Variability in the Perilymphatic Diffusion of Gadolinium Does Not Predict the Outcome of Intratympanic Gentamicin in Patients With Ménière’s Disease

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OBJECTIVES/HYPOTHESIS: To assess the utility of imaging in planning intratympanic (IT) gentamicin (Gent) treatment in Ménière’s disease (MD), we compared the dosage and outcomes of ITGent with the severity and extent of endolymphatic hydrops (EH), as evaluated by three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) sequence in a 3-T magnetic resonance imaging (MRI) unit, after IT gadolinium administration.

STUDY DESIGN: Retrospective review.

METHODS: A total of 18 patients (10 males and 8 females; age, 28–78 years; median age, 53.2 years) with definite MD participated in the investigation. The duration of the disease ranged from 8 months to 9 years (median, 2 years), with a prevalence of vertigo spells ranging from 0.8 to 8 per month (median, 2.2), as calculated in the last 6 months. A 3D-FLAIR MRI was performed 24 hours after IT injection of diluted gadobutrol. ITGent injection was performed within a variable period of time, from 1 week to 3 weeks after 3D-FLAIR MRI. The degree and extension of EH as evaluated by 3D-FLAIR MRI were compared with the number of injections necessary to cure vertigo attacks. Vertigo results, functional level scale modifications, variations in caloric excitability, and pure-tone average modifications.

RESULTS: No statistically significant correlation was observed between severity of EH and outcomes of ITGent administration.

CONCLUSIONS: The hypothesis of a reduced effect of Gent administered intratympanically in the presence of severe EH, owing to obstructed diffusion along the perilymphatic compartments, has not been confirmed in the present investigation.

KEY WORDS: Endolymphatic hydrops, vertigo, magnetic resonance imaging, 3 Tesla.

LEVEL OF EVIDENCE: 4.

INTRODUCTION

Three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) sequence in 3-T magnetic resonance imaging (MRI) unit, after intratympanic (IT) gadolinium (Gad) administration enables visualization of endolymphatic hydrops (EH) in patients suffering from Ménière’s disease (MD).1–3 Enlargement of the space occupied by nonenhancing endolymph-filled membranous structures reduces visualization of perilymphatic compartments enabling the detection of EH.1 This has opened very interesting perspectives in the diagnosis of MD and the comprehension of the role of EH. One of the desired advantages of this technique is the evaluation of absorption and diffusion of drugs administered intratympanically in an attempt to predict their efficacy. This could be particularly useful when an IT gentamicin (Gent) administration is planned in MD patients, to individualize the treatment as a function of penetration of the drug in the inner ear compartments. In fact, it is conceivable that diffusion of Gent should be inversely proportional to the severity of EH, and massive hydrops might require higher total dosage of the drug.

To assess the utility of imaging in planning ITGent treatment, we have performed the present investigation, which compares the dosage and outcomes of ITGent with the extent of perilymphatic enhancement defect, as evaluated by 3D-FLAIR MRI performed after ITGad administration.

MATERIALS AND METHODS

From January 2008 to August 2009, 18 patients (10 males and 8 females; age, 28–78 years; median age, 53.2 years) with definite MD4 were examined with 3D-FLAIR MRI using ITGad as a contrast medium and submitted to ITGent injection afterward. The patients were included in the study on the basis of the following criteria: unilateral disease, recurrent disabling vertigo attacks, and no history of middle ear and neurological disorders. Both the tympanic membranes were of normal appearance at otomicroscopy with the absence of calcification plaques. Most of the patients had been treated before MRI examination with different medical therapy regimens, mainly based on low-salt diet and diuretics, which were withdrawn at...
least 1 month prior to the time of MRI examination. However, symptomatic drugs, such as benzodiazepine and antiemetics, were occasionally administered after an acute vertigo spell during this period of time.

The duration of the disease ranged from 8 months to 9 years (median, 2 years), with a prevalence of vertigo spells of 0.8 to 8 per month (median, 2.2), as calculated in the last 6 months. Functional level scale (FLS) score ranged from 3 to 6, with a median of 4. The pure-tone average (PTA) at 500 to 3,000 Hz, ranged from 22 dB hearing level (HL) to 91 dB HL with a median of 4. The pure-tone average (PTA) at 500 to 6 months. Functional level scale (FLS) score ranged from 3 to 6, 0.8 to 8 per month (median, 2.2), as calculated in the last years (median, 2 years), with a prevalence of vertigo spells of this period of time.

