RESEARCH ARTICLE

Safety of Intratympanic Dexamethasone to Treat Inner Ear Diseases

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Abstract

Introduction: Corticoids are often used in medicine, mainly for their anti-inflammatory properties. Although their action in the inner ear is not well known, they are employed to treat diseases like sudden hypoacusis or Ménière's disease with good results. Nowadays, the intratympanic (IT) delivery is frequently used as a treatment strategy to reduce the systemic secondary effects of corticoids. Administering IT dexamethasone (DXM) is considered a safe treatment and does not alter the hearing function.

Objective: Demonstrate the safety of IT dexamethasone treatment at high doses over long periods.

Materials and method: This study forms part of a clinical trial. The sample comprises a group of patients with neoplastic disease, managed by using cisplatin. The treatment protocol consists in applying a daily IT dexamethasone dose of 8 mg/24 hour for the time that chemotherapy treatment lasts. The auditory threshold was evaluated by tone audiometry. A basal examination was performed and, before each cisplatin cycle, both treated ears and control contralateral ears were explored.

Results: Twenty-three patients were recruited with a mean age of 60 years. The mean IT dexamethasone treatment time, with a daily administered dose of 8 mg/mL, was 8.3 weeks, within a 2- to 18-week range and a median of 8 weeks. At the end of IT dexamethasone treatment, the difference between the mean auditory threshold between the treated and the control ears did not exceed 10 dB, which was considered to be clinically significant.

Discussion: The safety of IT treatment with corticoids has been demonstrated in experimental studies with animals, in which hearing did not become worse. In the works performed with patients diagnosed with sudden hypoacusis or Ménière's disease and treated with IT dexamethasone, the incidence of hypoacusis related to treatment was very low, although the typical characteristics of these pathologies may have influenced the results (fluctuating hypoacusis or spontaneous improvement). The data obtained in our study about previously healthy ears showed no significant hearing alterations in the ears treated with IT dexamethasone, even after maintaining treatment for longer periods and at higher doses than those of previously published works.

Conclusion: Using high doses of IT dexamethasone treatment for long periods does not lead to significant clinical hearing alterations in humans.

Keywords: Corticoids, Dexamethasone, Intratympanic treatment, Safety, Hypoacusis.

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Introduction

Corticoids are used in usual medical practice mostly for their anti-inflammatory properties.[1] The full action of corticoids inside the inner ear is not completely known. Apart from being anti-inflammatory, other mechanisms are proposed that could influence how the inner ear responds to treatment with corticoids. Some of these mechanisms include enhanced cochlear blood flow, antioxidant action, modulated ion homeostasis, or cellular apoptosis inhibitor effect.[2–4]

Corticoids are constituted by liposoluble molecules. They can penetrate cells by simple diffusion through either the lipid bilayer of the cell membrane[5] or corticoids bind to membrane receptors.[6,7] The presence of receptors for glucocorticoids in the cochlea has been demonstrated, as has an unequal expression in its different zones. The higher concentrations of receptors are found in neuronal cells, in the spiral ligament, and in vascular stria, and fewer receptors are detected in bristle cells.[8,9]

Corticosteroids, and dexamethasone in particular, are employed to manage various inner ear disorders, such as acoustic trauma,[10,11] sudden hearing loss,[2] Ménière's disease,[12] and tinnitus.[13,14] The most conclusive results are indicated for treating Ménière's disease and sudden hearing loss, for which oral, intravenous, and intratympanic (IT) corticoids are applied for lengthy periods.

Presently, IT delivery is one of the main strategies adopted to treat inner ear diseases. This application form has emerged as an alternative to manage certain illnesses in which treatment with oral or intravenous corticoids has proven efficiency. The purpose of this IT administration is to reduce systemic secondary effects and to reach higher local drug concentrations.[4,15]

The effectiveness of IT treatment can be altered by several factors,[16] of which the most important are the concentration of the administered drug and the contact time with the round window membrane.[17]

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The studies conducted by Spandow et al.[1] questioned the safety of topically applying corticoids to ears as these authors attributed a possible ototoxic effect. Nevertheless, the results obtained in subsequent works revealed that IT delivery is a safe and simple method to treat inner ear diseases if performed using local anesthetic during otorhinolaryngology consultations.[18,19]

The objective of this study is to demonstrate the safety of IT dexamethasone treatment applied at high doses for lengthy periods to maintain treated patients' hearing.

