Research Paper

# A pilot study of rizatriptan and visually-induced motion sickness in migraineurs

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## Abstract

**Background:** Limited evidence suggests that rizatriptan given before vestibular stimulation reduces motion sickness in persons with migraine-related dizziness. The present study was designed to test whether rizatriptan is also effective in protecting against visually-induced motion sickness and to test whether rizatriptan blocks the augmentation of motion sickness by head pain.

**Material and Methods:** Using randomized double-blind, placebo-controlled methodology, 10 females, 6 with migrainous vertigo (V+) and four without vertigo (V-) received 10 mg rizatriptan or placebo two hours prior to being stimulated by optokinetic stripes. Visual stimulation was coupled with three pain conditions: no pain (N), thermally-induced hand pain (H) and temple pain (T). Motion sickness and subjective discomfort were measured.

**Results:** Motion sickness was less after pre-treatment with rizatriptan for 4 of 10 subjects and more for 5 of 10 subjects. Augmentation of motion sickness by head pain was seen in 6 of 10 subjects; this effect was blunted by rizatriptan in 4 of these 6 subjects. Subjective discomfort was significantly more noticeable in V+ subjects as compared with V- subjects.

**Conclusions:** These pilot data suggest that rizatriptan does not consistently reduce visually-induced motion sickness in migraineurs. Rizatriptan may diminish motion sickness potentiation by cranial pain.

Key words: anxiety, optokinetic, pain, vertigo, vestibular

## Introduction

Migrainous vertigo is accepted as a common cause of episodic vertigo, affecting about 1% of the population [1]. A recent survey comparing the occurrence of vestibular complaints in 327 migraine patients and 324 controls without frequent headache reported dizziness or vertigo in 52% of migraine patients versus 32% of controls (*P*<0.0001) [2]. Furthermore, 23% of those migraine patients with vestibular complaints met criteria for the diagnosis of migrainous vertigo. Patients with migraine with aura had significantly more migraine attacks associated with vestibular complaints always (15% vs. 10%) or sometimes (22% vs. 5%) (*P*<0.0001).

Vestibular abnormalities have been identified in migraineurs when asymptomatic between headache episodes. A small study comparing interictal vestibular function in individuals with migraine with and without vertigo and controls (N=15) showed reduction in mean gain of the semicircular canal-ocular reflex, a larger modulation component of the otolith-ocular reflex, and increased postural sway during optic flow testing among individuals with migrainous

vertigo [3]. Recently, a larger study similarly testing vestibular function in patients with migraine or controls (N=75) identified saccadic pursuit, unilateral caloric hypofunction, and increased sway velocity on posturography in individuals with migrainous vertigo [4]. Others have failed to differentiate migraineurs with and without vertigo, based on specialized vestibular testing [5, 6].

Motion sickness provides an easily reproduced vestibular symptom. Motion sickness can be induced by stimulation of the vestibular receptors via actual motion or motion of visual surroundings, such as optokinetic stimuli. Such visually-induced motion sickness is often accompanied by a sensation of self motion indistinguishable from sensations experienced during actual motion. Visually-induced motion sickness can be as severe as that induced by actual motion. Drummond reported motion sickness symptoms after exposure to individual motions (e.g., boat, car, or amusement park rides) in 30-40% of migraineurs, with motion sickness after viewing visual stimuli (e.g., simulators or movie screens) in about 20-30% [7]. Interestingly, motion sickness induced by actual motion did not predict motion sickness from visual stimuli. Research by Drummond and Granston showed that visually-induced motion sickness in migraineurs can be potentiated by combining head pain with a provocative visual stimulus [8].

