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Potential ototoxicity from triamcinolone, neomycin, gramicidin and nystatin (Tri-Adcortyl™) cream

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Abstract

Although rare, ototoxicity from the use of aminoglycoside drops is well recognized. Ototoxicity has not been described with the use of combination aminoglycoside-steroid-antifungal creams or ointments. We present the case of a 60-year-old man with a perforated tympanic membrane who suffered a total hearing loss after the instillation of cream containing triamcinolone, neomycin, gramicidin and nystatin (Tri-Adcortyl™ cream) into his ear canal. On balance, we believe that a number of potentially ototoxic constituents in this cream were responsible. Other possible causes of sensorineural hearing loss and the possible mechanisms of ototoxicity of this cream are discussed. The reasons why such creams may be particularly ototoxic, compared with drops, are also considered. The authors caution against the use of such creams or ointments in the ear if there is any suspicion of a tympanic membrane perforation.

Key words: Cochlea; Toxicity; Triamcinolone; Neomycin; Gramicidin; Nystatin

Case report

A 60-year-old man with a long history of intermittently active, bilateral tympanic perforations was seen in the Ear, Nose and Throat (ENT) out-patient department, with a three-week history of discharge from his left ear. Examination revealed infected debris, a diffusely atelectatic tympanic membrane and an antero-inferior central perforation. A provisional diagnosis of active mucosal disease without cholesteotoma was made. He underwent microsuction and was treated with a seven-day course of topical antibiotic drops. This failed to resolve the infection and was therefore repeated six weeks later. In

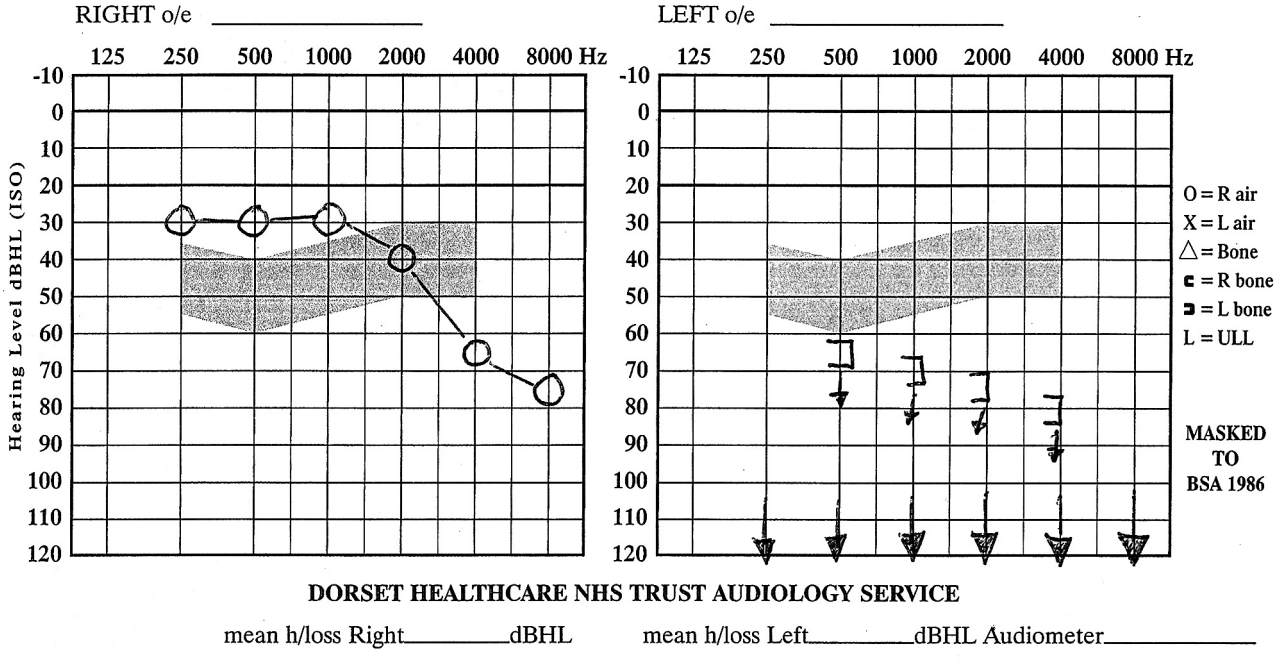

FIG. 1
Audiometry one month after the event.

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view of ongoing inflammation, triamcinolone, neomycin, gramicidin and nystatin (Tri-Adcortyl™) cream was applied to the surface of the tympanic membrane and associated granulation tissue. A month later the ear was dry but he complained that he could no longer hear anything in that ear. During microsuction at the previous visit, he could hear the sucker but shortly after instillation of the cream he developed marked pain in the ear, which was followed over the next few days by a decline in his hearing which failed to reverse. He denied any tinnitus or vertigo. Audiometry (see Figure 1) revealed a total hearing loss in the left ear. Subsequent blood tests, magnetic resonance imaging of the internal auditory meatus, computed tomography of the petrous bone and an examination of the ear under anaesthetic failed to uncover an alternative cause for his hearing loss. A medicolegal review of the case by an independent consultant concluded that '…on the balance of probabilities the hearing loss was caused by a direct toxic effect on the cochlea … by the combination of all the ingredients together' [i.e. in the cream].

