УДК 615.038 3.3.6 Фармакология, клиническая фармакология

DOI: 10.37903/vsgma.2025.1.5 EDN: DCDJXE

THE EFFECTIVENESS OF A TRIAZINE-INDOLE DERIVATIVE IN THE TREATMENT OF MOTION SICKNESS: A RANDOMIZED CLINICAL TRIAL

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Abstract

Objective. To investigate the effectiveness of a triazine-indole derivative in treating motion sickness under the Coriolis acceleration cumulative test.

Methods. During the randomised double-blind clinical trial individuals from the experimental group were administered a single dose of a triazine-indole derivative (trisan) 250 mg per os. Individuals from the control group received placebo followed by the Coriolis acceleration cumulative test and a psychophysiological examination. Follow-up tests were done 1, 2 and 3 weeks after the initial trial. 59 apparently healthy males aged 18-20. 19 were excluded for not meeting the inclusion criteria. 40 subjects included in the trial (randomized into experimental group (n=26) and control group (n=14) had no more than 2 min. tolerance of cumulative Coriolis acceleration. There were no refusals or replacements. Interventions: administration of a single dose of a triazine-indole derivative 250 mg per os. Main Outcomes and Measures: a single administration of 250 mg. of a triazine-indole derivative is expected to improve functional state and performance of subjects under the Coriolis test.

Results. Individuals from the experimental group demonstrated a 29.4% improvement in Coriolis tolerance time (from 72.4±6.1 to 93.7±5.8) with simultaneous reduction in vestibulo-sensory, vestibulo-vegetative and vestibulo-somatic reactions.

Conclusions. the obtained data make it possible to recommend a single administration of a triazine-indole derivative 250 mg per os to improve vestibular performance in individuals controlling high-speed and high-manoeuvrability vehicles and craft. An improvement in the tolerance of high-acceleration stimuli overall holds promise for prospective studies into the anti-motion sickness effectiveness of a triazine-indole derivative under different dosing regimen.

Keywords: triazine-indole derivative, motion sickness, Coriolis acceleration cumulative test

ЭФФЕКТИВНОСТЬ ПРОИЗВОДНОГО ТРИАЗИН-ИНДОЛА В ЛЕЧЕНИИ БОЛЕЗНИ ДВИЖЕНИЯ: РАНДОМИЗИРОВАННОЕ КЛИНИЧЕСКОЕ ИССЛЕДОВАНИЕ

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Резюме

Цель. Изучить эффективность производного триазин-индола при лечении болезни движения с помощью кумулятивного теста ускорения Кориолиса.

Методика. В ходе рандомизированного двойного слепого клинического исследования участникам экспериментальной группы вводили однократную дозу производного триазин-индола (трисан) в дозе 250 мг внутрь. Участники контрольной группы получали плацебо с последующим выполнением кумулятивного теста ускорения Кориолиса и психофизиологическим обследованием. Тесты повторяли через 1, 2 и 3 недели после первоначального исследования. В

исследовании приняли участие 59 практически здоровых мужчин в возрасте 18-20 лет. 19 человек были исключены из исследования в связи с несоответствием критериям включения. В исследование были включены 40 человек (рандомизированных в экспериментальную группу (n=26) и контрольную группу (n=14), у которых продолжительность исследования не превышала 2 мин. допустимого уровня совокупного ускорения Кориолиса. Отказов или замен не было. Меры предосторожности: однократное введение производного триазин-индола в дозе 250 мг внутрь. Ожидалось, что применение производного триазин-индола в указанной дозе улучшит функциональное состояние и работоспособность испытуемых при проведении теста Кориолиса.

Результаты. Испытуемые из экспериментальной группы продемонстрировали улучшение переносимости совокупного теста на ускорение Кориолиса на 29,4% (с 72,4±6,1 до 93,7±5,8) при одновременном снижении вестибулосенсорных, вестибуловегетативных и вестибулосоматических реакций.

Заключение. Полученные данные позволяют рекомендовать однократное введение производного триазин-индола в дозе 250 мг внутрь для улучшения вестибулярных функций у лиц, управляющих высокоскоростными и высокоманевренными транспортными средствами и плавсредствами. Улучшение переносимости стимулов, связанных с ускорением, в целом является перспективным для проведения проспективных исследований эффективности производных триазин-индола против укачивания при различных режимах дозирования.

