The Journal of Laryngology & Otology (2007), ***121***, *333–337.*

doi:10.1017/S0022215106004932
Printed in the United Kingdom
First published online 30 November 2006

Main Article

Topical antibiotic ototoxicity: does it influence our practice?

E C Ho, A Alaani*, R Irving†

Abstract

Introduction: We hypothesised that general practitioners and ENT specialists manage discharging ears differently. This study was designed to investigate this further.

Methods and materials: Postal questionnaires were sent to all general practitioners in the Birmingham area and all UK consultants on the British Association of Otolaryngology–Head and Neck Surgery address list.

Results and discussion: In the presence of an intact tympanic membrane, 99 per cent of consultants and 90 per cent of general practitioners would use topical antibiotics. In the presence of a perforated tympanic membrane, 97 per cent of consultants would continue to use topical antibiotics, compared with only 43 per cent of general practitioners. This was attributed to a fear of ototoxicity. If a topical non-ototoxic antibiotic of proven efficacy could be made available, 93 per cent of consultants and 88 per cent of general practitioners in this study would seriously consider using it as first line treatment.

Conclusion: The majority of general practitioners would not use topical antibiotics in the presence of a perforated tympanic membrane. Most doctors would consider using a non-ototoxic topical antibiotic as first line treatment should one be made available.

Key words: Antibiotics; Topical Anti-infective Agents; Aminoglycosides; Quinolones; Otitis Media; Otitis Externa; Ototoxicity; Questionnaire

Introduction

A significant proportion of the patients referred by general practitioners to ENT out-patient departments have discharging ears that have been inadequately treated. At present, all currently licensed ototopical antibiotics in the United Kingdom are known to be ototoxic. To quote the *British National Formulary*:

> The CSM (Committee on Safety of Medicine) has stated that topical treatment with ototoxic antibiotics is contra-indicated in the presence of a perforation. However, many specialists use ear drops containing aminoglycosides (e.g. neomycin) or polymyxins if the otitis media has failed to settle with systemic antibiotics; it is considered that the pus in the middle ear associated with otitis media carries a higher risk of ototoxicity than the drops themselves.[1]

Bickerton *et al.*, in their 1988 survey, found that 66 per cent of North Staffordshire general practitioners would not prescribe topical medication if the tympanic membrane was perforated.[2] A 1991 study in south London showed that treatment of post-grommet otorrhoea with oral antibiotics alone was favoured by 66.7 per cent of general practitioners (*vs* 7.8 per cent of ENT consultants).[3]

The 2002 Cochrane review of interventions for chronic suppurative otitis media (CSOM) assessed 24 randomised trials involving 1660 patients. The conclusions regarding resolution of otorrhoea were: (1) topical antibiotics or antiseptics were better than systemic antibiotics; (2) topical antibiotics with aural toilet was the most effective treatment method; (3) topical antibiotics together with systemic antibiotics were no more effective than topical antibiotics on their own.[4]

What is the current practice in the United Kingdom? Based on our observations, we hypothesised that: (1) there was a dichotomy in the management of discharging ears, between general practitioners and ENT specialists; (2) in the presence of a perforated tympanic membrane, general practitioners were reluctant to use topical antibiotics, primarily due to concerns about ototoxicity; and (3) most doctors (general practitioners and specialists)

From the Department of ENT Surgery, Warwick Hospital, Warwick, the *Department of ENT Surgery, Derbyshire Royal Infirmary, Derby, and the †Department of ENT Surgery, Queen Elizabeth Hospital, Birmingham, UK.
Presented at the Royal Society of Medicine Section of Otology Short Papers Meeting, 2nd April 2004, London, UK.
Accepted for publication: 17 February 2006.

would consider using a non-ototoxic topical antibiotic as first line treatment should one be made available.

Methods and materials

To test our hypotheses, we designed a postal survey. A standardised questionnaire was sent to all general practitioners in the Birmingham area and all UK ENT consultants on the British Association of Otolaryngology–Head and Neck Surgery address list (see Appendix 1).

