Scopolamine Treatment and Adaptation to Airsickness

Omer Doron; Orit Samuel; Daphne Karfunkel-Doron; Dror Tal

BACKGROUND: Airsickness is a clinical syndrome manifesting in a variety of symptoms, particularly nausea and vomiting during flight. Studies of habituation to motion sickness in humans treated by scopolamine have produced conflicting results. The drug accelerated habituation, but a rebound effect on symptom severity was observed after its withdrawal. The purpose of the present study was to investigate whether scopolamine affects the adaptation process. We also evaluated the relationship between initial symptom severity and adaptation to airsickness.

METHODS: Aviator cadets in the first two stages of their training were divided into two groups, treated and not treated by scopolamine. Airsickness severity was evaluated using both simulator sickness and motion sickness questionnaires, and drug administration was recorded.

RESULTS: A statistically significant higher rate of adaptation was observed among the scopolamine-treated group compared with the nontreated group. On the simulator sickness questionnaire, rate of adaptation for the two groups was -0.21 ± 0.53 and -0.1 ± 0.17, respectively, and for the motion sickness questionnaire -2.34 ± 1.54 and -0.91 ± 1.41, respectively. Examination of a possible connection between initial symptom severity and adaptation rate failed to reveal a significant relationship.

CONCLUSIONS: We recommend the use of oral scopolamine to accelerate habituation and find it a relatively safe short-term treatment for airsickness. Our results support the notion that scopolamine accelerates the natural adaptation process.

KEYWORDS: scopolamine, airsickness, adaptation, simulator sickness questionnaire.

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Airsickness is a distinct form of motion sickness. The clinical syndrome manifests in a variety of symptoms, particularly nausea and vomiting during flight. Among the remaining well-known symptoms are malaise, pallor, cold sweating, abdominal discomfort, changes in gastric motility, and changes in the level of circulating hormones.[10,15] The incidence of airsickness among flight academy cadets has been investigated in a number of studies, reaching as much as 88%.[13,14] Despite the high incidence of airsickness reported by student aviators, symptoms tend to fade over a relatively small number of sorties. The phenomenon usually affects subjects only at the beginning of their flight training, as most individuals will quickly adapt to the novel environment.

In a large study of U.S. student aviators, 88% were symptomatic during at least one of the first three sorties, while an abrupt drop to about 10% was reported during the fourth. At later stages in the course, changes in the flight acceleration characteristics resulted in the reappearance of symptoms.[18] The first transport flight of military parachutists produced symptoms in 64% of these service personnel, decreasing to 25% after five consecutive flights.[1] In contrast, Lucertini et al.[10] found that 12.2% of students at the Italian aviation academy were "slow adaptors," defined as having symptoms after the sixth sortie. Most of the subjects in this subgroup were women. In the Swiss aviation academy, however, no airsickness symptoms were observed after the seventh sortie.[15] Despite the fact that pharmacological treatment was prohibited, the authors found no reason to propose that airsickness should serve as a criterion for candidate selection.

Airsickness, as a subcategory of motion sickness, is considered to result from similar physiological processes, and is described by the widely accepted "neural mismatch and sensory rearrangement theory." It is believed that a neural mismatch

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occurs when inputs from the vestibular, visual, and proprioceptive sensory systems are inconsistent with past motion experience. While inducing the symptoms of motion sickness, the mismatch simultaneously initiates a sensorineural rearrangement.[3,12] The conventional treatment for motion sickness is the anticholinergic scopolamine (hyoscine hydrobromide 300–600 μg). This pharmacological treatment was also embraced as the drug of choice for airsickness, such as in the case of British Royal Air Force cadets.[2]

In the military flight academy, the selection of the best candidates generates a distinctive challenge. The academy physician may also face a number of treatment options that could be contradictory. During their first flights, airsickness might prevent candidates from fully revealing their skills and they should, therefore, be offered treatment with scopolamine. On the other hand, the drug might lead to a number of cognitive side effects. In addition to the possible short-term side effects, scopolamine may also affect long-term adaptation processes. Takeda et al.[17] demonstrated that scopolamine accelerated the process of habituation to a double rotation stimulus in a rat model. Kohl et al.[7] also noted accelerated adaptation when they examined a combination of scopolamine and amphetamine compared with placebo. Wood et al.[20] reported a conflicting set of results regarding habituation to rotation stimulus in humans. The drug was found to accelerate habituation, but a rebound effect on symptom severity was observed after its withdrawal. These findings suggest that the neuronal cholinergic system may be involved in the process of habituation to motion sickness. However, Lackner and Graybiel[8] failed to demonstrate changes in adaptation rates following intramuscular injection of scopolamine (0.5 mg).

