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Triamcinolone acetonide can be detected in cerebrospinal fluid after intratympanic injection

Valerie Dahm [a], Matthias Millesi [b], Julia C. Gausterer [c], Alice B. Auinger [a], Franz Gabor [c], Gottfried Reznicek [d], Dominik Riss [a], Ursula Schwarz-Nemec [e], Christian Matula [b], Christoph Arnoldner [a,*]

[a] Medical University of Vienna, Vienna, Austria, Department of Otorhinolaryngology, Head and Neck Surgery, Austria
[b] Department of Neurosurgery, Medical University of Vienna, Vienna, Austria
[c] Department of Pharmaceutical Technology and Biopharmaceutics, University of Vienna, Vienna, Austria
[d] Department of Pharmacognosy, University of Vienna, Vienna, Austria
[e] Medical University of Vienna, Vienna, Austria, Department of Radiology, Division of Neuroradiology and Musculoskeletal Radiology, Austria

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ABSTRACT

Intratympanically applied treatments are of increasing interest to the otologic community to treat sudden sensorineural hearing loss or vestibular disorders but also to deliver gene therapy agents, or biologics to the inner ear. Further diversion from the middle ear and perilymph to blood circulation and cerebrospinal fluid via the cochlear aqueduct are one of the limiting factors and so far not understood well enough.

In this study, intratympanically applied triamcinolone acetonide was determined in cerebrospinal fluid. Additionally, perilymph was sampled through the round window membrane as well as at the lateral semicircular canal to determine drug levels. Of the twenty-one included patients, triamcinolone acetonide was quantifiable in cerebrospinal fluid in 43% at very low levels (range 0 ng/ml–6.2 ng/ml) which did not correlate with perilymph levels. Drug levels at the two different perilymph sampling sites were within a range of 13.5 ng/ml to 1180.0 ng/ml. Results suggest an equal distribution of triamcinolone acetonide to semicircular canals, which might support the use of triamcinolone acetonide as a treatment option for vestibular pathologies such as Menières disease. On the other hand, the distribution to cerebrospinal fluid might be limiting current approaches in gene therapy where a central distribution is unwanted.

1. Introduction

Intratympanically (IT) applied substances have been of increasing interest in recent years since intravenously and orally applied drugs have limited access to the inner ear due to the blood-perilymph barrier. Additionally, systemically applied drugs lead to side effects, which can be circumvented. Steroids or gentamicin are injected through the intact tympanic membrane and meant to take effect on the inner ear. Dexamethasone or dexamethasone phosphate are the most commonly used IT glucocorticoids, mainly for sudden sensorineural hearing loss and are assumed to influence hair cells or afferent nerve fibers. Gentamicin is applied IT for therapy of Menière's disease and should mainly target the vestibular part of the inner ear. After application of substances into the middle ear cavity, fluids diffuse over the round window membrane (RWM) and reach the perilymph and endolymph. Their passage through the RWM depends on the lipophilicity, polarity and size of molecules. Several communication routes between the inner ear and the intracranial spaces have been described: the cochlear aqueduct, the internal auditory canal, the endolymphatic sac, via cranial nerves (facial nerve branches, trigeminal nerve branches) and via dissemination to the vasculature [1,2]. This communication pathways have led to the concern that new agents targeted at hair cell regeneration could potentially reach the central nervous system. Many studies assessing drugs applied IT are derived from animal studies which inherently

* Corresponding author at: Waehringer Guertel 18-20, 1090 Vienna, Austria.
E-mail addresses: valerie.dahm@meduniwien.ac.at (V. Dahm), matthias.millesi@meduniwien.ac.at (M. Millesi), julia.clara.gausterer@univie.ac.at (J.C. Gausterer), alice.auinger@meduniwien.ac.at (A.B. Auinger), franz.gabor@univie.ac.at (F. Gabor), gottfried.reznicek@univie.ac.at (G. Reznicek), dominik.riss@meduniwien.ac.at (D. Riss), ursula.schwarz-nemec@meduniwien.ac.at (U. Schwarz-Nemec), christian.matula@meduniwien.ac.at (C. Matula), christoph.arnoldner@meduniwien.ac.at (C. Arnoldner).

