Diluted gadoteridol (ProHance®) causes mild ototoxicity in cochlear outer hair cells
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ABSTRACT

Visualization of Endolymphatic hydrops (EH) has become possible using three-dimensional fluid-attenuated inversion recovery (3-D FLAIR) magnetic resonance imaging (MRI). Direct intratympanic (IT) injection of gadolinium-based MRI contrast agents (GBCAs) has rapidly gained wide acceptance because images obtained after IT injections have higher quality than that of images obtained after routine intravenous injection.

Four types of GBCAs have been clinically used in Japan. These are Omniscan®, Magnevist®, and gadoteridol (ProHance®), each forming chelate complexes with gadolinium ions. The inner ear toxicity of gadolinium ions is well known. To avoid potential toxic effects of GBCAs, the gadolinium ion must be strongly held in the chelate complex [1]. Gadoteridol is the newest addition in the GBCA series. This contrast agent is non-ionic, with a unique macro-ring chelate structure. These features make it more stable and less prone to dissociation of gadolinium ions. Therefore, the newly developed gadoteridol may be less toxic than other GBCAs, but its effects on inner ear cells are still not clearly understood.

The specific aims of this study were twofold: (i) to document gadoteridol-induced alterations in guinea pig physiology using distortion product otoacoustic emission (DPOAE) after IT gadoteridol injection; and (ii) to assess the safety of gadoteridol in isolated guinea pig cochlear outer hair cells (OHCs).

METHODS AND MATERIALS

1. GBCA IT injection and DPOAE measurement

Animals
We used 12 adult pigmented guinea pigs (250-300g).

Experimental setup
Test solutions were prepared by diluting commercially available gadoteridol (ProHance®, Bracco Eisai Co. Ltd, Tokyo, Japan) by 8- or 16-fold with saline. The animals were divided into 8 groups (n = 4) and saline (control; n = 4) groups, and a test solution (0.1 ml) was injected into the left ear of each animal.

DPOAE measurement
DPOAE was measured using the CUBIS 3.00-C DPOAE system (Mimosa Acoustics, NJ, USA). The 2f1/f2 ratio was 1.2 and the intensity of the stimulus was 65 dB. To monitor hearing changes, DPOAE was measured before and 1, 2, and 4 weeks after IT injections of the test solutions. We defined the difference between DPOAE amplitude and background noise amplitude as the DPOAE level.

2. Effects of gadoteridol on the morphology of isolated guinea pig cochlear OHCs

Animals
We used 12 adult pigmented guinea pigs (300-500g).

Cell culture
All animals were anesthetized deeply with pentobarbital and then immediately decapitated. The temporal bones were quickly harvested. The organs of Corti were excised and bathed in Hank’s balanced salt solution (HBSS) buffered at pH 7.2 and 305 ± 2 mOsm with 10 mM HEPES. To obtain a primary culture of isolated OHCs, strips of the organ of Corti were incubated for 20 minutes in HBSS containing 0.25 mg/ml collagenase. Further dissociation was performed mechanically in a perfusion chamber. The isolated hair cells were collected for subsequent experiments.

RESULTS

Diluted gadoteridol decreases DPOAE levels only at high tone frequencies

DPOAE amplitudes were not decreased up to the background noise level at any frequency level except at F2 = 8016 Hz 4 weeks after application of 1/8 diluted gadoteridol (Fig. 1A, arrow).

Quantitative analysis 1 year after IT injection of test solutions revealed significant differences at F2 = 12000 Hz between 1/8 diluted gadoteridol and control (*P<0.05).

Diluted gadoteridol causes mild morphological changes in isolated OHCs

Table 1. Numbers of OHCs examined and Morphological changes in OHCs

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of OHCs</th>
<th>Morphological changes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/8 Gadoteridol</td>
<td>25</td>
<td>24% (6/25)</td>
</tr>
<tr>
<td>1/16 Gadoteridol</td>
<td>33</td>
<td>3% (1/33)</td>
</tr>
<tr>
<td>Saline</td>
<td>22</td>
<td>0% (0/22)</td>
</tr>
<tr>
<td>GdCl3 (2.36 mg/ml)</td>
<td>10</td>
<td>80% (8/10)</td>
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</table>

*P<0.05 in comparison with groups administered 1/16 gadoteridol and saline

CONCLUSIONS

1/16 diluted gadoteridol did not induce significant physiological (DPOAE) changes as compared to 1/8 diluted gadoteridol.

In the second set of experiments, cell shape changes were shown in 24% (6/25) and 3% (1/33) OHCs after application of 1/8 and 1/16 diluted gadoteridol, respectively. The occurrence of morphological damage was significantly lower after application of 1/16 diluted gadoteridol compared to 1/8 diluted gadoteridol. Future studies are necessary to confirm the usefulness of gadoteridol dilutions as contrast agents.

REFERENCES

