Meclizine seasickness medication and its effect on central nervous system oxygen toxicity in a murine model

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Abstract
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Introduction: Diving utilising closed circuit pure oxygen rebreather systems has become popular in professional settings. One of the hazards the oxygen diver faces is central nervous system oxygen toxicity (CNS-OT), causing potentially fatal convulsions. At the same time, divers frequently travel by boat, often suffering seasickness. The over-the-counter medication meclizine is an anticholinergic and antihistaminergic agent that has gained popularity in the treatment of seasickness. Reports have shown the inhibitory effect that acetylcholine has on glutamate, a main component in the mechanism leading to CNS-OT seizure. The goal of the present study was to test the effect of meclizine on the latency to CNS-OT seizures under hyperbaric oxygen conditions.
Methods: Twenty male mice were exposed twice to 608 kPa (6 atmospheres) absolute pressure while breathing oxygen after administration of control solution (carboxymethyl cellulose solvent) or drug solution (meclizine) in a randomised crossover design. Latency to tonic-clonic seizures was visually measured.
Results: Mean latency to seizure did not significantly differ between the control group (414 s, standard deviation [SD] 113 s) and meclizine group (434 s, SD 174 s).
Conclusions: Based on results from this animal model, meclizine may be an appropriate option for divers suffering from seasickness, who plan on diving using pure oxygen rebreather systems.

Introduction

Military diving operations are becoming increasingly more complex and demanding. They often require long durations and compact gear, particularly in clandestine missions. Breathing systems that fulfil these requirements usually deliver oxygen (O_2) rich gas in a closed-circuit design. In addition, many divers suffer from seasickness while travelling to the dive site, and even during the dive. Thus, seasickness medications are in demand amongst divers.

Divers breathing pure O_2 are exposed to significantly higher partial pressures of oxygen (pO_2) than at sea level. Exposure to elevated PO_2 may impose toxic effects on the central nervous system (CNS) and lungs, which may be life-threatening. Thus, the likelihood for CNS O_2 toxicity (CNS-OT) must be considered during dive planning.[1,2]

The hallmark of CNS-OT is a generalised tonic-clonic seizure. There may be prodromal symptoms such as sensory anomalies (aura, blurred vision, tinnitus, tingling of extremities, dizziness) and changes in mood and mental status.[3,4] The seizures manifest with a sudden loss of consciousness and stiffening of the body (tonic phase) followed by twitching and jerking of the face, arms, and legs (clonic phase). These events will ultimately prove fatal if pO_2 is not reduced.[3] If such seizures should occur during a dive, death by drowning may occur. As the risk for CNS-OT is a function of exposure time and PO_2, efforts have been made over the decades to create predictive risk analysis tools.[1,5]

Divers must also cope with seasickness, affecting 25–75% of sea vessel passengers.[6] Meclizine, an anti-motion sickness medication, operates in the CNS as both a histaminergic receptor antagonist and a nonspecific muscarinic receptor antagonist.[7] Thus, it also blocks CNS acetylcholine receptors.[8,9] The neurotransmitter basis for oxygen toxicity seizures involves elevated levels of acetylcholine and glutamate in the CNS. Studies show that the first tonic phase is induced by over-stimulation of muscarinic acetylcholine receptors (mAChRs), while the second clonic phase is a result of high levels of glutamate.[10–12] The mAChR receptors have been found to downregulate glutamate activity,[13] while antagonists of mAChR prevent the tonic

phase seizures.[10] The inhibitory effect of acetylcholine on glutamate is probably mediated by GABAergic neurons.[14,15] This GABAergic population of cells appears to produce inhibitory control of glutamate's excitatory activity. Under these conditions, susceptibility to CNS-OT could be curbed. Compounds having antimuscarinic activity, such as scopolamine and meclizine, block the excitatory effect of acetylcholine receptors. In this manner, the GABA downregulatory effect on glutamate would be reduced. This cascade has the potential to hasten the onset of full tonic-clonic seizures. Nevertheless, uncertainty remains regarding how different acetylcholine receptor antagonists affect the risk of CNS-OT.[3]

Previous studies have tested the interaction of high PO_2 with other anti-motion sickness medications,[16,17] yet meclizine remains untested. Meclizine is becoming increasingly popular thanks to its global availability as an over-the-counter drug and minimal side effects. The present study aimed to evaluate the effect of meclizine on the latency to CNS-OT under hyperbaric conditions in a murine model.

Methods

ETHICAL APPROVAL

The Animal Research Committee of the Israel Ministry of Defence approved the experimental procedures, and husbandry and handling were in accordance with internationally accepted humane standards.

STUDY POPULATION

Twenty male C57BL/6 mice (Envigo RMS, Jerusalem, Israel) aged eight weeks and weighing between 16 and 20 grams were included in the study.