Reducing motion sickness can be accomplished by avoidance of a provocative stimulation or using vestibular suppressants. Triptans have been inconsistently shown to decrease symptoms in patients diagnosed with migrainous vertigo [9, 10]. A recent case report of three women with migrainous vertigo noted head pain induction or aggravation with resolution of vertigo after triptan treatment (sumatriptan in 2 patients and rizatriptan in one patient) of usual vertigo attacks [11]. Our previous research has suggested in a small pilot study that rizatriptan, when given orally two hours prior to exposure to a complex vestibular stimulation, reduces motion sickness in persons with migraine-related dizziness [12]. Based upon this apparent protective effect of rizatriptan for motion sickness induced by actual motion in migraineurs, we embarked upon a comparable study of visually-induced motion sickness. We were especially interested in replicating and extending research by Drummond and Granston [8] that showed that visually-induced motion sickness in migraineurs can be potentiated by combining head pain with a provocative visual stimulus, the "Drummond Effect". In the present study, using a small number of subjects, we addressed the hypotheses that rizatriptan acts as a protective agent against visually-induced motion sickness in migraineurs and that rizatriptan interferes with the Drummond Effect.

## Methods

This double-blind placebo controlled pilot study compared the development of visually-induced motion sickness after pre-treatment with a typical migraine dose of the serotonin agonist rizatriptan or placebo. Rizatriptan was selected for this study based upon its superior ability to cross the blood-brain barrier [13]. This trial was conducted in accordance with the guidelines of the International Conference on Harmonization for Good Clinical Practice and the study protocol was approved by a local Institutional Review Board. Each study participant provided informed consent prior to study enrollment.

For this pilot study, data from ten females with migraine headache and a history of motion sickness are reported. Eligible subjects were identified via local paid advertisements. Subjects were required to be 21-45 years old with a diagnosis of ICHD-II migraine with or without aura [14]. Subjects were initially screened by telephone for migraine using the previously-validated Migraine Assessment Tool [15], with the diagnosis confirmed through clinical evaluation by a board-certified neurologist. Eligible subjects were required to report a typical migraine frequency of at least 2 episodes per month and have previously demonstrated tolerability to any triptan medication. Subjects were also required to report a history of motion sickness symptoms with actual or visually-induced motion. Subjects were excluded if they had heart disease, uncontrolled hypertension, a family history of early myocardial infarction, were current smokers, or were pregnant. Subjects were also excluded if they had neurologic or otologic disease aside from migraine or migraine-related dizziness or a diagnosis of hemiplegic or basilar migraine. Subject candidates were subsequently evaluated by a neurotologist using the validated Structured Interview for Migrainous Vertigo [16] and clinical assessment to categorize subjects as having migraine with (V+) or without (V-) migrainous vertigo, based on previously published criteria by Neuhauser, et al. [17].

During the screening visit, subject candidates were evaluated with testing of visual and auditory acuity, along with vestibular screening tests. Eye position data were collected using infrared cameras housed in form-fitted goggles for the following tests: ocular motor screen, gaze and spontaneous nystagmus search, positional nystagmus search, caloric irrigation, and earth vertical axis rotational testing. During ocular motor screening, subjects were placed in front of a screen onto which a laser target or dark bars

were projected. Subjects were instructed to watch the laser target as it moved in different patterns or count stripes as they moved in a clockwise or counter-clockwise manner. For gaze and spontaneous nystagmus search, subjects were asked to look straight ahead and then left, right, up, and down for 10-15 seconds in each position. The testing was repeated with and without visual fixation. Positional nystagmus assessed using infrared goggles with eyes open in darkness. Subjects were asked to recline in the supine position, then with head turned right and left and finally on his/her right side and then left side. Each position was held approximately 20 seconds. Caloric irrigation was performed using a closed-loop irrigator with the ear stimulated with water at 30° and 44°C. Both temperatures were performed in each ear. Subjects were asked to count by 2's for 40 seconds after irrigation completion to keep from suppressing the vestibular response. For earth vertical axis rotational testing, subjects were rotated sinusoidally in the dark with frequencies varying from 0.02 to 1.0 Hz and amplitudes of 25 to 150 degrees/second and constant velocity of 60 degrees/second. Subjects were excluded if, on baseline screening, they had corrected vision worse than 20/40 in each eye or abnormalities on clinical audio-vestibular laboratory testing.

