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ORIGINAL RESEARCH



Comparative study of the effect of bilastine and cetirizine on cognitive functions at ground level and at an altitude of 4,000 m simulated in hypobaric chamber: a randomized, double-blind, placebo-controlled, cross-over study

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ABSTRACT

Introduction: Antihistamines are easily accessible and cover the vast majority of the medical therapy of allergic rhinitis. However, their systemic administration may more frequently associate with their well-known side-effect, sedation, which is a serious problem in persons in safety-critical jobs such as aviation. We have a poor understanding whether a non-sedative antihistamine has an impact on vigilance when hypobaric hypoxia occurs during flight.

Methods: In this randomized, placebo-controlled, double-blind, cross-over study the effect of 20 mg bilastine was compared to 10 mg cetirizine and to placebo (20 mg pyridoxine) in 33 individuals at ground level and at 4,000 m altitude simulated in hypobaric chamber. Levels of vigilance, ultrashort memory, combined distributive attention, monotony tolerance and peripheral blood oxygen saturation (SpO₂) were assessed.

Results: Bilastine did not impair the tested abilities in comparison with the control groups either at ground level or hypobaric hypoxia. Administration of cetirizine increased the number of errors at ground level. At the simulated altitude, already impaired results were additionally demonstrated with regards to the distributive attention test.

Conclusions: From the two examined antihistamines, bilastine should be the preferred medication for by individuals who require constant attention and are exposed to hypobaric hypoxia.

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Antihistamine; attention; aviation; cognitive capability; hypobaric hypoxia; sedation; vigilance

1. Introduction

Today, in industrialized countries, the frequency of allergic rhinitis (AR) is estimated at 10–20% [1]. In 2015, according to our own survey, its prevalence was 14.03% among healthy young adults applying for military service in Hungary [2]. It is known that the disease may cause daytime feeling of drowsiness and fatigue, which in turn, impairs cognitive functions. Essentially, this impairment is not due to the inferior quality of sleep caused by the general symptoms of the disease, it is rather a result of the systemic effect of the released mediators and cytokines associated with it [3]. A prior study showed that nasal pollen provocation in patients with allergic rhinitis caused significantly worse driving performance of the subjects than of the placebo group. This deterioration is equivalent to a 0.05% blood alcohol level [4]. This bears a negative impact on the individual's quality of life, and the resulting reduction in working capacity and the cost of treatment due to high-prevalence have a substantial impact on the economy at large. According to calculations, the economic burden stemming from reduced work productivity and capacity due to allergic diseases (allergic rhinitis, allergic asthma, atopic dermatitis) amounted to an estimated 55–155 billion euros in the EU countries in 2014, a cost of almost 2,400 euros per patient [5]. Antihistamines, i.e. H₁-receptor inverse agonists are the basic

compounds for the treatment of allergic rhinitis. First-generation antihistamines cross the blood–brain barrier, so they can block cortical histamine receptors, resulting in drowsiness, fatigue and concentration loss. Their use today is not recommended for the treatment of AR any longer [1,6]. Second-generation agents, such as loratadine, desloratidine, cetirizine, levocetirizine, fexofenadine, bilastine, have the same efficacy as first-generation antihistamines, but have an improved side-effect profile. This is attributable to their increased H₁ receptor specificity and their massive lateral chains, which make their crossing through the blood–brain barrier more difficult. As a result, second-generation antihistamines have higher affinity to the peripheral histamine receptors than to the ones in the central nervous systems, so their side-effects here are more favorable than those of the first-generation antihistamines. Even so, some second-generation antihistamines may still cause certain degree impairment in cognitive functions [1,7–9].

In activities and occupations that require long-term vigilance, such as driving, and especially participation in aviation that is based upon the integration of higher levels of cognitive functions (distributive attention, long-term attention, and complex calculations), diseases causing perceptual constraints such as AR and the antihistamines used to treat them, can be very dangerous on their own [8,10].

According to a survey by Maurer and Zuberbier, half of the patients with allergic rhinitis did not seek medical assistance [11]. A third of them took 'over-the-counter' (OTC) antihistamines. Although the instructions for most of such medicines contraindicate their use by persons working at elevated platforms as well as by drivers and vehicle operators, it is difficult to check and assert such administration. While the prohibition of alcohol consumption while driving is evident now, the ban on the use of other sedating substances has a lesser degree of public awareness. It is important to note that sedation can occur without its subjective perception [12].

Research aimed at reducing morbidity serves a major public health objective, one direction of which is to minimize the side-effect profile of antihistamines while maintaining and increasing their efficacy. Today, antihistamines are available, which do not influence daily activities at ground level conditions, with respect to sedation [13–17]. In the case of air crews, allergic rhinitis, besides the usual symptoms of the disease, is a significant additional disturbance factor. At the time of ascending and descending, and especially during landing when the pilot's attention is a critical factor, the change in air pressure can cause pain in the nasal sinuses and in the ear (barotrauma). Another problem may be that the visual disturbance caused by allergic conjunctivitis may make it difficult to continuously monitor vital devices, which could jeopardize the safety of low-altitude flight; and sneezing may also distract the pilot's attention [18].

Treatment of allergic rhinitis and the elimination of its symptoms enhance the safety of aviation by improving the air crew's sense of well-being. However, the drugs they are allowed to take must undergo rigorous control as to whether or not they constitute an increased risk by impairing the cognitive performance of crew members. The choice of antihistamines that can be used safely in aviation is made difficult by the fact in such cases, altitude dependent hypobaric hypoxia is also present simultaneously, unlike in ground conditions. It was observed in other drug groups, for instance in the case of cholesterol-lowering pravastatin, that as an unexpected side-effect not experienced in ground conditions, intolerable migraine occurred in hypobaric hypoxia [19]. For safety reasons, it is indispensable to know that antihistamines that are non-sedative at normal atmospheric pressure, retain their beneficial properties in hypobaric hypoxia.

It is plausible that antihistamines, that are non-sedative under normobaric conditions could lower cognitive reserves below a critical threshold in real-life flight conditions, i.e. in hypobaric hypoxia. Based on existing results of tests performed so far, we do not yet have a reliable answer.

