**<R/Heads>PHARMACOLOGY**

**Adverse drug reactions**

Hina Lodhi MB BS FCAI is a Specialty Doctor in Anaesthesia and Critical Care at University Hospitals of Leicester NHS Trust, Leicester, UK. Conflicts of interest: none declared.

Jonathan Thompson BSc (Hons) MD FRCA FFICM is Honorary Professor in Anaesthesia and Critical Care at the University of Leicester and a Consultant at the University of Leicester Hospitals NHS Trust, Leicester, UK. Conflicts of interest: none declared.

**Abstract**

Adverse drug reactions (ADRs) are a common and important cause of morbidity and mortality. They occur frequently in patients undergoing anaesthesia or in Intensive Care. ADRs occur by a number of mechanisms, some of which remain unclear, but several risk factors have been identified. It is increasingly recognised that pharmacogenetic factors are important in determining susceptibility to ADRs. Medical practitioners should be aware of their responsibility to report ADRs and know how to report them.

**Keywords:** Adverse drug reaction; adverse drug event; drug reaction classification; drug reaction mechanism; Medicines and Healthcare products Regulatory Agency.

**Royal College of Anaesthetists CPD matrix:** 1A02

**Learning Objectives**

After reading this article, you should be able to:

* Classify adverse drug reactions
* List the risk factors and describe common mechanisms associated with adverse drug reactions
* Describe the process of recognising and reporting any adverse drug reaction to the MHRA

An adverse drug reaction (ADR) is described by the World Health Organisation as a ‘response to a medicine which is noxious and unintended, and which occurs at doses normally used in man’. ADRs are relatively common: they are responsible for approximately 6.5% of all hospital admissions with a projected annual financial cost to the NHS of £466 million and a mortality of 2%.1 However it is recognised that admissions related to ADRs are under-reported.2

Anaesthesia-associated ADRs are a significant cause of mortality and morbidity. One review of all data from the Medicines & Healthcare products Regulatory Agency (MHRA) up to 2005 found 11,199 reported reactions for common anaesthetic agents, 9% of which were fatal. The majority of ADRs in this report were not allergic and were generally associated with induction of anaesthesia.3 However, allergic reactions are generally under-reported, particularly for older drugs. The incidence of perioperative anaphylaxis reported by the Royal College of Anaesthetists’ 6th National Audit Project (NAP6) was around 1:10000.4 The drugs most often responsible for perioperative anaphylaxis in the NAP6 report are listed in Box 1.

Adverse drug events are subtly different from ADRs. Adverse drug events (ADE) occur when there is a reaction associated with exposure to a drug but not necessarily caused by that drug. ADEs occur frequently, particularly after the introduction of a new therapeutic agent. They are important as the reporting of ADEs helps identify ADRs associated with new drugs.

**Classification**

The traditional classification for ADRs comprises Type A (augmented) reactions and Type B (bizarre or idiosyncratic) reactions and generally encompasses most observed ADRs. Subsequently four further divisions were added to produce a six category classification (A – F) (Table 1). A more recent classification (Table 2) accounts for the **d**ose relatedness, **t**ime course and **s**usceptiblity of the patient (DoTS) to a reaction; this classification is increasingly used.5 Malignant hyperpyrexia, for example, occurs at any dose in susceptible individuals (**Do**), occurs on first dose (**T**), and individual susceptiblity is an inherited mutation for the ryanodine receptor (**S**).

***Type A and B Reactions***

The MHRA continues to refer to the simple, ‘classical’ classification, and this suits discussion of drug reactions occurring in anaesthesia and Intensive Care. In type A reactions, the adverse reaction occurs in proportion to the dose of drug given and tends to be related to pharmacokinetics. Thus the hypotension associated with propofol is a dose-related and predictable adverse reaction. Fasciculations associated with suxamethonium is another such Type A reaction, but so is the subsequent rise in intra-ocular pressure – a secondary adverse reaction occurring as a consequence of an initial reaction. Such reactions are usually revealed in developmental clinical trials and so are already well recognised before the marketing of a new drug.

