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Restricted sedation and absence of cognitive impairments after administration of intranasal scopolamine

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Abstract

Introduction: Space motion sickness in astronauts during spaceflight causes significant discomfort, which might impede their functionality. Pharmacological treatment has been mainly restricted to promethazine. Transdermal and oral scopolamine have also been used in space; however, their use was reduced due to unpredictable effectiveness and side effects. Recently, intranasal scopolamine administration has gained much interest, since this route ensures fast and reliable absorption with a decreased incidence of undesirable side effects. The aim of this study was to evaluate the effect of intranasal scopolamine on cognitive performance and to determine its side effects.

Methods: This double-blind, placebo controlled, repeated measures study evaluated vigilant attention, short-term memory, implicit memory and working memory. Side effects were reported on a 22-item questionnaire and sleepiness was assessed by the Karolinska, Stanford and Epworth Sleepiness Scales.

Results: Scopolamine had no effect on cognitive function. Only the Karolinska score was significantly increased for scopolamine compared to placebo. Participants reported a dry mouth and dizziness after receiving scopolamine.

Discussion: Results show that intranasal scopolamine did not impair cognitive performance. Intranasal scopolamine might be a good alternative to promethazine for the alleviation of space motion sickness, since the agent has minimal sedative effects and does not hamper cognitive performance.

Keywords

Space motion sickness, intranasal scopolamine, working memory, short-term memory, implicit memory

Introduction

Space motion sickness is a condition that resembles terrestrial motion sickness and that typically manifests in 70% of astronauts during the first three days in space (Davis et al., 1988; Lackner and Dizio, 2006). Symptoms may vary from dizziness and cold sweats to episodes of projectile vomiting. Depending on the severity of the symptoms, the discomfort experienced by astronauts can range from being mild to completely incapacitating. It is clear that the occurrence of such symptoms affects the astronauts' normal spatial activities and that it might lead to hazardous situations when they arise during emergency egress or other critical events. Astronauts are therefore not allowed to perform extra-vehicular activities during the first few days of spaceflight (Freeman, 2000). To date, promethazine has been reported as the standard pharmacological countermeasure used in space programmes notwithstanding that the drug is known to cause significant sedation. This is a major drawback since the cognitive abilities of astronauts should be preserved in order to keep their operational skills at the highest possible level. Therefore, in order to counteract such a side effect, psychostimulants such as dextedrine have been given in combination with promethazine. However, reports concerning the efficacy of the combination of promethazine with dextedrine are contradictory and astronauts tend to be reluctant to use such combinations since amphetamines have a high likelihood of addiction and dependence (Souvestre et al., 2008). Recently, the opportunity to fly to space has been made possible for the general public, making

space motion sickness no longer an issue that only astronauts encounter. Indeed, space motion sickness symptoms will tend to develop in space tourists, which will negatively influence their spaceflight experience, as well as their general well-being.

The anti-muscarinergic drug scopolamine has been used for the symptomatological treatment of motion sickness and is considered as being the most effective one for decades (Shaw and Urquhart, 1981; Wood and Graybiel, 1968). The drug has been

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mostly administered orally or transdermally, but these administration routes have several drawbacks. First, oral scopolamine is known to have a poor absorption and an important hepatic first-pass metabolism, causing a low bioavailability of the drug (Ahmed et al., 2000; Putcha et al., 1989). Second, peak plasma concentrations (C_{max}) are only reached 12–16 hours after application of dermal patches, which causes blood concentrations to be elevated for a long period of time and significantly increases the risk of developing adverse effects such as dry mouth, drowsiness and blurred vision (Shaw and Urquhart, 1980). Transdermal scopolamine has been administered prophylactically during space programmes, but its use was reduced as the drug also caused blurred vision and significant sedation, which also required the addition of psychostimulants (Paule et al., 2004).

The development of an intranasal scopolamine formula has gained more interest over the past few years. This novel route of administration seems very useful during spaceflight as it is non-invasive, rapidly absorbed and ensures a fast onset of therapeutic action (Tonndorf et al., 1953). Additionally, the likelihood of developing sedation, blurred vision or other side effects would be decreased due to low dosage and thus lower blood concentration over a shorter period of time. All these advantages, together with the fact that scopolamine is considered as the most effective agent against motion sickness, make intranasal scopolamine an interesting alternative to promethazine for the treatment of space motion sickness. In the present paper, the adverse effects of intranasal scopolamine (0.4 mg) and its influence on psychomotor performance and different cognitive functions such as working memory, implicit memory and short-term memory will be further discussed.

