A novel GLP-1 analog delivered orally reduces postprandial glucose excursions in a porcine model

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Introduction

The incretins (GLP-1 , GLP-1 analogs and DPP IV- inhibitors) possess putative effects with potential benefit to diabetes management. These drugs have proven to preserve β-cell function, reduce oxidative stress, improve cardiac function, lower blood pressure, improve lipid profiles, reverse fatty liver, heighten insulin sensitivity and reduce postprandial hyperglucagonemia. However, to date, GLP-1 and its analogs are only available in parenteral dosage forms. In this study, we sought to examine whether ORMD-0901, a novel GLP-1 analog with a prolonged half-life, can be enterically delivered using Oramed's drug delivery platform and retain its reported pharmacodynamic effect of reducing postprandial glucose excursions.

Experimental Methods

Five single-dose, enterically-delivered ORMD-0901 formulations were assessed in a postprandial glucose excursion porcine model. Each formulation was tested on 3 pigs (avg wt: 40 kg), whereby, ORMD-0901 was directly administered through an indwelling jejunal cannula. Animals were challenged with an oral glucose load (3gr/kg or 5gr/kg) 30 minutes after oral administration of ORMD-0901. Post-load glucose excursions were compared to those of controls challenged with equal amounts of glucose without ORMD-0901 pretreatment. Tolerance and adverse effects were also assessed.

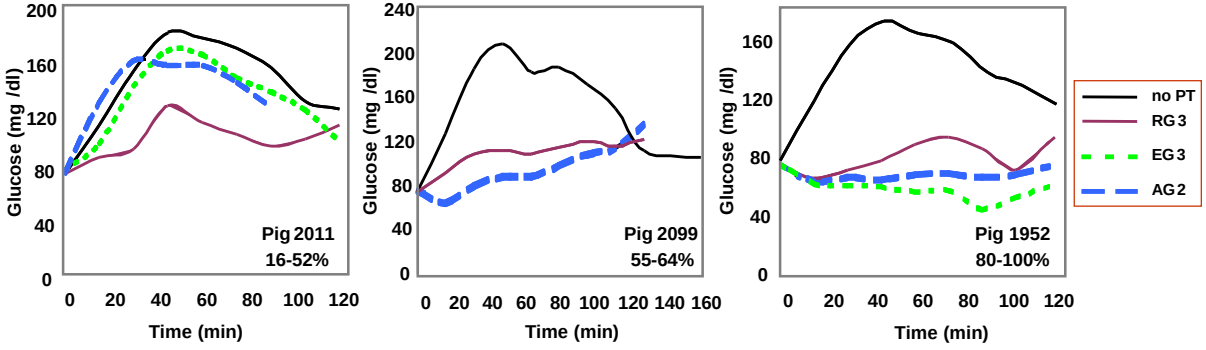

Fig 1. Normalized blood glucose levels after treatment of healthy, cannulated pigs with ORMD-0901 prior to glucose challenge. Pigs (n=3) were treated with various formulations of ORMD-0901, 30 minutes prior to a 5 g/kg glucose challenge. Controls were administered glucose with no pretreatment (no PT) ORMD-0901 dose. Blood was drawn every ten minutes and blood glucose levels were determined. Percent drop in glucose peak values are indicated on each response curve, where 75 mg/dl glucose was considered baseline.

Results

Enteric delivery of ORMD-0901 was well tolerated by all animals and no adverse reactions were noted. Postprandial glucose excursions were significantly reduced in pigs receiving ORMD-0901 before a 5 g/kg glucose challenge (Fig 1). Mean area under the curve (AUC) values of pigs pretreated with ORMD-0901 Formulations RG3 or AG2 were significantly lower than in their non-ORMD-0901 counterpart sessions (p=0.004 and 0.041, respectively, Fig 2). AUCs were up to 34% lower than control animals treated with glucose alone.

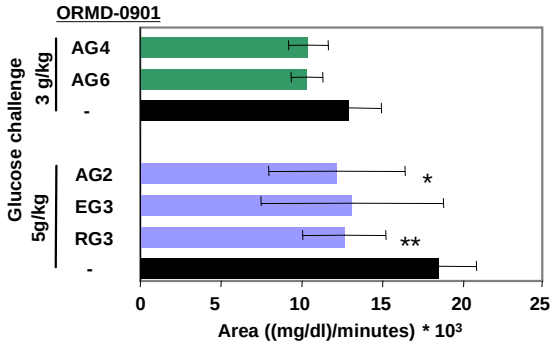

Fig 2. AUC of glucose responses of healthy, cannulated pigs to ORMD-0901. Pigs were treated with various formulations of ORMD-0901 as described in Fig 1. Controls were administered glucose with no prechallenge ORMD-0901 dose. Normalized plasma glucose response curves were plotted as a function of time and AUC values were calculated.
* p=0.041, ** p=0.004

Summary and Conclusions

- Enteric administration of the novel ORMD-0901 GLP-1 analog prior to a glucose load, exhibited a potent curbing effect on postprandial glucose excursions, replicating the effects of parenterally-administered GLP-1.
- Oral delivery mimics the physiologic route of GLP-1 secretion and absorption and establishment of a portal/peripheral gradient. It may hold more and yet unknown beneficial effects.
- High portal vein GLP-1 concentrations together with low peripheral concentrations are likely responsible for the lack of side effects.

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