Results

The response rate at two months was 43 per cent (242/562) for general practitioners and 36 per cent (236/648) for ENT consultants. Three of the ENT consultants did not manage adults on a regular basis, which left 233 valid, completed questionnaires in the consultant group. We analysed the results that were pertinent to this paper. For statistical analysis, we used the chi-square test.

Prior to initiating treatment, 12 per cent of general practitioners and 26 per cent of consultants reported taking a microbiology swab. In the presence of an intact tympanic membrane, 99 per cent of consultants and 90 per cent of general practitioners would use topical medication as first line treatment. An overwhelming majority of consultants (90 per cent) would use a topical medication on its own, whilst only 54 per cent of general practitioners would do so. A combination of oral and topical treatment would be given by 9 per cent of consultants and 36 per cent of general practitioners. Only one (0.4 per cent) consultant would prescribe an oral antibiotic on its own as first line treatment, compared to 9 per cent of general practitioners (Table I).

In the presence of a perforated tympanic membrane, or if the tympanic membrane could not be visualised, 97 per cent of consultants would still use topical antibiotics (alone or in combination with oral antibiotics) as first line treatment, versus 43 per cent of general practitioners. Out of the 218 general practitioners who were happy to prescribe topical antibiotics (alone or in combination) if the tympanic membrane was intact, only 104 (48 per cent) would continue to do so if the tympanic membrane was perforated. These figures included the 25 per cent of consultants and 29 per cent of general practitioners who would use combination treatment. More consultants (72 per cent) would use topical medication on its own, compared with general practitioners (15 per cent) (Table I).

The most popular topical antibiotics amongst both consultants and general practitioners were Gentisone, Sofradex, Otomise and Locorten-Vioform (Table II). Interestingly, 16 per cent (38/233) of consultants were already using quinolone (ciprofloxacin and ofloxacin) eye drops in the presence of a perforated tympanic membrane (i.e., an unlicensed indication) (Table II). An analysis of these 38 consultants showed that 82 per cent (31/38) would prescribe a non-quinolone medication if the tympanic membrane was intact.

Sixty-one per cent of consultants and 70 per cent of general practitioners reported that the ototoxic risk of topical antibiotic use in cases of tympanic membrane perforation was of concern and influenced their practice (Table III). Should a topical non-ototoxic antibiotic of proven efficacy (i.e. as good as or better than the currently available antibiotic) be made available, 93 per cent of consultants and 88 per cent of general practitioners reported that they would seriously consider using it as first line treatment (Table III).

Discussion

This study demonstrated that, contrary to the Committee on Safety of Medicines reminder but in line with the Cochrane review findings, the overwhelming majority of ENT consultants would use a topical

TABLE I

RESPONSES TO QUESTIONS 2 & 3

	Cons*		GPs†		p‡
	% (n)	Rx (days) [Mean (range)]	% (n)	Rx (days) [Mean (range)]	
Question 2					
In the presence of an intact TM, my first line treatment would be:					
(a) Topical medical (alone)	90 (210)	10.5 (5–42)	54 (131)	9.6 (5–28)	<0.001
(b) Oral antibiotics (alone)	1 (1)	7 (7)	9 (21)	8.8 (5–14)	<0.001
(c) Combination topical & oral	9 (22)	10.3 (7–14)	36 (87)	9.4 (5–42)	<0.001
(d) Topical (alone or in combination)	99 (232)		90 (218)		<0.001
Question 3					
In the presence of a perforated TM, my first line treatment would be:					
(a) Topical medical (alone)	72 (167)	10.4 (7–42)	15 (35)	8.9 (7–21)	<0.001
(b) Oral antibiotics (alone)	1 (2)	10.8 (7–14)	55 (132)	7.0 (5–21)	<0.001
(c) Combination topical & oral	25 (59)	9.6 (7–14)	29 (69)	9.2 (5–42)	0.43
(d) Topical (alone or in combination)	97 (226)		43 (104)		<0.001