Ключевые слова: производное триазин-индола, болезнь движения, совокупный тест на ускорение Кориолиса

Introduction

Technological progress has brought about a significant increase in the use of high-speed and high-manoeuvrability means of transportation, which are now used by people of different age and gender. At the same time there is a steady increase in the number of accidents involving such vehicles due to low statokinetic stability of pilots. Safe operation of high-speed vehicles and craft requires the pilot to have an optimal functional state, fitness for work and enough physical and psychological resources [1]. The latter requirement is often neglected and excessive acceleration often gives rise to various vestibulo-somatic, vestibulo-vegetative and vestibulo-sensory reactions that adversely affect bioelectric activity of the brain, conditioned reflexes, memory, attention and spatial orientation [2, 9, 12].

Thus, it is highly important to offer professionals controlling high-speed vehicles and craft effective drugs that would improve their functional state and performance. However, our review of pharmaceutical drugs for motion sickness shows that many of them are detrimental to the pilot's capacity and performance. In this respect, antihypoxic drugs show a lot of potential [4].

The majority of extreme stimuli, including acceleration, share a common pathogenic mechanism, i.e., the disruption of oxygen and energy homeostasis. Antihypoxic drugs have shown to offer protection from a wide range of stimuli: anoxic and circulatory hypoxia, G loads, high temperature, and trophic deficiency of the vestibular system, etc. [4].

In this research, we studied the effectiveness of 3-[(2-morpholinoethyl) thio]-5H-1,2,4 triazine-indole dihydrochloride monohydrate derivative (Trisan) (Fig. 1). The drug has passed clinical trials and has been approved for medicinal use by Russia's Ministry of Health. Prior research demonstrated that triazine-indole derivative eliminated hemodynamic imbalance and excessive afferent signalling by peripheral receptors that occurred due to acceleration. Inner ear homeostasis was preserved in the face of excessive excitation of peripheral receptors and influence of ototoxic drugs.

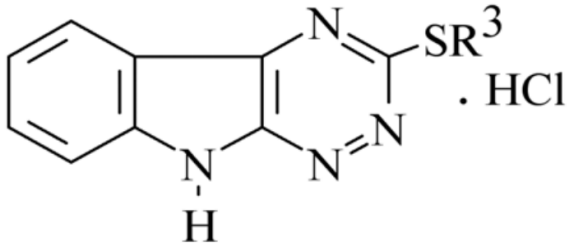

Fig. 1. The structural formula of the 3-[(2-morpholinoethyl) thio]-5H-1,2,4 triazine-indole dihydrochloride monohydrate derivative (Trisan)

Antihypoxic drugs were shown to improve the resistance of the human brain and internal organs to extreme factors of circulatory anoxia, preserved performance in extreme conditions and increased performance in regular conditions [1]. It was found that hyperlactacidemia is most prominent in individuals prone to motion sickness, which indicates reduced aerobic and increased anaerobic glycolysis. Aircraft pilots with lower acceleration resistance showed a six-fold increase of lactate and reduction of pyruvate in their bloodstream [2].

Extreme conditions lead to excitation of the brain, resulting in an increase of glucose consumption and a build-up of lactic acid. This inhibits aerobic glycolysis leading to lower ATF production. Antihypoxic drugs reduce the lactate which results in up to 40 per cent reduction in oxygen consumption. Antihypoxic drugs normalize bioenergetic processes, preserve physical endurance, functional performance of the central nervous system and improve metabolism [6].

The goal of this research was to determine the influence of a triazine-indole derivative on the vestibular performance.

Methods

The research was conducted at the Department of Otorhinolaryngology, S. M. Kirov Military Medical Academy (Saint Petersburg, Russia). Research subjects included 40 apparently healthy males aged 18-20. They were informed about the research protocol and methods and had given a written consent for inclusion. At the preparatory stage, the Coriolis acceleration cumulative test (the Coriolis test) was used to select individuals who within the first 1-2 minutes of the test exhibited 3rd grade vestibular and vegetative reactions.

