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Dose Escalation Pharmacokinetics of Intranasal Scopolamine Gel Formulation

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Abstract

Astronauts experience Space Motion Sickness requiring treatment with an anti-motion sickness medication, scopolamine during space missions. Bioavailability after oral administration of scopolamine is low and variable, and absorption from transdermal patch is slow and prolonged. Intranasal administration achieves faster absorption and higher bioavailability of drugs that are subject to extrahepatic, first pass metabolism after oral dosing. We examined pharmacokinetics of 0.1, 0.2, and 0.4 mg doses of the Investigational New Drug formulation of intranasal scopolamine gel (INSCOP) in 12 healthy subjects using a randomized, double-blind cross-over study design. Subjects received one squirt of 0.1 g of gel containing either 0.1 mg or 0.2 mg/0.1 mL scopolamine or placebo in each nostril. Serial blood samples and total urine voids were collected after dosing and drug concentrations were determined using a modified LC-MS-MS method. Results indicate dose-linear pharmacokinetics of scopolamine with linear increases in C_{max} and AUC within the dose range tested. Plasma drug concentrations were significantly lower in females than in males after administration of 0.4 dose. All three doses were well tolerated with no unexpected or serious adverse side effects reported. These results suggest that intranasal scopolamine gel formulation (INSCOP) offers a fast, reliable, and safe alternative for the treatment of motion sickness.

Keywords

scopolamine, intranasal, pharmacokinetics, dose escalation

Of all the neurovestibular disturbances experienced by astronauts immediately after exposure to the microgravity environment of space flight, Space Motion Sickness (SMS) causes acute symptoms and discomfort requiring treatment with medications during the early, mission critical time of space flight. Nearly 40% of all medications used by astronauts during flight has been for the treatment of SMS.¹

Approximately 70% of Space Shuttle crewmembers experience symptoms of SMS during the first few days of flight. These symptoms can include malaise, anorexia, headache, lack of motivation, impaired concentration, stomach awareness, and vomiting.^{2,3} The severity of these symptoms can be debilitating and are most severe early in spaceflight beginning on the first day of microgravity and continuing for several days; later in flight, frequency of SMS and severity of symptoms appear to diminish. The frequency and severity of SMS symptoms have led to restrictions on extravehicular activities (no sooner than 72 hours after launch) and mission duration (no less than 3 days).

Astronauts use a variety of medications to prevent or reduce severity of SMS symptoms. Promethazine (PMZ) has been the primary pharmacologic countermeasure used to treat SMS since 1988 and, although effective, it has long-lasting side effects that include drowsiness and dry mouth. Seventy five percent (75%) of crewmembers who take PMZ during flight experience drowsiness.³ The sedative side effect is undesirable and potentially

dangerous during missions especially in an emergency, or during other mission-critical activities like Shuttle-station docking which demand optimal alertness and cognitive function. Similarly, another commonly used medication for motion sickness, diphenhydramine, also has sedative side effects. Although it is perceived by the crew that the benefit of PMZ treatment for SMS outweighs the risk from sedative side effects of the drug, a potential for untoward adverse event still exists.

Scopolamine is a historically known belladonna alkaloid used as an anticholinergic/antiemetic for a long time. It is a very common prescription medication for the prevention of nausea and vomiting associated with motion sickness. Earlier reports indicate that scopolamine is the most effective drug for suppressing nausea and vomiting caused by motion sickness.^{4–6} Wood and Graybiel⁷

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compared 16 drugs and drug combinations administered orally for the prevention of motion sickness induced by slow rotating room and found the most effective treatment for motion sickness to be a combination dose of scopolamine and dextroamphetamine. Another recent study also compared the efficacy of current choices of motion sickness medications and reported that scopolamine was the most efficacious treatment for suppression of both nausea and vomit reflex induced by Vertical Rotating Chair (VRC). Of the medications tested in the study, only scopolamine had a positive treatment effect of prolongation of mean duration of rotation time in the VRC. Additionally, accuracy of Delayed Matching-to-Sample Test (DMTST), a short term memory and attention test, was found to be unaffected by scopolamine whereas other medications negatively affected DMTST scores; these results confirm that scopolamine does not impair cognitive performance like the others tested in this study.⁸ Based on these scientific reports and operational experience from the Navy, NASA's Reduced Gravity Office uses scopolamine tablets (0.8 mg) and scopolamine combined with dextroamphetamine (0.8/10 mg) dispensed in a capsule for the treatment of motion sickness on board DC-9 parabolic flights, a microgravity analog environment for training astronauts and testing flight equipment.

