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EFFICACY OF INTRANASAL SCOPOLAMINE GEL FOR MOTION
SICKNESS TREATMENT IN AVIATION CANDIDATES

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Executive Summary

Introduction: Motion sickness in astronauts, aviators, and military personnel often leads to decrements in operational performance. Scopolamine administered as oral and transdermal formulations has been minimally effective due to slow absorption, low bioavailability, and unpredictable therapeutic effect. Results from preliminary studies indicate that intranasal scopolamine (INSCOP) has faster absorption, higher bioavailability and reliable therapeutic index than oral or transdermal forms and may be used for both prophylaxis and rescue. The objective of this study was to determine the efficacy of INSCOP for the treatment of motion-induced sickness in a simulated/analog environment, and to estimate the rate of absorption.

Method: After completing baseline physiological (heart rate and blood pressure), biological (blood samples) and cognitive assessments, 16 motion sickness susceptible aviation candidates were given 0.4 mg of INSCOP and a placebo in a randomized, crossover design. Subjects experienced Coriolis cross-coupling in a staircase progression, beginning with one rpm, which continued for 40 minutes or until moderate nausea was reported. Each of the two sessions was scheduled at least one week apart to prevent motion adaptation. After exposure to the provocative motion stimulus, subjects provided iterative physiological, biological, cognitive, and subjective sleepiness assessments, for the remainder of the testing period. Efficacy was determined by the number of head movements tolerated between treatment and placebo conditions. Physiological side effects were determined by changes in heart rate and blood pressure for each treatment over time, and scopolamine absorption was estimated by blood assay. Cognitive performance changes were determined from scores on the ANAM[®] Readiness Evaluation System (ARES[®]) cognitive battery and a delayed recall task from the ANAM[®] 4th edition. Medication side-effects were assessed from scores on the Karolinska Sleepiness Scale (KSS) and self-reports of adverse events. **Results:** Analysis indicates that subjects tolerated significantly more head movements after treatment with intranasal scopolamine compared to placebo, ($M = 45.19$, $SD = 81.93$), $t(15) = 2.21$, $p < .05$. Analyses conducted on systolic blood pressure showed no significant effects, however, analysis of diastolic blood pressure did show that participants have significantly lower diastolic blood pressure after administration of INSCOP when compared to placebo, $p < .05$. Analysis of heart rate revealed significantly lower heart rates among participants who were given intranasal scopolamine at certain time points when compared to participants who were given a placebo, $p < .05$. Blood concentration levels of scopolamine over time are also provided. The analyses revealed no significant cognitive performance effects over time between the placebo and treatment condition for the ARES[®] battery or for the code substitution test (delayed recall) included from the ANAM[®] battery, $p > .05$. Likewise, the analysis conducted on self-report of sleepiness (KSS) revealed no significant differences between treatment conditions. **Conclusions:** Intranasal scopolamine is efficacious for the treatment of motion sickness in susceptible individuals, with no significant cognitive or sedative effects, and offers an excellent alternative for use in dynamic operational environments.

Introduction

Motion sickness is a malady that affects military personnel in numerous dynamic training and operational settings. A review of the historic records for military Student Naval Aviators (SNA) and Student Naval Flight Officers (SNFO) indicates that 10-38% of SNA and approximately 50% of SNFO show some degree of airsickness during training with concomitant decreases in flight performance ratings (Banks, Salisbury & Ceresia, 1992; Dobie, 1974; Money, 1970). In addition, motion sickness has historically been the stated cause of attrition for an estimated 1% percent of SNA and 5% of SNFO (Banks et al., 1992; Brand, 1970; Chinn, 1951; Dobie & May, 1994; Hixon, Guedry & Lentz, 1984; Jones, Levy, Gardner, Marsh, & Patterson, 1985; Money, 1970; Royal, Jessen & Wilkins, 1984; Ryback, Rudd, Matz, Jennings, 1970; Wood, Graybiel, McDonough, Kennedy, 1965). More recent attrition statistics for SNA and SNFO training show that motion sickness accounted for as much as 16% of attrition during Fiscal Year (FY) 2003- FY 2007, with an average financial loss of \$160K and \$115K per attrited SNA and SNFO, respectfully (Arnold & Phillips, 2009). In military operational settings, whether over land or water, and in related occupations such as astronauts, the detrimental effect of motion sickness on cognitive and physical performance has also been well documented (Cowings, Toscano & DeRoshia, 1998; Cowings, Toscano, DeRoshia & Tauson, 1999; Davis, Vanderploeg, Santy, Jennings & Stewart, 1988; Heer & Paloski, 2006; Reschke et al., 1998; Rickert, 2000; Stevens & Parsons, 2002).

Oral or transdermal scopolamine is the standard prescriptive therapy for motion sickness in naval training and military operational environments (Ambrose et al., 1991). Although not the first line of defense, oral scopolamine is an option for U.S. astronauts suffering from space motion sickness. Successful treatment with scopolamine is directly related to the speed of medication onset and optimal dosing. Several studies have shown that oral scopolamine preparations are not rapidly absorbed and also have significant first-pass effect resulting in relatively low bioavailability. Further issues with oral scopolamine include slow onset of symptom relief and, if administered after symptom onset, loss of medication during emesis (Putcha, Cintron, Tsui, Vanderploeg, & Kramer, 1989; Putcha et al., 1996; Renner, Oertel & Kirch, 2005; Tonndorf, Hyde, Chinn, & Lett, 1953). Transdermal delivery of scopolamine delays the time to reach peak plasma levels, an average of 8 hrs compared to 60-90 minutes with oral, and reported side effects are often severe with significant detrimental impacts on physiological and cognitive parameters (Fung, Ho, Lee, Manaretto & Tsai, 2003; Nachum et al., 2001; Parrott 1986; Parrot, 1989; Renner et al., 2005).

Intranasal administration of scopolamine has shown promise for achieving rapid absorption and onset of medication effect, superior efficacy, and increased bioavailability (Chinn, Hyde & Milch, 1955; Chinn, Milch & Dugi, 1953; Hyde, Tonndorf & Chinn, 1953; Putcha et al., 1996; Simmons, Phillips, Lojewski, & Lawson, 2008; Tonndorf et al., 1953). Military research laboratories examining motion sickness countermeasures in the 1950's tested intranasal scopolamine (INSCOP) in spray and liquid formulations and found rapid absorption of scopolamine, rivaling intravenous injection, with a significant increase in effectiveness when compared to oral scopolamine and placebo (Chinn et al., 1955; Chinn & Smith, 1953; Hyde et al., 1953, and Tonndorf et al., 1953). A similar, but separate study conducted by Chinn et al., (1955)

tested the efficacy of intranasal scopolamine after symptom onset in flight. Chinn used military aircraft to provide the standardized flight profile, with subjects being treated 15 minutes after take-off, a time based on previous flights where no vomiting would have occurred, however, vasomotor disturbances and nausea would be present. The data clearly showed that intranasal administration given after symptom onset significantly reduced the incidence of vomiting, while oral administration was deemed “ineffective”. Due to a lack of precise dosing control and objective measures of absorption, intranasal testing of scopolamine was shelved for almost 40 years.

Work with intranasal scopolamine resumed with a pharmacokinetic study by Putcha and colleagues in 1996. The study compared the bioavailability of 0.4 mg doses of oral, intravenous, and intranasal scopolamine (liquid drops) with similar results to studies previously cited. Intranasal scopolamine had a rapid rate of absorption (mean absorption rate of 0.37 hrs) and the onset, duration, and magnitude of effect more closely resembled intravenous dosing than oral. In 2000, Ahmed et al., evaluated the effects of pH and dose on the absorption of intranasal scopolamine. The study assessed two doses of intranasal scopolamine (0.2 mg, and 0.4 mg) at three pH levels (4.0, 7.0, and 9.0) and found similar rates of absorption as Putcha et al., (1996). A review of the literature revealed two recent studies that tested intranasal scopolamine in a provocative motion environment. Klocker, Hanschke, Toussaint, and Verse (2001) dosed subjects 30 minutes prior to exposure in a rotating chair with 0.1% or 0.2% of scopolamine hydrobromide or placebo. The experimenters collected seasickness scores (SKS) every minute for five minutes and found that the 0.2% formulation was more efficacious than placebo in deterring motion sickness symptoms. In the second study, Buckey, Alvarenga, Mackenzie, Wang, and Das (2008) tested intranasal scopolamine gel in two different dosages (0.2 and 0.4 mg) and reported a significant increase in stimulus duration tolerated for both intranasal doses compared to placebo. Results from recent efficacy studies, in combination with early intranasal work, indicate that nasal administration of scopolamine may provide a mechanism for more rapid drug absorption, increased efficacy at lower dosing, ease of use in dynamic, operational environments, and possible use as rescue therapy.

The objectives of the present study were to determine the efficacy of a 0.4 mg dose of intranasal scopolamine gel as a countermeasure for motion sickness and to determine the potential cognitive and medication side effect profile.

Method

Subjects

Sixteen aviation candidates (13 male and 3 female) with a mean age of 23.5 (SD = 2.96) volunteered to participate in the study. Descriptive statistics for all subjects are shown in Table 1. The study protocol was approved by the Naval Aerospace Medical Research Laboratory, Institutional Review Board and written informed consent was obtained from each volunteer prior to participation. All participants were healthy, aviation candidates possessing a current flight physical and who were at least minimally susceptible to provocative motion as evidenced by a minimum score of 3.0 on the Motion Sickness Susceptibility Questionnaire (Appendix A).

Participants were additionally screened for any health-related habits or problems that would exclude them from a medication or motion study and were asked to refrain from the use of any alcohol, tobacco products, herbal supplements, and prescription or over the counter medications while taking part in the study (Appendix B). Female participants were given a urine pregnancy test upon arrival at the laboratory on both test days and were excluded if a positive result was indicated.

Motion Stimulus

The Human Disorientation Device (HDD) provided passive, Coriolis cross-coupling stimulation by rotating the subject about the earth's vertical and horizontal axes in combination (Hixon & Niven, 1969). Subjects sat in a chair, which was located inside a metal sphere, and were restrained with an aviator-style 4-point seat belt and a padded head fixture to prevent extraneous movement and to ensure head-centered movement during rotation. The subject's gaze was directed to a black visual field inside the device. The staircase profile of counter-clockwise rotation about the vertical began with a velocity of one rpm and increased in increments of one rpm/min, while rotation about the horizontal consisted of a 40° roll to the right, back to center, then left in a 3 second/direction sequence (Stott, Barnes, Wright, & Ruddock, 1989). A roll to the right and back to center constitutes one head movement. At the end of each minute, the horizontal rolls paused for 12 seconds to allow symptom collection and then automatically continued rotation at one rpm greater than the previous minute. During symptom collection, the subjects were asked to rate several standard motion sickness symptoms as minimal, moderate, or major. The motion sickness endpoint for test termination was a self-report of moderate nausea that persisted for one minute or a maximum rotational speed of 40 rpm. The staircase profile and the HDD have been used in previous studies, and have been successful in provoking motion sickness symptoms in 93% of research subjects (Simmons et al., 2007). In the current study, the test-retest correlation, with at least 1 week between sessions, was $r = .74, p < .001$.

