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Main Articles

Topical aminoglycosides in the management of active mucosal chronic suppurative otitis media

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Abstract
Debate has currently re-emerged following a renewed warning issued from the Committee on the Safety of Medicines (CSM) regarding the relative risk of ototoxicity from the use of aminoglycoside-containing drops in patients with tympanic membrane perforations. We present the findings of a survey of ENT consultants, questioning their views and current practice, and we add to the debate by means of a review and discussion of the literature.

Key words: Otitis media, suppurative; Therapy; Toxicity

Methods and results

A questionnaire was issued to all consultant members of the BAORL (British Association of Otorhinolaryngologists – Head and Neck Surgeons) living within the UK and Ireland, with a reply rate of 308/525. The questionnaire enquired if they routinely used topical aminoglycoside-containing drops as part of their management of active mucosal chronic suppurative otitis media (CSOM), offering only a yes/no alternative, of which 93 per cent did. We subsequently asked if they believed there was a definite risk of ototoxicity when using these drops in ears with a known tympanic membrane perforation, again limiting replies to yes and no, of which only 48 per cent thought there was. Finally we asked those who thought there was a risk, but still used them, how they justified this risk; the results of which are found in Table I.

TABLE I
QU: IF YOU BELIEVE THAT THERE IS A RISK OF SENSORINEURAL HEARING LOSS WITH AMINOGLYCOSIDE CONTAINING DROPS IN THE MANAGEMENT OF ACTIVE MUCOSAL CSOM, BUT STILL USE THEM, HOW DO YOU JUSTIFY THIS RISK?

	Numbers
The risk is no greater than the risk imposed by active infection	64
Because the risk is so small	63
There is only a risk in cases of prolonged use	42
The benefits justify the risks	27
There is no risk when the middle ear mucosa is inflamed	14
Because I have never seen a case	18
There are no non-surgical alternatives	10
Oral medication is ineffective	4

N.B. Respondents not limited to a single choice.

Discussion

It is estimated that approximately five per cent of adults within the UK have chronic suppurative otitis media, of whom at any one time approximately two per cent will have an associated mucopurulent discharge indicating active infection (Browning *et al.*, 1988). Hence much time and resources are involved in the management of these patients by both primary care physicians and specialists. In 1997 a current review circulated by the CSM warned of the risks of ototoxicity when using aminoglycoside-containing drops in any ear with a perforated tympanic membrane (that we must presume includes those patients with active mucosal chronic suppurative otitis media). This differed from their previous publication in 1981 warning against the use of such topical agents in the management of otitis externa with a co-existing tympanic membrane perforation. This more specific warning seemed to highlight the possibility that in the process of treating a patient's otitis externa, one may get potentially ototoxic drops into a non-diseased middle-ear cleft, if they have a co-existing tympanic membrane perforation. The renewed warning therefore advocates we preclude the use of aminoglycoside-containing drops in the

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management of active mucosal chronic suppurative otitis media; an issue which is now central to current debate.

The use of aminoglycoside-containing drops stems from its wide spectrum of antibacterial activity, its efficacy against the commonest organism cultured in active CSOM; *Pseudomonas aeruginosa* (Kenna *et al.*, 1986; Wintermeyer and Nahata, 1994; Yuen *et al.*, 1995) and the relative resistance of this organism to the more commonly used antibiotics. It must still seem bizarre to many specialities outside our field that we continue to use potentially ototoxic aminoglycosides. The vestibulotoxic effects of intratympanic gentamicin are well documented in the treatment of incapacitating Menière's disease, albeit in much higher concentrations (i.e. ± 24 mg per ml for chemical ablation versus 4 mg per ml in commercially available drops) (Marais and Rutka, 1998). Despite this, ototoxicity with such preparations is rarely reported (Murphy, 1970; Dumas *et al.*, 1980; Nomura, 1984; Podoshin *et al.*, 1989). Some of these cases involve the administration of drops in the absence of inflammatory middle-ear oedema and in other cases it is difficult to separate aminoglycoside ototoxicity from the ototoxic effect of the infection itself, which is a commonly recognized complication of CSOM (Hulka, 1941; Paparella *et al.*, 1970; Kawabata, 1971; Paparella *et al.*, 1972; English *et al.*, 1973). A recent literature review looked at nine (12 ears) well documented, incontrovertible cases of iatrogenic vestibulotoxicity in patients using a topical aminoglycoside-containing preparation, Garasone™, in ears with documented tympanic membrane perforations. Presentation in six out of nine cases was with an acute unilateral vestibular loss following topical treatment for unilateral disease, whilst three out of nine presented with bilateral peripheral vestibular losses following topical treatment for bilateral disease. At the time of onset of vestibular symptoms, the mean length of time that the drops had been used for was 5.4 weeks, and they had been continued, on average, for 18.4 days after the cessation of otorrhoea (Marais and Rutka, 1998).