Scopolamine has been reported to have a low absolute bioavailability of approximately 4% from an oral dose given as a tablet⁹ because of extensive first pass metabolism of the drug after oral administration. A tablet formulation, Scopase, an over the counter medication, is no longer available, and the transdermal patch is available by prescription for use by travelers who may experience low to medium severity of motion sickness. The patch is a low dose, sustained release dosage form intended for treatment over a long period of 3 days. Despite the ease of use and convenience of transdermal patches, they have been notoriously inconsistent in rate and amount of drug released.¹⁰

In addition to SMS symptoms which affect oral bioavailability of drugs, spaceflight is also known to influence gastrointestinal (GI) function by reducing GI motility.¹¹ To alleviate this reduction in bioavailability, an aqueous intranasal dosage form of scopolamine was compounded and absolute bioavailability assessed in healthy human subjects in a phase I Investigational New Drug (IND) study under FDA sponsorship. Results of this study indicated that intranasal administration of scopolamine facilitates rapid absorption with significantly higher and more reliable absolute bioavailability than an equivalent oral dose (83% vs 3.7%, $P < 0.05$).⁹ In this Phase II IND study, we examined pharmacokinetics after administration of a custom manufactured intranasal scopolamine gel formulation (INSCOP). This FDA sponsored clinical trial was designed to characterize dose linearity of INSCOP for optimizing dose range and dosing interval to facilitate clinical trials to establish

safety and efficacy of treatment for motion sickness with this IND formulation.

Subjects and Methods

The clinical protocol was reviewed and approved by the NASA Johnson Space Center Committee for the Protection of Human Subjects and the Investigational Review Board of MDS Pharma Services (Lincoln, Nebraska) where this IND clinical protocol was implemented. Twelve healthy, non-smoking human subjects between 21 and 47 years of age with matching astronaut's age group participated in the study after giving a written informed consent briefing. Subjects were brought into the MDS research clinic on the night before for an overnight stay and were given the first dose at approximately 8 AM the next morning. Subjects who had a history of nasal surgery were excluded from the study. Caffeinated beverages and grapefruit containing products were restricted during the study period. Fluid intake was monitored on study days to maintain adequate hydration.

Treatments

Two intranasal gel formulations with 0.1 and 0.2 mg of scopolamine hydrobromide in 0.1 g of gel were custom manufactured by Natestch Pharmaceuticals, Inc., Bothell, Washington and were dispensed in actuator pumps (Pfeiffer of America, Princeton, New Jersey). The carrier gel was custom compounded as a proprietary undisclosed formulation by Natestch. A fully randomized double blind crossover study design was used for drug and placebo treatments with a seven-day washout period between treatments. Each subject received three doses of scopolamine, 0.1, 0.2, and 0.4 mg and a placebo and order of treatments was randomized amongst subjects. Treatments were administered following an 8–10 hour overnight fast starting at bed time on the day before each treatment. All treatments were administered by a study nurse to deliver one squirt of the gel into each nostril; for 0.1 mg dose, subjects received a squirt of placebo in one of the nostrils.

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 into heparinized vacutainers from an indwelling catheter (Intracath[®], Becton and Dickinson, Downers Grove, Illinois) placed in the antecubital vein in the arm. Samples were gently mixed by inversion and centrifuged at 3,000 rpm to separate plasma, transferred into cryotubes, and stored frozen at -40°C until analysis.

Urine voids were collected at scheduled time intervals from 5 min to 24 h after dosing. Samples were stored frozen at -80°C until analyzed.

