Dose response to oral insulin capsules in fasting, healthy subjects

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BACKGROUND

Oral alternatives to injectable insulins are expected to better mimic physiological portal vein insulin gradients, while inducing far fewer side effects than systemically delivered insulins. However, orally administered insulin, much like most proteins and peptides, is both subjected to the harsh proteolytic forces of the gastrointestinal tract and fails to traverse the intestinal epithelium. Oramed Pharmaceuticals has developed an oral drug delivery platform, based on a simple blend of the active ingredient with protease inhibitors and an absorption enhancer, which involves no new chemical entities. Previous studies have established the safety and efficacy of an oral insulin formulation (ORMD-0801), designed along the principles of this technology. The ratios of the provided excipients are proposed to support delivery of proteins sizes of up to 100 kDa and a broad span of concentrations.

OBJECTIVES

- To assess the capacity of the excipient content of the current ORMD-0801 formulation to support delivery higher concentrations of insulin.
- To assess the pharmacodynamics (PD) of orally administered. insulin in healthy subjects
- To compare PD responses to equal amounts of insulin delivered in one versus two capsules.

DESIGN

Following informed consent, a single capsule containing 8 mg or 16 mg insulin, or two capsules containing 8 mg insulin each, were administered to ten fasting, healthy, male subjects. This interim analysis focused on blood glucose concentrations, which were monitored over the ensuing 300-minute period. Subjects demonstrating a PD response in any of the three treatment sessions were included in the analysis. A PD response was defined as a Cmin ≥15% lower than baseline blood glucose values.

Table 1. Mean glucose responses to ORMD-0801

Treatment	C_{min} [SD] (mg/dL)	T_{min} [SD] (min)	AUC [SD] (mg/dL*min)
8 mg	64.6 [6.2]	169.3 [67.5]	22425.0 [2152.6]
8+8 mg	47.9 [11.3]	188.6 [72.9]	19470.7 [2126.5]
16 mg	57.3 [8.4]	139.3 [48.0]	20610.4 [1427.6]

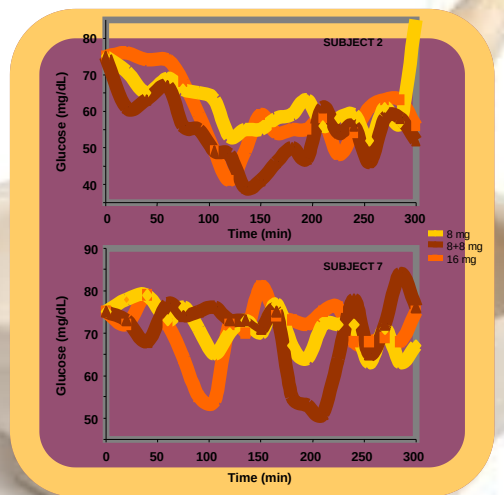

Figure 1. Blood glucose profiles of two healthy subjects following treatment with ORMD-0801. ORMD-0801 capsules, containing 8 or 16 mg insulin were administered to fasting healthy subjects. Blood glucose concentrations were monitored for 5 hours thereafter.

RESULTS

No adverse events were observed or reported for any of the treatment regimens. PD responses were observed in 7/10 subjects. Maximal glucose responses for all treatments were observed following a ≥60-min lag period, as expected of enteric-coated capsules (Table 1, Figure 1). Dose responses were manifested by significantly lower mean blood glucose C_{min} following the 8+8mg (47.9 ± 11.3 mg/dL, p=0.006) and 16mg (57.3 ± 8.4 mg/dL, p=0.001) treatments, when compared to that which followed 8mg dosing (64.6 ± 6.2 mg/dL) (Table 1, Figure 1). Moreover, glucose area under the curve (AUC) was significantly lower following both 8+8mg and 16mg treatments (13.2% and 8.1%, respectively), when compared to 8mg (p=0.003 and 0.008, respectively) (Table1).

CONCLUSIONS

- The ORMD-0801 excipient ratios effectively deliver doses higher than those tested to date.
- Blood glucose response intensity positively correlated with the insulin content in ORMD-0801.
- One and two-capsule regimens for delivery of 16 mg insulin were equally effective in lowering blood glucose concentrations.

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