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Postaurical injection is a systemic delivery supported by symmetric distribution of Gd-DOTA in both the ipsilateral and contralateral ears☆

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Abstract

Postaurical injection of therapeutics was recently applied in clinical practice to treat inner ear diseases based on supposed existence of a direct channel from the postaurical area to the inner ear. Doubting on the associated reports and aiming to provide evidence on the inner ear uptake mechanism, the present study tracked the dynamic distribution of gadolinium-tetra-azacyclo-dodecane-tetra-acetic acid (Gd-DOTA) in rat inner ears after postaurical injection using MRI. A targeted tympanic medial wall delivery was utilized as control. The results showed that, at the early time points after postaurical injection, Gd-DOTA distributed mainly in tissues surrounding the bulla, temporal bone and skull and neck space. In the inner ear, there was gradual uptake of Gd-DOTA on both the ipsilateral and contralateral sides with equal signal intensities. There was no sign of direct channel carrying the agent from the postaurical area to the inner ear. Targeted tympanic medial wall delivery induced significantly greater uptake of Gd-DOTA in the inner ear than did postaurical injection. At 30 min post-administration, targeted tympanic medial wall delivery yielded 4.6-folds higher signal intensity than did postaurical injection. The total dose of Gd-DOTA delivered by the targeted tympanic medial wall approach was only 0.1% of that delivered by postaurical injection. In conclusion, postaurical injection is a systemic administration, which is similar to hypodermic injection, rather than a focal delivery method. By contraries, targeted tympanic medial wall delivery induces fast and abundant uptake of Gd-DOTA in the ipsilateral inner ear without significant distribution in unwanted areas.

Keywords: Focal drug delivery; Inner ear; Intratympanic delivery; Hypodermic injection; Magnetic resonance imaging

1. Introduction

Focal drug delivery in inner ear therapy, especially through transtympanic injection, has recently gained increasing popularity, partially because of its convenience, efficiency, and reduced systemic drug exposure and associated adverse effects (Schuknecht, 1956; Zou et al., 2014). Alternatively, Yang et al. (2007) reported that postaurical single injection of betamethasone was more effective in treating intractable low-frequency sensorineural hearing loss than oral administration of Merislon and Sibelium for two weeks (Yang et al., 2007). Subsequently, postaurical injection of therapeutics was also employed to treat sudden deafness and tinnitus (Diao et al., 2013; Li et al., 2015; Wu et al., 2015). Potential existence of a direct transportation channel from the postaurical area to the inner ear was reported to support the postaurical injection approach (Lin and Yu, 2009). Postaurical injection reportedly induced greater distribution of gadolinium chelate in the inner ear of guinea pigs than did intravenous injection (Li et al.,

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2012). The authors believed that postaurical injection was a noninvasive method of focal drug delivery (Li et al., 2012).

I doubt on the reports associated with postaurical injection. Based on anatomy, there is no direct transportion channel from the postaurical area to the inner ear. Theoretically, postaurical injection is a type of hypodermic injection that would never induce different distribution of agents in the inner ear between the ipsilateral and the contralateral sides. Defining postaurical injection as a noninvasive method is conceptually incorrect because the needle has to penetrate the skin, which is an invasive procedure (Li et al., 2012). In order to support my opinion, the present study tracked the dynamic distribution of gadolinium-tetra-azacyclo-dodecane-tetra-acetic acid (Gd-DOTA) in the surrounding tissues and inner ear of rat after postaurical injection by following a previously reported protocol (the reported concentration should be 0.5 mol/L instead of 0.5 mmol/L) (Li et al., 2012).

2. Materials and methods

Nine male Sprague Dawley rats, weighing between 266 g and 635 g, were provided by and maintained in the Biomedicum Helsinki Laboratory Animal Centre of the University of Helsinki. Four rats were assigned in the experimental group of postaurical injection of Gd-DOTA and five rats were employed as controls receiving targeted tympanic medial wall delivery (Zou et al., 2011). All the animal experiments were approved by the Ethical Committee of the University of Tampere (permit number: LSLH-2006-4143/Ym23). Animal care and the experimental procedures were conducted in accordance with the pertinent European legislation. During the experiments, animals were anesthetized with isoflurane (Piramal Healthcare, Boise, USA) using a 5% isoflurane–oxygen mixture (flow-rate 1.0 L/min) for induction and 3% isoflurane–oxygen mixture for maintenance via a facemask with the animals' eyes protected with Viscotears® (Novartis Healthcare A/S, Denmark).

