Pharmacokinetics of Scopolamine Intranasal gel Formulation (INSCOP) during Antiorthostatic Bedrest

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Introduction

- Space Motion sickness (SMS) is an age old problem for space travelers - on short and long duration space flight
- Oral antiemetics are not very effective in space due to poor bioavailability
- Scopolamine (SCOP) is the most frequently used drug by recreational travelers - patch, tablets available on the market
- Common side effects of antiemetics, in general, include drowsiness, sedation, dry mouth and reduced psychomotor performance
- Severity and persistence of side effects are often dose related
- Side effects can be detrimental in high performance demanding settings, e.g. space flight, military
The Oral Scopolamine Story

A representative saliva concentration -time profile in a crewmember

Mean Plasma concentration -time curve in normal subjects
Intranasal Scopolamine

- Oral, injectable and transdermal formulations of SCOP are either invasive, unsuitable or ineffective for the treatment of SMS
- Intranasal dosage form of scopolamine offers great promise for the treatment of MS on Earth and in space
- Advantages of intranasal dosage forms in general are:
  - Noninvasive
  - Rapid absorption facilitating rescue and treatment options with the same formulation
  - Enhanced and reliable bioavailability allowing precise and reduced dosing options
Results from a Phase I IND study showed 83% bioavailability of INSCOP versus 3.7% bioavailability of oral SCOP.

**Study Population:** 12 healthy male subjects

**Study Design:** Randomized Crossover Design

**Treatments:** 0.4 mg of IV, PO, or IN Scopolamine

**Blood Samples:** Pre-dose, 0.42, 0.83, 0.17, 0.33, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12hr post dose.

Requirements for Therapeutics in Space

- Medications used for treatment in space must be commercial products for efficacy and safety reasons.

- Investigational New drug (IND) protocols must strictly adhere to FDA guidelines for conducting Phase I - IV clinical trials to establish efficacy, safety and commercial potential.
Pharmacotherapeutics of Intranasal Scopolamine - A NSBRI sponsored Drug Development project of INSCOP

Four FDA sponsored clinical trials were designed to characterize pharmacokinetics (PK) and pharmacodynamics, and evaluate the safety and efficacy of INSCOP

<table>
<thead>
<tr>
<th>SPECIFIC AIMS</th>
<th>FDA PROTOCOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific Aim # 1: Establish PK of INSCOP with three escalating dose levels of 0.1, 0.2 and 0.4 mg</td>
<td>INSCOP 002-A: Dose Ranging PK Study (MDS)</td>
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<tr>
<td>Specific Aim # 2: Perform a dose ranging Efficacy study of INSCOP</td>
<td>Dose/ Efficacy Studies:</td>
</tr>
<tr>
<td></td>
<td>INSCOP 002-B (Dartmouth)</td>
</tr>
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<td>INSCOP 002-D (NAMRL)</td>
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<tr>
<td>Specific Aim # 3: Determine if bioavailability and PD of IN SCOP are altered in a simulated microgravity environment</td>
<td>INSCOP 002-C: Bioavailability Study during ABR (MDS)</td>
</tr>
</tbody>
</table>
Specific Aim #1: Protocol 002-A

A Phase I, Randomized, Double-Blind, Placebo-Controlled, Dose Ranging Study of Pharmacokinetics and Pharmacodynamics of Intranasal Scopolamine

- Dose escalation of INSCOP at 0.1, 0.2 and 0.4 mg dose levels
- 12 normal healthy subjects (6 male/6 female) received INSCOP in a placebo-controlled randomized crossover design
- Assessment of primary PK parameters of INSCOP as a function of dose
Results

Plasma Concentration - Time profiles of Scopolamine

- Dose=0.1mg
- Dose=0.2mg
- Dose=0.4mg
Specific Aim #2: Protocol 002-B

A Phase II, Randomized, Double-Blind, Placebo-Controlled, Efficacy Study of Intranasal Scopolamine

