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Ciproxin HC eardrops application for funding

The New Zealand Society of Otolaryngology Head and Neck Surgery (NZSOHNS) published a position statement on the use of potentially ototoxic topical antibiotic ear drops in the *New Zealand Medical Journal*, 20-July-2007, Vol 120 No 1258 (http://www.nzma.org.nz/journal/120-1258/2646). The NZSOHNS recommended avoiding, wherever possible, the use of potentially ototoxic drops in patients with ears at risk and this is consistent with Australian and American recommendations.

The only ototopical antibiotic medication available in New Zealand (NZ) which to date has not been shown to be ototoxic isciprofloxacin with hydrocortisone (Ciproxin HC). Unfortunately it is not funded in NZ and therefore significantly more expensive than commonly available and potentially ototoxic eardrops.

Last year the NZSOHNS made an application to PHARMAC for funding of ciprofloxacin with hydrocortisone eardrops (Ciproxin HC). Regrettably, PHARMAC has now declined this application.

In contrast to the NZSOHNS opinion, in their response PHARMAC maintains that there was no evidence that ciprofloxacin with hydrocortisone (Ciproxin HC) was a better or safer alternative to commonly funded antibiotic eardrops. Safety in the presence of a tympanic membrane perforation was not proven and not guaranteed by the manufacturer.

The New Zealand Society of Otolaryngology Head and Neck Surgery stands by their position statement (below). Further efforts to achieve funding for ciprofloxacin with hydrocortisone eardrops will be made.

STATEMENT FROM THE NEW ZEALAND SOCIETY OF OTOLARYNGOLOGY HEAD AND NECK SURGERY ON THE USE OF EARDROPS WITH OTOTOXIC POTENTIAL IN THE PRESENCE OF TYMPANIC MEMBRANE PERFORATION, VENTILATION TUBES AND MASTOID CAVITIES WITH OPEN MIDDLE EAR

1. It is preferable to use non ototoxic drops in the presence of tympanic membrane perforation, ventilation tubes and mastoid cavities with open middle ear.
2. If potentially ototoxic eardrops are used then they should be used only in the presence of infection and discontinued immediately after infection has resolved. The treatment should preferably be limited to a maximum of two weeks.
3. If potentially ototoxic eardrops are prescribed for the treatment of ear infection, with either a tympanic membrane perforation, ventilation tube or open middle ear/mastoid cavity, then the reason for use and the potential ototoxicity should be discussed with the patient/parent and documented (risk 1:1,000 to 1:10,000).
4. If potentially ototoxic drops are prescribed, then the patient should be advised to return to the doctor if vertigo, hearing loss or tinnitus develop during or soon after treatment.
5. Use of potentially ototoxic eardrops is acceptable in the presence of an intact tympanic membrane.

William J Baber
President

Michel Neeff
Secretary

New Zealand Society of Otolaryngology Head and Neck Surgery
Auckland

Response from PHARMAC

Thank you for the opportunity to respond to Drs Baber and Neef about ciprofloxacin/hydrocortisone (Ciproxin HC) eardrops.

Clinical aspects of this issue are explained by the relevant minutes of the Pharmacology and Therapeutics Advisory Committee (PTAC), available online at http://www.pharmac.govt.nz/2008/02/01/PTAC%20minute%20-%20February%202008.pdf. The application, for the treatment of otitis media with tympanic membrane perforation and associated conditions such as chronic suppurative otitis media, was considered by PTAC at its February 2008 meeting.

In essence, PTAC has recommended that the application for funding be declined because of insufficient evidence to suggest greater efficacy than currently funded ear drops or better safety in the presence of tympanic membrane perforation. The Committee also suggested the applicants approach the manufacturer for evidence on safety of use and, if applicable, request a change in the manufacturer's data sheet to reflect this. (PTAC had noted that the data sheet (http://www.medsafe.govt.nz/profs/datasheet/c/Ciproxinhcotic.htm) indicates that safety and efficacy have not been studied in the presence of a perforated tympanic membrane, and the eardrops are therefore contraindicated in patients with known or suspected perforation, or where there is a risk of perforation).

Note: The relevant record from that meeting is as follows; sections of the minute have been withheld under Section 9 (2)(a) of the Official Information Act 1982, as indicated by "[ ]".

Peter Moodie
Medical Director
PHARMAC

Relevant minutes of the Pharmacology and Therapeutics Advisory Committee Meeting held on 21 & 22 February 2008:

Ciprofloxacin/Hydrocortisone (Ciproxin HC) for treatment of otitis media with a perforated tympanic membrane (TM) and associated conditions such as chronic suppurative otitis media (CSOM)

The Committee reviewed applications from Dr J Gathercole and the New Zealand Society of Otolaryngology Head and Neck Surgery for the listing of ciprofloxacin 0.2% with hydrocortisone 1.0% ear drops (Ciproxin HC) on the Pharmaceutical Schedule for the treatment of otitis media with a perforated tympanic membrane (TM) and associated conditions such as chronic suppurative otitis media (CSOM).

The Committee noted that an earlier application for the funding of ciprofloxacin with hydrocortisone ear drops was made in 2003 and at that time the Antibiotic Subcommittee recommended declining the application in light of concern about quinolone resistance and insufficient information supplied to validate the statements made in the application.

The Committee noted that the New Zealand Society of Otolaryngology Head and Neck Surgery and Dr Gathercole were concerned about the ototoxic potential of currently funded aminoglycoside ototopical agents when used to treat middle ear infections in the presence of a non-intact tympanic membrane. Members noted that both applicants suggest ciprofloxacin with hydrocortisone ear drops are non-ototoxic and should be funded.