Materials and Method

The analyzed data form part of a clinical trial with Protocol Code: OTO4008, Number EudraCT: 2015-003953-16, entitled: "Clinical trial in phase IIIB to evaluate the efficacy of dexamethasone to protect irreversible hearing loss in patients on ototoxic cancer treatment". Otoprotection in cancer treatment.

The clinical trial has received a favorable report from the Ethical Committee of Clinical Research (CEIC) for meeting Good Clinical Practice rules. Eligible patients could only enroll after providing the informed consent approved by the CEIC.

The sample was made up of a group of patients from a tertiary hospital who had been diagnosed with neoplastic disease between May 2016 and April 2018. Of the inclusion criteria, the presence of cisplatin as the basis for the chemotherapy treatment protocol stood out. Our patients were aged 18 years or more with no previous hearing problems, except for presbycusis and/or acoustic trauma. Those patients with previous hearing diseases (Ménière's disease, sudden hearing loss, middle ear disease, inner ear autoimmune disease) were excluded, as were patients being treated with previous or simultaneous radiotherapy on head and neck, and those diagnosed with diabetes mellitus.

The treatment that the clinical trial evaluated is based on applying IT dexamethasone at a dose of 8 mg/mL via a device placed in their ear called Microwick®. It consists in transtympanic drainage, and a polyvinyl sponge that allows medication to pass from the external auditory canal (EAC) to the inner ear. The drug is administered to patients' EAC as drops. Treatment starts on the same day as patients undergo the first chemotherapy cycle, and continues up to 3 weeks after the last cisplatin cycle.

Only one ear was treated in each patient recruited for the clinical trial, while the contralateral ear was taken as the control. The treated ear was chosen randomly by a computer system.

The protocol consists in instilling 20 drops (1 mL/8 mg) of dexamethasone once a day while maintaining cisplatin treatment. Patients lie down with their head turned 45° toward their untreated side for 45 minutes to help medication passively move through a round window (Fig. 1).

With each patient, the IT dexamethasone treatment time was adapted to the chemotherapy protocol prescribed by the oncology service.

The auditory threshold was evaluated by tone audiometry. A basal examination took place before starting IT dexamethasone treatment, before each cisplatin cycle, and then every 2 or 3 weeks depending on the chemotherapy protocol.

Clinically significant hearing loss was defined in accordance with American Speech Language Hearing Association (ASHA) criteria as hearing loss of 20 dB, or more, at one frequency, or of at least 10 dB at two consecutive frequencies or more.[20]

To detect differences in both the experimental and control ear groups of >20 dB at one frequency or >10 dB at two consecutive frequencies, and bearing in mind that variability may range from 6 to 12 dB (standard deviations in published trials), we had to recruit a maximum of 23 patients.

A descriptive analysis was carried out with central tendency and dispersion measurements (quantitative variables) and absolute/relative frequencies (qualitative variables). Comparisons were made between groups using paired analysis tests (Student's *t* and analysis of variance (ANOVA) for paired data, or their nonparametric equivalents: Wilcoxon and Friedman). The changes in the different cycles attributed to treatment were estimated with a analysis of covariance (ANCOVA) by bearing in mind the baseline levels and fittings for the other variables. All the comparisons were interpreted with a 5% alpha risk (p <0.05). Calculations were performed with the PASW 18.0 statistics package (SPSS Inc.).

Results

The study recruited twenty-three patients, 18 men (78.3%) and 5 women (21.7%). Their mean age during their first visit was 60 years (standard deviation 7.5 years, range: 44.2–74.8 years).

Of our twenty-three patients, 12 had lung cancer (52.2%), 10 had bladder cancer (43.5%), and one diagnosed case presented cervical metastasis with a primary tumor of unknown origin (4.3%).

The right ear was treated in 47.8% of the cases (11 patients), and the left ear in 52.2% (12 patients).

The number of cisplatin cycles ranged between one and six. The mean daily IT dexamethasone treatment time was 8.3 weeks, within a 2- to 18-week range and a median of 8 weeks. Of all twenty-three patients, 47.8% received four cycles, which implied applying IT dexamethasone daily for between 8 and 12 weeks (Table 1).