Eligible candidates were then scheduled to return for two experimental visits, scheduled at least one week apart. Subjects were required to have been without any headache for 48 hours prior to each testing visit and have not used any triptan for at least 1 week prior to each experimental visit. Vital signs were recorded and then subjects were treated orally in a blinded fashion with either 10 mg of rizatriptan (R) or a placebo (P) in identical capsules two hours prior to exposure to optokinetic stripes. Each subject received R on one testing day and P on the other. The order of treatment was determined randomly by the independent pharmacists, who created the randomization scheme by drawing treatment assignments from a blinded container. The investigator administering the drug, the technicians performing testing, and the subject were blinded to treatment assignment. The Investigational Drug Service provided the unidentifiable drug in a container labeled only with the visit number. The randomization scheme was not unblinded until the data were collected for the entire study. Blood pressure, heart rate, and the development of any adverse events were monitored for the two hours after ingestion of study drug. Two hours was selected as the optimal time for exposure to a potentially motion-sickness provoking stimulus so that rizatriptan could obtain its peak migraine-relieving effect [18].

Two hours after study-drug administration, subjects were exposed to three 15-minute trials of full-field optokinetic stripes rotated horizontally using a constant velocity of 30 degrees/second. Either clockwise or counterclockwise motion was used for all trials for each subject. Testing was identical on both experimental days. Prior to visual stimulation, subjects were assessed using the Motion Sickness Scale (MSS) [19] to establish a baseline. Subjective Units of Discomfort (SUDs) also were assessed. The MSS includes assessments of nausea, skin color, cold sweating, increased salivation, drowsiness, headache, and dizziness with eyes open and closed. Severity of abnormalities in each category are rated by the subject and technician, with a range of scores for nausea of 0 to 16, for skin color of 0 to 8, for cold sweating of 0 to 8, salivation of 0 to 8, drowsiness of 0 to 8, and headache and dizziness as described below. If MSS exceeded 16 at any time, the trial was discontinued. SUDs rates anxiety from 0 (none) to 10 (panic level anxiety). MSS and SUDs, recorded approximately every 2 minutes during and after exposure. On each day of testing, subjects were exposed to three different pain conditions presented in random order that were coupled with the optokinetic visual stimulation: no pain (N), hand pain (H), and temple pain (T). During the N condition, subjects viewed rotating vertical black and white stripes projected onto a wall. Every 2 minutes during the N trial, subjects were asked to rate their motion sickness and anxiety. During the H condition, 2 minutes after beginning stripe viewing, the subject's non-dominant hand was immersed in 32°C water for 2 minutes then immersed in 2°C ice water for 30 seconds and then back into the warm bath. Ice water immersion was repeated at 8 and 12 minutes, with subjects rating motion sickness and anxiety throughout. During T, subjects were asked to place a small block of ice at their temple using a gloved hand for 30 seconds, starting 4 minutes after stripe viewing. Subjects were asked to select that side of the head that was most commonly affected with pain during a migraine. Ice to the temple was repeated at 8 and 12 minutes. Subjects rated their motion sickness and anxiety throughout. The order of pain conditions was assigned to each subject randomly, with at least 2 minutes of rest time between trials. Testing was discontinued at the subject's request or if the MSS reached 16 or above.

### Data analysis

The overall motion sickness score for each pain condition was determined by subtracting the MSS score obtained just prior to exposure to the optokinetic stimulus for that pain condition from the aver-

age MSS score obtained during and 2 minutes after the 15-minute exposure. Overall SUDs for each pain condition was determined by subtracting the SUDs score obtained just prior to exposure to the optokinetic stimulus for that pain condition from the average SUDs score obtained during and 2 minutes after the 15-minute exposure.

