Clinical Neurophysiology 127 (2016) 2350–2354

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Vestibular evoked myogenic potentials and motion sickness medications

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ARTICLE INFO

Article history:
Accepted 7 March 2016
Available online 19 March 2016

Keywords:
Vestibular evoked myogenic potentials
Scopolamine
Cinnarizine
Dimenhydrinate
Seasickness
Motion sickness

HIGHLIGHTS

- We examined cVEMP as a means of evaluating the action of anti-seasickness drugs.
- Action of scopolamine was demonstrated by changes in cVEMP latencies.
- cVEMP may be used to evaluate the effect of drugs on the vestibular system.

ABSTRACT

Objective: Seasickness is a widespread problem among naval crew, and has a major impact on their performance at sea. The three pharmacological agents most commonly employed in the treatment of seasickness are dimenhydrinate, cinnarizine, and scopolamine. At present, the effectiveness of anti-seasickness drugs is tested by a process of "trial and error", while sailing and exposed to sea conditions. A physiological test to evaluate the action of a drug might save crew members long periods of suffering, as well as simplifying the procedure of selecting the appropriate treatment for each individual. The cervical vestibular evoked myogenic potentials (cVEMP) test has come to be recognized as a reliable procedure for the objective evaluation of saccular function. It was the hypothesis of the present study that cVEMP otolith responses may be affected by anti-motion sickness drugs, which might thus make cVEMP a useful clinical neurophysiological tool for the assessment of drug absorption and efficacy.
Methods: Thirty male sailors who regularly took medication for the treatment of seasickness participated in the study. Participants underwent the cVEMP test pre- and 1 h post-drug administration.
Results: A statistically significant decrease in p13 latency was found after administration of scopolamine compared with baseline (14.46 ms vs. 15.09 ms, $p = 0.0049$), with significant prolongation of the binaural average inter-latency in this group. No differences were found in the dimenhydrinate and cinnarizine study groups.
Conclusions: This study demonstrated that scopolamine absorption can be verified by changes in cVEMP latencies.
Significance: The potential of the cVEMP test for predicting action of scopolamine on the vestibular system.

1. Introduction

Seasickness represents a major problem for ships' crew. Its symptoms are both vegetative and cognitive, with the consequence that the crew's ability to perform their daily duties is often severely limited. Some crew members undergo habituation to seasickness after 3–6 months experience at sea, although others remain sensitive to sea conditions. Symptoms occur with varying severity in 20–60% of sailors, depending on the sea state and the length of the voyage (Golding and Gresty, 2015).

It becomes clear from a review of the literature that the vestibular system plays a significant role in the development of motion sickness. Support for this may be found in the fact that both animals and humans with bilateral vestibular loss are immune to motion sickness (Cheung et al., 1991). Furthermore, motion sickness drugs act via a bilateral vestibular blocking mechanism (Takeda et al., 1993). Riccio and Stoffregen (1991) and Stoffregen (2011) postulated a relationship between the vestibular system and body sway prior to stimulus exposure. The authors pointed out differences in body sway between those persons who developed motion sickness symptoms and those who did not. Simulator studies have

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http://dx.doi.org/10.1016/j.clinph.2016.03.010
1388-2457/

demonstrated that the vertical linear acceleration component of ship motion (heave) is the most provocative stimulus of seasickness, particularly in the range 0.17–0.23 Hz. The saccule is responsible for monitoring vertical acceleration in the upright position, and therefore it is suggested that the saccule may play an important role in seasickness (Lawther and Griffin, 1987; Tal et al., 2006).

In recent years, the cervical vestibular evoked myogenic potentials (cVEMP) test has been used to evaluate saccular function by provoking the inhibitory bipolar myogenic potential of the sternocleidomastoid (SCM) muscle. The response is considered a unilateral reflex, and is measured by surface electrodes located on the SCM ipsilateral to the stimulated ear (Colebatch et al., 1994; Murofushi et al., 2004). It is mediated by a synaptic pathway leading from the vestibular nuclei to the SCM motor nucleus (Phelan et al., 1990).

Animal and human studies have documented the presence of muscarinic acetylcholine receptors, as well as histamine receptors, in the peripheral vestibular system and the vestibular nuclei. The activity of the vestibular system is modulated by excitation and inhibition of these receptors. A number of studies have shown the influence of vestibular suppressant drugs on vestibular reflexes (Ishiyama et al., 1997; Phelan et al., 1990; Shupak et al., 1994). Motta et al. (2011) recorded auditory brain response and cVEMP reflexes in anesthetized guinea pigs. Whereas the auditory brain response could be measured normally during anesthesia, the cVEMP response was not recordable.

