

Effects of prochlorperazine on normal vestibular ocular and perceptual responses: A randomised, double-blind, cross-over, placebo-controlled study.

Patel M¹, Nigmatullina Y¹, Seemungal BM¹, Golding JF^{1,2}, Bronstein AM¹

¹ Division of Brain Sciences, Imperial College London, Charing Cross Hospital, London. W6 8RF.

² University of Westminster, Department of Psychology, London. W1B 2UW.

Short title: Effects of prochlorperazine on vestibular motion

Key Words: Vestibular, Velocity Storage, Perception, Eye Movement, Dizziness

Address for correspondence:

Professor Adolfo M Bronstein, Dept. of Clinical Neurosciences,

Division of Neuroscience and Mental Health,

Imperial College London,

Charing Cross Hospital,

London, W6 8RF

a.bronstein@imperial.ac.uk

Abstract

Background: The present study investigated whether prochlorperazine affects vestibular-ocular reflex (VOR) and vestibulo-perceptual function. **Methods:** We studied 12 healthy naïve subjects 3 hours after a single dose of oral prochlorperazine 5mg in a randomised, placebo-controlled, double-blind, cross-over study in healthy young subjects. Two rotational tests in yaw were used: 1) a Threshold task investigating perceptual motion detection and nystagmic thresholds (acceleration steps of 0.5deg/s/s) and 2) Suprathreshold responses to velocity steps of 90deg/s in which vestibulo-ocular (VO) and vestibulo-perceptual (VP) time constants of decay, as well as VOR gain, were measured. **Results:** Prochlorperazine had no effect upon any measure of nystagmic or perceptual vestibular function compared to placebo. This lack of effects on vestibular-mediated motion perception suggests that the drug is likely to act more as an antiemetic than as an anti-vertiginous agent.

Introduction

Acute vestibular disorders induce severe vertigo usually associated with nausea and vomiting. Relief of these symptoms is the first task for the clinician. In many countries including the United Kingdom, prochlorperazine is perhaps the drug most commonly prescribed in the acute scenario [Patka et al., 2011] and the British National Formulary (“BNF”) lists its indications as “severe nausea, vomiting, vertigo, labyrinthine disorders [JointFormularyCommittee, 2012]. Prochlorperazine suppresses vomiting by modulating messages from the vestibular system to the vomiting centres at the chemo-receptor trigger zone (CTZ) [Yang and Neff, 1974] yet any anti-vertiginous effect is unproven.

The hypothesis of the study was that oral prochlorperazine modulates vestibular-motion (ocular reflex and perceptual) signals. This is important to try to establish if the drug beneficial effects is due to action on the vestibular system *per se* i.e. truly anti-vertiginous. If prochlorperazine has no effect on vestibular parameters one would have to conclude that the mechanism of action of the drug is only antiemetic. Significant suppression of vestibular responses by prochlorperazine (our primary outcome) would also impact the reliability of clinical testing in acute vestibular patients taking the drug. As many vertiginous patients included in clinical research projects are under the effects of this drug, the findings in our study may

clarify if some of the vestibulo-ocular and vestibulo-perceptual abnormalities detected acutely in patients may be due to the effects of the drug rather than the vestibular lesion itself. In particular, vestibulo-perceptual time constants are particularly shortened in acute vestibular neuritis patients and it was suggested that this represented a cortical ‘shut down’ with a net anti-vertiginous effect [Cousins et al., 2013]. However, the possibility that this perceptual effect was drug induced was not directly investigated. We now address these questions as a double-blind, randomised, cross-over, placebo controlled, non-clinical drug trial on healthy subjects.

Methods

12 healthy naïve, right-handed subjects (aged 19-34 years, mean 22.7 years, 6 females), verified by clinical history, participated and gave signed consent. The study was approved by the local ethics committee. The number of subjects included was based on previous experiments using this vestibular methods in normal subjects, as in the current study [Kyriakareli et al., 2013].

Prochlorperazine and Placebo

The local hospital pharmacy supplied prochlorperazine as the brand “Stemetil” as a single 5mg unmarked film-coated tablet in an unremarkable bottle (Stemetil 5mg tablets are bioequivalent to prochlorperazine 5mg tablets (MHRA guidelines, PL17907/0072)). The Placebo (indistinct lactose) was issued identically. A computer generated randomisation list was unknown to the authors. The 5mg dose was chosen as it is the BNF [JointFormularyCommittee, 2012] starting oral recommended dose (3mg for the buccal preparation).