Caloric testing was performed using a standardized sequence of 30-second irrigations with 200 mL of water (44°C and 30°C for each ear), and nystagmus activity was recorded by electrooculography. Canal paresis was defined, using Jongkees formula5 as a difference of >25% between maximum slow-phase velocity measurements for each ear when compared with the sum of slow-phase velocities. Canal paresis was present in 15 patients, with absence of any response in one patient, whereas caloric response was normal in three patients.

All the patients were submitted to ITGad solution (gadobutrol, 1 mmol/mL) administration in the affected ear 24 hours prior to 3D-FLAIR MRI investigation with a 3-T unit, according to techniques detailed in previous articles.6–8 Each portion of the labyrinth (i.e., basal, middle, and apical turns of the cochlea), vestibule, superior, posterior, and lateral semicircular canal was separately evaluated and judged to have a normal, reduced, or absence of enhancement on the basis of criteria detailed in previous articles.7,8

ITGent injection was administered within a variable period of time from 1 week to 3 weeks after 3D-FLAIR MRI. A single-shot administration protocol was attempted with additional injections administered on demand in the case of relapsing vertigo spells.9,10 At least a 1-month interval between the administrations was observed. Thirty minutes after topical anesthesia, 0.3 mL of gentamicin sulfate (40 mg/mL) solution diluted with 0.3 mL of 8.4% sodium bicarbonate were administered intratympanically. The patient was kept supine with the head rotated 45° contralaterally for 30 minutes after the injection. After ITGent application, patients were kept under observation for balance symptoms on a weekly basis. Symptoms, such as dizziness, instability, vertigo, or hearing loss were carefully recorded. The cochlear function was controlled by pure-tone audiometry. Spontaneous and evoked nystagmus was detected using Frenzel glasses. No further application of ITGent was performed in the absence of recurrence of vertigo spells. Additional criteria considered in excluding further ITGent injections were worsening of the PTA >15 dB and the appearance of clinical signs of vestibulotoxicity, such as imbalance or persistent spontaneous or head-shaking nystagmus beating away from the injected ear.

Patients were followed up for 2 years after the first ITGent administration. Ultimate outcomes were calculated in the last 6 months of this follow-up period. The efficacy of ITGad injection was evaluated by considering the number of injections necessary to cure vertigo attacks. Vertigo results,4 FLS modifications, variations in caloric excitability (>25%), and PTA (>10 dB HL) were also taken into consideration. These parameters were compared with the degree and extension of EH as evaluated by 3D-FLAIR MRI. To this end, the number of inner ear sites involved by EH (reduced or absent enhancement) was considered.

RESULTS

All patients showed impaired perilymphatic enhancement of variable degrees in the affected inner ear. Absent or reduced enhancement spanned from only one site involved in two subjects to all seven sites involved in one (median, 3.5 sites involved). Absent enhancement was observed in only one site in five subjects, in two sites in one subject, and in three sites in one subject.

Figure 1 shows the 3D-FLAIR MRI findings observed in a patient with left MD, 24 hours after bilateral ITGad administration. Complete perilymphatic enhancement was observed in all portions of the right inner ear. The left cochlea showed a complete perilymphatic enhancement at the level of the basal turn, whereas the middle and apical turns produced a reduced enhancement suggestive of EH occupying the perilymphatic space. The semicircular canals were completely enhanced, whereas reduced enhancement was detected in the vestibule. The patient received a single shot of ITGent in the left ear 2 weeks after MRI, yielding complete control of vertigo spells.

Figure 2 shows the survival actuarial curves depicting the time elapsed between the first administration of ITGent and the possible recurrence of vertigo in two groups of patients, arbitrarily divided on the basis of the
number of inner ear sites involved by EH (i.e., one to three or more than three). Descriptive analysis showed a similar behavior between the groups. No statistical comparison was attempted owing to the small number of subjects for each group.

In 10 out of the 18 patients, only one application of gentamicin was necessary. Six patients needed two injections, and only two required three administrations.