*$n = 233$. †$n = 242$. ‡Comparing number of consultants (Cons) and general practitioners (GPs). Rx = treatment; TM = tympanic membrane

https://doi.org/10.1017/S0022215106004932 Published online by Cambridge University Press

TABLE II

TOPICAL ANTIBIOTICS USED AS FIRST LINE TREATMENT

Antibiotic	Intact TM (*n*)		Perforated TM (*n*)	
	Cons	GPs	Cons	GPs
Gentisone	79	61	72	21
Sofradex	68	48	77	9
Otomise	41	53	27	14
Locorten-Vioform	18	34	9	13
Otosporin	6	5	5	0
Ciprofloxacin	7	0	31	0
Ofloxacin	0	0	7	0

Note that the majority of respondents gave one answer, but more than one answer was also accepted. TM = tympanic membrane; Cons = consultants; GP = general practitioners

antibiotic regardless of the status of the tympanic membrane. However, in the presence of a perforated tympanic membrane, 57 per cent of general practitioners would not use a topical antibiotic; this was attributed to the fear of ototoxicity. If a topical non-ototoxic antibiotic of proven efficacy were made available, 93 per cent of consultants and 88 per cent of general practitioners in this study would seriously consider using it as first line treatment. A study in 1993 (before non-ototoxic topical antibiotics were available) suggested a similar attitude and practice amongst United States otolaryngologists.[5]

It was first demonstrated in 1986 that topically applied aminoglycosides easily penetrate the round window membrane.[6] The use of topical gentamicin for therapeutic vestibular ablation in cases of Ménière's disease is also well established.[7] What then, is the risk of ototoxicity from ototopical antibiotics? In a survey of 2235 United States otolaryngologists, 3.4 per cent stated that, during their lifetime practice, they had witnessed antibiotic-related ototoxicity.[5] However, in a subanalysis of 11 trials within the 2002 Cochrane review, there was negligible or no change in hearing levels following topical treatment.[4]

TABLE III

RESPONSES TO QUESTIONS 4 & 5

	Cons* [% (*n*)]	GPs† [% (*n*)]	*p*
Question 4			
The ototoxic risk of topical antibiotic with TM perforation is of concern and influences my practice	61 (141)	70 (168)	0.042
Question 5			
If a topical non-ototoxic antibiotic with proven efficacy as good as or better than the currently available antibiotic were made available, I would seriously consider using it as first line treatment	93 (216)	88 (214)	0.112

*$n = 233$; †$n = 242$. TM = tympanic membrane

In their prospective study of 150 patients, Podoshin *et al*. (1989) found that patients with CSOM who were treated with topical antibiotics experienced a significant worsening of sensorineural hearing loss compared with those treated with topical steroids alone. This was more likely to occur in patients who had a prolonged, continuous course of treatment.[8]

The precise incidence of iatrogenic ototoxicity attributed to topical antibiotics is difficult to quantify. Seven cases have been reported in the English literature.[9–13] Roland (1994) reviewed 41 cases of ototoxicity reported in the literature (many in foreign language articles) and felt that many of the reports did not conclusively prove that the ototoxicity was iatrogenic in nature.[14] Roland also analysed Lundy and Graham's 1993 paper[5] and estimated the incidence of iatrogenic 'otoxicity' at less than 1 in 10 000.[14] On the other hand, Kellerhals (1978), in his survey of Swiss otolaryngologists, estimated the risk at approximately 1 in 3000.[15] An attempt to report a larger series was hampered by poor documentation which meant that many suspected cases of sensorineural hearing loss could not be conclusively classified as iatrogenic.[13]

Ototoxicity encompasses both cochleotoxicity and vestibular toxicity, either in isolation or combination. Most articles have addressed sensorineural deafness in isolation. Antibiotics identified as ototoxic include framycetin, polymyxin B, neomycin and gentamicin.[13,14,16] Many aminoglycosides (especially gentamicin) are predominantly vestibulotoxic rather than cochleotoxic. Marais and Rutka (1998) believed that iatrogenic vestibulotoxicity due to topical antibiotics was under-recognised, as there was a tendency to attribute any vestibular symptoms to the 'natural course' and symptoms of otitis media.[17]

The first case of iatrogenic vestibulotoxicity was reported by Leliever in 1985.[10] This was followed by another two cases reported by Longridge in 1994.[12] Wong and Rutka (1997) and Bath *et al*. (1999) then reported larger series of five and 22 cases, respectively.[18,19] Many patients sustained some sensorineural hearing loss as well, and some were left with disabling vestibular symptoms.

