

	Group 1 Diamorphine (n=20)			Group 2 Morphine (n=16)		
	Mean	SEM	Range	Mean	SEM	Range
Age (yr)	58.0	2.3	44-80	62.3	2.1	50-78
Weight (Kg)	66.4	3.7	44.5-115	68.5	3.5	46-92
Duration of surgery (min)	117.0	11.5	60-300	112.1	7.2	60-177
Intraoperative	10.2	0.9	5-20	9.3	0.5	5-15

There were no significant differences between the diamorphine and morphine groups with respect to mean (SEM) doses of morphine administered intraoperatively; 10.2 (0.95) mg in the diamorphine group and 9.3 (0.55) mg in the morphine group (p=0.43; Table 11.1).

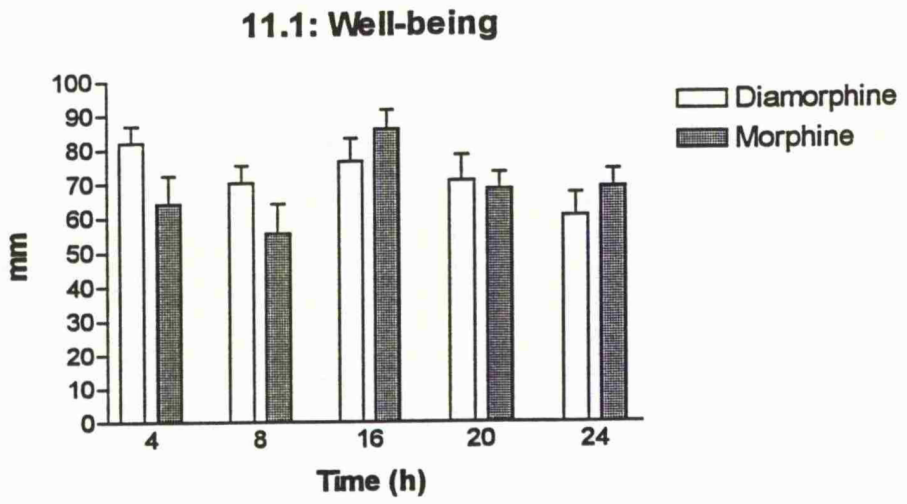
Postoperatively, mean (SEM) requirements for diamorphine were 20.2 (2.4) mg compared with 44 (6.8) mg morphine (p=0.004). No patient self-administered the maximum dose of opioid available.

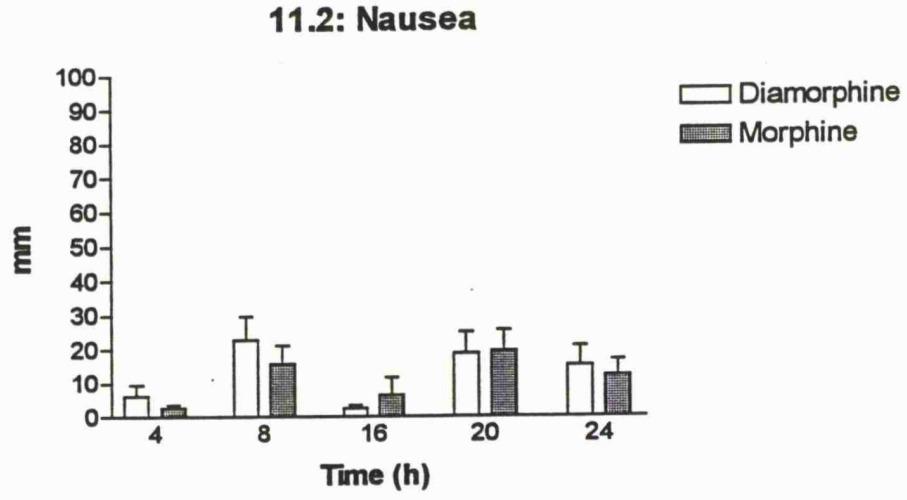
There were no significant differences between the groups in the requirements for metoclopramide (p=0.50; Table 11.2) or in the VAS for well-being (Fig. 11.1), nausea (Fig. 11.2) or sedation (Fig. 11.3). The verbal three-point scores for overall experience of pain, nausea and well-being are shown in Table 11.3. There were no significant differences.

Table 11.2 Number (%) of metoclopramide doses administered intramuscularly. No significant differences.

Doses	Group 1 Diamorphine (n=20)		Group 2 Morphine (n=16)	
(n)	(n)	(%)	(n)	(%)
0	10	50	10	62
1	5	25	3	19
2	3	15	2	13
3	2	10	0	0
4	0	0	1	6

Figure 11 Mean (SEM) visual analogue scores. No significant differences.