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include uncertainties. Animals often examined for hearing research, such as guinea pigs, mice or rats have a patent cochlear aqueduct to such an extent that perforating the bony otic capsule or the round window leads to a substantial rate of CSF driven fluid efflux [2,3]. Research in humans is scarce, so far. As stated above, steroids are one of the most common drugs applied IT, not only in the setting of sudden sensorineural hearing loss or Menière's disease, but also before or during cochlear implantation to possibly reduce scaring and impedances [4]. Triamcinolone acetonide (TAC) is not used as often as other substances such as dexamethasone or methylprednisolone for IT application [5]. It is poorly water solubile due to its lipophilicity, therefore forming a suspension if present at concentrations above the saturation concentration being dependent on temperature and solvent. It causes a depot effect at other sites of application, probably due to its crystalline texture [6]. Further, this steroid has been shown to have a longer half-life than dexamethasone and is equally distributed over the cochlea in a guinea pig model [7]. The aim of the current study was to investigate the dissemination of IT injected TAC to CSF. The second aim was to assess TAC perilymph levels at the RWM in comparison to the perilymph at the lateral SCC.

2. Methods

The study was conducted in compliance with the principles of the local ethics review board (#1550) and with approval of the Austrian Agency for Health and Food Safety Ltd. Each subject gave informed consent to participate in the study. The study was registered at clinicaltrials.gov, NCT04658836.

2.1. Participants

Patients undergoing vestibular schwannoma resection older than 18 years were asked to participate in our study. In total, 21 patients were included, nine of which underwent simultaneous translabyrinthine (TL) vestibular schwannoma resection and cochlear implantation. Twelve further patients underwent retrosigmoid (RS) (n = 4) or middle fossa (MF) (n = 8) resection of their vestibular schwannoma. Patients received IT application of 40 mg/ml TAC on the day before surgery. All patients included in the study undergoing TL resection of vestibular schwannoma had no serviceable hearing on the affected side [8] and were offered cochlear implantation simultaneously, explaining why a round window access was part of the surgical procedure. Exclusion criteria were as follows: regular steroid therapy or steroid therapy within two weeks before surgery, contraindication against TAC IT application.

2.2. Transtympanic injection

Patients were placed in a supine position. The head was turned to the contralateral side. The tympanic membrane and the ear canal were locally anesthetized with xylocaine spray (10 mg/puff). The entire ear canal was filled and patients were asked to stay in this position for at least 20 min. After suctioning the xylocaine fluid, the suspension containing TAC was applied IT via a 25G (0.50x90mm, 3.50 IN) needle. Individuals were then asked to stay in the lying position without talking and as little swallowing as possible for further twenty minutes. Subjects were able to continue their normal routine after the injection.

2.3. Triamcinolone acetonide

The substance used in this study was Volon® A 40 mg/ml crystal suspension (Dermapharm GmbH, Grünwald, Germany). It contains 9.9 mg of benzyl alcohol per 1 ml, sodium carboxymethyl cellulose, polysorbate 80, sodium chloride and water.

2.4. Sampling

Nine patients underwent TL vestibular schwannoma resection and cochlear implantation. During the surgery, an extended mastoidectomy is performed, followed by a posterior tympanotomy. After identification of the round window membrane (RWM) and drilling of the bony overhang, the lateral semicircular canal (SCC) was blue lined. Perilymph was sampled through the intact RWM as well as through the intact membranous labyrinth of the SCC with a sterile disposable aspirator with a diameter of 0.4 mm. An amount of 20 µl of perilymph was aspirated. The sample was immediately transferred to a 0.2 ml safe lock tube. Specimens were stored at − 80 °C. In two cases the perilymph sample of the SCC was < 1 µl making any further analysis impossible. Cerebrospinal fluid (CSF) could be sampled in all 21 cases. 200 µl CSF was taken in every case and stored in a 2 ml safe lock tube at − 80 °C.

2.5. Quantification of triamcinolone acetonide

2.5.1. Sample preparation quantification of TAC in CSF

Perilymph samples were diluted with ice-cold methanol to a total minimum volume of 20 µl to ensure a sample volume sufficient for HPLC-MS analysis of triplicates (dilution range: 1:3 to 1:20). Samples were centrifuged and supernatants were stored at 4 °C until HPLC-MS/MS analysis. CSF samples were simultaneously analyzed (1) after dilution with ice-cold methanol, i.e. 100 µl of CSF were mixed with 100 µl of ice-cold methanol (dilution factor 1:2) and stored at 4 °C and (2) as undiluted, pure CSF samples. Final TAC levels in CSF did not differ/vary between samples prepared according to (1) or (2).

