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A Benefit-Risk Assessment of Ofloxacin Otic Solution in Ear Infection

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Contents

Abstract

Ofloxacin is a fluoroquinolone antibacterial with potent bactericidal activities and the topical otological preparation of this drug has been clinically utilised since the late 1980s. The rate of eradication with ofloxacin ranges from 83.3% to 100% for all pathogens commonly isolated from middle ear effusions in cases of otitis media and otitis externa. Despite the significant length of its usage, emergence of resistant pathogens has been rarely encountered in clinical trials; only two strains

of *Pseudomonas aeruginosa* have been documented with decreased susceptibility to ofloxacin following the use of the otic solution.

Ear infections, including otitis externa, chronic suppurative otitis media and otorrhoea associated with tympanostomy tubes, are common problems in clinical practice. The potential complications associated with ear infection can be otological, extratemporal, or even psychosocial. They are sometimes fatal and the effect can be long-lasting and detrimental. The use of an effective topical antibacterial with high cost-effectiveness is definitely warranted. As regards various clinical aspects, including overall success rate, symptomatic relief of otalgia and otorrhoea, ofloxacin otic solution was found to be more effective than comparator agents, be it a topical antibacterial, a systemic antibacterial or combination drugs.

The systemic absorption of fluoroquinolones is minimal after topical application. Ofloxacin otic solution 0.3% has been shown to have a low rate of adverse drug reactions. Adverse reactions to ofloxacin otic solution were generally mild. The lack of ototoxic effect from ofloxacin eardrops, even in the concentration higher than 0.3%, has been demonstrated in animal studies. In the clinical setting, no increase in bone-conduction threshold has been shown after the treatment of topical ofloxacin otic solution. There have not been any reports of ototoxicity with ofloxacin otic solution since its approval.

To conclude, ofloxacin otic solution 0.3% is clinically effective in the treatment of otitis externa and chronic suppurative otitis media in particular with respect to the overall cure rate, relief of otalgia and otorrhoea. It is well tolerated, with minimal adverse effects. It is not associated with any ototoxicity both experimentally and clinically.

1. Ofloxacin Otic Solution

1.1 General Overview

Ofloxacin is a fluoroquinolone antibacterial with potent bactericidal activity against Gram-positive and Gram-negative organisms. It was first launched in Japan in June 1985. The ofloxacin otic solution was initially launched in Asian countries including China and Hong Kong, and became widely available in North America, Europe and Australia in the 1990s.

Topical ofloxacin otic solution 0.3% was approved by the US FDA for the treatment of otitis externa in adults and children in 1997. It was the first ototopic antibacterial to gain approval for acute otitis media in children with tympanostomy tubes, and in chronic suppurative otitis media in adolescents (≥12 years) and adults with chronic perforation of the tympanic membrane, which are its main indications for use in clinical practice.

An ideal topical agent applied to the ear should be effective against the common pathogens in ear infections without causing any ototoxic effects. It should have a high local drug concentration with minimal systemic absorption to have a maximal local effect against bacterial activities without a risk of systemic adverse effects. Ofloxacin, which is not associated with ototoxicity and can achieve high local concentrations when used topically, is a drug potentially capable of fulfilling these requirements.[1,2] Safety issues in terms of hearing impairment have always been the main concern. This will be discussed in section 6.2.

1.2 Global Consumption

Annual consumption of ofloxacin otic solution globally has been significant. In the US the equivalent of more than 2 million bottles of the

standard 5mL pack size of ofloxacin otic solution were sold in 2001. According to recently available US data (March 2002), 34% of usage was made by paediatricians, 26% by primary-care physicians, 22% by otorhinolaryngologists, 2% as an emergency medication, and 16% was by other sources.[3]

In Asia, more than 850 000 bottles of ofloxacin otic solution were cumulatively sold in the year 2001 in the markets of China, Korea, Taiwan, Philippines, Indonesia, Hong Kong, Thailand, Malaysia and Singapore. In Japan more than 1.7 million bottles were sold in the same year. From a retrospective analysis done in Japan in 1999 over a 4-year period, of the 3381 patients using ofloxacin otic solution, 14% of patients were treated for otitis externa while 84% were treated for various forms of otitis media.[4]

1.3 Chemical Structure and Preparation

The commercially available proprietary ofloxacin otic solution 0.3% is a sterile aqueous antiinfective (antibacterial) solution for otic use. The ofloxacin molecule has three condensed 6-membered rings that are made up of a fluorinated carboxyquinolone with a benzoxazine ring. Its chemical name is (±)-9- fluoro-2,3-ihydro-3-methyl -10-(4-methyl-l -piperazinyl)-7-oxo-7H-pyrido [1,2,3-de]-1, 4-benzoxazine-6-carboxylic acid. The empirical formula of ofloxacin is C18H20FN3O4 and its molecular weight is 361.38. The otic solution contains 0.3% (3 mg/mL) ofloxacin, the preservatives benzalkonium chloride (0.0025%), sodium chloride (0.9%), and water for injection. Hydrochloric acid and sodium hydroxide are also added to adjust the pH to the near neutral of 6.5 ± 0.5.[5]

1.4 Mechanism of Action

The principal target of ofloxacin is the A unit of DNA gyrase. Through antagonising the activity of DNA gyrase, ofloxacin inhibits the detachment and winding of the superhelixes of bacterial chromosomes in growing bacteria. Consequently, the reading of the genes and therefore the synthesis of protein are blocked.[6] This characteristic mechanism of so-called gyrase antagonists does not lead to plasmid-induced resistance as easily as does the use of beta-lactam antibacterials.[6] Its strong and rapid bactericidal effects explain its high efficacy against many microbes.[7] Besides, by having good tissue penetration, ofloxacin poses advantages in the treatment of ear infections.[8,9]

