A protective effect of 5-HT3 antagonist against vestibular deficit? Metoclopramide versus ondansetron at the early stage of vestibular neuritis: A pilot study

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KEYWORDS
5-HT3 antagonist; Vestibular neuritis; Neuroprotection

Summary
Objectives: Ondansetron is an antiemetic 5-HT3 receptor antagonist with proven efficacy in central balance disorder. A pilot study investigated impact on acute unilateral vestibular neuritis.

Patients and methods: A randomized clinical trial included 20 vestibular neuritis patients. Subjects received methylprednisolone-valacyclovir, associated to 5 days’ metoclopramide (30 mg/d; group M, n = 10) or ondansetron (8 mg/d; group O, n = 10). Assessment was based on early and 1 month videonystagmography, duration of hospital stay and time to first independent walking. Blinded intention-to-treat analysis used univariate (Student test) and multivariate (linear logistic regression) analysis.

Results: Early caloric vestibular deficit was significantly lower in group O than group M (56.53% versus 84.38%; P = 0.03). Vestibular preponderance did not differ between groups (8.2°/s in O versus 10.34°/s in M). At 1 month, trends were observed for vestibular deficit (43% in O versus 63.4% in M; P = 0.07) and preponderance (1.67°/s in O versus 1.74°/s in M; P = 0.4). Hospital stay and time to first independent walking were significantly shorter in O (2.88 versus 4.5 days (P = 0.03); and 1.25 versus 2.25 days (P = 0.001), respectively).

Conclusion: Early treatment with ondansetron associated to corticosteroids and antiviral treatment reduced vestibular deficit in acute-phase vestibular neuritis as compared to reference histamine H1 receptor antagonists. The treatment did not affect central compensation. Benefit includes improved tolerance of vertigo syndrome and reduced hospital stay. These results should be confirmed on a larger series, particularly to determine the mechanism of action of 5-HT3 antagonists on vestibular function.

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Introduction

The physiopathology of vestibular neuritis is poorly understood; viral infection and/or microcirculation disorder are currently the main hypotheses [1]. Whatever the mechanism, it induces neuronal dysfunction in Scarpa’s ganglion or the brainstem [2].

The usual antiemetics prescribed to treat the associated vegetative signs are histamine H1 receptor antagonists. Apart from their antiemetic effect, these receptors have been shown to be present on and affect the function of vestibular neurons [3]. H1 antagonists may thus play a role in vestibular function as such [4].

More recently, other antiemetics, serotonin 5-HT3 receptor antagonists, were used in nausea and vomiting, being more effective than H1 antagonists. In animals, 5-HT3 receptors are expressed in the neurons of Scarpa’s ganglion and medial brainstem vestibular nuclei [5]. We therefore sought to investigate their as yet undetermined role in regulating vestibular physiology.

Given the proven efficacy of 5-HT3 receptors in post-traumatic neuroprotection [6], the present pilot study focused on the preventive effect of a 5-HT3 antagonist, ondansetron, on vestibular deficit in acute-phase vestibular neuritis.

Patients and methods

An open-label, randomized comparative study was conducted within the ENT department of the Montpellier (France) University Hospital Center from September 2007 to December 2008. The study drugs were already authorized for the indication in question; local ethics committee approval was obtained.

All cases (n = 34) of suspected vestibular neuritis with onset at least 48 hours before initiation of treatment were included. In case of misdiagnosis corrected on videonystagmography (VNG: central signs or less than 25% deficit) or imaging within 48 hours of initiation of treatment, the subject was excluded from analysis.

All patients received methylprednisolone-valacyclovir, associated blindly to 5 days’ metoclopramide (30 mg/d) or ondansetron (8 mg/d). Assessment was based on early (24–48 hours after symptom onset) and 1 month VNG, analyzing vestibular deficit in terms of slow horizontal phase speed (/s) and directional preponderance (/s) on caloric testing.

Duration of hospital stay and time to first unassisted walking were also recorded.

At end of treatment, the two groups were compared for: patient age, early and 1 month post-onset percentage vestibular deficit on the caloric test calibrated according to de Jonckees, early and 1 month post-onset directional preponderance on caloric test (/s), date of first walking and date of discharge home.

Statistical analysis comprised univariate analysis (Student t test) plus multivariate analysis on stepwise logistic regression, with a threshold of 0.15 at each step. The significance threshold was systematically set at 5% (Systat 10.2 software, SYSTAT Inc.).

Results

After checking inclusion criteria, 10 patients were included in either arm and 14 were excluded (seven for interval to treatment more than 48 hours, five for central signs on VNG, and two for unilateral deficit less than 25%) (Fig. 1).