Over the past decades, the involvement of the cholinergic system in memory and learning processes has been the subject of thorough investigation within cognitive research. Numerous pharmacological studies examining the effects of anticholinergics such as scopolamine have been elaborated. Drachman and Leavitt (1974) were the first to report scopolamine-induced amnesia in young healthy subjects and, ever since, the drug has been widely used to provoke amnesia in experimental settings. Studies of short-term memory with digit span, where subjects are asked to recall previously shown numbers, revealed that immediate recall was minimally affected by scopolamine but elucidated an impairment of delayed recall, suggesting a disrupted memory consolidation caused by the agent (Drachman and Leavitt, 1974; Ghoneim and Mewaldt, 1975). Moreover, performance during mental rotation tasks, during which subjects have to compare two three-dimensional objects, has also shown not to be impaired by scopolamine. These aforementioned observations tend to argue that the drug affects neither the phonological loop nor the visuospatial loop of short-term memory (Rusted, 1988). Studies have further demonstrated that scopolamine does not impair retention of information stored before drug administration, suggesting it rather has an influence on the acquisition of novel information (Petersen, 1977; Safer and Allen, 1971). Broks and co-workers (1987) investigated the effects of scopolamine on attention and spatial and verbal learning tasks by means of an extensive cognitive test battery. Results from that study showed that short-term memory remained unaffected; however, for long-term memory, spatial learning remained intact while verbal learning was impaired. Furthermore, the drug seemed to affect sustained attention, but not vigilance for single stimuli (Broks et al., 1987). It was

further claimed by former studies that scopolamine has no influence on working memory; however, more recent studies have refuted that idea. Muscarinic receptors have been shown to play a modulatory role in spatial and non-spatial working memory processing (Ellis et al., 2006; Rusted and Warburton, 1988). Moreover, Green and colleagues (2005) demonstrated scopolamine-induced impairments in both spatial and object working memory performance. All of these previous findings suggest that scopolamine affects cognitive performance in such a way that it might be detrimental for the functionality of astronauts during spaceflight. Hereto, only one study, performed by Simmons and co-workers (2010), has investigated the effects on cognition of a 0.4 mg dosage of scopolamine delivered intranasally. The results of that study showed no significant decrements on memory or reaction time (RT) after intranasal administration of the drug, but the authors did recommend that studies should focus on specific operational tasks where memory and recall are tested (Simmons et al., 2010). It is hypothesized that, since scopolamine is delivered at a low dose and under the best pharmacokinetical conditions as a nasal spray, the likelihood of developing cognitive impairments or other side effects would be reduced.

Keeping the importance of maximizing crew performance in mind, the present study investigated the following cognitive functions by means of a computer-driven test battery: psychomotor performance; working memory; short-term memory; implicit memory.

Material and methods

Subjects

After a medical screening for eligibility, a total of 19 healthy male volunteers (mean age 24.4 years; range 20.15–29.32 years) were included for participation. None of them exhibited a history of neurological, auditory or vestibular deficits. The study was commissioned by the European Space Agency and approved by the Institutional Review Board of the Antwerp University Hospital (reference no. B30020072398). Each participant provided a signed informed consent form for both the screening and the actual test sessions. All clinical investigations have been conducted according to the principles expressed in the Declaration of Helsinki.

Study design

A double-blind, placebo controlled and repeated measures design was adopted. Participants were accustomed to the cognitive test battery by a training session that took place during the medical screening, before the actual start of the clinical study. During the study, cognitive function tests were performed at the same hour of the day in order to exclude the interference of circadian effects. The nasal spray was administered by the investigator at the start of each session in an identical manner for both scopolamine (0.4 mg) and placebo. Product order was randomly assigned and a wash-out period of minimally four weeks was foreseen between each product. Participants, each of them a non-smoker, were instructed to stop alcohol consumption one day before the testing day and no caffeine or quinine containing beverages were allowed during the testing days. The intake of any other medication had to be reported to the investigator and the medical doctor supervising the study.

