Intranasal Scopolamine Spray Provides Motion Sickness Protection While Demonstrating Rapid Absorption Rates and No Impact on Cognitive Performance

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BACKGROUND

- Motion sickness (MS) continues to be a problem for the modern military across the Services.
- The anticholinergic scopolamine is the most efficacious prophylaxis against MS, yet most delivery methods suffer significant drawbacks. Oral dosage suffers from significant first-pass metabolism; transdermal application requires 6-8 hours before therapeutic plasma levels are achieved; and intravenous, intramuscular, and subcutaneous routes are impractical in operation settings. All are associated with increased sedation.
- A low-dose, moderate pH aqueous intranasal formulation of scopolamine (INSCOP) was developed by the Pharmacotherapeutics Laboratory of the SK3 Human Adaptation and Countermeasures Office at NASA under Dr. Lakshmi Putcha.
- In 2011, a pilot study with 6 subjects receiving 0.2 mg of INSCOP showed rapid absorption and no cognitive or sedative effects.
- From 2014-2015, in partnership with Repurposed Therapeutics, Inc., we conducted a two-part Phase II clinical trial of an intranasal formulation of scopolamine (INSCOP): a pharmacokinetic (PK) phase aimed at identifying bioavailability parameters by repeating the pilot study with an expanded sample size, and an Efficacy phase aimed at determining INSCOP's effectiveness against MS when compared to placebo.

METHODS

- INSCOP clinical trial material was produced in two separate lots, identified by production year: 2011 and 2014. Both lots were used in each phase.
- In the PK phase (including the pilot study), 19 subjects received 0.2 mg INSCOP followed by 8 hours of cognitive assessments and monitoring.
- In the Efficacy phase, 22 subjects underwent two counterbalanced sessions of mechanical rotation approx. 40 minutes after receiving either 0.2 mg of INSCOP or saline placebo in double-blinded fashion. While rotating, subjects performed paced head tilts intended to elicit Coriolis Cross-Coupling. Beginning at 1 rpm, rotation speed increased 1 rpm potentially to a maximum of 40 rpm. End point was one minute of unabated "stomach awareness" or a full minute at 40 rpm. The two sessions were separated by a minimum of one week. Post-dose cognitive assessments and monitoring were conducted over 3.5 hours.
- Both phases used identical measurements:
  - Cognitive performance was measured using six tests from the Automated Neuropsychological Assessment Metrics (ANAM©) program. Tests included: Code Substitution – Learning (CDS), Code Substitution – Delayed Memory (CDD), Logical Relations (LRS), Matching to Sample (M2S), Running Memory (CPT), and Simple Reaction Time (SRT).
  - Subjective fatigue was measured using the Karolinska Sleepiness Scale (KSS).
  - ANAM test batteries and the KSS were applied prior to dosage, and then at 20, 65, 125, 185, and 365 minutes post-dose for PK, and at baseline, 20, 85, 125, and 185 minutes post-dose for Efficacy.
  - Vitals, blood samples, and any adverse events were collected pre-dose and at 5, 15, 30, 45, 60, 120, 180, 240, 360, and 480 minutes post-dose for PK, and at pre-dose, 5, 15, 25, 80, 100,120, and 180 minutes post-dose for Efficacy.

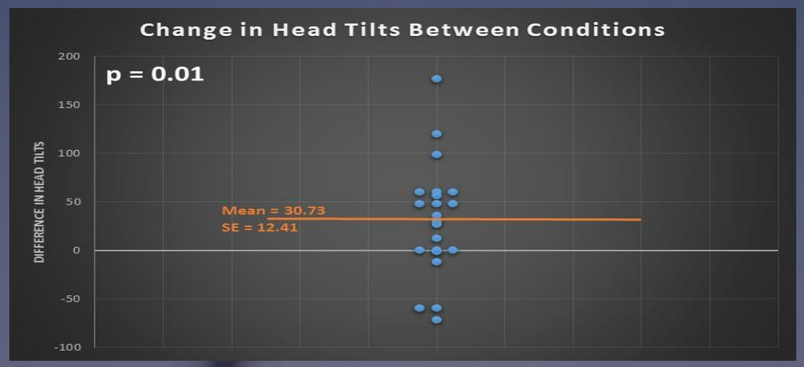

Figure 1: Change in Head Tilts Tolerated Between Conditions.

RESULTS

Efficacy – Rotation Analysis

- Figure 1 displays the mean difference in head tilts tolerated between conditions: 30.7 head tilts, SE=12.41.
- A paired samples t-test $t_{(21)}$=2.6, p = 0.01, showed a 19% increase in the number of head tilts tolerated between INSCOP and placebo.
- A Pearson correlation found a moderate positive relationship between plasma concentration levels prior to rotation and the difference in head tilts tolerated between conditions, r=.490, n=20, p=.028.

