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Main Article

Resistance of *Pseudomonas* to ciprofloxacin: implications for the treatment of malignant otitis externa

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Abstract

For fifteen years oral ciprofloxacin has been the standard treatment for malignant otitis externa, a sometimes fatal osteomyelitis of the skull base usually caused by *Pseudomonas aeruginosa*. Resistance to ciprofloxacin is developing. Over a 16-month period, we saw five cases where malignant otitis externa progressed, with the development of cranial nerve palsies in four cases, despite oral ciprofloxacin. Prolonged intravenous antibiotic therapy became necessary. One case was managed largely as an out-patient, but four patients spent many weeks in hospital. Only two cases had diabetes and this was monitored and controlled. *Pseudomonas aeruginosa* was isolated in four of the five cases, but antibiotic sensitivity to ciprofloxacin was not determined. In one case a later isolate was tested and found to be ciprofloxacin resistant. Progress was monitored by serial C-reactive protein (CRP) and white cell count. For diagnosis and assessing response to treatment we considered serial magnetic resonance imaging or computed tomography more useful than isotope bone scan. There must be a readiness to use intravenous antibiotics, as a response to ciprofloxacin can no longer be assumed. Bacterial isolates must be tested for sensitivity to antibiotics including ciprofloxacin, and further biopsy and culture are essential if treatment fails.

Key words: Otitis Externa; Osteomyelitis; Ciprofloxacin; Drug Resistance, Microbial

Introduction

Malignant otitis externa is a severe infection of the external auditory meatus and bony tympanic plate that may spread to the skull base. It typically occurs in elderly diabetic patients and presents with severe otalgia, purulent otorrhoea, and granulations in the ear canal at the bone-cartilage junction;[1] cranial nerve palsies may arise (Figure 1), and the mortality rate is high (51 per cent in the presence of facial nerve palsy in older series[2]). The causative organism in 90 per cent of cases is *Pseudomonas aeruginosa*.[3]

Meltzer described malignant otitis externa in 1959,[4] and in 1968 Chandler[5] published a series of 13 cases, of whom 11 had diabetes, all underwent surgical debridement and six died. Ciprofloxacin was introduced in the late 1980s. This oral treatment greatly reduced the need for surgical intervention and hospital admission and rapidly became the antibiotic of choice.[6,7,8] Unfortunately, ciprofloxacin resistant *Pseudomonas aeruginosa* is an emerging problem.[8,9,10,11] In the past 16 months at St Michael's Hospital in Bristol we have seen five patients who developed cranial nerve palsies despite oral ciprofloxacin. These cases illustrate the need to reconsider intravenous antibiotic therapy, serial monitoring by C-reactive protein (CRP) and imaging (Figure 2), and the likely value of testing the antibiotic sensitivities of bacterial isolates *in vitro*.

Methods

Cases of malignant otitis externa requiring admission to hospital over a 16-month period from November 2003 to April 2005 were identified at St Michael's Hospital in Bristol (where there were 4680 new out-patients and 6097 follow-up attendances in 2005). Relevant literature was found by a search of Medline and Embase for *malignant otitis externa* alone and in conjunction with the MeSH headings *Ciprofloxacin* and *drug resistance, bacterial*.

Results

Despite treatment with oral ciprofloxacin, five patients required admission to hospital over a 16-month period because of increasing pain and in four cases the development of cranial nerve palsies.

