Intranasal Scopolamine for Motion Sickness

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INTRODUCTION: Rapid onset, noninjection methods are required to provide "as needed" therapy for motion sickness. Intranasal scopolamine (IN SCOP) is attractive because it can be fast acting and work when gastric motility is slowed. Intranasal administration can provide a time to maximal concentration (T_{max}) of drugs (e.g., naloxone and midazolam) of 30 min or less. We evaluated the efficacy, pharmacodynamics, and pharmacokinetics of IN SCOP in a placebo-controlled, randomized, double-blind, dose-ranging study, and compared pharmacokinetic outcomes against other published results.

METHODS: There were 18 healthy adult volunteers (10 M, 8F) who received placebo, low dose (0.2 mg), and high dose (0.4 mg) IN SCOP intranasally using a pump device and a gel formulation. Participants rode in an off-vertical axis rotation (OVAR) chair 1.25 h after dose administration and completed neurocognitive tests to evaluate secondary drug impacts. Pharmacokinetics (PK) and pharmacodynamics (PD) were assessed in eight subjects. PK data were compared to results from previously published studies.

RESULTS: Low and high dose IN SCOP increased chair time significantly compared to placebo. No significant sleepiness or cognitive impairment was seen, likely due to the small sample size. T_{max} was long for both dosages (High dose 75.0 $\pm$ 49.4 min, Low dose 61.9 $\pm$ 37.1 min), compared to other intranasally administered drugs and some previous studies with IN SCOP. Average T_{max} was not superior to previously published values for dose-matched (0.4–0.5 mg), orally-delivered SCOP.

DISCUSSION: IN SCOP has potential as a rapid administration route for relieving MS symptoms, but more work is needed to identify optimal intranasal formulation and dispensing methods.

KEYWORDS: Motion sickness, pharmacokinetics, scopolamine, intranasal administration.

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Motion sickness (MS) reduces performance in altered motion environments (e.g., in naval, aviation, and space operations). While several pharmacologic options exist for the treatment and prevention of MS, including promethazine, meclizine, and diphenhydramine, previous findings suggest that scopolamine (SCOP) is one of the most effective drugs for suppressing MS symptoms (e.g., nausea and vomiting).[28]

Although SCOP and other MS drugs are effective when given orally, they must be administered well in advance of symptom onset because they are largely ineffective once MS symptoms have developed. If the medications are administered in advance to prevent motion sickness, some individuals may experience significant side effects (e.g., sedation) even though they might not have developed MS symptoms. Injections provide a rapid onset but require needles and training which makes them undesirable in many operational settings. Currently, a noninjectable, rapid onset treatment that can be administered immediately before entering the motion environment or once symptoms have arisen is not available. Easily administered, rapidly acting, and effective treatment with minimal side effects are therefore needed for the optimal management of MS symptoms.

Intranasal (IN) SCOP is an attractive treatment option because: 1) it has a short elimination half-life, and could be used for multiple administrations as needed; 2) it may have better bioavailability and more reliable absorption than oral

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medications, so may be more effective;[22] and 3) an intranasal dosage form could be administered and absorbed after the onset of gastrointestinal MS symptoms such as nausea and vomiting. Whether intranasal administration can provide a rapid onset comparable to injectable forms reliably, however, remains to be determined.

Scopolamine is a muscarinic, cholinergic antagonist with antiemetic, antiparkinsonian, and mydriatic effects. Although its mechanism of action for MS is unknown, SCOP likely inhibits MS by blocking cholinergic vestibular input to the central nervous system (CNS). Scopolamine acts as an unselective antagonist across all five muscarinic receptors M1 to M5. Most of the unwanted cognitive and autonomic side-effects are associated with the M1 to M3 and possibly M4 receptors, whereas it appears likely that the desired antimotion sickness action is at the M5 receptor.[15] Major side effects of SCOP include drowsiness, sedation, amnesia, euphoria, cycloplegia, risk of seizures, hallucinations, restlessness, psychosis, urinary difficulties, and the possibility of triggering acute narrow-angle glaucoma. CNS effects of the drug may also include memory impairment and reduced psychomotor performance. These adverse effects are thought to be associated with both dose and duration of drug exposure.[18]