Plasma Analysis

- Two subjects each in PK and Efficacy phases were excluded from plasma analysis due to missing data.
- Figure 2 displays mean plasma concentration levels for the PK (N=11) and Efficacy (N=20) phases and by lot. Table 1 displays pharmacokinetic parameters by phase and by lot.
- There were discrepancies noted in the plasma levels by lot. Lot 2011, which was also used in the pilot study, shows consistent parameters across studies. Lot 2014, however, shows differences in plasma concentrations at multiple time points, suggesting potential errors during the manufacturing process.
- However, there was no correlation between number of head tilts and plasma levels by lot.

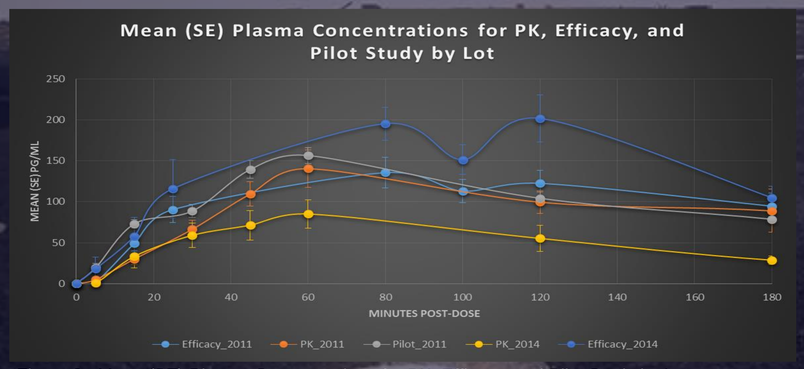

Figure 2: Mean (SE) Plasma Concentrations for PK, Efficacy, and Pilot Study by Lot.

PK						
	Total (N=11)		Lot 2011 (N=5)		Lot 2014 (N=6)	
	Mean	SE	Mean	SE	Mean	SE
Cmax (pg/mL)	117.5	17.1	156.3	21.3	85.2	17.5
Tmax (Minutes)	70.9	10.9	84	24.1	60	0
AUC (pg/ml * h-l)	320.5	178.3	455.4	159.6	208.1	99.2
Efficacy						
	Total (N=20)		Lot 2011 (N=15)		Lot 2014 (N=5)	
	Mean	SE	Mean	SE	Mean	SE
Cmax (pg/mL)	175.3	14	158.5	14.6	225.4	25.5
Tmax (Minutes)	87	8.9	82.7	11.44	100	9
AUC (pg/ml * h-l)	340.2	32.3	308.9	36.11	434.2	56
Pilot Study (Lot 2011)						
	Total (N=6)					
	Mean	SE				
Cmax (pg/mL)	165.6	22.7				
Tmax (Minutes)	57.5	2.5				
AUC (pg/ml * h-l)	500.4	61.4				

Table 1: Pharmacokinetic Parameters by Phase, Study, and Lot.

Cognitive Analysis

- As noted in Fig 3, a decline in cognitive performance was noted in both treatment and placebo following rotation which corresponded to an increase in sleepiness. However, there were no differences between treated and untreated subjects indicating that INSCOP does not significantly increase drowsiness compared to placebo.
- There was a significant interaction between condition and time for CPT, F (2.56, 53.7) = 4.49, p = .010 , driven by a mean drop in throughput score of 10.9 points in INSCOP condition compared to only 3.1 in placebo. This interaction was limited to the 5 subjects receiving lot 2014 for which manufacturing accuracy concerns exist.

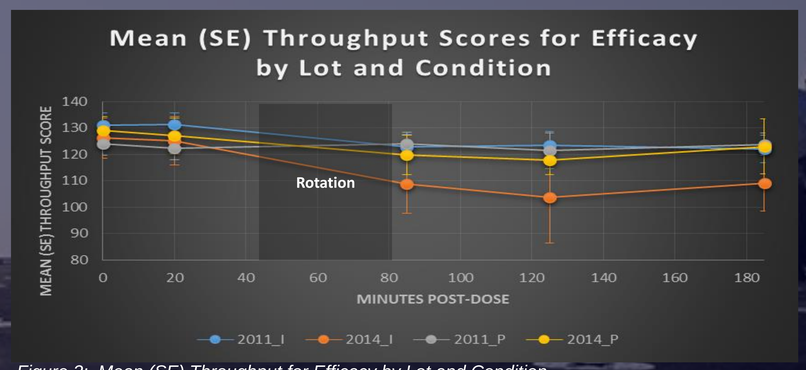

Figure 3: Mean (SE) Throughput for Efficacy by Lot and Condition.

CONCLUSION

- The results of this study indicate that INSCOP is a highly effective anti-MS countermeasure, and improves capacity to tolerate provocative motion without impacting cognitive performance or causing serious side effects.
- Evidence suggests higher plasma levels of INSCOP afford greater MS protection.
- Discrepancies in both PK and Efficacy measurements noted only in the 2014 lot reinforce the importance of attention to manufacturing processes.
- These results indicate that INSCOP may be a promising alternative to current FDA-approved formulations which often have significant cognitive impairment as a side effect.