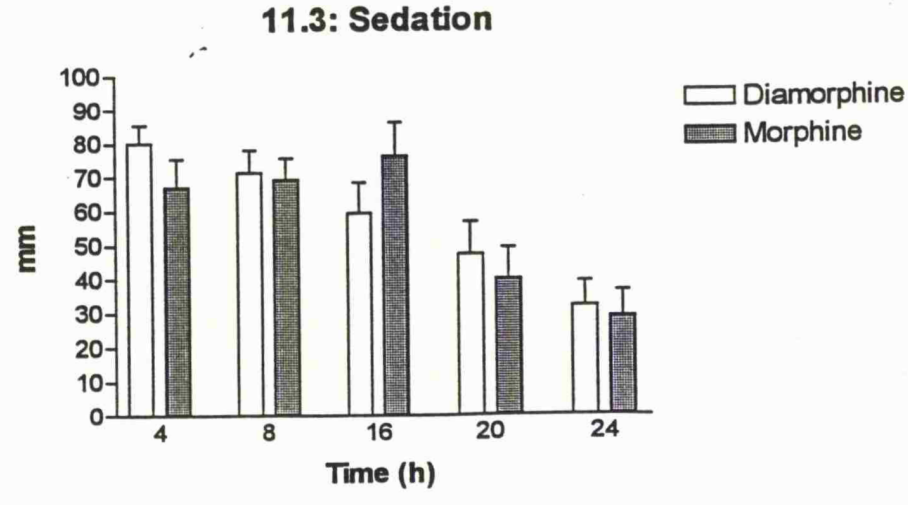


Table 11.3 Three-point VRS for pain, nausea and well-being.

No significant differences.

	Group 1 Diamorphine (n=20)		Group 2 Morphine (n=16)	
	(n)	(%)	(n)	(%)
Pain				
1. Severe	2	10	3	19
2. Moderate	13	65	9	56
3. Slight/none	5	25	4	25
Nausea				
1. Severe	1	5	3	19
2. Moderate	4	20	3	19
3. Slight/none	15	75	10	62
Well-being				
1. Miserable	3	15	1	6
2. Average	4	20	9	56
3. Happy	13	65	6	38

11.4 Discussion

No significant differences were found between the groups over a 24 hour period in the degree of euphoria, nausea and vomiting or sedation, as assessed by subjective VAS, or in pain relief, nausea and euphoria as assessed by VRS. There was, in addition, no significant difference in the requirements for antiemetics between the two groups. Both groups demonstrated relatively low nausea scores. The mean amount of morphine demanded was approximately twice that of diamorphine.

The relatively high levels of patient well-being recorded by VAS (Fig. 11.1) contrast with the VRS (Table 11.3) where 75% of the patients in each group reported moderate to severe pain and yet, 65% of the diamorphine group and 38% of the morphine group reported their overall feeling of well-being as "Happy".

The scientific basis for the alleged superiority of diamorphine over morphine (Tattersall, 1981; Katz et al., 1984; Levine et al., 1986; Sellers, 1986) is dubious and since diamorphine is metabolized into analgesically active 6-monoacetylmorphine, morphine and M6G, it would be surprising if there were a marked difference. Very few studies authenticate this claim of superiority and this study is no exception. If a pain is opioid responsive it will respond equally well to both morphine and diamorphine (Twycross, 1994). The major advantage of diamorphine over morphine is that, when injections are necessary, the high solubility of diamorphine means that larger doses can be given in small volumes.

Smith and Beecher (1962) reported that impairment of mental function, described usually as euphoria, following diamorphine but not morphine was probably caused by the increased speed of onset of action of diamorphine when given in equianalgesic doses. Intramuscularly, diamorphine has a slightly earlier onset of action than morphine, whereas intravenously morphine (in equipotent doses) acts more quickly (Morrison et al., 1991). Twycross (1977) and Inturrisi and colleagues (1984) did not find diamorphine to have any clinical advantage over morphine in terms of both analgesic efficacy and euphoria when given by oral or intramuscular (retrospectively) routes. There was no evidence of increased rate of onset, or of euphoria, in diamorphine compared with morphine, in this study. One of the reasons for the popularity of diamorphine amongst drug abusers is its solubility which may account for a previous assumed speed of onset of physic effects.

Dundee and colleagues (1966) in their study of opioids given as premedication reported no significant difference in the frequency or intensity of subjective effects of diamorphine, but they did report that the effects after diamorphine were of shorter duration (by about 25%) than those of morphine. They found the toxicity of morphine and diamorphine was similar but that morphine caused more emesis than diamorphine and that the latter was more efficacious. It was stressed that these opioids were given only in single doses and that repeated doses may lead to different results. However, in this study there was no evidence that morphine was associated with more emesis than diamorphine.