In contrast, type B reactions tend to be unpredictable (‘bizarre’), and unrelated to the known pharmacology of the drug in question. These reactions tend to be more severe and potentially fatal but are relatively rare. The most familiar examples in anaesthesia are anaphylaxis, suxamethonium apnoea and malignant hyperpyrexia (MH). These reactions are idiosyncratic, infrequent and influenced by immunological and genetic factors. Some Type B reactions present less dramatically, for example halothane hepatotoxicity or fluoride nephrotoxicity. For all these reasons Type B ADRs are often missed in clinical trials and are discovered during post-marketing surveillance, often some years later.

**Risk Factors**

One of the difficulties in understanding ADRs is that the mechanisms by which they occur are largely unknown. However, some predisposing factors have been identified.

***Age***

Patients at the extremes of age are at increased risk of ADRs for several reasons. In the elderly, multiple medications are commonly taken to treat coexisting conditions. Therefore the risk of an ADR arising *per se* or from drug interactions is increased. Ageing is also associated with impaired drug metabolism, decreased physiological reserve (especially renal, hepatic and cardiovascular function) and nutritional deficiency. Therefore elderly patients are both more susceptible and less able to tolerate the adverse effects of a given drug. Of those drugs relevant to anaesthesia, hypnotics, antihypertensives, anticoagulants and NSAIDs are particularly associated with adverse events in the elderly.

Children, and particularly neonates, have other physiological differences including a greater proportion of extravascular total body water, immature renal and hepatic function, reduced plasma protein concentrations and a relatively permeable blood-brain barrier. These factors contribute to susceptibility to ADRs. Furthermore, children unwell enough to require hospitalisation usually require multiple drug therapy, which increases the risk of adverse events. For some reactions the mechanism is unclear, such as the association of aspirin with Reye’s syndrome. Of concern to anaesthetists is that of the 331 deaths in children reported to the MHRA via the Yellow Card scheme in the UK before the year 2000, 30 were attributable to anaesthetic agents.6

***Polypharmacy***

Multiple drug therapy is an independent risk factor for the development of an ADR. A prospective analysis of in-hospital ADRs in a UK centre demonstrated that the addition of each extra medication was independently associated with a 1.14 times increased hazard of an ADR.7 Importantly, additional medication was the only significant predictor of an ADR in this study, and was most frequently associated with diuretics, opioids and anticoagulants. The risks associated with polypharmacy are probably related to drug interactions or altered pharmacokinetics, in addition to associations with age and disease state.

***Disease***

The nature or severity of a disease influences the pharmacodynamic effects of a drug. For example the injection of a given dose of propofol in a patient with systemic sepsis is more likely to result in hypotension; and respiratory depression is more likely after morphine in a patient with renal disease compared with the same doses in healthy individuals. This is important in the critically ill where life-threatening adverse drug events are estimated to occurring in over 20% of patients. Recent evidence suggests that kidney injury and thrombocytopenia are particularly associated with an increased risk of an ADE. Since intravenous drugs are also associated with increased risk, it is clear that the critically ill are particularly susceptible to adverse drug reactions. 8

***Pharmacogenetic factors***

In addition to the effects of age, disease or physiology, genetic factors are involved in some ADRs. Examples include G6PD deficiency, acute intermittent porphyria, and ‘slow acetylators’. These predispositions are also associated with geographic and ethnic variability and can influence the choice of medication (Table 3).

Drug metabolism seems particularly subject to genetic variance with considerable heterogeneity seen in the liver microsomal cytochrome P450 system. The CYP2D6 subtype is especially relevant and is involved in the metabolism of many drugs including codeine, tramadol, ondansetron and beta-blockers. Individuals can be classed as having poor, intermediate, extensive (normal) or ultra-rapid CYP2D6 metabolic activity. For example, poor CYP2D6 metabolism is commoner in Black patients than Caucasian, resulting in reduced effectiveness of codeine (dependent on CYP2D6 for its conversion to morphine). Chinese patients demonstrate extensive metabolism, but activity remains lower compared with Caucasians. Furthermore, 1 – 10% of Caucasians carry extra CYP2D6 genes associated with ultra-rapid metabolism. The net effect is overall CYP2D6 activity is generally lower in Chinese and other East-Asian populations.

CYP2C19 and CYP2C9 also demonstrate geographic polymorphism. CYP2C19 is important for metabolising tricyclic antidepressants, diazepam and clopidogrel, whilst CYP2C9 metabolises NSAIDs and warfarin. CYP2C19 function is absent in 30% of Chinese people compared with 15% Caucasian, with genotyping being recommended by the American Heart Association and American College of Cardiology for those at high cardiovascular risk being treated with clopidogrel. Similarly CYP2C9 shows significant heterogeneity: activity is more frequently reduced in Western compared with Japanese populations, leading to increased warfarin dosing.

