Effect of the anti-motion-sickness medication cinnarizine on central nervous system oxygen toxicity

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Ariel R, Shupak A, Shachal B, Shenedrey A, Ertraacht O, Rashkovan G. Effect of the anti-motion-sickness medication cinnarizine on central nervous system oxygen toxicity. Undersea Hyper Med 1999; 26(2):105-109.—Severe seasickness could pose a serious problem in diving, and anti-seasickness medication should therefore be prescribed for the seasickness-susceptible diver. Cinnarizine may be used as a medication if it does not increase the risk of central nervous system (CNS) oxygen toxicity when diving with closed-circuit oxygen or O2-enriched gas mixtures. Twenty-six male, white Sprague–Dawley rats were exposed to high O2 pressures (507 and 608 kPa) before and after cinnarizine ingestion (3.3 mg kg–1), until the appearance of the first electrical discharge (FED) in the electroencephalogram (EEG) which precedes the clinical convulsions. Each rat was tested on five exposure protocols (control and cinnarizine at 507 kPa O2, control, cinnarizine, and 15 h starvation as a control for cinnarizine at 608 kPa O2) at intervals of at least 2 days or until the EEG connector became detached (a mean of 3.1 exposures per rat). Latency to the FED increased after cinnarizine ingestion in 16 of the 17 pairs of measurements at 507 kPa O2 (by more than 61%, P < 0.002) and in 17 of the 19 pairs of measurements at 608 kPa O2 (by 36%, P < 0.002). There was no significant effect of 15 h starvation. Cinnarizine can be further considered for use in seasickness-susceptible divers as it does not increase the risk of CNS O2 toxicity.

hyperosia, hyperbaric oxygen, seizure, diving

Seasickness is a problem occasionally encountered by divers during surface transportation or when diving in shallow water. Severe seasickness could pose a serious problem in diving. Anti-seasickness medication should therefore be prescribed for the seasickness-susceptible diver. One such medication is cinnarizine. Cinnarizine (Stunaron) was found to be efficient in alleviating the symptoms of seasickness (1,2). Cinnarizine, a piperazine derivative, blocks H1 receptors, Ca++ channels, and dopamine (D2) receptor (3). Cinnarizine inhibits the transfer of calcium ions from the endolymph to the hair cells in the ampulla of the semicircular canals, and in the macula of the utricle and the saccule, thus depressing vestibular input (1). Cinnarizine is easily absorbed from the alimentary system. In humans, the plasma level of cinnarizine reached a maximum 3 h after oral intake of 75 mg (4).

Central nervous system (CNS) oxygen toxicity may manifest as generalized seizures which may be followed by a loss of consciousness. This is a major risk in closed-circuit O2 diving, and should also be taken into consideration in a relatively new but expanding field in which sport divers use oxygen-enriched gas mixtures. Before cinnarizine can be considered for the prevention of seasickness during dives employing high pressure O2, it is important to assess whether this drug has any effect that may enhance CNS O2 toxicity.

The interaction between cinnarizine and O2 at high partial pressures might also be of relevance for divers using cinnarizine in open-circuit diving, who require hyperbaric oxygen (HBO2) therapy, for arterial gas embolism due to pulmonary barotrauma, and for decompression sickness. This mode of therapy, which is the treatment of choice for these diving accidents, uses high partial pressure of O2. In such cases, any potential enhancement by cinnarizine of CNS O2 toxicity would be important. The first electrical discharge (FED) in the electroencephalogram (EEG), which precedes the clinical convulsions of CNS O2 toxicity, is a well-defined phenomenon (5,6). We used this in a previously described rat model (7,8) to investigate the effect of cinnarizine on CNS O2 toxicity.

MATERIALS AND METHODS

Animals

Twenty-six Sprague–Dawley rats [335 ± 38 g (SD)] were used. Rats were implanted with EEG electrodes. The electrodes were stainless steel screws penetrating the skull in the parietal area. Insulated wires attached to a female miniconnector were soldered onto the screws, and the miniconnector was fastened to the skull with dental cement. The experimental procedure was approved by the animal care committee of the Israel Defence Forces, and the rats
were handled in accordance with internationally accepted humane standards.

**Experimental system and procedure**

*Experimental cage:* The experimental cage is a metal, double-walled cage (25 × 20 × 12 cm, volume 6.0 liters). One wall for observation of the animal and the top cover which can be opened are made of Plexiglas. Thermoregulated water can be pumped through the double wall to control the ambient temperature. The incoming gas flows through a metal container attached to the cage wall for temperature equilibration before entering the cage. The metal walls of the cage are covered on the outside with thermal insulating material. A cable with a male miniconnector for EEG recording passes through the top cover. A humidity and temperature measuring device (EE20FT, EE Electronics, Austria) was inserted into the top cover of the cage.