2.5.2. HPLC-MS/MS analysis

TAC in biological fluids was quantified with high performance liquid chromatography. The samples were analyzed using liquid chromatography/mass spectrometry (LC-MS/MS) on an Ultimate 3000 RSLC-series system (Thermo Fisher Scientific, Sunnyvale, California, USA) coupled to a triple quadrupol mass spectrometer (AB Sciex Instruments API 4000, Concord, Ontario, Canada) equipped with an orthogonal ESI source operated in positive mode.

LC separation was performed on an Acclaim RSLC 120 C18 column (3 µm, 100 × 2.1 mm I.D., Thermo Fisher Scientific), preceded by an Acclaim 120 C18 guard cartridge (5 µm, 10 × 2 mm I.D., Thermo Fisher Scientific), at a flow rate of 0.5 ml/min and a column temperature of 25 °C. The mobile phase consisted of a linear gradient mixed from 0.1% aqueous formic acid (mobile phase A) and acetonitrile (mobile phase B). The gradient ranged from 20% B at 0 min. to 95% B in 5 min., purging with 95% B for 1 min., then again 20% B to equilibrate the column for 4 min. before application of the next sample (total analysis time 10 min.), TAC eluted at 4.13 min. TAC was selectively and sensitively detected and quantified using MS/MS fragmentation of TAC giving a quasimolecular ion at m/z 435.4 [M + H] + . MRM m/z 435.4/415.0 (quantifier) as well as m/z 435.4/213.1 (qualifier) were used for calibration curves with external standard TAC (injection volume 5 µl) to give a linear concentration range from 0.1 ng/mL to 5000 ng/mL (y = 559x + 3050, correlation coefficient 0.9986). The lower limit of detection (LLOD) was 0.1 ng/ml, and the lower limit of quantification (LLOQ) was set at 0.5 ng/ml. The triple quadrupol mass spectrometer operated with the following parameters: ESI pos., IS 5500, EP 10, CUR 10, GS1 40, GS2 40, TEM 500 °C, CAD 4, CEM 3000, DF −100. MRM m/z 435.4/415.0: DP 66, CE 11, CXP 26, MRM, m/z 435.4/213.1: DP 81, CE 37, CXP 34, dwell time for each MRM150 ms.

2.6. Computed tomography

High resolution computed tomography examinations of the temporal bone were performed on a 64-detector row scanner (Philips Brilliance 64, Philips Medical Systems, Best, the Netherlands). A standard protocol was used including the following parameters: 140 kV, 200 mAs, pitch

0.3, 20 × 0.6 collimation, 768 × 768 matrix, 0.75 sec. rotation time and slice thickness of 0.67 mm.

All examinations were anonymized and randomly presented on a picture archiving and communication system (IMPAX, AGFA HealthCare, Bonn, Germany) to a radiologist (U.S.-N. with six years of experience in head and neck imaging), who was not aware of any clinical data

First, for the assessment of semicircular canal dehiscence, multiplanar reformation images in three planes were reconstructed to best visualize the superior, posterior and lateral semicircular canals on both sides. A canal was considered to be dehiscent if its bony covering could not be detected.

Second, for the measurement of cochlear aqueduct width, the intracranial opening of the cochlear aqueduct was localized on axial images on both sides and the widest part was measured with an integrated measuring tool.

2.7. Statistical analysis

Due to the small sample size of seven (SCC), nine (RWM) and twenty-one (CSF) samples, results are reported as individual data, mean and median, where appropriate. Median values (interquartile range, IQR) are given for description of continuous variables.

3. Results

3.1. Cerebrospinal fluid

Twenty-one patients received IT TAC 40 mg/ml at a median volume of 0.7 ml (IQR 0.45–0.8 ml). The injection was performed on the day before surgery. The median time interval between drug application and sampling of CSF was 22 h, 5 min (IQR 21 h 15 min–22 h 37 min). TAC could be quantified in the CSF of nine (43%) of these patients. In 57% (n = 12) TAC was below the LLOD. The median TAC level of all 21 patients was 0 ng/ml (range 0 ng/ml–6.2 ng/ml, IQR 0–1.4 ng/ml). The median TAC levels of the patients with detectable TAC concentrations was 1.6 ng/ml with a range of 0.8 ng/ml up to 6.2 ng/ml. Results are depicted in Fig. 1.