Scopolamine hydrobromide (HBr) is available as a transdermal patch (Transderm Scōp®) for the prevention of nausea and vomiting associated with motion sickness, seasickness, and airsickness. Despite its effectiveness as a potent antimotion sickness drug, current formulations and administration methods of SCOP remain suboptimal. Intravenous injection of SCOP offers the fastest time to onset, on the order of minutes, but is invasive, and injectable formulations of SCOP are currently not readily available commercially. Transdermal applications, while effective, are slow, with the patch designed to deliver 0.5 mg of SCOP per day over a 3-d period.[3] As an oral medication, SCOP has limited use due to its poor bioavailability (e.g., due to extensive first-pass metabolism of the drug, less than 28% of an oral dose is bioavailable[21,22]) and slow time to maximal concentration (T_{max}), on the order of 30 min to 1 h.[23]

A proposed alternative route of noninvasive SCOP delivery that may offer quicker onset of symptom relief is intranasal (IN) administration.[27] Previous findings have suggested IN SCOP offers more consistent and higher bioavailability (e.g., absolute bioavailability of 83% following a single dose[22]), supporting the notion that an intranasal preparation of SCOP could significantly improve treatment delivery for MS symptoms. IN delivery also presents the possibility of circumventing the first pass metabolic breakdown of the drug encountered with oral delivery, and previous animal model studies suggest that IN administration may offer a more effective delivery pathway to the brain.[20,25] In a study applying an aqueous saline solution of hyoscine (scopolamine) directly into the nasal cavity using a blunt needle and calibrated syringe, Tonndorf et al. demonstrated that nasal administration offered faster onset latencies (as represented by saliva production impact), when compared with oral delivery.[27]

But, the question of whether IN SCOP reliably offers a rapid onset approach to motion sickness treatment remains unresolved. Some studies have shown rapid absorption and onset of action with intranasal administration, while others have not. Chinn et al. and Klocker et al. showed antimotion sickness effects of the drug within 30 min of intranasal administration.[8,16] Tonndorf et al. showed rapid effects on salivary flow with nasal drops (approximately 30% suppression within 30 min),[27] as did Putcha et al. (approximately 60% suppression in 30 min).[22] The pharmacokinetics in the Putcha et al. study showed a T_{max} for scopolamine (administered as nasal drops) of 22 min. Other studies, however, have not shown rapid intranasal absorption of the drug. Wu et al. examined the pharmacokinetics of a gel formulation and calculated a T_{max} of over an hour (78 ± 30 min) for a 0.4 mg dose,[29] which is longer than the T_{max} for oral scopolamine calculated in the 1989 Putcha et al. study (47 ± 6 min).[21] Similarly, although the Simmons et al. study had five subjects with a T_{max} under 30 min, the average T_{max} was 80 min for the remainder of participants.[26] By contrast, other medications used intranasally to provide a rapid absorption without using injections, such as naloxone or midazolam, typically show T_{max} values in the 15–20 min range.[4,17] The overall results from previous investigations show inconsistent performance for IN SCOP as a rapid onset medication, likely due to differences among studies in the formulation and administration of the drug.

The objectives of the current study, therefore, were as follows: 1) to present our experience with a gel formulation of IN SCOP and compare this to other studies; 2) to review the existing data on the onset of action of IN SCOP; and 3) to make recommendations for future studies. The ultimate goal is to help realize the therapeutic potential of this novel dosage form as a fast-acting MS treatment.

METHODS

To evaluate the safety and efficacy of intranasal scopolamine administration for the treatment of motion sickness symptoms, a phase II placebo controlled, randomized, double-blind, dose-ranging study was conducted with 18 healthy, motion-sickness-susceptible volunteers. Three treatment conditions were administered to participants: placebo, low-dose IN SCOP (0.2 mg), and high-dose IN SCOP (0.4 mg). Participants were randomized into one of six counterbalanced orderings of treatment administration and received each of the treatment doses once. Each dose was delivered intranasally using a pump device. One dose was delivered per treatment sessions, and sessions were conducted on separate days, spaced out by a drug wash out period of at least one week. In every condition, subjects rode in an off-vertical axis rotation (OVAR) chair 1.25 h after intranasal dose administration to elicit symptoms of MS.