Drug preparation

The intranasal scopolamine gel and intranasal placebo gel preparations were provided by the Pharmacotherapeutics Laboratory, Johnson Space Center, Houston, TX. Study medications were blinded and delivered in individual vials with pre-marked participant numbers. Physiochemical properties for intranasal scopolamine gel; scopolamine hydrobromide trihydrate, MW = 438.33 g/mole, pH = 3.5/0.2 mg dose, pKa = 7.55 @ 23° C. The intranasal placebo was a saline-infused gel. The dose selection of 0.4 mg, versus the typical oral dose of 0.8 mg, was based on results from Putcha et al., (1996) reporting enhanced bioavailability of intranasally delivered scopolamine. Both the active and placebo intranasal gel was delivered by a single pump of the actuator to each nostril.

Measures

Motion Sickness Questionnaires

Modified Motion Sickness Susceptibility Questionnaire- Short Form (MSSQ-Short). This questionnaire is designed to determine how susceptible an individual is to motion sickness and what kinds of motion stimuli were most effective in causing sickness during childhood and over the past 10 years. Sickness was defined as feeling queasy or nauseated after exposure to a variety of motion stimuli involving land, sea, and air travel, as well as amusement rides (Golding, 2003; 2006). Previous researchers have identified the need for susceptibility screening for motion sickness studies and have used cut-off scores to identify the most appropriate subject population (Golding, Mueller & Gresty, 2001; Golding, Kadzene & Gresty, 2005). The current study used a cut-off score of 3.0 on the MSSQ-Short to exclude the least susceptible subjects.

Motion Sickness Symptom Assessment- The symptom report was derived from symptoms listed in the Pensacola Motion Sickness Questionnaire (MSQ; Hutchins & Kennedy, 1965) and was used to guide the subject's self-report of common motion sickness symptoms including: nausea, dizziness, sweating, salivation, warmth, drowsiness, and headache for each minute of motion exposure. Subjects were asked to rate experienced symptoms as minimal, moderate, or major based on pre-established definitions. Stomach awareness and stomach discomfort were reported as present or not present. Symptoms were collected at the end of each minute just prior to advancement to the next higher rpm. One pre-rotation symptom assessment was conducted to determine any pre-existing symptoms and one post-rotation assessment was completed prior to the subject exiting the motion device to assess recovery.

Biological Assessments

Blood Sampling

There were four blood samples taken over the course of approximately two hours. Specifically, there was a baseline blood draw prior to dosing and then three draws at 15, 25, and 80 minutes post-dose. Blood draws were done using standard blood collection procedures (21 gauge BD Vacutainer® Push Button Collection Device or a PROTECTIV® 20 gauge indwelling catheter, Model # 3057; Carlsbad, CA). Blood samples were collected using a 4 mL BD Vacutainer® with a lithium heparin additive (BD Franklin Lakes, NJ). After the first, second, and third samples the catheter was flushed with 0.9% saline, and prior to taking the 4 mL sample for the blood assay, a 3 mL tube of blood was taken to release the saline from the line. The indwelling catheter (if used) was removed immediately after the last sample was taken. Samples were then centrifuged (Allegra X-22R Centrifuge, Beckman Coulter, Fullerton, CA) at 3000 rpm at a temperature of 4° C for ten minutes to separate the plasma. The plasma samples were then separated equally into cryovials for each time point, labeled, and placed in a -80° C freezer in preparation for shipment and analysis.

Physiological Monitoring

Blood Pressure & Temperature

The Welch Allyn Propaq Encore[®] (Model 206 EL) was used to measure blood pressure and heart rate and Welch Allyn's Sure Temp Plus[®] was used to determine the subject's temperature. Measures were taken prior to administration of the medication, and then 15, 25, 80, 115, 145, and 190 minutes post-dose. This information was collected for safety and to provide additional information regarding potential medication effects.

Cognitive Assessments

ARES[®] and ANAM[®]

A Palm[®] Pilot PDA (Tungsten E Model) was used to administer the Automated Neuropsychological Assessment Metrics Readiness Evaluation System (ARES[®]) cognitive battery, a customized, Tri-Service Test Battery of objective cognitive tests consisting of: Simple Reaction Time, Running Memory, Logical Reasoning, and Matching to Sample (Elsmore & Reeves, 2004). Baseline testing occurred prior to dosing, and was repeated 5, 90, 120 and 160 minutes post-dose. Two tests from the Automated Neuropsychological Assessment Metrics (ANAM[®]) battery were administered on a personal computer (PC): Code Substitution Learning and Code Substitution Delayed Retrieval. These tests emphasize scanning, paired associative learning of symbol-number pairs, and delayed recall. To decrease chances of proactive interference, delays of at least 30 minutes separated each trial and session of testing. For example, a subject would complete the Code Substitution Learning trial, wait at least 30 minutes, and then complete the Code Substitution Delayed Retrieval trial. Subjects would then wait an additional 30 minutes prior to the next trial of Code Substitution Learning and that procedure would continue for the remainder of the trials. These particular cognitive tests were chosen as they are sensitive to medication-induced performance effects (Elsmore, Reeves & Reeves, 2007; Kane, Roebuck-Spencer, Short, Kabat & Wilken, 2007; Lewandowski, Dietz, & Reeves, 1995).

Subjective Assessments

Karolinska Sleepiness Scale (KSS)

The KSS measures sleepiness using a nine point scale based on five states ranging from "extremely alert" to "extremely sleepy, fighting sleep". There are four intermediary states that are not designated with words. Previous research has found that the KSS is closely linked to the objective measures of encephalographic and oculographic signs of sleep onset (Akerstedt & Gilberg, 1990; Kaida et al., 2006). Scores on the KSS were used to determine the potential impact of medication on alertness.

Experimental Procedures

Practice and Physical Examination Days

Subjects reported to the lab prior to experimental days for the following: 2 practice blocks of the ANAM[®] tests (Code Substitution Learning and Code Substitution Delayed Recall) separated by at least one day, a Brief Aeronautical Exam by a physician, and one block of combined ANAM[®] tests and 6 ARES[®] cognitive battery trials. The ANAM[®] only practice sessions always occurred before the combined ANAM[®] and ARES[®] session. The practice sessions served to mitigate practice effects for the cognitive tasks. In addition, during the practice sessions, subjects were briefed on the timeline for the experimental days, specifically covering the symptoms of motion sickness, and the definitions for minimal, moderate, and major motion sickness symptoms to assist with symptom collection during their rotations in the HDD.

Experimental Days

Subjects reported to the lab at 0715. The compliance questionnaire was administered, baseline physiological data was collected and urine pregnancy tests were completed (as applicable). An indwelling catheter for blood draws was inserted and baseline blood samples were taken. Subjects then completed baseline performances on the cognitive tests and the KSS. Intranasal dosing (0.4 mg intranasal scopolamine or intranasal saline placebo) was administered at 0830, followed by post-dose blood draws, cognitive testing, and the KSS. Rotation began 40 minutes post-dose, and was discontinued when one of the following conditions was met: the subject reported moderate nausea that did not abate after one minute, the subject requested that the rotation be discontinued, or the subject rotated for a total of 40 minutes. After rotation, one final blood draw was taken, physiological assessments, cognitive testing, and the administration of the KSS continued for approximately 130 minutes. Specific timeline details can be found in Table 2.

Efficacy and Pharmacotherapeutics

Efficacy was determined by the average number of head tilts tolerated per condition. Each minute of stimulation was equal to 12 head tilts. The stimulus profile was controlled by Labview[®] software, as was the collection of the total number of head tilts and ride duration. The plasma concentrations of intranasal scopolamine were determined by a liquid chromatographic mass spectrometric method conducted by the Pharmacotherapeutics Laboratory, Johnson Space Center, Houston, TX.

Statistical Analyses

Statistical analyses were performed using SPSS version 12.0 for Windows[®] (SPSS Inc., Chicago IL). A paired samples t-test was conducted to determine whether intranasal scopolamine resulted in a significant increase in the total number of head movements tolerated compared to placebo. Plasma concentration time profiles of scopolamine were analyzed for absorption and bioavailability variables using moment analysis (Gibaldi, 1984). In addition, two paired samples t-tests were performed comparing dose weights, to determine dose

standardization and consistency. One t-test compared dosage weights between ride one and ride two. The second t-test compared INSCOP dosage weights to placebo. A Pearson correlation was conducted to examine whether higher INSCOP dose weights are associated with more head movements tolerated in the treatment condition.

Three 2 x 7 repeated measures ANOVAs were conducted to compare changes in heart rate and blood pressure (systolic and diastolic) between the treatment and control groups. These analyses each possessed two within-subject factors (treatment, 2 levels and block, 7 levels). Effects were indicated by significant interactions between order and block. Any significant findings were followed by least significant differences post hoc analyses.

A series of two factor repeated measures ANOVAs were conducted to determine whether there were any significant cognitive performance effects associated with intranasal scopolamine. The analyses each possessed two within-subject factors (block and treatment). Cognitive tests included Simple Reaction Time, Running Memory, Logical Reasoning, and Matching to Sample from the ARES[®] battery and Code Substitution Learning and Code Substitution Delayed Retrieval from the ANAM[®] battery. Cognitive performance effects were indicated by significant interactions between treatment and block. For a more complete description of these analyses see Table 3. A two factor ANOVA was conducted to compare subject self-report of sleepiness (KSS) between the placebo and treatment conditions. This analysis possessed one within-subject factor (block) and one between-subject factor (treatment). Again, significant results were indicated by significant interactions between treatment and block (See Table 3). Any significant findings were subjected to post hoc analyses.