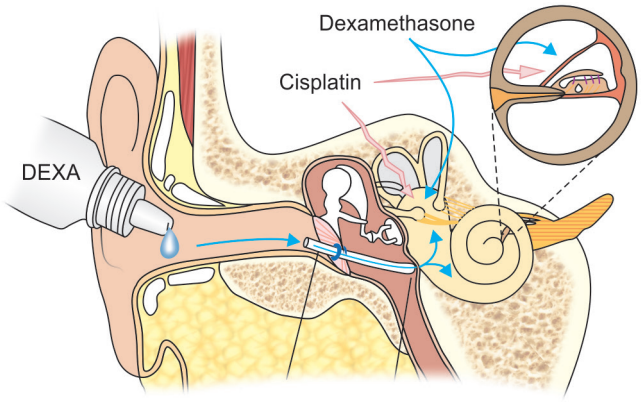
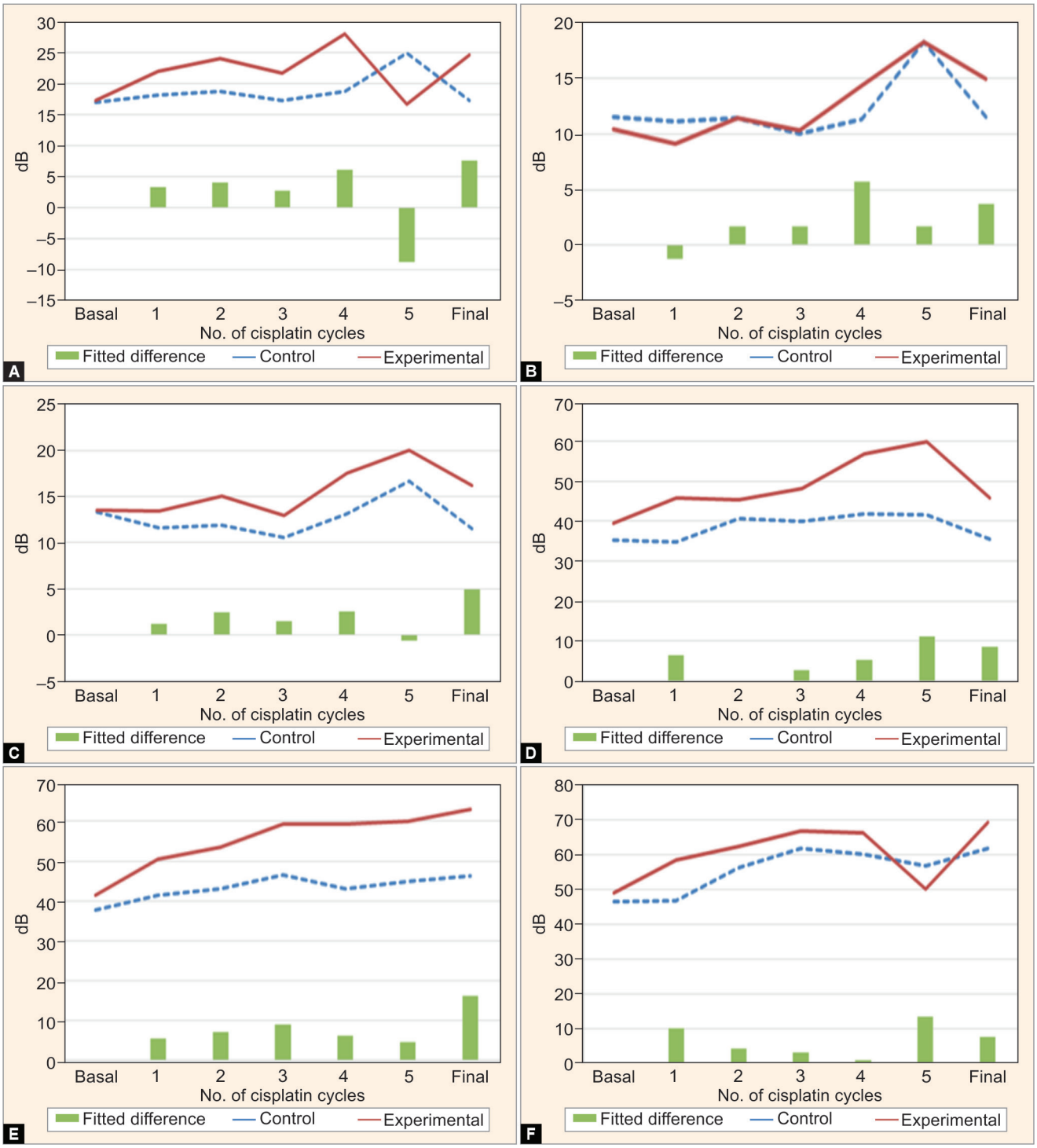


