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 regulating drug absorption patterns in humans.

METHODS

An intestinal fistula was created by isolating a 25 cm-long intestinal section, creating an intussuscepted 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. Enteroic 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. When applied to the intestinal area, the nipple-valve long-term access technique maintains intestinal function, and can be easily minimized via simple excision of the surrounding skin, followed by suturing. Long-term jejunal access via a nipple-valve has been provided in over 75 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 subcutaneous tissue.

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.