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Intratympanal gentamicin in Meniere's disease: Effects on individual semicircular canals

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ABSTRACT

Objective: In this retrospective study the aim of the authors was to examine the effect of gentamicin on the individual semicircular canals after low dose, single injection intratympanal gentamicin therapy in Meniere's disease.
Methods: Data of 32 patients treated between 2011 and 2015 were collected. The high frequency, high acceleration vestibuloocular reflex (VOR) gain was measured in the individual semicircular canals using video head impulse test immediately before the first intratympanal gentamicin instillation and approximately two months later.
Results: In all cases 'AAO-HNS Class A' vertigo control could be attained at least for several months. In 13 cases only one instillation was necessary. In the other 19 cases the attacks returned after a few months. In 11 cases the injection had to be repeated a second time, in 4 cases 3 injections, in 2 cases 4, in 1 case 5 injections and in another 6 injections were necessary. The initial VOR gain was normal in all cases and two months after one injection it decreased in average by 40% in a highly significant manner. However, there were cases in which, although the patients became free of attacks, the gain values remained normal.
Conclusion: It was possible to demonstrate a significant correlation between the gain decrease of the individual canals. There was no prognostic correlation between the initial gain decrease after the first injection and the necessity of further injections. Gain values also decreased slightly but significantly in the lateral and posteriors canals on the contralateral, untreated side, possibly because of the missing disfacilitation from the treated side.

1. Introduction

In the last few years it has been demonstrated, that in Meniere's disease (MD) it is possible to prevent vertigo attacks by mild inhibition of peripheral vestibular function using intratympanic gentamicin (ITPG) injection [1,2]. By infrequent administration of single ITPG injections it is possible titrate the desired vestibular inhibition and the side effects (such as hearing loss) can be held on an acceptably low level [3,4]. Based on two randomised, controlled trials a Cochrane review found that intratympanal gentamicin seems to be effective against vertigo compared to placebo [5]. It has been shown that a single dose of ITPG markedly reduced AVOR gains for the semicircular canals on the treated side [4,6]. According Carey et al. [4] it does not cause complete hair cell destruction allowing the preservation of baseline afferent discharge on the treated side. Hirvonen et al. [7] showed that, at least in chinchilla, a single intratympanic gentamicin injection causes partial damage and loss of vestibular hair cells, particularly type I hair cells or their calyceal afferent endings, does not damage the afferent spike initiation zones, and preserves enough hair

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cell synaptic activity to drive the spontaneous activity of vestibular afferents.

The mild peripheral inhibition seems to be well suited to inhibit vertigo attacks without causing symptoms of chronic vestibular insufficiency, which occurs sometimes (in 15%: [8]) after vestibular neurectomy or labyrinthectomy.

Although in the last four years it has been possible to measure the vestibulo-ocular reflex gain (VOR gain) in individual semicircular canals using the three-dimensional video-head impulse test, reports on the effect of the drug on the individual semicircular canals are scarce. In several early studies magnetic search coils were used [4,6,9] and we found two recent studies carried out using video head impulse testing [10,11].

In 2004 we adopted the single injection strategy at our department and during the last 12 years we treated 117 MD patients because of intractable vertigo attacks with good results [12,13]. Since 2012 we have been measuring the VOR gain using video head impulses before and after the ITPG-therapy. In this retrospective study our aim was to assess the effects of the successful ITPG-therapy on the individual semicircular canals on the treated and on the intact side, respectively. We also wanted to determine if the long-term effectiveness of the ITPG therapy can be predicted by the degree of initial VOR gain inhibition after the first injection.

2. Materials and methods

Cases with the diagnosis "definite Meniere's disease [14]" were collected from the period between November 2011 and May 2015. Before data collection permission has been obtained from the Ethical Commission of Lower Austria (GS4-EK-4/319-2015). Cases were included if admission occurred after 1st August, 2012 and all follow up examinations were completed before 30th May, 2015.

Inclusion criteria were: adults over 18 years of age; final diagnosis: "definite Meniere's disease [14]"; results of video head-impulse testing done before and two months after ITPG injection were available. Exclusion criteria: missing results of follow up examination. ITPG injection was done basically as recommended by Carey et al. [4] and as documented in Refs. [12,13]. Briefly, the middle ear was filled with an unbuffered gentamicin solution (gentamicin sulfate, Sandoz, 40 mg/1 ml) after myringotomy. The gentamicin was held in the middle ear (the patients are laying in the lateral horizontal position and instructed not to swallow) for one hour. The effect of this injection develops over several days and lasts usually at least for several months. Should the vertigo spells recur (usually in form of weak attacks) a second (or a third or fourth etc.) injection can be given.

We identified 32 cases with MD treated at our department between August 2012 and May 2015 (15 men, 17 women, 11 on the right side, 21 on the left). In all cases only one side was affected and the contralateral side showed normal VOR gain. In 6 cases only the horizontal semicircular canal (SCC) was measured (the tool for the measurement of the vertical canals was not available that time), in the remaining 26 cases all three SCC could be measured before and after therapy. Average age at the time of the first injection was 57 years (min.= 39; max. = 81). Follow up VOR gain measurement occurred in average after 63 days (min. = 31; max. = 77). All patients had been having frequent attacks for months at least for five months before therapy. As a measure of the activity of the symptoms we use the number of attacks during the last two weeks. We did not administer ITPG-injection unless the patients had at least two attacks in the last two weeks.

All examinations, except audiometry were done by the same experienced examiner (B.B.). During data acquisition the following parameters were collected retrospectively: date of admission and of the first measurements, age and sex of the patients, gain of the different semicircular canals as measured by video-head-impulse test at approximately 160 °/s head velocity on the day of ITPG injection and at the follow-up examination, which occurred approximately after two months. vHIT-Test was carried out using Otometrics ICS Impulse Otosuite Vestibular V 1.2. Gain-values were determined using the average value of software-calculated individual gain values of separate impulses with a velocity between 140–180 °/s. In order to filter out artefacts, the presence of corrective saccades in the time period up to 200 ms after the impulse was considered obligatory for the validation of decreased gain values. The result of the vHIT was considered pathological in the horizontal canal if the gain was under 0.8. In the case of the vertical canals the VOR gain under 0.7 was pathological (as established in our laboratory after having measured 35 normal values and determining average ±2 standard deviation). Audiometry was done using Interacoustics Equinox Affinity Suite AC440. Statistics were done using Graphpad Prism® Software.

3. Results

In all cases 'AAO-HNS Class A' [14] vertigo control could be attained at least for several months. In our experience [13], ITPG-injection is typically followed by a 3–5 days latency without any effect, during which sometimes even attacks occur. Then the attacks cease and unsteadiness develops, which lasts for 2–3 weeks. In 13 cases only one instillation was necessary. Although in this paper we only analyse the effects of the first ITPG injection, we mention here that in the other 19 cases the attacks returned after several months. Out of these, in 11 cases the injection had to be repeated a second time, in 4 cases 3 injections, in 2 cases 4, in 1 case 5 injections and in another 6 injections were necessary. The initial VOR gain in the horizontal canal was normal (greater than 0.8) in all cases. Anterior canal gain was lower than normal in three cases and the posterior canals gain was decreased in one case before the first injection. The following analysis describes the effects of the first injection. VOR gain measured two months after the first injection decreased in average by 40% in a highly significant manner (Fig. 1 and Table 1). However, there were cases in which, although the patients became free of attacks, the gain values remained normal.

On the contralateral side after the injection the VOR gain values decreased slightly but significantly in the horizontal and posterior canals and there was no significant difference in the

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