The first reports assessing the combined effects of antihistamines and hypoxia on aviation were published in the early 1970s [20]. Since then a few studies have addressed whether antihistamines influence flight performance of cabin crew. Some gained results at ground level and proposed recommendations on antihistamine selection [18]. Studies simulating flight circumstances by using reduced oxygen breathing device (ROBD) did not reproduce the phenomenon of hypobaric hypoxia arising at high-altitudes [12]. Of antihistamines, loratadine was the first to be evaluated in a hypobaric chamber, in a device that can imitate the most realistic flight situation [21].

Further investigations focused on the psychologic effects of desloratadine and bilastine however our understanding derived from these hypobaric chamber experiments is limited up to 2,438 m simulated altitude [22–24].

This study focuses on this issue comparing the effect of cetirizine, bilastine and placebo on cognitive functions in healthy volunteers, under ambient atmospheric conditions and in a hypobaric chamber that best simulates real flight circumstances, under the conditions of hypobaric hypoxia corresponding to an altitude of 4,000 m [12,24].

2. Patients and methods

2.1. Subjects of the study

This study was approved by the institutional review board of the Medical Centre, Hungarian Defence Forces (Reg.No. 2303/385/2016). Written informed consent was requested from each participant.

The participants were healthy volunteers above 18 years of age, with normal BMI. Only non-smokers were allowed to take part in the study, individuals with no history of associated chronic illnesses and not being on medication on a permanent basis. Those candidates were excluded who within one month prior to the tests took, even if only once, systemic or local steroids, or within one week took anti-leukotriene derivatives, beta blockers, antidepressants, antipsychotics, alpha-adrenergic preparations (also including nasal drops), beta-agonists, or theophylline. The only permitted drug was contraceptive pill. Participants' initial pulse oximetry oxygen saturation values were > 95%. No such individuals were allowed to participate in the study who were diagnosed any time even if only by skin test, determination of allergen-specific IgE values, medical examination with allergic rhinitis or asthma. Potential pregnancy and drug use were also reasons for exclusion. In case of participants with a history of catarrh of the upper respiratory tract, the conditions for participation were two weeks without symptoms assessed subjectively and, in each case, a negative otolaryngology examination. Subjects were asked to refrain from the use of alcohol during the day before each test and caffeine containing products during the six hours preceding the tests, and to sleep at least six hours during the previous night. Another request was that medication interfering with the gastrointestinal system was not allowed to be taken within the two hours prior to or following the administration of the medications related to the study. Subjects self-reported any violation of the exclusion requirements, if they violated any of the exclusion criteria, they were banned from participation in the study.

Of the applicants a total of 34 individuals met the selection criteria. Of them, 33 participants completed all the tasks. In the 33 there were 17 men and 16 women, with an average age of 37.06 years (sd = 9.09 years).

2.2. Drugs of interest: bilastine and cetirizine

Both bilastine and cetirizine are authorized drugs in Hungary. Currently, bilastine is a prescription medicine, while cetirizine is available in the pharmacies as an OTC drug. Bilastine and

cetirizine are routinely administered in 20 mg and 10 mg dose once a day respectively. The average elimination half-

life of bilastine is 14.3 h and that of cetirizine is 8.3 h. The peak serum level is reached by both drugs at 90 min following administration [25]. As a placebo control subjects received a single dose of 20 mg pyridoxine (Vitamin B₆; Egis Pharmaceuticals PLC.). Only original medicines were used in the study: Zyrtec® 10 mg (cetirizine; UCB Hungary Ltd.), Lendin® 20 mg (bilastine; Menarini International Operations Luxembourg S.A.). Blinding and dispensing of the medicines were performed by the institutional pharmacy personnel.

2.3. The course of the test

A randomized, double-blind, placebo-controlled, single-center, four-period, cross-over study was conducted in the Aeromedical, Military Screening and Healthcare Institute, Medical Centre, Hungarian Defence Forces, Kecskemét, Hungary. The effect of bilastine on cognitive performance was compared to cetirizine as an active control and to a placebo as a passive control. Participants, meeting the selection criteria, took part in the tests for the first time without taking the medication. The results of these tests were the baseline control values without medication (No). Volunteers subsequently carried out the same tests for three more times, in a randomized fashion, with the two drugs of interest and placebo, after a minimum washout time of seven days.

For the standardization of the conditions, the participants were fasting for 6 h prior to the tests. The potential negative effect of hypoglycemia on cognitive and psychomotor functions is well known. To preclude the potentially damaging effects of low blood glucose levels, participants were given scones, fruit juice and water after the taking each type of pill. The food being digested has no substantial effect on the absorption of antihistamines.

All the tests were started 90 min after the administration of medication, at the peak of their plasma concentrations. Naturally, there was no time threshold applied in the case of tests performed without any medication administered (No). First the measurements were taken at 0-meter altitude followed by the hypobaric chamber simulation of the 4,000-meter elevation immediately thereafter. Although the town of Kecskemét is about 120 m above sea level, in the tests it was considered the starting point, i.e. 0-meter altitude.

Measurements were made following the establishment of the state of equilibrium, in the sequence of the tests made at

0 m altitude. 'Landing' was performed with a safe pressure equalization to avoid barotrauma. A simplified study protocol is summarized in Figure 1.

2.4. Psychophysiologic measurements

2.4.1. Pulse oximetry

The O₂ saturation value of peripheral blood (SpO₂) was monitored by a finger pulse oximeter (Hellige Vicom SMU-EVO). Given the fact that with respect to oxygen saturation, performance is influenced by the most severe hypoxia, always the lowest value was recorded during the test.

2.4.2. Level of vigilance

Participants used a 10 cm long visual analogue scale (VAS) to determine the subjective level of vigilance. They were asked to mark their real-time condition on the scale from one to ten. The two endpoints were 'I feel extremely sleepy' and 'I feel wide awake'.