Sample Analysis

Concentrations of scopolamine in plasma and urine were measured by a modified LC-MS/MS method.¹² Plasma

samples were extracted with ice cold acetonitrile and drug concentrations determined using Waters[®] LCMSMS system (Waters Corporation, Milford, Massachusetts). Briefly, separation and quantitation of scopolamine concentrations in the sample extracts was achieved using a Waters Acquity UPLC system combined with Micro-mass Quattro Micro[™] API MS/MS detector using an electrospray interface. Positive ions were monitored in the Multiple Reaction Monitoring (MRM) mode. Chromatographic separation was accomplished with an Agilent Zorbax SB-CN 50 × 2.1 mm, 5 μm, column and a mobile phase of 90:10 (v/v), methanol: 2 mM ammonium acetate, pH adjusted to 5.0 ± 0.1, with a flow rate of 0.2 mL/min, injection volume of 10 μL, and run time of 4 minutes. Precision and accuracy of the assay were acceptable with $r^2 = 0.99$ or better for the linearity established by the regression of response areas across the detected concentrations range between 100 and 1000 pg/mL with LLOQ of 50 pg/mL. Inter- and intra-day coefficients of variation were below 10%. The extraction recoveries were 77.2% for 100 pg/mL and 86.4% for 1000 pg/mL and the coefficient of variation for percent extraction recovery was below 5% at all concentrations.

Scopolamine glucuronide levels in the urine were determined by difference between unconjugated and total scopolamine concentration. Total scopolamine concentration consisting of unconjugated parent drug and glucuronide conjugate was determined after incubation of samples with β-glucuronidase at 37°C for 12 h to cleave scopolamine and glucuronide before solid phase extraction.

Data Analysis

Plasma concentration versus time data were fitted to a one-compartment model using WinNonlin (version 6.3, Mountain View, CA) to estimate pharmacokinetic parameters.¹³ Area under the curve was determined by trapezoid rule by extrapolation to infinity from the last predicted time point using the terminal elimination rate. Dose linearity of area moment pharmacokinetic parameters was tested using SAS proc glm (Cary, North Carolina). Differences of PK parameters between sexes were determined using a non-parametric Wilcoxon–Mann–Whitney test, with level of significance set at $\alpha = 0.05$.

Urinary excretion data were analyzed by non-compartmental analysis using WinNonlin (version 6.3) to estimate pharmacokinetic parameters.

Results

All subjects had normal values for hepatic and renal functions (albumin, ALT, ALP, AST, bilirubin, BUN, hematocrit, GGT, urinary creatinine clearance) as well as indices of cardiovascular function (blood pressure, pulse rate). Details of subject demographics are presented in Table 1.

Table 1. Demographics of Study Subjects

Gender	Male	Female
N	6	6
Age (mean ± SD)	37 ± 8.5	29 ± 5.4
Body weight (mean ± SD)	88.7 ± 9.6	72.8 ± 14.3
Average BMI	26	

SD, standard deviation; BMI, body mass index.

Side Effects Profile

The INSCOP was well tolerated with no reports of clinically significant unexpected adverse events. Vital signs were not significantly different among treatments. The most commonly reported Expected Adverse Event was sleepiness or drowsiness which was experienced by nine of twelve subjects and this effect was not statistically correlated with dose. Three female subjects reported dizziness or lightheadedness within three hours after dosing of 0.4 mg. Two other female subjects reported nasal burning within 10 minutes after dosing, one after a 0.2 mg dose and another after the 0.4 mg dose. One female subject reported aftertaste within fifteen minutes of dosing. All of these minor discomforts were resolved within 30 minutes after dosing.

Pharmacokinetics

Mean plasma concentration versus time profiles for the three doses of scopolamine in 12 subjects are presented in Figure 1(a) and separately for males and females in Figures 1(b) and (c), respectively. Absorption of the drug was fast, reaching maximum plasma concentrations within one hour after dosing, and declined exponentially thereafter reaching concentrations below the LLOQ of 50 pg/mL in most subjects in 6 hours after the 0.1 mg dose, in 8 hours after the 0.2 mg dose, and 12 hours after the 0.4 mg dose. Increase in C_{max} and AUC were linear with dose administered (Figure 2, $r^2 = 0.99$). Mean values of pharmacokinetics parameters calculated for the three dose levels are presented in Table 2. These data suggest that there are no significant differences between sexes after 0.1 and 0.2 mg dosing. However, after administration of 0.4 mg dose, mean maximum plasma concentration (C_{max}) of INSCOP in males was lower than that in females ($P < 0.05$); clearance and volume of distribution in males were higher than in females ($P < 0.05$).