Participants were divided into two groups: 1) in 8 of 18 subjects, efficacy of treatment, pharmacokinetics (PK), and pharmacodynamics (PD) were assessed (Group A); 2) the remaining 10 subjects participated only in the drug efficacy and

PD testing (Group B). Efficacy was evaluated by amount of run time in the OVAR chair, as a proxy for tolerance of motion sickness inducing stimulus as described previously.[6,7] PK studies were conducted through the collection and analysis of blood samples at multiple time points as described in **Table I** and **Table II**, and neurocognitive tests were administered to evaluate secondary impacts of the drug (PD measures). All research procedures were reviewed and approved by the Committee for the Protection of Human Subjects at the Geisel School of Medicine at Dartmouth. Informed consent was obtained from each subject.

To compare the results from this study to other published studies, the PK data were compared to oral PK results from studies by Putcha et al.[21] and Ebert et al.[9] as well as to PK results from other intranasal scopolamine studies.[1,12,22,26,29]

Subjects

The study population consisted of 10 male and 8 female subjects 21–49 yr of age who were susceptible to motion sickness based on answers to a motion sickness susceptibility questionnaire.[13] Subjects had no active illnesses and were not taking any medications. They were included if they had normal BMI, electrocardiogram, audiogram, neurological exam, renal function, and liver function. Individuals who were pregnant, potentially pregnant, or with a history of vertigo, Meniere's disease, labyrinthine dysfunction (or other neuro-otological diseases), hypertension, coronary artery disease, significant cardiac arrhythmia, gastrointestinal disorder, anemia, asthma, seizure disorder, narrow-angle glaucoma, urinary retention problems, tobacco use within 1 yr, alcohol or other substance abuse, allergy to scopolamine or other belladonna alkaloids, or chronic or current antihistamine use were excluded.

Procedures

The motion sickness stimulus and protocol has been described previously.[6,7] Motion sickness symptoms were produced using off-vertical axis rotation (OVAR). For each run, the chair was tilted to 15° off vertical, and accelerated at $5° \cdot s^{-2}$ to 17.5 rpm (approximately 0.3 Hz). When the chair starts rotating, subjects initially perceive rotation, but semicircular canal output returns to normal after approximately 30 to 45 s of rotation. At this point subjects generally no longer perceive rotation, but instead sense a gentle rocking motion. The frequency of this rocking motion is similar to the frequency of wave motion associated with the onset of seasickness. No provocative head motions are required, which minimizes subject fatigue and need for training. Opaque goggles were placed over subjects' eyes to minimize visual sensory stimulation. For safety, participants were restrained with a seat belt and shoulder harness, with heads secured to the headrest with a strap to prevent rapid head movements. OVAR has been shown to produce motion sickness symptoms with a high test-retest reliability.[19]

All subjects completed an initial familiarization run in the OVAR chair. Prior to the familiarization ride, subjects were informed about the symptoms they might experience, how to report their symptoms,[5] and were instructed on how and when to stop the test. During the familiarization run, they were instructed to ride in the chair until they either experienced severe nausea or felt so ill that they needed to stop, but not to the point of vomiting.

OVAR rides lasted up to 20 min, or until subjects either requested discontinuation of the test or reported they had reached a score of 10 on the subjective motion sickness ratio scale (0 = no sickness, 10 = wanting to stop the chair).[5] Severity of motion sickness experienced under different treatment

Table I. Study Procedures.

		0 h	TO 1.25 h	1.25 h	TO 12 h	
	PREDOSE TESTING	MEDICATION ADMINISTRATION	POSTDOSE, PRE-OVRC TESTING	OVRC	POSTDOSE, POST-OVRC TESTING	DISCHARGE DAY 1
Group A: Efficacy, PK, PD [*N* = 8]	Mood and effort Vital signs Adverse events Blood collection Urine collection Saliva collection ARES KSS		Vital signs Adverse events Blood collection Saliva collection KSS at 0.25, 0.5, 0.75, 1, 3, 4, 6, 8, and 24 h postdose	MS assessment Ride duration ARES, pre- and postride	Mood and effort Vital signs Adverse events Blood collection Urine collection Saliva collection ARES KSS	Discharge at 12 h postdose
Group B: Efficacy, PD [*N* = 10]	Mood and effort Vital signs Adverse events Blood collection ARES KSS		Vital signs Adverse events Blood collection KSS at 0.5 and 1 h postdose	MS assessment Ride duration ARES, pre- and postride	Vital signs Adverse events	Discharge at 3 h postdose

OVRC: off-vertical axis rotation; PK: pharmacokinetics; PD: pharmacodynamics; ARES: ANAM Readiness Evaluation System; KSS: Karolinska Sleepiness Score; MS: motion sickness.
All subjects completed baseline assessment, an OVAR ride, motion sickness assessments, and biosample collections, according to the schedule presented. Participants were divided into two groups: A (efficacy, PK, and PD testing) and B (efficacy and PD assessment only).