Maximum potency of a 5mg stemetil tablet (Bristol Laboratories Limited, UK) is achieved after 3.1 hours (MHRA, PL17907/0072). Testing was performed 3.0 hours after taking the tablet, at the same time of day for each subject and all were asked to avoid caffeine. Testing took approximately 40 minutes and conducted in two sessions separated by one week (i.e., cross-over design).

Experimental Protocol

Subjects sat in a vibration-free Barany Chair (Contravez Inc) with head restrained by a chin rest and in complete darkness. White noise was amplified through two speakers

fixed to the chair behind the head to mask any surroundings sound clues that may indicate rotation.

Given that the result of the study could be related to drug-induced changes to alertness [Nigam et al., 1985], we performed a simple reaction time test immediately before rotational testing: pressing a button as fast as possible with the thumb of the dominant hand upon hearing a loud beep. Mean reaction time was calculated from 5 trials.

Vestibular Tests

Two tests were performed; a vestibular threshold motion detection task and a supra-threshold task in which vestibulo-ocular and perceptual time constants were measured. The order of these tests was randomised. A detailed explanation of the measurements and analysis is provided elsewhere [Cutfield et al., 2011; Okada et al., 1999]. Below summarises the methods in brief:

Vestibular threshold test

The chair rotated about the yaw plane (i.e., horizontally), increasing in velocity in steps of 0.5 deg/s^2 every 3 seconds. Subjects were rotated in total ten times, 5 times to the left and 5 times to the right in random order. A one minute rest was given between each rotation.

Subjects held a two button box controller with both hands, pressing the left button to indicate a perceived leftward rotation and the right button when they perceived a rightward rotation. Each subject was given an identical instruction to press the right/left button as soon as they felt motion, and to not press any button if they had any doubt about motion or direction. The time to button press indicates the vestibulo-perceptual threshold (Figure 1A), which can be expressed as either time (s) or chair velocity (deg/s).

Eye movements were simultaneously captured through electro-oculography (EOG) sampled at 250 Hz. EOG signals were passed through a low-pass filter (cut-off 30 Hz) prior to analysis. The nystagmic or vestibulo-ocular threshold i.e., onset time of nystagmus, was obtained from the raw eye movement trace and a differentiated and de-saccaded eye movement trace (see [Cousins et al., 2013; Okada et al., 1999] for further technical details).

An average perceptual and eye movement onset time was obtained.

Suprathreshold vestibular task

The chair was rapidly accelerated (1s) in the yaw plane to a constant velocity of 90°/s using a rotational step stimulus [Okada et al., 1999]. The velocity was constant until the nystagmus had stopped and never less than 60s. A total of 4 rotations, two in each direction, and four stopping responses were obtained. The direction order was randomised.

Subjects signalled their perceived or subjective angular velocity by turning a tachometer wheel with their right hand at the onset of perceived rotation in either direction (onset and stopping responses). Instructions were given to subjects to turn the wheel as fast as comfortably possible initially on chair acceleration/deceleration for the first couple of seconds. From then on they should slow down the wheel turning congruently with their perceived angular velocity until they no longer felt rotating, at which point they should stop turning the wheel. All subjects turned the wheel in the direction of actual motion. An output voltage proportional to the angular velocity of the wheel was digitally sampled at 250 Hz. An average waveform was normalised for size variations between subjects; accordingly amplitude units are arbitrary and hence not considered further herewith.

Eye movements were simultaneously captured with EOG sampled at 250 Hz and passed through a low-pass filter (cut-off 30 Hz) prior to analysis. The EOG signals were displayed raw and also differentiated, de-saccaded and visible artefacts removed (i.e., blinks). An averaged, calibrated and normalised in amplitude slow phase eye movement trace was obtained for each subject.

Analysis of tachometer-wheel (vestibulo-perceptual) and slow phase eye movement (vestibulo-ocular) supra-threshold responses (Figure 1B) was the average of the combined 8 accelerations/decelerations as right and left rotations produced similar responses. The duration of the differentiated slow phase nystagmic response and of the perceptual responses, and the (normalised) Area under Curve was obtained. Also, an exponential was fitted to the perceptual and slow phase eye velocity movements attaining the time constant of decay of the vestibulo-ocular and vestibulo-perceptual responses; in this way the ocular and perceptual velocity storage mechanisms are assessed [Bertolini et al., 2011; Shaikh et al., 2013]. The time constant was derived from the best fit exponential line by visual overlap of a computer generated curve and response curve and high correlation coefficient (r)

(Figure 1C). This measure is amplitude independent. Gain of the slow phase eye movement response (VOR) was calculated, defined as peak eye velocity / peak stimulus velocity (90 deg/s).