A huge variety of micro-organisms have been cultured from the ears of patients with CSOM. Pseudomonas species were the commonest bacteria found in many studies, constituting between 48.6 and 72 per cent of CSOM cultures.[12,20,21,22] In the presence of cholesteatoma, pseudomonas was also more frequently found.[23] Topical quinolones such as ciprofloxacin and ofloxacin have a spectrum of activity against *Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*[16] and methicillin-resistant *S aureus*.[24] An *in vitro* study showed that topical quinolones compared well against polymyxin B but were far superior to neomycin in treating pseudomonas species.[25] Clinical studies confirmed the efficacy of quinolones in treating CSOM when given orally[26,27] and

https://doi.org/10.1017/S0022215106004932 Published online by Cambridge University Press

topically, even in the presence of pseudomonas.[20,28] Quinolones are more effective than non-quinolones, according to the conclusions of both the Cochrane review[4] and another systematic review.[29]

So far, none of the quinolones have been shown to be ototoxic. In animal testing, topically applied ciprofloxacin has been shown not to cause any significant hearing loss nor any histological evidence of hair cell loss.[20] Certain ingredients of topical antibiotic drops (not exclusive to the quinolones), such as benzalkonium chloride, can cause middle-ear mucosal changes which can result in small but insignificant conductive hearing losses.[30] Furthermore, clinical trials involving ciprofloxacin[28] and ofloxacin[31] have not demonstrated any ototoxic effects.

- **It has been established that topical antibiotics are better than systemic antibiotics in the treatment of discharging ears**
- **Ototoxic topical antibiotics carry a theoretical iatrogenic ototoxic risk, but this is difficult to quantify**
- **Topical quinolones have been proven safe and effective for topical aural use**
- **This study found that a majority of general practitioners in the west Midlands region would not use topical antibiotics in the presence of a perforated ear drum for fear of ototoxicity**
- **However, an overwhelming majority of general practitioners and ENT consultants would consider using a non-ototoxic topical antibiotic (e.g. quinolones) if made available**

The American Academy of Otolaryngology–Head and Neck Surgery 2000 consensus panel report has recommended the following: (1) the initial treatment of healthy patients with uncomplicated CSOM and acute otitis externa should consist of ototopical drops and aural toilet; (2) in healthy patients with uncomplicated acute otitis externa, any topical antibiotic can be used as first line treatment, including the aminoglycosides; (3) in healthy patients with uncomplicated CSOM, a non-ototoxic topical antibiotic such as the quinolones should be considered as first line treatment; (4) oral antibiotics should be added if there are any complications, concurrent respiratory infections or systemic symptoms, and other risk factors such as craniofacial anomalies, Down's syndrome and immunocompromise; and (5) use of systemic antibiotics should be guided by microbiological culture.[16]

Conclusion

An overwhelming majority of the general practitioners and consultants responding to our questionnaire indicated that they would consider using a non-ototoxic topical antibiotic as first line treatment, should one be made available. Topical quinolones have been proven effective and safe for aural use. Currently, none of the quinolone preparations have been licensed for aural use in the UK. Nevertheless, that has not deterred some ENT consultants from using ciprofloxacin and ofloxacin optic preparations in the ear, especially when a tympanic membrane perforation is present. The efficacy of these optic preparations could be suboptimal as they lack the beneficial effects of the steroids found in the aural preparations, which are not available in the UK.

Even though the response rates to our questionnaire were less than 50 per cent, we feel that the results should not be ignored. In our cohort of responders, an obvious, dichotomous pattern in the treatment of patients with discharging ears was demonstrated. While the degree of this dichotomy may have differed with a higher response rate, it would be highly improbable that such a difference would disappear. Quinolone ototopical drops are already widely used in the United States, in many European countries and in Australia. Are there good reasons why non-ototoxic ototopical antibiotics still remain unlicensed in certain countries?