1.5 Pharmacodynamics and Pharmacokinetics

In vitro activity of an antibacterial is assessed according to the minimal inhibitory concentration required for 50% or 90% of strains (MIC_{50} and MIC_{90}, respectively). According to the US National Committee for Clinical Laboratory Standards (NCCLS), the susceptibility breakpoint for ofloxacin is ≤2 mg/L.[10] This breakpoint is calculated for systemically administered drug. The local concentration of ofloxacin achieved under standard dosage of the otic solution is 3000 mg/L.[8,9] Under this remarkably high concentration, the topically administered ofloxacin is expected to have greater bacterial efficacy. A review by Simpson et al.[7] showed that, with ofloxacin treatment, the rate of eradication ranged from 83.3% to 100% for all pathogens commonly isolated from middle ear effusions in cases of otitis media and otitis externa. Besides, the rate of persistence/recurrence was also very low (<0.3%). This makes ofloxacin a good choice of antibacterial for ear infections.

1.6 Drug Resistance

Antibacterial resistance is always a concern. The possible mechanisms of drug resistance include promoting the emergence of mutant resistant organisms, or allowing the overgrowth of organisms inherently resistant to the antibacterial agent administered. The mechanisms of developing resistance to fluoroquinolones, including ofloxacin, involve alterations in the A subunit of DNA gyrase which will lead to decreased affinity for the fluoroquinolones. Changes in the outer membrane porin proteins or other factors that affect the membrane permeability of the organism, will also result in diminished accumulation of the drug inside the cell. In almost all

cases, resistance to ofloxacin is chromosomal-related rather than plasmid-mediated.

Spontaneous mutations that reduce fluoroquinolone susceptibility usually result in only modest increase of the MIC of 2- to 8-fold, and these were demonstrated to be rare in an *in vitro* study.[11] Mutation frequencies were originally estimated to be between 10^{-9} and 10^{-11} but data from the same study indicated a higher frequency. Among the organisms responsible for ear infections, *in vitro* resistance to ofloxacin can be produced in certain strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus* by serial passage in the presence of increasing concentration of the drug. Two or more mutations are required for the emergence of highly resistant strains for most organisms. Large increase in MIC values (≥16-fold) occurred in 19% of strains (including *P. aeruginosa* and *S. aureus*) exposed to super inhibitory concentration of ofloxacin *in vitro*. As reviewed by Simpson et al.,[7] concern about the emergence of resistant pathogens was not supported by data from clinical trials; only two strains of *P. aeruginosa* were documented with decreased susceptibility to ofloxacin following the use of the otic solution. The clinical observation thus confirmed the rare occurrence of bacterial resistance predicted in *in vitro* studies.

2. Prevalence of Ear Infections

2.1 Otitis Externa

The bony external ear canal is lined by a thin layer of stratified squamous epithelium. Otitis externa, infection of the external ear canal, is a common disorder in clinical practice. Infection is often introduced by minor abrasions or injuries to the layer or by the presence of water in the ear canal. It is therefore a very common condition among swimmers and in warm and humid climates. An estimated 10% of all persons have had an acute otitis externa infection at some time in their lives.[12] From the 1998 National Ambulatory Medical Care Survey and the National Hospital Medical Care Survey for office, outpatient department and emergency department visits, there were about 2 247 000 visits with International Classification of Disease (ICD)-9 codes 380.1 (otitis externa infective) and 380.2 (otitis externa other), and this accounted for 0.22% of all visits.[13]

2.2 Chronic Suppurative Otitis Media

Chronic otitis media (chronic middle ear infection) is also a common condition in otological practice. Often a long history of recurrent ear discharge (otorrhoea) with multiple doctor visits is given. Despite advances in public health and medical care, chronic suppurative otitis media is still prevalent around the world. The prevalence of chronic otitis media in developing countries is higher than that in developed countries, and is in relation to the level of hygiene, living environment, availability of medical service and antibacterials. Certain racial groups such as Maoris of New Zealand, Australian Aborigines and Native Americans and Canadians are particularly prone to chronic middle ear suppurations.[14] The overall prevalence was reported to be 0.94–6.86%,[15-17] a figure not to be ignored in clinical practice. In developing countries and among various disadvantaged indigenous population groups in developed countries, it therefore remains a major cause of ear pathologies.[14]

2.3 Otorrhoea Associated with Tympanostomy Tubes

The insertion of grommets (also known as ventilation or tympanostomy tubes) is one of the most common surgical procedures performed on children. In the US, it was reported that more than 1 million such procedures were performed each year.[18] In England, for the year 2000–2001, 41 619 patients had grommets inserted.[19] There are two main indications for this operation: one, for adequate ventilation of the middle ear with resolution of the 'glue-ear' (chronic otitis media with effusion), and the other, to prevent recurrent acute otitis media (middle ear infections). Unfortunately, postoperative otorrhoea (ear discharge) is the most common complication, with a reported incidence ranging from 10 to 50%,[20,21] and may occur shortly after insertion or at any time until the grommet is extruded. Children

with tympanostomy tubes inserted, therefore, constitute a special high-risk group for ear infections.

3. Potential Complications of Ear Infections: Risks of No Treatment

In the pre-antibacterial era, it was not uncommon to see women succumb to puerperal infections and children to complications from ear infections. Although fatal complications are much less common nowadays, without treatment, ear infection can result in significant morbidity. In a group of patients who had continuous or intermittent purulent ear discharge which lasted for months or even years, there was gradual destruction of the bones of the middle ear, resulting in worsening conductive as well as sensorineural hearing impairment.[22] Besides, other complications of ear infections can also affect the inner ear and the extra-temporal region. Therefore, the sequelae of ear infections should not be understated.

3.1 Middle Ear and Inner Ear Complications

Middle ear complications include tympanosclerosis, adhesions or scarring of the middle ear, cholesterol granuloma and bony destructions of the ossicles. Inner ear complications include labyrinthitis and vestibular dysfunction, which can result in balance problems. Cochleitis can cause sensory hearing loss. Erosion of the infected area into the facial nerve can lead to facial nerve paralysis.