Table II. Data Collection Schedule.

	COLLECTION TIMES	
TEST	**GROUP A: EFFICACY, PK, PD ($N = 8$)**	**GROUP B: EFFICACY, PD ($N = 10$)**
Efficacy Data		
Subject response	Collected verbally every minute during OVAR Questionnaire completed following OVAR	
Mood and effort	Questionnaire completed predose and immediately following each ARES test	
Safety Data		
Vital signs Adverse events	Predose, postdose, immediately following OVAR, following each blood and saliva collection, and prior to discharge	Predose, postdose, immediately following OVAR, following each blood collection, and prior to discharge
Pharmacokinetic (PK) Data		
Blood collection	Predose and 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 24 h postdose	Predose, 0.5 h and 1 h postdose
Saliva collection	Predose and 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 24 h postdose	None
Urine collection	Predose, PRN voids for 24 h postdose	None
Pharmacodynamic (PD) Data		
ARES	Predose, postdose, immediately following OVAR, and following each blood and saliva collection	None
Sleep Logs/KSS	Predose, postdose, immediately following OVAR, and following each blood and saliva collection	None

Measures of efficacy, safety, pharmacokinetics, and pharmacodynamics were collected.
OVAR: off-vertical axis rotation; PK: pharmacokinetics; PD: pharmacodynamics; ARES: ANAM Readiness Evaluation System; KSS: Karolinska Sleepiness Score; PRN: as needed.

conditions was assessed through the total number of minutes subjects rode in the chair before stopping.

The effects of drug administration on cognitive performance and neurological functioning was assessed using the Automated Neurological Assessment Module (ANAM™) Readiness Evaluation System (ARES®),[10] and the Karolinska Sleepiness Score (KSS), a subjective measure of sleepiness and alertness.[2] Specific components of the ARES® cognitive battery used in the side-effect analysis included: Simple Reaction Time (SRT), Running Memory (RM), and Matching to Sample (MRT) ARES®. The analyses of Simple Reaction Time (SRT) included the following variables: mean reaction time (MRT), throughput (TP) and impulsivity (IMP). Variables included in the analyses of Matching to Sample and Running Memory included MRT, percent correct (PC) and TP. Subjects completing ARES testing underwent three training sessions to become familiar with the ARES software and answered questions regarding their mood and perceived effort required to complete tasks following each ARES testing session. ARES test results were evaluated using the ARES Data Man© software (Activity Research Services, Chula Vista, CA).

Intake CBC and chemistry laboratory tests were done for inclusion screening only. Blood samples and other tests were collected according to the schedule in Table II, and results were recorded on case report forms (CRF) for each participant. Blood samples (7 ml) were collected into heparinized vacutainers from an indwelling catheter (Intracath ®, Becton and Dickinson) placed in the antecubital vein of the arm. Urine and saliva samples were also collected but are not included in this analysis.

The participants were randomized to receive a series of three medication doses (placebo, 0.2 mg IN SCOP, and 0.4 mg IN SCOP) separated by a drug washout period of no less than one week; this interval also helped prevent habituation to the rotating stimulus. Both study administrators and study participants were unaware of the dose of study medication administered. Intranasal scopolamine hydrobromide formulation used in this study was a glycerin-based gel obtained from Nastech Pharmaceuticals, Inc., Bothell, WA, in strengths of 0.1 mg/0.1 g gel (pH 4.0) and 0.2 mg/0.1 g gel (pH 3.5). No detergents or dispersive agents were included in the formulation. Subjects received each of the treatment doses once in a divided dose with one pump of the gel being administered in each nostril (i.e., one pump in each nostril of the 0.1 mg/0.1 gel for the 0.2 mg dose, and one pump in each nostril of the 0.2 mg/0.1 gel for the 0.4 mg dose). The operators were instructed to deliver the squirts of the gel at least 1 centimeter into the nasal passage. Actuator pumps for delivery of the study medication were also obtained from Nastech Pharmaceuticals Inc. Study medication was stored at room temperature (25°C) and protected from light.