Mean age in group M was 48 years 9 months (range: 31–75 years) and in group O 61 years 4 months (range: 43–88 years) (P = 0.05 on Student test).

Mean early vestibular deficit was greater in group M than group O (84.38 ± 20.57% versus 56.53 ± 27.78%; P = 0.049 on Student test; Fig. 2). Mean early preponderance was 10.34 ± 4.26 /s and 8.2 ± 5.63 /s (P = 0.40 on Student test) in groups M and O respectively (Fig. 2).

First unassisted walking was earlier in group O than group M (1.25 ± 0.52 versus 2.25 ± 0.89 days; P = 0.01 on Student test; Fig. 3). Mean hospital stay was 4.5 ± 1.48 and 2.88 ± 1.17 days (P = 0.03 on Student test) in groups M and O respectively (Fig. 3).

Assessment at 1 month found a mean vestibular deficit of 63.4 ± 34.30% in group M and 43 ± 31.25% in group O (non-significant on Student t test: P = 0.07; Fig. 2), and mean preponderance of 1.74 ± 0.60 /s and 1.67 ± 0.63 /s (P = 0.40, Student t test), respectively (Fig. 2).

Multivariate analysis on linear logistic regression showed early vestibular deficit to correlate with early preponderance (P = 0.004) and treatment group (P = 0.03). The age difference between treatment groups did not account for the difference in early vestibular deficit. One-month vestibular deficit correlated with the early value (P = 0.009), but not with treatment group or age. Hospital stay correlated with age and treatment group (P = 0.01 each), but not with early vestibular deficit: advanced age and metoclopramide treatment were associated with longer hospital stay.

Discussion

These results indicate that ondansetron, administered early in association with corticosteroid and antiviral therapy, was
more effective than associated metoclopramide in reducing hospital stay in vestibular neuritis patients.

The explanation of this effect is two-fold. On one hand, it may lie in improved tolerance for the vegetative signs (nausea and vomiting) associated with vertigo, against which ondansetron is more effective than metoclopramide [7]. On the other hand, ondansetron may also act on the early vestibular deficit found on the first VNG examination.

Early vestibular deficit was lower in group O than group M. The 5-HT3 antagonist effect of ondansetron may play a role in vestibular synapse neuromodulation, limiting possible excitotoxicity secondary to excessive glutamate release, as seen in the cochlea following acoustic trauma and in the vestibule following aminoside [8,9] or AMPA receptor antagonist treatment [10].

It has been shown in stroke models that 5-HT3 receptors play a role in aggravating post-infarction toxic lesions [6]; as they are expressed in animals in Scarpa’s ganglion neurons and medial brainstem vestibular nuclei [5], the question arises as to their role in vestibular physiology.

These receptors are very probably activated under physiological conditions, given their presence in the area postrema and solitary tract, which are areas involved in the nausea-vomiting reflex [11] and which project toward the vestibular nuclei [12,13]. Their role, however, can hardly be more than one of modulation, since clinical use of 5-HT3 antagonists induces neither vertigo nor astasia.

These arguments are particularly supported by several reports of the interest of ondansetron in the treatment of vertigo and astasia following cerebral trauma and brainstem damage related to multiple sclerosis [14,15].
For neuroprotective purposes, very early application is probably needed for a clinical effect to be induced. Here lies the main limitation of the present study. There was a group difference in early vestibular deficit: but, when this was measured, the patients were already receiving metoclopramide or ondansetron, and it is impossible to know, for obvious reasons of examination tolerance, whether the two groups had comparable deficits before initiation of treatment. Only a larger series could answer this question.

At all events, ondansetron does not impair the capacity for central compensation, as seen in the absence of any difference in directional preponderance between the two groups, with scores less than 2°/s in both.

The medium-term effect of ondansetron is harder to assess. While there was a notable, if non-significant, group difference at 1 month, this seemed purely related to early deficit values: if the early deficit was indeed related to treatment, it may be supposed that ondansetron, by its acute-phase effect, limits the worsening or promotes recovery of the early deficit.

These hypotheses thus remain to be confirmed, and dose-response studies on larger series and animal models of acute vestibular deficit will be needed to determine the action mechanism of 5-HT3 antagonists in vestibular neu-ritis.

Conclusion

The results of the present pilot study suggest that ondansetron administered in the acute-phase of vestibular neuritis in association with corticosteroid and antiviral therapy reduces vestibular deficit and hospital stay in comparison with reference anti-H1 antiemetic treatment in the same association. Specificity and action mechanism, however, remain unknown and should be explored in animal models and a larger series in order to determine whether the present findings can be generalized in the management of this pathology.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References