3.2 Extratemporal Complications

Extratemporal complications are the most serious potential complications in ear infections. These can include petrositis of Gradenigo's syndrome, an infection of the apex of the petrous region of the temporal bone, resulting in cranial nerve palsies. Furthermore, due to the proximity of the ear to the thin dural plate protecting the brain, unchecked infection has the potential to erode into the brain itself, resulting in meningitis, encephalitis or brain abscess, which can be fatal. The annual risk in an adult with active chronic otitis media of developing an abscess is about one in 10 000. Serious intracranial complications developed in about 3% of cases without the use of antibacterials. However, with the use of antibacterials, the incidence of intracranial complications has fallen to about 0.15%.[23]

3.3 Developmental and Psychosocial Sequelae

Hearing loss is an obvious result of damage to any of the functional parts of the auditory system. The severity of hearing loss experienced can be of mild or moderate grade severity (≥40dB) and is generally related to the duration of the infection, with chronic and recurrent otitis media more problematic than acute otitis media. Loss of hearing in young children is a serious situation that has many potential developmental and psychosocial sequelae including speech and language problems. When it occurs during the first 2 years of life, the consequent hearing loss may have serious effects on the critical period of a young child's language development, and can cause significant delays in school progress.[24]

In view of these potential complications that are sometimes fatal and can cause long-lasting detrimental effects, the use of an effective antibacterial is highly justified in the management of active ear infections.

4. The Efficacy and Benefit of Ofloxacin Otic Solution for Ear Infections

The cost of systemic antibacterial treatment and hospitalisation is high when compared with ambulatory treatment in the form of topical antibacterials. Besides, medical services are relatively deficient in developing countries. The fact that ear infections are more prevalent in developing countries may have an influence in the choice of the appropriate form of treatment. In view of the financial status and the prevalence of ear infections in developing countries, a treatment with high cost-effectiveness would have an obvious advantage and a much greater impact.

In subsequent paragraphs, we will discuss the treatment effectiveness of ofloxacin otic solution and other topical or systemic antibacterials in detail. The efficacy of antibacterial treatment in otitis externa, chronic suppurative otitis media and tympa-

nostomy tube otorrhoea are discussed in accordance with the indications for use of ofloxacin.

4.1 Otitis Externa

Otitis externa is a bacterial or fungal infection of the skin of the external auditory canal. This commonly seen condition has a higher prevalence in summer months. The most common bacterial pathogens are *P. aeruginosa* and *Staphylococcus* species. Diagnosis is made clinically with otalgia, otorrhoea and swollen mucosa under otoscopic examination and empirical treatment could be instituted. In the immunocompromised or diabetic patient, necrotising or 'malignant' otitis externa can occur and it is a very serious condition requiring systemic antibacterial treatment. In most cases of uncomplicated otitis externa, in addition to meticulous aural cleansing, topical antibacterials serve as the first-line treatment. Meatal external auditory canal swelling can be treated by inserting a gauze wick impregnated with an antimicrobical drug into the ear canal to keep it open. In the management of otitis externa, the integrity of the tympanic membrane may not be assured as the swollen and tender canal can deter an accurate otoscopic examination. Under these circumstances, the ototoxic potential of the topical antibacterials should be considered as the drug can enter the ear canal and then in turn penetrate the inner ear through an undiscovered tympanic membrane defect.

Jones et al.[25] performed a prospective controlled study to compare the safety and efficacy of ofloxacin otic solution administered twice daily with that of the fixed combination neomycin-polymixin B-hydrocortisone otic solution administered four times daily as treatment for otitis externa. Two evaluator-blind, multicentre groups were included in the study in children aged 1–11 years and adults aged >12 years. Treatment was randomly assigned. For the ofloxacin group, ofloxacin otic solution 0.3% was administered twice daily approximately 12 hours apart, with the adults and children receiving 0.5mL (10 drops) and 0.25mL (5 drops), respectively. For the neomycin-polymixin B-hydrocortisone group, treatment was given four times daily approximately 6 hours apart, with the adults and children receiving 0.2mL (4 drops) and 0.15mL (3 drops), respectively. A total of 314 adults and 287 children (601 subjects) were enrolled, of whom 247 adults and 227 children (474 subjects) were clinically evaluable. No significant differences in sex, race, laterality of infection, duration and severity of disease, number of organisms, or number of pathogens were noted between treatment groups on enrolment among children or adults.

Overall, clinical cure was found in 97% of ofloxacin-treated children and 95% of children treated with neomycin-polymixin B-hydrocortisone ($p = 0.48$). Clinical cure was also reported in 82% of ofloxacin-treated adults and 84% of adults treated with neomycin-polymixin B-hydrocortisone ($p = 0.56$). The rates of success in the overall clinical and microbiological responses were also comparable between treatment groups. The results reported herein indicate that ofloxacin otic solution 0.3% administered twice daily is as effective and well tolerated as neomycin-polymixin B-hydrocortisone otic solution in the management of otitis externa in both children and adults. As commented by the authors, different regimens of neomycin-polymixin B-hydrocortisone and ofloxacin might influence compliance in daily practice and the twice-daily regimen of ofloxacin otic solution was more favoured in that respect.

