

Absorption of orally ingested insulin in human type I diabetic subjects: proof of concept study

Donald C Whitelaw¹, Christine A Kelly¹, Wendy Ironmonger¹, Clare Cunliffe², Roger New³, James N Phillips³

¹Department of Diabetes & Endocrinology, Bradford Teaching Hospitals NHS Trust, Bradford UK; ²Akela Consultancy Ltd, London UK; ³Diabetology Ltd, London UK



Introduction

Previous attempts to deliver insulin therapy by the orally ingested route have been unsuccessful because of digestion of the protein structure by gut enzymes.

We have developed a formulation containing insulin which, taken in capsule form, protects insulin from enzymatic digestion and facilitates absorption across the intestinal mucosa (DTY001).

Previous studies in diabetic dogs and in healthy human subjects suggest that ingestion of DTY001 raises plasma insulin concentrations.

We have examined here for the first time the absorption of DTY001 in human diabetic subjects.

Subjects

Eight otherwise healthy male type 1 diabetic subjects were recruited from the Diabetic Clinic and gave informed consent

Approval was obtained from local research ethics committee and from UK MHRA

All subjects had good overall glycaemic control on multiple daily insulin injections (see table for baseline characteristics)

Methods

Subjects attended after an overnight fast, having omitted bedtime basal insulin the previous night.

We administered 150U insulin with water as a single capsule to all subjects. Each subject underwent repeat assessment with the 300IU dose 5-28 days later.

Subjects remained fasting throughout the procedure.

Venous blood glucose and plasma insulin concentrations were measured every 15 minutes for up to 8 hours.

Statistical analyses

Data were analysed to examine changes in plasma insulin concentration and time to peak insulin concentration (primary endpoints).

Changes in glucose concentrations were also analysed (secondary endpoint)

Insulin and glucose concentrations were analysed by 2-way ANOVA (insulin after log transformation).

Data are shown only for the six subjects who completed both assessments

Figure 1: insulin concentrations

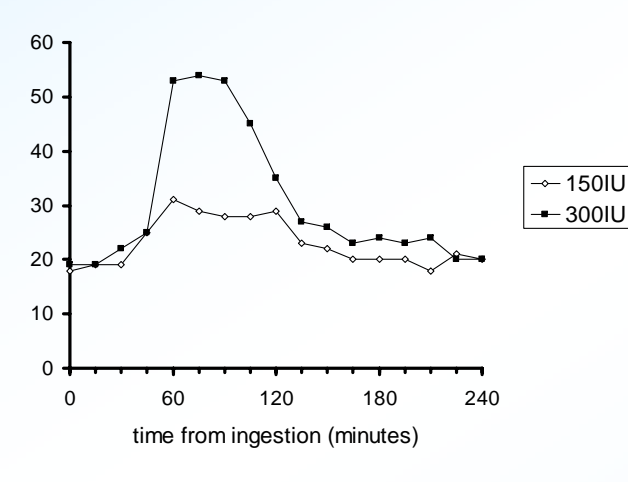


Figure 2: mean glucose change from baseline

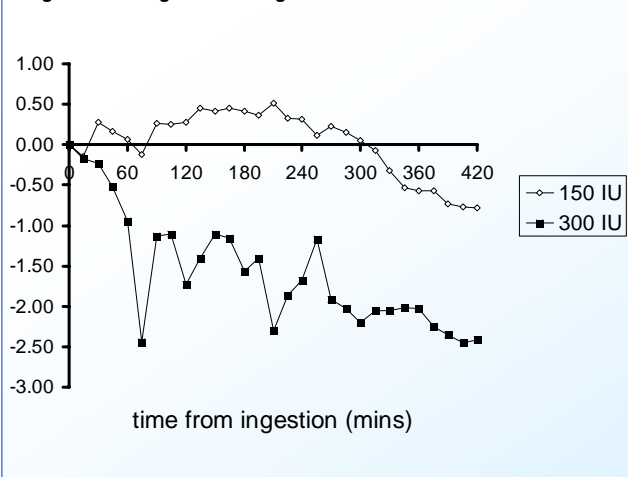


Table: subject characteristics

| | Mean | median | range |
|---------------------------|------|--------|-----------|
| Age (yrs) | 30.2 | 31 | 21-41 |
| Weight (kg) | 80.2 | 80 | 63.5-98.4 |
| BMI (kg m ⁻²) | 26.1 | 25.7 | 23.6-29.8 |
| Duration of DM (yrs) | 4.3 | 2.5 | 1-10 |
| HbA1c (%) | 7.6 | 7.5 | 6.7-8.0 |

Results

Peak plasma insulin concentrations were reached at 80-90 minutes after ingestion -

150IU: 87.5mins (range 45-120)

300IU: 83.6 mins (60-105)

Both doses of insulin resulted in a significant increase in plasma insulin concentration ($p=0.014$ by ANOVA)

300IU insulin produced a greater increment in plasma insulin levels ($p<0.0001$)

Significantly greater falls from initial blood glucose were observed at the higher insulin dose (mean 1.6mmol/l vs 0.02mmol/l; $p<0.0001$)

Unadjusted AUC for insulin and glucose did not differ significantly between doses

Considerable between-subject variation in response was observed

One subject developed symptomatic, biochemically confirmed hypoglycaemia (with 150IU insulin only); one subject was withdrawn because of severe hyperglycaemia at baseline

Conclusions

We have developed a preparation of insulin which can be ingested orally and absorbed to have a measurable effect on plasma insulin concentrations

This offers the potential for therapeutic use of oral insulin in diabetes and may be a more physiological means of delivering insulin

Further studies are required to assess the clinical potential of oral insulin in both type 1 and type 2 diabetes

Acknowledgements Dr G Wark, Guildford. Dr M Cooper, Bradford.

Correspondence: Donald.whitelaw@bradfordhospitals.nhs.uk