Statistical Analysis

Data analysis of responses was performed by two blinded examiners. An unblinded statistician compared the responses between examiners and performed all statistics (J.G). Mixed ANOVAs with factors: drug, order, examiner were employed as well as paired t-tests for specific investigations (reaction time test, examiner effect, direction of rotation). Significance level was set as double tailed $p < 0.05$.

Results

The two examiners analyses of rotational responses were similar and no interaction between examiner and drug effect was found. The mean from the two blinded examiners' analyses was therefore used.

Blinded participants were unable to distinguish between the two tablets and none experienced an adverse response. Oculomotor recordings from one subject (Subject 7) were lost.

Mean reaction time was very similar and not significantly different between prochlorperazine (0.25s) and placebo (0.23s).

Vestibulo-ocular and vestibulo-perceptual threshold tasks

Upon perceiving angular movement, all subjects pressed either the right or left button as instructed. On three occasions, different subjects pressed the incorrect button for direction and this response was excluded (once on placebo). Nystagmic thresholds were attained quicker than perceptual thresholds, as observed in previous research [Cousins et al., 2013]. There was no significant difference between leftward and rightward rotations.

As illustrated in figure 2, nystagmic threshold for prochlorperazine was 6.3s (S.E.M \pm 0.24) and placebo 6.7s (S.E.M \pm 0.2) from the onset of rotation, corresponding to a mean chair rotational velocity of 4.9 and 5.7 deg/s respectively. Perceptual threshold for prochlorperazine was 10.0s (S.E.M \pm 1.17) and placebo 10.23s (S.E.M \pm 1.18), which correspond to a mean chair rotational velocity of 11.0

and 11.8 deg/s respectively. ANOVA showed no drug or order effect for any measure of nystagmic or perceptual threshold during the vestibular motion detection task.

Vestibulo-ocular and vestibulo-perceptual supra-threshold task

During rotation all subjects turned the tachometer wheel in the direction of movement, always stopping wheel rotation before 60s. Upon stopping the chairs' rotation, all subjects turned the wheel toward the opposite direction reflecting a perceived change in movement direction. There was no significant difference between leftward and rightward rotations.

Shown in figure 3, Nystagmic duration for prochlorperazine was 39.5s (S.E.M \pm 1.28) and placebo 42.5s (S.E.M \pm 1.19). Nystagmic time constant for prochlorperazine was 13.85s (S.E.M \pm 0.76) and placebo 14.65s (S.E.M \pm 0.74). Nystagmic area under Curve for prochlorperazine was 51.9 degrees (S.E.M \pm 15.0) and placebo 51.6 degrees (S.E.M \pm 9.99). VOR gain for prochlorperazine was 0.45 and placebo 0.52. Perceptual duration of rotation for prochlorperazine was 26.5s (S.E.M \pm 2.81) and placebo 31.43s (S.E.M \pm 3.27). Perceptual time constant for prochlorperazine was 15.02s (S.E.M \pm 1.64) and placebo 16.62s (S.E.M \pm 1.92). Perceptual area under Curve for prochlorperazine was 70.94 arbitrary units (a.u.) (S.E.M \pm 10.57) and placebo 82.06 a.u. (S.E.M \pm 11.36).

ANOVA showed no drug or order effect on any measure of nystagmus or motion perception i.e., there was no difference between prochlorperazine and placebo.

Discussion

We found no significant effects of prochlorperazine upon any measure of ocular or perceptual function.

Vestibular motion detection – threshold task

The vestibular motion detection technique used has previously shown elevated bilateral vestibulo-ocular and vestibulo-perceptual thresholds in acute unilateral vestibular neuritis [Cousins et al., 2013; Cutfield et al., 2011]. One pending question was whether the anti-vertiginous drugs some of these patients received (usually prochlorperazine in the UK) played any role in this bi-directional threshold elevation. This would make sense as ideally a vestibular suppressant drug should elevate vestibular thresholds, in particular perceptual. The present results attest

against this possibility and hence, the bilateral threshold elevation observed in acute vestibular neuritis, is likely the result of the reduced signal-to-noise ratio following the vestibular loss as postulated by Cousins et al. [Cousins et al., 2013].