4.2 Chronic Suppurative Otitis Media

Chronic suppurative otitis media (CSOM) is drainage of any duration through a chronic perforation of the tympanic membrane. It is a serious bacterial infection of the middle ear being unpleasant to those with the condition. CSOM usually follows untreated or inadequately treated acute otitis media, which is common in the first 5 years of life, and is associated with poor socio-economic conditions.[26] It is a far less common problem in developed countries than it was before the advent of antibacterials but world-wide it remains a major health issue especially in developing countries and among various disadvantaged indigenous population groups in developed countries.[14]

The most common pathogens associated with CSOM have been identified in a number of studies, and re-examined in a US multicentre study by Agro et al.[27] This study evaluated 207 patients from 27 centres, and demonstrated that the three most recognised organisms responsible for CSOM were *S. aureus*, *P. aeruginosa* and *Proteus mirabilis*. Infection can also be caused by Gram-negative organisms and coagulase-negative *Staphylococcus* spp. Their prevalence depends on the series and cases reported. The pathogens can originate from external auditory canal or ascend from the nasopharynx via the eustachian tube.

The management of CSOM are regular aural cleansing, such as dry mopping ('wicking') and/ or syringing, insufflations of topical antiseptics, administration of topical and/or systemic antibacterials (usually given following ear cleansing), and tympanoplasty if the drum fails to heal. Meta-analysis showed that treatment with antibacterials or antiseptics accompanied by aural cleansing was more effective in resolving otorrhoea than no treatment or aural cleansing alone.[28]

Surgical closure of the tympanic perforation is frequently necessary to cure CSOM permanently. Since this is neither feasible nor available to all patients with draining ears, especially in developing countries in which the medical facilities may not be readily available, conservative medical treatment plays an important role in controlling otorrhoea both as an alternative to and as a preparation for tympanoplasty.

Topical antibacterial eardrops have become a standard treatment option for patients with chronic otitis media and intermittent otorrhoea. Repeated application of an otic solution for a chronic case raises some concern for its ototoxic adverse effects. When administered to patients with suppurative otitis media, the drug may enter the middle ear and cause mucosal damage. If the drug enters the inner ear and the vestibule, cochlear and vestibular degeneration may occur with damages to the sensory cells of the Organ of Corti.

Topical fluoroquinolones are more effective than non-fluoroquinolones in the medical treatment of CSOM. At least five studies[29-33] found that topical ofloxacin or ciprofloxacin was more effective than intramuscular gentamicin, topical gentamicin, topical neomycin-polymyxin, or oral amoxicillin-clavulanic acid in resolving otorrhoea (odds ratio [OR] 0.26; 95% CI 0.16–0.41) and in eradicating bacteria (OR 0.30; 95% CI 0.17–0.52).[28] This may be accountable by the activities of the fluoroquinolones against *P. aeruginosa*, a commonly isolated pathogen.

A meta-analysis was completed recently to determine the effectiveness of ofloxacin otic solution for the treatment of suppurative otitis media compared with other antibacterials.[34] Nine randomised controlled trials[1,30,33,35-40] and two non-randomised controlled trials[27,41] were included, and all these studies used ofloxacin otic solution 0.3% as the experimental intervention (table I). Of these 11 studies, five chose the combination of neomycin-polymyxin B-hydrocortisone otic solution as the comparative drug.[33,35-38] In three of these studies, comparison was made with oral amoxicillin combined with clavulanic acid or chloramphenicol otic drops,[1,30] while one study compared with framycetin-gramicidin-dexamethasone otic solution.[40] Two others compared with 'current practices' but details were not specified.[27,41]

The main outcomes included in this meta-analysis were namely: (i) the overall cure rate; (ii) the resolution of the symptom of otalgia; (iii) the resolution of the symptom of otorrhoea; and (iv) the report of any adverse events. The overall cure rate was defined as the complete disappearance of otalgia, otorrhoea and other symptoms associated with suppurative otitis media after at least 1 week of treatment.

Nine of the trials[1,27,30,33,35-38,41] were included with a pooled total of 1290 patients (table II). Eight out of nine included studies showed a higher benefit increase among patients given ofloxacin otic solution 0.3% compared with the comparator treatment.[1,27,30,33,35-37,41] The pooled OR of benefit increase in patients given ofloxacin otic solution 0.3% was 2.67 (95% CI 2.04–3.50). The results were homogenous among the different studies (heteroge-

Table I. Summary of the regimens of ofloxacin otic solution and the comparative control groups in the studies included in a recent meta-analysis to determine the effectiveness of ofloxacin otic solution for the treatment of suppurative otitis media compared with other antibacterials[34]

Study	Ofloxacin 0.3% otic solution regimen	Control group regimen
Abes et al.[38]	5 drops twice daily for 2–4 weeks	Polymixin otic solution given as 3–5 drops to affected ear 3 times daily for 2–4 weeks
Agro et al.[27]	10 drops twice daily for 14 days	Current practice medications (not specified)
Boesoirie et al.[35]	6 drops twice daily for 7–14 days	Neomycin-polymixin B-hydrocortisone otic solution 6 drops to affected ear twice a day for 7–14 days
Dohar et al.[41]	5 drops twice daily for 10 days	Current practice medications (not specified but did not contain ofloxacin)
Gendeh[40]	6 drops twice daily for 2 weeks	Framycetin-dexamethasone-gramicidin otic solution 6 drops twice a day for 2 weeks
Goldblatt et al.[1]	5 drops twice daily for 10 days	Amoxicillin-clavulanic acid 40 mg/kg per day for 10 days
Helmi et al.[36]	6–10 drops twice daily for 14 days	Neomycin-polymixin B-hydrocortisone otic solution 3–5 drops three times daily for 14 days
Subramaniam et al.[37]	6 drops twice daily for 14 days	Neomycin-polymixin B-hydrocortisone otic solution 3 drops three times daily for 14 days
Supiyaphun et al.[39]	6 drops twice daily for 14 days	Amoxicillin 500mg three times daily for 14 days plus chloramphenicol otic solution 3 drops three times daily for 14 days
Tong et al.[33]	6 drops twice daily for 14 days	Neomycin-polymixin B-hydrocortisone otic solution 6 drops twice daily for 14 days
Yuen et al.[30]	Three times daily for 7 days[a]	Amoxicillin-clavulanic acid 375mg three times daily for 7 days[a]

a Number of drops was not stated.

neity test; p = 0.09). It was also noted that ofloxacin otic solution 0.3% was better than antibacterial otic solution given in combination with corticosteroids. Four randomised controlled trials[33,35-37] were included in a subgroup analysis to compare the efficacy of ofloxacin and other antimicrobials in combination with corticosteroids (table III). All four studies showed higher benefit increase among patients given ofloxacin otic solution 0.3% compared with those given other antibacterial otic solutions plus a corticosteroid. The pooled OR of benefit increase in patients given ofloxacin otic solution 0.3% was 2.73 (95% CI 1.52–4.90). The results were also homogenous among the four different studies (heterogeneity test; p = 0.96).

