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Results of Electrocochleography in Ménière's Disease after Successful Vertigo Control by Single Intratympanic Gentamicin Injection

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Key Words
Intratympanic · Gentamicin · Electrocochleography · Ménière's disease

Abstract
In the last several years, a promising new approach has been suggested in the therapy of Ménière's disease (MD): the low-dose intratympanic gentamicin therapy. By titrating the desired vestibular inhibition by single injections and infrequent administration, side effects concerning hearing can be held on an acceptably low level, while disease-related symptoms are often successfully eliminated. However, it is still unclear if endolymphatic hydrops actually decreases when the patients become symptom free. In the literature, hydrops is significantly associated with an enhanced ratio of summating potential/action potential (SP/AP). Our aim in this retrospective study was to answer the question if pathologically high SP/AP ratios normalize after successful low-dose intratympanic gentamicin treatment. Twenty-eight patients with MD received one, two or three intratympanic gentamicin injections. These injections inhibited vertigo spells without causing additional hearing loss. SP/AP ratios measured by noninvasive electrocochleography did not improve statistically when patients became symptom free. This indicates that the beneficial effect of gentamicin does not depend on the improvement of SP/AP ratios. Considering the well-established correlation between increased SP/AP and active MD, it thus seems unlikely that gentamicin treatment significantly reduces hydrops.

Introduction

Although spontaneously improving in many cases, Ménière's disease (MD) may cause severe complaints making normal everyday life almost impossible. Having 5–10 shorter or longer vertigo spells with nausea and vomiting during a 2-week period exerts a significant pressure on patient and doctor as well. In the last several years, a promising new approach has emerged in the literature: the low-dose intratympanic gentamicin therapy [Harner et al., 2001; Carey et al., 2002]. After having been suggested in the 1950s [Schuknecht, 1957], vestibular ablation using aminoglycosides initially fell into disfavor because of the high rate of sensorineural hearing loss accompanying it. Thanks to careful studies concerning the mechanism of action and the effects after administration [for review see Carey, 2004], it became clear that titrating the desired vestibular inhibition by low, infrequent administration of gentamicin, side effects concerning hear-

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ing can be held on an acceptably low level. In 2002, Carey et al. showed that even one single intratympanic injection of gentamicin causes a reduction in semicircular canal function similar to that of repeated injections [Carey et al., 2002]. In that study, single injection did not cause complete inhibition of the angular vestibulo-ocular reflex as it is the case with surgical deafferentation. Nevertheless, the relatively mild effect was obviously sufficient to obtain a symptom free period of at least several months. Mild chemical ablation is advantageous in a clinical setting, since the risk of posttreatment chronic vestibular insufficiency is reduced. So, in 2004 we adopted the single injection strategy at our department. In the last 5 years, we have treated 47 MD patients with intractable dizziness using single intratympanic gentamicin. In all cases, the vertigo spells were successfully inhibited at least for several months, in many cases for years.

As symptom-free periods due to intratympanic gentamicin seem to depend on markedly decreased semicircular canal function [Carey et al., 2002], vestibular hypofunction seems to be necessary for vertigo control. On the other hand, it is still unclear if the endolymphatic hydrops decreases when the patients become symptom free. Several authors have suggested that gentamicin acts by inhibiting endolymph production, thereby diminishing hydrops [Park and Cohen, 1982; Pender, 1985].

In the last few decades, it has been fairly well established that dilatation (hydrops) of the endolymphatic space is a histological marker of MD [Merchant et al., 2005]. It has also been suggested that, when in case of hydrops the basilar membrane is deflected towards scala tympani, this bias acts on sensory cells and generates a larger than normal DC response. This results in an increased summating potential (SP), whereas the magnitude of the action potential (AP) remains unchanged [Eggermont, 1976; Gibson et al., 1977].

To assist the correct diagnosis of MD, we are using a noninvasive extratympanic version of electrocochleography (EcochG). Extratympanic EcochG has evolved as an important tool in the diagnosis of MD and endolymphatic hydrops [Ferraro and Durrant, 2006]). It is completely painless and well tolerated, thereby making repeated measurements possible. In a study by Adamonis et al. [2000], a statistically significant reduction in the SP/AP ratio was observed after gentamicin administration. If this was true, the number of endolymph-producing dark cells should be diminished after gentamicin therapy. However, in a morphological study the decrease in the dark cell quantity could not be demonstrated [Cureoglu et al., 2003].