Many more microsomal polymorphisms exist. For example, CYP3A4 is involved in the metabolism of opioids, local anaesthetics and benzodiazepines. However, although variants of CYP3A4 are relatively frequent, they are not recognised as being clinically significant. Alfentanil is metabolised by both CYP3A4 and CYP3A5 enzymes, and the latter might contribute to interindividual variability in its metabolism.

Genetic polymorphisms also affect other aspects of drug action, for example cellular transport mechanisms, uptake pathways and receptor structure. The beta2 adrenergic receptor is one of the best studied: mutations in structure can attenuate the effectiveness of bronchodilator therapy as well influence disease severity. Within anaesthesia, a genetic mutation in the coding for the ryanodine receptor partly accounts for susceptibility to malignant hyperthermia in response to inhalational anaesthetics. Microsomal polymorphisms could account for some of the observed variations in pharmacodynamic responses to opioids and intravenous anaesthetics. The MOP opioid receptor (formerly µ) is polymorphic, with carriers of the abnormal G118 allele having a decreased response to opioids (both analgesia and adverse effects).

***Sex***

The risk of an ADR is 1.5 to 1.7 times higher in women owing to pharmacokinetic factors caused by differences in lean body mass, hepatic clearance or cytochrome P450 system activity. Hormonal differences may also be involved, and may underlie the increased frequency of drug-induced *torsade-de-pointes* in females.

***Immune System***

Most Type B reactions are probably mediated by the immune system (Table 4). A prime example of this is anaphylaxis, a type I hypersensitivity reaction where the binding of a drug to a protein induces cross-linking of IgE antibodies resulting in a widespread systemic inflammatory response.

Some immune-mediated drug-induced reactions are less well understood, e.g. the severe skin reactions of Stevens-Johnson syndrome and toxic epidermal necrolysis, particularly associated with sulphonamides and NSAIDs. The mechanism of hypersensitivity may involve the production of toxic metabolites, or those metabolites binding with endogenous proteins resulting in the formation of an antigenic molecule (a hapten). There may also be a cell-mediated component of induced keratinocytic apoptosis either through the actions of immune cells (e.g. T-lymphocytes) or via the secretion of soluble Fas ligand, Fas being a naturally expressed cellular receptor involved in programmed apoptosis.

Halothane hepatitis is also considered to have an immune basis. The oxidative metabolites of halothane appear to bind to hepatic proteins in susceptible patients forming haptens against which antibodies are formed. Cell-mediated reactions may also occur with Kupffer cells demonstrating antigen presentation in the presence of halothane.

**Preventing ADRs**

Various tools have been designed to help clinicians to anticipate drug-associated complications and ADRs. The purpose is to identify patients at risk, monitor them more carefully and attempt to minimise risk factors. However, all the tools available have limited ability to predict events in different populations and none is universally applicable. For example, the GerontoNet ADR risk prediction tool was designed to predict ADRs in Italian patients aged over 65 years. This tool included polypharmacy; a previous ADR; the presence of at least 4 comorbidities; and coexisting liver, renal or heart failure as risk factors. However the sensitivity of the GerontoNet tool was only 38% when it was later evaluated prospectively in a group of Irish patients.9 Therefore the clinician must use judgement and caution to minimise polypharmacy and excessive dosing in those at the extremes of age, with certain diseases, multiple comorbidities or other predisposing factors.

**Reporting ADRs**

One of the functions of a clinical trial is to demonstrate and quantify the incidence of common adverse effects. However many severe ADRs are rare, and it would require 30,000 participants for any trial to demonstrate an ADR that had an incidence of 1:10,000. Therefore other methods of identification of ADRS are needed, including case reports, cohort studies, population statistics and meta-analyses. These are sporadic in nature, sometimes expensive and a formal means of post-marketing surveillance is needed to determine rare but serious ADRs.