Foldes and colleagues (1964) estimated that diamorphine was 2-3.3 times more potent than morphine; whereas Dundee and colleagues (1966) observed that diamorphine 5 mg i.m. was approximately equipotent with morphine 10 mg i.m. and Morrison and colleagues (1991) found that diamorphine 1 mg i.v. was equipotent with morphine 2 mg i.v. This study, with self-administered intravenous diamorphine and morphine after hip replacement surgery, concurs with the observations made by these authors.

It would appear then that, with patient-controlled administration, there is little difference between morphine and diamorphine and there is no evidence to support the view held by many clinicians that diamorphine is superior to morphine in terms of the production of greater euphoria and less nausea and vomiting.

CHAPTER 12

An Assessment of the Emetic Sequelae of PCA

12.1 Background

Postoperative nausea and vomiting (PONV) are distressing side-effects of anaesthesia and surgery (Russell and Kenny, 1992), with a high incidence after gynaecological surgery (Madej and Simpson, 1986; Hovorka et al., 1990) and strabismus surgery in children (Karlsson et al., 1990; Kraus et al., 1991). An incidence as great as 83% has been reported in female patients after major orthopaedic surgery (Kauste et al., 1986) but Lerman (1992) puts the overall incidence at 30% for the first 24 hours after anaesthesia. Clinical observation from conducting the previous studies (Chapters 6-11) suggests the incidence to be more in the region of 50%.

Despite the extensive literature on PONV there is a lack of review articles in this field, the two largest reviews are separated by an interval of 8 years (Palazzo and Strunin, 1984a, 1984b; Watcha and White, 1992). This is because of the poor methodology, which often lacks standardization and the data is frequently difficult to interpret and therefore compare (Rowbotham and Smith, 1992).

In the early 1900s, Flagg described three causes of PONV. The first kind he attributed to anaesthetics, the second to a reflex action such as pain or the type of surgery, and the third to opioids such as morphine (Flagg, 1916). Three-quarters of a century later, despite the recent advances in modern anaesthesia, only modest progress has been made in our understanding and treatment of PONV (Lerman, 1992).

However, there are a number of other background factors which have been shown to influence the incidence and severity of PONV (Korttila, 1992). The frequency of

PONV in children is the same in both boys and girls, which is about twice that in adults (Vance et al., 1973), until it decreases after puberty (Rowley and Brown, 1982). PONV is more common in women than in men, a difference that is thought to be hormonal in origin (Bellville et al., 1960). Diamond and colleagues (1988) suggested that there might be a dose-dependent pharmacodynamic difference in the antiemetic action of metoclopramide, and that a dose of 50 mg in females is equivalent to 20 mg in males. After 70 years of age, gender ceases to have any effect on PONV (Purkis, 1964). A previous history of motion sickness (Kamath et al., 1990) and emesis after previous anaesthetics also contribute to a higher incidence of PONV (Korttila et al., 1987). In addition, it has been suggested that in women of childbearing age the menstrual cycle has some effect (Beattie et al., 1991; Honkavaara et al., 1991). The administration of antiemetic drugs prior to surgery may decrease the incidence or severity of PONV (Korttila et al., 1979, 1985). Recent work with orally administered ondansetron has produced favourable results (Kenny et al., 1992).

It is the impression of many clinicians that nausea and vomiting are more common with PCA than with intramuscular analgesia (Rowbotham and Smith, 1993). Whilst it is true that some patients may use more opioid with PCA than i.m. therapy, and subsequently suffer more nausea and vomiting, it may also be due to the natural tendency amongst staff to blame a new technique (PCA) for a wide variety of routine postoperative complications (Notcutt and Morgan, 1990) of which PONV is one.

In clinical use, whilst conducting the comparative studies for this thesis, three patients had suffered severe side-effects of nausea and vomiting, during the use of intravenous morphine by PCA, but it was not clear if the PONV was caused by the drug or delivery technique. The purpose of this study, therefore, was to compare the incidence of emetic sequelae in patients using PCA devices with a control group of patients receiving regular 4 hourly intramuscular injections of morphine for control of postoperative pain after elective surgery.

12.2 Methods

This study was carried out at Glenfield General Hospital, Leicester, where thirty-two patients scheduled to undergo cholecystectomy gave informed consent to this double-blind randomized controlled study.

Patients were instructed in the use of a Graseby PCAS at a preoperative interview. The VAS method that would be used to assess their experience of pain, nausea and sedation was also explained. Each linear analogue comprised a 10 cm unmarked line the ends of which denoted the extremes of the variables in question, i.e. no pain, worst possible pain; no nausea, worst possible nausea; wide awake, unable to stay awake.