Four trials[33,37,39,40] were included in the evaluation of resolution of the symptom of otalgia with a total of 231 patients (table IV). The pooled OR of

Table II. Comparison of cure rate between ofloxacin otic solution 0.3% and other medical treatments[34]

Study	Cure rate (no. cured/total no. treated)		Odds ratio	95% CI
	ofloxacin solution	other treatment[a]		
Abes et al.[38]	22/23	18/22	3.93	0.63–24.75
Agro et al.[27]	148/162	38/54	5.74	2.36–13.95
Boesoirie et al.[35]	38/38	33/54	8.31	0.16–42.14
Dohar et al.[41]	121/143	140/218	2.76	1.72–4.42
Goldblatt et al.[1]	107/140	101/146	1.44	0.86–2.42
Helmi et al.[36]	23/69	11/69	2.53	1.17–5.48
Subramaniam et al.[37]	26/30	19/30	3.40	1.07–10.83
Tong et al.[33]	25/28	19/24	2.14	0.48–9.57
Yuen et al.[30]	22/30	7/30	7.16	2.62–19.55
Total	**532/663**	**386/627**	**2.67**	**2.04–3.50**

a See table I for details of comparator group regimens.

Table III. Comparison of cure rate between ofloxacin otic solution 0.3% and otic solution containing an antibacterial in combination with a corticosteroid[34]

Study	Cure rate (no. cured/total no. treated)		Odds ratio	95% CI
	ofloxacin solution	antibacterial + corticosteroid[a]		
Boesoirie et al.[35]	38/38	33/54	8.31	0.16–42.14
Helmi et al.[36]	23/69	11/69	2.53	1.17–5.48
Subramaniam et al.[37]	26/30	19/30	3.40	1.07–10.83
Tong et al.[33]	25/28	19/24	2.14	0.48–9.57
Total	**112/165**	**82/157**	**2.73**	**1.52–4.90**

a See table I for details of comparator group regimens.

benefit increase in patients given ofloxacin otic solution 0.3% was 2.41 (95% CI 1.20–4.82). The results were homogenous among the different studies (heterogeneity test; p = 0.50). There was a higher benefit increase in terms of resolution of otalgia among patients given ofloxacin otic solution 0.3% than all the other types of medical treatment.

All 11 studies[1,27,30,33,35-41] were included in the evaluation of resolution of otorrhoea with a total of 1266 patients (table V). All studies showed a benefit in terms of proportion of resolution of otorrhoea among patients receiving ofloxacin otic solution 0.3% compared with the comparator treatment. The pooled OR of benefit increase in patients given ofloxacin otic solution 0.3% was 2.78 (95% CI 2.12–3.65). The results were homogenous among the different studies (heterogeneity test; p = 0.25). It was also noted that ofloxacin otic solution 0.3% was found to be superior to orally administered antibacterials. Three randomised controlled trials[1,30,39] were included in a subgroup analysis to compare the effect of ofloxacin otic solution and an oral antimicrobial. All three studies showed higher benefit increase in terms of resolution of otorrhoea among patients given ofloxacin otic solution 0.3% than those given oral antibacterials. The pooled OR of benefit increase in patients given 0.3% ofloxacin otic solution was 1.99 (95% CI 1.28–3.09). The results were also homogenous among the four different studies (heterogeneity test; p = 0.06).

The duration of treatment for CSOM by ofloxacin otic solution 0.3% has also been explored. Tong et al.[42] studied whether a short duration of antibacterials given topically has the same efficacy as the recommended duration of therapy. In this study, group A patients (n = 33) received 10 minutes of treatment (i.e. patients kept their head in the lateral position for 10 minutes following instillation of the ear drops), group B (n = 33) received 3 minutes of treatment and group C was the control group. In group A, 64% of cultures were positive pre-treatment cultures, but only 14% were positive post-treatment. Group B had an 82% positive rate before treatment, but it fell to 15% after therapy. Group C (control group) had a 60% pretreatment positive culture and an 86% post-treatment positive culture. This demonstrated that a duration of treatment as short as a 3-minute application of ofloxacin in a patient's ear achieves a similar efficacy (85% negative culture rate), compared with taking the drug for 10 minutes (86%). This emphasises the excellent activity of ofloxacin, even when given for a very short duration. However, a more rapid application time could possibly enhance patient compliance.

4.3 Otorrhoea with Tympanostomy Tube

As mentioned in section 2.3, the widely practised procedure of tympanostomy tube insertion in children with recurrent otitis media, otitis media with effusion or secretory otitis media, not uncommonly results in problems of tympanostomy otorrhoea.[20,21] During a viral upper respiratory tract infection in the child with the tube in place, otorrhoea frequently ensues. Inflammation caused by the upper respiratory tract infection spread to the middle ear directly via the eustachian tube. The otorrhoea is further amplified by reflux of nasopharyngeal secretions into the middle ear. The mucopu-

Table IV. Comparison of resolution of otalgia between ofloxacin otic solution 0.3% and other medical treatment[34]

Study	Resolved otalgia (no. cured/total no. treated)		Odds ratio	95% CI
	ofloxacin solution	other treatment[a]		
Gendeh[40]	32/36	21/34	4.28	1.45–12.67
Subramaniam et al.[37]	15/16	14/14	0.15	0.00–7.80
Supiyaphun et al.[39]	34/39	32/40	1.67	0.51–5.46
Tong et al.[33]	25/28	19/24	2.14	0.48–9.57
Total	**106/119**	**86/112**	**2.41**	**1.20–4.82**

a See table I for details of comparator group regimens.

rulent discharge eventually flows out through the tympanostomy tube and the child presents with otorrhoea. The tube also acts as a foreign body with potential dead space for bacteria to grow. As described earlier, this condition may occur shortly after insertion and at any time until the grommet is extruded.