In our study, we performed a retrospective study to answer the question if pathological SP/AP values normalize after successful low-dose intratympanic treatment of MD.

Methods

Subjects

Over the last 5 years, we have treated 47 patients with 'definite' MD (Committee on Hearing and Equilibrium [Monsell et al., 1995]) using single intratympanic gentamicin injection (ITP-G). Out of this group, 28 patients were included in this retrospective study. Inclusion criteria were: reproducible, good quality EcochG measurement before and after ITP-G therapy and sufficiently long observation time (at least 9 months) after the last ITP-G injection. Before diagnostic and therapeutic procedures, the patients were extensively informed and written consent was obtained. In most cases with diagnosed MD, salt-free diet and mild diuretic therapy has been suggested and a permanent or temporary improvement occurred. In order to avoid treating cases using an ablative method when possibly spontaneous improvement may occur, we restricted ITP-G injection to cases with severe symptoms, when debilitating vertigo made normal life almost impossible. Since we diagnose 30–50 cases of MD each year, this corresponds to 20–30% of cases. Also, when an EcochG curve could be measured, we never offered the injection if the SP/AP ratio was not pathologic according to our criteria (see below). None of the patients had had MD on the other (presumably healthy) side; this has been ensured using anamnestic data and analyzing hearing thresholds. On the 'healthy' side, the SP/AP ratio was normal in every case.

The group consisted of 17 female and 11 male patients, 15 with left-sided and 13 with right-sided MD. None of these patients had bilateral MD. The average age was 58 years (range: 41–82 years). The examination consisted of the following tests: history of complaints, microscopic examination of the ear drum, routine ENT examination, pure tone audiometry, impedance measurement of the middle ear, neurootological status (examination of spontaneous nystagmus and head shaking nystagmus under Frenzel's glasses, head impulse test (HIT), positional and positioning nystagmus), and noninvasive EcochG. Impedance measurement was carried out in order to assess a possible disturbance of middle ear ventilation, since a tympanotomy was planned.

Vertigo Spells before Therapy

All patients had been having frequent attacks for months (in one case for 1 month, in all the other cases at least for 6 months) before therapy. The average duration of vertigo complaints before injection was 35 months [range: 1–80 months, median: 30 months, interquartile range: 12(Q1)–60(Q3) months]. Out of 28 patients, 6 had two vertigo attacks during the last 2 weeks (these lasted 2–3 h with severe vegetative reactions). The other patients had on average eight attacks (range 4–20) during the last 2 weeks before examination and injection.

Time since Last ITP-G Injection

Before the first and after the last ITP-G injection, we carried out noninvasive EcochG. Before the control EcochG measurement presented in this paper, all patients had been symptom free

Table 1. Average EcochG parameters before and after therapy (mean ± SE; n = 28)

	Before therapy		After therapy		Change (after – before therapy)	
	normal ear	affected ear	normal ear	affected ear	normal ear	affected ear
SP amplitude, μV	0.29 ± 0.04	0.68 ± 0.09	0.24 ± 0.02	0.56 ± 0.07	–0.05 ± 0.05	–0.12 ± 0.07
AP amplitude, μV	1.24 ± 0.13	1.14 ± 0.14	1.04 ± 0.09	1.06 ± 0.16	–0.19 ± 0.13	–0.07 ± 0.1
AP latency including acoustic delay, ms	2.32 ± 0.03	2.45 ± 0.04	2.3 ± 0.04	2.52 ± 0.04	–0.03 ± 0.02	–0.07 ± 0.05
SP/AP ratio, %	23 ± 1.41	60 ± 2.47	24 ± 1.44	58 ± 3.93	–0.76 ± 1.43	–1.75 ± 4.33

for at least 9 months. On average, the last ITP-G injection was made 26 months before the EcochG measurement; during this time, the patients were free of symptoms (range: 9–56 months).

Noninvasive EcochG

We used the evoked response audiometer ICS ChartrEP®, with gold-plated skin electrodes (noninverting to the contralateral ear, ground to the forehead). The inverting electrodes (Bio-Logic™-EcochGtrode) were pushed into the ear canal until they touched the tympanic membrane. This setup results in an upward deflection for AP.