The initial plan was to begin OVAR 30 min after drug administration. During pilot testing, however, the pilot subjects were not experiencing dry mouth or motion sickness relief 30 min after taking the medication. To compensate for this, the protocol was changed to start the chair rides 1.25 h after drug administration. Any symptoms that developed after OVAR or medication administration were followed until the subject returned to baseline. All subjects also completed motion sickness assessments and PD assessments (ARES cognitive performance testing and KSS measure of sleepiness and alertness). In addition to the efficacy and PD testing described above, 8 of the 18 subjects (Group A) also underwent additional testing to study the pharmacokinetics (PK) of INSCOP (Table I). For these participants, blood samples were taken at 12 time points throughout the study session (Tables I and II).

For all 18 study participants, safety parameters, including incidence of adverse events (AE) and monitoring of vital signs, were recorded pre- and postdosing and prior to discharge. Vitals signs included temperature, blood pressure, respiratory rate, and pulse, which were measured using a Critikon Dinamap 1846-SX device (Critikon, Inc). Subjects remained at the study site until 3 h postdose or until the completion of the 12-h

and 24-h postdose data collection, and all subject were examined by a physician prior to discharge.

Statistical Analysis

Three categories of analyses were conducted on the data collected in this study: 1) efficacy exploration, comparing mean time in the OVAR under placebo, high dose IN SCOP, and low dose IN SCOP administration conditions; 2) pharmacodynamic (PD) analysis, to evaluate the extent of drug-related side effects experienced, including impacts on cognitive performance (ARES) and drowsiness (KSS); and 3) pharmacokinetics (PK), to establish peak drug concentration levels (C_{max}) and time to peak serum drug concentration, T_{max}, for the two SCOP treatment dose conditions. The scopolamine versus time blood sample data were analyzed using a noncompartmental model for the estimation of PK parameters using MATLAB® Simbiology 2018b.

For efficacy and PD data, two-way, repeated measures Analysis of Variance models (ANOVAs) were used to compare results for placebo, and low and high doses of SCOP across all variables of interest, with follow-up paired-samples *t*-tests used to decompose omnibus ANOVA findings. For PK parameters, pairwise *t*-tests compared T_{max} and C_{max} for the high and low SCOP dose administration conditions. To compare the PK results between study conditions, pairwise *t*-tests were used for T_{max} and C_{max} values. A series of mixed two-factor ANOVAs were conducted to analyze data collected from the ARES® cognitive battery to examine the side-effect profiles of each treatment condition over time. Each analysis possessed one within subject variable, (Time) and one between subject variable (Treatment). These analyses were done using SPSS, version 25.

All statistical tests are reported two-tailed with α at 0.05. Where necessary, Greenhouse-Geisser corrections were applied when sphericity could not be assumed (Mauchly's sphericity test < 0.05).

RESULTS

Eight women and ten men participated in this study, and mean age of all participants was 32.6 yr (SD = 5.9 yr). Participants reported an average motion sickness susceptibility quotient (MSQ) of 43.5 (SD = 18.7), corresponding to a rating of moderate susceptibility to motion sickness.

The volume of drug actually administered per trial was calculated by weighing the administration pump syringe before and after IN delivery. Average administered dose was 1.2 g across all trials, with an SD of 0.5 g.

We determined the efficacy of IN SCOP to prevent or alleviate MS symptoms by comparing mean time in the OVAR for placebo and at different IN SCOP dose levels. Results showed that administration of both low and high IN SCOP doses significantly increased the time in the chair (M = 10.2 min, SD = 6.9 min; M = 10.6 min, SD = 5.9 min, respectively) compared to placebo (M = 7.6 min, SD = 5.4 min), [$F(1.71, 29.05) = 3.47$, $P = 0.05$]. No significant difference in chair time was observed between high dose IN SCOP and low dose IN SCOP [$t(17) = -0.32$, $P = 0.75$]. The effect size for the changes (d) was $d = 0.53$ for high dose and $d = 0.42$ for low dose. For comparison, Golding et al. examined the effect size for motion sickness relief using scopolamine in parabolic flight, which was $d = 0.6$.[14]