The organisms typically responsible for otorrhoea include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *P. aeruginosa* and *S. aureus*. The occurrence of otorrhoea after placement of tympanostomy tubes presents a significant therapeutic problem and adds substantially to the healthcare costs of this disorder. The average number of episodes of otorrhoea per case was 1.46 in a retrospective analysis of 491 children,[43] with an even higher incidence rate during summer months.

Goldbatt[44] reported a study to compare the efficacy of the topically applied ofloxacin otic solution with that of oral amoxicillin-clavulanic acid therapy in children with tympanostomy tubes in place and purulent otorrhoea. This was a multicentre, randomised, parallel group, evaluator-blind study involving 240 patients aged 1–12 years with purulent otorrhoea from acute otitis media in the presence of tympanostomy tubes. Patients were treated for 10 days with either 40 mg/kg/day amoxicillin-clavulanic acid in three divided doses per day orally, or 5 drops of ofloxacin otic solution 0.3%, 0.25mL topically twice daily applied directly to the ear canal. Patients with systemic symptoms, such as fever, vomiting or diarrhoea, were excluded. The clinical cure rates were 76.3 and 68.3% in the ofloxacin otic solution treatment arm and the amoxicillin-clavulanic acid-treated arm, respectively. The cure rates and failure rates between the two groups were not statistically different.

Post-treatment microbiologic evaluation for recovered organisms in the ofloxacin group revealed

Table V. Comparison of resolution of otorrhoea between ofloxacin otic solution and other medical treatment[34]

Study	Resolved otorrhoea (no. cured/total no. treated)		Odds ratio	95% CI
	ofloxacin solution	other treatment[a]		
Abes et al.[38]	20/23	17/22	1.91	0.42–8.67
Agro et al.[27]	148/162	38/54	5.74	2.36–13.95
Boesoirie et al.[35]	34/38	23/36	4.16	1.42–12.21
Dohar et al.[41]	121/143	33/47	2.54	1.10–5.88
Gendeh[40]	30/36	18/34	4.02	1.47–10.94
Goldblatt et al.[1]	107/140	101/146	1.44	0.86–2.42
Helmi et al.[36]	57/69	42/69	2.90	1.39–6.07
Subramaniam, et al.[37]	26/30	19/30	3.40	1.07–10.83
Supiyaphun et al.[39]	36/39	34/40	2.04	0.51–8.12
Tong et al.[33]	21/28	11/24	3.35	1.10–10.16
Yuen et al.[30]	22/29	7/27	7.13	2.52–20.16
Total	**622/737**	**343/529**	**2.78**	**2.12–3.65**

a See table I for details of comparator group regimens.

100% eradication of *P. aeruginosa*, 100% of *S. pneumoniae*, 93% of *H. influenzae*, 96% of *S. aureus* and 93% of *M. catarrhalis*. Eradication rates with oral amoxicillin-clavulanic acid therapy, however, were notably lower, with eradication rate of 43% of *P. aeruginosa*, 87% of *S. pneumoniae*, 77% of *H. influenzae*, 48% of *S. aureus*, and 90% of *M. catarrhalis*. The differences in eradication rates between therapies were not statistically significant for *S. pneumoniae*, *H. influenzae*, *and M. catarrhalis* but were statistically significant for *P. aeruginosa* and *S. aureus* ($p < 0.05$ for both) with ofloxacin otic solution being more effective at eradicating the latter two organisms. The superior efficacy was suggested to be due to the higher local concentrations of antibacterial achieved topically, which can exceed MIC by >1000-fold, in comparison with those achieved systemically. Although this study revealed that 10-day treatment of ofloxacin otic solution 0.3%, 0.25mL topically twice daily showed an overall clinical cure rate comparable to oral amoxicillin-clavulanic acid, 40 mg/kg per day in three divided doses (76% vs 69%, respectively), with the simpler treatment regimen, ofloxacin otic solution is expected to have potentially better treatment compliance.

5. Review of Safety of Other Commonly Used Topical Antibacterials

Ototoxicity is defined as the tendency of certain therapeutic agents and other chemical substances to cause functional impairment and cellular degeneration to the tissues of the inner ear and especially of the end organs and neurons of the cochlear and vestibular divisions of the VIIIth cranial nerve.[45] In clinical practice, ototoxicity normally points to medications which are cochleotoxic or vestibulotoxic.

There are always issues on the safety of otic solutions, especially the effect of ototoxicity as the otic solutions may be applied directly to the middle ear through a perforated tympanic membrane. Otic solutions can potentially penetrate the inner ear through the round window, which in turn can give rise to cochlear and vestibular toxicity. Outer hair cells are more easily affected, especially for those at the basal turn of the cochlear that is responsible for high pitch hearing.[13] High frequency sensorineural hearing loss on audiometry is, therefore, an important sign for early detection of cochlear damage.[46]

The cardinal symptoms are tinnitus, hearing loss and balance disturbances, with a feeling of pressure in the ears being a frequently added complaint. The onset is, however, variable. Ototoxicity may appear rapidly with short-term exposure, slowly during administration or even some time after the therapy has stopped. The effects may only be detected by special tests (audiometry, speech tests and electronystagmography). In view of the insidious nature of these effects and the minimal symptoms, significant functional hearing and vestibular loss may occur before ototoxicity is clinically manifested.