- Clinical efficacy study with 0.2 and 0.4 mg and INSCOP given as pre-treatment for motion sickness induced by off-axis Vertical Rotation Chair (VRC)
- 18 male/female, motion sickness susceptible subjects
- Establish concentrations of INSCOP for efficacy as well as assess PK (10 subjects ONLY) of the two doses of INSCOP
Results

Mean Plasma conc. - time profiles of INSCOP

Scopolamine conc. (pg/ml)

Time (hr)

- dose=0.2mg
- dose=0.4mg
Specific Aim #3: Protocol 002-C

**A Phase II, Randomized, Double-Blind, Bioavailability Study of Intranasal Scopolamine in a Simulated Microgravity Environment**

- Estimate the bioavailability of a 0.2 mg dose and 0.4 mg dose of INSCOP during ambulation (AMB) and simulated microgravity, Antiorthostatic Bed Rest (ABR)

- 12 normal healthy subjects (6 male/ 6 female) received INSCOP in a four-way crossover design

- Evaluate PK/PD, safety and side effect profile of the two doses during AMB vs. ABR
Results

Concentration - time profiles of scopolamine in plasma
# Primary PK Parameters

<table>
<thead>
<tr>
<th>Parameters (Mean±SE)</th>
<th>Units</th>
<th>Dose(mg)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMB</td>
</tr>
<tr>
<td>Cmax/D</td>
<td>pg/ml*mg</td>
<td>2.24±0.30</td>
</tr>
<tr>
<td>Tmax</td>
<td>h</td>
<td>1.27±0.23</td>
</tr>
<tr>
<td>AUC(_{inf}/D)</td>
<td>h<em>pg/mL</em>mg</td>
<td>9.02±1.72</td>
</tr>
<tr>
<td>(V_s)</td>
<td>L</td>
<td>578.03±93.55</td>
</tr>
<tr>
<td>(Cl_s)</td>
<td>L/h</td>
<td>141.70±16.45</td>
</tr>
<tr>
<td>(t_{1/2})</td>
<td>h</td>
<td>3.23±0.56</td>
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*P<0.05  
**P<0.005
Comparative Profiles

A

B

C

Scopolamine conc. (ng/ml) vs Time (hr)

Dose=0.2mg of A

Dose=0.2mg of B

Dose=0.2mg of C

Time (hr)
PK Results (002 A)

- Dose-related nonlinearity between 0.2 and 0.4 with clinically significant primary PK parameters, Cmax and AUC

- Dose and dosing intervals may be adjusted to account for nonlinearity at higher doses
PK Results (002 C)

- No difference between AMB and ABR in PK parameters after 0.2 mg dose

- $\text{Cls}$ decreased with a concomitant increase in $\text{Cmax}$ and $\text{AUC}$ during ABR after 0.4 mg dose

- This difference in $\text{AUC}$ and $\text{Cls}$ at the higher but not the lower dose during ABR is in agreement with the nonlinear kinetics with dose observed at these doses (002 A)

- Dosing adjustment may be required for treatment with INSCOP in space
Overall Results

- Inter-site differences in profiles - may be a result of dosing discrepancies between study sites

- The dosage form for A and B are from a different vendor than for C

- Data for all protocols (0.2 and 0.4 ambulatory) will be pooled for obtaining statistical rigor for modeling
Data Analysis in Progress

Extremely Rich data facilitating complex analysis options - Some trend analysis and interpretation currently in progress with respect to:

PK

• Gender differences

• Dose - related metabolism differences

• PK modeling combining all ambulatory subjects data

• Plasma/saliva simultaneous fitting and correlation

• Metabolite kinetics
Data Analysis in Progress

**PD** Dose - Effect analysis with

- BP, HR data
- ARES Performance Parameters
  - Reaction time
  - Accuracy
  - Short and running memory recall

PK/PD Modeling with applicable response parameters

*Stay tuned for next update!*