Acknowledgements

We thank Peter Nightingale (Statistician, Wellcome Trust Clinical Research Facility) for providing statistical support. This work was supported by an unconditional grant from Alcon Laboratories UK.

References

1 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary 49*. London: Pharmaceutical Press: 2005;540
2 Bickerton RC, Roberts C, Little JT. Survey of general practitioners' treatment of the discharging ear. *Br Med J (Clin Res Ed)* 1988;**296**:1649–50
3 Robb PJ, Johnston D. The clinical management of otorrhoea following grommet insertion: a survey of otolaryngologists and general practitioners. *Clin Otolaryngol* 1991;**16**:367–70
4 Acuin J, Smith A, Mackenzie I. Interventions for chronic suppurative otitis media (Cochrane Review). In: *The Cochrane Database*. Oxford. [www.cochrane.org/reviews]
5 Lundy LB, Graham MD. Ototoxicity and ototopical medications: a survey of otolaryngologists. *Am J Otol* 1993;**14**:141–6
6 Harada T, Iwamori M, Yoshitaka N, Nomura Y. Ototoxicity of neomycin and its penetration through the round window membrane into the perilymph. *Ann Otol Rhinol Laryngol* 1986;**95**:404–8
7 Blakley BW. Update on intratympanic gentamicin for Meniere's disease. *Laryngoscope* 2000:**110**:236–40
8 Podoshin L, Fradis M, David JB. Ototoxicity of ear drops in patients suffering from chronic otitis media. *J Laryngol Otol* 1989;**103**:46–50
9 Tommerup B, Moller K. A case of profound hearing impairment following the prolonged use of framycetin ear drops. *J Laryngol Otol* 1984;**98**:1135–7
10 Leliever WC. Topical gentamicin induced positional vertigo. *Otolaryngol Head Neck Surg* 1985;**93**:553–5
11 Lind O. Deafness after treatment with ear drops containing neomycin, gramicidin and dexamethasone. A case report. *J Otorhinolaryngol* 1986;**48**:52–4
12 Longridge NS. Topical gentamicin vestibular toxicity. *J Otolaryngol* 1994;**23**:444–6
13 Linder TE, Zwicky S, Brandle P. Ototoxicity of ear drops: a clinical perspective. *Am J Otol* 1995;**16**:653–7