Vestibular velocity storage mechanism – suprathreshold task

The normal prolongation of vestibular-ocular and perceptual time constants to values of 13-16s (i.e. double those of the vestibular nerve time constant [Ramat and Bertolini, 2009] is due to a central integrator known as ‘velocity storage’ [Raphan et al., 1979]. Professional dancers, figure skaters and jet fighter pilots [Cohen et al., 2003] show reduced vestibular time constants due to a process of vestibular habituation thought to involve velocity storage processing. For this reason, we expected that any anti-vertiginous or vestibular suppressant effects (as these drugs are often referred to) of prochlorperazine would involve the velocity storage mechanism, presumably shortening vestibular nystagmic and/or perceptual time constants. However, we found no effect of prochlorperazine on the time constants of decay of the vestibulo-ocular or vestibulo-perceptual post-rotational responses or the gain of the VOR. Contrastingly, baclofen, a GABA-B agonist, reduces the vestibular time constant [Dai et al., 2006], whereas promethazine (a drug with antihistaminic H1/anticholinergic properties) has no effect [Cohen et al., 2003].

Prochlorperazine reduces vomiting by inhibiting dopamine (D2) receptors (Yang and Neff 1974). As we found no effect of prochlorperazine on vestibular function tests, and given that the primary mechanism of action of prochlorperazine is as a dopamine antagonist, our results suggest that dopaminergic involvement in the vestibular system is small. Indeed, only a small number of dopaminergic neurones can be found in the medial vestibular nucleus (MVN) of rats [Cransac et al., 1996].

Study limitations

Although the current experiment was performed in a young cohort, the responses were consistent with those of older adults, age-matched to vestibular neuritis patients [Cousins et al., 2013]. In addition, we used healthy subjects as opposed to patients who might have a different response to prochlorperazine. However, our past investigations show that patients taking prochlorperazine respond within the same range to patients who are not on the drug during the same vestibular tests used here

[Cousins et al., 2013]. Still, the drug effects in patients would need to be specifically studied.

Conclusions

Whilst oral prochlorperazine is an accepted therapy for vomiting and nausea, it seems to have no effect on vestibular motion detection or on the vestibular velocity storage mechanism (ocular and perceptual). Therefore it would seem to offer little relief for unwanted vestibular-mediated motion feelings (vertigo) in dizzy patients. Prochlorperazine is unlikely to affect clinical assessments of vestibular function (nystagmic or perceptual) in dizzy patients, but it has to be acknowledged that our study was only conducted in normal subjects. The beneficial effects of prochlorperazine, and perhaps related drugs, may be due to anti-emetic action. Higher doses of this drug may well have an effect on vestibular function but clinical experience and pharmacological studies [Nigam et al., 1985] indicate that, at higher doses, general CNS effects, alertness and cognitive in particular, would be very difficult to disentangle from true central vestibular effects.

References

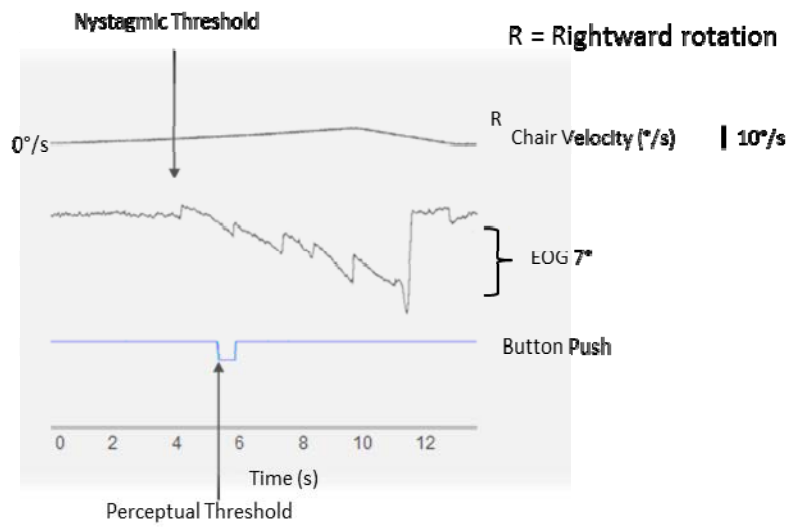
- Bertolini G, Ramat S, Laurens J, Bockisch CJ, Marti S, Straumann D, Palla A: Velocity storage contribution to vestibular self-motion perception in healthy human subjects. *J Neurophysiol* 2011;105:209-223.
- Cohen B, Dai M, Raphan T: The critical role of velocity storage in production of motion sickness. *Annals of the New York Academy of Sciences* 2003;1004:359-376.
- Cousins S, Kaski D, Cutfield N, Seemungal B, Golding JF, Gresty M, Glasauer S, Bronstein AM: Vestibular perception following acute unilateral vestibular lesions. *PloS one* 2013;8:e61862.
- Cransac H, Cottet-Emard JM, Pequignot JM, Peyrin L: Monoamines (norepinephrine, dopamine, serotonin) in the rat medial vestibular nucleus: Endogenous levels and turnover. *J Neural Transm* 1996;103:391-401.
- Cutfield NJ, Cousins S, Seemungal BM, Gresty MA, Bronstein AM: Vestibular perceptual thresholds to angular rotation in acute unilateral vestibular paresis and with galvanic stimulation. *Ann N Y Acad Sci* 2011;1233:256-262.
- Dai M, Raphan T, Cohen B: Effects of baclofen on the angular vestibulo-ocular reflex. *Exp Brain Res* 2006;171:262-271.
- JointFormularyCommittee: British national formulary, ed 63. London, British Medical Association and Royal Pharmaceutical Society of Great Britain, 2012.
- Kyriakareli A, Cousins S, Pettorossi VE, Bronstein AM: Effect of transcranial direct current stimulation on vestibular-ocular and vestibulo-perceptual thresholds. *Neuroreport* 2013;24:808-812.