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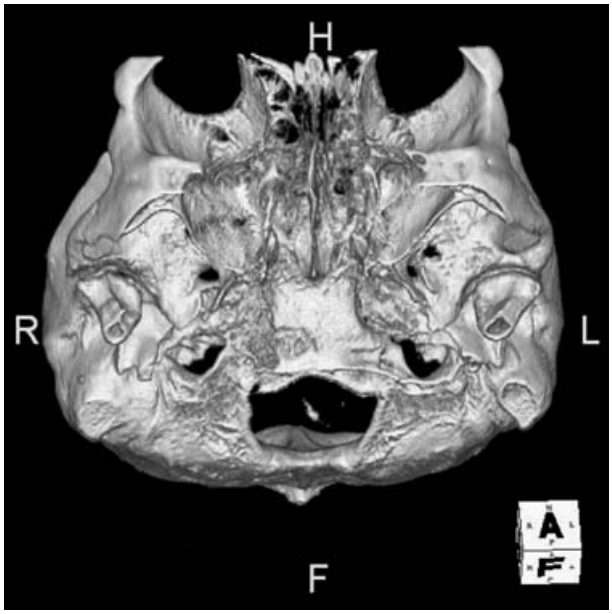

FIG. 1
Three-dimensional computed tomography reconstruction of the skull base from Case Two, showing erosion of the right petrous apex, hypoglossal canal and clivas.

Case reports

Case One

A 71-year-old man with non-insulin dependent diabetes mellitus and widespread arteriosclerosis presented with an eight-week history of right otalgia. Otoscopy revealed otorrhoea and an aural polyp. Nasendoscopy revealed a nasopharyngeal mass, and computed tomography showed a heterogeneous contrast-enhancing mass with bony erosion of the right skull base and expansion of the hypoglossal canal and hypoglossal foramen. A carcinoma or lymphoma was suspected but biopsy revealed pus with no evidence of malignancy, and microbiology revealed commensal bacteria including *Staphylococcus aureus*. Magnetic resonance imaging of the skull base demonstrated erosion of the petrous apex in keeping with osteomyelitis. Oral ciprofloxacin was commenced for a diagnosis of malignant otitis externa.

A partial right facial nerve palsy developed within 10 days. Progressive weight loss, fatigue and renal impairment were noted on admission to hospital. The CRP was elevated at 41 mg/l, and the white cell count was 11.5×10^9/l. Ciprofloxacin was discontinued after a total of three weeks, and intravenous meropenem was given for six weeks during which time there was resolution of the otalgia and facial nerve palsy. After six months he remained symptom free. Computed tomography showed residual bone loss and some healing.

Case Two

A 76-year-old man with non-insulin dependent diabetes mellitus presented with a two-week history of right aural discharge shortly after syringing of the external auditory meatus in primary care.