Fig. 1: Method to administer dexamethasone by Microwick®

Table 1: Treatment time with intratympanic dexamethasone (IT DXM) depending on the number of cisplatin cycles that patients received

Treatment time with IT DXM (weeks)	*No. of cisplatin cycles*	*Patients (n)*
18	6	1
15	5	1
12	4	4
9	3	4
8	4	7
6	3	1
3	1	3
2	1	2



Figs 2A to F: Comparative graphs of the mean auditory thresholds for the experimental ears group (unbroken red line) and the control ears group (dashed blue line) throughout intratympanic dexamethasone treatment at the different evaluated frequencies (A, 125 Hz; B, 250 Hz; C, 500 Hz; D, 4000 Hz; E, 6000 Hz; F, 8000 Hz)

The fitted difference in the low frequencies (125, 250, 500 Hz) between the two studied groups did not exceed 10 dB at any follow-up point (Fig. 2).

At the high frequencies (4000, 6000, 8000 Hz), fitted differences appeared for >10 dB after five treatment cycles at 4000 and 8000 Hz [fitted difference 11.2 (–30.9; 53.3) and 13.3 (–337; 364), respectively], and also in the final control at a frequency of 6000 Hz [fitted difference 16.0 (3.2; 28.7)].

Discussion

Nowadays, IT corticoids administration in different hearing diseases is usual to mainly treat sudden hearing loss and Ménière's disease.

Many authors consider it to be a safe treatment, and one that does not make the internal ear function any worse[21,22] despite no conclusive studies conducted in humans demonstrating this based on evidence and on risk-benefit evaluations.

Hearing loss is described for the possible complications of IT treatment with corticoids, along with pain, otitis media, perforated eardrum, and vertigo.[23]

Hence, some controversy exists about the time and dexamethasone dose to be used, and also about it causing ototoxicity or not.

The safety of IT treatment with corticoids has only been demonstrated in animal experiments. The study by Calli et al.[12] employed control animals that received only IT dexamethasone as a single dose (4 mg/mL) with no other ototoxic drugs. This study indicated no changes in the auditory threshold. Similar results have been reported in the work by Hill et al.,[24] who administered a higher IT dexamethasone dose in one ear (24 mg/mL), and saline solution in the contralateral ear, in a sample of mice. The auditory threshold measurements by brainstem-evoked potentials showed no changes in hearing in the IT dexamethasone-treated ears.

Auditory evaluations in humans have been analyzed for different dexamethasone doses, and dexamethasone is one of the most widely studied corticoids for IT use. Chandrasekhar et al.[25] treated eleven patients suffering sudden hearing loss with IT dexamethasone at doses of 2 and 4 mg/mL. They detected hearing loss in two treated ears. At a higher dose (8 mg/mL), other works have recorded no changes in hearing.[26] However at the same dose, the results obtained in the study of Arriaga et al. indicated that hearing became worse in three treated ears (20%).[27]

In larger series, like that published by Sakata et al., who administered IT dexamethasone to treat tinnitus in 1,466 ears and, despite their work not providing details about the audiometric results, these authors indicated no hearing loss after treatment.[28]

Most evaluated series have been made in patients diagnosed with Ménière's disease or sudden hypoacusis, and it is no easy task-relating cases of hearing loss with treatment because of the fluctuating nature of hypoacusis in Ménière's disease, and the possibility of the disease itself progressing or spontaneous recovery in sudden hearing loss.

Our study was conducted with healthy ears in people with no known hearing disease, which means that any auditory changes that took place could be due to chemotherapy treatment. The obtained results showed no clinically significant threshold differences in the examined ears between the experimental and control groups. Hearing slightly worsened in the experimental group, but no significant clinical changes took place according to the ASHA criteria.[20]

The dexamethasone doses employed to treat both sudden hearing loss and Ménière's disease in published studies were lower than those administered in our clinical trial, and our patients received dexamethasone daily for a long period (a mean of 8 weeks).

We found no published studies that reported using IT dexamethasone treatment for such a long time as that which we employed in our study.

The results of our study evidence the safety of IT dexamethasone treatment, as reflected by the fact that, despite having administered high doses of this drug for a long time, we found no toxic effects for the hearing of treated ears compared to untreated ears.

Conclusion

Using high doses of IT dexamethasone treatment for a long time does not lead to a significant and clinically worse hearing in humans.

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