- Nigam P, Rastogi CK, Kapoor KK, Gupta AK: Prochlorperazine in anxiety. *Indian J Psychiatry* 1985;27:227-232.
- Okada T, Grunfeld E, Shallo-Hoffmann J, Bronstein AM: Vestibular perception of angular velocity in normal subjects and in patients with congenital nystagmus. *Brain* 1999;122 (Pt 7):1293-1303.
- Patka J, Wu DT, Abraham P, Sobel RM: Randomized controlled trial of ondansetron vs. Prochlorperazine in adults in the emergency department. *West J Emerg Med* 2011;12:1-5.
- Ramat S, Bertolini G: Estimating the time constants of the rvor. A model-based study. *Ann N Y Acad Sci* 2009;1164:140-146.
- Raphan T, Matsuo V, Cohen B: Velocity storage in the vestibulo-ocular reflex arc (vor). *Exp Brain Res* 1979;35:229-248.
- Shaikh AG, Palla A, Marti S, Olasagasti I, Optican LM, Zee DS, Straumann D: Role of cerebellum in motion perception and vestibulo-ocular reflex-similarities and disparities. *Cerebellum* 2013;12:97-107.
- Yang HY, Neff NH: The monoamine oxidases of brain: Selective inhibition with drugs and the consequences for the metabolism of the biogenic amines. *J Pharmacol Exp Ther* 1974;189:733-740.

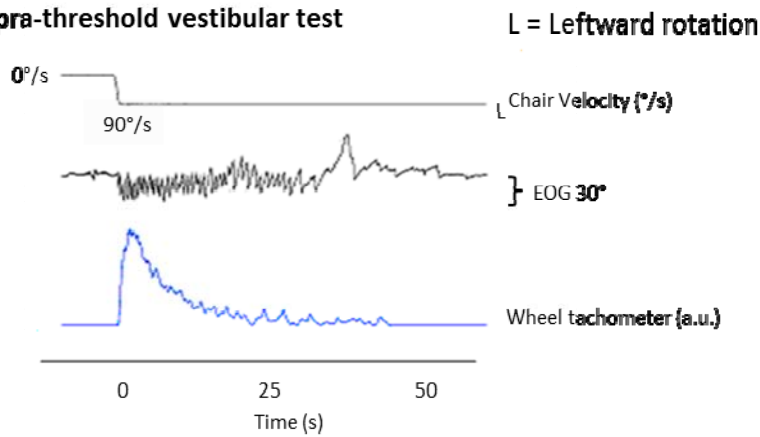
Conflicts of Interest

The authors have no conflicts of interest. This work was generously supported by an MRC grant to A.M.B. (MC_U950770497). MP is funded by the Meniere's Society, UK.