It therefore seems crucial to define the appropriate scopolamine treatment protocol, in order to minimize interference in natural adaptation processes. Furthermore, from our review of the literature, we were unable to obtain a clear picture of the association between initial airsickness severity and the ability to adapt. Thus, the physician may not be able to rely on a candidate's initial sensitivity to predict future adaptation processes.

The purpose of the present study was to investigate whether the process of adaptation to airsickness might be affected by scopolamine. We also sought to examine the relationship between initial airsickness severity and subsequent adaptation.

METHODS

Subjects

Of the total 506 student aviators in the first and second stages of light aircraft training who were approached, 331 volunteered to participate in the study. Only 256 of these met the minimum criterion for qualification, which was the completion of a Simulator Sickness Questionnaire (SSQ) on four or more occasions. Subjects were followed up in a prospective study. During flight, 92 were asymptomatic and 164 symptomatic. Of the symptomatic subjects, 19 were assigned to the treatment group (T), and 145 (137 men, 8 women) were not treated (NT) and, therefore, served as a control group. Subjects' ages ranged from 18.3 to 23.68 yr (mean 19.34 yr), with no significant difference between the study groups. The study was approved by the Israel Defense Forces Medical Corps Human Research Committee, and informed consent was obtained from all participants. No other medications were taken by subjects in the course of the study. Airsickness symptoms were self-reported by means of an SSQ.[5] All participants attended a lecture on the etiology, symptoms, and treatment of airsickness. Subjects were assigned to the two study groups in accordance with their own decision whether to volunteer for pharmacological treatment.

Subjects were students at the Academy in 2013–2014. All subjects underwent an annual medical examination at the Israel Air Force Military Academy Clinic, and were proven to be healthy, fit individuals. The first stage of flight training lasted 5 mo and comprised 15 sorties. The second stage began 12 mo after the beginning of training and comprised 10 sorties. During the 6–10 mo break between the two stages of training, subjects had no exposure to flight whatsoever.

For inclusion in the study, subjects had to be healthy (as approved by the Academy Clinic), male or female student aviators ages 18 to 40, not suffering from any acute illness during the week prior to the flight session, and not taking any drugs in the 24 h preceding flight. Any cadet suffering from otitis or subjective hearing loss, having vestibular pathology of any kind, or a contraindication to scopolamine was excluded.

Materials

No questionnaire has ever been developed specifically for airsickness. Motion sickness was historically assessed by means of a motion sickness questionnaire (MSQ), numerous variants of which have been developed by generations of investigators. With the development of flying simulators, the MSQ was adapted for use in the evaluation of simulator sickness as the SSQ. Further adaptations of the SSQ enabled its use for seasickness and for airsickness in aviation during hurricane-strength storms.[5] The SSQ is designed to emphasize the visual aspects of artificial flight simulation. The MSQ focuses on acceleration effects during real motion in three dimensions, summing up subjects' rating of the symptoms to give the MSQ score.

Lane and Kennedy[9] adapted their approach to simulator sickness for the aeronautical environment. Since then, it has become well accepted for use in the assessment of airsickness. Symptoms are classified into three subcategories: nausea, oculomotor symptoms, and disorientation. The sum of these three categories is then calculated to give the final SSQ score. Kennedy et al.[6] later grouped symptoms into six categories: 0 = "No symptoms"; 0–5 = "Negligible symptoms"; 5–10 = "Minimal symptoms"; 10–15 = "Significant symptoms"; 15–20 = "Symptoms are a concern"; 20 and above = "A problem simulator."

