

NATIONAL UNIVERSITY OF PUBLIC SERVICE

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**Examination of the effect of antihistamines on cognitive
functions with respect to military and aero-medical
suitability**

THESES OF THE DOCTORAL (PhD) DISSERTATION
(THESIS BOOK)

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INTRODUCTION

TIMELINESS OF SELECTING THE SUBJECT

One of the most important milestones in the evolution of mankind was the discovery of aviation, the ability of lifting off the ground, making the dream of Icarus come true after several millennia. The military use of the capability, only a desire until that point, had also come true. Following the experimental balloon flights of the 18-19th century, aircraft deployed by the time of the First World War were not only suitable for reconnaissance but also air fight and bombing. The speed of airplanes grew from the initial 70-80 km/h to 190-220 km/h, their flight altitude rose from 2000-3000 m to 5000-6500 m. By the time of the Second World War, the developments reached the limits of technical possibilities of aircraft powered by internal combustion engines. The maximum speed grew to 700-750 km/h and the flight altitude increased to 10000-12000 m. And in the era of jet propulsion - after 1947 - and also in our times, man could exceed the speed of sound and could also fly into the outer space since 1961. Defence technology research from the very beginning, and also now, has been the most powerful driver of development. Aviation is no longer an instrument for breaking always the records of speed and flight altitude. By today, it has grown into a capability which fundamentally defines the application of the military force. Owing to its favourable possibilities of use (wide range of altitude and speed, long distance flights, omni-presence, multi-task capability, quick response, possibility of concentration) its use is inevitable not only in the offensive and defensive military operations but also in the international security and peace operations, rescue and humanitarian tasks as well as disaster management.

While implementing its tasks, the air force uses the atmosphere above the ground surface - in specific cases, also the outer space, the cosmos. In view of its characteristics, air as medium deviates both from land and sea. In the course of flights, the air imposes conditions which are partly different from the customary conditions and are partly unknown, e.g., air pressure decreasing with the growth of altitude (hypobaric condition), diminishing of level of oxygen (hypoxia) and temperature drop (hypothermia). In addition to these impacts, which are not insignificant and stressful on their own, further major challenges are presented for the flight crew by the operation of equipment becoming increasingly complex and more powerful owing to the technical developments. The parameters demanded by the application of the new technical solutions may already exceed the limits of human capacities. All over again, we are confronted with the problem that man is becoming the weakest link in the systems applied.

As more and more people become involved in aviation it has been recognised that not all persons can meet these complex challenges. The first steps towards selecting the personnel capable of optimally performing the aviation tasks included the scientific discovery of the physiological processes caused by the unfavourable effects on participants due to altitude and the use of such information. The system of the aero-medical suitability examination so established has a double function. Partly it permits the exclusion of the clearly unsuitable candidates and partly it allows the selection of the candidates optimally suited for the specific tasks. Medical support of aviation safety partly aims at the maximum protection of the personnel having received expensive training, protection of the expensive infrastructure by this manner and the prevention of the eventual ground damage and casualties through avoiding air accidents.

Both military medicine and aero-medicine are motivated for continuous development by the need to attain as optimal as possible medical compliance with the requirements imposed on human resources by the innovations in aviation technology. The task of these disciplines includes not only the application of the latest knowledge in medical science, but also the examination whether this knowledge is applicable in the same way under the special conditions arising in the course of flight. The new body of knowledge must also prevail in the course of the selection, training and educational activities, in the examination of medical suitability, fatigue management and therapy protocols. By virtue of our obligations in the Alliance, this knowledge should be applied under unified principles through the conventions, STANAG (Standardization Agreement for procedures and system and equipment components) of the NATO Standardisation Organisation (NSO).

As a specialist of oto-laryngology in my daily practice, I constantly face the fact that by today allergic rhinitis (RA is the accepted acronym in scientific literature) has become an ever more frequently occurring clinical picture, an endemic disease. This disease has a steadily growing significance also due to the number of patients requiring treatment growing year after year, the impact of the disease on the quality of life and the economy.

DESCRIPTION OF THE SCIENTIFIC PROBLEM

The illness presents a serious problem for the authorities dedicated to and responsible for the decisions about the health suitability of the military personnel. The diagnosis of this illness, pursuant to the effective regulations, may preclude suitability for service, including aviation. If the ground or flight crew suffering from this clinical picture is declared as unsuitable, then about one-fifth of the population suitable from other aspects and available for service is lost by

definition, including the potentially excellent pilot candidates. A further problem is that allergic rhinitis mainly becomes manifest from the young adult age and it cannot be diagnosed in a medical examination performed in the symptom-free period. Therefore, it may happen that the subsequent deployment of the flight personnel trained with the investment of significant amounts in the period still free of symptoms, will be prevented by the disease. In case of the disease emerging during the years of the military service, it is impossible to count on voluntary confession due to the fear of losing the actual post commissioning.