Results

The paired samples t-test indicated that significantly more head movements were tolerated by participants after receiving 0.4 mg of intranasal scopolamine than after receiving a placebo ($M = 45.19$, $SD = 81.93$), $t(15) = 2.21$, $p < .05$, $d = .55$ (Figure 1). This suggests that 0.4 mg of intranasal scopolamine delays the onset of motion sickness and that the effect is both statistically and clinically significant. The second paired samples t-test revealed no significant differences in the weight of compounds delivered between test day one and test day two. This indicates that the intranasal delivery device provided a consistent dosage of treatment across administrations (Figure 2). The internal consistency of weight dose across the sixteen administrations of INSCOP is depicted in Table 4. The paired samples t-test comparing dosage weights between INSCOP and placebo detected significant differences $t(14) = -2.45$, $p < .05$, $d = .63$. These differences are potentially associated with either a slight difference in viscosity or consistency between the INSCOP and saline-infused placebo gel. Dose weights within INSCOP showed high levels of internal consistency across the 16 administrations. Twelve out of 16 participants received 0.2 mg of INSCOP, three participants received 0.15 mg of INSCOP and one participant received 0.25 mg. The Pearson correlation conducted between INSCOP dosage weight and head movements revealed a significant positive relationship $r = .462$, $p < .05$ which suggests that higher dosage weights are associated with a higher number of head movements tolerated in the INSCOP condition.

The analyses conducted on systolic blood pressure showed no significant effects for treatment, block, or treatment by block interactions. However, analysis of diastolic blood pressure did show a significant treatment effect $F(1, 15) = 5.70, p < .05, \eta_p^2 = 0.28$ (Figure 3 & Table 5). Examination of means showed that participants have significantly lower diastolic blood pressure after administration of INSCOP when compared to placebo. Analysis of heart rate revealed a significant effect for treatment $F(1, 15) = 17.81, p < .05, \eta_p^2 = 0.54$, block $F(6, 90) = 42.09, p < .05, \eta_p^2 = 0.74$, as well as a significant treatment by block interaction $F(6, 90) = 8.94, p < .05, \eta_p^2 = 0.37$ (Figure 4 & Table 5). Post hoc analyses showed significantly lower heart rates among participants who were given intranasal scopolamine at time points four, five, six, and seven when compared to participants who were given a placebo. Mean differences between the treatment and placebo conditions across these time points were 6.94, 9.0, 9.56 and 7.94 beats per minute, respectively. Scopolamine is known to be associated with a decreased heart rate; therefore, these results support the argument that the medication is well absorbed. The analyses revealed no significant cognitive performance effects over time between the placebo and treatment condition for the tests included from the ARES[®] battery or for the code substitution test (delayed recall) included from the ANAM[®] battery ($p > .05$; Tables 6 & 7 and Figures 5-9). Likewise, the analysis conducted on self-report of sleepiness (KSS) revealed no significant differences between treatment conditions over time (Figure 10). This suggests that no significant cognitive or sedative effects were associated with intranasal scopolamine at the current dosage.

Discussion

The purpose of the present study was to determine whether scopolamine, delivered intranasally, would confer greater motion sickness protection than placebo without detrimental cognitive or medication side effects. As hypothesized, when motion sickness susceptible participants received intranasal scopolamine gel they tolerated more provocative motion than under placebo condition (Figure 1). While serving in the treatment condition, participants were able to tolerate an average of 45 more head movements during exposure to a very provocative motion. These results are similar to the findings by Klocker et al. (2001), whose subjects in the 0.2% intranasal scopolamine spray condition reported a significant decrease in seasickness scores when compared to dimenhydratate or placebo. In a related study, Buckey et al. (2008) used two intranasal scopolamine gel formulations (0.2 and 0.4 mg doses), and found subjects in both treatment conditions were able to withstand a significantly greater time in the rotating chair when compared to placebo, with no difference between the 0.2 and 0.4 mg doses. The only other efficacy studies involving intranasal scopolamine are from historical military studies, which also reported significant findings for intranasal scopolamine in spray and drop formulations when compared to oral scopolamine and placebo (Chinn et al., 1955; Hyde et al., 1953; Tonndorf et al., 1953). Scopolamine is known to be an effective motion sickness deterrent, but these noteworthy findings for low dose, intranasally delivered scopolamine hold significant promise for operational personnel in a variety of dynamic environments.

The results of the blood plasma data showed a moderate level of systemically available scopolamine beginning at the first collection time point (15 minutes; Figure 4). There was concern that a gel formulation with a large particulate size may not be readily absorbed, however, the rate of absorption as determined by the slope of concentration v. time graph

indicates that detectable, and potentially efficacious, levels of scopolamine may have been in the system well before the 15 minute collection point. It appears the levels were below the threshold typically reported with negative visual or cognitive anticholinergic effects, but high enough to deliver motion sickness protection. This study was not designed to determine the complete pharmacokinetic properties of intranasal scopolamine, but to estimate absorption. Even with the positive results from the present study, it stands to reason that scopolamine in aqueous solution or nebulized form, with a significantly smaller particulate size, would provide faster and more complete absorption than a gel. Future studies should consider a finer particulate formulation in a lower dose, 0.1-0.2 mg, to increase absorption and decrease time to reach C_{max} ¹.

Other evidence of adequate scopolamine absorption was found in the heart rate data (Figure 4). The analysis of medication effects on physiological variables showed a significant linear decrease in heart rate over time in the intranasal scopolamine condition, similar to findings reported by Golding & Stott (1997) using oral scopolamine, Klocker et al., (2001) using intranasal scopolamine and Parrott (1989) administering transdermal scopolamine. Heart rate data from the present study indicate that 0.4 mg of intranasal scopolamine significantly decreased heart rate more than placebo over time, with differences being found at 80, 115, 145, and 190 minutes post-dose. The decrease in heart rate was anticipated as administration of small doses of muscarinic receptor antagonists act to block M_1 receptors on postganglionic parasympathetic neurons, not only seen with scopolamine but also with atropine (Brown & Taylor, 2001; Golding & Stott, 1997). In addition to the blood plasma assays indicating adequate absorption of scopolamine, the significant change in heart rate data act as a strong confirmation of medication absorption.

Examination of diastolic and systolic blood pressure readings yielded mixed results. Comparison of systolic blood pressure data revealed no significant change over time between the INSCOP and placebo groups; however, diastolic readings differed significantly between the treatment condition and placebo over time (Table 5 & Figure 3). Significant changes in blood pressures were not expected as the systemic vasculature is considered to lack sufficient cholinergic innervation and the vessels supplying skeletal muscles do not appear to be involved in normal regulation of tone (Brown & Taylor, 2001). Also, numerous researchers (Brown and Taylor; Kanto, Kentala, Kaila & Philajandaki, 1989; and Nachum et al., 2001) reported no significant changes in blood pressures after administration of scopolamine in doses ranging from 0.3 to 0.6 mg through oral, transdermal or parenteral delivery. The significant decrease in diastolic blood pressure found in the present study is similar to the results of Klocker et al. (2001), who found analogous changes in diastolic blood pressure after administration of 0.2% intranasal scopolamine when compared to dimenhydrinate and placebo. The nature of the change in diastolic blood pressure in the current study, although statistically significant, was not found to be clinically remarkable as the mean change across time was only 2.55 mmHg. Overall, blood pressures were fairly stable; however, further research comparing blood pressure and bioavailability levels may assist in determining the potential effect of intranasal scopolamine on the cardiovascular system, as well as, other physiological variables.

The current study examined the amount of gel dispensed to each subject in the treatment and placebo conditions to determine consistency of dose and effectiveness of the dispenser.

¹ C_{max} refers to the maximum concentration of a drug in the body after dosing.

There were no significant differences in amount of scopolamine gel dispensed between subjects. The dose weight required to achieve a 0.4 mg dose of scopolamine was 0.2 g. Twelve of the 16 subjects received 0.2 g, three received 0.15 g and one received 0.25 g. One interesting difference was found in the weight of the scopolamine gel. Subjects receiving the higher gel weight dose did tolerate a significantly greater number of head movements than subjects dispensing lesser amounts of gel. This suggests a linear effect of dose and gel weight, and therefore, greater efficacy. Dispensing of the placebo was also very consistent, but when a deviation occurred it was always on the higher side (0.25 g). This difference is most likely due to the placebo gel being saline infused and potentially less viscous than the scopolamine gel. Dose weight results are outlined in Table 4 and Figure 2.

No significant effects on cognitive performance were found between the treatment and placebo conditions following administration of 0.4 mg of intranasal scopolamine (Tables 6 & 7; Figures 5-9). Although no significant differences were shown, trends appeared for throughput on the delayed recall portion of the code substitution task ($p = .066$). The data indicate that participants performed better in block two while in the placebo condition when compared to the INSCOP condition (Fig. 9). The interpretation of this trend is complicated by two factors; the lack of treatment effects in block three (Fig 9) and the possible synergistic effect of scopolamine and rotation. If the trend resulted solely from the treatment, one would expect to find a significant difference between treatment and placebo in block three. In this case, no differences were found between the treatment and placebo conditions in block three (Fig. 9). Previous work by Koller et al., (2003) specifically investigating the effect of scopolamine on delayed retrieval found that subcutaneous injections of 0.3 and .06 mg of scopolamine were associated with detriments in delayed retrieval on memory tests. Although the results are similar, a direct comparison between intranasal and subcutaneous scopolamine administration is problematic. The negative effect of high doses of scopolamine on memory is widely accepted (Parrott et al., 1989), but at lower doses the effect on memory is less clear.

The potential for scopolamine to act synergistically with provocative motion must be considered as a factor in the trend shown for the code substitution/delayed recall task. Paule, Chelonis, Blake, and Dornhoffer (2004) found that rotation alone significantly decreased task accuracy and choice response speed, especially at longer recall delays, in a delayed matching-to-sample task. The same study compared several anti-emetic agents and reported that scopolamine alone decreased accuracy, and when combined with rotation, produced a significant decrease in speed. One might expect the synergistic effect to stem from the combined drowsiness effect of a muscarinic receptor antagonist and motion, but there were no significant differences in drowsiness between the treatment and placebo conditions (Figure 10). The trend for delayed recall can most likely be attributed to the combination of medication and rotation but more information is needed to gain a clear understanding of the exact contribution of each component on performance. The current data do not suggest that intranasal scopolamine at 0.4 mg significantly impairs memory encoding or retrieval in a young, healthy population. Future studies should focus on testing the effects of low dose intranasal scopolamine on specific operational tasks where memory and recall are factors.