In a questionnaire survey in the US published in 1993, of the 2235 respondents, 94% of American otolaryngologists affirmed their use of ear drops containing potentially ototoxic antibacterials in the treatment of otorrhoea in the presence of draining perforations (84.1%) and drainage through ventilation tubes (93.7%).[47] Of those surveyed, 3.4% thought they had witnessed inner ear damage secondary to topical therapy. It was calculated that an ototoxic event occurred in about 1 out of 10 000 prescriptions.[47]

5.1 Neomycin-Polymixin B-Hydrocortisone Otic Solution

Ototoxic effects are well documented, clinically important adverse effects of parental aminoglycoside use. For topical aminoglycoside otic solution, controversy still exists in the literature as their safety in the presence of a membrane defect.[48-50]

Neomycin-polymixin B-hydrocortisone otic solution and gentamicin 0.3% are commonly used topical antibacterials. *In vitro* and *in vivo* animal studies have demonstrated the ototoxicity of these widely used drugs.[51,52] A study in baboons demonstrated cochlear damage when a commercially available preparation of neomycin-polymixin B-hydrocortisone otic solution was introduced into the middle ear.[53]

Isolated case reports have revealed patients with profound bilateral sensorineural hearing loss attributable to excessively administered ear drops in the presence of a tympanic perforation.[48] In a retrospective study by Podoshin et al.[54] involving 150 patients with chronic otitis media, it was shown that the treatment with ear drops containing very commonly prescribed topical antibacterials, namely neomycin and polymyxin B, played a part in the sensorineural loss and the effect of these ototoxic antibacterials should not be ignored. The mean difference in the sensorineural hearing threshold in the group with neomycin-polymixin B-hydrocortisone treatment was 6.0dB and –0.9dB in the control group ($p < 0.025$).

Barlow et al.[52] conducted an animal study to compare the cochlear and middle ear toxicity of commonly used otic solutions. The solutions included neomycin-polymixin B-hydrocortisone, gentamicin ophthalmic solution 0.3%, benzakolium chloride 0.026 and 0.05%, and ofloxacin 1%. Saline 0.9% was used as the control. Male and female juvenile albino Hartley strain guinea-pigs with a standard starting weight were used as the animal model. The agents were instilled daily for 7 days into the bulla of the animal and the animals were sacrificed on the 14th day. The Organ of Corti was examined under light microscope and scanning electron microscopy. The average cochlear hair cell damage was 66% for neomycin-polymixin B-hydrocortisone, 6.5% for gentamicin ophthalmic solution 0.3% and 1% for ofloxacin. For the control group and the benzakolium chloride 0.26 and 0.05% groups, the hair cell losses are 1.4, 1.0 and 1.1%, respectively. Neomycin-polymixin B-hydrocortisone produced statistically significant hair cell damage compared with the control group ($p < 0.05$).

Russell et al.[51] performed an *in vitro* experiment to assess the ototoxicity of some common otic preparations by direct exposure to isolated chinchilla cochlear outer hair cells. The neomycin-polymixin B-hydrocortisone group showed statistically shorter time to cell death, when compared with the control, the ciprofloxacin and ofloxacin groups morphologically ($p < 0.05$). The cells in neomycin-polymixin B-hydrocortisone group were also significantly shorter in size than the control group ($p < 0.05$). This demonstrated that neomycin-polymixin B-hydrocortisone may be the most toxic among the commonly used otic preparations.

5.2 Gentamicin-Betamethasone

Another commonly used ototopical antibacterial is gentamicin in combination with betamethasone. In 1996 the Canadian Adverse Drug Reaction monitoring Program[55] reported seven cases in which the use of gentamicin-betamethasone eardrops in the presence of tympanic membrane perforation resulted in ototoxicity. All patients were prescribed the eardrops to treat middle disorders with or without otorrhoea. Complaints were of imbalance, vertigo, ataxia, oscillopsia (visual blurring with head movement), tinnitus and hearing loss. Subsequent investigations (vestibular testing and audiometry) confirmed the absence or reduction of vestibular function as well as high-frequency sensorineural hearing loss in all cases (bilateral in five cases, unilateral in two cases). Patients were severely affected by the ototoxicity and some were even incapacitated.

6. Safety and Adverse Events of Ofloxacin Otic Solution

6.1 Adverse Drug Reactions

The overall incidence for all adverse reactions associated with systemic ofloxacin reported ranges from 4.4 to 16.5%.[56] The most commonly reported adverse effects include arthropathies, CNS toxicity and nephropathy.[56]

Systemic use of fluoroquinolones is restricted in children because of its potential damage to articular cartilage. An animal study conducted by Kato et al. the local application of ofloxacin into the middle ear did not show any chondrotoxicity.[57] In this study, the effect of ofloxacin otic solution 0.3% on the cartilages constituting the epiphyses of the auditory ossicles and the wall of the auditory tube was examined after 30-day repeated intratympanic administration to juvenile aged 4 weeks male guinea-pigs.

Table VI. Comparison of the development of any adverse event between ofloxacin otic solution 0.3% and other medical treatments[34]

Study	Adverse event (no. with an adverse event/total no.)		Odds ratio	95% CI
	ofloxacin solution	other treatment[a]		
Abes et al.[38]	6/23	4/23	1.65	0.41–6.59
Boesoirie et al.[35]	2/39	1/36	1.83	0.18–18.18
Goldblatt et al.[1]	13/228	77/246	0.19	0.12–0.30
Tong et al.[33]	6/28	7/24	0.67	0.19–2.32
Total	**27/318**	**89/329**	**0.28**	**0.19–0.42**

a See table I for details of comparator group regimens.

There was no significant change detected histologically.