All 21 patients had a tympanic membrane without any pathologies. The middle ear could not be evaluated in all cases, since a majority (57%) of patients underwent middle fossa or retrosigmoid resection of vestibular schwannoma.

3.2. TAC levels (round window, lateral semicircular canal)

Perilymph could be sampled and evaluated in nine patients through the round window membrane. Seven patients underwent perilymph sampling at the SCC. There were no adhesive bands or thickened mucosa in the middle ear of any of these patients. Perilymph TAC levels of nine patients sampled at the round window membrane were at a median of 283.8 ng/ml (mean 435.3 ng/ml) with a range of 21.8 ng/ml to 1180.0 ng/ml. Perilymph TAC levels at the SCC were at a median of 302.2 ng/ml (mean 302.8 ng/ml) with a range of 13.5 ng/ml to 639.0 ng/ml. Results of the individual groups are depicted in Fig. 2.

3.3. Comparison of TAC levels

In seven patients, perilymph could be sampled both at the round window and at the lateral SCC. Results are depicted in Fig. 3. The median round window TAC level was 283.3 (mean 430.3 ng/ml) with a range of 21.8 ng/ml to 1180.0 whereas a median level of 302.2 ng/ml (mean 302.8 ng/ml) with a range of 13.5 ng/ml to 639.0 ng/ml was found at the lateral SCC. Of these seven patients TAC was under the LLOQ in the CSF of four patients and 0.8 ng/ml in two further patients as well as 1.1 ng/ml in one patient. Results are depicted in Fig. 3. There was no correlation between the perilymph levels and the CSF level of TAC as

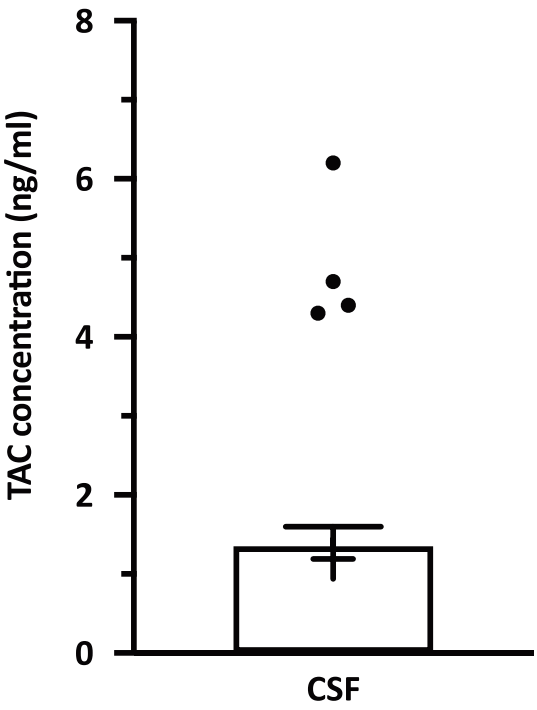

Fig. 1. Triamcinolone acetonide (TAC) concentration in cerebrospinal fluid (CSF) of 21 patients. The horizontal line shows the median (0 ng/ml), while the + signifies the mean (1.2 ng/ml). The boundaries of the box represent the lower and upper quartiles. The whiskers reaching from the edge of the box to the largest and smallest values that are outside the box but within 1.5 standard deviations. Values outside this range (outliers) are denoted with circles. Results of TAC levels are given in ng/ml.