The intranasal scopolamine gel was well tolerated and no significant adverse events were reported by any subject. Analysis of the medication side effect data did not reveal significant

effects between the INSCOP and placebo conditions (Tables 5 & 8; Figures 3, 4 & 10). The only negative subject feedback concerning the gel was several reports of a full feeling in the nasal cavity and one person stated that the compound had a slight odor. There were no complaints of nasal or esophageal irritation or burning from the gel. The absence of side effects is in contrast to other studies that reported an increase in the incidence and/or severity of medication-induced side effects with intranasal administration (Chinn & Smith 1953; Hyde et al., 1953; Ahmed et al., 2000). Chinn et al., (1955) and Putcha et al., (1996) reported an increase in the incidence of dizziness and dry mouth after intranasal administration of doses ranging between 0.2 to 0.6 mg. There have also been several studies reporting cases of scopolamine intoxication, psychosis, and recurrent migraine attacks after scopolamine administration at higher dosages, such as those delivered by the transdermal patch. Subjects from the current study reported mostly mild side effects and no reports of the aforementioned severe side effects (Gordon, Mankuta, Shupak, Spitzer, & Doweck, 1990; Osterholm & Camoriano, 1982). Table 8 shows the frequency of symptoms at several time points, including baseline, pre-dose, post-dose, during rotation and post-rotation throughout the study. A majority (83%) of the symptoms reported post-rotation were reported by those same participants during rotation, providing evidence that the symptoms may be related to the rotation, and not necessarily the medication.

Future Studies

The military is rightfully reluctant to medicate personnel in high-risk occupations. With this in mind, a potential area for future testing is the use of intranasal scopolamine for rescue. Considerable research has examined the efficacy of scopolamine in various administration forms, mainly as a prophylactic for motion sickness, but only one published study to date has explored the efficacy of intranasal scopolamine after the onset of symptoms (Chinn et al., 1955). The success of a “just in time” anti-motion sickness medication would allow service members to medicate only when absolutely necessary and not pre-medicate during more routine operations. Because of intranasal scopolamine’s rapid absorption profile, and potentially more rapid in a nebulized form, further investigation regarding its efficacy as a rescue therapy is warranted. It is also recommended that future testing focus on field trials and operational settings rather than purely laboratory-type experiments.

Conclusion

The data suggest that intranasal scopolamine is effective, safe, and a practical alternative route of medication administration in dynamic military and space environments. The absorption rate of intranasal scopolamine in the current study appeared to have a superior absorption rate when compared to oral scopolamine, without cognitive detriment or increasing symptomatology. Intranasal delivery also provides a field expedient solution, overcoming administration challenges experienced with other delivery methods.

Military Significance

With discussion among the military services regarding implementation of Sea Power 21, and the concept of sea-basing, motion sickness will become a greater problem, not only for Navy, but for Army and Air Force personnel. The results from the present study suggest that this novel route of administration holds promise as a fast-acting, field expedient, motion sickness countermeasure. In addition to the U.S. military, the National Aeronautics and Space Administration (NASA) has been seeking a highly effective motion sickness countermeasure with the potential of rescue treatment. Initial bioavailability results show great promise for action in less than 15 minutes. Future testing should concentrate on a finer mist or inhaled formulation with controlled laboratory tests, and then field testing, to prove the real value of intranasal scopolamine.

Disclaimer

The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.

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Human Research Protections/IRB statement

The study protocol was approved by the Naval Aerospace Medical Research Laboratory Institutional Review Board in compliance with all applicable Federal regulations governing the protection of human subjects.

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Table 1. Demographic Information (*n* = 16)

	N	%
Gender		
<i>Male</i>	13	81
<i>Female</i>	3	19
	Mean	<i>SD</i>
Age (years)		
<i>Total</i>	23.50	2.96
<i>Male</i>	23.77	3.24
<i>Female</i>	22.33	0.58
Height (inches)		
<i>Total</i>	69.25	2.65
<i>Male</i>	69.77	2.46
<i>Female</i>	67.00	2.65
Weight (pounds)		
<i>Total</i>	168.75	21.17
<i>Male</i>	171.62	20.64
<i>Female</i>	156.33	22.81
Body Mass Index (BMI)		
<i>Total</i>	24.71	2.49
<i>Male</i>	24.78	2.67
<i>Female</i>	24.37	1.84
MSSQ-Short Score		
<i>Total</i>	11.31	4.65
<i>Male</i>	10.85	4.60
<i>Female</i>	13.27	5.32
Race	%	
<i>White</i>	87.5	
<i>Black</i>	6.3	
<i>Asian American</i>	6.3	
<i>Hispanic/Latino (a)</i>	0	
<i>Other</i>	0	

Note: MSSQ-Short = Motion Sickness Susceptibility Questionnaire- Short Form

Table 2. Timeline of Experimental Days

Time	Event(s)
0715	Subject arrival
0730	Reaffirm Consent
0735	Compliance Check, Pregnancy Test if applicable, ARES warm-up (x 1 on Rotation 1 and x 2 on Rotation 2)
0745	Baseline: ANAM [®] CSL & ARES [®]
0755	Baseline: KSS
0800	Baseline: Blood, Vital Signs
0805	Baseline: ANAM [®] CSDR
0830	0.4 mg Intranasal Scopolamine <i>or</i> Placebo intranasal gel administration
0835	ARES [®] , KSS
0845	Blood, Vital Signs
0855	Blood, Vital Signs, Adverse Events
0910	Rotation, Motion Sickness Symptom Assessment (1 x pre-rotation, 1 x every minute of rotation, and 1 x post-rotation)
0950	Maximum time spent in HDD; Blood
1000	ANAM [®] CSL & ARES [®]
1010	KSS
1025	Vital Signs, Adverse Events
1030	ANAM [®] CSDR & ARES [®]
1045	KSS
1055	Vital Signs, Adverse Events
1110	ANAM [®] CSL & ARES [®]
1135	KSS
1140	Vital Signs, Adverse Events
1145	ANAM [®] CSDR
1200	Vital Signs, Debrief and Discharge

Note. ARES[®] = Automated Neuropsychological Assessment Metrics Readiness Evaluation System, ANAM[®] = Automated Neuropsychological Assessment Metrics, CSL = Code Substitution Learning, KSS = Karolinska Sleepiness Scale, CSDR = Code Substitution Delayed Retrieval

Table 3. Summary of Analyses of Cognitive and Sedative Effects

Test	Design	Within		Dependent Variables
Matching to Sample	2x6	Treatment	Block	MRT, TC, TP
Logical Reasoning	2x6	Treatment	Block	MRT, TC, TP
Running Memory	2x6	Treatment	Block	MRT, TC , TP
Simple Reaction Time	2x6	Treatment	Block	MRT, IMP
Code Substitution (Delayed Recall)	2x3	Treatment	Block	MRT, TC, TP
KSS	2x5	Treatment	Block	Total Score

Note. KSS = Karolinska Sleepiness Scale; MRT = Mean Reaction Time, TC = Total Correct, TP = Throughput, IMP = Impulsivity

Table 4. Intranasal Scopolamine Dose Weights and Head Movements for Each Subject

Subject	Weight (g)	Dose (mg)	Total Head Movements, INSCOP condition
1	0.15	0.3	192
2	0.15	0.3	213
3	0.20	0.4	136
4	0.15	0.3	230
5	0.20	0.4	201
6	0.20	0.4	239
7	0.20	0.4	469
8	0.25	0.5	501
9	0.20	0.4	183
10	0.20	0.4	289
11	0.20	0.4	477
12	0.20	0.4	178
13	0.20	0.4	276
14	0.20	0.4	360
15	0.20	0.4	337
16	0.20	0.4	133

Note. INSCOP = intranasal scopolamine

Table 5. Group Means ($\pm$ SE) for Heart Rate and Blood Pressure over Time.

<i>Minutes Post-Dose</i>	Heart Rate (bpm)			
	Placebo		INSCOP	
Baseline	67.4	$\pm$ 2.3	70.6	$\pm$ 2.0
15	64.4	$\pm$ 2.8	62.4	$\pm$ 2.1
25	62.5	$\pm$ 2.2	59.6	$\pm$ 2.3
80*	60.6	$\pm$ 2.3	53.6	$\pm$ 2.5
115*	59.4	$\pm$ 2.5	50.4	$\pm$ 1.9
145*	57.3	$\pm$ 2.4	47.8	$\pm$ 1.6
190*	57.8	$\pm$ 2.2	49.8	$\pm$ 2.0
<i>Minutes Post-Dose</i>	Systolic Blood Pressure (mmHg)			
	Placebo		INSCOP	
Baseline	119.5	$\pm$ 3.2	117.9	$\pm$ 2.7
15	116.6	$\pm$ 2.8	113.4	$\pm$ 2.8
25	114.1	$\pm$ 3.3	115.9	$\pm$ 2.8
80	113.9	$\pm$ 2.9	114.1	$\pm$ 3.7
115	111.4	$\pm$ 2.9	110.3	$\pm$ 3.3
145	117.1	$\pm$ 3.3	112.4	$\pm$ 3.6
190	117.1	$\pm$ 2.6	111.8	$\pm$ 2.4
<i>Minutes Post-Dose</i>	Diastolic Blood Pressure (mmHg)			
	Placebo		INSCOP	
Baseline	64.2	$\pm$ 1.5	64.6	$\pm$ 2.1
15	64.6	$\pm$ 2.0	63.0	$\pm$ 1.4
25	67.2	$\pm$ 2.0	65.1	$\pm$ 1.7
80	67.1	$\pm$ 2.0	65.6	$\pm$ 1.8
115	67.1	$\pm$ 2.6	62.6	$\pm$ 1.6
145	68.0	$\pm$ 2.7	63.8	$\pm$ 2.3
190	66.4	$\pm$ 2.2	65.3	$\pm$ 2.4

Note. bpm = beats per minute; mmHg = millimeters Mercury; INSCOP = 0.4 mg intranasal scopolamine; * = significant difference between INSCOP and Placebo at 80, 115, 145, and 190 minutes post-dose, $p < .01$.