Sleepiness was measured using the KSS rating scores, and cognitive impairment was assessed with response time on the ARES task. There was no significant difference in perceived sleepiness ratings between conditions, and the Time × Treatment interactions for Simple Reaction Time (MRT, TP, and IMP), and Matching to Sample and Running Memory (MRT, PC, and TP), were not significant. Despite the lack of significant results among these analyses, insufficient statistical power for the neurocognitive data precludes strong statements regarding the absence of treatment-related cognitive effects.

Pharmacokinetic (PK) parameters of IN SCOP at high and low doses were examined in a subgroup of participants ($N = 8$) and are summarized in **Table III**.

Peak plasma concentration (C_{max}) of SCOP was greater for high dose (M = 273.6 pg · ml^{-1}, SD = 127.6 pg · ml^{-1}) as compared with low dose (M = 136.8 pg · ml^{-1}, SD = 67.2 pg · ml^{-1}), [$t(7) = -3.377$, $P = 0.01$]. The mean time to reach peak plasma concentration (T_{max}) tended to be later for high dose (M = 75.00 min, SD = 49.43 min) than for low dose IN SCOP (M = 61.88 min, SD = 37.12 min), though this difference was not significant [$t(7) = -0.70$, $P = 0.51$]. **Fig. 1** shows the pharmacokinetic results graphically. No subjects had a $T_{max} < 30$ min for either high dose or low dose. The variability of the absorption is also apparent. In general, high dose led to higher C_{max} levels but this was not always true (subjects 2 and 6). For some individuals the absorption was very slow (subjects 1 and 15 low dose).

When compared to T_{max} of dose matched (0.4–0.5 mg) orally delivered SCOP from the published literature ($N = 5$, M = 46.92 min, SD = 42.14 min, Putcha et al.[21]; $N = 14$, M = 23.50 min, SD = 8.20 min, Ebert et al.[9]), IN delivery via gel formulation did not offer significant improvement in T_{max} [$t(11) = 1.05$, $P = 0.32$, when compared with the Putcha et al. data], and in fact in some cases performed significantly worse [$t(20) = 3.88$, $P < 0.001$, as compared with the Ebert et al. findings] (**Table IV**). The T_{max} findings were also comparable to other intranasal studies using a gel formulation.[26,29]

DISCUSSION

IN delivery of SCOP was shown to be effective in alleviating MS symptoms, as measured by chair time, even at a level (0.2 mg) lower than current standard therapeutic doses of scopolamine (1.5 mg transdermal and 0.4–0.8 mg oral). IN SCOP was also associated with minimal neurocognitive side effects (e.g., sleepiness and cognitive impairment), although the sample size was limited and changes could have been missed. From other studies, scopolamine is well known to produce unwanted side-effects such as drowsiness and reduced cognitive performance.

Table III. Overall Results for Group A Alone (Efficacy, PK, PD Data Group, $N = 8$).

SUBJECT ID	CHAIR TIME PLACEBO (min)	CHAIR TIME HIGH DOSE (min)	CHAIR TIME LOW DOSE (min)	C_{max} HIGH DOSE ($pg \cdot ml^{-1}$)	C_{max} LOW DOSE ($pg \cdot ml^{-1}$)	T_{max} HIGH DOSE (min)	T_{max} LOW DOSE (min)
1	15	20	20	169.5	54.5	120	120
2	2	7	4	98.5	99.9	45	45
4	8	20	20	377.2	270.4	30	60
6	9	5	10	173.0	156.2	30	45
10	4	7	3	239.6	151.7	120	45
13	4	10	7	473.5	128.8	60	180
15	17	20	20	376.1	161.6	45	45
17	4	8	4	281.0	70.9	45	60
Average	8	12	11	273.6	136.8	62	75
Standard Deviation	5.5	6.7	7.8	127.6	67.2	37.1	49.4

The chair time data for all 18 subjects is presented in the text. Chair time, C_{max}, and T_{max} are presented for each subject across the two dosage conditions (high, low). A high degree of variability was observed in both C_{max} and T_{max}.