Comparisons between pain conditions and between testing sessions within each subject were evaluated using non-parametric analyses. Comparisons between V+ and V- groups and between groups with and without visual motion sensitivity were performed using the Wilcoxon rank sum test.

## Results

Fourteen persons were identified as possible study candidates. Of these, one was excluded because of abnormal baseline caloric responses, one was excluded due to technical reasons, and two subjects withdrew prior to completing the study. The 10 subjects completing the study were all female, ranging in age from 25 to 42 years old (mean 34.6 +/- 6.9 years). (See Table 1.) Six subjects met Neuhauser criteria for migraine-related vertigo (V+) and four had no complaints of vertigo (V-). Each of the ten subjects tolerated the experimental procedures well and had no adverse effects from the drug or the induction of pain. There were no changes in heart rate or blood pressure that required discontinuation of an experiment. Three trials were terminated early because MSS exceeded 16.

Motion sickness induced by moving optokinetic stripes was higher on average during placebo trials than during rizatriptan trials in 4 of 10 subjects, higher with rizatriptan in 5 of 10 subjects, and unchanged for one subject. Motion sickness was not different between the V+ group and the V- group based on the Wilcoxon rank-sum test. Motion sickness was higher for the T condition than for the H condition for 6 of 10 subjects for placebo trials. For these 6 subjects, 4 of them showed a decreased or absent Drummond Effect with rizatriptan. That is, rizatriptan interfered with the potentiation of motion sickness symptoms by concomitant temple pain in 4 of 6 subjects. This effect of rizatriptan was equally apparent in the V+ group and V- groups. Motion sickness was not different between those subjects with a history of visually-induced motion sickness vs. those subjects without a history of visually-induced motion sickness using the Wilcoxon rank-sum test.

Data regarding the amount of anxiety induced by the combinations of pain and visual motion based on SUDs indicated that during testing following ingestion of rizatriptan the V+ group was more anxious overall than the V- group (p<.05) based on the Wilcoxon rank-sum test. Rizatriptan did not appear to consistently either reduce or increase anxiety during testing.

**Table 1.** Demographics of the subject group.

| Subject Number | Age | Gender | Aura/No Aura | Diagnosis | Motion Sickness History | | Prior headache response to triptan |
|---|---|---|---|---|---|---|---|
| | | | | | Actual | Visual | |
| 1 | 32 | Female | Aura | Vertigo | x | | Sumatriptan – benefit |
| 2 | 39 | Female | No Aura | Vertigo | x | x | Sumatriptan – benefit |
| 3 | 37 | Female | Aura | Non-Vertigo | x | x | Rizatriptan, Sumatriptan, Eletriptan – no benefit<br>Frovatriptan – benefit |
| 4 | 23 | Female | Aura | Vertigo | x | | Sumatriptan – no benefit; Rizatriptan- benefit |
| 5 | 40 | Female | Aura | Vertigo | x | | Sumatriptan – benefit |
| 6 | 29 | Female | No Aura | Non-Vertigo | x | x | Zolmitriptan – no benefit; Eletriptan – benefit |
| 7 | 41 | Female | Aura | Non-Vertigo | x | | Sumatriptan, Rizatripitan (benefit unknown) |
| 8 | 43 | Female | Aura | Vertigo | | x | Sumatriptan – benefit; |
| 9 | 26 | Female | Aura | Vertigo | x | | Frovatriptan – benefit |
| 10 | 33 | Female | Aura | Non-Vertigo | | x | Eletriptan – benefit |

## Discussion

Our initial pilot study regarding the effect of triptans on motion sickness combined actual motion, i.e., vestibular stimulation, with rizatriptan [12]. That study suggested a possible protective effect of a serotonin agonist for motion sickness in migraineurs with migraine-related dizziness. The pilot study reported herein extends this line of research by combining a visual motion sickness-inducing stimulus with pain and pre-treatment with rizatriptan. In this study, rizatriptan does not appear to reduce visually-induced motion sickness but rizatriptan may reuce the potentiation of motion sickness by cranial pain. This effect does not appear to be greater in subjects with migrainous vertigo. That is, we found that rizatriptan

may interfere with a previously recognized phenomenon wherein laboratory-induced head pain but not extremity pain potentiates visually-induced motion sickness in migraineurs, i.e., the Drummond Effect [8]. The exact mechanism whereby rizatriptan interferes with the Drummond Effect is uncertain. Rizatriptan may interfere with connections between central pain pathways and the vestibular nuclei.