In the UK such surveillance is mediated via the MHRA, which in 2003 took primary responsibility for the collection and analysis of ADRs. Spontaneous reporting is managed via the Yellow Card Scheme, referring to the reporting card that can be found in the BNF, MIMS, or in the ABPI Medicines Compendium. Clinicians, and more recently patients can report any suspected reaction via this scheme, whilst for the pharmaceutical industry it is a statutory requirement to report any serious ADR. Any drug can be reported via the scheme. New drugs need particular attention and are marked with a black inverted triangle for a five-year period but for more established drugs, the MHRA recommends that only serious adverse reactions are reported. Serious reactions include ones that involve prolonged hospitalisation; may be life-threatening; cause disability or congenital abnormalities; or are fatal. Drugs can be reported to the MHRA in a number of ways: commonly either by completing and posting a Yellow Card, or by completing an online form at <https://yellowcard.mhra.gov.uk/>. Four essential pieces of information are required (Box 2), in addition to any medical information that the reporter thinks is relevant.

It is generally accepted that less than 10% of all serious adverse drug reactions are spontaneously reported via the Yellow Card scheme. Despite this, ADRs have been determined for a number of drugs, for example the doses of alendronate and ketorolac were revised and warnings added after initial reports of toxicity.

**Severe ADRs and anaphylactic reactions in the perioperative period**

Severe ADR and anaphylactic reactions may sometimes be difficult to recognise in the perioperative period because of physiological variations during and after general anaesthesia and surgery, or delays in presentation. Anaphylactic or severe ADRs should be managed according to the Association of Anaesthetists’ guidelines. It is the responsibility of the treating clinician to refer to the MHRA when the contributing drug is identified.10

**Conclusions**

Adverse drug reactions are common and are associated with significant morbidity. Within anaesthesia ADRs are often immediately apparent. However other ADRs are delayed both in time and in the recognition of their importance e.g. adrenocortical suppression with etomidate; or the metabolic acidosis, rhabdomyolysis, and cardiovascular collapse associated with propofol infusions. Clinicians need to be aware of both the common occurrence of ADRs and their responsibility to report them.

**References**

1. Pirmohamed M., Walley T.J., Park B.K. et al. Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18 820 patients. *BMJ.* 2004; **329**:15-9.

2. Patel H, Bell D, Molokhia M, et al. Trends in hospital admissions for adverse drug reactions in England: analysis of national hospital episode statistics 1998-2005. *BMC Clin Pharmacol*. 2007; **7:** 9.

3. Holdcroft A. UK drug analysis prints and anaesthetic adverse drug reactions. *Pharmacoepidemiol Drug Saf*. 2007;16 (3) 316-28.

4. Cook T.M., Harper N.J.N., Farmer L. et al. Anaesthesia, surgery, and life-threatening allergic reactions: protocol and methods of the 6th National Audit Project (NAP6) of the Royal College of Anaesthetists. *Br J Anaesth.* 2018; **121:**124-33.

5. Aronson JK, Ferner RE. Joining the DoTS: new approach to classifying adverse drug reactions. *BMJ*. 2003; **327**:1222-5.

6. Clarkson A, Choonara I. Surveillance for fatal suspected adverse drug reactions in the UK. *Arch Dis Child*. 2002; **87:**462-6.

7. Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, Pirmohamed M. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. *PLoS One*. 2009; **4:** e4439.

8. Kane-Gill SL, Kirisci L, Verrico MM, Rothschild JM. Analysis of risk factors for adverse drug events in critically ill patients. *Crit Care Med.* 2012;**40:** 823-8.

9. Lavan, A.H., Gallagher, P. Predicting risk of adverse drug reactions in older adults.*Thera Adv Drug Saf.* 2016; **7:** 11-22.

10. Patton K., Borshoff D.C. Adverse drug reactions. *Anaesthesia*. 2018; **73: Suppl 1:** 76-84.

**TABLE 1. Classification of drug reactions**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Type of Reaction** | **Mnemonic** | **Features** | **Examples relevant to Anaesthesia/Intensive Care** |
| A | Dose-related | Augmented | Common | Hypotension after propofol, fasciculations with suxamethonium |
| Related to pharmacological action of drug |
| Predictable |
| Low mortality |
| B | Non-dose-related | Bizarre | Uncommon | Anaphylaxis, suxamethonium apnoea, malignant hyperpyrexia |
| Unrelated to pharmacological action of drug |
| Unpredictable |
| High mortality |
| C | Dose-related & time-related | Chronic | Uncommon | Propofol infusion syndrome |
| Related to cumulative dose |
| D | Time-related | Delayed | Uncommon | Tricholorethylene carcinogenesis, fluoride nephrotoxicity |
| Usually dose-related |
| Occurs or becomes apparent some time after use of drug |
| E | Withdrawal | End of Use | Occurs soon after drug withdrawal | Rebound hypertension with clonidine cessation  Opioid withdrawal syndrome |
| F | Unexpected failure of therapy | Failure | Common | Rifampicin (or other enzyme inducing drug) associated therapeutic failure of oral contraceptive |
| Dose-related |
| Often caused by drug interactions |

Adapted with permission from Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet*. 2000; 356: 1255-1259.