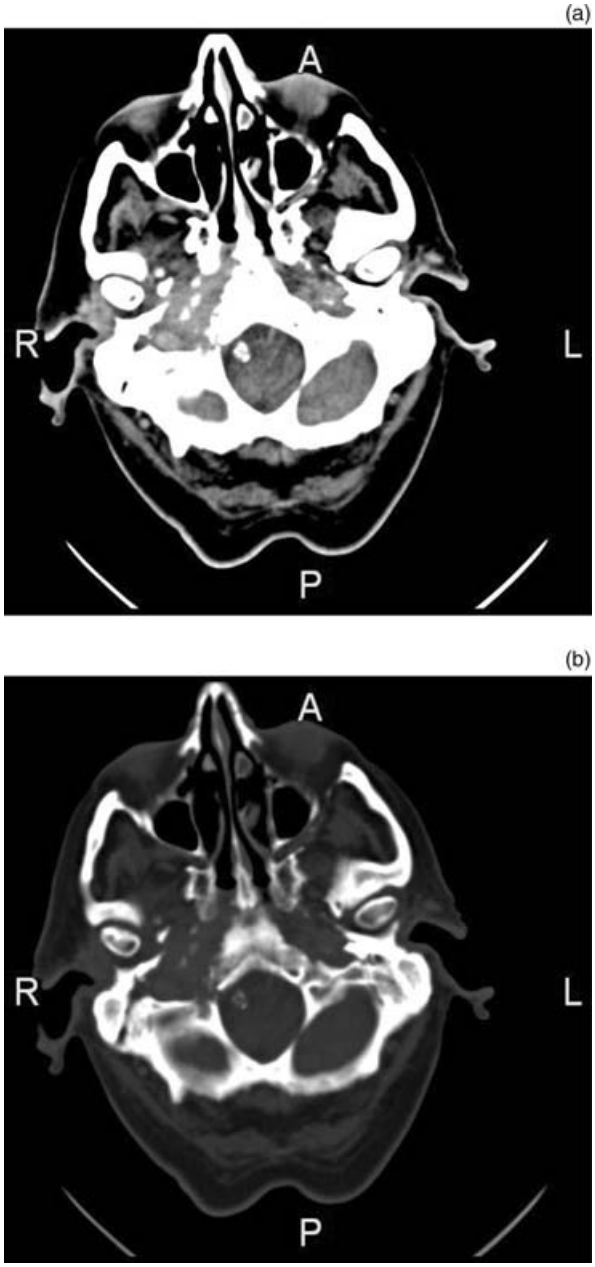

FIG. 2
Axial computed tomography of Case Two showing extensive soft tissue changes in (a) and bone erosion involving the right temporal bone extending to the foramen magnum and involving the lower cranial nerves (IX^{th}, X^{th}, XI^{th} and XII^{th}) in (b).

Examination revealed discharge, swelling of the ear canal and granulations. After three weeks using Sofradex drops the canal remained painful, swollen and occluded. A swab revealed *Pseudomonas aeruginosa* and Candida species; antibiotic sensitivities were not obtained. Right facial nerve palsy developed four weeks after presentation. Biopsy confirmed granulations. Oral ciprofloxacin was given for six weeks and after three weeks of treatment the facial nerve palsy resolved.

Seven months after presentation he was readmitted with severe otalgia and palsies of the right vocal fold, right side of the tongue and right

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trapezius and sternomastoid as well as the facial nerve. The CRP was 143 mg/l, the white cell count rose to 21.4×10^9/l (neutrophils 17.1×10^9/l), and blood glucose had deteriorated. A six-week course of intravenous Tazocin® (tazobactam and piperacillin) was commenced. Computed tomography demonstrated destruction of the floor of the right middle cranial fossa in the region of the jugular foramen and carotid canal. By day 14 of Tazocin® therapy, the CRP was 44 mg/l and the white cell count 18.3×10^9/l. By day 35, the CRP was below 10, the palsies of X, XI and XII had resolved, and there was less pain.

Two months after discharge and twelve months after initial presentation, he was admitted again with severe otalgia and continuing facial nerve palsy. The postnasal space appeared normal, but magnetic resonance imaging demonstrated right skull base inflammation with extension into the middle cranial fossa. Meropenem was given for six weeks, with relief of the pain and facial nerve palsy by the fourth week.

One month later he was again admitted to hospital with otalgia, dysphagia, right facial nerve palsy, and bilateral vagus nerve palsies. Computed tomography showed bone destruction at the anteroinferior end of the clivus extending into the skull base and bilateral prevertebral soft tissue swelling extending to both jugular foramina. He was aspirating and so was fed by nasogastric tube, and then by percutaneous gastrostomy. He was treated with meropenem for six weeks with gentamicin for the first week; otalgia and facial nerve palsy resolved. Swallowing remained unsafe and he was still gastrostomy-fed five months later.

Case Three

An 80-year-old man with arterial diseases, but not diabetes mellitus, sensorineural hearing loss and a five-year history of recurrent bilateral otitis externa presented with left otalgia and swelling of the ear canal. The white cell count was normal. Examination under anaesthesia revealed granulations in the ear canal. *Pseudomonas aeruginosa* was isolated and shown to be sensitive to polymixin and gentamicin, but sensitivity to quinolones was not tested. Computed tomography revealed anterior and posterior bony external auditory meatus erosion. With intravenous ceftazidime for four weeks, otalgia, otorrhoea and granulations resolved.