Premedication was with oral diazepam 10 mg given 60-90 minutes before surgery. Anaesthesia was induced with thiopentone via an indwelling intravenous cannula, and tracheal intubation was facilitated by the use of a non-depolarizing muscle relaxant. The lungs were ventilated with 67% nitrous oxide in oxygen, supplemented with a volatile agent. Intraoperative opioid was limited to morphine 0.1-0.2 mg/kg. Surgery was performed through a subcostal incision in all cases.

In the recovery room, intravenous morphine was administered in 2 mg increments, at the anaesthetist's discretion, until satisfactory analgesia was achieved.

Patients were assigned randomly on return to the ward to one of two groups: group 1 used a PCAS with morphine and received 4 hourly i.m injections of saline; group 2 used a PCAS with saline and received 4 hourly i.m injections of morphine. Syringes for both the PCAS and i.m injections were prepared by the hospital pharmacy. They were assigned a numerical value and issued in chronological order as each new patient entered the study. The PCAS was programmed to deliver 1 ml of solution: either 2 mg morphine in 1 ml solution (group 1) or 1 ml of saline (group 2). The lockout interval

was set to 10 minutes, thus the maximum hourly patient-controlled dose was 12 mg in group 1. Morphine/saline administration was recorded by a Hewlett Packard thermal printer.

Morphine or saline was prescribed for all patients to be given i.m 4 hourly: 1 ml (10 mg morphine in group 2) for those weighing less than 75 kg, or 1.5 ml (15 mg morphine in group 2) for those weighing more than 75 kg. The ward nurses were instructed to halve or omit these 4 hourly doses if they considered the patient was oversedated or pain-free.

Prochlorperazine (12.5 mg) was prescribed as an antiemetic, to be given only when required, and not routinely. Additional prescriptions of morphine 5-10 mg were available as escape analgesia. VAS for assessment of pain, nausea and sedation were completed at 2, 4, 6 and 24 hours postoperatively.

Patients completed a short questionnaire (Table 12.1) at the end of the study period designed to elicit specific information about the occurrence and frequency of vomiting. The questionnaire contained several dummy questions in the attempt to avoid the possibility of bias. (There was a risk that heightened awareness of the possibility of nausea/vomiting might increase patient compliance). The ward nurses, who were also unaware of the patient's group, recorded the incidence of nausea and vomiting, on a separate chart designed for this purpose, over the 24 hour postoperative period.

Data were analysed by unpaired Student's t-test and Wilcoxon rank sum test as appropriate. MANOVA for repeated measures was used for VAS scores. Chi-squared analyses were applied to administration of antiemetics, episodes of nausea and vomiting and the results of the patients' questionnaires, with Yates' correction as appropriate.

The number of patients was chosen to give the study an 80% power with a probability of < 0.05 to detect a difference of 20 mm in VAS for nausea, the variable at issue. The power was calculated by applying Altman's nomogram (Altman, 1980) and confirmed by the formula: $n = \frac{2\kappa.\sigma^2}{\Delta^2}$ (Bourke et al., 1984).

Table 12.1 Patient's Questionnaire

1)	Have you experienced any HEADACHES over the last 24 hours?	Yes/No
2)	Have you experienced any DIZZINESS over the last 24 hours?	Yes/No
3)	Have you experienced any ACHES IN THE LEGS over the last 24 hours?	Yes/No
4)	Have you experienced any VISUAL DISTURBANCE over the last 24 hours?	Yes/No
5)	Did you VOMIT at all in the last 24 hours?	Yes/No
6)	Did you have any other unpleasant feelings during this 24 hour period? If yes, please describe them....	Yes/No

12.3 Results

Two patients were excluded because they received the other's injection in error, despite clear labelling. Data were thus available for 30 patients (4 males and 11 females in each group) who were well matched for age and duration of operation, but group 2 (i.m.

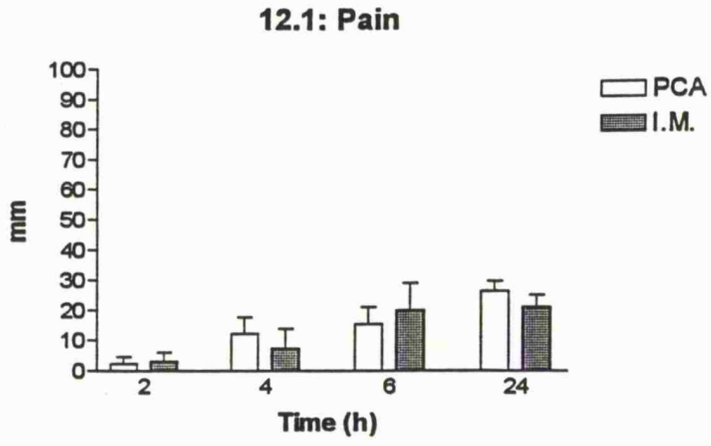
morphine) patients were significantly heavier than group 1 (p = 0.006, Table 12.2). There were no significant differences in the mean (SEM) quantities of morphine used in the operating theatre; 11.4 (1.2) mg in the PCA group and 12.2 (1.3) mg in the i.m. group (p=0.69), or in the 24 hour postoperative consumption; 34.8 (5.0) mg in the PCA group and 30.2 (6.7) mg in the i.m. group (p=0.17; Table 12.2).