Procedure

The first two sorties in each stage were conducted without any pharmacological treatment in order to evaluate airsickness severity. Subsequently, a 300-μg scopolamine tablet (Kwells, Bayer, Newbury, Berkshire, UK) was offered to those who desired

to begin treatment. The tablet was administered orally 1 h before any sortie. In accordance with the expected habituation phase of six sorties, cadets on their seventh sortie received no treatment. Subjects symptomatic on this flight had the option of receiving scopolamine tablets for the rest of their training.

Statistical Analysis

Statistical analysis was carried out using SPSS 12.0 software (SPSS Inc., Chicago, IL, USA). Differences between the T and NT groups for sensitivity and adaptation rate were analyzed using a paired sample *t*-test and the Mann-Whitney test for parametric and nonparametric data, respectively. Multivariate analysis of the symptom severity groups was calculated using ANOVA. The rebound effect was analyzed using a paired *t*-test. A *P*-value of 0.05 was taken as representing statistical significance.

RESULTS

Data were analyzed for the 256 participants who had completed at least four SSQ. A total of 1624 questionnaires were filled out in the first stage and 562 in the second. The average number of questionnaires collected per subject for the two stages was 7.6 and 6.9, respectively. No major side effects were reported during treatment. One subject reported a minor side effect of blurred vision.

To calculate the adaptation rate, SSQ scores were normalized to each subject's first sortie. Linear regression was derived for each subject's scopolamine-free flights and a slope was calculated representing the individual adaptability rate. An example may be seen in **Fig. 1**. Adaptation rate in the T group was calculated using their scopolamine-free flights. Such "windows" were enabled by the treatment protocol, which precluded the use of scopolamine in flights 1, 2, and 7, and by subjects choosing not to take the drug in other specific flights. All sorties were included in calculation of the adaptation rate for the NT group.

To test the effect of scopolamine on the adaptation process, we compared the adaptation rates of the T and NT groups in 16 and 106 cadets, respectively (**Table I**). Because there was an insufficient number of subjects in the T group during the second stage of training, these adaptation rates represent only the first stage. The Mann-Whitney test revealed a statistically significant higher adaptation rate among the T group compared with the NT group (-0.21 ± 0.53 and -0.1 ± 0.17, respectively; $P = 0.01$). Moreover, MSQ scores revealed significant differences in the adaption rates between T and NT groups (-2.34 ± 1.54 and -0.91 ± 1.41, respectively; $P = 0.0001$).

To assess whether there is a relationship between initial symptom severity and the adaptation rate, only the control group (NT) was included, to avoid the effect of scopolamine. Subjects were subdivided into two groups for each training stage according to symptom severity. Subjects with minimal symptoms (0–10) were assigned to the mild severity group ($N = 48$ in the first and $N = 21$ in the second training stage). Those with severe symptoms (10 and greater) were assigned to a second group ($N = 58$ in the first and $N = 18$ in the second training stage). As can be seen in **Table II**, no significant difference was found between the slopes for the mild and severe groups in the first stage (-0.12 ± 0.24 and -0.09 ± 0.05, respectively; nonparametric Mann-Whitney test, $P = 0.1$). Similarly, we found no significant difference between the slopes for the mild and severe groups in the second stage of training (-0.12 ± 0.17 and -0.12 ± 0.04, respectively; Student's unpaired *t*-test, $P = 0.99$).

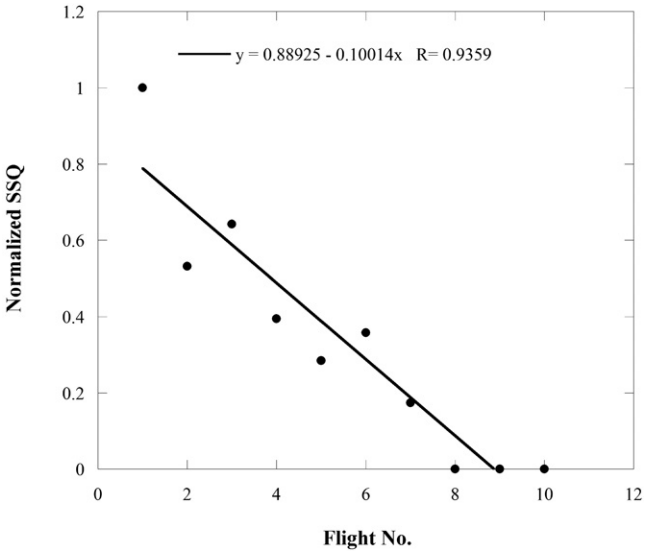

Fig. 1. Linear regression curve for normalized simulator sickness questionnaire (SSQ) scores recorded for an individual cadet from the group not treated (NT) with scopolamine.

