Pulmonary Insufflation of ROSE-010 (GLP-1 Peptide Analogue) Completely Suppresses the MMC in the Conscious Rat: Comparison with the Intravenous and Subcutaneous Routes

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Abstract

Introduction: Subcutaneous administration of ROSE-010, a GLP-1 analogue, reduces bowel spasm and relieves acute pain in patients with irritable bowel syndrome (IBS). The feasibility of non-invasive, pulmonary therapy for IBS was studied in the rat migrating myoelectric/motor complex (MMC) model. The test article was a dry powder formulation of ROSE-010 prepared using Technosphere® technology. Technosphere® technology provides rapid systemic drug delivery by inhalation of a powder containing the drug and a novel excipient.

Objective: To compare ROSE-010 in the MMC model when insufflated as ROSE-010 Technosphere® powder compared to ROSE-010 administered by subcutaneous (SC) or intravenous (IV) injection.

Methods: Studies were carried out in 10 rats with a jugular vein catheter and bipolar electrodes implanted at 5, 15, and 25 cm distal to the pylorus. Total myoelectric activity was recorded over 6–8 hours. After a control period of four MMC cycles, animals were briefly (4 min) anesthetized with 3–4% Isoflurane and rapidly insufflated with air or ROSE-010 Technosphere® powder at doses of 0.1 and 0.2 mg/kg ROSE-010. Alternatively, ROSE-010 was administered by IV or SC injection at 0.1 mg/kg. Recording was continued until four MMC cycles were resumed.

Results: Pulmonary insufflation of ROSE-010 Technosphere® powder (0.2 mg/kg ROSE-010) increased MMC cycle length from 18.7 ± 7.3 to 105.9 ± 9.5 min (n = 6), and 0.1 mg/kg ROSE-010 from 19.4 ± 2.9 to 102.6 ± 18.3 min (n = 3). IV or SC ROSE-010 (0.1 mg/kg) prolonged the MMC cycle from 18.3 ± 2.5 and 14.8 ± 2.0 min to 124.1 ± 27.3 and 148.1 ± 49.4 min, respectively (n = 6/group). As a control, there was no increase in MMC cycle length in animals administered air by insufflation.

Conclusion: MMC inhibition following pulmonary insufflation of ROSE-010 Technosphere® powder is comparable to inhibition following IV or SC injection of ROSE-010 at similar doses.

Conflict of Interest: The research was funded in part by MannKind Corporation and Rose Pharma.

Introduction

Subcutaneous administration of GLP-1 reduces bowel spasm and relieves acute pain in patients with irritable bowel syndrome (IBS).[1,2] The feasibility of non-invasive, pulmonary therapy for IBS was studied in the rat migrating myoelectric/motor complex (MMC) model. The therapeutic agent was ROSE-010, a GLP-1 analogue, and the test article was a dry powder formulation of ROSE-010 prepared using Technosphere® technology. This technology provides rapid systemic drug delivery by inhalation of a powder containing the drug and a novel excipient.[3-6]

ROSE-010

The chemical structure of ROSE-010 is:

His-**Val**-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-
Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly

(7 10 15 20 25 30 35 37)

- ROSE-010 is an analogue of Glucagon-Like Peptide 1 (GLP-1, 7-37), one of a family of endogenous polypeptide hormones produced in the GI tract.
- GLP-1 is a prominent inhibitor of gastrointestinal secretion and motor activity, but has an extremely short half-life (approximately 90 seconds).
- ROSE-010 has a longer half-life and duration of action because the primary structure was modified by substituting valine for alanine at position 8.
- Non-clinical and clinical studies indicate ROSE-010 given by injection relaxes smooth muscles of the gut to relieve pain associated with IBS.

Technosphere® Technology

The primary component of Technosphere® powder is the novel excipient fumaryl diketopiperazine (FDKP; (E)-3,6-bis[4-(N-carboxy-2-propenyl)amidobutyl]-2,5-diketopiperazine) (Figure 1). Technosphere® particles are prepared by the pH-induced self-assembly of FDKP nanocrystals. These microparticles have a median diameter of 2 to 2.5 µm and dissolve rapidly at physiological pH.

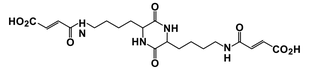

Figure 1. Fumaryl diketopiperazine (FDKP)

Preparation of ROSE-010 Technosphere® Powder

For this study, ROSE-010 was adsorbed onto Technosphere® particles to prepare an inhalation powder containing 10% ROSE-010 (w/w). (See Figure 2)

Characterization of ROSE-010 Technosphere® Powder

The ROSE-010 content of the Technosphere® powder was within 10% of target. Based on cascade impaction data (Andersen cascade impactor), at least 20% of the particles from the sample exhibited an aerodynamic diameter less than 5.8 µm (respirable fraction). (See Table 1)