2.4.3. Cognitive performance

To evaluate a subject's cognitive performance the ultrashort visual memory, the combined distributive attention and the monotony tolerance were assessed. With the crossover design of the test, that is, having all eight task groups performed by the same people, an effort was made to minimize the variable parameters. In view of this, one of the most important aspects of selecting the tests to be performed was to avoid repetitive sequences which could be recognized, so as to prevent learning them. The aim was to prevent getting better and better results by repeatedly performing the assignments, i.e. it becoming a routine exercise. A digital tachistoscope (DTC-1 EM-05.74, Struktúra Instruments Ltd., Hungary) was used for measuring the ultrashort visual memory (STS = Short-Term Store) of participants. Functions of memory, vigilance, localization, retention and recovery of information could be tested with this instrument. Triggered by the participant, 5 fields pop up simultaneously on the screen of the device divided into 4 × 4 fields, with a duration of 30 ms. The task is then to identify, memorize and recall the image elements displayed in the stimulus, and then reproduce the pop-up fields using the pushbuttons of the 4 × 4 matrix. There is no time constraint. During the test, the task is repeated ten times consecutively. The instrument scores the correct hits of the 10 × 5 pop-up displays, one correct hit is one point, so a total of 50 points can be achieved at the

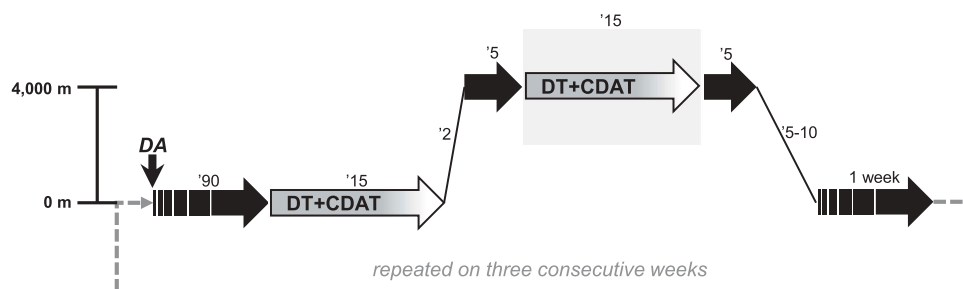


Figure 1. Study design for the eligible subjects. At the first visit medicine wasn't dispensed during drug administration (DA). During three more cycles drugs were given double-blinded according to randomization. (DA: drug administration, DT: digital tachistoscopes, CDAT: combined distributive attention test, SpO₂: finger pulse oximetry).

maximum score. There is no option to correct the selections. When using Combined Distributive Attention Tester (EM-05.54/55, Struktúra Instrument Ltd, Hungary) participants were required to constantly watch a simple stimulus field, where occasional small changes occur (flashes). The task is to respond to these changes correctly and quickly. In cases like this, the attention is divided, since the stimulus field is composed of many small, individual elementary units capable of flashing. The task is simple and monotonous, lasting for a long time (5 min) with respect to its character, which can cause psychological saturation. Recording the correctness of the responses of the person under testing during the entire measurement, a picture is obtained about the functioning and characteristics of the subject's distributive attention. The total number of the correct hits primarily refers to the level of attention, while the number of misses, i.e. of the errors, is indicative of its precision. Changes in the data per minute provide information on the consistency of attention. The results are characteristic of the performance of the individuals in monotonous tasks requiring long-term distributive attention.

From each of the two devices described above, only one unit was available, so the participants worked in pairs. Consequently, at a single 'take-off' only two subjects could be tested, who performed their own task simultaneously, and then swapped instruments. The time spent at the simulated altitude of 4,000 m in hypobaric hypoxia was 25 min on average. The control of the hypobaric chamber and the recording of the test results were performed by O₂ breathing personnel. Medical supervision of participants was also ensured.

2.5. Statistical methods

The characteristics of the participants referring with respect to their cognitive functions and the comparisons in the changes in their level of vigilance were determined through summarizing statistical calculations, and the changes in their level of vigilance were compared. The statistical design was aimed to detect the eventual differences between the application of 10 mg cetirizine and 20 mg bilastine. Parametric statistical procedures as one-sample and paired *t*-tests were used. Where the distribution of the data was unknown, calculations were made with the Wilcoxon signed-rank test. For similar data, however, in the case of several parameters, the Kruskal–Wallis test was applied. To mitigate inaccuracy due to the eventual small number of participants and to reconstruct near real-life scenario, the statistical method of stochastic simulation was used. Statistical analyses were carried out using R in RStudio environment (RStudio Inc., Boston, US).

3. Results

During the course of the tests, one person dropped out due to barotrauma, so 33 individuals completed all the tasks. Each of the participants carried out a total of 16 instrument-supported tests and 8 subjective vigilance self-assessment tests. The 33 subjects generated a total of 792 separate data sets. Half of the data sets, i.e. 396 sets were recorded under normobaric conditions, and the other 396 sets were obtained under conditions of hypobaric hypoxia.

3.1. Level of vigilance

Paired *t*-tests were used for comparing the VAS results applied for determining the subjective level of vigilance of the participants. There was no significant change ($p < 0.05$) on the basis of the statistical comparison of the data of different test groups (at 0 m and 4,000 m; no drug: No; placebo: Plac; cetirizine: Cet; bilastine: Bi). Only one case produced a near-significance result. There was a difference between men and women at 0-meter altitude in the test, with no medication (No) (average of men: 8.117, average of women: 7.375; $t = 2.0042$; $df = 30.459$; $p = 0.05401$), according to which men, in a default condition, self-reported themselves to be more vigilant compared to women. This figure can be evaluated as merely of weak significance ($p < 0.1$).

3.2. Short-term memory test

3.2.1. Performance

Applying a digital tachistoscope to test ultra-short visual memory, for the comparison of hit results of measurements performed on all groups to detect differences, a paired *t*-test was used ($T = 0.126$; $df = 131$; $p = 0.9001$), no significant difference could be confirmed.

3.2.2. Saturation

At 4,000 m we tested whether there was a decrease compared to the baseline O₂ > 95% saturation values recorded at 0 m in the different study groups. Since the distribution of the saturation values was not known, we could not use parametric statistical procedures such as the *t*-test. A specific, one-variable nonparametric analysis was required, so the Wilcoxon signed-rank test was applied. The $p = 2.2 \times 10^{-16}$ (pseudo-median: 87.50%) value confirmed with a strong significance that saturation fell below 95% for all measurements taken at 4,000-meter altitude.