Eight months later there was recurrent left otalgia with aural discharge and granulations. Oral ciprofloxacin and Sofradex® (neomycin and dexamethasone) drops for four weeks led to no improvement. He was treated as an out-patient for six weeks with daily gentamicin and thrice daily intravenous ceftazidime. Four months later, there was bilateral discharge but no otalgia. *Pseudomonas aeruginosa* resistant to ceftazidime, gentamicin and ciprofloxacin was isolated. Treatment continued with topical Sofradex® and aural toilet in clinic.

Case Four

A 94-year-old non-diabetic woman presented with a two-month history of increasing left otalgia and otorrhoea. Granulations were seen in the left ear canal and confirmed on histology. *Pseudomonas aeruginosa* was isolated, but antibiotic sensitivities were not tested. Oral ciprofloxacin was commenced.

Four weeks later, an abscess of the cartilaginous part of the external auditory meatus was drained, and she was admitted to hospital. The CRP was elevated at 50 mg/l, and the white cell count was 11.3×10^9/l. Computed tomography showed extensive erosion of the skull base in keeping with malignant otitis externa. Ciprofloxacin was given for seven weeks in all. Pain and otorrhoea improved.

Six months after the first presentation, she was admitted to hospital following a fall and found to have palsies of left cranial nerves VII, X and XII, including a left vocal fold palsy and impaired swallowing. Intravenous meropenem was given for six weeks. The CRP fell from 26 mg/l to below 10 mg/l by the tenth day of treatment. By six weeks, the cranial nerve palsies had resolved, and computed tomography showed no progression of bone destruction. Four months later there had been no recurrence of otalgia although she had been admitted on three occasions for pneumonia.

Case Five

An 82-year-old non-diabetic man presented with a ten-day history of right otalgia after recent aural syringing. The external auditory meatus was swollen and contained discharge. *Pseudomonas aeruginosa* and Candida species were isolated; antibiotic sensitivities were not obtained. Despite Sofradex® drops and then Canesten® (clotrimazole) drops, swelling, discharge and pain increased over the course of three weeks. Oral ciprofloxacin was commenced.

Two weeks later he was admitted with a partial right facial nerve palsy and worse pain. The CRP was 32 mg/l, and the white cell count 6.2×10^9/l. Biopsy under general anaesthesia gave normal histology and no bacterial growth. Computed tomography showed soft tissue swelling in the ear canal and opacification of the mastoid air cells and middle ear; isotope bone scan showed activity in the mastoid bone extending along the petrous block. Intravenous Tazocin® was given for six weeks, and within four weeks the CRP was normal, otalgia had settled, and the facial palsy had resolved.

He was readmitted one month later with severe otalgia, dysphagia, weight loss, and adductor vocal fold palsy, with no recurrence of the facial nerve palsy. Intravenous meropenem was given for six weeks, with gentamicin for the first five days, and the condition improved.

Two weeks after completing meropenem, otalgia had worsened. Oral ciprofloxacin was given as three four-week courses, with a temporary improvement in otalgia. A second isotope bone scan, after an interval of six months, showed a greater signal in the mastoid and petrous temporal bones. However, serial computed tomography and magnetic resonance imaging over the same period showed improvement in the soft tissue infiltration of the mastoid air cells and no further bone erosion, so the increased activity in the bone

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scan was thought to reflect healing rather than continuing infection. Two years after presentation this man died of rapidly progressive motor neurone disease that may have been responsible for the dysphagia.

Discussion

Oral ciprofloxacin is thought to be a simple and effective treatment for malignant otitis externa, but our five cases illustrate the difficulty of eradicating infection from the skull base. Oral ciprofloxacin was the first line of systemic antibiotic therapy in four cases and was unsuccessful in all five. Cranial nerve palsies developed in four cases despite the concurrent use of oral ciprofloxacin. Eventually, all five patients received intravenous antibiotics for several weeks (tazobactam and piperacillin [Tazocin], meropenem, or ceftazidime, and adjuvant gentamicin in two cases), and in three cases intravenous antibiotics had to be repeated for recurrence. Changes in symptoms and inflammatory markers were helpful in judging response or relapse. However, we saw relapses even when there was a good early response and intravenous treatment was continued for six to eight weeks (Table I).