**TABLE 2. DoTS (dosed relatedness, time course and susceptibility) classification of adverse drug reactions. 5**

|  |  |  |
| --- | --- | --- |
| **Classification** | **Sub-classification** | **Explanation / further classification** |
| **DOSE** | Toxic | Reactions occurring at supra-therapeutic doses |
| Collateral | Reactions occurring at standard doses |
| Hyper-susceptibility | Reactions at sub-therapeutic doses in susceptible individuals |
| **TIME COURSE** | Time independent | Occur at any time during therapy |
| Time-dependent | Related to *rapid* administration |
| Occur after the *first dose* of a medication, but not always after subsequent doses |
| *Early reactions* that resolve (usually because of tolerance) |
| *Intermediate reactions* that occur after some time, usually non-allergic hypersensitivity reactions |
| *Late reactions* incidence increases with longer duration of drug administration, or withdrawal reactions |
| *Delayed reactions* occur much later after administration, even after cessation of the drug (e.g. carcinogenesis) |
| **SUSCEPTIBILITY** | Genetic | Factors associated with risk of a reaction to a particular drug. May be single or multiple factors. |
| Age |
| Sex |
| Physiological variation |
| Exogenous factors |
| Diseases |

**TABLE 3. Examples of genetic differences in drug response or metabolism and main geographical or ethnic distribution**

|  |  |  |
| --- | --- | --- |
| **Affected enyzme or pathway** | **Geographical Variance** | **Affected or related drugs** |
| N-Acetyltransferase | Slow acetylator phenotype common in Caucasian & African populations (50 - 65%) | isoniazid, hydralazine |
| Fast acetylator common in East Asians (80 - 90%) |
| CYP2C19 | Deficient enzymatic activity in Chinese populations (~20%) | diazepam, tricyclic antidepressants |
| CYP2D6 | poor metabolisers: Black (0 - 19%) > White (5 - 10%) > Asian (1%) | codeine, tramadol, ondansetron, beta blockers |
| extensive metabolisers: Lower activity in Chinese compared with Caucasian |
| ultrarapid metabolisers: Saudi Arabia & Ethiopian populations |
| plasma pseudocholinesterase | E1a mutation associated with deficient enzyme activity | suxamethonium, mivacurium |
| Asian & Middle Eastern > Caucasian (4%) > Black population |
| G6PD deficiency | Haemolytic anaemia in susceptible individuals | sulphonamides, nitrofurantoin |
| Commonest in Mediterranean, African and Asian populations |
| Porphobilinogen deaminase deficiency | Acute intermittent porphyria | barbiturates, nitrofurantoin |
| Commonest in Switzerland, Sweden and the Netherlands |

**TABLE 4. Immune-mediated hypersensitivity reactions**

|  |  |  |  |
| --- | --- | --- | --- |
| I | Anaphylactic | Anaphylaxis, angioedema, atopy | IgE |
| II | Cytotoxic | Goodpasture's syndrome, transfusion reaction | IgG, IgM |
| III | Immune Complex | SLE, rheumatoid arthritis | IgG, IgM |
| IV | Delayed | Contact dermatitis, tuberculin test | T-cells |

**Box 1. Agents most commonly responsible for anaphylactic drug reactions in the perioperative period in the NAP6 report.4**

|  |
| --- |
| Antibiotics (47%) |
| Neuromuscular blocking agents (33%) |
| Chlorhexidine (9%) |
| Patent blue dye (5%) |

**Box 2. Essential information for completion of a Yellow Card**

|  |  |
| --- | --- |
|  | The adverse event or reaction; seriousness and treatment given |
|  | Information about the affected individual (age, sex, initials) |
|  | The name of the suspected drug |
|  | The reporter's name & address, so that the report can be acknowledged and enable the MHRA to request further information if required |