Urinary excretion rate profiles of scopolamine as a function of time after administration for all three doses are presented in Figure 3; amount excreted in the urine as scopolamine and its glucuronide metabolite after administration of the three doses are presented in Table 3. The percentage of dose excreted in the urine as scopolamine

Figure 1. Mean plasma concentration versus time profiles of scopolamine after administration of INSCOP to normal subjects (mean $\pm$ SE). (a) Mean plasma concentration profiles of scopolamine in all subjects ($n = 12$), (b) mean plasma concentration profiles of scopolamine in male subjects ($n = 6$), (c) mean plasma concentration profiles of scopolamine in female subjects ($n = 6$).

was consistent for all three doses, with less than 1.5% of the administered dose being eliminated unchanged confirming that hepatic metabolism, not renal excretion is the major pathway for elimination of scopolamine in

humans. However, the percentage of dose excreted as scopolamine glucuronide, a significant metabolite excreted in the urine was less than 5.2% of all doses, suggesting existence of other metabolites from hepatic metabolism

Figure 2. Absorption parameters of scopolamine as a function of dose after administration of INSCOP to normal subjects (mean $\pm$ SE). (a) C_{max} vs. Dose, (b) C_{max}/D (dose* body wt.) vs. Dose, (c) AUC vs. Dose, (d) AUC/D (dose*body wt.) vs. Dose.

Table 2. Pharmacokinetic Parameters of Scopolamine After INSCOP Administration to Normal Subjects

Parameters		Dose (0.1 mg)			Dose (0.2 mg)			Dose (0.4 mg)		
		All	Female	Male	All	Female	Male	All	Female	Male
N		12	6	6	12	6	6	12	6	6
C _{max}	(ng/mL)	0.1 ± 0.04	0.1 ± 0.02	0.1 ± 0.02	0.2 ± 0.07	0.2 ± 0.07	0.1 ± 0.05	0.3 ± 0.1	0.4 ± 0.07 ^a	0.2 ± 0.1
C _{max} /(D*BW)	(ng/mL)	0.7 ± 0.4	0.8 ± 0.4	0.5 ± 0.3	0.6 ± 0.4	0.8 ± 0.5	0.5 ± 0.3	0.7 ± 0.6	1.1 ± 0.7 ^a	0.4 ± 0.2
T _{max}	(h)	1.3 ± 0.4	1.4 ± 0.3	1.3 ± 0.8	1.2 ± 0.3	1.1 ± 0.3	1.2 ± 0.2	1.3 ± 0.5	1.4 ± 0.4	1.3 ± 0.6
K _a	(h ⁻¹)	1.1 ± 1.7	0.7 ± 0.2	1.4 ± 1.3	1.5 ± 1.2	1.5 ± 0.9	1.5 ± 0.8	1.5 ± 1.8	1.0 ± 0.7	2.1 ± 1.7
AUC	(h*ng/mL)	0.3 ± 0.2	0.4 ± 0.1	0.3 ± 0.1	0.6 ± 0.2	0.6 ± 0.3	0.5 ± 0.2	1.3 ± 0.6	1.6 ± 0.6	1.1 ± 0.4
AUC/(D*BW)	(h*ng/mL)	2.5 ± 1.2	3.1 ± 1.3	1.8 ± 0.8	2.4 ± 1.8	2.8 ± 2.3	1.9 ± 1.1	2.9 ± 2.9	4.3 ± 3.8	1.6 ± 0.6
Vd/F	(L)	627.6 ± 351.9	514.3 ± 425.2	763.5 ± 80.2	1146.5 ± 987.2	851.2 ± 554.3	1441.8 ± 1246.7	876.9 ± 535.9	500.0 ± 266.2 ^a	1253.7 ± 457.0
CL/F	(L/h)	442.9 ± 346.1	412.6 ± 438.6	479.4 ± 144.2	695.3 ± 795.2	570.8 ± 450.8	819.8 ± 1048.5	432.0 ± 193.5	322.8 ± 157.2 ^a	589.4 ± 88.2
T _{1/2}	(h)	1.1 ± 0.31	1.0 ± 0.2	1.2 ± 0.3	1.4 ± 0.4	1.1 ± 0.3	1.6 ± 0.5	1.4 ± 0.4	1.1 ± 0.2	1.6 ± 0.4