Thereafter, it was analyzed whether the 4,000-meter groups had deviations in the minimum values of saturation. The distribution of the values was not known in this case either, but several variables were available, so the Kruskal–Wallis process was used for the evaluation. On this basis, there was no significant difference between the minimum saturation values of the groups ($p = 0.118$, Kruskal–Wallis chi-square = 5.87; $df = 3$). While the $p = 0.118$ value comes close to the threshold of $p < 0.1$ of weak significance but does not surpass it. However, the visualization on a Boxplot diagram shows that the minimum saturation values of the additional groups are uniformly higher than the saturation values of those without drug administration (No) (Figure 2).

3.3. Distributive attention test

3.3.1. Performance (number of correct responses, own tempo)

Own tempo of individuals was assessed by summation of correct responses per each minute. The visual display and comparison of the data were performed with the Boxplot diagrams of the *explorative data analysis* (EDA).

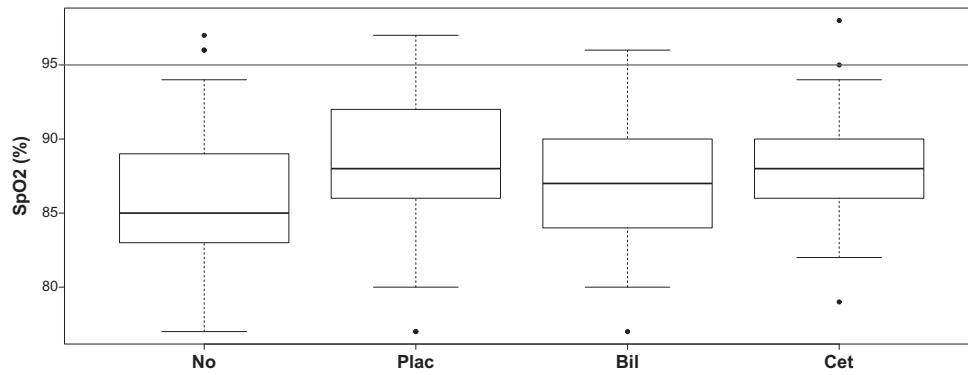


Figure 2. The lowest saturation values of digital tachistoscope tests for ultrashort visual memory at 4,000 m simulated altitude. (No: no medication was administered; Plac: vitamin-B₆ as placebo was administered; Bil: measurements after bilastine administration, Cet: after the administration of cetirizine; ▬: median value, ○: mean value, ●: outlier data point(s), boxes cover IQR, whiskers cover 2xIQR).

In the first step, the data of the eight groups are presented individually and then broken down into the minute intervals of the test, placed side by side (Figure 3).

In the groups without medication inferior results were obtained, deviating from the results of the drug-taking groups, more prevalently at 0 m and less so at 4,000 m.

It is observable at 0 m that after having taken all the pills, an improvement can be detected during the minutes following the first minute, while in the 5th minute deterioration occurs. This is most apparent in the case of cetirizine. Bilastine yielded results equivalent to those obtained with the placebo. At 4,000 m, there is an improvement compared to the initial performance only in the case of no drugs and placebo, followed by a decline, however, the results here are not worse than those observed in the first minute. At 4,000 m, bilastine and cetirizine show a deterioration after the first minute, which is of a higher rate for cetirizine.

3.3.2. Errors

We also used Boxplot diagrams to display the mistakes made. Cetirizine yielded the worst results already at 0 m. Bilastine caused no more errors when compared with the results of the

tests with no medication and placebo, respectively. At 4,000 m, there were more mistakes observed in all cases. The results obtained with bilastine were identical to the no-drug and placebo cases. Most of the errors were caused by cetirizine, more than at 0-meter level and this was the most pronounced in the fifth minute (Figures 4 and 5).

3.3.3. Joint testing of performance (number of correct hits, own tempo) and mistakes

We were wondering if the own tempo and the mistakes could be measured together. The background to this was that while an individual could produce flawless results, it is not of much use if he/she is very slow. Conversely, somebody may get many correct hits, when he/she makes many mistakes due to the high-speed. Either of these cases are optimal for performing the task. We created the term 'own efficacy' to jointly evaluate performance and errors. This test was assessed by following formula:

$$\text{own efficacy} = \frac{a \times \text{own tempo} - b \times \text{error}}{c \times \text{own tempo} + d \times \text{error}} \quad (1)$$

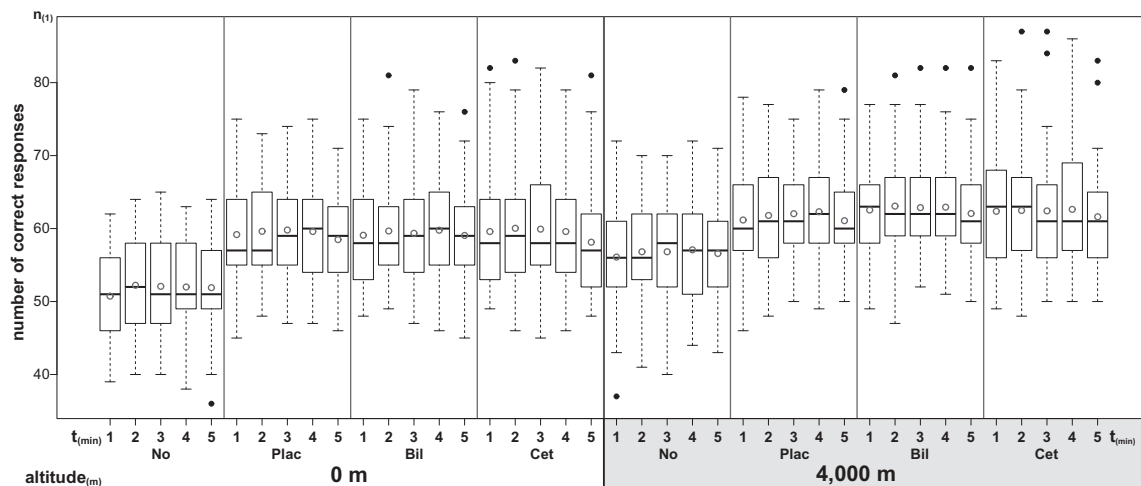


Figure 3. Number of correct responses of the distributive attention test in different groups, per minute, at 0 m and at 4,000 m simulated altitude. (No: no medication was administered; Plac: placebo; Bil: bilastine, Cet: cetirizine; t: time interval in minutes; ▬: median value, ○: mean value, ●: outlier data point(s), boxes cover IQR, whiskers cover 2xIQR).