Nasal spray device and drug administration

The nasal spray devices were manufactured under good manufacturing practice conditions by the School of Pharmacy, Department of Pharmaceutical Sciences located at the University of Maryland, Baltimore, USA. Both placebo and scopolamine formulations were filled into Aptar® bidose nasal spray devices. Each scopolamine nasal spray device delivered two puffs, with a concentration of 0.1 mg/0.1 mL per puff. In order to achieve a total delivery of 0.4 mg of scopolamine, two nasal spray devices (and thus a total of four puffs), one in each nostril, were administered to the subjects. For administration of placebo, the same amount of nasal sprays and puffs were used.

A bioavailability study performed by Putcha and colleagues (1996) has shown that intranasal administration of 0.4 mg of scopolamine results in $C_{\max}$ after 0.37 ± 0.05 hours and a mean residence time (the average time a molecule spends in the body) of 1.57 ± 0.12 hours.

Cognitive tests

The effects of scopolamine on cognitive performance were evaluated approximately three hours after drug/placebo administration by means of a test battery comprising four computer-driven tasks. Written instructions were provided at the start of each test and the test sequence was similar in all conditions.

Psychomotor vigilance task. Vigilant attention is measured by means of the psychomotor vigilance task (PVT), which is a test of simple RT (Dinges and Powell, 1985). Participants are asked to click the left mouse button as soon as a visual stimulus (a flashbulb) appears on the computer screen. The stimuli are shown randomly with different intervals (2000, 4000, 6000, 8000 and 10000 ms). The RT is set at 500 ms and each response exceeding that time is registered as a lapse. Total duration of the test is 10 minutes. The mean RT (ms) for all the correct responses is calculated and the number of lapses is determined.

The Sternberg working memory task. During this test, which follows a classic matching-to-sample paradigm, short-term memory function is assessed (Sternberg, 1969). An array of numbers, varying from one to six, is shown on the computer screen and subjects are asked to memorize the array. Subsequently, a number is presented and subjects have to indicate whether this appeared in the previously presented series of numbers. The mean RT (ms) and accuracy (number of correct answers) are calculated.

Implicit memory. The implicit memory test (Jacoby, 1983) starts with words that are shown on the computer screen and have to be read out loud by the participant. The presented words are based on an available lexicon and are matched for length and frequency. During the second part of the test, words, some of them presented in the previous series, are shown very briefly on the computer screen. The subject is then asked to reproduce the word he thought he recognized. The accuracy (total number of correctly reproduced words) is determined at the end of the test.

Automated operation span task. Working memory is assessed by means of the automated operation span (Ospan) task (Conway and Engle, 1996). During the experiment, participants are asked

to simultaneously solve mathematical problems and memorize letters that are presented between each maths operation in the correct order.

Before the actual start of the experiment, a practice session is provided in order to familiarize the participant with the conduct of the test. First, letters are shown on the screen and the subject is asked to memorize these and to recall them in the order they were shown. Second, a calculation appears (e.g. $(7*3)-3 = ?$) and the participant is asked to click the mouse once he knows the answer. A possible solution is then presented and the participant has to indicate whether the suggested solution is 'true' or 'false'. The average time needed to solve the calculation plus 2.5 SD is calculated and used as a time limit for the further maths operations in order to detect whether the subject is rehearsing the order of the presented letters while simultaneously solving the maths operations and thus being slower on mathematical processing. After this, letter recall and calculations have to be performed together. The experimental block starts immediately after the last practice exercise and consists of three sets of each set size (the total amount of letters that have to be recalled ranges from three to seven). Hence, a total of 75 letters and maths operations are presented throughout the experimental block. Furthermore, the percentage of maths accuracy is shown on the upper right corner of the screen and the subject is asked to keep this accuracy at or above 85%. A total of five scores are computed when the experiment is finished: Ospan score (sum of letters in all the correct recalled letters sets); Ospan total (sum of the letters recalled in the correct position regardless of whether the entire set was correct); Ospan accuracy error (number of wrongly answered maths operations); Ospan speed error (number of answers beyond the allowed time); Ospan maths error (sum of Ospan accuracy error and Ospan speed error).