We used the following setup parameters: amplification gain = 100000; high pass = 10 Hz; low pass = 3 kHz; notch filter = on; artifact rejection = off; sweep time = 8 ms; sweeps = 2000; delay = –1 ms; stimulus rate = 20 click/s; number of clicks = 100; click type = alternating, at 80–95 dB HL. Clicks were administered through an insert phone (EARTone, 3A insert earphone, EAR-Auditory Systems), with a tubing of 23 cm causing an acoustic delay of 0.67 ms to eliminate stimulus artifacts.

We consider the EcochG curve suggestive of endolymphatic hydrops when the SP/AP ratio is higher than 40%, or when there is a strong (threefold) asymmetry of the SP/AP ratio (e.g. 10% on the healthy side and 30% on the side with sensorineural hearing loss) [for review see Hall, 1992]. In this study, the ratio was in all cases higher than 40%. Normal values were determined 5 years ago when SP/AP ratios in 50 normal, healthy ears were measured (upper limit of normal: average SP/AP ratio in normals +2 SD, data not shown).

Intratympanic Gentamicin Injection

We used the protocol suggested by Carey [Carey, 2004], except that we used an unbuffered gentamicin solution (gentamicin sulfate, Sandoz, 40 mg/1 ml). The term 'single injection regimen' is used here to signify the titration of ablative effect using single intratympanal gentamicin injections administered infrequently and according to recurrence of complaints. At the first session, only one ITP-G injection is given. The effects of this injection develop over several days and last usually at least for several months. Should the vertigo spells recur (usually in form of weak attacks) a second (or a third or fourth) injection can be given.

Head Impulse Test

HITs were carried out by a skilled examiner. Ten impulses were analyzed visually in order to register possible covert saccades [Weber et al., 2008]. The results were divided into three possible categories:

- negative HIT (no saccades during at least seven impulses)
- slightly positive HIT (covert saccades during at least seven impulses)
- positive HIT (overt saccades after at least seven impulses).

Audiometry

Pure tone audiometry was performed on the day of the EcochG using an Interacoustics AC40 Audiometer. Acoustic impedance was measured using an Interacoustics AT22 Impedance Bridge.

Statistical Analysis

When not explicitly mentioned otherwise, we compared data using a two-tailed paired t test, and a significance level of 0.05. The comparison of parameters between pre- and post-gentamicin therapy for healthy and affected side was also done using analysis of variance in a repeated-measures design with two groups (factors healthy ears against affected, time before versus after).

Results

Effects of ITP-G Injection on Vertigo Complaints

In all cases, the ITP-G injection caused a prolonged imbalance for 1–4 weeks with a latency of 3–5 days, and the attacks ceased 1 week after ITP-G injection (for at least several months).

In 19 patients (68%), one ITP-G injection was sufficient to eliminate vertigo spells completely. Five patients received two injections; after the first injection, these patients encountered a period of 4–12 months without vertigo spells before the complaints started to reappear. After several attacks, a second ITP-G injection was delivered, which eliminated the vertigo. Four patients received a third ITP-G injection, several months after the second.

Amplitude and Latency of EcochG Potentials and SP/AP Ratio

Average EcochG parameters before and after therapy are summarized in table 1.

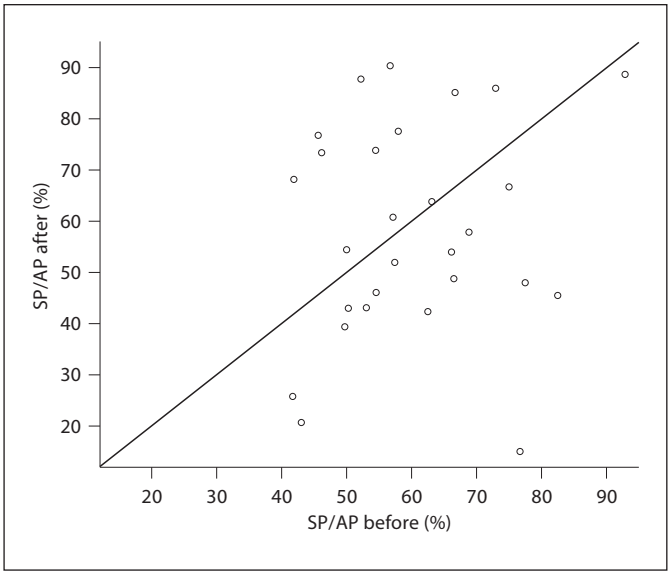

Fig. 1. SP/AP ratios before therapy against values measured after ITP-G in all 28 patients. Straight line: x = y.