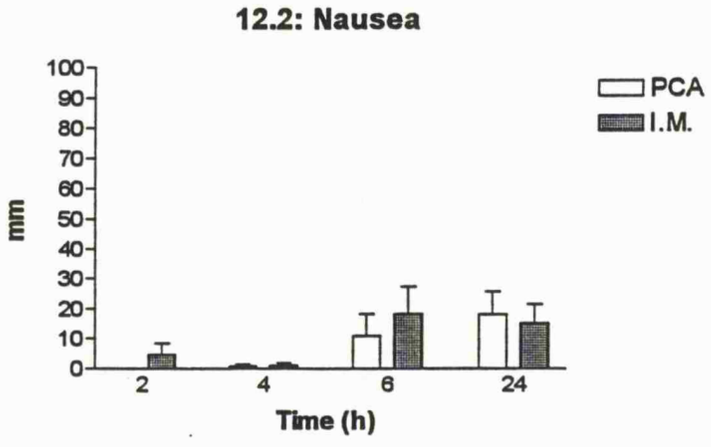
Table 12.2 Patient data, intra and postoperative dose of morphine (mg). *p=<0.05.

	Group 1 PCA (n=15)			Group 2 i.m. (n=15)		
	Mean	SEM	Range	Mean	SEM	Range
Age (yr)	60.1	3.5	30-78	55.3	4.3	26-77
Weight (Kg)	66.7	2.7	45-79	77.7	2.6	45-100*
Duration of surgery (min)	90.0	6.6	45-150	90.0	58.8	30-180
Intraoperative	11.4	1.2	5-23	12.2	1.3	7.5-23
Postoperative	34.8	5.0	2-74	30.2	6.7	0-60

Three patients required escape analgesia. One patient in the PCA group needed two doses of 5 mg morphine and two patients in the i.m. group required 2 doses of 10 mg morphine. All patients continued to use the PCAS and completed the study. Three patients in the i.m. group, who used the PCAS, were sufficiently pain-free to refuse the routine injections and therefore did not receive any postoperative analgesia. There were no significant differences between the two groups in the overall requirements of antiemetics (p=0.69; Table 12.3) or in the frequency of nausea and vomiting as recorded by the ward nurse. Eight (53%) patients in the PCA group were not nauseated, did not vomit and did not require antiemetics compared with 4 (27%) patients in the i.m. group (p=0.14).

Figure 12 Mean (SEM) visual analogue scores. No significant differences.





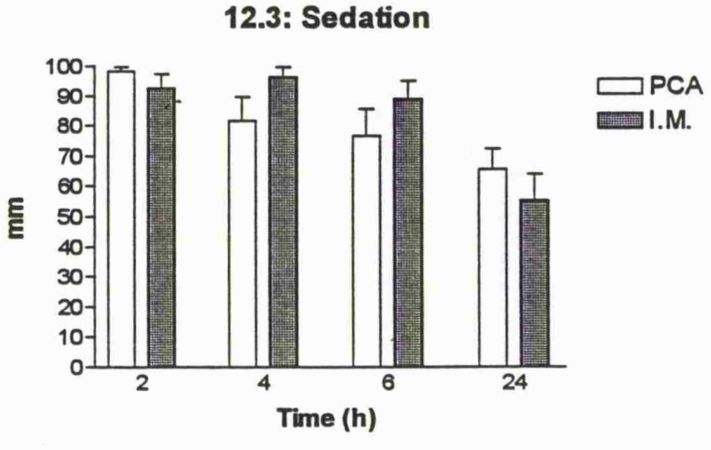


Table 12.3 Number (%) of doses of prochlorperazine administered intramuscularly. No significant differences.

Doses	Group 1 PCA (n=15)		Group 2 i.m. (n=15)	
(n)	(n)	(%)	(n)	(%)
0	8	53	5	33
1	4	27	4	27
2	2	13	3	20
3	1	7	2	13
4	0	0	1	7

Linear analogue scores for pain (Fig. 12.1), nausea (Fig. 12.2) and sedation (Fig. 12.3) were not statistically different between the groups. The results of the patients' questionnaires were not statistically significant and corresponded with the ward nurses' assessments of nausea and vomiting.