Questionnaires

Participants were asked to complete several questionnaires at the beginning of each test session. By means of the Karolinska Sleepiness Scale (Åkerstedt and Gillberg, 1990) and the Stanford Sleepiness Scale (Hoddes et al., 1972), subjects indicate to what degree they have experienced sleepiness during the intake of scopolamine by marking one of the suggested states of sleepiness. The lowest score, 1, reflects an alert, awake state and the highest score, 9 for the Karolinska and 8 for the Stanford Scale, reflects a very sleepy or sleepy state respectively. A third sleepiness scale, the Epworth questionnaire (Johns, 1991), was used to assess the overall state of sleepiness of the participants over the past month, which is thus not related to the intake of the drug. Each subject was asked to indicate the chance that he would have fallen asleep during different daily activities such as reading, watching TV, driving, etc. Finally, the occurrence of side effects after administration of scopolamine or placebo was evaluated by means of a questionnaire comprising 22 different symptoms. Participants indicated for each item to what degree they had experienced the adverse effect by means of a score between 0 and 3 (0 = symptom did not occur, 1 = symptom occurred to a small degree, 2 = symptom occurred moderately, 3 = symptom occurred severely).

Statistical analysis

Outcomes of the cognitive tests during scopolamine intake were compared to placebo by means of a parametric paired t-test.

Table 1. Mean values ($\pm$ SD) for both placebo and scopolamine for the cognitive tests.

Cognitive test and parameters	Placebo	Scopolamine
PVT – reaction time (ms)	295 $\pm$ 30.5	297 $\pm$ 28.7
Sternberg working memory test – reaction time (ms)	878 $\pm$ 236	940 $\pm$ 244
Sternberg working memory test – accuracy	0.955 $\pm$ 0.0341	0.948 $\pm$ 0.0372
Implicit memory – accuracy	0.943 $\pm$ 0.0469	0.944 $\pm$ 0.0484
Ospan – score	42.9 $\pm$ 15.5	38.0 $\pm$ 16.8
Ospan – total	60.0 $\pm$ 11.0	56.6 $\pm$ 15.5
Ospan – accuracy error	3.84 $\pm$ 2.71	4.58 $\pm$ 2.61
Ospan – speed error	1.32 $\pm$ 1.42	1.95 $\pm$ 1.93
Ospan – maths error	5.16 $\pm$ 3.78	6.53 $\pm$ 3.72

Comparison of data from the questionnaires was performed with a Wilcoxon signed-rank test. A significance level of 0.05 was chosen. Statistical analysis was performed with SPSS V20.

Results

The significant results are summarized in the following paragraphs.

Cognitive tests

Due to a technical problem that occurred during the recording of the PVT responses, data from eight subjects could not be retrieved for analysis. Hence, for that test, data from 11 subjects were analysed.

Statistical analysis on the outcomes of the PVT, the Sternberg working memory task, the Ospan and the implicit memory test revealed no significant effect of scopolamine after comparison with placebo. The means and SD can be found in Table 1.

Questionnaires

Statistical analysis of the data from the sleepiness questionnaires revealed a significant increase of the Karolinska score for scopolamine intake (median: 4) when compared to placebo (median: 3) (Wilcoxon, $p = 0.024$). The median of the difference between scopolamine and placebo calculated for each subject was 1. No significant effects were observed on the scores of the Epworth or the Stanford Sleepiness Scales.

Results from the side effects questionnaire revealed a significant increase of the scores given to the items dry mouth and dizziness when comparing scopolamine with placebo. Table 2 shows the percentage of ratings given by the participants for those two symptoms with the corresponding p -values.

Discussion

The occurrence of space motion sickness during the first days of spaceflights is known to be potentially incapacitating for astronauts. Moreover, in the context of space tourism, space motion sickness might also become a potential obstacle in the experience and well-being of tourists during their journey. Pharmacological countermeasures have been mainly restricted to promethazine but the drug requires concomitant administration of psychostimulants to counteract drug-induced sedation. Scopolamine, oral or

Table 2. Percentage of ratings for the significant items on the 22-item side effects questionnaire.

Items	Score (%)	0	1	2	3	p -value
		None	Little	Moderately	Severely	
Dry mouth	Placebo	58	42	0	0	0.007
	Scopolamine	32	21	32	16	
Dizziness	Placebo	69	26	5	0	0.046
	Scopolamine	32	58	10	0	

transdermal, has been successfully used against motion sickness for many years. However, the two routes of administration have several drawbacks, such as low oral bioavailability and an increased risk of developing adverse effects due to prolonged and elevated blood plasma concentrations.

