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EASD Abstract

The metabolic effects of an SGLT2 inhibitor (dapagliflozin) during a period of acute insulin withdrawal and development of ketoacidosis in people with type 1 diabetes.

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Background and aims

SGLT2 inhibitors may offer advantages in the management of people with type1 diabetes with improvement in glycemic control and, reductions in hypoglycemic events, insulin doses and weight. Significant safety issues have been highlighted in clinical trials with increased rates of ketoacidosis. Using stable isotope techniques this study explored the effect of dapagliflozin on glucose flux, lipolysis and ketone body concentration during acute insulin withdrawal in people with type 1 diabetes.

Methods

A double-blind placebo controlled cross over study with a 4-week wash out period was performed in 12 People (4M & 8F) with type 1 diabetes (age 40.7±3.9 y, BMI 26.2±1.5 kg/m2) using insulin pump therapy. Subjects received dapagliflozin or placebo in random order for 7 days. On day 7, they were transferred to a soluble variable insulin infusion to maintain blood glucose at 5 mmol/l. [6,6-2H2]glucose was infused throughout to measure glucose Ra and glucose Rd and [1,1,2,3,3 5H2]glycerol to measure lipolysis. At isotopic steady state insulin was withdrawn, study medication given and blood glucose allowed to increase. Measurements were taken for plasma glucose and glycerol enrichment, NEFA, beta hydroxybutyrate (BOHB), glycagon and spot urine for glucose. The study was terminated at 600 min or in the event of one of the rescue parameters being reached; blood glucose of 18mmol/L, bicarbonate <15mmol/L, venous pH <7.35 or point of care capillary beta hydroxybutyrate level of >5.0mmol/L. Data was modelled using the Steele Equation.

Results

Baseline

Glucose Ra (micromol/min/kg) at 0 min was higher with dapagliflozin compared with placebo 13.1 ± 0 vs 11.68 ± 0.65 p=0.011 and glucagon/insulin (ng/pmol) at 0 min was 0.28 ± 0.06 vs 0.16 ± 0.02 p=0.031, respectively. The statistical differences were lost during insulin withdrawal.

Following insulin withdrawal

Plasma glucose concentration at end point was 8.5 ± 0.7mmol/L for dapagliflozin and 14.4 ± 1.1 for placebo p=0.0005. Urinary glucose excretion during 0-120 min (micromol/kg/min) (n=6) for dapagliflozin 5.10 ± 0.80 vs 0.029 ± 0.01 p=0.003.

AUC0-180 min Glucose Rd (micromol/min/kg \*min) was higher for dapagliflozin 2727± 222 vs 2006 ± 140 for placebo p=0.0004.

AUC0-180 min BOHB (mmol/L\*min) was significantly different 149 ± 26 for dapagliflozin vs 12 ± 18 for placebo p=0.044.

Figure 1- Concentration of beta hydroxybutyrate (mmol/L) at arrival (-120), at equilibrium (0 min) and after insulin withdrawal at 0 to 600 min at the end of 7 days treatment with either dapagliflozin (o) or placebo (•). Dapagliflozin or placebo was administered at 0 min. Study was terminated when one of the rescue parameters was reached. Results are mean ± SEM.

There was no statistical difference in lipoplysis with AUC0-180 min Glycerol Ra (micromol/min/kg \*min) 585 ±7 7 for dapagliflozin vs 543 ± 56 placebo p=0.22 and AUC0-180 min NEFA (mmol/L\*min) 192 ± 15 vs 188 ± 14 p=0.55.

Conclusion

During insulin withdrawal lipolysis was not significantly different between dapagliflozin and placebo but beta hydroxybutyrate was significantly higher with dapagliflozin suggesting a potential metabolic switch to ketogenesis within the liver. Glucagon insulin ratio was higher at baseline and lost during insulin withdrawal.