Therefore, unified protocols are available set up for the diagnosis and care of the personnel involved in accordance with the principles of *evidence based medicine (EBM)* - based upon the results of objective, double-blind, placebo controlled examinations.

The recognised illness can be treated, therefore, the suitability can be retained with respect to health condition. The fundamental medications of treatment are the antihistamines, which, in addition to their beneficial effects - eliminating the symptoms - have also known negative influence on the central nervous system.

Both the illness and the medications available for its treatment may equally have an unfavourable influence on performance, which may represent a major problem in case of the military personnel and - within that - especially in case of the flight crew. The fact is known both from our practical experience and data of literature that the undesirable side effects caused by the members of the antihistamine group of drugs are different from compound to compound and do not occur in each patient.

The medications available for treatment - excluding a few exceptions - are today available as OTC drugs, therefore, in case of such symptoms, the patients have the possibility to receive medical treatment from pharmacy staff having no adequate knowledge regarding military and aero-medical criteria or even to perform self-healing.

The treatment of allergic rhinitis and achieving a symptom-free condition - through the improvement of general well-being of the pilot - increases the safety of flight. However, the medications permitted for the flight crew must undergo strict testing to ascertain that these do not represent an enhanced risk through the deterioration of cognitive capabilities.

As of today, antihistamines are already available which have no influence on the daily activity with respect to sedation based on evidence, when applied in therapeutical dosage under the ground conditions. 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. For safety reasons, it is indispensable to know

whether antihistamines, that are non-sedative at normal atmospheric pressure, retain their beneficial properties in hypobaric hypoxia.

JUSTIFICATION OF THE SELECTION OF SUBJECT

The first generation antihistamines as well as cetirizine were confirmed to lead to automobile and air accidents due to their sedative effect. In the course of processing the air accident data between 1990 and 2015, while analysing 5383 tragedies also involving fatalities, first generation antihistamine could be identified in the organism of the pilots in 338 cases. In 103 of the 338 cases, only antihistamine could be detected (one kind in 94 cases and two kinds in 9 cases). Based upon the conclusions of the investigations conducted by the National Transportation Safety Board of the USA, the cause triggering the accident was clearly the administration of antihistamines in 12 of the 338 incidents. In additional 50 cases, this could be identified as one of the factors leading to the disasters.

It is possible, that antihistamines non-sedating under ground conditions diminish the cognitive reserves already below the critical threshold under real-life flight conditions, i.e. together with hypobaric hypoxia. Based on existing results of tests performed so far, we do not yet have a reliable answer.

CLASSIFICATION OF THE DISSERTATION BY DISCIPLINES

With respect to their classification by subject matters and science taxonomy, the research activities presented deal with questions equally bearing on specific fields of natural sciences (physics, chemistry, biology), medicine social sciences (military science). The subject I selected and researched is interdisciplinary, which includes, in addition to the subject of military health care and within that, particularly aero-medicine, includes also references to otolaryngology, public health as well as physiology with respect to the examination of cognitive functions. The practical applicability of the results should be recognised not only with respect to otolaryngology and aero-medicine, however, with respect to transport safety and public hygiene.

RESEARCH HYPOTHESES

In the course of analysing the impacts of allergic rhinitis and of the antihistamines used for its treatment, influencing the aero-suitability, transport safety and military suitability, the hypotheses below were formulated:

1. I wanted to prove that the occurrence of allergic rhinitis with noticeable increase as shown in literature and the everyday otolaryngology patient care has a prominent significance in military medicine.
2. By conducting prevalence research I intended to certify the increasing occurrence of RA among the candidates applying for military service.
3. According to my assumption, the examination of the potentially sedative side effect of antihistamines applied for the treatment of this illness under simulated flight conditions is inevitable with respect to drug safety.
4. According to my assumption, such examination methods measuring cognitive functions can be selected and applied through which the side effect profile of the different pharmaceutical ingredients can be made measurable.
5. I assumed that by means of the testing methods so selected, it is possible to detect the eventually occurring effect in deteriorating the cognitive performance under real flight conditions of the antihistamines, which are non-sedative under ground conditions.
6. I assumed that in case an antihistamine can be identified in the course of examination, which does not deteriorate the cognitive functions and can also be applied with respect to aviation safety, then this knowledge can also be applied regarding the review of regulations which currently define military suitability.