12.4 Discussion

This study has demonstrated that morphine administered by PCA causes no more nausea and vomiting than regular 4 hourly intramuscular therapy.

There was a statistically significant difference in weight between the two groups, but others have not found weight to correlate with opioid usage from a PCAS (Tamsen et al., 1979; Dahlstrom et al., 1982) and, since all patients titrated their needs to an acceptable level of comfort, this variable does not affect the conclusions drawn from this study.

There was a total of 20 episodes of vomiting in the active intramuscular group and the patients required 20 doses of antiemetic compared with 11 and 8 (respectively) in the active PCA group. Four patients in the PCA group vomited compared with 10 patients in the intramuscular group, whilst eight patients in the PCA group did not vomit and were not nauseated (and therefore did not require antiemetics) compared with four patients in the i.m. group. In addition, the nausea scores at 2 hours were nil for the PCA group (Fig. 12.2). This trend may indicate a favourable aspect of opioid analgesia administered via PCA and concurs with Welchew (1983) who assessed the emetic sequelae in a study comparing intramuscular analgesia with PCA. However, in Welchew's study, although nausea was found to be significantly less frequent in patients in the regular intramuscular morphine group, he used fentanyl in the PCA group and therefore the use of two different opioids may invalidate this finding.

The possibility of a Type II error was minimized in this study by selecting a difference of 20 mm in respect of nausea and vomiting, which, together with the number of patients in each group and an estimate of the standard deviation for nausea of 20 mm found from previous work (Colquhoun and Fell, 1989), gives the study a power of approximately 80% (Altman, 1980).

Pain and sedation VAS between the groups did not vary significantly and it is interesting to note that three patients in the i.m. group did not receive any postoperative analgesia yet all had triggered the PCA device. This confirms the work of others (Dahlstrom et al., 1982) which has shown the wide variation for postoperative analgesic requirements. It also suggests a placebo effect of PCA. Patients are far more relaxed before surgery with the knowledge that they are to be in control and will not have to wait for a nurse to administer analgesia. This is particularly true of patients who have previously undergone surgery (Evans et al., 1976; Peck, 1986; Egan, 1990).

This study has demonstrated that if analgesia is given via the intramuscular route on a regular basis (i.e. 4 hourly) it may be as satisfactory as PCA but unfortunately this rarely occurs in a ward. It would have been unethical to compare PCA with on demand morphine because this would have necessitated giving placebo on demand for pain which is clearly unacceptable. Instead the ward nurses were asked to omit or reduce the intramuscular injections if the patient refused analgesia or if they thought that the patient was oversedated; thus customary practice was not followed precisely in this study.

Owen and colleagues (1989a) examined three different dosages of morphine (0.5, 1 and 2 mg boluses, each with a lockout interval of 5 minutes) administered via PCA in a range of postoperative conditions and, whilst they found that the optimum dose for analgesia was 1 mg they did not find any difference in the incidence of nausea, vomiting and administration of antiemetics between the groups.

This study has demonstrated that morphine administered via PCA for postoperative analgesia causes no more nausea and vomiting than regular i.m. therapy. This view is supported by other investigators who have measured this variable and have not found significant differences (Albert and Talbott, 1988; Eisenach et al., 1988; Harrison et al., 1988; Hecker and Albert, 1988; Rayburn et al., 1988; Berde et al., 1991). Clinical impressions following this study suggest that patients who self-administer morphine may require fewer antiemetic injections compared with those who receive regular intramuscular morphine therapy.

Conclusion

This thesis set out to investigate PCA by comparisons of an electronic bedside device against electronic and nonelectronic ambulatory devices and as a research tool to evaluate alternative methods of providing postoperative analgesia.

The initial pilot (Chapter 6) revealed the potential problems of patient recruitment and the importance of educating staff, patients and relatives regarding the technique. It also highlighted the necessity of having an anaesthetist (or designated nurse), familiar with PCA therapy, available 24 hours in order to troubleshoot, should the occasion arise.

Comparative studies of portable and electronic devices revealed no overall advantages for one device over another in terms of clinician and patient satisfaction. In addition, the Bionica MDS 110 (Chapter 7) was withdrawn from the market before satisfactory assessment could be made. From the nurses' perspective, there appeared to be a trend in favour of this portable device in the second postoperative day. From the researcher's point of view, however, the device was deficient in a number of ways (Chapter 4).