Table 6. Group Comparisons of Mean Reaction Time, Percent Correct, and Throughput ($\pm$ SE) for the ARES[®] Cognitive Battery

	Time											
	1		2		3		4		5		6	
	Mean Reaction Time (ms)											
SRT _{IN}	220.5	± 6.6	222.6	± 6.6	225.7	± 6.8	222.2	± 6.3	222.9	± 5.4	226.2	± 7.6
SRT _P	234.8	± 7.0	221.8	± 6.3	226.4	± 7.5	225.4	± 6.7	221.4	± 4.6	221.3	± 4.3
RM _{IN}	414.8	± 13.3	406.4	± 13.6	408.1	± 13.1	413.6	± 14.2	418.6	± 16.3	421.2	± 16.8
RM _P	418.0	± 14.4	414.9	± 14.4	413.6	± 15.4	413.9	± 17.2	414.0	± 12.8	421.3	± 16.8
MS _{IN}	1084.8	± 116.5	1004.5	± 75.0	1047.3	± 91.4	1127.6	± 144.8	1001.6	± 83.6	1161.3	± 122.3
MS _P	1118.0	± 95.1	1001.6	± 83.6	1025.9	± 87.5	1043.2	± 74.3	929.9	± 58.5	1038.7	± 82.1
LR _{IN}	1471.9	± 134.6	1349.7	± 77.6	1394.3	± 112.1	1386.0	± 111.1	1491.6	± 118.0	1520.1	± 119.4
LR _P	1432.2	± 121.2	1471.6	± 136.3	1425.0	± 113.1	1486.2	± 127.3	1511.6	± 126.5	1480.9	± 132.0
	Total Correct*											
RM _{IN}	76.4	± 1.5	78.0	± 0.5	77.4	± 0.7	76.9	± 0.6	75.8	± 1.3	75.4	± 1.2
RM _P	76.7	± 0.8	77.2	± 0.6	77.2	± 0.5	75.9	± 0.7	76.7	± 0.5	76.4	± 0.8
MS _{IN}	9.8	± 0.1	9.4	± 0.2	9.6	± 0.1	9.3	± 0.2	9.8	± 0.1	9.4	± 0.2
MS _P	9.8	± 0.1	9.6	± 0.1	9.6	± 0.2	9.5	± 0.3	9.6	± 0.2	9.5	± 0.2
LR _{IN}	22.6	± 0.3	22.5	± 0.4	23.4	± 0.3	22.4	± 0.4	22.0	± 0.3	22.3	± 0.3
LR _P	22.9	± 0.3	23.1	± 0.4	22.6	± 0.3	22.8	± 0.3	22.0	± 0.5	22.6	± 0.3
	Throughput											
RM _{IN}	138.8	± 5.9	145.9	± 4.3	143.6	± 4.7	141.9	± 5.0	138.6	± 6.3	136.4	± 6.4
RM _P	139.2	± 4.6	141.9	± 4.3	139.9	± 4.7	140.2	± 5.1	139.9	± 4.7	138.3	± 5.4
MS _{IN}	63.5	± 6.4	61.6	± 5.7	62.8	± 4.7	58.6	± 6.2	66.9	± 5.7	56.9	± 5.5
MS _P	55.8	± 4.6	58.6	± 4.5	59.6	± 5.3	56.8	± 4.4	64.2	± 4.8	59.2	± 5.3
LR _{IN}	41.6	± 3.1	42.8	± 2.2	44.3	± 2.8	43.1	± 2.9	39.3	± 2.7	39.6	± 3.3
LR _P	42.9	± 3.1	43.4	± 3.4	42.0	± 3.0	42.1	± 3.8	39.3	± 3.0	40.8	± 3.1

Note. All Mean Reaction Time scores in milliseconds. _{IN} = intranasal scopolamine; _P = Placebo; SRT = Simple Reaction Time; RM = Running Memory; MS = Matching to Sample; LR = Logical Reasoning. Times 1-6 correspond with Warm-up, Baseline, 5, 90, 120, and 160 minutes post-dose. * = RM out of 80; MS out of 10; and LR out of 24 total stimuli.

Table 7. Group Comparisons of Mean Reaction Time, Mean Percent Correct and Throughput($\pm$ SE) for Code Substitution: Delayed Retrieval Over Three Observations

	Time		
	1	2	3
MRT _{IN}	888.5 $\pm$ 54.6	1051.8 $\pm$ 46.2	1120.9 $\pm$ 72.4
MRT _P	904.7 $\pm$ 32.8	983.0 $\pm$ 42.0	1065.5 $\pm$ 45.7
PC _{IN}	93.4 $\pm$ 1.5	85.8 $\pm$ 2.5	81.4 $\pm$ 2.7
PC _P	92.9 $\pm$ 1.4	90.3 $\pm$ 2.9	80.9 $\pm$ 2.4
TP _{IN}	65.9 $\pm$ 3.5	49.0 $\pm$ 3.2	45.3 $\pm$ 3.9
TP _P	61.3 $\pm$ 2.9	56.1 $\pm$ 3.3	45.6 $\pm$ 2.7

Note: MRT = Mean Reaction Time (ms); PC = Percent Correct; _{IN} = intranasal scopolamine; _P = Placebo; Time 1-3 correspond with Baseline, 120, and 195 minutes post-dose.

Table 8. Group Frequencies (and Percentages) of Adverse Events Pre-Treatment, Post-Treatment, and Post-Rotation

Pre-Treatment (Baseline)			
	Placebo	INSCOP	
Drowsiness		1 (6)	
Anxiety	1 (6)	1 (6)	
15 min Post-Treatment, Pre-Rotation			
	Placebo	INSCOP	
Drowsiness	1 (6)	1 (6)	
Anxiety		1 (6)	
Increased Salivation		1 (6)	
25 min Post-Treatment, Pre-Rotation			
	Placebo	INSCOP	
Anxiety		1 (6)	
80 min Post-Treatment, Post-Rotation			
	Placebo	INSCOP	
Drowsiness	5 (31)	3 (19)	
Dizziness	5 (31)	9 (56)	
Stomach Discomfort	4 (25)	6 (38)	
Nausea	5 (31)	4 (25)	
Headache	2 (13)	3 (19)	
Increased Salivation			
Lightheadedness		1 (6)	1 (6)
Body Warmth		2 (13)	2 (13)
Symptoms during Rotation¹			
	Placebo	INSCOP	
Drowsiness	4 (25)	2 (13)	
Dizziness	5 (31)	9 (56)	
Stomach Discomfort	4 (25)	6 (38)	
Nausea	5 (31)	4 (25)	
Headache	2 (13)	2 (13)	
Increased Salivation			
Lightheadedness			
Body Warmth			
115 min Post-Treatment, 35 min Post-Rotation			
	Placebo	INSCOP	
Drowsiness	4 (25)	4 (25)	
Dizziness	3 (19)	5 (31)	
Stomach Discomfort	2 (13)	2 (13)	
Nausea	1 (6)	2 (13)	
Headache	2 (13)	2 (13)	
Lightheadedness			
Symptoms during Rotation			
	Placebo	INSCOP	
Drowsiness	3 (19)	4 (25)	
Dizziness	3 (19)	5 (31)	
Stomach Discomfort	2 (13)	2 (13)	
Nausea	1 (6)	2 (13)	
Headache	1 (6)	0	
Lightheadedness		1 (6)	
145 min Post-Treatment, 55 min Post-Rotation			
	Placebo	INSCOP	
Drowsiness	3 (19)	4 (25)	
Dizziness	1 (6)	2 (13)	
Stomach Discomfort		2 (13)	
Nausea	1 (6)	2 (13)	
Headache		2 (13)	
Symptoms during Rotation			
	Placebo	INSCOP	
Drowsiness	3 (19)	3 (19)	
Dizziness	1 (6)	2 (2)	
Stomach Discomfort		2 (13)	
Nausea	1 (6)	2 (13)	
Headache		1 (6)	
190 min Post-Treatment, 110 min Post-Rotation			
	Placebo	INSCOP	
Drowsiness	1 (6)	3 (19)	
Dizziness		1 (6)	
Stomach Discomfort		1 (6)	
Headache		1 (6)	
Symptoms during Rotation			
	Placebo	INSCOP	
Drowsiness	1 (6)	2 (13)	
Dizziness		1 (6)	
Stomach Discomfort		1 (6)	
Headache		1 (6)	

Note. INSCOP = Intranasal Scopolamine, 0.4 mg; ¹ Symptoms During Rotation calculated to demonstrate possible side effects of rotation, rather than intranasal scopolamine.

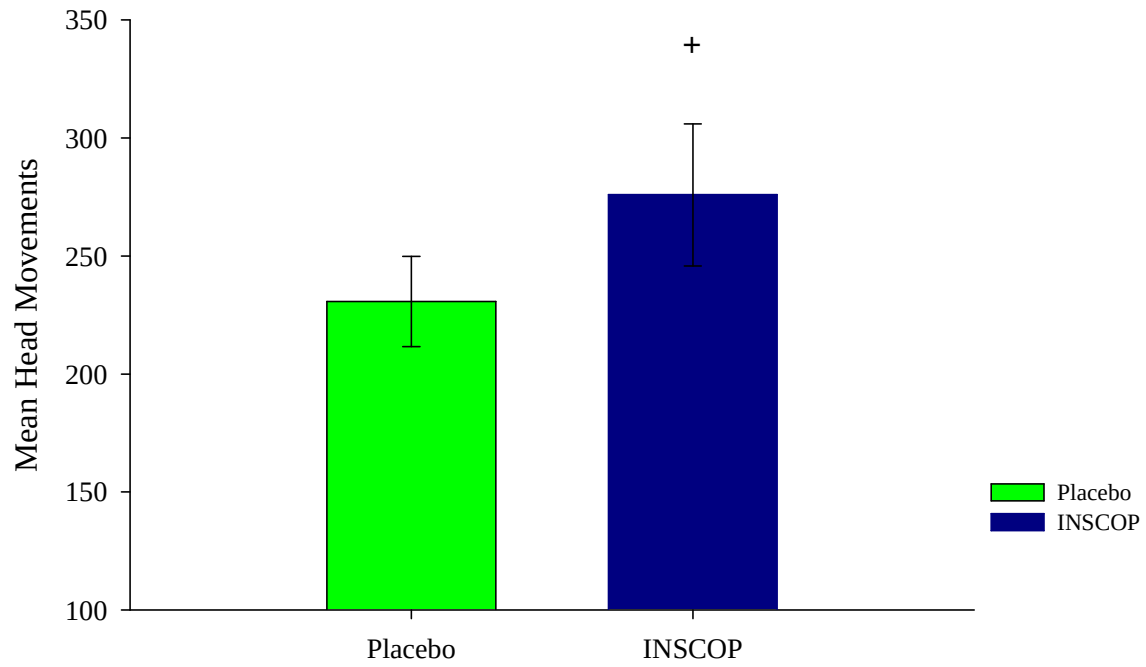


Figure 1. Motion tolerance as measured by head movements to moderate nausea for Intranasal Scopolamine (INSCOP) and Placebo. (+) denotes a significant difference in number of head movements tolerated between the two conditions, $t(15) = 2.21$, $p < .05$, $d = .55$.

