Name of Sponsor/Company
University of Dundee

Title of Study
Use of Diazoxide in Acute Hypoglycaemia

Investigators
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Study centre(s)
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Publication (reference)
1. PS George, R Tavendale, C NA Palmer, RJ McCrimmon. Diazoxide improves hormonal counterregulatory responses to acute hypoglycemia in long-standing Type

Date of first enrolment Jan 2012 **Date of last completed** April 2013	**Phase of development** Phase IV

Objectives
To determine if the non-selective potassium channel opener (KCO) diazoxide amplifies epinephrine release during insulin-induced hypoglycaemia.

Methodology
A randomized, double-blind, placebo-controlled cross-over trial using a stepped hyperinsulinemic hypo- glycemia clamp was performed in 12 T1D subjects with prior ingestion of diazoxide (7 mg/kg) or placebo. Counter-regulatory hormones, Symptoms and Cognitive responses were assessed at each of the glucose nadir.

Number of patients planned
12

Number of patients analysed

Diagnosis and main criteria for inclusion
1. Type 1 Diabetes (aged 18-55) with >5 years disease duration
2. On intensive insulin therapy (CSII or multiple daily injections)
3. HbA1C <8.0%
4. Ability to give written informed consent to participate in the study
5. BMI between 20-29

Test product dose
Diazoxide 7 mg/kg

Duration of treatment
One off dose prior to the hyperinsulinaemic, hypoglycaemia clamp

Reference therapy

Matched placebo

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Criteria for evaluation

Primary Endpoint

The primary endpoint was defined as the magnitude of epinephrine responses at a glucose level of 2.5 mmol/l

Secondary Endpoints

Secondary outcomes examined whether oral Diazoxide would affect glucose thresholds for

Statistical methods

Data are presented as mean (SE). Normally distributed data were compared using paired samples t tests, while non-normally distributed data were compared using the Wilcoxan signed rank test. Statistical analyses were conducted using Graphpad Prism 6 and $p<0.05$ was considered statistically significant. Repeated measures ANOVA was used for analysis of Glucose falls, BP and Pulse, to determine if there were any significant changes.

Glucose thresholds for onset of symptoms, counterregulatory hormone responses and cognitive function were determined according to published protocols. Glucose thresholds for onset of hormone responses were defined as the time of onset of a sustained (≥2 successive time points) increase in hormone concentrations ≥ 2 SDs above the mean of the two baseline measurements for that hormone. Thresholds for the total symptoms were determined as the time at which the symptom score increased ≥2 over baseline on ≥2 successive time points. If no defined change occurred, then the lowest measured glucose was used as the threshold for that individual, in a similar fashion to other published literature. The glucose level at which there was a greater than 4% in the error rate was used to define thresholds of the Four Choice Reaction test

Summary Conclusions

Results

The primary outcome measure for this trial was the epinephrine response during the maximal hypoglycaemic stimulus (2.5 mmol/l). In support of our hypothesis, we found that following oral administration of Diazoxide, there was a 37% increase in mean (SEM) epinephrine responses (0.40 (0.06) vs. 0.29 (0.05) ng/ml; D vs. P respectively, p<0.05) and a 44% increase in norepinephrine (0.85 (0.07) vs. 0.59 (0.06) ng/ml; D vs. P respectively, p<0.05)

Although, glucagon levels remained, as expected, suppressed during hypoglycaemia there was a non-significant trend towards higher glucagon levels in the Diazoxide arm (57.8 (11) vs. P; 50.0 (7.1) ng/l; D vs. P, respectively, p=0.241). Glucose infusions were also non-significantly lower in those who had received Diazoxide.(D. 75.5 (11.5) vs P.69.5 (14.0) p=0.41 (see Table 2)

Following administration of Diazoxide participants also reported greater total symptom scores of hypoglycaemia during the 2.5 mmol/l plateau although this difference did not prove significant (D v P; 21.5(3) vs 19.3 (3.0) p=0.33. Similarly, although there was an overall increase in autonomic symptoms following Diazoxide but this was not significant (10.3 (1.5) vs. 8.9 (1.4) p=0.21). Performance on three of the four cognitive tasks did not differ following Diazoxide administration [TMB-T (32.5(4.7) vs 30.3(4.2) (D vs. P, respectively, p=0.65), Dig-B (6.3(0.7) vs 6.7(0.6), D vs. P, respectively, p=0.38) as well as 4CRT (546.9(21.2) vs 542.6(18.0), D vs. P, respectively, p= 0.82). In contrast, there was a significant deterioration in DSS following Diazoxide administration (71.7(8.5) vs 81.3(8.2); D vs. P, respectively, p=0.048) (see Table 3).

Conclusion

In summary, we have shown for the first time in human subjects that the K_{ATP} channels are integral to hypoglycemia detection and in the generation of an ade- quate CRR to acute hypoglycemia. We report that the K_{ATP} channel opener diazoxide, when given orally before a hypoglycemic stimulus to subjects with long-standing T1D and IAH, results in a 37–44% increase in the magni- tude of the catecholaminergic counterregulatory hormonal response.

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