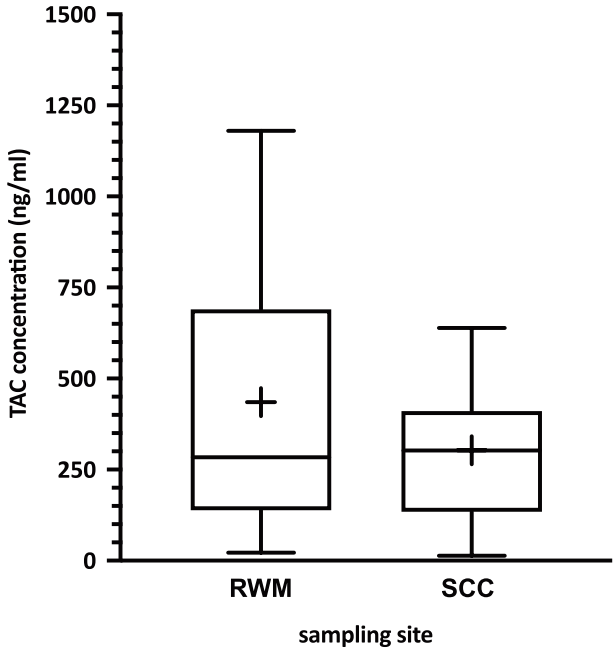

Fig. 2. Boxplot of triamcinolone acetonide (TAC) concentration in perilymph samples at the round window membrane (RWM) n = 9, and samples at the lateral semicircular canal (SCC) n = 7. The horizontal line shows the median, while the + signifies the mean. The boundaries of the box represent the lower and upper quartiles. The whiskers reaching from the edge of the box to the largest and smallest values that are outside the box but within 1.5 standard deviations. Results of TAC levels are given in ng/ml.

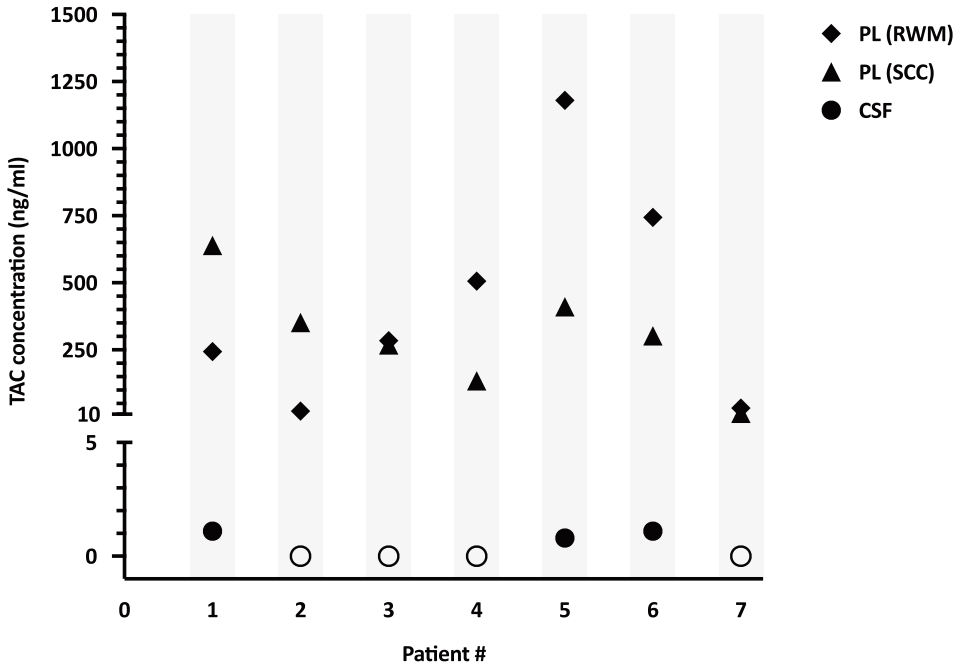

Fig. 3. Comparison of triamcinolone acetonide (TAC) concentration in perilymph (PL) sampled at RWM and SCC and CSF (n = 7). Results of TAC levels are given in ng/ml for each patient individually. Empty circles are patients with non - detectable TAC levels in CSF. Full black circles are patients with detectable TAC levels in CSF.

seen in Fig. 3.

3.4. Correlation of TAC in CSF and age

The median age of included patients was 53.0 years with a range of 26 to 74 years (IQR 47.5 years–60.5 years). Nine patients had detectable TAC CSF levels (0.8–6.2 ng/ml), which were in the age range between 46 years and 74 years. There was no correlation of CSF TAC levels and age as seen in Fig. 4.