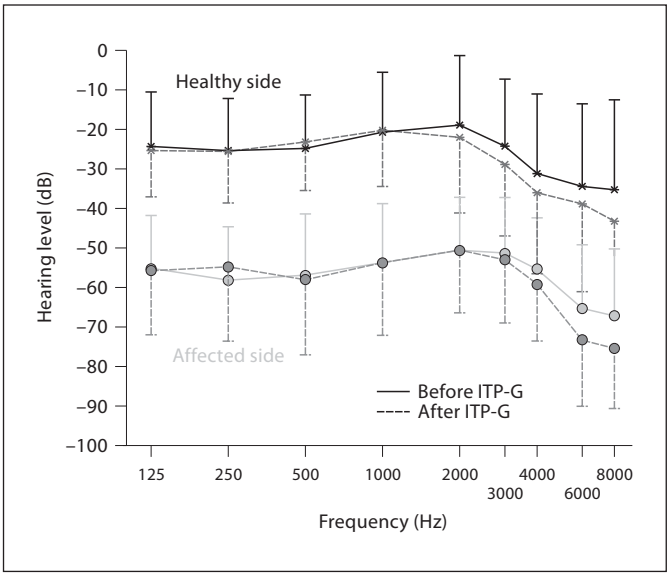

Fig. 2. Mean hearing thresholds (±SD) before and after therapy (n = 28).

As expected, SP amplitudes and SP/AP ratios differ significantly between healthy and involved side (two-tailed paired t test, $p < 1e{-}6$). SP and AP amplitudes and SP/AP ratios did not differ significantly before and after therapy (see also fig. 1). Using a two-way ANOVA for repeated measures (with 'side' and time as 'before therapy' vs. 'after' as factors), SP and AP amplitudes did not change after versus before therapy on either side ($p = 0.07$ and $p = 0.19$, respectively). SP was significantly higher in ears with MD ($p < 0.0001$), whereas AP was not ($p = 0.75$). There was a significant difference in the SP/AP ratio between healthy and affected ears ($p < 0.0001$), and this concerned only the side, not the 'time' of measurement ('time' alone: $p = 0.82$, time vs. symptoms: $p = 0.59$).

Effect of ITP-G on Hearing

In the statistical analysis of the results of the audiometry, we considered low frequencies (below 1 kHz) and high frequencies (over 2 kHz) separately. There were no significant changes in the low frequencies after ITP-G. After the ITP-G injection, the hearing level was slightly but significantly reduced for high frequencies ($p < 0.05$ ipsilateral for frequencies above 4 kHz, and contralateral for frequencies above 2 kHz), with a maximum reduction on both sides of 8 dB at 8 kHz (see fig. 2). The reduction on the ipsilateral side correlated slightly but significantly with the reduction on the contralateral side ($r^2 = 0.07$, $p < 0.001$).

The comparison of hearing thresholds between pre- and post-gentamicin therapy for healthy and affected side was also done in a repeated-measures design with two groups. The ANOVA revealed a significant difference between the healthy and affected sides ($p < 0.0001$), occurring before as well as after therapy. The interaction term was not significant ($p = 0.58$), indicating that evolution (after injection vs. before) did not differ between both sides.

Head Impulse Testing

In all patients a normal, bilateral vestibulo-ocular reflex could be elicited during HIT before ITP-G. In 9 patients, the results of HIT were normal after the therapy; in the other 19 patients, the HIT was slightly positive in the direction of the affected ear.

Discussion

Since the high rate of spontaneous fluctuation of symptoms and spontaneous recovery with MD, we took special care with the patient selection. We administered ITP-G injection only if frequent symptoms made everyday life almost impossible. In our study, the – sometimes repeated – administration of ITP-G eliminated intractable vertigo symptoms of MD, with little or no hearing loss.

It has been suggested previously that a single ITP-G-injection should be beneficial for treating patients with MD [Harner et al., 2001; Carey et al., 2002; Flanagan et al., 2006]. Recently it has been shown, in animal experiments as well as in humans, that a single ITP-G injection causes partial damage and loss of vestibular hair cells, but preserves enough hair cell synaptic activity to retain the spontaneous discharge and/or rotational sensitivity of afferents [Carey et al., 2002; Hirvonen et al., 2005]. Apparently, this reduction in peripheral vestibular sensitivity is sufficient to inhibit pathological fluctuations of afferent input, but gentle enough not to provoke the symptoms of chronic vestibular insufficiency, elicited in 20% of cases with unilateral vestibular loss [Reid et al., 1996; Badke et al., 2002]. This could make ITP-G administration an ideal candidate for the therapy in severe MD.

