ABSTRACT
An intranasal gel dosage formulation of scopolamine (INSCOP) was developed for the treatment of Space Motion Sickness (SMS). The bioavailability and pharmacokinetics (PK) were evaluated under IND guidelines. The aim of the project was to develop a PK model that can predict the relationships among plasma, saliva and urinary scopolamine concentrations using data collected from the IND clinical trial with INSCOP, and estimate the PK parameters of INSCOP described from a multiple compartmental PK model.

METHODS:

**Subjects and Treatments:**
- Twelve healthy human subjects (6 male/6 female) participated in the study, with an average age of 38.9 ± 8.1 yr., height of 175.6 ± 11.3 cm and weight of 80.8 ± 14.3 kg.
- A randomized double blind crossover study design was used with a seven-day washout period between treatments.
- All subjects were administered at three dose levels (0.1, 0.2 and 0.4 mg) of INSCOP

**PK Evaluation:**
- Serial blood samples (7 ml) were collected at 0, 0.083, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 24 h after each treatment.
- Serial saliva samples (0.4-2 ml) were collected at 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 24 hr. after each treatment.
- Urine samples for PK analysis were collected over the following intervals: Pre-dose (single void) and at intervals of 0-3, 3-6, 6-10, 10-12, 12-24 hours.
- Plasma saliva and urine samples were assayed for concentrations of INSCOP using a validated LC/MS/MS method.
- A Waters Acquity UPLC system combined with Micromass Quattro MicroTM API MS/MS detector was used, and concentrations range were between 100 and 1000 pg/mL with LLOQ of 50 pg/mL.

**PK Modeling:**
- Initial estimates of individual compartmental PK parameters were evaluated using Phoenix. Concentrations of Scopolamine (and its glucuronide metabolite) in plasma, saliva and urine were fitted simultaneously.
- Actual dosing and sampling times were used for the compartmental modeling.
- Model discrimination was performed on data using Phoenix, by minimizing the Akaike Information Criteria (AIC) and by comparison of the quality of fit plots (e.g. observed data vs. fitted, weighted residual vs. time).

RESULTS

The aim of this project was to develop a PK model that can describe the relationships among plasma, saliva and urinary scopolamine concentrations, using data collected from the IND clinical trial with INSCOP, and estimate the PK parameters of INSCOP described from a multiple compartmental PK model.

Subjects and Treatments:
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**BACKGROUND:**
- An intranasal gel dosage formulation of scopolamine (INSCOP) was developed for space motion sickness (SMS), and bioavailability and pharmacokinetics (PK) were evaluated under approved protocol in IND guidelines.
- Understanding the PK of INSCOP is crucial for the use of this drug in space.
- Pharmacokinetic modeling can be used to describe the PK of INSCOP in plasma as well as in saliva and urine over time.

**CONCLUSIONS:**
- The PK model developed for INSCOP satisfactorily estimated the PK of scopolamine in plasma, saliva and urine after administration.
- The model can be utilized to predict scopolamine plasma concentrations from saliva and urine data, which will be useful for the assessment of PK of scopolamine in space and other remote environments without requiring invasive blood sampling.
- A future objective is to use the validated model to fit data from the bed rest study to predict PK changes of scopolamine after INSCOP administration.

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