Due to the large number of subjects in the first stage, we were able to redistribute the NT population among three severity groups according to their SSQ scores: 0–10; 10–20; and 20 and above. No statistically significant difference was found in adaptation rate between the three groups [$N = 48$, -0.12 ± 0.24; $N = 26$, -0.08 ± 0.05; and $N = 32$, -0.01 ± 0.05, respectively; ANOVA, $F(2103) = 0.55$, $P = 0.58$].

The data also enabled us to examine whether previous flight experience might influence a subject's airsickness severity or adaptation processes in the subsequent stages of the course. We therefore compared initial airsickness severity in the NT group for the first and second stages of training (**Table III**). No significant difference was found for symptom severity between the first flight of the first stage and the first flight of the second stage (13.27 ± 11.94 and 17.53 ± 16.77, respectively; Mann-Whitney test, $P = 0.25$). However, the adaptation rate was higher in the

Table I. Normalized Slopes for the Adaptation Rate in Treated and Not Treated Cadet Groups in Non-Scopolamine Flights.

STAGE	T	ADAPTATION RATE	NT	ADAPTATION RATE	*P*-VALUE
1st	$N = 16$	–0.21 ± 0.53	$N = 106$	–0.1 ± 0.17	0.01
2nd	N/A	N/A	N/A	N/A	N/A

Data are expressed as mean ± SD. T = treated; NT = not treated; N/A = not applicable.

Table II. The Relation Between Initial Severity and Adaptation Rate, Normalized Slope for the Two Severity Groups in the Different Stages.

STAGE	MILD SYMPTOMS (0-10)	ADAPTATION RATE	SEVERE SYMPTOMS (≥ 10)	ADAPTATION RATE	*P*-VALUE
1st	*N* = 48	–0.12 ± 0.24	*N* = 58	–0.09 ± 0.05	0.10
2nd	*N* = 21	–0.12 ± 0.17	*N* = 18	–0.12 ± 0.04	0.99

Data are expressed as mean ± SD.

second stage than in the first (−0.11 ± 0.08 and −0.09 ± 0.01, respectively). This finding was statistically significant (Mann-Whitney Test, $P = 0.01$).

The possibility of a rebound effect (exacerbation of symptoms after withdrawal of the medication) was examined by comparing the SSQ scores for a flight with scopolamine administration and the following flight without scopolamine for 26 pairs of data which met this criterion. We found no rebound effect between the scopolamine and no-scopolamine flights (16.38 ± 19.98 and 19.00 ± 22.37, respectively; paired *t*-test, df = 25, $P = 0.49$).

DISCUSSION

The military flight academy's training program is interspersed with long periods of academic study lasting up to 1 yr, during which the cadets do not fly. It is not clear what may be the effect of these prolonged breaks in flying activity, as well as their impact on airsickness severity and adaptation, particularly when medication is involved. The purpose of the present study was to evaluate airsickness severity and adaptation in relation to scopolamine.

We demonstrated a 61% incidence of airsickness symptoms in flight academy cadets during the first stage of their training. These rates are higher than previously reported, the differences perhaps being due to the techniques employed for the evaluation of airsickness. Most previous studies used only severe nausea and vomiting as evidence of airsickness without referring to other known symptoms. The SSQ employed in our study covered additional symptoms other than simply nausea and vomiting, thus taking into account a broader spectrum of airsickness.

The main finding of the present study was a significantly higher airsickness adaptation rate among cadets treated with scopolamine compared with those not treated. The findings from these flights in which cadets experienced airsickness agree with those of previous animal and human laboratory rotation studies of motion sickness.