RESEARCH OBJECTIVES

The objectives of my research work were:

1. to demonstrate and professionally justify that allergic rhinitis, an endemic disease today, is an important problem in military hygiene and aviation safety due to the performance degradation it causes.
2. to highlight that this illness, of increasing prevalence, has a particular significance, not only through its diagnosis but also through the treatment regarding the examination of military suitability, as both the underlying disease and the eventual medical treatment in itself may mean a risk to safety.
3. to determine the actual prevalence of allergic rhinitis among the applicants for military service.
4. selection from among the various objective measuring methods of cognitive functions the ones, through which the side effect of antihistamines used for the treatment of the illness and causing side effect of sedation may optimally be examined in the course of the domestic aero-medical examinations, also in a baro-chamber.

5. comparative analysis of the sedative side effect profile of the antihistamines in frequent application using these measuring methods in order to identify their difference in safety among ground and special - simulated flight - conditions (baro-chamber).
6. the aim of the determination of measuring processes and methodology I have applied was to make them suitable for application also in the course of examining the ingredients of other groups of drugs and make them capable of the examination of their effect and/or side effect spectra deviating from the ones at ground condition.
7. to formulate therapeutical recommendations, based upon the research results, also for the personnel employed in safety critical jobs, who suffer from allergic rhinitis.

RESEARCH METHODS

In the course of elaboration of my dissertation, the first two chapters are based upon the review and analysis of the national and international literature and the medical-health suitability regulations related to the subject of research.

The third chapter is devoted to the examination of percentage proportion of prevalence of allergic rhinitis among the applicants for military service. A questionnaire covering the symptoms related to the eventual allergy of respiratory tract was distributed in the survey, in which validated series of questions proposed by national and international guidelines were applied to allow 'structured interview'. The results were assessed by means of descriptive statistical methods.

The 4th chapter presents the randomised, placebo-controlled, crossover, double-blind examination conducted with voluntary participation of 33 healthy individuals. The effects of two antihistamines, cetirizine and bilastine, as well as of the placebo were compared on the basis of results obtained from the instrument-aided measurements of several parameters. The examinations were partly carried out under atmospheric pressure at ground level and partly in a baro-chamber best simulating the real flight conditions, under the conditions of hypobaric hypoxia corresponding to an altitude of 4000 meters, which was greater than the altitude used in the earlier tests. The characteristics of the participants related to cognitive functions were determined by summarising statistical calculations and the variability of their vigily level was also compared. The statistical setting were aiming at the detection of any eventual difference which might arise in the application of the two antihistamines. Parametric statistical procedures (two-sample t-test and paired t-tests) or non-parametric procedures were applied as a statistical method for evaluation, depending on the distribution of the results (Wilcoxon test, in case of a single variable, and the Kruskal-Wallis test in case of several variables). In the comparative

examination of oxygen saturation values of the different examination groups at 4000 m altitude, in addition to the Kruskal-Wallis test - due to the small number of cases - we also resorted to the statistical method of stochastic simulation to confirm the accuracy of results. The simulation was made by RStudio in R environment. The visual presentation and comparison of the data were performed using the charts of the *EDA (explorative data analysis)* box (boxplots).

STRUCTURE OF THE DISSERTATION

1. The introduction presents the actuality of the selection of subject, the research hypotheses and objectives as well as the research methodology.
2. The **first chapter** provides the fundamental knowledge of anatomy, physiology, pathophysiology and of pharmaceutical effects important for allergic rhinitis under the national and international literature covering the subject.
3. The **second chapter** is devoted to the increasing prevalence data of allergic rhinitis in Hungary and abroad. Based upon the latest results of the science, the effects of the illness on aero-physiology, traffic safety and military suitability and of the antihistamines applied for treatment are presented in detail. Special attention is devoted to the relevant regulations of the NATO countries as well as their comparison with the Hungarian regulations of military and civil aero-medical practice.
4. The **third chapter** presents the questionnaire prevalence research performed with the involvement of 510 participants for the determination of percentage of occurrence in Hungary among the applicants for military service with the results obtained. The survey determines that the proportion of applicants for the military service in Hungary suffer from allergic rhinitis in 14.03%, which is a higher figure compared to the data of the earlier tests.
5. The **fourth chapter** deals with the measuring methodology developed for the examination of the effects of antihistamines on cognitive functions and the analysis of these effects at ground conditions and under simulated flight circumstances at 4000 m altitude. The physiological impacts of hypobaric hypoxia subject to altitude are presented. The baro-chamber used as the site of research, the measuring instruments applied in the tests, and the cognitive properties they measure, are described. The process of selection of participants and the statistical analysis of the performed randomised, placebo-controlled, crossover, double-blind examination and the statistical analysis of its results are presented. In the test presented, the effect of bilastine on cognitive performance was compared to that of cetirizine, as an active control and to