Complete control of vertigo spells (class A) was achieved in 14 patients, whereas substantial control (class B) occurred in three patients, and moderate control was observed in one patient (class C). Postoperative FLS ranged from 1 to 3 (median, 1.5).

Post-treatment PTA threshold ranged from 20 dB to 95 dB HL, with a median of 51.5 dB HL. Three patients (17.6%) had a deterioration in hearing thresholds (>10 dB), nine patients (50%) showed a stable HL, and six patients (33.3%) demonstrated an improved HL (>10 dB).

After the treatment, canal paresis was observed in 17 ears, with absence of response in two; one ear displayed a normal response. Caloric response improved in two subjects (11.1%), did not change in 10 subjects (55.5%), and worsened in six subjects (33.3%).

Table I shows the outcomes of the correlation analysis (Spearman test) between the severity of hydrops, as estimated by the number of inner ear sites involved by EH, with a series of parameters such as the number of injections necessary to cure vertigo, variation in FLS, change in hearing threshold, change in caloric excitability, and class of vertigo results. No statistically significant correlation was observed for all these parameters.

**DISCUSSION**

Intratympanic administration of Gent is a common treatment option for patients with MD, enabling complete or substantial control of vertigo spells in 75% to 96% of subjects.11–14 The efficacy of ITGent relies on its diffusion to the inner ear, where it realizes an ototoxic effect, in particular toward the vestibular sensory cells.15–17

Currently, some information on inner ear penetration of a drug administered intratympanically may be obtained in humans by observing perilymphatic enhancement at the 3D-FLAIR MRI following ITGad injection.1–3 This might be shown as particularly useful in predicting pharmacokinetics of ITGent, although chemical differences between the two substances should lead to caution in the interpretation of the data. Absorption, diffusion, and active elimination of a drug from the inner ear is quite a complex phenomenon that depends on a number of factors, such as molecular weight, water solubility, and pathological alterations. The balance between absorption and clearance is of fundamental importance in determining the diffusion gradient in the inner ear of a substance applied to the round window membrane (RWM).18–20 In particular, low clearance substances tend to be more evenly distributed with respect to drugs that are quickly eliminated.18 In this regard, a particular role can be played by the differences in the molecular weight between Gad-based contrast agents (>600 g/mol) and Gent (449.5–477.6 g/mol, depending on the different components of the drug).21 In addition, atrophic changes in the spiral ligament or vestibular fibrosis, which have been documented in MD,22,23 may differentially impair diffusion and active elimination mechanisms of Gent and Gad in the inner ear.

Gentamicin passes the interfaces between the middle and inner ear, represented mainly by the RWM and secondarily by the annular ligament in the oval window. Transfer of substances through the semipermeable RWM...
to the scala tympani of the inner ear is a passive process, and therefore the passage is facilitated by a low molecular weight. Contact with the RWM may be blocked by fibrous tissue or mucosal folds, partially or totally obstructing the round window niche in 18% to 32% of the ears. Yoshioka et al. investigated the absorption of Gad in 42 patients with EH and 13 patients with various nonhydropic inner ear disorders, using MRI after the ITGad administration. The authors found no or reduced enhancement, probably because of poor absorption through the RWM, in 13% of the ears, and this occurred in half of the cases in ears showing calcification of the tympanic membrane or inflammation of the mastoid cells. The time course of Gad diffusion inside the human inner ear was studied by Nakashima et al. in their Original Report in 2007. The authors found that the intratympanically administered Gad entered the scala tympani of the cochlea through the RWM. On 3D-FLAIR MRI taken 2 hours after the injection, Gad was observed in the vestibular perilymph, parts of the lateral semicircular canals close to the vestibule, and the scala tympani of the basal turn of the cochlea. One day after the IT injection, the Gad was observed almost entirely inside the perilymph of the inner ear. These outcomes are indicative of complex modality of perilymphatic diffusion, which cannot be merely longitudinal. In patients with MD, Fiorino et al. found a pattern of perilymphatic enhancement incompatible with a longitudinal diffusion, which would imply a predictable enhancement defect distally to a perilymphatic region occupied by hydropic membranous structures. Observations such as a reduced or absence of enhancement of the vestibule and a regular enhancement of the semicircular canals, as evidenced in some of the patients, implied a radial diffusion capable of bypassing the block of perilymphatic sites owing to EH. The longitudinal pattern of diffusion has also been contradicted by other evidence, such as the very slow rate of <$2 nL/min, of longitudinal flow of cochlear perilymph. Therefore, some direct pathways between the scala tympani and scala vestibuli bypassing the helicotrema, and passage through the annular ligament across the stapedio-ovalar joint have also been suggested. A particular role may be played by alternative pathways along the osseous, perineural, or perivascular routes. Zou et al. found that Gad injected intratympanically in guinea pigs appeared to progress from the scala tympani to the modiolus, and then to the scala vestibuli, beginning in the basal turn and slowly progressing distally. The authors suggested that this radial communication is mediated mainly through the vasculature of the modiolus, or through the intercellular space of the spiral ligament, which has a loose fibrous structure. Combined light and scanning electronic microscopy showed that perilymph and fluid spaces in the modiolar periphery form a common system. The modiolar wall of the scala vestibuli and tympani in the first and second cochlear turns is porous, forming a perilymphatic communication route to the perivascular and perineural spaces in the modiolus. A perimodiolar lymph can be identified in the modiolar periphery, indicative of a rich fluid exchange between the modiolus and perilymph. This canalicular system may play a role in the circulation of perilymph in the human cochlea, and from there to the vestibular structures. This fluid exchange pattern is compatible with the findings observed in humans by Kaway et al., who visualized increased enhancement of the cochlear modiolus after IT injection of Gad using 3D-FLAIR turbo spin echo with real reconstruction sequence with high spatial resolution and a 32-channel head coil at 3 T.