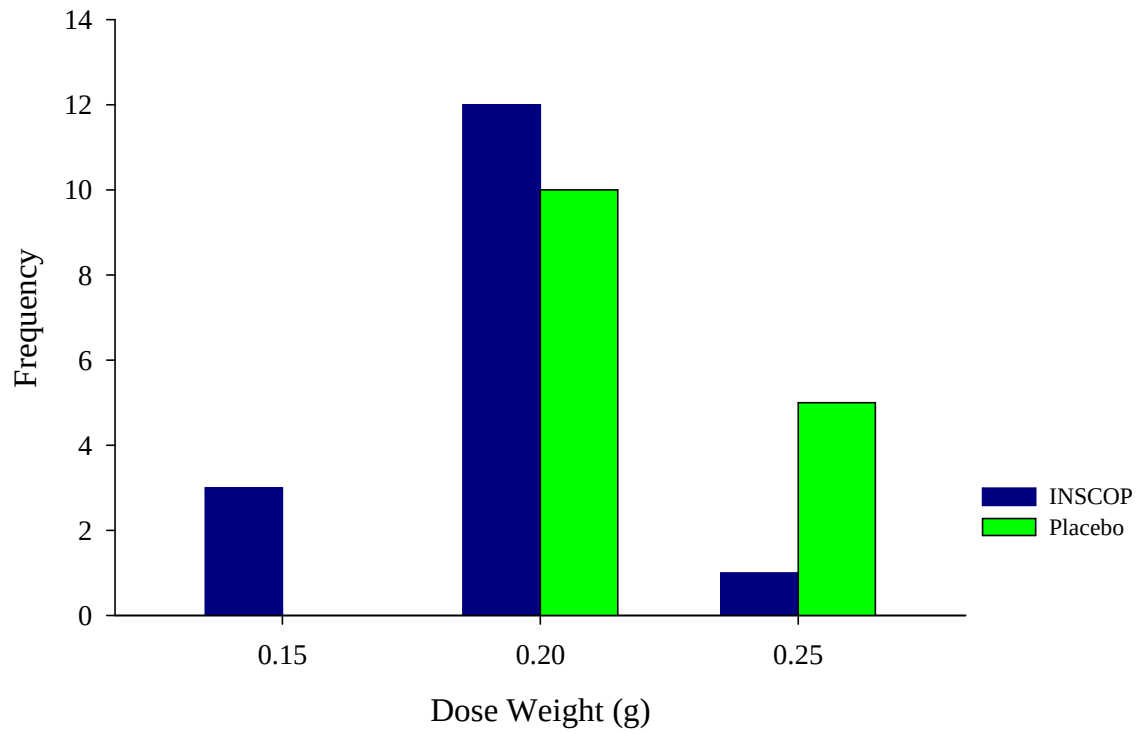


Figure 2. Frequency of gel weights dispensed in the intranasal scopolamine (INSCOP) and placebo conditions. No significant differences were found in gel delivery between subjects in either condition ($p > .05$).

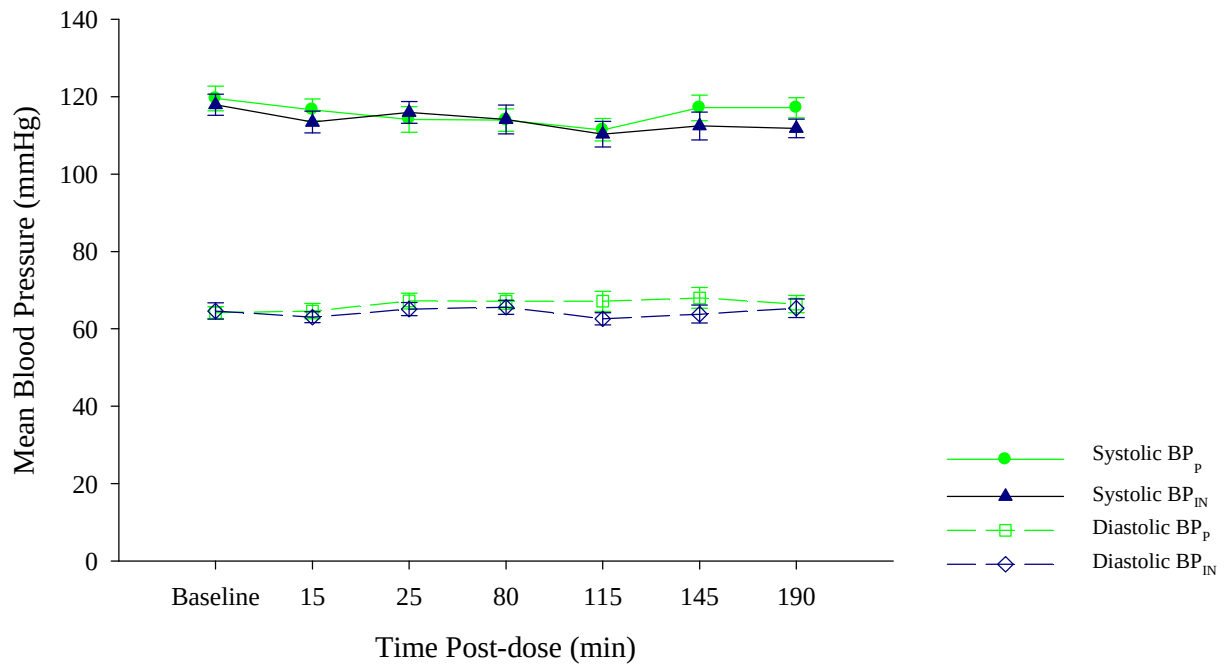


Figure 3. Mean blood pressures were recorded at baseline and six time points post-dose, annotated in minutes. The analyses conducted on systolic blood pressure showed no significant effects of treatment, time, or an interaction between treatment and time. However, analysis of diastolic blood pressure did show a significant treatment effect over time, with participants having a significantly lower diastolic blood pressure after intranasal scopolamine when compared to placebo, $p < .05$. BP_P = Blood Pressure, Placebo, BP_{IN} = Blood Pressure, Intranasal Scopolamine

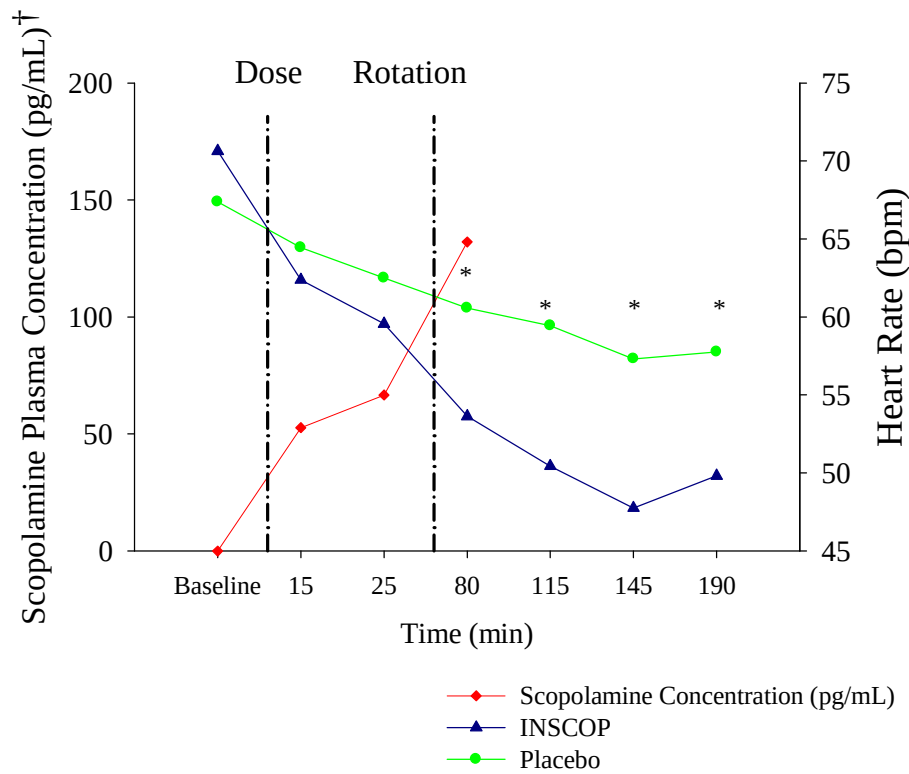


Figure 4. Comparison of Scopolamine Plasma Concentration Levels and Heart Rate recorded at baseline and six time points post-dose in the treatment and placebo conditions. A significant difference for heart rate was found between INSCOP and Placebo (*) at 80, 115, 145, and 190 minutes post-dose, $p < .01$. The increase in plasma concentrations, with the concomitant decrease in heart rate for the INSCOP group, indicate the quick and effective properties of INSCOP. † = Plasma concentration values were provided by the Pharmacotherapeutics Laboratory, Johnson Space Center, Houston, TX.

ARES[®] : Simple Reaction Time

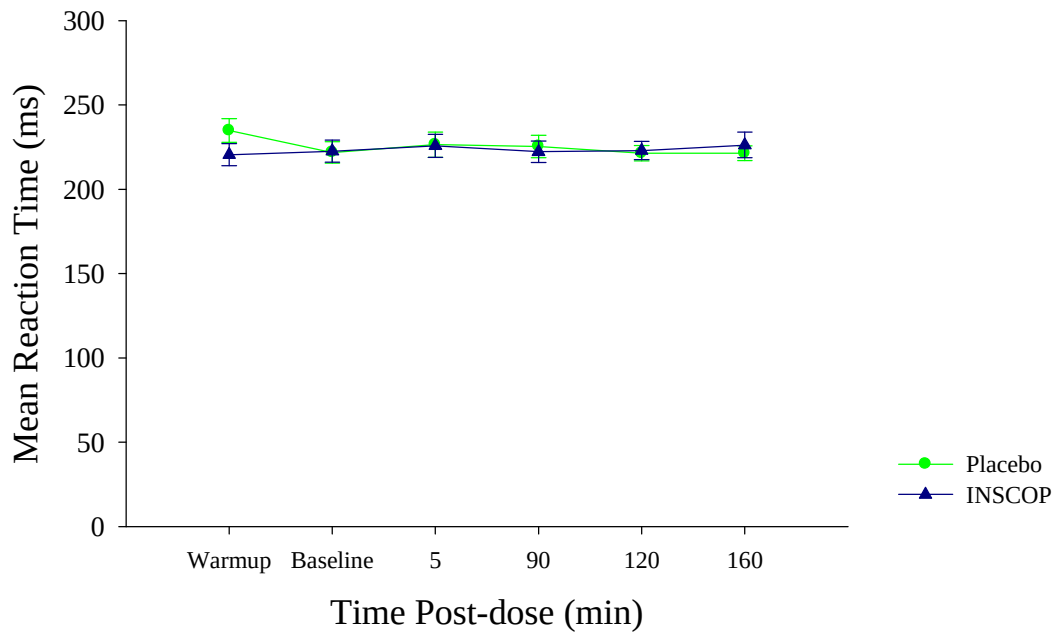


Figure 5. Mean Reaction Time (ms) for the ARES[®] Simple Reaction Time task. To protect against practice effects, one warm-up was completed to restore performance to asymptote. The test was administered again to determine baseline and four tests were completed post-dose. No significant differences were found between INSCOP and Placebo conditions, $p > .05$.