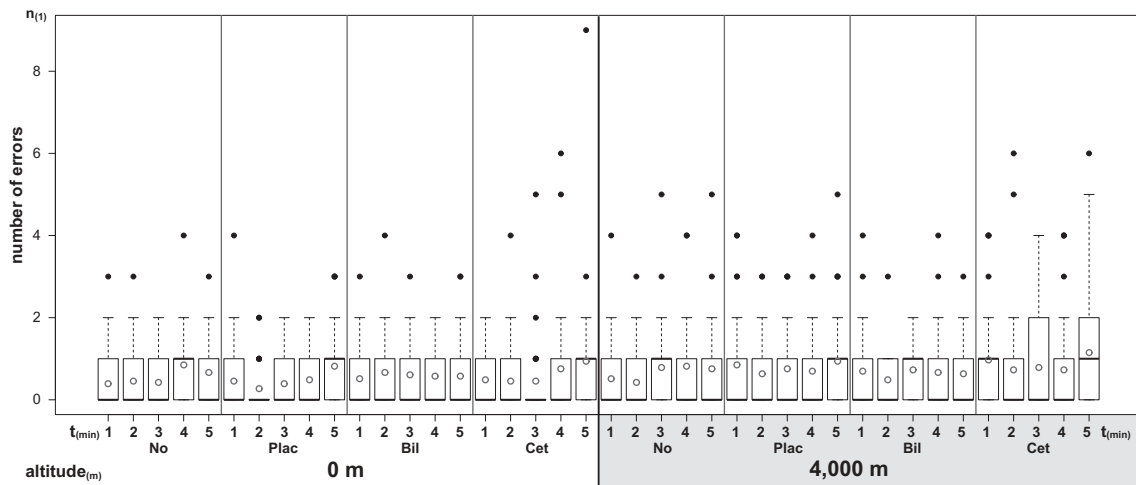


Figure 4. Comparison of error counts of distributive attention testing between groups at 0 m and 4,000 m simulated altitude, per minute. (No: no medication was administered; Plac: placebo; Bil: bilastine; Cet: cetirizine; t: time interval in minutes; ■: median value, ○: mean value, ●: outlier data point(s), boxes cover IQR, whiskers cover 2xIQR).

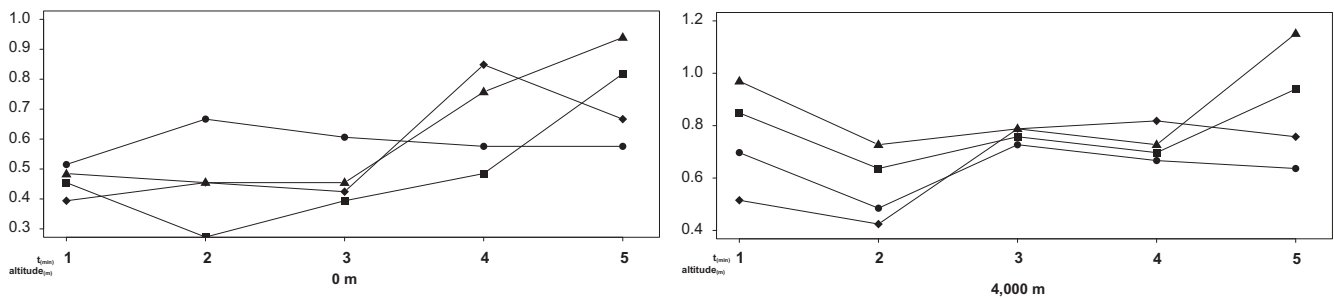


Figure 5. Displaying mean values of error counts of distributive attention test at different altitudes in a minutal timeframe (◆: no medication was administered, ■: placebo, ●: bilastine, ▲: cetirizine, t: time interval in minutes).

where **a**, **b**, **c**, **d** coefficients were defined as 1. On the basis of the statistical calculation, the closer the obtained result was to one [1], the more optimal the performance was deemed to be. Based on the comparison of the boxplots, also considering the lengths of the lower stems (covering data from the average to the 2x-dispersed range) and the outliers, bilastine performed equivalent to the no-drug and the placebo results. Cetirizine gave poorer results, especially at 4,000 m, in the fifth minute (Figures 6 and 7).

3.3.4. Oxygen saturation

It was investigated whether the lowest oxygen saturation values measured during the five minutes of testing of distributive attention obtained according to the distribution of the sequence of minutes at 4,000 m were lower than the starting > 95%. In this respect, in all cases the values were significantly below the 95% level. *Kruskal–Wallis* test: chi-square: 3.1523; df = 4; **p** = **0.5327**.

Through further analysis, it was investigated whether there was a justifiable difference between the minimum saturation values according to the various administered agents, broken down per minute. There was no significant difference observed between the active agents in our population in any one minute (Table 1). We wondered if the lack of significant differences among groups was only due to the statistically small number of cases. To eliminate

this, the method of stochastic statistical simulation was used to reconstruct a near real-life scenario. Using this method, we compared the average of differences in saturation values across specific groups by performing ten thousand simulations (Table 2).

Displaying the simulation values in Boxplots, when the no-drug group was compared to the groups administering active agents, saturation levels were lower in each group and in every minute. When pills taken were compared, bilastine gave a similar result to placebo. In the bilastine vs. cetirizine comparison, higher saturation values were found in the case of bilastine (Figure 8).