This complex modality of drug diffusion in the inner ears is probably one of the main reasons of the occurrence of therapeutic and adverse effects of Gent, even in the presence of endolymphatic space dilatation. The hypothesis of a reduced effect of Gent administered intratympanically in the presence of severe EH, owing to obstructed diffusion along the perilymphatic compartments, has not been confirmed in the present investigation. No difference in drug dosage or cochlear and vestibular effects has been found between MD subjects showing different degrees of EH.

Additional factors may also explain this behavior. A possible reason for free diffusion of Gent is the low prevalence of hydropic involvement of the basal turn of the cochlea. This may enable Gent to freely enter the scala tympani and reach, via radial communications, the scala vestibule of the basal turn, which is connected to the vestibulum via an open communication, enabling further diffusion to the remaining perilymphatic spaces. Gadolinium has a molecular weight that is at least one-third greater than that of Gent. This may be trivial for the passage through the RWM, but may be significant for diffusion in the inner ear.

In fact, there is much evidence of different distribution modalities between Gad and Gent, which may render inapplicable to predict inner ear diffusion of Gent by the behavior of the contrast medium. Gentamicin is able to penetrate the endolymph when administered either intravenously or transtympanically. This is inferred indirectly by its pharmacological effect on the cochlear and vestibular sensory cells, and by a series of experimental outcomes, as staining of hair cells after administration of the drug conjugate with a marker. The mechanisms by which aminoglycosides enter endolymph, passing the blood/labyrinth barrier and perilymph/endolymph barrier, remains undetermined. There are three possible routes: 1) from strial capillaries to marginal cells, followed by clearance into endolymph; 2) by transcytosis across the epithelial perilymph/endolymph barrier; or 3) by passage in the scala tympani through the basilar membrane into extracellular fluids within the organ of Corti and from there enter hair cells by traversing their basolateral membranes. On the other hand, round window application of Gad in animals and humans has been demonstrated to enhance the perilymphatic space but not the endolymphatic space, indicating absence of or minimal diffusion through the perilymphatic/endolymphatic barrier. This phenomenon may be due to impermeability of the perilymphatic/endolymphatic barrier to Gad, or a low concentration in the endolymph not capable of producing an enhanced signal. To the best of our knowledge,
there are no studies on the kinetics of Gad responding to this issue.

CONCLUSION
The hypothesis of a reduced effect of Gent administered intratympanically in the presence of severe EH, owing to obstructed diffusion along the perilymphatic compartments, has not been confirmed in the present investigation. Absorption, diffusion, and clearance of a drug from the inner ear is quite a complex phenomenon. Pharmacokinetic differences make it inapplicable to predict the effectiveness of IT Gent by perilymphatic diffusion of Gad.

BIBLIOGRAPHY