3.5. Correlation of TAC and computed tomography findings

A bony dehiscence of the superior semicircular canal was present in four patients, as seen in Table 1. None of these patients had detectable TAC levels in CSF. The widest point of the cochlear aqueduct (CA) was measured on CT and correlated to TAC CSF levels, as seen in Fig. 5. The

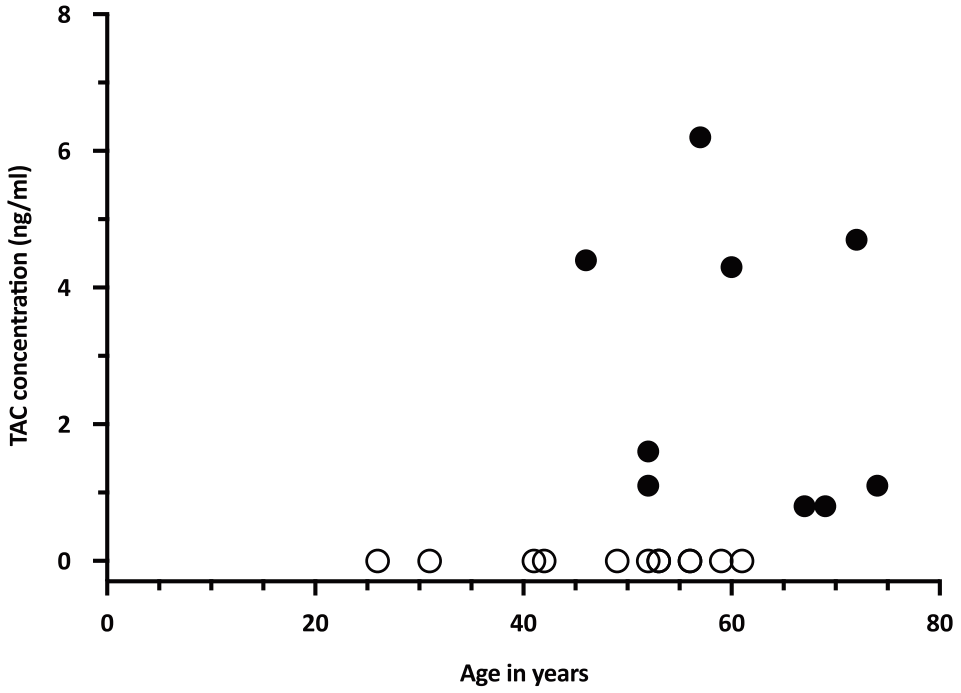

Fig. 4. Scatterplot showing age versus TAC levels in CSF. Triamcinolone acetonide (TAC) concentration in CSF given in ng/ml on the y-axis. The x-axis shows the age in years. Each circle represents one patient. Empty circles are patients with non - detectable TAC levels in CSF. Full black circles are patients with detectable TAC levels in CSF.

Table 1
Computed tomography findings of each individual patients. ID refers to each individual patient. Sup. SCC – superior semicircular canal, Post. SCC – posterior semicircular canal, Lat. SCC – lateral semicircular canal, 0 = no dehiscence, 1 = bony dehiscence, CA – cochlear aqueduct. Largest width of the CA given in mm. Cerebrospinal fluid (CSF) triamcinolone acetonide (TAC) levels given in ng/ml. n.d. – not detectable.

ID	Sup. SCC	Post. SCC	Lat. SCC	CA width (mm)	CSF-TAC (ng/ml)
1	0	0	0	3.3	0.8
2	1	0	0	3.1	n.d.
3	0	0	0	2.5	n.d.
4	0	0	0	2.2	n.d.
5	0	0	0	2.4	6.2
6	0	0	0	2.3	1.1
7	0	0	0	1.9	n.d.
8	0	0	0	2.3	n.d.
9	0	0	0	1.2	n.d.
10	1	0	0	3.4	n.d.
11	0	0	0	3.5	n.d.
12	1	0	0	2.3	n.d.
13	0	0	0	2.3	4.4
14	0	0	0	1.6	n.d.
15	0	0	0	2.3	n.d.
16	1	0	0	1.6	4.7
17	0	0	0	2.6	n.d.
18	0	0	0	1.8	0.8
19	0	0	0	1.9	4.3
20	0	0	0	1.7	1.1
21	0	0	0	2.1	1.6

median CA width was 2.3 mm (IQR 1.85–2.55 mm) in all patients. The median CA width in the group without detectable TAC levels was 2.3 mm (IQR 1.98–2.98 mm) as well as 2.1 mm (IQR 1.75–2.35 mm) in the group with detectable CSF TAC levels.