4. Discussion

Hypobaric hypoxia at an altitude of 3,600 m and above may already cause deterioration in psychomotor functions [26]. According to Ernsting's observations, this deterioration is certain to occur in everyone in altitudes above 4,500 m [27]. Based on this assumption, the altitude of 4,000 m was selected in our study, whereby hypobaric hypoxia was reasonably expected to decrease the abilities but could not yet mask the potential influence of antihistamines. In the classical division, the 2,000–4,000-meter range is, in a physiological sense, a perfect compensation range where no physiological decompensation occurs in a healthy person over a time interval corresponding to a few hours

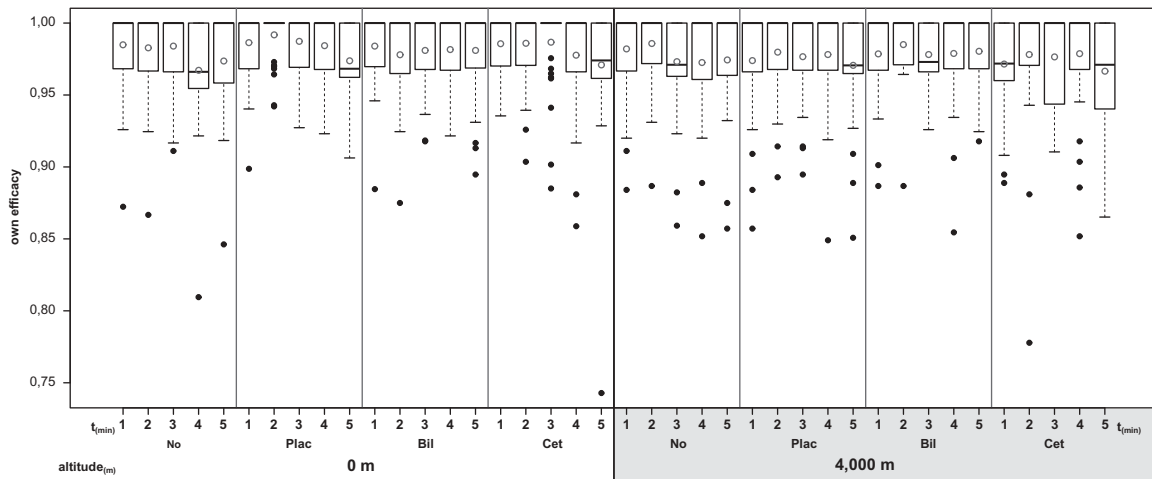


Figure 6. Visualization of *own efficacy* calculated from performance and mistakes made per minute by different groups at 0 and 4,000 m simulated altitude, according to equation N°1. (No: no medication was administered; Plac: placebo; Bil: bilastine, Cet: cetirizine; t: time interval in minutes; $\square$: median value, $\circ$: mean value, $\bullet$: outlier data point(s), boxes cover IQR, whiskers cover 2xIQR).

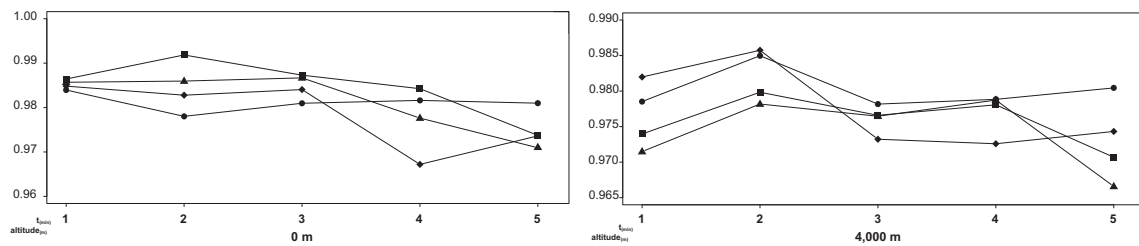


Figure 7. Displaying mean values of *own efficacy* at different altitudes in a minimal timeframe ($\diamond$: no medication was administered, $\blacksquare$: placebo, $\bullet$: bilastine, $\blacktriangle$: cetirizine, t: time interval in minutes).

in flight by increasing cardiovascular reflexes and sympathetic activity via the release of epinephrine and adrenal steroids. Beyond 4,000 m above sea level, however, in the so-called imperfect compensation zone, time-dependent depletion of these reflexes must be considered [28]. In the airtight cabin and passenger compartment used in air transport, crew and passengers are protected by the cabin pressure set to the boundary of the indifferent and perfect compensation zones, matching the pressure at an altitude of 1,500–2,400 m.

Table 1. Kruskal–Wallis analysis of minimum saturation values in a minimal timeframe during the combined distributive attention test.

Kruskal–Wallis analysis of minimum saturation values in a minimal timeframe					
timeframe	1	2	3	4	5
p-value	0.149	0.6234	0.648	0.6399	0.7564
Degrees of freedom	3	3	3	3	3
Chi-square	5.3319	1.6712	1.6483	1.6864	1.1857

According to Dalton's Law, the Boyle-Mariott Law and Avogadro's Law, the partial pressure of the gases is reduced, depending on the altitude above sea level [29]. In the case of oxygen, hypoxia occurs during ascent, i.e. there is a decreased oxygen supply of the body as a whole and of some vital organs such as the heart and brain cells, which may drastically impair the air crews' ability to work, potentially escalating to a state of emergency. Due to the laws of physics, in the cabin air, in addition to oxygen, the same partial pressure drop also occurs with respect to all the other gases, such as carbon dioxide. This provokes carbon dioxide loss from the body through the respiratory tract even without an increase in respiratory rate. This is a 'passive' hyperventilation in case of CO₂ diffusion. As a result of this, in addition to hypoxia, in the short term significant hypocapnia also arises in the body's fluid spaces, leading to respiratory alkalosis. In case of long-term hypobaric hypoxia this situation also occurs, but due the prevailing anaerobic metabolic

Table 2. Average and standard distribution of stochastic simulations of the saturation differences among the groups at 4,000 m. (No: no medication was administered; Plac: placebo; Bil: bilastine, Cet: cetirizine).