that of a placebo, as a passive control. The results were also compared with the data of a drug-free examination. Hypobaric hypoxia was simulated with the 4000 m simulated altitude in order to optimally serve the objective of observation - more realistically than in earlier papers already published on the subject. Based on the results of complex instrument-aided measurements, it was found that the effect of 20 mg bilastine on the inevitably necessary cognitive capabilities of the flight crew does not deviate significantly from that of the groups receiving no medication or receiving placebo, therefore, this can be applied safely. On the other hand, 10 mg cetirizine, which is virtually non-sedative under ground conditions and causes no psychomotor performance impairment on its own, when combined with a simulated 4000 m altitude, already caused – in addition affecting the short-term memory capabilities - performance degradation in complex and divided 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.

6. The **closing chapter** provides the summary analysis and conclusions of the results found, with the proposals and recommendations for the practical application of the new body of knowledge acquired.

SUMMARY OF THE RESEARCH

The fundamental motivation of my dissertation was to review and analyse the actual clinical information, prevalence data, treatment protocols, drug therapy possibilities and the related eventual side effects in connection with allergic rhinitis. I have also devoted special attention to the implications in foreign and domestic military medicine in general and aero-medicine in particular.

The illness has a steadily growing significance - due to its prevalence, the number of cases growing year after year, its impacts on the quality of life and military suitability.

Pursuant to the currently effective regulations of medical suitability of the Hungarian Defence Forces, allergic rhinitis, with the exception of a slight case of the illness, leads to unsuitable qualification. It is impossible to diagnose the illness in the course of a medical examination performed in the symptom-free period. In case of the disease emerging during the years of the military service, it is impossible to count on voluntary confession due to the fear of losing the actual post of commissioning. The medications available for treatment - excluding a few exceptions - are today available as OTC drugs, therefore, in case of such symptoms, the patients have the possibility to receive medical treatment from pharmacy staff having no adequate

knowledge regarding military and aero-medical criteria or even they can even resort to self-healing.

In its active period, the disease in itself and also because of the side effect profile of the incorrectly selected treatment, represents a safety risk regarding the task to be fulfilled, due to the reduction of cognitive reserves of the individual.

The optimum treatment of allergic rhinitis is important and possible in the civil and military medicine and aviation. After consultation of the oto-laryngologist specialist in charge, with the observation of appropriate safety rules, properly selected medical treatment, it is possible to retain the military suitability of the personnel having received expensive training and no enhanced risk prevails in the deployment of the personnel, including flight missions.

The military-medical specifications of the issue are not uniform in an international comparison. These new evidence-based experiences are not yet integrated in the regulations of several countries, including here also the Hungarian regulations.

FINAL CONCLUSIONS

In the following, I summarize my answers given to my hypotheses formulated in the course of investigating the effects of allergic rhinitis and of the antihistamines applied for its treatment, influencing the aviation-physiology, transport safety and military suitability:

1. I could prove my assumption that the increased occurrence of allergic rhinitis in reference data and the everyday oto-laryngology patient care has an outstanding military-medical significance.
2. I provided evidence by prevalence research that the increasing occurrence of RA can also be demonstrated among the candidates applying for military service.
3. My assumption, namely that the investigation of the potential sedative side effect of antihistamines used for the treatment of the illness under simulated flight conditions is inevitable with respect to pharmaceutical safety could be confirmed.
4. I could select and apply such testing methods and instruments measuring the cognitive functions, through which the side effect profile of the various pharmaceutical ingredients - deviating under flight conditions from the one detected at ground level - can be measured.
5. I could prove that by the so selected testing methods, it is possible to detect the cognitive performance deteriorating effect of the antihistamines, which are non-sedative under ground conditions, which eventually occurs under real flight conditions.

6. My assumption was confirmed that through my research it was possible to identify the antihistamine type which does not degrade the cognitive functions and can also be applied with respect to aviation safety.