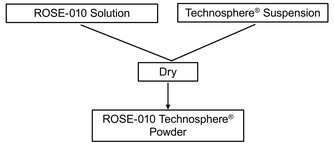

Figure 2. Preparation of ROSE-010 Technosphere® Powder

Table 1. Drug Content and Respirable Fraction of ROSE-010 Technosphere® Powder

Powder	wt%ROSE-010	Respirable Fraction
10% ROSE-010	9.1	24.4%

Scanning Electron Microscopy

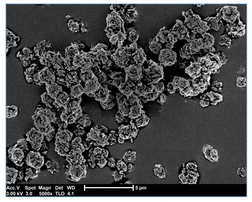

Figure 3a. ROSE-010 Technosphere® Powder at 5000x

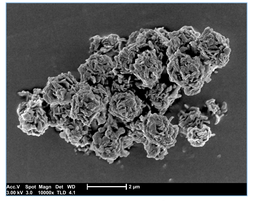

Figure 3b. ROSE-010 Technosphere® Powder at 10000x

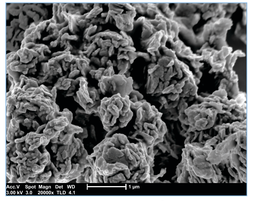

Figure 3c. ROSE-010 Technosphere® Powder at 20000x

Methods

ROSE-010 Pharmacodynamics

Migrating Myoelectric/Motor Complex (MMC) Model

The MMC represents gastrointestinal tract motor patterns observed in the fasting state of several species including rats and man.[1,2] The MMC is propagated along the gut and consists of three different phases: phase I with no myoelectric activity, phase II with sporadic irregular myoelectric activity (spikes), and phase III with regular myoelectric activity on top of each slow wave (basal electrical rhythm). Phase III occurs at regular intervals in the fasted state (rat about 15 min, man about 120 min) and these intervals define the MMC cycle length. A rat MMC model was used to evaluate the effect of ROSE-010 on gut motility following injection or pulmonary administration.

Administration of Test Articles

The animals were fasted and had a stable MMC pattern. After a control period of four MMC cycles (about 60 min), male Sprague Dawley rats received either ROSE-010 alone by IV or SC injection (0.1 mg/kg ROSE-010) or ROSE-010 Technosphere® powder by pulmonary insufflation (0.1 or 0.2 mg/kg ROSE-010). Animals dosed by injection were not anesthetized; insufflated animals were briefly (~ 4 min) anesthetized with 3–4% isoflurane to permit dosing. ROSE-010 Technosphere® powder was delivered using a Penn-Century Dry Powder Insufflator™ (Model DP-4; Figure 4).[7] After dosing, recording was continued until four more MMC cycles had been completed. Total myoelectric activity was recorded over 6–8 hours.

Figure 4. Penn-Century Dry Powder Insufflator™

Results

ROSE-010 Pharmacodynamics

Insufflation of ROSE-010 Technosphere® at a ROSE-010 dose of 0.1 mg/kg prolonged MMC inhibition (Figures 5 and 6). A similar prolonged MMC inhibition was observed following SC and IV injection of 0.1 mg/kg ROSE-010. No MMC pattern changes were observed in control animals receiving either air insufflation or injected saline. In the insufflation groups, MMC recording was interrupted briefly during the insufflation procedure.

Pulmonary insufflation of ROSE-010 Technosphere® powder (0.2 mg/kg ROSE-010) increased MMC cycle length from 18.7 ± 7.3 to 105.9 ± 9.5 min (n = 6), and 0.1 mg/kg ROSE-010 from 19.4 ± 2.9 to 102.6 ± 18.3 min (n = 3). IV or SC ROSE-010 (0.1 mg/kg) prolonged the MMC cycle from 18.3 ± 2.5 and 14.8 ± 2.0 min to 124.1 ± 27.3 and 148.1 ± 49.4 min, respectively (n = 6/group). There was no increase in MMC cycle length in animals administered air by insufflation. This study demonstrated that MMC inhibition following pulmonary insufflation of ROSE-010 Technosphere® powder is comparable to inhibition following intravenous or subcutaneous injection of ROSE-010 alone at similar doses.

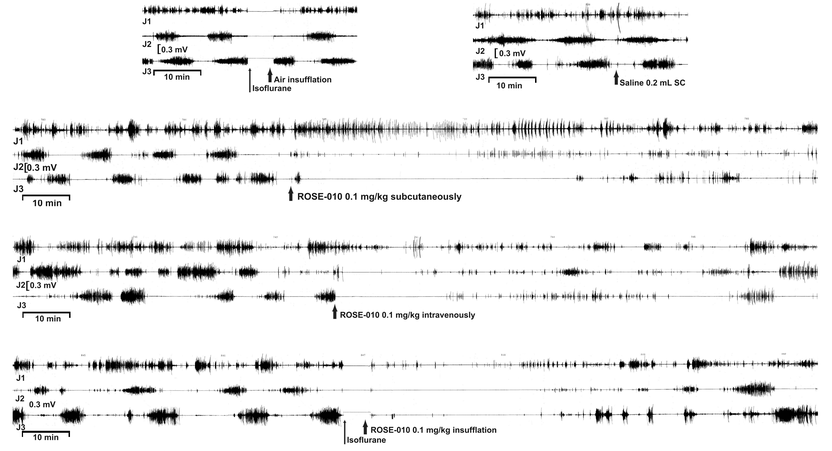

Figure 5. Migrating myoelectric/motor complex raw data from air insufflation, saline 0.2 mL SC, Rose-010 0.1 mg/kg SC, Rose-010 0.1 mg/kg IV and Rose-010 0.1 mg/kg insufflation. The electrodes implanted at 5, 15, and 25 cm distal to the pylorus correspond to recordings J1, J2, and J3, respectively.

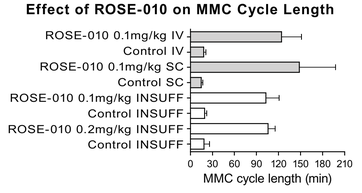

Figure 6. Duration of MMC suppression in male Sprague Dawley rats administered ROSE-010 alone by intravenous injection or subcutaneous injection or ROSE-010 Technosphere® powder by pulmonary insufflation and corresponding controls.

Conclusions

MMC inhibition following pulmonary insufflation of ROSE-010 Technosphere® powder is comparable to inhibition following IV or SC injection of ROSE-010 alone at similar doses. These data suggest that ROSE-010 administered by the pulmonary route as a ROSE-010 Technosphere® powder has potential for the treatment of irritable bowel syndrome by inhibition of gut motility.

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