Our cases were typical in being elderly and in two having diabetes (which was monitored and controlled). However, the frequency of cranial nerve palsy was higher than expected, and in all four cases developed during ciprofloxacin therapy. Cranial nerve palsies arise from the progression of osteomyelitis in the petrous temporal bone leading to constriction at the stylomastoid foramen and the more distant jugular foramen.[5,12] In keeping with this anatomy, facial nerve palsy is more frequent than glossopharyngeal, vagus, and accessory nerve palsies. Two of our patients developed hypoglossal nerve palsy despite the hypoglossal foramen being even further distant from the origin of infection.

The appearances on magnetic resonance imaging and computed tomography included soft tissue swelling and bone erosion as in four of our cases and may mimic malignancy,[13] as in one of these cases. Computed tomography, magnetic resonance imaging and isotope bone scanning have been used to assess progress.[1,14] Our patients underwent serial imaging with computed tomography, three also with magnetic resonance imaging, and one also with serial isotope bone scanning. Deciding whether there is progression is important but can be difficult. Improvement in the computed tomography appearances of Case Five led us to ascribe increased uptake on the bone scan to healing rather than increasing infection. Thus, computed tomography or magnetic resonance imaging is probably preferable to isotope bone scan for judging the response to treatment.

TABLE I

INVESTIGATION, INPATIENT ANTIBIOTIC TREATMENT, AND OUTCOME

	Microbiology	Histopathology	Intravenous antibiotic treatment	Inflammatory markers *(on admission, and day of normalization*)*	Outcome
Case One	Polybacterial growth on pus and tissue culture	First biopsy suspicious of lymphoma; second – no evidence of lymphoma or carcinoma	Meropenem for 6 weeks	CRP 41, normal at day 38; WCC not raised	No recurrence at 6 months
Case Two	*Pseudomonas aeruginosa*; heavy growth of Candida species	Granulation tissue, exudate and stratified squamous epithelium; no neoplasm	1. Tazocin® for 6 weeks; 2. meropenem for 6 weeks; 3. meropenem for 6 weeks and gentamicin for 1 week	CRP 143, normal at day 36; WCC 21.4	Continues PEG feeding; still aspirating
Case Three	*Pseudomonas aeruginosa*; polymixin and gentamicin sensitive initially; became ciprofloxacin and ceftazidime resistant	Granulation tissue showing a heavy active chronic inflammation; no evidence of tumour	1. Ceftazidime for four weeks; 2. ceftazidime and gentamicin for 6 weeks	CRP 14, normal at day 30; WCC not raised	Well at six months; persistent bilateral otitis externa
Case Four	*Pseudomonas aeruginosa*; gentamicin and polymixin sensitive	Granulation tissue; no evidence of neoplasm	Meropenem for 6 weeks	CRP 50, normal at day 26; WCC not raised	Alive without further recurrence; episodes of pneumonia
Case Five	Candida species Pseudomonas aeruginosa	Nil abnormality detected	1. Tazocin® for 6 weeks; 2. meropenem for 6 weeks	CRP 32, normal at day 30; WCC not raised	Deceased; motor neurone disease

*Day of normalization of inflammatory markers was measured from the day of commencement of first treatment with intravenous antibiotics. CRP = C-reactive protein; WCC = white cell count; PEG = percutaneous endoscopic gastrostomy

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The high mortality of malignant otitis externa is a consequence partly of age and diabetes, and partly of complications including dural sinus thrombosis, meningitis and cerebral abscess. In Chandler's 13 cases, of the six deaths, four appear to have been cardiovascular and one cerebrovascular.[5] It has become evident that systemic inflammation is an important risk factor for arterial thrombosis,[15] so it is likely that persistent malignant otitis externa increases the risk of myocardial infarction and stroke in these vulnerable patients.

