A dose-response of blood glucose concentrations to orally delivered insulin in healthy subjects

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BACKGROUND

Effective oral delivery of therapeutic proteins is significantly hampered by the natural barriers impeding their integrity and bioavailability. Oramed Pharmaceuticals has developed a technological platform supporting the oral delivery of proteins and peptides, by concomitantly administering protective agents and absorption enhancers. Its oral insulin product (ORMD-0801) has been proven effective in curbing glucose excursions in both type 1 and type 2 diabetes patients and in stabilizing glucose profiles in unstable type 1 diabetes patients.

OBJECTIVES

To determine the capacity of a base oral delivery formulation to support increasing doses of insulin, as measured by its glucose-lowering effect in healthy subjects.

METHODS

Enteric-coated capsules containing the base formulation with either 8 or 16 mg insulin/capsule were administered to ten healthy, fasting volunteers at four independent visits at the following doses: 8 mg insulin, 16 mg insulin, 8+8 mg insulin (2 capsules) and 8+16 mg insulin (2 capsules).

Blood glucose and c-peptide concentrations were monitored over the ensuing 300-minute period.

Analyses compared the mean area under the curve (AUC) of baseline measurements (0-40 minutes post-dosing) to that of the treatment period (40-300 min post-dosing) and of the best response period, defined as the 2-5-point range with each subject's best response. AUC measurements were normalized to time.

Table 1. Comparison of mean baseline versus best-period glucose AUC (entire cohort)

GLUCOSE				
Dose	baseline AUC (mg/dL)	best-period AUC (mg/dL)	ΔAUC	Relative change (%) in AUC
8mg	84.4	76.6	- 8.2	-9.6
16mg	80.6	67.8	- 12.8	-15.7
8+8mg	81.2	69.7	-11.5	-13.9
8+16mg	79.6	65.3	-14.2	-17.6

Table 2. Comparison of mean baseline versus best-period glucose AUC (excluding nonresponders)

GLUCOSE				
Dose	baseline AUC (mg/dL)	best-period AUC (mg/dL)	ΔAUC	Relative change (%) in AUC
8mg	84.8	75.2	- 9.6	-11.2
16mg	76.6	64.8	- 14.4	-17.9
8+8mg	81.2	66	-15.2	-18.4
8+16mg	78.4	64.5	-14	-17.5

Table 3. Comparison of mean baseline versus treatment c-peptide AUC (entire cohort)

c-peptide				
Dose	baseline AUC (ng/mL)	Treatment period AUC (ng/mL)	ΔAUC	Relative change (%) in AUC
8mg	2.1	1.7	- 0.4	-18.1
16mg	1.8	1.4	- 0.3	-18.2
8+8mg	1.9	1.5	-0.4	-18.3
8+16mg	1.8	1.5	-0.3	-18.0

Table 4. Comparison of mean baseline versus best-period c-peptide AUC (entire cohort)

c-peptide				
Dose	baseline AUC (ng/mL)	Treatment period AUC (ng/mL)	ΔAUC	Relative change (%) in AUC
8mg	2.1	1.4	- 0.7	-31.7
16mg	1.8	1.1	- 0.7	-40.3
8+8mg	1.9	1.2	-0.7	-36.3
8+16mg	1.9	1.1	-0.7	-37.5

RESULTS

No adverse events were recorded throughout the study sessions.

Seven of the ten subjects demonstrated responses to treatment (≥10% drop from baseline glucose values).

Best response periods exhibited significantly lower mean glucose AUCs when compared to baseline AUCs of the same dose ($p<0.01$), with an average relative decrease of 14.2% (range: 9.6-17.6%), for the entire cohort and 16.3% (range: 11.2-18.4%), when excluding the three nonresponders (Tables 1-2). When comparing between doses, subjects demonstrated a significantly greater response to the 8+16 mg regimen, when compared to the 8 mg regimen ($p=0.012$, and $p=0.047$ when including and excluding the nonresponders, respectively). A significantly lower mean treatment c-peptide AUC when compared to baseline AUC, was observed for all tested doses ($p<0.003$), with an average relative decrease of 18.2% and 36.4% in c-peptide levels calculated for the entire post-treatment period and best response period, respectively Tables 3-4).

CONCLUSIONS

The tested oral drug delivery formulation is safe and supports delivery of increasing doses of insulin.

Due to the innate differences between healthy and diabetic individuals in responsiveness to exogenous insulin, a similar dose-response study will be conducted in the target population.

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