The three main drugs employed in the conventional treatment of motion sickness are dimenhydrinate, a histamine antagonist, cinnarizine, an antihistamine and calcium channel blocker, and scopolamine, which acts via blocking of the muscarinic acetylcholine receptor (Golding and Gresty, 2015). One of the challenges faced by the physician in the motion sickness clinic is to select the appropriate drug for the patient. Difficulties arise due to high variability in the response to the different medications. In the case of seasickness, the current procedure is to examine the drug's efficacy during real-time exposure to sea conditions. This could involve prolonged suffering on the part of the patient until a suitable treatment is found. However, the major concern is when the patient fails to respond to any of the above mentioned drugs. In such a case, when there is a known history of seasickness, the physician should advise the patient to reconsider his choice of occupation as a crew member aboard a sea-going vessel. The purpose of the present study was therefore to evaluate the effect of seasickness medications on the cVEMP response.

2. Methods

2.1. Subjects

Thirty naval crewmembers volunteered to participate in the study. Subjects' ages ranged from 19 to 41 years (24.59 ± 7.11). A review of their medical history, together with an otoneurologic examination and pure tone and speech audiometry, ruled out any previous inner ear pathology or conductive hearing loss that might affect cVEMP results. Subjects were instructed not to take any medications, drugs or alcohol in the 48 h preceding cVEMP testing. All subjects gave their written informed consent, and the study was approved by the Israel Defense Forces Medical Corps Human Research Committee.

2.2. Experimental protocol

2.2.1. Pharmaceutical agents

The study population was divided randomly into three drug groups, 10 subjects in each. The pharmaceutical agents employed in the study were dimenhydrinate 100 mg ("Travamin", Rekah, Holon, Israel), cinnarizine 25 mg ("Stunarone", Janssen, Latina, Italy), and scopolamine 0.3 mg ("Kwells", Bayer, Newbury, Berkshire, UK). Adverse effects were documented 1 h after application of the drug. Side effect severity was graded on a four-point scale: 0 – no symptom; 1 – mild; 2 – moderate; 3 – severe. An average score for the three groups was calculated for each symptom. Documented symptoms were far-sighted blurred vision, near-sighted blurred vision, dazzle, eye irritation, drowsiness, headache, fatigue, difficulty concentrating, dryness of the mouth, physical weakness, and mental weakness.

2.2.2. Cervical vestibular evoked myogenic potentials

cVEMP was performed bilaterally using the Navigator Pro system (Bio-Logic Systems Corp., Mundelein, IL, USA). Surface electromyographic (EMG) activity was recorded in the supine position, with the subject lying on a firm medical bed, as previously documented (Li et al., 1999; Tal et al., 2006, 2013). Sternocleidomastoid (SCM) muscle voltage was measured using surface Ag/AgCl electrodes fixed to the skin with Ten20 electrode paste. The active electrodes were firmly attached over the main bulk of the muscle, approximately half the distance between the mastoid tip and the sternal notch. A reference electrode was placed over the upper sternum. A ground electrode was placed on the center of the forehead. The cVEMP tests were performed by the same operator for all subjects. The position of each electrode was marked in the pre-medication test in order to reattach it at the same spot in the post-drug test.

Stimuli were in the form of bilateral tone bursts, presented to the external ear canal through insert earphones covered with foam plugs. To achieve sufficient activation of the SCM, and thus produce the inhibitory reflex arc, subjects were instructed to lift their head up to an angle of about 30°. EMG activity was recorded bilaterally to avoid asymmetric muscle tension, and also due to the purely unilateral nature of the reflex.

Tone bursts were presented at 4.3 Hz, with a central frequency of 500 Hz. The duration of sampling was 53.3 ms from the beginning of each click, and was amplified and filtered to a frequency range of 10–1500 Hz. Each VEMP signal was derived from an average of 200 responses to click stimuli. Inclusion criteria for VEMP waves were two sequential responses with a correlation above 0.75 and a signal-to-noise ratio (SNR) of at least 2 (Tal et al., 2006, 2013).

The cVEMP parameters evaluated for a 90 dB nHL intensity stimulus were p13 wave latency (ms), n23 wave latency (ms), p13–n23 wave inter-latency (ms), p13 wave amplitude (μV), n23 wave amplitude (μV), p13–n23 wave inter-amplitude (μV), and interaural amplitude difference (IAD) ratio. The IAD ratio was defined as the interaural peak-to-peak amplitude difference divided by the sum of the amplitudes in both ears.

2.3. Statistical analysis

Statistical analysis was carried out using SPSS 12.0 software (SPSS Inc., Chicago, IL, USA). Differences between baseline values and those obtained after administration of the drug were analyzed for the binaural averages of the cVEMP parameters using a paired sample *t*-test and the Wilcoxon matched-pairs signed-rank test for parametric and non-parametric data, respectively. The adverse effects of the drugs were analyzed by an ANOVA test. A p value of 0.05 was taken as representing statistical significance.

3. Results

cVemp waves were successfully recorded in all subjects. The values obtained for the binaural mean latencies of the parameters evaluated are given in Tables 1–3.