CASE REPORT

Gentamicin induced ototoxicity during treatment of enterococcal endocarditis: resolution with substitution by netilmicin

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Enterococcal endocarditis can be very difficult to eradicate, requiring prolonged treatment with a combination of a penicillin and an aminoglycoside. In this patient with a pacemaker associated enterococcal endocarditis, ototoxicity occurred due to total gentamicin dose despite plasma concentrations consistently within the treatment range. Substitution with netilmicin, without a break in aminoglycoside treatment, resulted in a rapid improvement in hearing and allowed the required course of aminoglycoside to be completed. The risk factors for ototoxicity with gentamicin are reviewed, in particular the dangers of increasing age and of multiple and prolonged courses. Close treatment monitoring does not totally avoid this risk, especially when prolonged aminoglycoside treatment is required. This case emphasises the need for prompt investigation and adequate, definitive treatment of enterococcal endocarditis to avoid the increased risk consequent on repeated courses of antibiotics. The resolution of the ototoxicity with netilmicin is consistent with other reports of lower cochleotoxicity than with other aminoglycosides.

Enterococcal endocarditis is a difficult infection to eradicate, with relapse or death occurring in about 20% of cases. In the western world it is a disease of the elderly and accounts for 5–15% of all cases of endocarditis.¹ International guidelines recommend treatment with a β lactam in combination with an aminoglycoside for 4–6 weeks.^{2–3} Gentamicin is the most commonly used aminoglycoside. Monitoring of plasma concentrations is routine and generally effective in avoiding nephrotoxicity and ototoxicity caused by the drug's narrow treatment window.⁴ Nevertheless, toxicity can occur despite apparently satisfactory drug concentrations. We report a case of severe ototoxicity caused by prolonged treatment with gentamicin for pacemaker associated enterococcal endocarditis, despite close treatment monitoring, which rapidly resolved when the drug was replaced by netilmicin.

CASE REPORT

A 76 year old man was admitted with pyrexia, confusion, and rigors associated with positive blood cultures for *Enterococcus* species. A ventricular demand pacemaker had been implanted three years previously for atrial fibrillation with symptomatic ventricular pauses. His medical history included myocardial infarction, pulmonary embolism, and non-insulin dependent diabetes mellitus. This was his fourth admission with proven enterococcal septicaemia over seven months. Despite extensive investigation, no source had been identified for his bacteraemia and he had received several short courses

of antibiotics (one of which included gentamicin), none of more than four weeks. On this occasion, he was transferred to Papworth Hospital, where a transoesophageal echocardiogram showed a 1.5 cm vegetation attached to the tricuspid valve at the point of contact with the pacing lead.

The lead and pacemaker were completely removed under general anaesthesia. A temporary pacing system was not required, as the patient was found not to be pacing dependent. Before pacemaker removal he had received benzylpenicillin 2.4 g intravenously six times daily and gentamicin 80 mg intravenously twice daily (2.3 mg/kg/day, patient weight 69 kg) for nine days. As the duration of endocarditis was greater than three months, microbiological advice was (in accordance with American Heart Association guidelines) to continue this regimen for a total of six weeks.² Gentamicin dosing was adjusted to achieve target concentrations of $< 1 \mu\text{g/ml}$ before and 3–5 $\mu\text{g/ml}$ after administration. Seven days postoperatively, the patient experienced impaired hearing and was referred to the ear, nose, and throat clinic. He was already known to have mild presbycusis. Audiometry at day 10 showed a mixed conduction and sensorineural deafness with notable high tone loss. This was initially attributed to age and sinusitis and he was treated with decongestants and clarithromycin 500 mg orally twice daily without resolution. By day 16 he had become profoundly deaf, to the extent that communication was possible only with pencil and paper. Gentamicin concentrations, monitored on average every three days throughout his treatment, had been satisfactory (consistently $< 1 \mu\text{g/ml}$ before and maximum 3.4 $\mu\text{g/ml}$ after administration). Nevertheless, ototoxicity secondary to gentamicin was felt to be the likely cause of the high tone loss. The gentamicin was therefore substituted with netilmicin 80 mg intravenously twice daily (2.3 mg/kg/day) following microbiological advice. Three days later his hearing had greatly improved and he was able to understand normal speech, with further improvement until discharge three weeks later. He received netilmicin for 15 days with treatment monitoring and was able to complete the intended total course of aminoglycoside. Concurrent oral medications at the time of hearing loss were digoxin 250 μg , gliclazide 80 mg, bendrofluzide 2.5 mg, and lansoprazole 30 mg, each once daily. He remains well with no evidence of endocarditis 18 months later.

DISCUSSION

Gentamicin ototoxicity, leading to hearing loss or deranged vestibular function, has been widely reported and is often irreversible. The prevalence of clinically evident ototoxicity with multiple daily regimens has been estimated at 11%. In contrast, the prevalence with once daily regimens has been given as 0.2–6.2%, although it may be significantly higher in at risk groups, and these regimens are not advocated for treatment of endocarditis.^{4–6} Hearing loss is partially or

completely reversible in at least half of the cases caused by multiple daily aminoglycoside regimens. Recovery may start from 24 hours after stopping the aminoglycoside.⁷ In our patient pre- and post-dose concentrations remained within the target range. However, the course of treatment was prolonged, adding a total dose of 4.16 g gentamicin to that received in his previous course. In this situation gentamicin can accumulate in the tissues, leading to ototoxicity despite normal serum concentrations. Initial studies suggested that uptake of gentamicin by the inner ear rapidly leads to saturation but the drug is only slowly released. Prolonged exposure of hair cells to aminoglycoside is the probable cause of damage. More recent studies have proposed that interference by aminoglycosides with phosphoinositide metabolism in the hair cells and binding of the drug to acid glycosaminoglycans may also be important in cochleotoxicity.^{5 8 9}

Gentamicin is 90% renally cleared, principally through glomerular filtration. The elderly are especially at risk from aminoglycosides, as their creatinine clearance may be significantly reduced without increase of serum creatinine. Other risk factors suggested for aminoglycoside induced ototoxicity are a large cumulative dose, repeated courses of treatment, bacteraemia, fever, hypovolaemia, liver dysfunction, noise exposure, pre-existing disorders of hearing, and other ototoxic drugs especially loop diuretics.^{5 7-9} In this case, only the most recent of four previous courses of antibiotics contained gentamicin, which was started four months before the current admission. The total dose had been 6.52 g over 23 days, giving a cumulative total of 10.68 g. He had mild pre-existing presbycusis. Plasma creatinine was normal before ototoxicity developed but formal creatinine clearance was not measured, nor was he taking other ototoxic drugs, including loop diuretics.

The improvement in hearing was strikingly correlated temporally with the change from gentamicin to netilmicin. In both animal and human studies netilmicin has been shown to be the least cochleotoxic aminoglycoside.^{4 9} The change of antibiotic in this case allowed continued aminoglycoside treatment, which was considered to be essential to clear the infection and avoid the high mortality associated with enterococcal endocarditis or the risks of a further course of treatment.

This case illustrates three important points. Firstly, enterococcal endocarditis, though often an apparently indolent infection, requires full investigation and early definitive treatment (in this case pacemaker removal and a full course of combination antibiotics). Secondly, large cumulative doses of gentamicin and coexisting risk factors can lead to ototoxicity despite close adherence to treatment monitoring. Thirdly, substitution with netilmicin may allow resolution of gentamicin ototoxicity alongside completion of a required course of antibiotics. Physicians should be reminded of the problem of ototoxicity in long term aminoglycoside treatment, especially in the elderly and in patients with additional risk factors.

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