The Committee reviewed the evidence provided by both applicants and further evidence regarding efficacy of ototopical quinolones, ototoxicity of aminoglycoside ear drops 0and antibiotic resistance from the use of ototopical agents.

Members considered that evidence for efficacy of ciprofloxacin with hydrocortisone ear drops in otitis media with perforated TM was limited. The Committee reviewed one randomised, double blind, controlled trial (*Couzos et. al. MJA, 2003*) comparing topical 0.3% ciprofloxacin with framycetin (0.5%), gramicidin and dexamethasone (Sofradex) for CSOM in 147 children aged 1-14 years. A highly significant absolute difference of 24.6% in clinical cure (resolution of otorrhoea) was reported in favour of ciprofloxacin compared with Sofradex (76.4% vs 51.8%; P=0.009). However, only those children who had a post-treatment assessment (n=111) were included in the statistical analysis; an intention-to-treat analysis was not undertaken. There was no difference in TM perforation size or hearing.

The Committee noted further evidence regarding the efficacy of topical quinolones (without steroid) from two Cochrane reviews by Macfadyen et.al., 2005 and Macfadyen et.al., 2006 (*Macfadyen et.al., The Cochrane Library, 2007*). The reviews indicated that topical quinolones were superior to systemic antibiotics and topical antiseptics but the difference between topical quinolones and non-quinolones was unclear. The reviewers considered that the studies evaluated in the reviews were of varying methodological quality and poorly reported, and while the evidence presented related to short-term clearance of aural discharge, long-term outcomes and safety were unclear.

The Committee noted the position statement from the New Zealand Society of Otolaryngology Head and Neck Surgery on the use of potentially ototoxic ear drops. Members considered that the statement is consistent with Australian and American guidelines and that there is a small risk of ototoxicity (in the order of 1:1000 to 1:10,000) from the use of ototopical aminoglycosides in situations where there is a direct pathway to the middle ear. Members also noted that the Society recommends, where possible, avoiding the use of potentially ototoxic ear drops in the presence of a non-intact TM.

The Committee reviewed further evidence regarding ototoxicity of aminoglycoside ear drops from a review by Roland et al (*Otolaryngology – Head and Neck Surgery, 2004*) and Matz et al (*Otolaryngology – Head and Neck Surgery, 2004*) and noted that the evidence was largely from animal studies with some case reports in humans. Members noted that there are anatomical differences between the human ear and experimental animal ear and, as such, data needs to be extrapolated with caution. Members also considered that ototoxicity in humans may be underappreciated because the earliest and most severe auditory manifestations may occur at higher frequencies which are usually not tested in humans; the vestibular manifestations, if unilateral, may be subtle; and some damage may be misattributed to the condition.

The Committee also noted an opinion from [ ], consultant otolaryngologist regarding ototoxicity of ototopical ear drops. The Committee noted [ ] views on the use of ototoxic ears drops and [ ] concern around the safety of quinolone ear drops and antibiotic resistance. The Committee noted that there was no evidence provided in support of [ ] view. The Committee agreed that there was insufficient evidence regarding the safety of quinolone ear drops when used in the presence of a non-intact TM.

The Committee noted that quinolone resistance has been raised as a concern because of increasing quinolone use. The Committee reviewed evidence from a review by Weber et al (*Otolaryngology – Head and Neck Surgery, 2004*) on development of resistance with the use of ototopical antibiotics. The Committee noted that there was grade B evidence to indicate that no significant antibiotic resistance develops from use of ototopical antibiotics. Members noted further support for this from a review article by J Kline (*Amer J Managed Care, 2002*), which recommends using ototopical antibiotics rather than systemic antibiotics for treating middle ear infections to reduce the risk of developing bacterial resistance. The Committee also noted the opinion of Dr Mark Thomas, a member of the Anti-infective Subcommittee, who considered that the use of ciprofloxacin ear drops would provide relatively minor selection pressure for emergence of resistant organisms.

The Committee acknowledged the New Zealand Society of Otolaryngology Head and Neck Surgery's concern around the medico-legal risk from the use of potentially ototoxic ear drops in treatment of otitis media in the presence of a non-intact TM. However the Committee noted that potentially ototoxic ear drops had been used, off-label, to treat middle ear infections in the presence of a non-intact TM for many years and considered that the risk of ototoxicity from aminoglycoside ear drops was low.

The Committee considered that there may be an unmet need for a safer alternative in certain populations such as low socio-economic, Maori, and Pacific Island people in whom chronic middle ear conditions are more prevalent.

However, the Committee considered that there was insufficient evidence to suggest ciprofloxacin with hydrocortisone ear drop were a safer alternative to use in the presence of a non-intact TM. The Committee noted that the manufacturer of ciprofloxacin with hydrocortisone ear drops states that the safety and efficacy of ciprofloxacin with hydrocortisone ear drops have not been studied in the presence of a perforated tympanic membrane and ciprofloxacin with hydrocortisone ear drops are, therefore, contraindicated in patients with known or suspected perforation, or where there is a risk of perforation of the tympanic membrane.

The Committee **recommended** that the application for funding of ciprofloxacin 0.2% with hydrocortisone 1.0% ear drops (Ciproxin HC) be declined because of insufficient evidence to suggest that they were more efficacious than currently funded ear drops or were safer to use in the presence of a non-intact TM.

The Committee also suggested that the applicants approach the manufacturer for evidence on safety of using ciprofloxacin with hydrocortisone ear drops to treat otitis media in the presence of a TM perforation and if applicable, a change in the manufacturer's data sheet recommendation to reflect this.

The Decision Criteria relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (vii) The direct cost to health service users, and (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.