The Baxter disposable PCA device (Chapter 8), although not demonstrated to be superior to the Graseby, must surely have a place in postoperative pain management. It is easy to operate, small, lightweight, easily portable and low tech, therefore less intimidating for many patients. Clinically, it was apparent that the nurses were happy with this device. Its lack of software equated with minimum maintenance. However, it is not a device suited for research purposes as it is impossible to monitor the precise amount of opioid delivered, nor keep a record of amount, time and demand for analgesia. Other clinicians, despite the fixed regimen, have also found it to be satisfactory for postoperative opioid analgesic requirements (Wermeling et al., 1987; Mackey et al., 1993).

There can be little dispute that PCA is an efficient research tool. In comparative studies with alternative methods of providing analgesia, it is unethical to deny patients analgesia and therefore PCA plays an important role in providing a more accurate measurement of patients' requirements. Unlike conventional i.m. therapy, PCA patients demand to an endpoint and PCA can therefore be used to assess the analgesic contribution of other agents or methods (Owen, 1990).

TCENS was not shown to be advantageous following total hip replacement but in the evaluation of TCENS, the use of PCA was able to demonstrate that there was no obvious placebo effect. Possibly the most important finding in this study was the inadequate monitoring of patients, for arterial desaturation, postoperatively (Chapter 9.4). The postoperative practice in the hospital where the research was carried out, changed in deference to this finding.

Similarly, infiltration with bupivacaine to the wound, following Caesarean section did not show any differences, but again PCA provided an accurate assessment of patients' requirements and, equally important, provided 90% of patients with good/very good postoperative analgesia (Chapter 10.4).

Using PCA to assess the efficacy of diamorphine provided more evidence to dismiss the popularly held belief that diamorphine causes more euphoria and less emesis than morphine. No differences in efficacy of analgesia or side-effects of diamorphine, when compared with morphine, were found. This again, would have been difficult to assess if analgesia had been administered on a 4 hourly i.m. basis. In addition, the equianalgesic dose of morphine was confirmed to be twice that of diamorphine (Chapter 11.4).

Interestingly, no difference was demonstrated between PCA and i.m. therapy with regard to emetic sequelae. However, there was a definite trend towards fewer episodes of nausea and vomiting and lower requirements for antiemetics in the PCA group. As

the studies progressed it soon became obvious that, as the nurses were not responsible for initiating PCA, the patients were not getting prophylactic antiemesis as they usually did with i.m. analgesia. This failing is now being addressed. The amount of morphine administered was not found to correlate with emesis and as this study (Chapter 12.3) has demonstrated, 53% of patients in the PCA group did not require antiemetics.

The subject of postoperative nausea and vomiting became of great interest to me whilst I was conducting the clinical work for this thesis. I found that the incidence of postoperative nausea and vomiting was higher than I had anticipated (Glaxo, 1992). Unfortunately for me time did not permit, but in recent years other investigators have taken up the theme of patient-controlled emesis (PCE) and so far the results look promising (Bishop et al., 1993; Sharma and Davies, 1993; Williams et al., 1993; Tuckey and Margot, 1995). It is still an area, in my opinion, that requires further research.

This thesis, in setting PCA into context, has also reviewed the complexities of the physiology of pain (Chapter 1). It is clear from the literature that investigations into this area are far from complete. Indeed McQuay and Dickenson (1990) describe an "exciting time in neuroscience".

Whilst the incidence of postoperative pain (Chapter 2.2) is unlikely to change significantly it is equally clear that there remains room for improvement of its management (Chapter 3). The long-standing problems of under prescribing and under dosing due to fear of opioid addiction (Marks and Sachar, 1973) and lack of adequate explanation (Egbert et al., 1964) are hard to resolve. Postoperative pain can be managed effectively in individual cases, but the main problem is that it is not being managed effectively in many cases (Raj, 1993). Several authors have advocated postoperative analgesia tailored for individual requirements, often combining therapies, i.e. local anaesthetic agents with NSAIDs (Ogilvy and Smith, 1992).

The development of PCA (Chapter 4), together with the advent of Acute Pain Teams, has undoubtably led to improvement in the management of postoperative pain. PCA is now well established in areas such as: obstetrics (Harrison et al., 1988; Sinatra et al., 1989; Wheatley et al., 1991), burns (Wermeling et al., 1986; Kinsella et al., 1988; Choiniere et al., 1992), paediatrics (Rodgers et al., 1988; Berde et al., 1991), chronic and terminal pain (Keeri-Szanto, 1976) all with good effect.

One area that has been explored with PCA relatively recently is anxiolysis (Galletly et al., 1989; Egan et al., 1992). The results of these studies suggest that this application for patient-controlled delivery of drugs also warrants further investigation.

In summary, this thesis has shown that comparative studies of electronic and portable PCA devices reveal little difference in terms of clinician and patient satisfaction. As a research tool, PCA has proved useful in evaluating alternative methods of providing postoperative analgesia and in assessing the dose requirements and effect of diamorphine. In addition, there is some evidence in support of the administration of fewer antiemetics with PCA.