A number of studies have examined the neuropharmacology of antimotion sickness drugs. Takeda et al.[16,17] classified the drugs by mechanism. According to their model, each of the three classes has a specific effect on habituation due to its intrinsic properties. Class A drugs block the sensory input that is liable to lead to sensorineural mismatch. Because this input is not received, the habituation process is postponed. Class B drugs modify neural storage, the holding center for patterns of past experience. Consequently, these drugs act to accelerate habituation by attenuating any mismatch. Finally, Class C drugs block signals arriving at the emetic center, thus precluding the expression of motion sickness symptoms and preventing any effect on habituation.

Based on the results of double rotation in a rat model, the authors ascribed scopolamine to Class B. They hypothesized that acetylcholine transmits past sensory memory information into neural storage via the muscarinic receptors. Blockage of acetylcholine by scopolamine prevents this transfer, instead enabling acquisition of a new sensory pattern. A common claim is that scopolamine suppresses integration of the sensory stimuli in the vestibular nuclei.[11] Modifying neural input is thought to contribute to the cerebellar and reticular systems in order to readjust spatial orientation.

Wood et al.[20] reported a similar effect using a rotation stimulus in humans. They found that scopolamine accelerated adaptation and decreased motion sickness symptoms, also noting a rebound effect in which symptoms were exacerbated after discontinuation of the medication. A reduction of seasickness symptoms in sailors using the scopolamine patch as opposed to placebo was described by van Marion et al.[19] After removal of the patch, subjects displayed a higher degree of symptoms in comparison with the placebo group. The authors suggested that this rebound effect was due to hypersensitivity of the scopolamine receptors after stopping the drug.

These observations are not borne out by our study results, which failed to demonstrate a statistically significant rebound effect in student aviators after discontinuing scopolamine. This may be attributed to the low scopolamine dose given in our study (300 μg), in contrast with previous studies. In the majority of cases, the rebound effect was correlated with higher doses of scopolamine, such that a gradual reduction of the dose has been recommended in order to avoid this.[11]

We hypothesize that in nonevolutionary conditions (travel by sea, air, car, etc.), the vestibular system has inherent errors that result in susceptibility to motion sickness. Another property of the vestibular system is its ability to adapt. Both of these are considered independent intrinsic properties. Our subjects were divided into groups based on their initial response during the first stage of training. When adaptation rates were normalized to the initial response, we were unable to find

Table III. Normalized Initial Airsickness Severity and Adaptation Rates for the NT (Not Treated) Group in the First and Second Stages of Training.

SEVERITY OF SYMPTOMS IN THE FIRST FLIGHT			ADAPTATION RATE		
1st STAGE	2nd STAGE	*P*-VALUE	1st STAGE	2nd STAGE	*P*-VALUE
13.27 ± 11.94	17.53 ± 16.77	0.25	–0.09 ± 0.01	–0.11 ± 0.08	0.01
N = 106	*N* = 28		*N* = 106	*N* = 28	

Data are expressed as mean ± SD.

a significant difference between the study groups. This finding is consistent with our hypothesis. The two independent intrinsic properties of initial susceptibility and subsequent adaptation may result from a diversity of neurophysiological pathways. Preliminary sensitivity may arise via pathways in the brain stem, whereas adaptation is thought to follow a cortical pathway. The cerebral cortex and the limbic system, including the hippocampus, are considered the major sites of spatial orientation information processing. The neural mismatch signal activates cholinergic neurons, and seemingly stimulates the development of adaptation processes by updating the neural store.[17]

Although symptoms did reappear during the second stage, the adaptation rate was accelerated. It appears that adaptation processes were deactivated between training stages, with a subsequent return of sensitivity to flight stimuli. However, re-exposure to flight appears to reactivate the adaptation process in an accelerated manner. This is in agreement with the findings of Hu and Stern,[4] who demonstrated almost full retention of adaptation after 1 mo and partial retention after 1 yr.

Based on the findings of previous studies and the present investigation, we would recommend the use of oral scopolamine as a relatively safe, short-term pharmacological treatment for airsickness. Our results also suggest that scopolamine accelerates the natural adaptation process.

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