The mainstay of treatment for malignant otitis externa has been high-dose oral ciprofloxacin. Its introduction in the 1980s led to earlier treatment and improvements in morbidity and mortality. In 1989 Hickey *et al.* reported two cases free of disease at five months after treatment with oral ciprofloxacin alone for periods of four and five months.[6] In 1991 Levenson *et al.* reported 10 cases free of disease for at least 18 months after oral ciprofloxacin given for a mean of 10 weeks.[7]

Pseudomonas aeruginosa resistant to quinolones such as ciprofloxacin is an increasing problem. Quinolones inhibit two bacterial replication enzymes, DNA gyrase and topoisomerase IV; mutations in these enzymes confer resistance.[16] Bacteria may also adapt by producing a coating of polysaccharide and hence a biofilm that impedes penetration of the antibiotic.[17] Resistance is selected by excessive, injudicious and inadequate use of antibiotic therapy. The frequent use of topical quinolones may be adding to this problem.

- **Malignant otitis externa is a potentially fatal skull base osteomyelitis usually caused by *Pseudomonas aeruginosa***
- **Elderly, diabetic patients and children are at risk**
- **Clinical features include severe otalgia, granulations in the ear canal and cranial nerve palsies**
- **Oral ciprofloxacin out-patient therapy has increasingly replaced intravenous antibiotics**
- **Progress should be assessed by repeated clinical examination, monitoring of the acute phase response, and serial imaging**
- **The presentation may be mistaken for malignancy**
- **Oral ciprofloxacin fails on occasion to control malignant otitis externa**
- **Determining antibiotic sensitivity, including ciprofloxacin, is a priority**
- **There must be readiness to change from ciprofloxacin to intravenous antibiotics**
- **Reculture or biopsy is essential if treatment fails**
- **Computed tomography and magnetic resonance imaging appear more sensitive than isotope bone scan for treatment response**

In 2002 seven cases of malignant otitis externa unresponsive to ciprofloxacin were reported by Berenholtz *et al.*, of which two occurred in the decade up to 1998 and five in the three years between 1998 and 2001.[9] Our experience has been similar, in that we believe our five cases represent a new wave of admissions to our hospital.

This study brought to our attention that isolates of *Pseudomonas aeruginosa* were not tested for antibiotic sensitivity, nor retained for future testing. This omission probably stems from the lack of recognition of ciprofloxacin resistance and from not making clear to the laboratory the distinction from ordinary otitis externa where systemic antibiotics are not usually indicated. In the one case where we demonstrated ciprofloxacin resistance, the organism was also resistant to ceftazidime and gentamicin. Three of our patients required repeated courses of intravenous antibiotics, so multidrug resistance may be a greater problem. In one Boston hospital rates of multidrug-resistant *Pseudomonas aeruginosa* increased from 1 per cent in 1994 to 16 per cent in 2002.[18]

If there is a poor response or deterioration on oral ciprofloxacin, there is now an urgent need to consider prolonged intravenous antibiotic therapy. Thought needs to be given to the logistics of arranging intravenous therapy on an out-patient basis, as in one of our cases, to avoid the expense and demoralization of a long stay in hospital.

Conclusion

Our findings lead to several recommendations if ciprofloxacin is to remain the first choice for patients well enough to be treated at home. Culturing the organism for antibiotic sensitivity is a priority. Oral ciprofloxacin should be prescribed early and at full dose for six to eight weeks (as indicated for osteomyelitis),[19,20] so long as there is early symptomatic improvement and improvement in inflammatory markers. Reculture, or biopsy for culture, is essential if treatment fails. There must be readiness to change from ciprofloxacin to an intravenous antibiotic.

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