ARES[®]: Running Memory

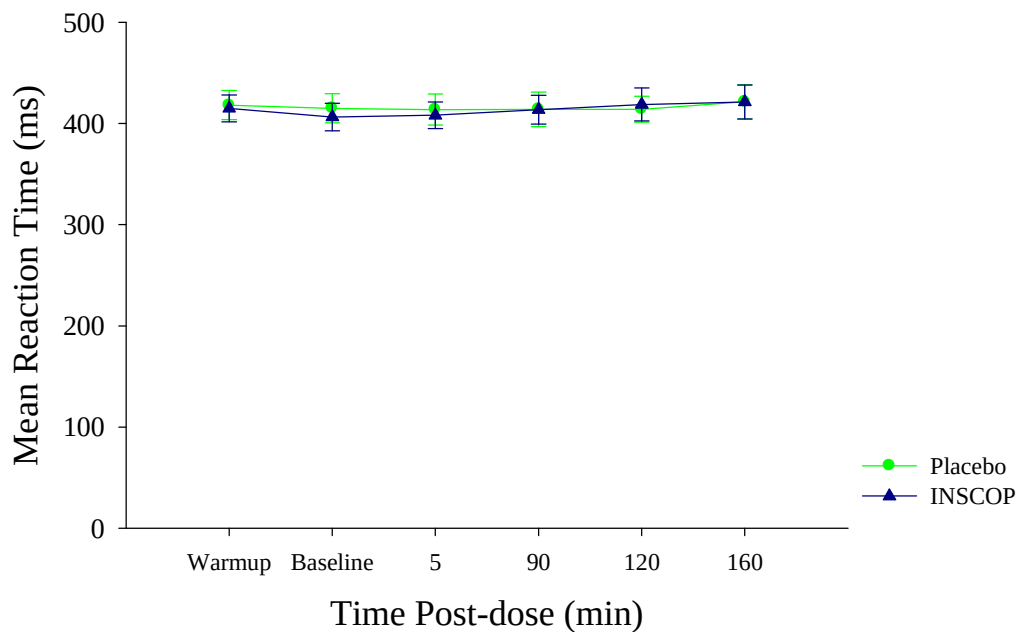


Figure 6. Mean Reaction Time (ms) for the ARES[®] Running Memory task. To protect against practice effects, one warm-up was completed to restore performance to asymptote. The test was administered again to determine baseline and four tests were completed post-dose. No significant differences were found between INSCOP and Placebo conditions, $p > .05$.

ARES[®] : Matching to Sample

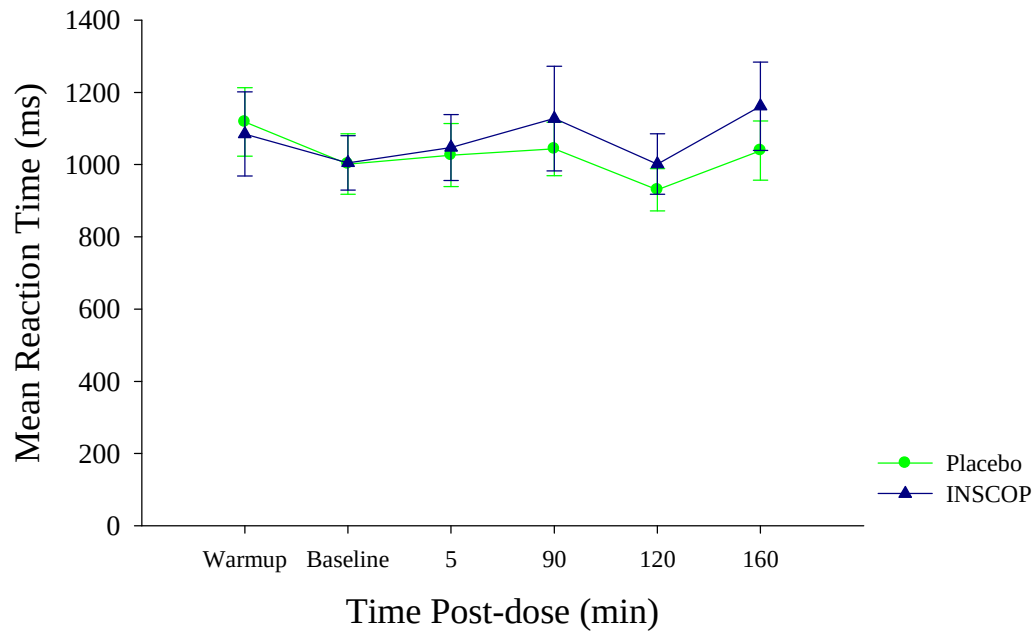


Figure 7. Mean Reaction Time (ms) for the ARES[®] Matching to Sample task. To protect against practice effects, one warm-up was completed to restore performance to asymptote. The test was administered again to determine baseline and four tests were completed post-dose. No significant differences were found between INSCOP and Placebo conditions, $p > .05$.

ARES[®] : Logical Reasoning

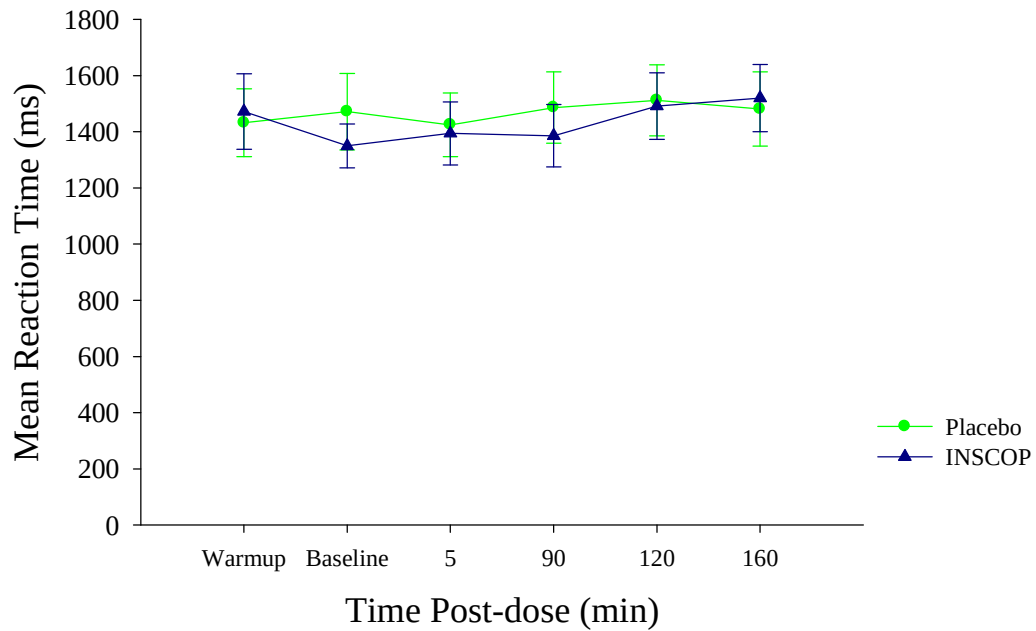


Figure 8. Mean Reaction Time (ms) for the ARES[®] Logical Reasoning task. To protect against practice effects, one warm-up was completed to restore performance to asymptote. The test was administered again to determine baseline and four tests were completed post-dose. No significant differences were found between INSCOP and Placebo conditions, $p > .05$.

ANAM[®] : Code Substitution (Delayed Retrieval)

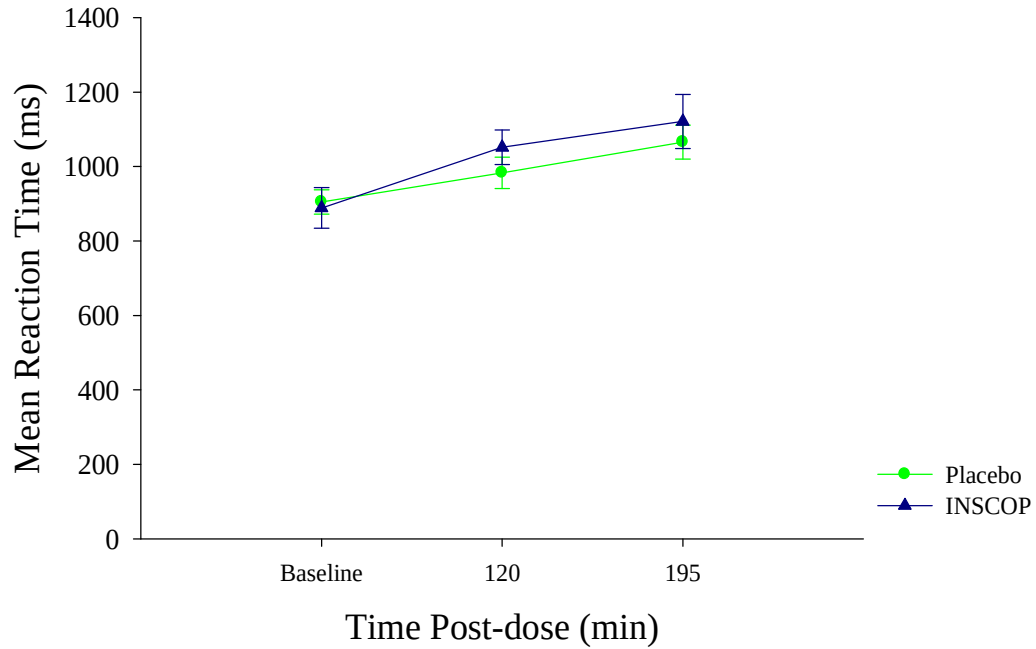


Figure 9. Mean Reaction Time (ms) for delayed retrieval during Intranasal Scopolamine (INSCOP) and Placebo conditions. The delayed retrieval portion of the test occurred 30 minutes post-Code Substitution Learning. No significant differences were found between the two conditions, $p > .05$.