Consistent with other studies using this gel formulation, however, this study did not demonstrate a faster time to maximal concentration for IN SCOP (mean T_{max} was over an hour) when compared with other established routes of administration for scopolamine, or compared with other intransally administered drugs (e.g., naloxone, midazolam).[4,24] Several possible reasons exist for these findings.

First, there were technical factors in this study that contributed to variability. The volume of drug delivered via the pump dispenser varied considerably across participants. This may have been reflected in the variability observed in the plasma levels of the drug, suggesting a high degree of variability in both the amount of drug delivered and the amount absorbed (Table III). Once the gel was administered, the amount of the drug that was absorbed through the nasal mucosa vs. the amount that was swallowed and absorbed through the gastrointestinal tract could not be determined. But, the fact that the T_{max} values were similar to oral administration, and that some T_{max} values were 2 h or longer, strongly suggest that at least some of the drug was absorbed through the gastrointestinal tract rather than through the nasal mucosa.

PK parameters may offer further evidence that the administration method was not effective for delivering SCOP to the nasal mucosa. Some studies of intranasal administration have shown two peaks in the PK data with the first peak thought to represent nasal absorption and the second later peak representing uptake from the gastrointestinal tract.[11] Our data did not demonstrate the two-peak time course associated with initial drug absorption by the nasal mucosal membrane followed by gastrointestinal absorption. Instead, we observed a single concentration peak in our PK analysis, which aligned more closely with expected time courses for oral SCOP, supporting the hypothesis the administered drug may have been absorbed gastrointestinally (i.e., flowing down the back of the throat), rather than being primarily absorbed through the nasal mucosa. It is also possible that an early peak might have been missed due to the sampling time intervals used.

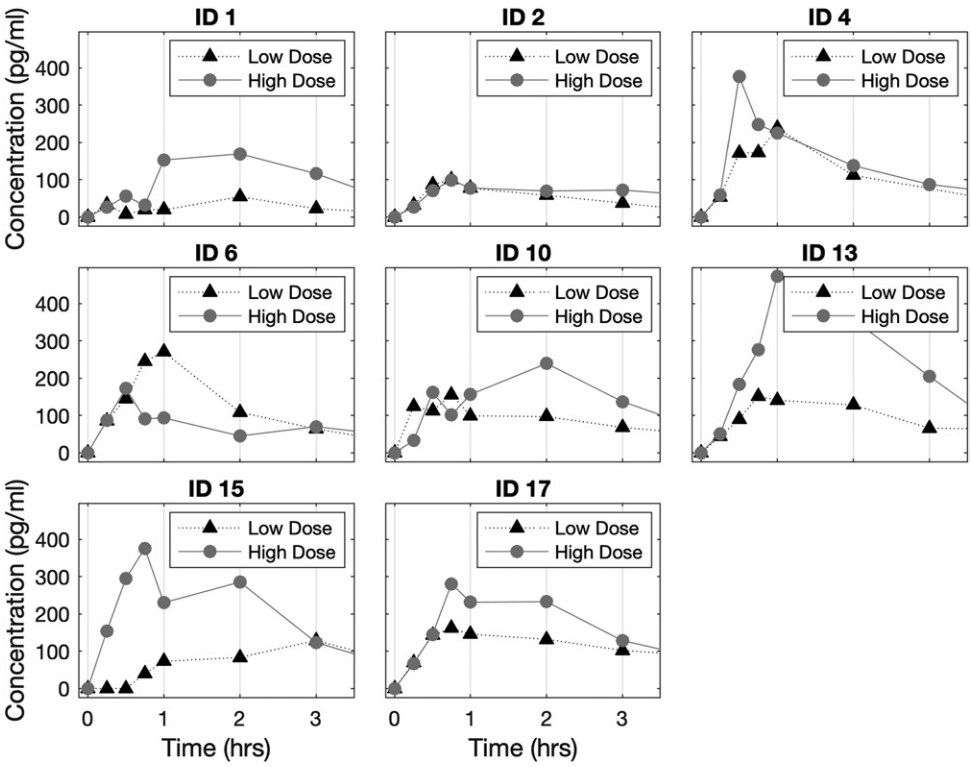

Fig. 1. Scopolamine vs. time blood sample data for the 8 PK subjects. No subjects had a $T_{max} < 30$ min for either high dose or low dose showing that the goal of rapid absorption was not achieved. Two subjects had higher C_{max} levels with low dose rather than high dose (ID2 and ID6), and for some individuals the absorption was particularly slow (ID1 and ID15 low dose).