The parameters recorded immediately after the test included: Coriolis tolerance time, duration of postrotational nystagmus, body sway, increased sweating, finger tremor and breath-holding time after inspiration. We also recorded the parameters of psychological and emotional state self-assessment, State-Trait Anxiety Inventory (the STAI), Critical Flicker-Fusion Frequency (the CFFF), Simple and Complex Reaction Time (the SRT and CRT). The analysis also included a statokinesiogram [28-31]. Then, the selected subjects were randomly split into the experimental (n=26) and control (n=14) groups. The experimental group received a triazine-indole derivative 250 mg per os, while the control group received a placebo. The administration of drugs was followed by another examination of patients. Follow-up tests were done 1, 2 and 3 weeks after the initial trial.

The Coriolis test followed the standard methodology by S.S. Makaryan with the use of Nydiag 200 Interacoustics and VF 405 Video Frenzel (Denmark). Self-assessment was done using the Doskin Test Chart. State anxiety was assessed with the Spielberger State-Trait Anxiety Inventory (2004). The postrotational nystagmus was assessed with the VO425 Interacoustics video nystagmography (Denmark) using the Kurashvili-Babiyak trapeze test programme (1975). The extent of body sway was assessed after the Coriolis test, using the S.S. Makaryan's methodology (1970). Increased sweating was assessed with DIANEL-5120 tool (Russia) by recording resistance, amplitude and galvanic skin response.

Tremorometria tool (Russia) was used to quantify the severity of tremor: patients extended the right arm and held a metal rod affixed to their index finger in the centre of a Ø5 mm opening for 15 seconds. The red Critical Flicker-Fusion Frequency was assessed with the CFFF-D tool (Russia). The subject watched the flickering of red diodes of increasing frequency and pressed a button when they started to perceive the light as continuous, thus recording their result (ten presentations).

Simple Reaction Time was recorded with the Reaction Time unit of the PMK tool (Russia), as the time of reaction to the stimuli (ten presentations). Complex Reaction Time was assessed using the 2nd programme of Reserves unit as part of the Physiologist-M tool (Russia): a sum of two digits and selection of an even or odd number option.

To assess the inspiratory breath-holding time, the subjects were asked to make two or three full inspirations and expirations, then make one more inspiration and hold their breath for as long as they were able.

Computerized posturography was carried out with Stabilan-01-2 (Russia). The subjects performed two sub-tests: sub-test 1 with eyes open and fixed on the object; sub-test 2 with eyes closed. The sub-test duration was 20 seconds with 1-minute break in-between. We recorded the average statokinesiogram elongation and extension rates; centre of gravity oscillation amplitude (the OA) and asymmetry factor (the AF) in sagittal and coronal planes and directions.

Statistical data processing was done in the Microsoft Excel 2010 software suite. For each data sample the distribution characteristics were calculated. The Student's t-test was used to assess the significance of difference between the two samples.

Results and discussion

The results indicate that a single dose of a triazine-indole derivative improves the Coriolis test tolerance. More specifically, the Coriolis tolerance time in the experimental group was longer by 29.4%. The parameters reflecting the functional state and performance of the subjects also improved: their general state, energy level and mood improved by 15.1%, while their state anxiety reduced by 12.5%; the duration of postrotational nystagmus fell by 15.6%, the extent of body sway by 33.3%, excessive sweating by 18.2% and finger tremor by 14.5%, with a 26.1% increase in breath-holding time after inspiration. The nervous activity and reaction time also improved: the CFFF time fell by 11.5%, the Simple Reaction Time by 17.1% and information processing speed by 18% (Table).