^aStatistically significant difference between females and males at $P < 0.05$ by Wilcoxon-Mann-Whitney test (N = 6 per group). C_{max}: maximum plasma concentration; C_{max}/(D*BW), maximum plasma concentration normalized with administered dose and bodyweight (70 kg); T_{max}: time to reach maximum concentration; K_a: absorption rate constant; AUC: area under the plasma concentration-time curve; AUC/(D*BW), AUC normalized with administered dose and body weight (70 kg); Vd/F: apparent volume of distribution; CL/F: apparent total body clearance; T_{1/2}: terminal elimination half-life; SD, standard deviation.

and/or from extra-hepatic pathways of metabolism of scopolamine in humans.

Discussion

Scopolamine is a legacy drug used for the treatment of motion sickness in the military, NASA manned space-flight program, and in the global settings as one of the first drugs approved for marketing by the US FDA. It has a long standing safety profile established in its currently marketed formulations for multiple indications with decades of post marketing drug safety evaluations. Current doses and dosage regimens of scopolamine are considered safe although care should be exercised when taking higher than recommended doses due to detrimental side effects which include drowsiness, memory impairment, dry mouth, and mydriasis.

At present, scopolamine transdermal patch is the only non-invasive formulation available on the market for the treatment of motion sickness. Doweck et al¹⁴ investigated the rate of scopolamine absorption through the skin and reported that therapeutic levels of scopolamine were achieved only 5–6 h after patch application. The main disadvantage of transdermal delivery is that therapeutic plasma levels are obtained very slowly, 6–8 h after application in the case of scopolamine.^{15–17} Thus, the use of TTS-scopolamine poses a problem when immediate treatment is required. Furthermore, the transdermal administration of scopolamine also has other limitations. For example, the peak plasma concentration (C_{max}) is not reached until 12–16 h after dosing. Moreover, this route provides unnecessary prolonged blood levels that result in a significant side effect profile which includes dry mouth, drowsiness, and blurred vision.¹⁸

Nasal administration gained attention of many pharmaceutical scientists due to its great potential utility for rapid drug delivery. It offers an attractive alternative for drugs with limited oral bioavailability that are destroyed by gastrointestinal fluids, or highly susceptible to hepatic first-pass or gut-wall metabolism.¹⁹ Results of earlier investigations from our laboratory indicated that while bioavailability of orally administration scopolamine was poor and variable, intranasal administration resulted in a fast, reliable, and more complete absorption of the drug.^{9,20} Klocker et al²¹ also reported that scopolamine nasal spray is an effective and safe treatment for motion sickness, with a fast onset of action within 30 minutes after administration. More recently, Renner et al²² also reported that pharmacokinetics and pharmacodynamics of scopolamine depend on the dosage form.

INSCOP offers less variability of systemic concentrations unlike oral administration with higher concentrations of the drug achieved more rapidly due to the fast absorption.^{9,22} The purpose of this study was to evaluate dose linearity of pharmacokinetics of this IND

Figure 3. Urinary excretion rate profiles of scopolamine after administration of INSCOP to normal subjects (mean $\pm$ SE). (a) Mean urinary excretion rates of scopolamine in all subjects ($n = 12$), (b) mean urinary excretion rates of scopolamine in male subjects ($n = 6$), (c) mean urinary excretion rates of scopolamine in female subjects ($n = 6$).

formulation for intranasal administration per FDA requirement of IND pharmaceutical preparations. This IND formulation is aimed at providing a rapidly acting, reliable, safe, and efficacious alternative for the treatment and prevention of motion sickness experienced by astronauts in space. Other target populations may be benefited from the use of this novel formulation as well, most notably, military aviators, military, and commercial seafarers. The formulation once approved for market release by the FDA is expected to facilitate administration of lower than normal therapeutic doses with no side effects in Space and on Earth.