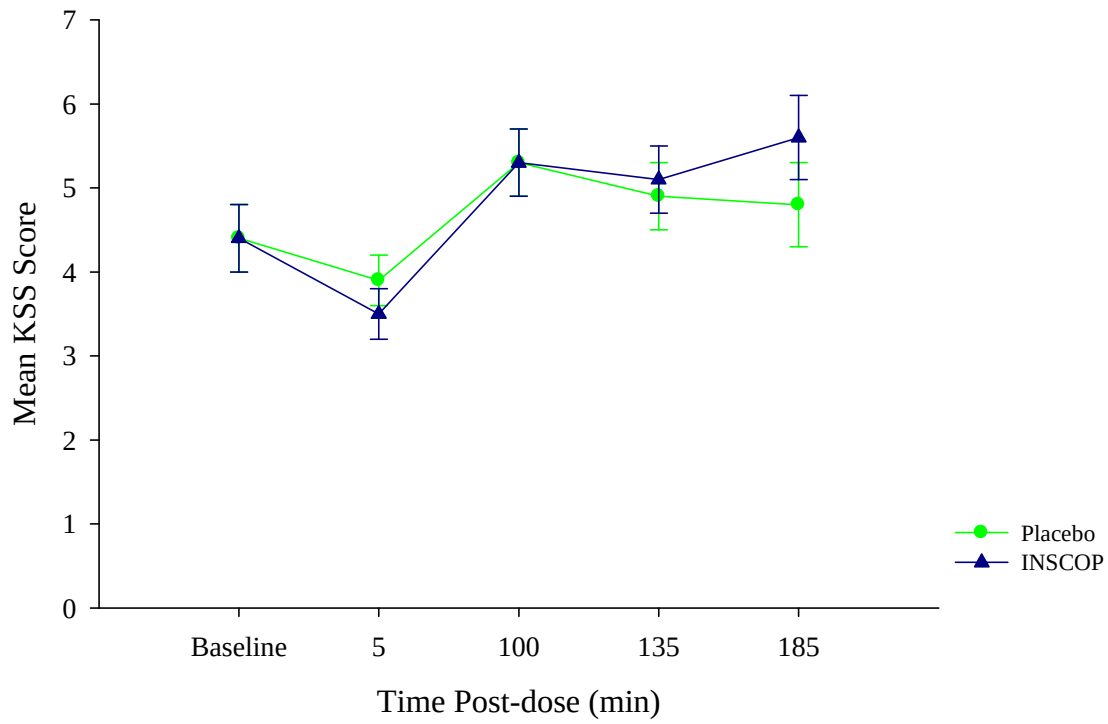


Figure10. Mean alertness score in points, derived from the Karolinska Sleepiness Scale (KSS). A baseline score was established and four scores were assessed over 185 minutes post-dose. No significant differences were found between the two conditions over time, $p > .05$.

Appendix A. Motion Sickness Susceptibility Questionnaire-Short Form

YOUR CHILDHOOD EXPERIENCE ONLY (BEFORE 12 YEARS OF AGE): Check the appropriate boxes for each section:

Experience Level					Level of Motion Sickness			
What was your experience with each motion stimulus?					How often did you feel motion sick?			
Cars	☐ High	☐ Medium	☐ Low	☐ Never Traveled	☐ Never	☐ Rarely	☐ Sometimes	☐ Frequently
Buses or Coaches	☐ High	☐ Medium	☐ Low	☐ Never Traveled	☐ Never	☐ Rarely	☐ Sometimes	☐ Frequently
Trains	☐ High	☐ Medium	☐ Low	☐ Never Traveled	☐ Never	☐ Rarely	☐ Sometimes	☐ Frequently
Aircraft	☐ High	☐ Medium	☐ Low	☐ Never Traveled	☐ Never	☐ Rarely	☐ Sometimes	☐ Frequently
Small Boats	☐ High	☐ Medium	☐ Low	☐ Never Traveled	☐ Never	☐ Rarely	☐ Sometimes	☐ Frequently
Ships (e.g., Channel Ferries)	☐ High	☐ Medium	☐ Low	☐ Never Traveled	☐ Never	☐ Rarely	☐ Sometimes	☐ Frequently
Swings in Playgrounds	☐ High	☐ Medium	☐ Low	☐ Never Traveled	☐ Never	☐ Rarely	☐ Sometimes	☐ Frequently
Roundabouts in Playgrounds	☐ High	☐ Medium	☐ Low	☐ Never Traveled	☐ Never	☐ Rarely	☐ Sometimes	☐ Frequently
Big Dippers, Funfair Rides	☐ High	☐ Medium	☐ Low	☐ Never Traveled	☐ Never	☐ Rarely	☐ Sometimes	☐ Frequently

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Did any of these experiences make you vomit while traveling?

☐ Yes ☐ No

If yes, which experiences made you vomit?

- | | | |
|--|---|---|
| ☐ Cars | ☐ Buses or coaches | ☐ Trains |
| ☐ Aircraft | ☐ Small boats | ☐ Ships |
| ☐ Swings in playgrounds | ☐ Roundabouts in playgrounds | ☐ Big dippers, funfair rides |

OVER THE LAST 10 YEARS: Check the appropriate boxes for each section:

Experience Level					Level of Motion Sickness			
What was your experience with each motion stimulus?					How often did you feel motion sick?			
Cars	☐ High	☐ Medium	☐ Low	☐ Never Traveled	☐ Never	☐ Rarely	☐ Sometimes	☐ Frequently
Buses or Coaches	☐ High	☐ Medium	☐ Low	☐ Never Traveled	☐ Never	☐ Rarely	☐ Sometimes	☐ Frequently
Trains	☐ High	☐ Medium	☐ Low	☐ Never Traveled	☐ Never	☐ Rarely	☐ Sometimes	☐ Frequently
Aircraft	☐ High	☐ Medium	☐ Low	☐ Never Traveled	☐ Never	☐ Rarely	☐ Sometimes	☐ Frequently
Small Boats	☐ High	☐ Medium	☐ Low	☐ Never Traveled	☐ Never	☐ Rarely	☐ Sometimes	☐ Frequently
Ships (e.g., Channel Ferries)	☐ High	☐ Medium	☐ Low	☐ Never Traveled	☐ Never	☐ Rarely	☐ Sometimes	☐ Frequently
Swings in Playgrounds	☐ High	☐ Medium	☐ Low	☐ Never Traveled	☐ Never	☐ Rarely	☐ Sometimes	☐ Frequently
Roundabouts in Playgrounds	☐ High	☐ Medium	☐ Low	☐ Never Traveled	☐ Never	☐ Rarely	☐ Sometimes	☐ Frequently
Big Dippers, Funfair Rides	☐ High	☐ Medium	☐ Low	☐ Never Traveled	☐ Never	☐ Rarely	☐ Sometimes	☐ Frequently

t

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Did any of these experiences make you vomit while traveling?

☐ Yes ☐ No

If yes, which experiences made you vomit?

☐ Cars

☐ Buses or coaches

☐ Trains

☐ Aircraft

☐ Small boats

☐ Ships

☐ Swings in playgrounds

☐ Roundabouts in playgrounds

☐ Big dippers, funfair rides

Appendix B. Confidential Medical Questionnaire

Screening Number: _____ Participant Number: _____ Date: _____

Gender (check one): Male ☐ Female ☐

Age: _____ Height: _____ Weight: _____

Part 1- Directions: **Circle “Yes”** if you currently suffer from or have ever been diagnosed with the condition **AND** explain below the question.

Circle “No” if they don't apply.

These questions are being asked to ensure your safety in this study.

ALL ANSWERS WILL BE KEPT CONFIDENTIAL

- | | | | |
|-----|--|-----|----|
| 1. | Do you have any drug allergies? | Yes | No |
| 2. | Do you currently or have you ever been diagnosed with asthma? | Yes | No |
| 3. | Do you have a history of or currently suffer from severe allergies? | Yes | No |
| 4. | Have you ever been diagnosed with sleep apnea? | Yes | No |
| 5. | Have you ever been diagnosed with a seizure disorder? | Yes | No |
| 6. | Do you currently or have you ever suffered from liver/kidney problems? | Yes | No |
| 7. | Do you have a history of urinary retention? | Yes | No |
| 8. | Have you ever been diagnosed with heart/circulatory disease? | Yes | No |
| 9. | Do you currently suffer from high blood pressure? | Yes | No |
| 10. | Have you ever been diagnosed with glaucoma? | Yes | No |

11.	Have you ever been diagnosed with emphysema?	Yes	No
12.	Have you ever been diagnosed with an enlarged prostate?	Yes	No
13.	Do you have a history of gastrointestinal disorders? (e.g. bowel distention, irritable bowel syndrome)	Yes	No
14.	Have you have been diagnosed with epilepsy?	Yes	No
15.	Have you ever suffered from pneumonia?	Yes	No
16.	Do you have a history of alcohol and drug dependency?	Yes	No
17.	Have you used any tobacco products in the last 6 months?	Yes	No
18.	Have you donated blood or plasma in the past 30 days?	Yes	No
19.	Have you, in the past or at present, experience discomfort in confined spaces?	Yes	No
20.	Do you take any prescribed medication on a regular basis?	Yes	No
21.	Have you taken a prescribed medication within the past 7 days?	Yes	No

Females:

22.	Are you currently pregnant or lactating?	Yes	No
23.	Do you tend to suffer regularly from premenstrual syndrome (PMS)?	Yes	No

Part II- Directions: Note any medication to which you currently or have ever had an allergic reaction or sensitivity to.

Scopolamine (Scopace)	Yes	No
Amphetamine (Adderal)	Yes	No
Other(s)	(Please list each medication)	

Part III- Directions: Answer the following questions to the best of your ability.

1. Are you in your usual state of fitness? (*circle one*) Yes No

a. If not, please indicate the reason: _____

2. Have you been ill in the past week (circle one) Yes No

a. If yes, please indicate the nature of the illness (e.g., flu, cold, etc.) _____

b. The severity of the illness (*Circle one*):

Very mild-----1-----2-----3-----4-----5-----Very Severe

c. Length of the illness Hours:_____ Days:_____

d. Major Symptoms: _____

e. Are you fully recovered? Yes No

3. Indicate all medication you have used in the past 24 hours.
(*circle all that apply*)

- a. None
- b. Sedatives/Tranquilizers
- c. Aspirin/Tylenol/any analgesic
- d. Antihistamines
- e. Decongestants
- f. Other (please specify)

4. Do you take any over the counter medications (e.g., antacids, Benadryl, Tylenol, etc.) two (2) or more times a month? Yes No

5. How many hours did you sleep last night? _____

Was this amount sufficient? Yes No

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