Comparison of contrast effect on the vestibular perilymph between two contrast media agents after single-dose intravenous administration

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Aims and objectives

• The diagnosis of endolymphatic hydrops (EH) with magnetic resonance imaging (MRI) relies on Inversion-Recovery sequences 4 hours after single dose intravenous injection of Gadolinium-based contrast agents (Gd) [1,2].

• Gd physiologically cross the blood-perilymph barrier thus the perilymph appears as a high-signal while the endolymph remains with low-signal because Gd does not pass the blood-endolymph and the perilymph-endolymph barriers due to the presence of tight junctions [3,4].

• One can hypothesize that the passage of the blood-labyrinth barrier also depends on biochemical properties of contrast media agents. The perilymph enhancement is particularly important to distinguish saccule from utricle structure, these inner ear structures were recently used to classify with imaging MD patients [2,5]. Enhancement of the semicircular canals has also shown to be useful to evaluate the location of hydrops in the lateral semicircular canal [6].

• Here, we compared the effect of two macrocyclic contrast agents (Gd-DOTA, Dotarem® and Gd-DO3A-butrol, Gadovist®), mainly different due to the Gd concentration, on inner ear structures in patients with Menière disease (MD).
Methods and materials

- **Population**

This was a single center parallel-group imaging study.

Twenty patients having a unilateral definite, probable or possible clinical diagnosis of MD based on the AAO-HNS guidelines [7] were recruited between December 2016 and April 2017. The side of the symptomatic ear was defined based on the clinical examination and/or the results of the electrophysiological tests. The patients didn't present renal disease.

- **Imaging**

Ten patients underwent an MRI scan with delayed acquisition 4 hours after a single intravenous dose of gadoteric megluminate (Gd-DOTA, Dotarem®, 0.1 mmol/kg, 0.5 mmol/mL, Guerbet, Roissy, France) and 10 others underwent an MRI after a single dose of gadobutrol (Gd-DO3A-butrol, Gadovist® 0.1 mmol/kg, 1 mmol/mL, Bayer Shering Pharma AG, Berlin, Germany). Imaging examinations were carried out on a 3T MRI scanner (General Electric Healthcare, Discovery®, Milwaukee, WI) with a 16-channel head-neck-spine (HNS) coil.

We performed a 3D-FLAIR MRI sequence with the CUBE® technique with the following parameters: TR: 8000ms, TE: 130ms, TI: 2059ms, 288x288, variable flip angle and isotropic voxel size of 0.8 mm for acquisition and 0.4 mm for reconstructions. We employed the ARC parallel imaging technique with an acceleration factor of 2, nex: 1, and a scan time of 7’30.

- **Analysis**

Images for each subject were evaluated independently with Osirix MD® by two readers who were blinded to the clinical data.

1. A quantitative assessment was carried out using the region of interest method as previously reported [8]. A 5 mm² circular ROI was set in the basal turn of the cochlea and a 50 mm² circular ROI was set at the same level in the medulla. The signal intensity ratio (SIR) was defined as the signal intensity of the basal turn divided by that of the medulla. The SIR was measured 3 times and the average SIR value was calculated for each ear.

2. A visual assessment based on a 2-grade scale was performed in order to evaluate the perilymph of each semicircular canal (0: no enhancement, 1: enhancement) and of the vestibule allowing the discriminate between the
utricle and the saccule (0: no distinction between the utricle and the saccule, 1: distinction between the utricle and the saccule).

3. We graded EH using the semi-quantitative grading system proposed by Nakashima et al [9]. We also graded EH using the saccular morphology classification as evaluated by the SURI sign (Saccule to Utricle Ratio Inversion) defined as the ratio between the area of the saccule and the area of the utricle, in axial and sagittal slices on one reference image [2,5]

- **Statistical analysis**

Data were analyzed using R software v3.3.2 (The R Foundation, Inc., USA).

Comparison between the SIR of each groups were assessed by Mann-Whitney test and comparison for the visual assessment between the two groups was studied by the Fisher test. In order to evaluate the reproducibility of the SIR measure by the two observators the Intraclass coefficient correlation (ICC) was used. Continuous data are presented as median with 25th and 75th percentile. Categorical data are reported as frequency and percentages. We set the significance threshold (p-values) at 0.05. Sensitivity and specificity were estimated by taking the clinical examination as gold standard.
Results

- **Population**

10 MD patients (5 women, 4 right-side MD, 6 left-side MD) were included in the Gd-DOTA group with a median age of 58.5 (48 ; 65) ranging from 27 to 81 years. There was 2 patients with the clinical diagnosis of possible MD, 1 of probable MD and 7 of definite MD.

10 MD patients (7 women, 5 right-side MD, 5 left-side MD) were included in the Gd-DO3A-butrol group with a median age of 45.5 (36 ; 56) ranging from 32 to 63 years. There were 4 patients with the clinical diagnosis of possible MD, 1 of probable MD and 5 of definite MD.

The Body Mass Index (BMI) was not significantly different (p=0.65) between the Gd-DOTA group (median: 25; 22.1, 30.3, ranging from 20.2 to 33.1) and the Gd-DO3A-butrol group (median: 25.4; 23.6, 31.7, ranging from 19 to 37.9).

- **Quantitative Analysis**

The median of SIR of Gd-DO3A-butrol in the symptomatic ear was 1.58 (1.46 ; 1.97), ranging from 1.03 to 3.25, while that of Gd-DOTA was 1.30 (1.15 ; 1.84) (Fig. 1) ranging from 1.02 to 2.9. The SIR difference between the two contrast media was not significant (p=0.18).