14 Roland PS. Clinical Ototoxicity of topical antibiotic drops. *Otolaryngol Head Neck Surg* 1994;**110**:598–602
15 Kellerhals B. Risk of inner ear damage from ototoxic eardrops [in German]. *HNO* 1978;**26**:49–52
16 Hannley MT, Denneny JC, Sedory Holzer S. Consensus panel report – use of ototopical antibiotics in treating 3 common ear diseases. *Otolaryngol Head Neck Surg* 2000; **122**:934–40
17 Marais J, Rutka JA. Ototoxicity and topical eardrops. *Clin Otolaryngol* 1998;**23**:360–7
18 Wong DLH, Rutka JA. Do aminoglycoside otic preparations cause ototoxicity in the presence of tympanic membrane perforations? *Otolaryngol Head Neck Surg* 1997;**116**:404–10
19 Bath AP, Walsh RM, Bance ML, Rutka JA. Ototoxicity of gentamicin preparations. *Laryngoscope* 1999;**109**:1088–93
20 Aslan A, Altuntas A, Titiz A, Arda HN, Nalca Y. A new dosage regimen for topical application of ciprofloxacin in the management of chronic suppurative otitis media. *Otolaryngol Head Neck Surg* 1998;**118**:883–5
21 Kenna MA. Microbiology of chronic suppurative otitis media in children. *Ped Infect Dis* 1986;**5**:223–5
22 Brook I, Finegold SM. Bacteriology of chronic otitis media. *JAMA* 1979;**241**:487–8
23 Karma P, Jokipii L, Ojala K, Jokipii AMM. Bacteriology of the chronically discharging middle ear. *Acta Otolaryngol* 1978;**86**:110–14
24 Ikeda K, Takasaka T. In vitro activity of ototopical drops against middle ear pathogens. *Am J Otol* 1993;**14**:170–1
25 Dohar JE, Kenna MA, Wadowsky RM. In vitro susceptibility of aural isolates of *Pseudomonas aeruginosa* to commonly used ototopical antibiotics. *Am J Otol* 1996;**17**: 207–9
26 Papastavros T, Giamarellou H, Varlejides S. Preoperative therapeutic considerations in chronic suppurative otitis media. *Laryngoscope* 1989;**99**:655–9
27 Piccirilo JF, Parnes SM. Ciprofloxacin for the treatment of chronic ear disease. *Laryngoscope* 1989;**99**:510–13
28 Esposito S, D'Errico G, Montanaro C. Topical and oral treatment of chronic otitis media with ciprofloxacin. A preliminary study. *Arch Otolaryngol Head Neck Surg* 1990;**116**:557–9
29 Generoso A, Espallardo N, Tong M, Subramaniam KN, Hermani B, Lasiminigrum L *et al*. A systematic review of the effectiveness of ofloxacin otic solution for the treatment of suppurative otitis media. *ORL J Otorhinolaryngol Relat Spec* 2003;**65**:106–16
30 Brownlee RE, Hulka GF, Prazma J, Pillsbury HC. Ciprofloxacin – use as a topical otic preparation. *Arch Otolaryngol Head Neck Surg* 1992;**118**:392–6
31 Ohyama M, Shigeru F, Ueno K, Katsuda K, Nobori T, Kiyota R *et al*. Ofloxacin otic solution in patients with otitis media – an analysis of drug concentrations. *Arch Otolaryngol Head Neck Surg* 1999;**125**:337–40

Appendix 1. Suppurative ear disease management questionnaire

A) My practice includes adult patients with discharging ears: Yes No
B) I routinely take a microbiology swab prior to initiating treatment: Yes No
C) I routinely perform aural toilet as part of my initial management: Yes No
D) I routinely refer patients for aural toilet as part of my initial management: Yes No

In the case of an adult with a discharging ear (either chronic or acute):

1) My plan of management depends on the presence of an intact tympanic membrane: Yes No
2) In the presence of an intact tympanic membrane, my first line treatment would be:
   a) Topical aural treatment drops/sprays: Yes No
      Preferred topical aural treatment/medication:___
      Period of initial prescription:___
   b) Oral antibiotics: Yes No
      Preferred oral antibiotic:___
      Period of initial prescription:___
   c) A combination ototopical medication and oral antibiotic: Yes No
      Preferred treatment/medication:___
      Period of initial prescription:___
   d) Other: Please state:___
3) ln the presence of a perforated tympanic membrane or if the tympanic membrane cannot be visualised, my first line treatment would be:
   a) Topical aural treatment/drops/sprays: Yes No
      Preferred topical aural treatment/medication:___
      Period of initial prescription:___
   b) Oral antibiotics: Yes No
      Preferred oral antibiotics:___
      Period of initial prescription:___
   c) A combination of topical medication and oral antibiotic: Yes No
      Preferred treatment/medication:___
      Period of initial prescription:___
   d) Other: Please state:___
4) The ototoxic risk of topical antibiotic with tympanic membrane perforation is of concern and influences my practice: Yes No
5) lf a topical non-ototoxic antibiotic with a proven efficacy as good as or better than the currently available topical antibiotic was made available, I would seriously consider using it as first line treatment: Yes No

Comments:___

(Note that question D was deleted from the version of the questionnaire sent to ENT consultants).

Address for correspondence:
Mr E C Ho
59 Spiceland Road,
Birmingham B31 1 NL, UK.

E-mail: euchinho@yahoo.co.uk

Dr Eu Chin Ho takes responsibility for the integrity of the content of the paper.
Competing interests: None declared