A review of the literature (and clinical experience) has shown PCA to be efficient in providing postoperative analgesia. When compared with more conventional regimens it is more flexible, it obviates the need for nurse dependency and it substantially reduces the delay in gaining pain relief.

Limitations

With hindsight it is always easier to see how things might have been performed to better effect. This thesis is no exception. There are several areas where a different approach would be recommended for future research.

One area is that of patient assessment. I found that postoperative patients (and this may differ from patients with chronic pain) generally did not want to be bothered with answering too many questions whilst they were recovering from surgery. It was for this reason that the majority of the VRS were 3-point scales. Experience drawn from the exceptions (the 4-point scale in Chapter 10 and the patient questionnaire in Chapter 12) resulted in the selection of 3-point scales for the remainder of the studies.

The review of literature did not conclude with any clarity the true value of VRS and VAS. However, the general view is that VAS are more sensitive for the type of studies undertaken in this thesis, i.e. analgesic comparisons (von Graffenried and Nuesch, 1980; Seymour, 1982; Wallenstein, 1991). Both VAS and VRS were performed in the majority of the studies and in designing this thesis it seemed appropriate to assess patients' analgesia and side-effects from two perspectives.

This approach resulted in one assessment contradicting the other! This contradiction can be seen quite clearly in Chapters 9 and 11 where 40% and 75% (respectively) of patients complained of moderate to severe pain, yet the VAS show relatively low pain scores and high well-being scores. One reason for such a result may well be that the VRS were performed at the end of the study period (i.e. in retrospect), unlike the VAS which were performed at intervals throughout the postoperative period. It may be more useful to conduct VRS at intervals also. However, it is probably unnecessary (and potentially irritating for the patient) to use both scales simultaneously.

Some of the VAS assessments were made at different time scales. VAS reported in Chapters 10 and 12 were both performed at 2, 4, 6 and 24 hours after surgery. At these intervals, postoperatively, VAS are more likely to be of value than, for instance, the first assessment at 6 hours (Chapter 8), 18 hours (Chapter 9) postoperatively, or the next day (Chapter 7).

In Chapter 11, VAS recorded well-being, nausea and sedation with a VRS for pain, nausea and well-being. Although the study was looking for the side-effects of euphoria, nausea and sedation in diamorphine compared with morphine, it may have been more informative to have used a VAS for pain rather than the VRS assessment.

The second area where changes could be made is that of patient numbers. In the comparative study of the Bionica MDS 110 and the Graseby PCAS (Chapter 7), for example, there were two occasions when the significance value ($p< 0.05$) was borderline ($p=0.06$ for postoperative morphine requirements and $p=0.057$ for patients using the devices whilst in a chair). Greater patient numbers may have altered the significance of these values.

Whilst conducting the studies for this thesis I was also using PCA to provide a postoperative pain service. It is my feeling that a more beneficial regimen of providing analgesia would be that of 1 mg morphine with a 5 minute lockout period (to replace the 2 mg morphine with a 10 minute lockout period that was used in the studies). This is supported by other users of PCA (Owen et al., 1989a; Notcutt and Morgan, 1990; Wheatley et al., 1991). Occasionally there would be a patient who "struggled" to obtain analgesia in the first hour or so. Although this may have been dependent on the amount of opiate the patient received whilst in theatre/recovery and the time taken between that and the commencement of PCA, more frequent administration may lead to improved patient comfort/satisfaction.

This leads to another point of practice for PCA. It is important to commence PCA immediately the patient recovers consciousness because it is easier to prevent acute pain than to cure it (Yeager, 1989). This practice was not followed in all of the studies in this thesis, partly because of the impracticability of transporting a lot of technical equipment (e.g. Chapter 9) and also because PCA was a new technique and initially it was felt safer to oversee its use in one area, i.e. on the ward.

In recent years much research has been conducted on PCA, particularly on the techniques of epidural PCA (Gambling et al., 1990; Grant et al., 1991 Welchew and Breen, 1991) and PCA with non-opioids (Oral et al., 1995; Pizzirani et al., 1995). PCA is still developing and is an area that will continue to benefit from further research.

Appendix 1

The American Society of Anesthesiologists' (ASA) Physical Status Classification (1974)

Grade 1	A normal healthy patient.
Grade 2	A patient with mild systemic disease.
Grade 3	A patient with severe systemic disease that is not incapacitating.
Grade 4	A patient with an incapacitating systemic disease that is a constant threat to life.
Grade 5	A moribund patient who is not expected to survive for 24 hours with or without operation.

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Italicized entries in this section refer to source material from third party material consulted during work on this thesis. They appear in recognition and acknowledgement of the original work undertaken by the respective authors.

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