In the contralateral asymptomatic ears (Fig. 1), the median of the SIR of Gd-DO3A-butrol (median: 1.62; 1.49, 1.7, ranging from 1.48 to 3.55) was significantly (p=0.009) higher than the SIR of Gd-DOTA (median: 1.21; 1.17, 1.42, ranging from 0.74 to 1.68). There was no significant difference of the SIR between the symptomatic ear and the asymptomatic ear in the Gd-DOTA group and in the Gd-DO3A-butrol group (p=0.14).

The ICC for the SIR between the two radiologists was excellent (0.964).

- **Visual analysis (Table 1)**

In the Gd-DOTA group (Fig. 2 and 3), the distinction between the utricle and the saccule was not possible in 7 out of 20 ears (35%).

A SURI sign was demonstrated in 2 out of 10 patients (Se=20%) always displayed on the side of the symptomatic ear (Spe=100%). By using the semi-quantitative method, EH was observed in 6 out of 10 patients on the symptomatic ear (sensitivity=60%) and also in 6 patients on the asymptomatic ear (Specificity=40%).
The enhancement of the semicircular canals (Fig. 2 and 3) was not observed in 16 out of 20 ears (80%).

In the Gd-DO3A-butrol group (Fig. 2 and 3), the distinction between the utricle and the saccule was not possible in 3 out of 20 ears (15%).

A SURI sign was observed in only 1 ear (Se=10%, Spe=100%). By using the semi-quantitative method, EH was observed in 6 out of 10 patients on the symptomatic ear (sensitivity=60%) and in 2 patients on the asymptomatic ear (Specificity=80%).

The enhancement of the semicircular canals (Fig. 2 and 3) was not demonstrated in 4 out of 20 ears (20%).

The Gd-DO3A-butrol was not significantly superior to Gd-DOTA in visualizing the endolymphatic structures (OR=2.96, IC95 0.54 ; 21.28, p=0.27) in the symptomatic ears but was significantly superior in the asymptomatic ears and to assess the semicircular canals (OR=14.5, IC95 2.8 ; 101, p<0.001).
Fig. 1: A-B: 3D-FLAIR axial slices at the level of the basal turn of the cochlea. In the Gd-DO3A-butrol group (A) the patient (51 years-old female, BMI=24.4) presented with a left definite MD and the SIR was estimated at 1.64 at right and 1.98 at left. In the Gd-DOTA group, the patient (47 years-old female, BMI=22.5) presented with a right definite MD and the SIR was estimated at 1.03 at right and 0.74 at left.
Fig. 2: A-B: 3D-FLAIR axial slices at the level of the utricle in the Gd-DOTA group (A) in an 81 years-old female (BMI=31.2) with a left probable MD and the Gd-DO3A-butrol group (B) in a 56 years-old male (BMI=37.9) with a left definite MD. (A) The enhancement of the lateral (white dotted arrow) and the posterior (white arrowhead) semicircular canals is weak and the utricle in low-signal (white arrow) is barely visible. (B) By contrast, in the Gd-DO3A-butrol group (B), the enhancement of the lateral (grey dotted arrow) and posterior (grey arrowhead) semicircular canals is strong and the utricle (grey arrow) in low-signal is surrounded by the perilymph in high-signal.

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Fig. 3: A-B: 3D-FLAIR axial slices at the level of the saccule in the same patients than the figure 3. In the Gd-DOTA group (A), the enhancement of the perilymph (white dotted arrow) and the posterior (white arrowhead) semicircular canal is low and the saccule in low-signal (white arrow) is barely visible. To the opposite, in the Gd-DO3A-butrol group (B), the enhancement of the perilymph (grey dotted arrow) and the posterior (grey arrowhead) semicircular canal is strong and the saccule (grey arrow) in low-signal is clearly observed.
Conclusion

The blood-perilymph barrier is similar to the blood-brain barrier allowing the penetration of low molecular-weight structures as taurine, mannitol, steroid hormones, drugs and Gd-contrast media [10].

Like Park et al [11] we have speculated that the differences in the physiochemical properties of Gd-contrast agents are determining factors to cross the blood-perilymph barrier. The concentration of Gd-DOA3-butrol is two times higher than the concentration of Gd-DOTA. The molecular weight is closely similar between the two Gd-contrast agents, however, the viscosity, the osmolality and the longitudinal relaxivity (r1) are higher with Gd-DO3A-butrol than with Gd-DOTA [12]. Contrast agents with higher r1 result with a higher signal on T1-weighted sequence [13]. We also believe that Gd-contrast agents with higher osmolality have more probability to come in contact with the surface of the blood-perilymph barrier and to pass it [11].

We showed that the SIR of the contralateral ear was significantly higher in the Gd-DO3A-butrol group than the Gd-DOTA group and that the visualization of different compartments of the inner ear after an intravenous administration of Gd-DO3A-butrol was better than with Gd-DOTA, allowing to discriminate the utricle from saccule in 85% of cases. Gd-DOTA does not allow the discrimination between the utricle and the saccule in cases without EH in 30% of cases rendering impossible the diagnosis of EH based on the saccular morphology [2,5]. The enhancement of both inner ears is crucial since 22 to 65% of MD patients could present bilateral EH with clinically silent ears [14].

The enhancement of the semicircular canals was significantly more displayed with Gd-DO3A-butrol (80%) than Gd-DOTA (20%). Interestingly, the BMI were closely similar between the two groups thus the enhancement of the perilymphatic space did not depend on the weight of the patients.
References


