A Single-Blind, Two-Period Study to Assess the Safety and Pharmacodynamics of an Orally Delivered GLP-1 Analog (Exenatide) in Healthy Subjects

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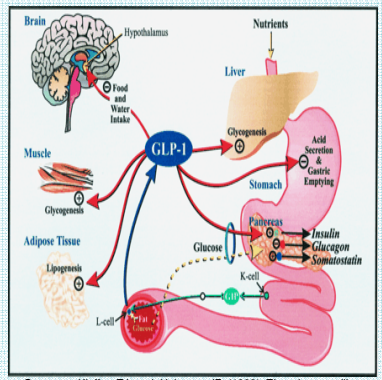
INTRODUCTION

Glucagon-like peptide 1 (GLP-1), secreted within minutes of food ingestion, is associated with a gamut of physiological processes, including induction of insulin release, support of normoglycemia, β-cell function preservation, improved lipid profiles, increased insulin sensitivity, inhibition of glucagon secretion and delayed gastric emptying[1,2]. Thus, GLP-1 harbors significant therapeutic potential for regulating Type 2 diabetes, where GLP-1 secretion is reduced. However, clinical use of the native GLP-1 is limited due to its rapid enzymatic inactivation resulting in a $t_{1/2}$=2-3 minutes. To overcome this obstacle, both natural and synthetic, long-acting degradation-resistant peptides, GLP-1 mimetic agents have been designed and introduced to the clinic. To date, GLP-1 analogs are only available as injectable dosage forms and its oral delivery is expected to provide physiological portal/peripheral concentration ratios while fostering patient compliance and adherence.



Source: Kieffer TJ and Habener JF (1999) The glucagon-like peptides. *Endocrine Reviews 20(6):876-913*

Physiological activities of GLP-1. GLP-1 stimulates insulin and somatostatin release via a glucose-dependent pathway and inhibits glucagon secretion. GLP-1 leads to reduction of gastric motility and is correlated with increased satiety signals. In addition, GLP-1 supports prolonged normoglycemia, improved lipid profiles and reversal of fatty liver.

RATIONALE

GLP-1 analogs are incretin mimetics with proven antihyperglycemic capacity and effectiveness in reducing weight. As such, this drug family is attracting increasing attention as a potential pharmaceutical alternative to management of diabetes. However to date, these agents are currently available as parenteral dosage forms only. This study was conducted to assess the physiological efficacy of ORMD-0901[3], an oral exenatide GLP-1 analog-based preparation designed with Oramed Pharmaceuticals' proprietary oral formulation technology. Insulin excursions after oral administration of ORMD-0901 or placebo followed by an oral glucose load, were compared.

OBJECTIVES

- To evaluate the safety and tolerance of ORMD-0901.
- To test the insulinogenic response of subjects orally treated with ORMD-0901 versus placebo before a glucose challenge.

DESIGN

First-in-human, single-blind, two-period study focusing on the induced insulinogenic responses to orally administered exenatide. Six fasting, healthy, male volunteers (ages: 18-19; BMI: 18.4-25.1) were administered a placebo or exenatide-based capsule (150 µg), on visits 1 and 2, respectively, (time: -60). Subjects were challenged with a 75 g oral glucose load 60 minutes after capsule administration (time: 0) and monitored for 150 min. Blood samples were collected at -60, -30, -15, 0, and every 15 minutes thereafter for up to 150 minutes. The data of six subjects were analyzed for safety evaluations, while those of four subjects were considered for the efficacy evaluations, due to adverse events reported upon glucose load at visit 1 (placebo).

SAFETY RESULTS/DISCUSSION

The oral formulation of exenatide was well tolerated by all six subjects (visit 2) and no serious adverse events occurred.
Nausea is the most frequently reported adverse reaction to subcutaneous exentide treatments and typically occur in a dose-dependent fashion. Other common side effects include vomiting, diarrhea and dyspepsia. Thus, the safety data collected from this preliminary study suggest improved exenatide tolerance when delivered via Oramed's oral formulation technology.

REFERENCES

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EFFICACY RESULTS/DISCUSSION

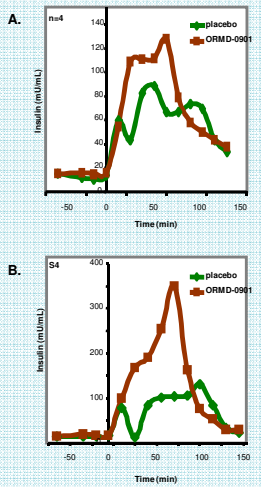

Figure 1. Insulin responses following oral administration of exenatide-based capsules Four healthy, fasting, male subjects were administered a placebo capsule (visit 1) or a single capsule containing 150 µg exenatide (visit 2). A 75 g glucose load was administered 60 minutes thereafter. Blood samples were drawn every 15 minutes throughout the monitoring session for evaluation of plasma insulin levels. (A) mean insulin values (B) insulin values of subject #4.

Insulin levels peaked in both placebo and exenatide-treated subjects within 60-75 minutes of glucose load (Figure 1). However, the mean peak insulin concentration in exenatide-treated subjects was 28% higher than in their counterpart placebo sessions (Figure 1A). In both sessions, insulin levels returned to close to baseline levels within the 150-minute monitoring session. The mean insulin AUC_{0-150} was 17.6% higher in exenatide-treated subjects, when compared to the placebo session (Table 1). These results reflect induced insulin release following exenatide absorption and bioactivity.

Table 1. Insulin vs. time area under the curve (AUC) values

	Insulin	
	Mean AUC_{0-150}	Std
Placebo	148.547	30.512
ORMD-0901	180.344	106.825
p value	0.523	

CONCLUSIONS

This first-in-human study has demonstrated that Oramed's proprietary technology provides for retained biological functionality or orally delivered exenatide. In addition, the drug preparation was safe and failed to induce any adverse events. These encouraging results provide a strong impetus for us to continue the development of this promising drug.
Development of oral delivery platforms for exenetide and other incretins and incretin mimetics may convey physiological advantages over their injectable counterparts, by better mimicking their physiological routes and gradients porto-hepatic environment.

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