*Experimental system:* The miniconnectors were mated, and the rat was placed in the experimental cage, which was placed in a 150-liter pressure chamber (Roberto Galeazzi, La Spezia, Italy). The flow of gas through the cage was controlled by a needle valve. The flow was checked by observation of a flowmeter located inside the pressure chamber. The outgoing gases exited via a bypass tube into the atmosphere of the pressure chamber. Water hoses were connected to ports in the pressure chamber and to the ports in the experimental cage for recirculation of the thermoregulated water (C/H Temperature Controller Bath and Circulator 2067, Forma Scientific, Marietta, OH). The temperature of the cage was checked at thermoneutral range 25°–30°C. The EEG was recorded on a chart recorder (Gould Inc, Cleveland, OH).

*Experimental procedure:* When the pressure in the chamber was being raised (at 100 kPa × min⁻¹), the gas flowing through the cage was air. When the desired pressure was reached, a period of 20 min was allowed for acclimation to the experimental conditions, during which air flowed through the cage at approximately 8 liters × min⁻¹. After the end of the acclimation period, the flow of air was immediately replaced by pure O₂ at high flow of approximately 30 liters × min⁻¹ for 1 min for fast replacement of the cage’s atmosphere, after which the flow was reduced to 8 liters × min⁻¹. The EEG signal was amplified and was recorded continuously on a chart recorder; ambient temperature and humidity were read and recorded. The rat was observed through a window in the pressure chamber. When the first FED was seen on the recorder, the time noted and decompression was commenced (at 100 kPa × min⁻¹). When no FED was seen, the exposure was terminated at 50 min to avoid the complication of pulmonary involvement (9). The cage was removed from the pressure chamber and the rat was freed from the experimental system.

**Experimental protocol:** Repeated measurements from the same rat were taken with at least a 2-day interval in between. The rat was deprived of food for 15 h (with access to drinking water) and was then given a piece of mashed bread containing ground cinnarizine (3.3 mg × kg⁻¹). We have previously shown that the sensitivity of latency to the FED to increased metabolic rate (10) or increased inspired CO₂ (11), decreases with the rise in P O₂. Thus for several P O₂’s that caused CNS O₂ toxicity, the effect of changing either metabolic rate or inspired P CO₂ on latency to the FED was maximal at the lowest P O₂. We therefore chose to test two different P O₂’s. Rats were subjected to a total of five different exposures, one every 2–3 days in random order (blind selection of the five protocols for each rat): 1) Control at 507 kPa O₂ without starvation. 2) 507 kPa O₂ exposure after cinnarizine ingestion. 3) Control at 608 kPa O₂ without starvation. 4) 608 kPa O₂ exposure after cinnarizine ingestion. 5) Control at 608 kPa O₂ after 15 h starvation and ingestion of a piece of bread 40 min before the exposure. This last exposure served as a control, because it has been shown that a longer period of starvation, 24 or 48 h, prolongs the latency to the FED (12). Each rat was subjected to the different conditions in random order until the connector became detached, therefore we did not obtain all five exposures for each rat. All exposures were conducted during the morning hours.

**Statistics:** Because we have shown in previous studies (7,8,10) that the variability in CNS O₂ toxicity between rats is much greater than the intra-rat variability, all the paired observations—cinnarizine and control at 507 kPa O₂, cinnarizine and control at 608 kPa O₂—and starvation and control at 608 kPa O₂—were analyzed statistically. When one or more rats in any of the paired observations failed to convulse during the maximal exposure of 50 min, this value was used for the analysis. Analysis of variance (ANOVA) with repeated observation was used to analyze control and cinnarizine effect (repeated) and 507 and 608 kPa O₂. Only paired observations were used, therefore there were no missing data. When ANOVA yielded significant effect of cinnarizine, because one or more rats in any of the paired observations failed to convulse during the maximal exposure of 50 min, a non-parametric Sign Test was used for each pressure as well. Control and 15 h starvation were analyzed using paired t test.

**RESULTS**

There were 3.1 ± 1.3 exposures (SD) per rat (range 2–5). The cage temperature was 27.6° ± 1.1°C (SD) and humidity at the end of the exposure was 58 ± 9% (SD). Because there was no difference in humidity in the various expo-
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sures, no effect of humidity is expected on the latency to CNS O₂ toxicity. ANOVA showed significant effect of Po₂ (P < 0.001) and of cinnarizine (P < 0.0005). Latencies to the FED at 507 kPa O₂ are shown in Fig. 1. Several rats did not convulse during the 50-min exposure after cinnarizine ingestion (Fig. 1, asterisks). We used 17 pairs of measurements for control and cinnarizine ingestion. In all rats but one, latency after cinnarizine ingestion was longer than in the control exposure. Although the rats differed in their sensitivity to CNS O₂ toxicity (some had shorter and others longer latency), non-parametric data analysis showed significant prolongation of latency to the FED after cinnarizine ingestion (P < 0.002). Results from the exposure to 608 kPa O₂ are presented in Fig. 2. As in the 507-kPa exposure, the variability in sensitivity between rats is greater than within the individual animal. Latency to the FED increased after cinnarizine ingestion in 17 of the 19 pairs of observations. Only one cinnarizine-treated rat failed to convulse within 50 min. The effect of cinnarizine on the prolongation of latency to CNS O₂ toxicity proved to be significant (P < 0.002). When the latency for the exposure during which a rat failed to convulse was taken as 50 min, the mean prolongation of latency to the FED by cinnarizine was 11.9 min (61% of the control latency of 29.7 min) and 5.8 min (36% of the control latency of 21.5 min) at a Po₂ of 507 and 608 kPa, respectively. The real difference between these two pressures would be even greater if an exposure period longer than 50 min had been employed. The results of food deprivation for 15 h are given in Fig. 3. Food deprivation for 15 h and eating a piece of bread 40 min before the exposure

