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A Model of Long-term Intestinal Access in the Pig

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INTRODUCTION

Due to the close resemblance between the pig and human gastrointestinal tract anatomy, physiology and eating patterns, the pig model is often considered most suitable for *in vivo* assessment of oral drug absorption. However, delayed gastric emptying and high variability in gastric pH preclude its application toward evaluation of oral drug formulations. Numerous bypass devices and techniques establishing long-term intestinal access in laboratory animals, have been described. However, their use is associated with infection and local sensitivity. Moreover, the majority of these devices do not lend themselves to capsule or tablet administration and are limited to liquid formulations only. To this end, we have developed a means of long-term intestinal access by generating a nipple valve which creates a unidirectional access port between the pig epidermis and the intestines. The method requires minimal surgical intervention and maintenance and has been proven effective in reflecting drug absorption patterns in humans.

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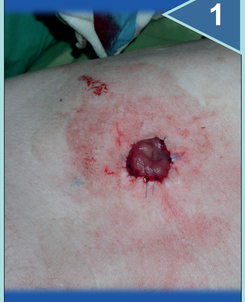

METHODS

An intestinal fistula was created by isolating a 25 cm-long intestinal section, creating an intususcepted nipple valve, and was then anastomosed end-to-side to the jejunum and exteriorized in the flank of the pig (Figure 1). Animals were allowed to rest for a minimum of seven days postsurgery before testing. ORMD-0801 and ORMD-0901 (Oramed Pharmaceuticals, Ltd.), drugs formulated to lower blood glucose and increase plasma insulin concentrations, were tested. Entericoated capsules containing ORMD-0801 were inserted via the access port in four pigs. The encapsulated formulation was tested four to six times per pig. Similarly, the ORMD-0901 suspension was orally administered via the nipple valve, and 30 min thereafter, pigs were exposed to an oral glucose challenge of 5 g/kg. Plasma glucose concentrations were monitored for two hours postadministration. **The same encapsulated ORMD-0801 and ORMD-0901 formulations were later evaluated in clinical trials and results are presented to demonstrate the effectiveness of the pig model in mimicking the human response to these oral drugs.**

RESULTS

ORMD-0801 induced a sharp reduction in blood glucose concentrations, which reached a minimum within 90 minutes of administration (Fig 2). In contrast, the nonformulated active ingredient (NC) was not absorbed, as evidenced by the stable glucose levels in these pigs. **While confirming the efficacy of the oral drug formulation, these findings also attest the intestinal integrity in these pigs.** An ORMD-0801 formulation adjusted for human use, induced a 7.0-7.5% decrease in glucose AUC values when compared to placebo-treated diabetics (Fig 3). Similarly, the ORMD-0901 formulations administered to pigs provided a potent curbing effect on postprandial glucose excursions. Mean area under the curve (AUC) values of pigs pretreated with ORMD-0901 were up to 34% lower than those of control animals challenged with glucose in the absence of ORMD-0901 (Fig 4). In a first-in-humans study testing ORMD-0901 efficacy when orally delivered 60 min before a glucose load, mean peak insulin levels were 28% higher and insulin $AUC_{0\text{-}150}$ values were 22% higher (180.3±106.8 vs. 148.5±30.5; p = 0.5) in ORMD-0901-treated subjects than those measured in their counterpart placebo sessions (Fig 5), **In summary, the parallel results observed in the porcine model and human trials reinforce the relevance of this model for oral drug testing.**

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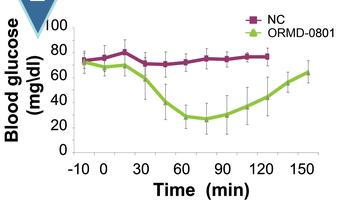

ORMD-0801 was administered to four nipple-valve-bearing pigs on sixteen independent test days. Plasma glucose concentrations were measured every 15 min thereafter, over a period of 2.5 hr postadministration. Drug effect was compared to that of a negative control formulation (NC) administered on four independent visits.

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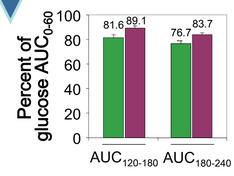

$AUC_{120\text{-}180}$ and $AUC_{180\text{-}240}$ calculations presented as ratios of $AUC_{0\text{-}60}$ (baseline period) of glucose levels measured following ORMD-0801 (green) and placebo (maroon) treatments. Error bars represent standard error means $AUC_{120\text{-}180}$ p=0.049, $AUC_{180\text{-}240}$ p=0.07

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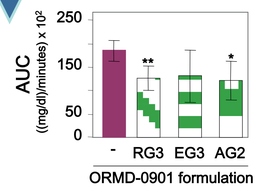

Pigs were treated with various formulations of ORMD-0901 30 minutes prior to a 5 g/kg glucose challenge. Blood was drawn every ten minutes from start of experiment and blood glucose levels were determined using a glucometer. Mean normalized plasma glucose response curves were plotted as a function of time and AUC values were calculated. (Formulation AG2, n=4; Formulations RG3 n=6; Formulation EG3 n=3) * p=0.041, ** p=0.004.

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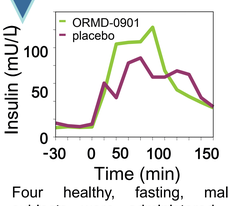

Four healthy, fasting, male subjects were administered a single ORMD-0901 or placebo capsule on two independent visits. A 75 g glucose load was administered 60 minutes thereafter. Blood samples were drawn every 15 minutes throughout the monitoring session for evaluation of insulin levels. Mean values are presented.

MODEL ADVANTAGES

- **Minimal postoperative complications**
- **Minimal maintenance requirements**
- **No effect on animal quality of life**
- **Supports capsule/tablet administration**
- **Object to be inserted can be up to 10 mm in diameter**
- **Drug can be administered to conscious pigs**
- **No use of foreign, nonbiological materials**
- **Extended animal usability**

Long-term jejunal access via a nipple-valve has been provided in over **40** pigs within the last three years. Our accrued experience has shown that epidermal overgrowth constitutes the central adverse reaction to this manipulation and can be easily minimized via simple excision of the surrounding skin, followed by suturing the intestine to the subcutane.

CONCLUSIONS

When applied to the intestinal area, the nipple-valve long-term access technique maintains intestinal integrity and allows for simple administration of investigational drug materials. The described model constitutes a bypass of the porcine stomach, an essential step in evaluating the effectiveness of oral drug formulations, in their encapsulated or suspension forms.

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