Intranasal delivery of scopolamine seems a more elegant route since it would ensure a facilitated drug uptake followed by a rapid onset of therapeutic actions. Moreover, since there is no first-pass effect, drug concentrations should not be elevated, decreasing the risk of developing side effects and thus eliminating the need for simultaneous administration of amphetamines (Ahmed et al., 2000; Putcha et al., 1996). As preservation of operational integrity is of crucial importance for astronauts, the present study aimed to evaluate the effects of scopolamine administered as a nasal spray on cognitive performance targeting vigilant attention, short-term memory, working memory and implicit memory. Furthermore, the side effects profile was determined by means of a 22-item questionnaire and the degree of induced sleepiness was evaluated by means of the Karolinska (Åkerstedt and Gillberg, 1990), Stanford (Hoddes et al., 1972) and Epworth (Johns, 1991) Sleepiness Scales.

The results of the study show that intranasal administration of scopolamine did not exert any detrimental effects on working memory, psychomotor performance, implicit memory and short-term memory. The score of the Karolinska Sleepiness Scale was significantly increased after intake of scopolamine. However, similar effects were not observed on the Stanford and the Epworth Sleepiness Scales. By means of the side effects questionnaire, participants indicated that they suffered from a dry mouth and dizziness, both known to be common side effects of scopolamine. Interestingly, symptoms related to fatigue were not given a significantly higher score after receiving the drug, notwithstanding the fact that an increased score was given to the Karolinska Sleepiness Scale. Comparison of the median of the scores of the Karolinska Scale given during placebo (3) and scopolamine (4) intake, show that the increase is rather restricted. A score of '3' reflects an 'alert' state, whereas a score of '4' indicates a 'quite alert' state. Hence, these results suggest that during intake of scopolamine, subjects indicated that they felt less alert, but not significantly sleepier.

The role of acetylcholine in cognitive processes has been extensively investigated and scopolamine has been used for a long time in animal models of Alzheimer since it has been shown to cause amnesia (Drachman and Leavitt, 1974). Findings in literature show that scopolamine impairs consolidation of new information, verbal learning in long-term memory, sustained attention and working memory performance (Broks et al., 1987; Green et al., 2005; Petersen, 1977; Safer and Allen, 1971). A study performed by Simmons and colleagues (2010) investigated the effects of a 0.4 mg dose of intranasal scopolamine gel on cognition by means of a simple RT task, a matching to sample

test, a running memory span and a test assessing logical reasoning. The running memory span task is considered as a tool that assesses updating and maintenance of working memory in the focus of attention (Broadway and Engle, 2010). The findings of the present study are in accordance with the findings of Simmons et al. (2010), since in both studies none of the investigated cognitive processes was affected after administration of intranasal scopolamine. In contrast, no significant side effects were observed during the study of Simmons et al., whereas in the present study participants reported suffering from a dry mouth and dizziness. This discrepancy can be explained by the fact that different formulas, i.e. nasal gel vs. nasal spray, were used throughout both studies. Furthermore, the incidence of adverse effects was assessed by means of different types of questionnaires.

It is worth noting that the function of different cognitive processes is a complex matter and that these processes are often considered to consist of multiple dimensions that are assessed by means of a variety of tests. In the present study, the cognitive functions that are important in the context of functionality were targeted and other cognitive processes such as long-term memory or more specified functions such as spatial working memory were not considered. It has to be kept in mind that cognitive data from eight subjects could not be retrieved and this obviously could have had an impact on statistical power. In addition, it should be noted that intranasal scopolamine might affect other cognitive functions that were not addressed.

Despite the fact that scopolamine is considered one of the most efficient countermeasures against motion sickness, the use of transdermal patches in space programmes was reduced due to induced drowsiness, which required the concomitant use of dexedrine or d-amphetamine (Paule et al., 2004). However, findings from the present study suggest that scopolamine administered as a nasal spray does not affect short-term memory, implicit memory, working memory or vigilant attention. Moreover, it has shown to decrease the likelihood of developing undesirable effects such as sedation. In conclusion, it is hypothesized that intranasal administration of scopolamine during spaceflights would minimally affect functionality, making it a useful candidate drug for fast and efficient relieve of space motion sickness.

Conflict of interests

None declared.

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