FIG. 2—Latency to the FED in the EEG at a Po₂ of 608 kPa, in the control exposure and after cinnarizine ingestion. Other symbols are as in Fig. 1.

FIG. 3—Latency to the FED in the EEG at a Po₂ of 608 kPa, in the control exposure and after 15 h food deprivation. Other symbols are as in Fig. 1. Non-significant P was calculated by a paired t test.

had no significant effect on latency to the FED at a Po₂ of 608 kPa (P = 0.22, paired t test). We derived results from seven rats both starvation and cinnarizine ingestion before exposure to 608 kPa O₂. The paired t test demonstrated significant prolongation of latency to CNS O₂ toxicity after drug ingestion (P < 0.04).

DISCUSSION

The possible interaction between anti-seasickness drugs and HBO₂ exposure is an important issue in closed-circuit O₂ diving. Such a possibility was previously studied in the case of scopolamine (13), and in the present study we have
done the same for cinnarizine.

In previous studies (7,8) we have shown that the preceding exposure has no effect on the time to the FED in the following one if there is a 2-day interval between them. Six exposures at 608 kPa O2 at 2-day intervals between them did not affect the latency to the FED for each of six rats 14.3 ± 7.0, 11.1 ± 3.7, 12.5 ± 4.1, 11.3 ± 4.4, 11.6 ± 4.4, and 11.7 ± 6.1 min sd (8). This procedure enabled repeated measurements to be taken from the same animal with reduced variability. We therefore have shown that intra-animal variability is much lower than inter-animal variability. Therefore we used repeated measurements from the same rat with at least a 2-day interval in between. The temperature of the cage was checked at thermoneutral range 25°–30°C to prevent the effect of increased metabolic rate on the latency to the FED (9). Lin and Jamieson (14) suggested that humidity in the inspired O2 might affect the latency to CNS O2 toxicity, and therefore the humidity in the cage was not controlled but monitored throughout the experiment. The dose per kilogram was calculated from the baseline of 75 mg for a 70-kg human. This value was corrected by the ratio of rat-to-human metabolic rate calculated from Stahl (15). VO2 = 11.6 × M0.76, where VO2 = ml × min-1 and M is body mass in kilograms. This yields 3.3 mg cinnarizine × kg-1 for the rat. Cinnarizine should be ingested by humans 1 h before exposure to sea conditions to achieve effective prevention of seasickness. To obtain this time interval for the rat, we used the relationship of time scale to body mass as M-0.25. The calculated interval from cinnarizine ingestion to drug effectiveness (and therefore to high O2 pressure exposure) for the rat was 40 min.

The exact pathways leading to CNS O2 toxicity are as yet unknown. The delaying effect of cinnarizine can be attributed to its blocking of Ca2+ channels, similar to the effect of Mg2+ ions (16) and the calcium antagonist flunarizine (17). Colton and Colton (18) showed that HBO2-induced seizures are blocked by excitatory amino acid antagonists. These excitatory amino acids induce calcium entry into the pathways that end in convulsions (excitotoxicity). Therefore, blocking this Ca2+ entry by cinnarizine, flunarizine, or Mg2+ can postpone CNS O2 toxicity. Cinnarizine might affect other routes besides that of excitotoxicity, as calcium potentiates O2 free radical injury to the mitochondria (19), and magnesium attenuates pulmonary O2 toxicity (20).

It has been established that metabolic rate (9) and inspired PCO2 (11) have a greater effect on latencies to the FED in the low range of PO2 that induces CNS O2 toxicity. In the present study, we found that the effect of cinnarizine on the prolongation of latency to the FED is also more pronounced at 507 kPa O2 (more than 61%) than at 608 kPa (36%). It may therefore be expected that in closed-circuit O2 diving and HBO2 therapy, where the PO2 does not usually produce CNS O2 toxicity, there may be a pronounced beneficial effect of cinnarizine.

Cinnarizine was proved to delay latency to the FED in the rat at the two O2 pressures tested. Therefore, cinnarizine taken as an anti-seasickness drug would not increase the risk of CNS O2 toxicity in the rat. A multi-purpose drug would be an optimal solution for any syndrome. A drug that can reduce both seasickness severity and the risk of CNS O2 toxicity, without impairing performance, is the ultimate solution for closed-circuit O2 divers who are susceptible to seasickness. Cinnarizine may be just such a remedy. However, further studies are required to evaluate the clinical significance of cinnarizine and HBO2 on humans.

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