Motion sickness is a behavioral response to both self-motion and visually-induced motion that has no known purpose [20]. Motion sickness is especially common in migraineurs [21, 22], occurring with a frequency of about 50% [23]. This increased susceptibility to motion sickness in migraineurs is of uncertain cause and can occur with both self motion, i.e., vestibular-induced motion sickness, and with visual motion, i.e., visually-induced motion sickness. We have theorized previously that increased activity in vestibulo-autonomic projections, possibly via serotonin, may account for increased symptoms in migraineurs [24, 25]. Recently, an alternate theory of motion sickness has been developed that links motion sickness to alterations in the so called "velocity storage" portion of the central vestibular system [26, 27]. Interestingly, although velocity storage appears to be unchanged in patients with migraine, our previous studies [3, 12] showed that both motion sickness and velocity storage decreased with rizatriptan.

Rizatriptan is known to influence the central nervous system [13, 28] and in particular, rizatriptan probably influences the vestibular nuclei since serotonin receptors have been found in the vestibular nuclei [29] and serotonin influences the activity of neurons in the vestibular nuclei [30]. Vestibulo-autonomic pathways [20] may be especially sensitive to rizatriptan in that rizatriptan is known to decrease nausea in migraine [31] but also may have a side effect of dizziness [32, 33]. Also, serotonin agonists have been shown to decrease emesis in animal models [34-36] and tryptophan depletion has been found to increase visually-induced nausea and dizziness in migraineurs [7]. Based on our results and the known effects of rizatriptan and serotonin, we hypothesize that rizatriptan provides benefit regarding motion sickness in some migraineurs by influencing central vestibulo-autonomic pathways both directly and indirectly.

Our subjects' anxiety, as reflected by subjective discomfort, was greater in the subjects with migrainous vertigo. This finding is consistent with the excessive vestibular symptoms in this group. Possibly, this finding is based on enhanced activity in the circuitry linking the vestibular nuclei to more rostral structures such as the parabrachial nucleus[37].

Although not uniformly successful, this pilot study provides additional impetus for the possibility of using triptans for prophylaxis against motion sickness, especially in those migraineurs who have dizziness associated with headache. The current treatment for motion sickness includes scopolamine as a prophylaxis agent [38]. To date, there is no literature aside from our pilot studies that suggest using a triptan for motion sickness prophylaxis.

Limitations of this study include the small number of subjects and the inclusion of only females. The gender inequality may have been less important given the finding by Park and Hu [39] that there was no gender difference for visually-induced nystagmus. Our sample also may be atypical of clinical samples of migraineurs given the high number of V+ subjects identified. Although Neuhuaser identified V+ in only 9% of migraineurs [17], a migraine sample recruited at our center for a previously reported study found V+ in 41% of adult migraineurs self-selecting to participate in a research study [16]. Future research in this area should include a larger number of subjects. Also, it may be of interest to assess motion sickness prophylaxis in migraineurs using a CGRP antagonist [40], when these agents become more widely available.

## Conclusions

These pilot data suggest that rizatriptan may interfere with the potentiation of visually-induced motion sickness in migraineurs by cranial pain. Rizatriptan did not appear to alter visually-induced motion sickness overall nor did rizatriptan alter subjective discomfort. Subjects with migrainous vertigo exhibited more discomfort during induction of visually-induced motion sickness.

## Acknowledgements

## Conflict of Interest

The authors have declared that no conflict of interest exists.

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