HUSBANDRY

Mice were housed in wire frame cages under standard conditions, with free access to drinking water, cardboard homes, and standard feed. They were kept in a 12-hour (h) light / 12 h dark cycle, and the ambient temperature was maintained at 24°C.

MECLIZINE PREPARATION

Carboxymethyl cellulose (CMC) solution 0.25% w/v, prepared by mixing CMC powder (MO512-100G, 4000 cP, Sigma) in single distilled water, served as the solvent and control solution. Meclizine solution was prepared with a single Bonine® tablet (25 mg meclizine hydrochloride, WellSpring Pharmaceutical Corporation) triturated by mortar and pestle and suspended in CMC solution via sonication. The final animal equivalent dose calculated and used was 5.2 $mg \cdot kg^{-1}$ per mouse, according to well-established methods.[18–20]

EXPERIMENTAL PROCEDURE

Each mouse was exposed twice to hyperbaric O_2 (HBO) in a randomised-crossover design. The exposure procedure was performed on each mouse individually. Since sensitisation to oxygen toxicity has been observed in small rodents after repeat exposures to HBO, the two sessions were performed a week apart to allow for any residual effects to dissipate.[21,22] Mice were denied food 12 h preceding HBO exposures, assuring more uniform drug pharmacokinetics.[23] Free access to fresh water was maintained at all times. Since the effects of drugs tend to be influenced by body mass, the body mass of the study groups was recorded and compared.

Mice were administered 0.2 mL of either control solution (CMC) or meclizine solution using a 20-gauge oral gavage needle, followed by placement in the test exposure box at standard ambient atmospheric conditions (101.3 kPa absolute pressure, 21% O_2). Mice were given 10 minutes to acclimatise in the exposure box, which is the time the drug was calculated to reach maximal blood concentration according to mouse equivalent pharmacokinetics.[24] The exposure box was placed in a hyperbaric chamber (Roberto Galeazzi, La Spezia, Italy) and pressure was increased at a rate of 101.3 $kPa \cdot min^{-1}$ (one atmosphere per minute) up to 608 kPa absolute pressure (six atmospheres absolute) with 100% O_2. While fully pressurised and breathing pure O_2, the mice were observed for clear signs of tonic-clonic seizures. Once seizures were evident and the time of exposure documented, the gas in the exposure box was replaced with air and the hyperbaric chamber was depressurised at a rate of 101.3 $kPa \cdot min^{-1}$ to avoid decompression illness. Mice were retested after seven days for the other treatment (control or meclizine). Every exposure session was recorded by video and subsequently further analysed to ensure the exact time of seizure onset was captured. A visual outline of the hyperbaric oxygen exposure procedure can be seen in Figure 1.

After completion of both sessions, mice were sacrificed by sedation with isoflurane vapour, followed by pentobarbital sodium overdose (200 $mg \cdot ml^{-1}$, CTS, Israel) and manual neck dislocation.

Data analysis was performed using GraphPad InStat 3.1 (GraphPad Software, San Diego, CA, USA) and KaleidaGraph 5.02 (Synergy Software, Reading, PA, USA).

Results

The mice exhibited the highly reproducible tonic-clonic seizures expected of CNS-OT, with an average (standard deviation [SD]) latency of 424 (SD 146) s. Comparing the latency to toxicity in control (414 [SD 113] s) versus meclizine-treated mice (434 [SD 174] s), no statistically significant difference was observed (paired Student *t*-test, $P = 0.37$). Additionally, plotting for the change in latency

Figure 1
Exposure profile of mice to hyperbaric oxygen conditions, and measurement of latency to onset of tonic-clonic seizures; during pressurisation, air is gradually switched to oxygen, and during decompression the oxygen is switched back to air. kPa – kilopascals; min – minutes; O_2 – oxygen

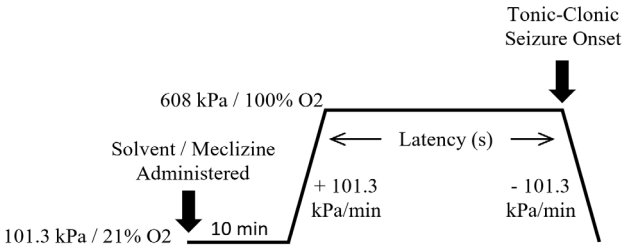

Figure 2
Latency for individual subjects for control and meclizine-treatment conditions. s – seconds

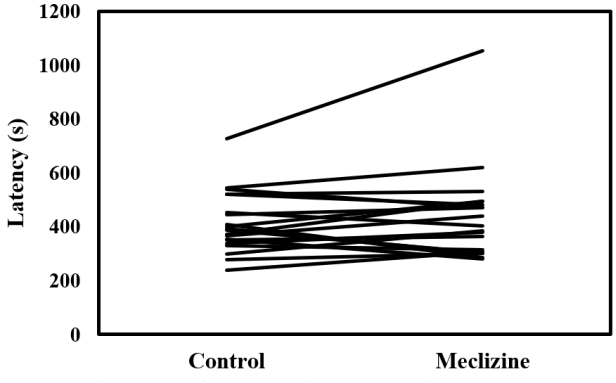

Figure 3
Latency versus mass of mice; oxygen toxicity latency did not vary with mass for either control (solid line) or meclizine-treatment (dashed line) groups. s – seconds; g – grams