The systemic absorption of fluoroquinolones is minimal after topical application and therefore these adverse effects would/should not be observed in patients receiving topical ofloxacin otic solution. A clinical study was performed with ofloxacin otic solution 0.3% administered topically in a single dose of 0.5mL in adults or 0.25mL in children with chronic suppurative otitis media and perforated tympanic membrane.[2] Serial sampling of serum up to 8 hours after administration revealed very low concentrations of ofloxacin. Ofloxacin was not detected in the serum of most patients. The highest concentration was 10 μg/L.[2] This level of systemic absorption is unlikely to give rise to any adverse effects associated with ofloxacin.

In the clinical setting, ofloxacin otic solution 0.3% was shown to have a very low rate of adverse effects. Only 1% of patients experienced rash, pruritus or diarrhoea, with negligible instances of vomiting.[1]

In a 4-year period retrospective study in Japan in 1999 involving 3381 cases, the occurrence rate of adverse drug reactions to ofloxacin otic solution 0.3% ranged from 0.03 to 0.06%. The adverse drug reactions were generally mild, and included local irritation, dizziness, vertigo, general discomfort, auditory, tinnitus and sensation of blockage. In Asia, other than Japan, no severe adverse drug reactions were reported.[58]

Since the launch of ofloxacin otic solution in the US in February 1998, only two adverse drug reactions have been reported to the manufacturer (one case of ear ache and one of otosalpingitis).[59]

The meta-analysis described in section 4.2 also assessed the adverse events of ofloxacin otic solution for the treatment of suppurative otitis media compared with other antibiotics.[34] Four trials[1,33,35,38] that included data on the rate of adverse reactions were included in the evaluation of the development of any adverse event with a pooled total of 647 patients (table VI), and they showed mixed results. Two of the small trials[35,38] showed higher but not statistically significant adverse event rates (5–26%) among patients given ofloxacin otic solution 0.3% compared with the rates seen with the comparators (2.5–17%). Another small trial[33] and a larger trial[1] showed lesser adverse event rates (21.4 and 5.7%, respectively) in the ofloxacin group compared with the rates seen with the comparators (29.1 and 31.3, respectively). The pooled OR for the development of adverse event in patients given ofloxacin otic solution was 0.28 (95% CI 0.19–0.42). The results were, however, heterogeneous among the different studies (heterogeneity test; $p = 0.01$).

This meta-analysis showed that there is lower risk of developing any adverse events in patients given ofloxacin otic solution 0.3% than those with all the other types of medical treatment.

6.2 Ototoxicity

There was evidence from animal studies that demonstrated the lack of ototoxic effect from ofloxacin eardrops.[52] In a study in guinea-pigs, ofloxacin solution at a concentration three times higher than the ordinary preparation, i.e. 1% showed no significant cochlear toxicity after 7-day instillations, when compared with neomycin-polymixin B hydrocortisone.[52]

In a similar study by Black et al.[60] ofloxacin otic solution 0.3% or 1.0% or neomycin 10% solution was delivered twice daily to the middle ear of guinea-pigs (5/sex/group) for 30 days. After 1 month of treatment, the ofloxacin otic solution had not caused any damage to the middle ear mucosa or ossicles. There was no evidence of change in the auditory brainstem response (a functional measure for hearing threshold) or to cochlear morphology. In addition there was no significant shift from baseline in mean threshold auditory responsivity when measured at 4, 10 and 20 kHz with either of the ofloxacin otic solutions. In contrast, neomycin 10% caused a marked shift, in the range of 35.0–47.8dB, in brainstem responses indicating substantial hearing loss caused by drug-induced ototoxicity.

In summary, animal studies of ototoxicity during topical ofloxacin otic solution administration have demonstrated a lack of local irritation, regardless of high concentrations of drug achieved locally. There has been no histological or functional evidence of adverse effects on the mucosa or ossicles of the middle ear and inner ear. Based on these data, ofloxacin otic solution appears to be a safe topical antibacterial for application to the middle ear and is well tolerated even at concentrations three times that recommended for clinical use.[61] Ofloxacin 0.3% eardrop is currently the only ototopical agent with US FDA approval for use in open middle ear.

Goldblatt et al.[1] showed that there was no increase in bone-conduction threshold (worsening of hearing acuity) after the treatment of topical ofloxacin otic solution when evaluated by change either in pure tone average or in hearing threshold at 4000Hz. It even showed a statistically insignificant improvement in pure tone average and hearing threshold. This supports the safety of topical treatment with ofloxacin in ear infections.

There have not been any reports of ototoxicity with ofloxacin otic solution since its appearance in the markets around the world since its availability from 1992 onwards.

7. Conclusion

From the information reviewed in this paper we have come to the following conclusions:

- Ear infections, including otitis externa, chronic suppurative otitis media and otorrhoea associated with tympanostomy tubes, are common problems encountered in clinical practice. Ototopical preparations are often employed in the management of these conditions.
- The complications associated with these ear infections are numerous and some of them are serious. In view of these potential complications which are sometimes fatal or can result in a long-lasting detrimental effect, the use of topical antibacterial to treat ear infections is highly justified.
- Treatment efficacy and safety are the main concerns for the choice of ototopical preparations. In view of the financial status and the high prevalence of ear infections in the developing countries, a treatment with high cost-effectiveness would be advantageous.
- As regards various clinical aspects, including overall success rate, symptomatic relief of otalgia and otorrhoea, ofloxacin otic solution was found to be more effective than comparator agents, be it a topical antibacterial, a systemic antibacterial or combination drugs.
- The duration of treatment can be as short as three minutes while maintaining its efficacy, representing an advantage in administration schedules compared with other preparations.
- Ofloxacin otic solution is well tolerated, with minimal adverse effects, which are mild and self-limiting in nature. It is not associated with any ototoxicity both experimentally and clinically.

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