Our results show that the SP/AP ratio measured by EcochG did not improve statistically when patients became symptom free. In many cases, mainly in older patients, even a slight increase of the SP/AP ratio could be observed. An increased SP/AP ratio can be considered an electrophysiological correlate of displacement of the basilar membrane into the direction of the scala tympani and thus of the presence of endolymphatic hydrops [Eggermont, 1976; Gibson et al., 1977; Ferraro and Durrant, 2006]. This ratio did not systematically improve after gentamicin injection, overall. Considering the well-established correlation between increased SP/AP and active MD, it thus may be concluded that hydrops, per se, is not likely resolved via gentamicin therapy.

It has been long known that gentamicin most likely reduces peripheral vestibular function by direct toxic effects on hair cells [Schacht, 1993; Song et al., 1998; Forge and Schacht, 2000]. Lin et al. [2005] showed that successful treatment of MD is closely related to attenuation of semicircular canal function as measured by horizontal canal angular vestibulo-ocular reflex gains, and Rabbitt et al. [2001] showed that endolymph pressure may modulate semicircular canal primary afferent discharge. So ITP-G may exert its beneficial effect in MD by decreasing the sensitivity of the vestibular labyrinth to endolymphatic pressure waves.

In contrast to these hypotheses, some authors have postulated that gentamicin may act by inhibiting endolymph production, thereby diminishing hydrops [Park and Cohen, 1982; Pender, 1985]. Adamonis et al. [2000] conducted a similar study to ours, measuring hydrops by noninvasive EcochG before and after ITP-G-treatment. They found a significant reduction in the SP/AP ratio in the gentamicin-treated group and postulated that 'gentamicin improves the electrophysiological function of the cochlea possibly by reducing the severity of the associated endolymphatic hydrops'. The differences between their results and the results of our study may be due to some important differences in the study design: in their study, the control EcochG measurements were performed only 1 month after the gentamicin therapy, so the posttreatment time was much shorter than in our study (at least 9 symptom-free months, on average more than 2 years). Also, in their study gentamicin was administered repetitively, by use of a catheter, until either nystagmus was observed, or the patients experienced unsteadiness with associated deterioration of tandem gait, or after 12 doses, or if hearing deteriorated. Also, the electrophysiological parameters differed between the two studies: the amplitude of the AP, which may serve as an indicator of the quality of the recording, was approximately half of the AP amplitudes recorded in our patients. Moreover, Adamonis et al. [2000] noted that 'the gentamicin induced decrease in the SP/AP ratio was caused primarily by an increase in the AP amplitude relative to the SP amplitude'. The authors do not provide a satisfactory explanation for this phenomenon: in our data, the average amplitude of AP was reproducible between measurement sessions.

When analyzing the results of the subjective audiometry, we did not find significant worsening of the hearing threshold in the low frequency range after ITP-G. Endolymphatic hydrops may be associated with low-frequency hearing loss [Tonndorf, 1976; Maier and Schipper, 2006]. The fact that low frequency hearing threshold did not deteriorate also shows that the functional consequences of endolymphatic hydrops did not change in our patient group.

We could observe a small but significant increase in the hearing level in the high-frequency region. Since this increase could also be demonstrated on the normal side, it was most probably not caused by the known high-frequency cochleotoxic effect of gentamicin. Rather, since on average more than 26 months elapsed between the first hearing test and the control measurement, this change can be interpreted as a slight effect of ageing. Consulting the table of age-related changes of hearing thresholds in a normal population (European Standard ISO 7029:2000) reveals similar predictable increase in thresholds in the high-frequency region [International Organization for Standardization, 2000].

According to some theories, endolymphatic hydrops results from disordered fluid homeostasis caused by disruption of regulatory elements within the spiral ligament [Merchant et al., 2005]. In that case, endolymphatic hy-

drops should be considered a consequence of MD, rather than a direct cause of the symptoms [Gates, 2006]. This interpretation would also be consistent with our results.

In conclusion, given our understanding of the SP/AP ratios, we believe that the beneficial effect of gentamicin does not depend on the improvement of endolymphatic hydrops, but more likely on a reduction in the sensitivity of the vestibular periphery. In our view, our study also confirms that single injection ITP-G therapy is an excellent option to treat patients with severe MD.

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