The importance of the delivery method has been seen in other studies. Tonndorf showed a slowed onset of action when the

Table IV. Comparison of the Pharmacokinetic Parameters from Studies on Intranasal and Oral Scopolamine.*

STUDY	*N*	FORMULATION	MODE OF ADMINISTRATION	LARGEST DOSE	T_{max} (minutes)	C_{max} (pg · ml^{-1})	NOTES
				–Oral–			
Putcha, 1989[21]	5	Tablet	Oral	0.4 mg	47 ± 42	529 ± 245	
Ebert, 2000[9]	14	Solution	Oral	0.5 mg	24 ± 8	540 ± 10	
				–Intranasal–			
Tonndorf, 1953[27]		Aqueous	Drops	0.6 mg			30% salivary suppression in 30 min
Putcha, 1996[22]	12	Aqueous	Drops	0.4 mg	22 ± 3	1680 ± 230	
Ahmed, 2000[1]	18	Aqueous	Spray	0.4 mg	8.8 ± 2.5	1380 ± 473	pH of 9
Simmons, 2010[26]	16	Gel	Nasal pump	0.4 mg	80 ± N.A.	156 ± 105	T_{max} for 11/16 subjects
Wu, 2015[29]	12	Gel	Nasal pump	0.4 mg	78 ± 30	300 ± 100	
Geyer, 2017[12]	11	Aqueous	Spray	0.2 mg	71 ± 36	118 ± 57	

* For comparison, the T_{max} of an oral dose of 0.4 mg scopolamine has been estimated at 47 min with a C_{max} of 529 pg · ml^{-1}.[21]

administration method for IN delivery was changed from an inserted dropper targeting deeper nasal passages to a spray bottle,[27] suggesting that when a drug formulation is not delivered beyond the anterior chamber of the nose, it does not reach the mucous membranes as readily. Large drops may form at the site of immediate contact, which may be carried down the throat. The gel formulation used in this study may not have penetrated deeply into the nasal passages and may not have had sufficient contact with the nasal mucosa. The problems with spray administration are also evident in Table IV. Geyer et al. used a spray in their study of aqueous intranasal scopolamine but the T_{max} did not differ from the results in this study or from others that used the gel formulation. Ahmed, however, achieved very rapid absorption using a nasal spray, suggesting that achieving rapid absorption with a spray is achievable,[1] but this may depend on several factors such as the depth of penetration of the spray nozzle, the velocity of the spray, and particle size. The formulation of the scopolamine is also likely to be important.

Tonndorf et al. showed that the use of a detergent improved scopolamine absorption from the nasal mucosa.[27] They hypothesized that the detergent helped to disrupt the endonasal mucosal film and so permitted better absorption. Ahmed et al. showed that pH was also a factor. They examined aqueous formulations with pH values of 4.0, 7.0, and 9.0. T_{max} improved with increasing pH, perhaps due to effects of pH on the solubility of scopolamine.[1] Klocker et al. formulated a nasal preparation of scopolamine dissolved in a neutral oil to improve the stability of the formulation over time.[16]

While current IN SCOP formulations and administration methods are not yet optimized, the potential still exists for IN delivery of SCOP to provide rapid motion sickness relief. Current published data suggest that a formulation with a high pH delivered in a way that maximizes contact with the nasal and pharyngeal mucosa would be optimal. This approach to treating motion sickness may have valuable implications for naval and aviation operations, for astronauts transitioning across different gravity environments, and for commercial spaceflight, but more work is needed to identify optimal intranasal formulations and dispensing methods.

In conclusion, in this study, we evaluated the efficacy, pharmacodynamics, and pharmacokinetics of an intranasal delivery approach for administering scopolamine for the fast-acting relief of motion sickness symptoms. While IN SCOP was shown to be efficacious for the alleviation of motion sickness, even at low dosage levels, T_{max} did not outperform previously published values for oral administration or for some previous intranasal studies using drops or sprays. The formulation and delivery method are key factors for successful, reliable intranasal administration, and future work should focus on depth of administration, particle size, spray velocity, and other factors.

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