Timeframe	No vs. Plac			No vs. Bil			No vs. Cet			Plac vs. Bil			Plac vs. Cet			Bil vs. Cet		
	Mean	$\pm$	SD	Mean	$\pm$	SD	Mean	$\pm$	SD	Mean	$\pm$	SD	Mean	$\pm$	SD	Mean	$\pm$	SD
1. min	-2.02	$\pm$	1.4	-2.22	$\pm$	1.32	-1.78	$\pm$	1.55	-0.21	$\pm$	1.21	0.23	$\pm$	1.31	0.45	$\pm$	1.1
2. min	-0.83	$\pm$	1.49	-0.89	$\pm$	1.57	-0.95	$\pm$	1.18	-0.07	$\pm$	1.46	-0.13	$\pm$	1.31	-0.08	$\pm$	1.29
3. min	-0.78	$\pm$	1.4	-1.25	$\pm$	1.64	-0.38	$\pm$	1.35	-0.46	$\pm$	1.36	0.41	$\pm$	1.38	0.86	$\pm$	1.26
4. min	-0.64	$\pm$	1.39	-0.88	$\pm$	1.48	-0.61	$\pm$	1.43	-0.25	$\pm$	1.31	0.02	$\pm$	1.45	0.27	$\pm$	1.44
5. min	-0.61	$\pm$	1.51	-0.58	$\pm$	1.42	-0.92	$\pm$	1.54	0.01	$\pm$	1.4	-0.33	$\pm$	1.54	-0.35	$\pm$	1.54

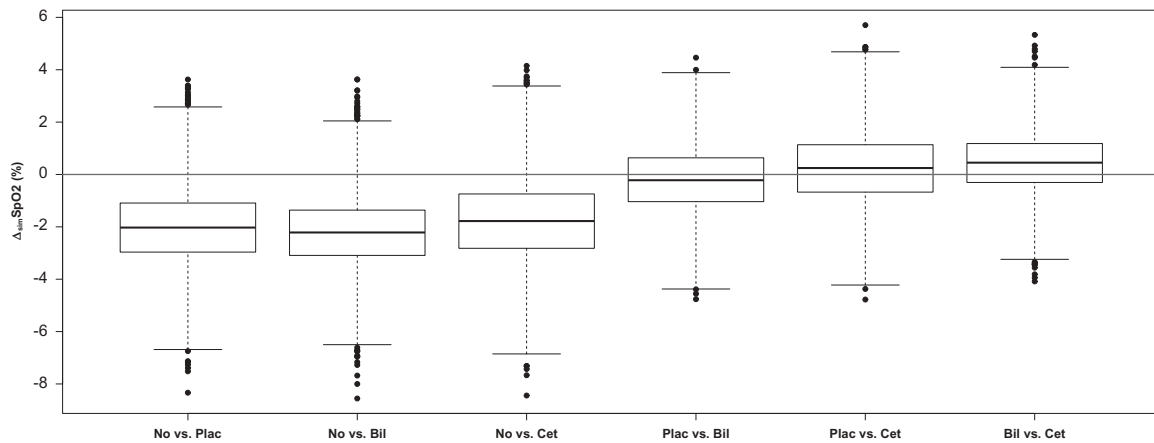


Figure 8. A simulation of the difference in saturation during the first test minute at an altitude of 4,000 m in the comparison of the individual groups (Δ_{simSpO_2 (%): simulation of difference in saturation, No: no medication was administered; Plac: placebo; Bil: bilastine; Cet: cetirizine; $\blacksquare$: median value, $\circ$: mean value, $\bullet$: outlier data point(s), boxes cover IQR, whiskers cover $2 \times \text{IQR}$).

processes, metabolic acidosis is superimposed on the respiratory alkalosis, to further reduce the CO_2 levels (mountain sickness). Hypocapnia, with the onset of oxygen deficiency, deteriorates by several factors the body's ability to use oxygen, which is available at sub-optimum levels in the first place. The controlling stimulus for the respiratory center is the pH of the cerebrospinal fluid. Its decrease causes hyperventilation, while alkalosis causes hypoventilation. There are many other factors that have an impact on breathing, all the afferentation of stimuli from the outside world and from the internal environment, cognitive and emotional factors as well, but the strongest stimulus of them all is the pH decrease. In alkalosis, therefore, the number of breaths and intensity of breathing will decrease, resulting in alveolar hypoventilation, which further increases the oxygen deficiency in all the fluid spaces. Thus, in hypobaric hypoxia in flight, alkalosis caused by CO_2 loss in a way catalyzes the aggravation of hypoxia, moreover, so that in the absence of a respiratory stimulus the subject is unaware of this, so there is nothing that would urge him/her to avoid the situation. This is a particularly unfortunate constellation from the point of view of aviation safety. Altitude-dependent physiological phenomena also influence the possible mechanism of action and side-effect profile of drugs, so its special modeling, analysis of cardiovascular and cognitive effects are also important in military aviation. In the framework of the relevant project of the NATO Working Group 26, the Hungarian Defence Forces also conducted pertaining studies, as hypoxia is still a realistic danger of potentially acute incapacity [30].

Vacchiano investigated the effect on the cognitive performance of fexofenadine and cetirizine. Under ambient conditions only hypoxia was simulated via a respirator, which supplied O_2 with partial pressure corresponding to altitudes of 3,000 and 4,500 m, respectively. Based on their results, cetirizine in a 10-mg dose also caused a decline in performance. However, 180 mg of fexofenadine in its effect on cognitive functions important to a pilot an aircraft did not deviate from placebo [12]. Based on the description of the study, the simulation of hypobaric condition was not performed, therefore in the absence of consequential CO_2 loss, the aforementioned alkalosis of outstanding physiological significance in aviation could not occur either. In a recent study in 24 volunteers, the effect of 20 mg bilastine was compared to

50 mg of hydroxyzine and placebo at an altitude of 2,438 m (8,000 ft) simulated in a hypobaric chamber. Such conditions refer to the lowest prescribed cabin pressure of civilian flights. According the results, 20 mg of bilastine did not cause functional deterioration in measured cognitive functions [24]. While this study was performed in a hypobaric chamber where hypobaric hypoxia could already have developed, the altitude of 2,438 m is still way below the 4,000 m altitude threshold, that can be compensated by the healthy body and it is closer to the indifferent 2,000-meter limit. Since there is still a smaller reduction in pressure, physiological decompensation cannot take place or it may evolve only very slowly. In our opinion, substantial hypoxia and further aggravating alkalosis, which differ substantially from the ground level conditions and which could influence results among healthy participants could not yet be reasonably established under such circumstances. Hypobaric hypoxia due to an altitude greater than 2,438 m is common in military aircrafts and in planes which are not sealed hermetically. In case of emergency, similar circumstances can develop even in commercial flights.