Results of this study clearly demonstrate that INSCOP was rapidly absorbed with measurable concentrations in plasma within 5 minutes after administration of all three doses in all the subjects, reaching maximum concentrations at 1.2–1.3 hours post dose (Table 2). Absorption and bioavailability appear to be linear at the administered dose range as indicated by C_{max} and AUC (Figures 2a and 2c). Ratios of body weight normalized AUC and C_{max} with dose (Figures 2b and 2d) are consistent confirming dose linear PK of INSCOP at 0.1–0.4 mg dose range (Figure 2). These results indicate consistency of absorption and bioavailability at all three doses,

Table 3. Urinary Excretion of Scopolamine and Scopolamine Glucuronide After INSCOP Administration to Normal Subjects

Parameters		Dose (0.1 mg)			Dose (0.2 mg)			Dose (0.4 mg)		
Mean $\pm$ SD	Unit	All	Female	Male	All	Female	Male	All	Female	Male
N		12	6	6	12	6	6	12	6	6
Urinary excretion of scopolamine										
X_u	μg	1.4 ± 0.6	1.5 ± 0.5	1.4 ± 0.7	3.2 ± 1.6	3.5 ± 1.9	2.9 ± 1.0	6.3 ± 2.4	6.4 ± 1.9	6.2 ± 2.8
PDEx	%	1.3 ± 0.8	1.2 ± 0.7	1.3 ± 1.0	1.4 ± 0.9	1.5 ± 1.1	1.4 ± 0.7	1.4 ± 0.6	1.5 ± 0.6	1.2 ± 0.6
AUXu	h*mg/mL	1.3 ± 0.6	1.3 ± 0.6	1.3 ± 0.7	2.9 ± 1.6	3.1 ± 1.8	2.7 ± 1.0	6.1 ± 2.6	6.4 ± 2.0	5.9 ± 1.7
Urinary excretion of scopolamine glucuronide										
X_u	μg	4.5 ± 1.6	4.5 ± 2.1	4.5 ± 2.4	11.2 ± 7.5	14.3 ± 9.1	8.1 ± 7.6	20.8 ± 9.7	19.3 ± 4.3	22.6 ± 14.5
PDEx	%	4.5 ± 1.6	4.5 ± 2.2	4.5 ± 2.4	4.2 ± 4.0	4.9 ± 4.3	3.5 ± 3.5	5.2 ± 2.5	4.8 ± 1.1	5.6 ± 3.7
AUXu	h*mg/mL	4.2 ± 1.4	4.9 ± 2.4	3.5 ± 1.7	10.5 ± 7.2	10.9 ± 6.2	10.2 ± 4.6	21.3 ± 9.5	20.5 ± 5.0	22.1 ± 7.0

X_u , total amount excreted in the urine; PDEx, percent of dose excreted in the urine; AUXu, area under the urinary excretion rate-time curve; SD, standard deviation.