Table. Psychological and physiological parameters of subjects before and after single administration of a triazine-indole derivative (X±δ)

#	Parameters	Experimental group		Control group	
		Before	After	Before	After
1	Coriolistolerancetime (s)	72.4±6.1	93.7±5.8*	71.8±5.9	72.3±5.6
2	Psychological and Emotional State (points)	5.3±0.2	6.1±0.3*	5.4±0.2	5.5±0.3
3	Anxiety (points)	36.8±2.6	32.2±3.1*	36.1±2.7	36.4±2.8
4	Nystagmus (s)	18.0±1.4	15.2±1.7*	18.1±1.4	17.9±1.2
5	BodySway (points)	0.9±0.08	0.6±0.09*	1.0±0.09	0.9±0.07
6	GalvanicSkinResponse (kΩ)	68.8±3.4	56.3±4.0*	65.9±4.1	66.6±3.9
7	Tremor (touches)	57.2±5.8	48.9±5.4*	57.3±4.9	57.8±5.3
8	Inspiratory Breath-holding Time (s)	49.0±2.7	61.8±2.0*	48.6±2.6	49.5±2.8
9	CFFF (Hz)	43.4±3.5	48.4±3.8*	42.8±3.9	42.4±3.7
10	SRT (bit/s)	158.6±6.2	169.5±6.8*	160±6.4	157.3±6.8
11	CRT programmetwo (ms)	310.2±10.3	254.5±9.9*	314.6±9.8	309.2±10.1
12	NumberofSubjects	36	36	24	24

Note: * – statistical significance is $p<0.05$ compared to initial data

The improvement in Coriolis performance is also supported the parameters of a statokinesiogram. More specifically, the experimental group demonstrated the following improvements: in the eyes open sub-test: significant improvements in the statokinesiogram elongation (by 14.7%) and extension (by 12.9%) rates; centre of gravity OA improvement in coronal (by 12.5%) and sagittal (12.3%) planes; AF improvement in coronal (by 11.4%) and sagittal (12.3%) directions; in the eyes closed sub-test: significant improvements in the statokinesiogram elongation (by 11.9%) and extension (by 11.2%) rates; centre of gravity OA improvement in coronal (by 11.3%) and sagittal (10.8%) planes; AF improvement in coronal (by 11.1%) and sagittal (10.9%) directions.

One of the goals of this research was to study the duration of the effect achieved by the drug administration. To this aim, the tests were repeated for both the experimental and control group after 1, 2 and 3 weeks. Experimental data indicate that the best Coriolis tolerance time was observed in the experimental group after a single administration of a triazine-indole derivative. Then, the Coriolis tolerance time gradually fell to its initial length: 72.4±6.1 before the drug administration; 93.7±5.8* after the administration; 77.2±5.9 one week later; 74.6±5.4 two weeks later; 73.5±5.8 three weeks later. We regret it is not possible to present all the recorded parameters due to article size limitation.

High vestibular performance is one of the indicators of sufficient functional capabilities under extreme dynamic conditions. Sufficiency of physical and psychological reserves is crucial to professional reliability of individuals performing in extreme dynamic conditions [7, 12].

Prior research established a link between vestibular disturbance and ischemic changes in relevant centres. This leads to underperformance of both analyzers and the single functional system of statokinetic stability [8]. Therefore, normalisation of cellular energy metabolism in neurons achieved by antihypoxic drugs

shows a lot of promise for alleviating statokinetic disturbances [5]. It has been established that a triazine-indole derivative has a positive impact on neuron energy metabolism by way of biochemical processes driven by a specific protein – hypoxia-inducible factor HIF-1α that plays a major role in the systemic evolutionary response to hypoxia and increases in quantity commensurately with lower blood oxygen tension [3, 10].

It is seen as the target molecule for various drugs addressing different types of hypoxia. This is due to the fact that higher HIF-1α level improves the cell's hypoxia resistance and is a transcription activator of genes influencing carbohydrate metabolism (aerobic enzyme synthesis genes), erythropoiesis (vascular endothelial growth factor (VEGF) gene) and iron metabolism. An Increase in VEGF expression due to HIF-1α activation promotes creation of new blood vessels in the area of hypoxia [3, 11].

A therapeutic dose of the drug administered two hours after the acoustic trauma produced the following effect: after a 5 mg/kg dose low-level HIF-1 expression in the hair cells and moderate HIF-1 expression in the cells of the spiral ganglion; after a 7 mg/kg dose moderate HIF-1 expression in the hair cells and the cells of the spiral ganglion; after a 10 mg/kg dose significant HIF-1 expression in the hair cells 1 and the cells of the spiral ganglion (Fig. 2).