Discussion

Ototoxicity from the use of aminoglycoside-containing drops is well recognized although the actual clinical risk is probably small.[1] However, we have not found in the world literature any reported cases of ototoxicity associated with creams or ointments containing an antibiotic-steroid combination (Medline, 1966 to the present). There are however a number of reasons why such creams may be particularly ototoxic compared with drops.

Firstly, these creams contain an aminoglycoside. The potential for drugs of this class to cause cochlear damage when applied to the middle ear is irrefutable in animal models.[2] The Committee on the Safety of Medicines recommends that the use of aminoglycoside ear drops is contraindicated when the tympanic membrane is perforated.[3] The British Association of Otolaryngologists and Head and Neck Surgeons has added an addendum to this advice,[4] in order to allow ENT surgeons to use these drops with caution and for limited periods of time. This advice relates to the use of drops; there is no specific guidance on the use of ointments.

In Tri-Adcortyl™ the aminoglycoside used is neomycin. This is known to be a particularly cochleotoxic aminoglycoside,[2] a feature which has limited its use to topical skin preparations and bowel sterilization. Certainly, one study has shown that long-term continuous treatment of chronic otitis media with topical drops containing neomycin, polymixin B and dexamethasone caused significantly greater sensorineural hearing loss than occurred in the untreated group.[5]

Secondly, the Triadcortyl™ cream preparation contains a number of other potentially ototoxic nonactive constituents (see Table I). Of these, polypropylene glycol,[6] ethanol[7] and benzyl alcohol[8] have been shown to cause ototoxicity in experimental animals. In addition, polypropylene glycol caused granulation tissue in the middle ear and destruction and ossification of the auditory bulla of rodents.[6] The cream also contains the potentially toxic ingredients hydrochloric acid and ethylene diamine. Although untested in animal ear models, the latter has been shown to be a potent sensitizer of asthmatic and skin reactions.[9]

Thirdly, whilst drops have a tendency to run out of the ear canal or down the eustachian tube, a cream or ointment persists for longer periods of time, allowing for more sustained presence of any potential ototoxic constituents in the vicinity of the round window.

The exact mechanism by which our patient developed a sensorineural hearing loss is not clear. Our patient describes a clear temporal relationship between the instillation of the cream and the onset of pain and hearing loss. This suggests that the cream itself is to blame rather the previous courses of aminoglycoside-containing drops or the ongoing infection itself. The absence of vertigo also makes a traumatic injury from microsuction or the cream instillation less likely. Although unlikely, the possibility of a completely coincidental, idiopathic sensorineural hearing loss cannot, however, be excluded.

TABLE I

INGREDIENTS OF TRI-ADCORTYL™ CREAM AND OINTMENT

Active ingredients
Triamcinolone acetonide 0.1%
Neomycin (as sulphate) 0.25%
Gramicidin 0.025%
Nystatin 100 000 units/g
Other ingredients
Cream
Aluminium hydroxide
Antifoam emulsion
Benzyl alcohol
Ethanol
Ethylenediamine
Hydrochloric acid
Macrogol ether
Perfume
Polysorbate 60
Propylene glycol
Sorbitol
Titanium dioxide
White soft paraffin
Water
Ointment
Liquid paraffin
Polyethylene resin

- **This is a case report of total sensorineural hearing loss following the instillation of cream containing triamcinolone, neomycin, gramicidin and nystatin (Tri-Adcortyl™ cream) to an ear with a tympanic membrane perforation**
- **The combination of neomycin and the excipients benzyl alcohol, propylene glycol, ethanol, hydrochloric acid and ethylene diamine may have acted synergistically to cause middle ear inflammation and cochlear damage, rendering the preparation particularly ototoxic**

Our patient developed marked pain in the ear within hours of instillation of the cream. The therapeutic instillation of aminoglycosides in the middle ear, such as in the treatment of Ménière's syndrome, is usually painless, suggesting that it was not the constituent to blame. However, the more vestibulotoxic aminoglycoside gentamicin, rather than neomycin, is usually used.

As mentioned above, a number of excipient ingredients have been shown to be ototoxic in animal models; propylene glycol in particular also has the potential to cause middle ear inflammation. This may have accounted for the pain that our patient experienced. The sustained presence of a combination of several different ingredients may have acted synergistically, firstly to cause middle ear mucosal inflammation and then cochlear damage leading to sensorineural hearing loss.

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We are aware of the use of antibiotic-steroid-containing ointments and creams in treating patients with otitis externa and discharging mastoid cavities (some of whom may have tympanic defects). It should be pointed out that only Tri-Adcortyl™ *ointment* and Tri-Adcortyl™ *otic ointment* (the same ointment packaged in a smaller tube with an otic nozzle) are licensed for use in the ear canal. These do not contain the potentially toxic excipients present in the cream preparation (see Table I). In our unit, the *cream* preparation has been completely withdrawn. The authors caution against the use of such preparations if there is any suspicion of an underlying tympanic membrane perforation.

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Mr S P Thomas takes responsibility for the integrity of the content of the paper.
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