suggesting safety and reliability of treatment in this dose range without the potential for adverse side effects. Increases in both observed and derived $C_{\max}$, observed AUC at last time point along with extrapolated AUC at time infinity were also linear with dose (Table 2). This dose linearity of PK in addition to the short half-life (1.1–1.4 hours) may allow administration of multiple doses without significant side effects. Results from an earlier study by authors⁹ indicated that an aqueous formulation of INSCOP achieved higher $C_{\max}$ and AUC values, compared to those of an equivalent oral dose. Both $C_{\max}$ and AUC were higher after administration of aqueous drops compared to those in this study (1.6 ± 0.2 vs. 0.3 ± 0.1 ng/mL and 2.8 ± 0.3 vs. 1.3 ± 0.6 ng·h/mL, respectively) suggesting that the aqueous formulation may offer more efficient absorption after intranasal administration. The pH of the gel was slightly lower than aqueous drops (3.5 versus 4) which may be a reason for lower absorption from the gel since Ahmed et al²³ reported that better bioavailability of scopolamine can be achieved by increasing the pH of nasal formulations. Simmons et al²⁴ in a double blind, placebo controlled clinical efficacy trial with INSCOP using Human Disorientation Device (HDD) for inducing motion sickness in aviation candidate subjects (mean age 23.5 y), collected four blood samples over 1.5 hours post dose to estimate drug levels associated with efficacy of treatment. They reported $C_{\max}$ and AUC values of 0.15 ng/mL and 0.1 ng·h/mL, respectively. These values are lower than those from our results (0.3 ng/mL and 1.3 ng·h/mL, respectively). However, $T_{\max}$ values in both studies are similar (1.3 hours post dose). These results lead us to believe that both $C_{\max}$ and AUC may be underestimated in their study due to lack of adequate sampling duration. Additionally, age of subject population and artificial motion environment could also contribute to differences in disposition of scopolamine in the two studies.

With respect to sex differences in pharmacokinetics of scopolamine, Ebert et al²⁵ reported that $C_{\max}$ was higher in males than in females after intravenous infusion of 0.5 mg dose for 15 minutes suggesting that females may need higher doses than males to achieve minimum effective concentration. Results from our study showed sex differences in some of the parameter estimates only at the higher dose of 0.4 mg. Mean $C_{\max}$ was lower in males than in females ($P < 0.05$), concurrently, clearance and volume of distribution values in males were higher than in females ($P < 0.05$). However, no significant difference in the AUC between males and females was detected by Wilcoxon rank-sum (Mann–Whitney) test ($P = 0.08$), most likely due to the highest degree of variability observed with dose dispensed for 0.4 mg treatment with a mean dose of 0.5 ± 0.3 mg ranging between 0.3 and 1.2 mg. Men and Venitz²⁶ also reported similar sex

differences in volume of distribution and half-life with males having a 45% higher V_{dss} and a 26% longer $t_{1/2}$ than females after a 6.7 mg/kg intravenous dose. The reported sex differences in the pharmacokinetic parameters of scopolamine may be attributed to possible physical and physiological differences between sexes, e.g., body weight, ratio of muscle tissue and body fat which could influence volume distribution and clearance, and possible differences in entero-hepatic metabolizing enzymes. While these authors also reported significant age-related differences in clearance and volume of distribution with elderly subjects having higher values than those in the young attributable to changes in plasma/tissue protein binding and/or extra-hepatic metabolism, no significant difference in AUC was observed in our study when subjects were divided into two age groups of 21–29 and 33–47 years. Age range for subjects in our study was intentionally kept narrow (21–47 years) in order to match age distribution of astronaut population.

Urinary recovery of unchanged scopolamine and its metabolite, glucuronide conjugate (Table 3), suggest that hepatic metabolism may be an important pathway of elimination of scopolamine after administration. Cumulative amount of scopolamine and glucuronide conjugate excreted in the urine increased linearly with dose, with amounts excreted higher after 0.4 mg dose. Concurrently, fraction of dose excreted as scopolamine and glucuronide conjugate in the urine were consistent and were not significantly different among the three dose levels with excretion ranging between 1.3% and 1.4% for scopolamine and 4.2% and 5.2% for glucuronide conjugate (Table 3). It is noteworthy that the cumulative percentage of dose excreted as scopolamine and glucuronide conjugate in the urine accounts for less than 10% of the administered dose for all three dose levels indicating the involvement of other significant metabolic pathways for scopolamine elimination in humans. Kentala et al²⁷ reported that following incubation of urine samples with β -glucuronidase and sulfatase, total scopolamine concentrations in the urine consisting parent drug and metabolites (glucuronide and sulfate conjugates) increased almost seven times without a significant increase in parent compound concentrations at all sample collection time points for 12 hours post dosing. These results indicate that glucuronide and sulfate conjugation are important metabolic pathways of scopolamine elimination in humans. In light of the fact that only less than 5.2% dose is excreted as glucuronide conjugate in our study, it is prudent to expect that sulfate conjugation is another significant metabolic pathway of scopolamine in human subjects. These results of overall low recovery of administered dose in this study also support existence of other extra-hepatic metabolism pathways of scopolamine suggested by earlier reports on the elimination of scopolamine.²⁵ No significant difference in urinary excretion rate of scopolamine and scopolamine

glucuronide across sexes was observed which is in agreement with earlier reports.²⁵