A. Threshold vestibular test



B. Supra-threshold vestibular test



C. Analysis of Supra-threshold vestibular test

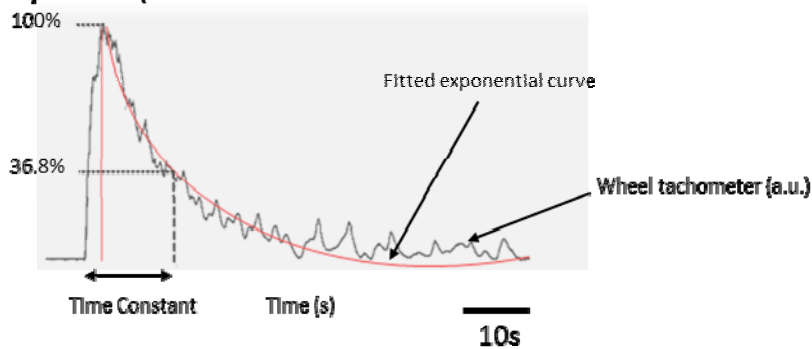


Figure 1 (A) Example response to a chair rotation and calculations of nystagmic and perceptual motion detection from the raw traces **(B)** Wheel tachometer output and Eye movements (VOR) **(C)** Example fitted exponential curve and time constant for the perceptual vestibular time constant (arbitrary units).

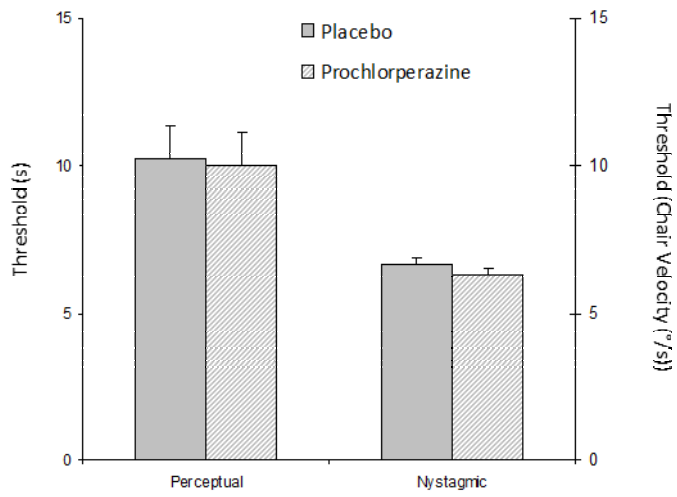


Figure 2: Mean vestibulo-ocular and vestibulo-perceptual thresholds and SEM for Placebo (grey) and Prochlorperazine (striped). There were no significant differences between prochlorperazine and placebo.

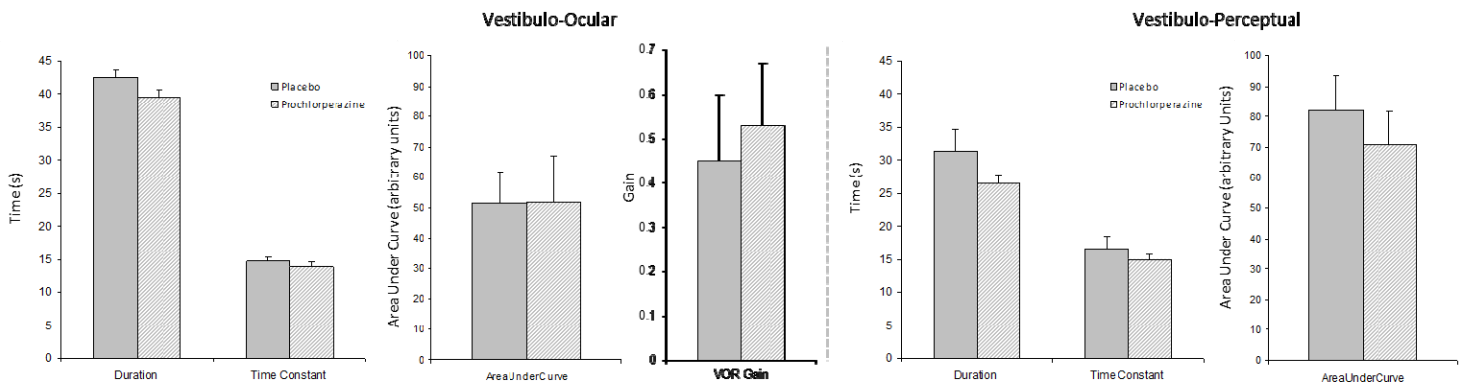


Figure 3: Mean and SEM for duration, time constant, VOR gain and Area under Curve from vestibulo-ocular (nystagmic) and vestibulo-perceptual (wheel tachometer) responses for Placebo (grey) and Prochlorperazine (striped). There were no significant differences between prochlorperazine and placebo.