4. Discussion

To our knowledge, this is the first study examining a correlation between IT applied steroids and distribution to CSF. TAC could be detected in the CSF of 43% of patients, even 24 h after injection. CSF levels do not correlate with perilymph levels. The cochlear aqueduct (CA) connects the perilymphatic space with the subarachnoid space and represents the most likely route of distribution of IT applied TAC. The CA extends from the basal turn of the cochlea to the inferior surface of the petrous pyramid in proximity to the jugular foramen and the glossopharyngeal nerve. It is a short bony canal, which has mainly been outlined in animal as well as cadaveric studies. Four types of patencies of the cochlear aqueduct have been described in humans previously: central lumen patent throughout length of aqueduct (34%), lumen filled with loose connective tissue (59%), lumen occluded by bone (4%), and obliteration of the aqueduct (3%) [9]. These outcomes from a cadaver study correspond well with the results presented in this study suggesting that TAC readily diffuses through the fully patent central lumen. CA width was measured at the widest point on CT of all included patients in the presented study. There was no correlation of CA width and presumed patency, which does not contradict the theory of the CA being the most likely path of distribution. These results simply show that the patency does not seem to correlate with the width of the CA and therefore cannot be predicted with CT imaging. Another distribution pathway of IT applied medication could be dissemination to the plasma. In a further study we could show that IT applied TAC disseminates to the plasma in a very small number of patients at very low levels[10]. TAC to CSF via blood circulation is therefore most unlikely. Further options that have been discussed are routes via the endolymphatic sac and through cranial nerves [1,2]. Both of these options are hard to prove or contradict. However, dissemination of IT applied substances to the endolymph have been described in several animal studies especially for the use of gentamicin [11,12], which might then further be transported to CSF. Since the endolymphatic space only comprises 17.3% of total labyrinth fluid in humans [13], spreading of injected drugs through the endolymphatic space to CSF via the endolymphatic sac can be expected to be minimal. Distribution of substances from perilymph to CSF via a bony dehiscence of semicircular canals has also been hypothesized [1]. Of our 21 presented patients, four had a dehiscence of the superior semicircular canal, none of which had detectable TAC levels in CSF.

Previous studies tried to analyze intratympanically applied drugs to CSF. A study by Naganawa et al. evaluated patients with endolymphatic

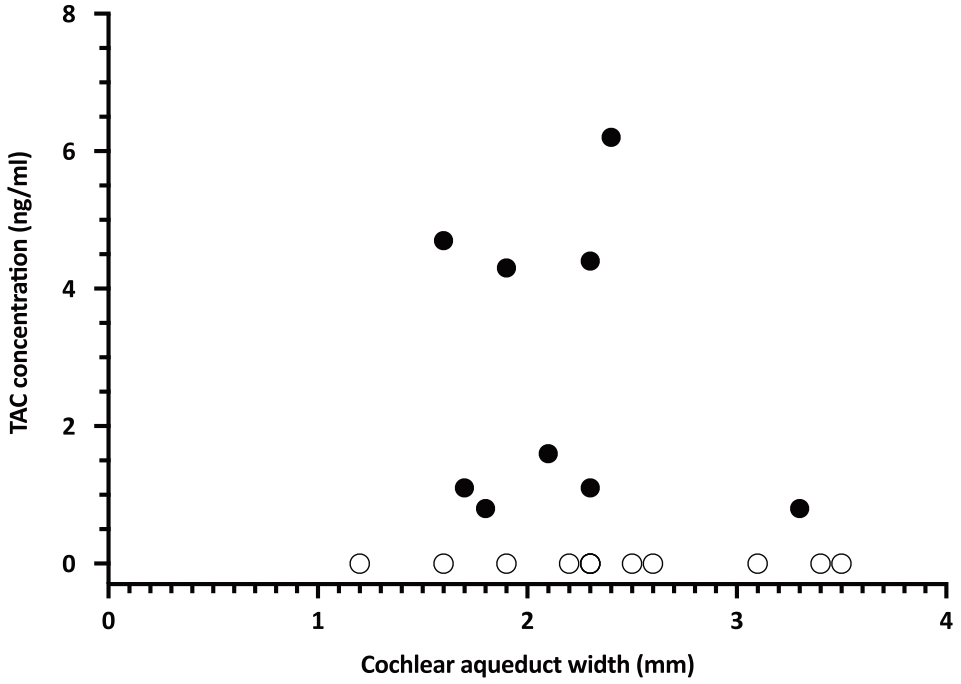

Fig. 5. Scatterplot showing cochlear aqueduct width (given in mm) versus TAC levels in CSF (given in ng/ml). Each circle represents one patient. Empty circles are patients with non - detectable TAC levels in CSF. Full black circles are patients with detectable TAC levels in CSF.

hydrops [14]. These patients were injected with intratympanic gadolinium diethyl- enetriaminepentaacetic acid. Twenty-four hours later MRI was conducted and showed contrast enhancement in the CSF space of the IAC. A further study measured CSF levels of intratympanically applied Gentamicin and could not find any distribution to CSF [15].