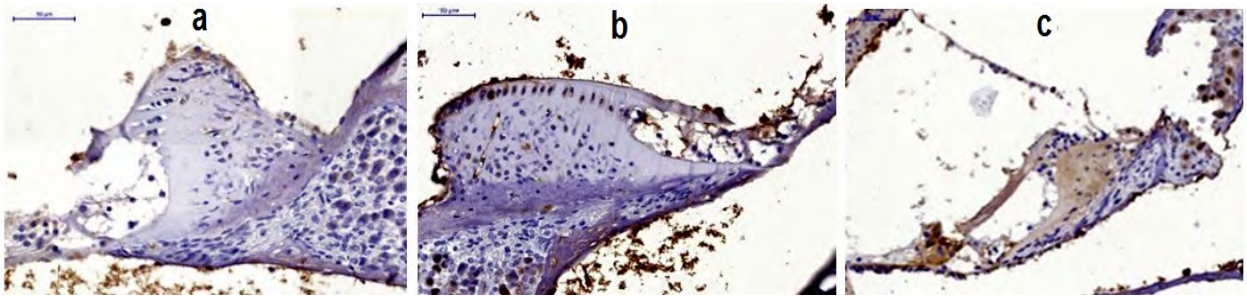

Fig. 2. a – a therapeutic dose of 5 mg/kg; b –7 mg/kg; c – 10 mg/kg

A therapeutic dose of the drug three days after the acoustic trauma produced the following effect: after a 5 mg/kg dose moderate HIF-1 expression in the hair cells and low-level HIF-1 expression in the cells of the spiral ganglion; after a 7 mg/kg dose moderate HIF-1 expression in the hair cells and the cells of the spiral ganglion; after a 10 mg/kg dose significant HIF-1 expression (Fig. 3).

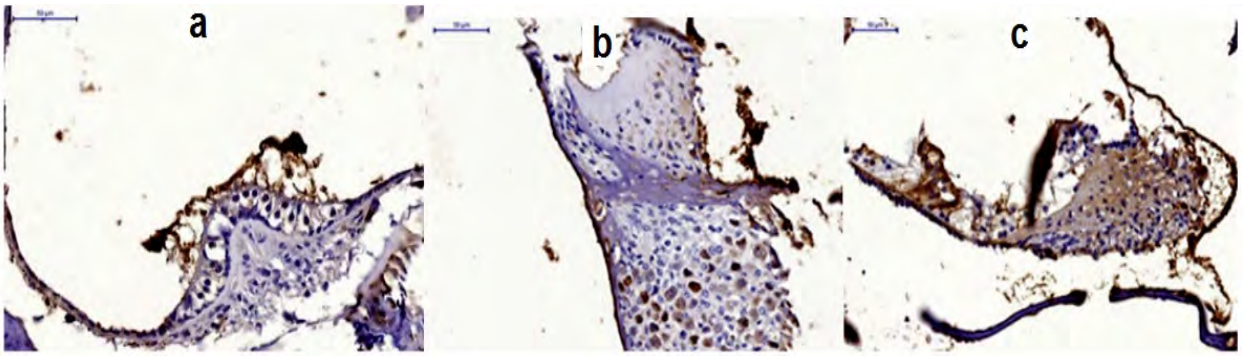

Fig. 3. a – a therapeutic dose of 5 mg/kg; b –7 mg/kg; c –10 mg/kg

The above data indicate that a triazine-indole derivative influences HIF expression. With a higher dose of triazine-indole derivative, a corresponding increase in HIF-1 expression is observed in hair cells and spiral and vestibular ganglia cells, which normalises cell energy metabolism in the cochlea.

Conclusions

1. A single administration of a triazine-indole derivative 250 mg significantly increases Coriolis tolerance time, at the same time reducing the extent of statokinetic disturbances. The best Coriolis tolerance time is observed immediately after the administration of a triazine-indole derivative; it then falls gradually and eventually returns to the initial level.
2. A triazine-indole derivative improves hypoxia resistance in the tissues of the inner ear by increasing HIF-1 expression in hair cells and spiral and vestibular ganglia neurons, which normalises cell energy metabolism in the cochlea and improves the overall condition of subjects

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Conflict of interest: The authors declare that there is no conflict of interest.

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Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Поступила 27.01.2025

Принята к печати 20.03.2025