NEW SCIENTIFIC RESULTS

1. I **certified** by questionnaire prevalence research the increasing occurrence of allergic rhinitis among the applicants for military service and **confirmed** the importance of the disease with respect to military-medicine and aero-medical suitability.
2. Applying the comparative, placebo-controlled, crossover, double-blind examination I **proved** also under hypobaric hypoxia conditions in a baro-chamber, corresponding to an altitude of 4000 m, that bilastine has no side-effect which would degrade the measured cognitive functions.
3. Among the antihistamines, I **proved** concerning the second generation cetirizine that it can be used as a passive control substance in the research comparing their side effect profiles influencing the cognitive capabilities.
4. I **proved** that the instruments used in the comparative baro-chamber examination (digital tachistoscope, combined distributive attention testing device), that through their use, it is possible to detect the effect degrading the cognitive functions of the specific active ingredients, which effects are not yet manifest at the ground level but already appear at higher altitudes.
5. In order to prove the difference existing among the second generation antihistamines through their impact on cognitive performance, I **have created** a characteristic presenting the quality of the solution of the task in a more optimum manner (the so-called own standard) by means of a mathematical formula, which can assess the complex performance simultaneously through a single value.

PRACTICAL APPLICABILITY OF THE RESEARCH RESULTS

I propose to assess the practical applicability of the research results not only in the fields of military-health and aero-medicine but also concerning civil health care, civil aviation and public road transport.

1. Through my dissertation, I directed the attention of military-medicine to the significance of allergic rhinitis of high prevalence. The new body of knowledge acquired through the pharmaceutical safety research conducted with antihistamines in baro-chamber can be used for the review of the currently effective regulations of military suitability. With

this help, the application of candidates with allergic rhinitis - e.g., potential future pilots - should not be turned down, on the one hand, and the personnel trained at great expenses can also be retained in service in case of a clinical picture arising during their military service, on the other hand, so that no further risk is presented by the disease already treated to the level of a no-symptoms status or by the administered antihistamine for the personnel, the performance of the actual task or the expensive infrastructure.

2. Sedation caused by the widely used antihistamines also available as OPC drugs, as a risk to transport safety should not be under-estimated with respect to public hygiene either. 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 when driving is evident now, the ban on the use of other sedating substances has a lesser degree of public awareness. The results of the baro-chamber research, particularly with respect to the examination of monotony tolerance, can also be applied in case of other persons performing highly critical work in the field of civil aviation, public road transport (professional drivers) or any other activity which requires permanent attention. Based upon the new result, educating such persons has a particularly great significance.
3. The instruments measuring the selected cognitive functions in the drug safety comparative test presented (digital tachistoscope, combined distributed attention monitoring device) have proved suitable for detecting the difference among the active ingredients at ground level and also under the circumstances of hypobaric hypoxia simulated in the baro-chamber corresponding to a simulated 4000 m altitude. Both instruments are widely applied now, they are validated testing instruments of career suitability (e.g., MÁV – Hungarian State Railways - , Hungarian Defence Forces), they are available commercially and their size allows their installation in the baro-chamber as well. In view of these points, the testing protocol I have created and the applied devices can be used for measuring the effect of additional pharmaceuticals, preparations of medicinal effect which have an impact on cognitive functions under flight conditions.

RECOMMENDATIONS, PROPOSALS

Based upon my scientific results formulated in my dissertation, I make the recommendations below:

1. Treatment of allergic rhinitis is important and possible in civil and military aviation and public road transport. After consultation with the otolaryngologist specialist in charge of treatment, with the observation of appropriate safety regulations, properly selected medication, no higher risk is presented for flight. Through my research I have determined that bilastine can be safely administered to the flight crew and to all persons working in the so-called critical safety positions.
2. My recent prevalence survey and the results of my research in baro-chamber proved bilastine to have a safe applicability even under flight conditions, which is a new piece of scientific knowledge. Under these altered conditions, it is proposed to change and alleviate during the new review the regulation of military medical suitability regulation, which defines allergic rhinitis and its treatment by medication, the MoD Decree (10/2015 (VII. 30)); the Joint Decree No. 22/2005 HM-EüM and the special instruction approved by MH EüCSF Hungarian Defence Forces, Medical HQ), the Professional Methodical Guide No. 675/2005.
3. I consider the new examination protocol presented in the dissertation as well as the instruments applied suitable, therefore, I propose it for the detection of effect eventually influencing the cognitive functions of additional ingredients, drugs or preparations of medicinal effect under flight conditions.

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- 1998-2007 Szent Rókus Hospital, Ward of oto-rhino-laryngology and head-neck surgery, chief physician, head of ward: prof Dr. György Lichtenberger
- 2007- Medical Center, Hungarian Defence Forces, Ward of oto-rhino-laryngology and head-neck surgery, chief physician, head of ward: Dr. Frigyes Helfferich PhD, col. med.
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- Lecturer of the Operational Medical Specialist training courses of the Hungarian Defence Forces
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- global post-laryngectomy rehabilitation
- head and neck endocrine surgery
- aero-medicine