A correlation between age and CA patency has been shown in a large cadaver study before, calling it the process of aging in the organism [16]. In said study 250 human cadavers and temporal bones with a wide age range (pre-term births up to 95 years of age) were studied. However, the majority of specimens (n = 200, i.e. 80%) were younger than 60 years of age. A patency for fluid (indirect test for patency) was shown in 32%, distributed over all groups under 60 years. Direct patency (dissection and staining) was found in 68% of cases with a steady decline with increasing age. In cases older than 60 years, 15–30% showed a patent CA. A different study conducted on 101 temporal bone cadavers with evenly distributed age groups between 0 and 100 years found no correlation with age [9]. Similarly, the results of the presented study show no correlation of CSF TAC levels, age and CA patency. One limitation is that only twenty-one subjects were included. Additionally, almost all patients were older than 50 years. Nevertheless, all nine patients with detectable TAC in CSF were older than 45 years. Not only cadaveric studies have suggested a patent or partially patent CA [9,16,17], the spread of pathogens with acute otitis media resulting in meningitis as well as labyrinthitis resulting from meningitis have also added to this theory [18,19]. Moller et al. investigated pneumococcal meningitis in a rat model by inoculating them intrathecally with Streptococcus pneumoniae [20]. Results showed that first the bacteria invaded the scala tympani of the cochlea through the CA, followed by a spread to scala vestibuli and the vestibular system.

The question of a patent CA is of utmost interest in recent years due to the fact that an increasing amount of gene therapies for hearing loss are under investigation [21]. Possible dissemination to CSF is one of the factors limiting these new approaches.

Results of the presented study show that TAC levels in CSF do not correlate with TAC levels in perilymph. Prevention of dissemination to CSF by dose reduction therefore does not seem promising. Nevertheless, TAC levels in CSF were not detectable in 57% of patients, in the remaining patients TAC levels were significantly lower in CSF than in perilymph. Consequently, the dissemination of TAC through whichever route seems to be minimal.

A further conclusion of the results presented in this manuscript is that perilymph TAC levels measured at the RWM and the lateral SCC are comparable even 24 h after IT injection. Similar to the missing correlation of intratympanically injected dose and distribution of TAC to CSF, we could not find a correlation of intratympanically injected TAC dose and perilymph levels in a previously published manuscript in 40 patients [10]. Consequently, the adequate dose of intratympanically injected TAC is not known, so far. While gentamicin has been used IT for several years, intratympanically applied steroids for Menière's disease is a fairly new treatment option. One of the most convincing studies in this field was conducted by Patel et al.; a randomised, double-blind, comparative study using methylpredinsolone and gentamicin IT for Menière's disease [22]. Results showed a significant improvement of vertigo attacks using either drug with no significant difference between them. Dexamethasone, dexamethasone phosphate, methylprednisolone and methylprednisolone succinate are by far the most commonly used drugs for IT injection. However, TAC has shown some superior qualities for perilymph absorption [23]. It can be assumed that treatment of Menière's disease is only successful, when the applied substance reaches the endolymph, which can be achieved through diffusion from perilymph but also through vessels of the stria vascularis, as shown in a study using fluorescent gentamicin [24]. Our results suggest that there is a good distribution of TAC after IT application to the SCC, which is an important foundation for further diffusion to the endolymph. A limitation of the study is that sampling of perilymph at the SCC was only possible in seven cases.

5. Conclusion

Characterizing pathways in and out of the middle and inner ear add to the knowledge on treatments for various pathologies such as hearing loss and Menière's disease. Results of the current study show that TAC applied IT is detectable in perilymph as well as in 43% of CSF samples, 24-hours after injection. Perilymph TAC levels measured through the RWM and at the lateral SCC are comparable.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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