A 4.7 T MR scanner with a bore diameter of 155 mm (PharmaScan, Bruker BioSpin, Ettlingen, Germany) in combination with a dedicated rodent head coil (linear birdcage coil, diameter 38 mm) was used for *in vivo* MR measurements. The body temperature of the rat was maintained by circulating warm water and respiration was recorded using the Physio Tool-1.0.b.2 program (Bruker, Ettlingen, Germany). After postaurical injection of Gd-DOTA on the left side at a dosage of 1.5 mmol/kg, the rat was placed in the MR scanner with ears positioned at the isocentre for imaging. In the control group, 2.5 μl Gd-DOTA (0.5 mol/L) (0.0031 mmol/kg in average) was injected onto the tympanic medial wall of the left ear using the custom-made device that was previously reported and the rats were kept in a lateral position with the injected ear up for 15 min before imaging (Zou et al., 2011). After establishing inner ear geometry using a T2-weighted rapid acquisition with relaxation enhancement (RARE) sequence, the Gd-DOTA uptake in the inner ear was evaluated using a T1-weighted RARE sequence and a fluid-attenuated inversion-recovery (FLAIR) sequence for 2-dimensional (2D) and 3D images as reported earlier (Zou et al., 2011, 2012a). The parameters for these sequences are as follows. RARE sequence for T2-weighted 2D images: TR/TE_{eff} 2500/40 ms, RARE factor 8, matrix size 256 × 256, slice thickness 0.8 mm, FOV 5.0 × 5.0 cm^2, resolution 0.195 × 0.195 mm^2, NEX 3. RARE sequence for T1-weighted images: TR/TE_{eff} 500/10 ms, RARE factor 4, matrix size 256 × 192, slice thickness 0.5 mm, FOV 2.5 × 2.5 cm^2, resolution 0.098 × 0.13 mm^2, NEX 33. RARE sequence for T1-weighted 3D images: TR/TE_{eff} 500/12 ms, RARE factor 16, matrix size 64 × 64 × 64, FOV 0.89 × 0.89 × 0.89 cm^3, resolution 0.139 × 0.139 × 0.139 mm^3, NEX 2. FLAIR sequence for 2D images: TR/TE_{eff} 8000/40 ms, inversion time 1800 ms, RARE factor 16, matrix size 256 × 192, slice thickness 0.5 mm, FOV 3.0 × 3.0 cm^2, resolution 0.117 × 0.156 mm^2, NEX 7. In the group of postaurical injection, distribution of Gd-DOTA from the injection site towards the surrounding area was followed from 5 min through 42 min after injection. Distribution of Gd-DOTA in the inner ear was followed from 45 min through 101 min after injection. MRI was repeated in one rat one week after the injection. Animals in the control group were imaged at the time points of 30 min, 43 min, 60 min, 70 min, 4 h, 6 h, and 2 d after administration.

The ParaVision PV 4.0 (Bruker, Ettlingen, Germany) software was used for post-processing and quantification of MR images. The IBM SPSS statistics 23 software was employed for statistical analysis. Signal intensities in the region of interests (the scala tympani, scala vestibuli and vestibulum), and the average values between the ipsilateral and contralateral ears during the period of 45–101 min were compared using paired-samples *t*-test. Signal intensities in the ipsilateral inner ear of the targeted tympanic medial wall delivery group at the time points of 30 min and 60 min were compared to that of the postaurical injection group at time points of 45 min and 73 min using independent-samples *t*-test (this arrangement would not underestimate the inner ear signal in the postaurical injection group because the uptake did not reach a plateau during the observation time of 101 min). p-values below 0.05 were considered statistically significant.

3. Results

Dynamic distribution of Gd-DOTA in the injection area and surrounding tissues is demonstrated in Fig. 1. Owing to T_2*-related signal loss (Hagberg and Scheffler, 2013), the MRI signal in the center of injection site (fluid), which mainly located hypodermically, was fully eliminated during the observation period of 42 min, but Gd-DOTA was always detected in the skin (Fig. 1A–D). At 5 min after postaurical injection, Gd-DOTA distributed mainly in the tissues surrounding the bulla, temporal bone and skull on the ipsilateral side (Fig. 1A). At 42 min, Gd-DOTA arrived at the nearby neck space and the temporal bone and skull on the contralateral side (Fig. 1B and C). The signal in the inner ear was weak (Fig. 1D). In the control group of targeted tympanic medial wall delivery, Gd-DOTA was absent in the tissues surrounding the bulla. However, dynamic accumulation of Gd-DOTA in the