Animal models usually using guinea pigs or chinchillas, which demonstrate ototoxicity with topical aminoglycosides, are less than ideal cross species comparisons because of anatomical differences. The anatomical relationship between the round window and tympanic membrane differs between humans and guinea pigs and chinchillas. The human round window is thicker compared to that of a rodent, also often being protected by an epithelial membrane (Meyerhoff *et al.* state that the human round window membrane is approximately 60 μm thick, and approximately 13–15 μm in the chinchilla) (Meyerhoff *et al.*, 1983). It may be that there is little risk of ototoxicity in active mucosal disease because of round window protection by thickened mucosa, and the presence of mucopus and fibrous bands (Newsletter BAORL, 1998). Animal studies have shown that when Eustachian tube dysfunction or middle-ear disease exist, concerns about otic drops reaching the round window are probably not justified (Meyerhoff *et al.*, 1983). Interestingly, it has been reported that in people with an inflamed middle ear mucosa, there is an increased perilymph concentration of gentamicin after systemic absorption (Voldrich, 1965). We often assume that the reported ototoxic effects of preparations are solely due to round window penetration, but seeing that routine aminoglycoside levels are not measured in these patients, this must remain an assumption. In a recent case report, a 62-year-old patient with chronic renal failure was found to have a serum gentamicin level of 6.2 μg/ml after using two Gentisone HC™ drops three times a day, for 37 days duration (Green *et al.*, 1997).

Little meaningful data is available to evaluate the relative risk of using these preparations in CSOM. Given the estimated risk of ototoxicity, the large numbers of patients needed in such a trial would probably preclude anyone from undertaking it (Browning *et al.*, 1988). In a trial performed by Browning *et al.* in 1988, 55 patients used Gentisone HC™ (four drops qds) for a four to six week period, having been deemed to be suffering from active mucosal chronic suppurative otitis media on clinical grounds. He showed that both the AC and BC thresholds failed to vary any more than they did in the untreated contralateral ear of the same patient or in a matched ear treated with placebo (McKelvie *et al.*, 1975; Browning *et al.*, 1988). In another study of 150 patients with sensorineural hearing loss and chronic otitis media, Podoshin states that the mean deterioration in bone conduction thresholds of patients treated with topical drops containing neomycin, polymyxin B and dexamethasone was 6.0 dB over 1.5 years or mathematically 4 dB a year (n = 124 with 64 per cent having otorrhoea which was purulent in 73 per cent of cases). This appears quite impressive when compared to the mean yearly sensorineural hearing loss of their patients with untreated chronic otitis media (1.5 dB). However the treated group also includes patients treated with topical aminoglycosides for a continuous period of follow-up of 1.5 years. Patients treated for a total of not more than six months of topical agents over the same period of follow-up only developed a mean sensorineural hearing loss of 1.8 dB, and even these patients massively exceed the current recommendation of a maximum of 10 days treatment with topical aminoglycoside-containing drops (Newsletter BAORL, 1998).

When completing their questionnaire, several members expressed an interest in topical ofloxacin as an alternative to topical aminoglycosides, and *in vitro* susceptibility results do indicate that ofloxacin can be an effective antibiotic in the treatment of active CSOM (Yuen *et al.*, 1995). Ofloxacin's spectrum of activity includes *S. aureus*, *Pseudomonas aeruginosa*, *Proteus mirabilis* and *Haemophilus influenzae* and is not known to be ototoxic when given either orally or topically (Gehanno-Cohen, 1993).

The question of ototoxicity with topical aminoglycosides will no doubt appear in and out of the literature for many years to come, unless someone provides conclusive data one way or the other from a large numbered randomized control trial. In the mean time, if non-ototoxic preparations (e.g. ofloxacin) do become widely available, and their efficacy is shown to be comparable with aminoglycosides as some evidence suggests (Gehanno and Cohen, 1993; Sumitsawan *et al.*, 1995; Jones *et al.*, 1997) then surely it would be a common sense substitution in the management of active mucosal CSOM.

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