Most pharmacodynamic studies with scopolamine thus far focused on the CNS effects of the drug. Pharmacodynamic measurements after intravenous and intramuscular scopolamine administration (0.5 mg scopolamine hydrobromide over a period of 15 minutes, and 0.5 mg in the upper right arm, respectively) indicated no interday variability of the baseline values of EEG.²⁸ Scopolamine was reported to produce a dose- and time-dependent impairment of memory and attention.²⁹ However, all of these studies used higher dose of parenteral administration. We reported significant suppression of salivary flow rate after intranasal administration of a low dose.⁹ A significant decrease in diastolic blood pressure after administration of intranasal scopolamine (0.4 mg or 0.2%) was also reported.^{24,21}

Limited information on the effective scopolamine concentrations for motion sickness treatment suggest that the mean scopolamine concentration in plasma required for seasickness prevention is 160 pg/mL.³⁰ Recent results on efficacy of INSCOP to prevent motion sickness symptoms using motion sickness simulation device HDD suggested that 0.4 mg of intranasal scopolamine delays the onset of motion sickness and that the effect is both statistically and clinically significant as indicated by significantly more head movements tolerated by subjects after receiving 0.4 mg of intranasal scopolamine than after receiving a placebo.²⁴ Klocker et al²¹ also showed that scopolamine nasal spray at a concentration of 0.2% was statistically superior to both placebo and dimenhydrinate in reducing seasickness score induced by whole body vibrations by a rotating chair. Neither of these studies, however, examined pharmacodynamics of scopolamine.

The number of intranasally administered drugs approved for marketing in the US by the FDA is limited, most of which are aqueous spray formulations, and reports on dose escalation studies in humans are available for only a handful of drugs that include sublingual desmopressin,³¹ intranasal insulin,³² nasal spray of zolmitriptan,³³ and intranasal ganirelix.³⁴

A gel formulation of Vitamin B12, Nascobol, was marketed by NASTECH which was subsequently abandoned and distributed at present as a spray formulation. Intranasal gel formulations are expected to provide increased retention time at the site of absorption, the nasal mucosal membrane, to enhance absorption and bioavailability compared to aqueous mists or sprays. However, gel formulations have inherent problems of inconsistent dose delivery resulting from sub-optimal specific gravity/viscosity characteristics and drug wastage due to priming volume requirements. Additionally, contamination with scopolamine during priming process of gel formulation can cause undesirable ocular side effects. Although the current gel formulation and the delivery devices

performed satisfactorily in the reduced gravity environment of parabolic flight suggesting that the dosage form may be suitable for the treatment of SMS, certain aspects of formulation like higher viscosity (1945–2050 cP) and lower than optimal pH are undesirable. While the current study found desirable pharmacokinetics of escalating doses of INSCOP, irregular dose delivery and excessive priming of the pump actuator required on occasions must be addressed for optimizing performance and efficacy of INSCOP.

In conclusion, INSCOP offers an attractive therapeutic alternative for motion sickness in light of its reliable and efficacious delivery characteristics in addition to being a simple and cost-effective formulation of an age-old drug with long standing safety record for use in modern medicine. It is expected that intranasal administration can provide higher concentrations more rapidly than oral doses that can enhance speed of onset and duration of therapeutic activity. Further, since nausea and vomiting are common symptoms of motion sickness, which can hinder absorption from an oral dose, exasperated by poor bioavailability due to extensive first pass metabolism after oral administration, it is hoped that treatment of motion sickness both on Earth and in space can be efficaciously managed before and after the onset of symptoms. Presently, clinical trials are underway with a modified aqueous spray formulation that will offset some of the aforementioned disadvantages encountered with the gel formulation.

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Declaration of Conflicting Interest

None of the authors has declared a conflict of interest.

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