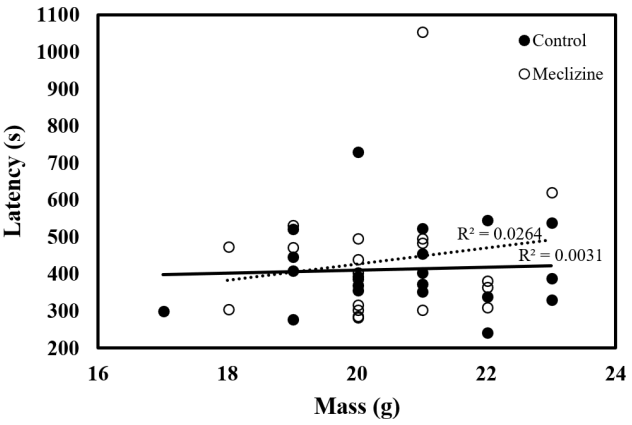

Table 1
Latency (s) to onset of seizures in control and meclizine-treated mice exposed to hyperbaric oxygen; s – seconds; g – grams

Group	Body mass (g)		Latency (s)	
	Mean (SD)	*P*	Mean (SD)	*P*
All sessions	20.5 (1.45)	–	424 (146)	–
Control	20.7 (1.60)	0.520	414 (113)	0.371
Meclizine	20.4 (1.31)		434 (174)	

for individual mice did not exhibit any clear trend, as may be seen in Figure 2.

Regarding the influence of body mass, there was no statistically significant difference between control and meclizine groups (mean 20.7 [SD 1.60] g and 20.4 [SD 1.31] g, $P = 0.52$). The mean chronological change in body mass between the sessions was + 0.50 (SD 1.96) g, $P = 0.27$. The dependency of latency to toxicity on body mass was also examined. Linear regression demonstrated no correlation between latency and body mass for either control or meclizine groups ($r^2 = 0.0031$, $P = 0.81$; $r^2 = 0.0026$, $P = 0.49$, respectively), as shown in Figure 3.

Latency and body mass data are shown in Table 1.

Discussion

Closed-circuit divers using pure oxygen rebreather apparatus have an elevated risk of CNS-OT. In many cases, these divers also develop motion sickness on their way to a dive location. To cope with seasickness, the use of medication is common. Some relevant drugs such as meclizine contain anticholinergic compounds, potentially increasing the risk of CNS-OT. The present study aimed to evaluate the effect meclizine may have on CNS-OT as defined by the clear appearance of tonic-clonic seizures in rats.

The main finding of the present study is that meclizine had no effect on the latency to CNS-OT resulting from high pO_2. To interpret this result, meclizine's pharmacology should be considered. Meclizine operates via different pathways to prevent motion sickness. It is considered to affect both histaminergic and cholinergic pathways.[25] Several studies have been conducted to examine the specific site of action of this drug. Although meclizine is defined as an antihistamine having additional antim uscarinic potency, it shows low affinity for the muscarinic receptors.[9] The antiemetic action of meclizine is attributed for the most part to blocking of the H1 histamine receptor.[26] Therefore, the mechanisms of action of this drug may explain the main result of the present study. Further support is provided by past studies which have also concluded that certain anticholinergic activity does not reduce the latency to CNS-OT.[16,17]

Since there was some variability in body mass, further analysis was undertaken to find out if this may have affected the results. The statistical analysis did not reveal a correlation

between body mass and latency to CNS-OT, in agreement with the literature. Arieli reviewed data of body mass and time to convulsion from several studies.[27] His analysis found that under hyperbaric conditions, time to convulsion did not correlate with body mass, either within a species or between species. Metabolic rate and free radical production, both at the basis of the biochemical mechanism for CNS-OT, increase with body mass. Arieli theorised that although free radical production increases, antioxidant production rates may also increase with body mass.[27] This would support the present study's main result.

Though the mouse and other small mammals are widely used in CNS-OT research,[3] the effects on humans may not be directly deduced due to differences in physiology. The acetylcholine antagonist scopolamine was tested for its effect on CNS-OT in rats over 30 years ago, and results did not show an increased risk.[16] Since then, scopolamine has become widely used by divers prior to oxygen diving. In this time, there have not been any reported CNS-OT cases involving this drug. With this knowledge and the results of the present study, a future human study can be conducted.

Conclusions

The results of the current study did not indicate any effect of meclizine in development of CNS-OT, as observed in mice. This may suggest that the pharmacological pathway and mechanism of this medication are not involved in the events leading to diving-related tonic-clonic seizures.

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Conflicts of interest and funding

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