In our study, due to the points above, we were not satisfied with low altitude testing and with the sole application of the hypoxia condition. The hypobaric chamber was, therefore, an indispensable means of testing, without endangering the health of the volunteers, but with the testing criteria satisfied with 4,000 m maximum simulated altitude.

When comparing the results of the VAS test used to determine the subjective level of vigilance of participants, the measured groups did not statistically differ from each other. This is interesting from the point of view that cetirizine showed detectably inferior results based on all of the evaluation criteria of the 4,000-meter test of distributive attention. This decline in performance was, therefore, not subjectively perceived by the participants. Consequently, the pilot's cognitive reserves can be exhausted while he feels in full possession of his abilities. This is an important aviation safety factor and is consistent with the results of previous observations [12]. When evaluating the VAS results, in one case of testing at 0 m with administration of no drug (No), a near-significance result was obtained for men and women. According to this, in the baseline situation, men found themselves more vigilant in comparison to women, but this did

not constitute an advantage in fulfilling their tasks. In our opinion, this self-perception may be rooted in social stereotypes, whereby men must always act prepared and confident.

Based on the results of the additional instrument aided tests, it can be stated that bilastine does not significantly affect the performance at any of the test altitudes in healthy adult volunteers, in comparison with placebo and drug-free controls, in functions necessary for piloting an aircraft, such as ultra-short visual memory, combined distributive attention and monotony tolerance.

In the ultrashort visual memory test, cetirizine did not cause detectable impairment, either. In the tests of combined distributive attention and monotony tolerance, at 0-meter, cetirizine caused worse performance only in the number of errors compared to other groups.

At 4,000 m, however, cetirizine produced worse results not only in the number of errors, but also in the joint test of the two parameters of the tempo and error number compared to drug-free control, placebo and bilastine. This is a result equivalent to previous observations [31,32]. Deterioration was the most pronounced in the fifth minute of the test. It can be concluded that cetirizine can cause disturbance in long-term, monotonous activities requiring distributive attention, which are already referred to by the error numbers recorded at 0 m, but this becomes significant at 4,000 m, due to the involvement of all parameters. It is known that hypobaric hypoxia equivalent to an altitude of 3,600 m or greater alone can cause a decrease in psychomotor capabilities [26]. At 4,000 m, a deterioration greater than the value recorded at 0 m with cetirizine is confirmed to be the consequence of a further, combined effect of hypobaric hypoxia. This was not detectable at 4,000 m in the case of bilastine, either. It can be stated that in the case of bilastine, the safety of the drug confirmed in earlier tests performed at ground level [13,14,24,33,34] was not impaired by the hypobaric hypoxia experienced at 4,000 m – unlike for cetirizine.

Oxygen saturation values measured at 4,000 m in all tests and in all groups were lower than those measured at 0 m. Within this range, the saturation values of participants of groups receiving pills including placebo were uniformly higher than those receiving no pills. It is believed that this is explained by the excitement caused by the administration of the pills, as our participants were otherwise healthy individuals under no medication.

It was observed that compared to the results of the test of distributive attention at 0 m and no-medication, after the ingestion of any pill, an increase in the number of correct hits was detected already at 0 m, which is also explained by excitement caused by the sensation 'I took a pill and it works!', as the test could not be learned or practiced, and further improvement trend was no longer detected with respect to this parameter at ground level (Figure 3). Continuing this line of thought, the results of the distributive attention test at 4,000 m showed a consistent improvement over the values recorded at 0 m. This is attributed to the subjective experience of combined physiological stressor effects of high-altitude, further increasing the excitement caused by taking the drug (decompression sound, cooling of the air, pressure changes in the air containing body cavities, etc.).

5. Summary

The treatment of allergic rhinitis ensures that the full working ability of those individuals, whose employment requires a constantly high-level of attention, can be preserved. For ground conditions, non-sedating antihistamines are already available and can be safely administered. However, in aviation, it is essential to know whether this beneficial property is maintained under hypobaric hypoxia or it reduces cognitive reserves below the critical threshold.

This study simulated hypobaric hypoxia more realistically than in previous literature addressing the topic, in a way that served the objectives of the study in an optimal manner. Based on the results of complex instrumental measurements, it was found that the effect of 20 mg bilastine on the cognitive functions essential for the flight crew does not differ significantly from the results obtained for subjects having taken no drug or having taken the placebo, therefore, it can be used safely. On the other hand, 10 mg cetirizine, which is virtually non-sedative under ground conditions and causing no psychomotor performance impairment on its own, but combined with a simulated 4,000 m altitude, already caused – in addition affecting the short-term memory capabilities – a loss of performance in complex and distributive attention tests as well as monotony tolerance. This objective deterioration of functions could not be justified with the subjective VAS vigilance test, suggesting that the subjects were not aware of this phenomenon. These findings can be useful beyond the realm of aviation safety and can be relevant in occupational and public health in other situations (for instance working at elevated geographic locations). The results should also be taken into account in the selection of active substances by individuals who require constant attention, vigilance and agility during their activity at high-altitude.

Our method can be suitable for modeling the effects of drugs and medicinal preparations on cognitive functions under flight conditions.

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Declaration of interest

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Author contributions

R.Á. devised the project, the main conceptual ideas, conducted the psychologic and physiologic experiments, processed the experimental data and drafted the manuscript. S.A. and T.Z. took part in experimental design and operation of the hypobaric chamber to simulate hypobaric hypoxia at high-altitude. G.A. and H.F. encouraged R.Á. to investigate the aviation aspect of antihistamine therapy and supervised the findings of this work. M.D. aided in interpreting the results and worked on the manuscript. All authors discussed the results, commented on the manuscript and approved the final version.

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