Immediate effects of tobramycin on human cochlea and correlation with serum tobramycin levels

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Summary

Electrocochleography was performed on three patients to monitor the intravenous administration of tobramycin. When peak serum tobramycin levels exceeded 8-10 μg/ml an immediate dramatic reduction in cochlear output was observed, which recovered fully as serum levels fell. The patients had no auditory or vestibular symptoms either during or after treatment.

Introduction

The aminoglycosides are a useful group of antibiotics, and gentamicin has gained widespread popularity for treating Gram-negative infections. Nevertheless, tobramycin is now probably the drug of choice in infections due to Pseudomonas aeruginosa since it is more active, at least in vitro, than gentamicin.1 These aminoglycosides occasionally produce ototoxicity. Of the 1327 patients studied by Arcieri et al, 31 (2.3%) had significant ototoxicity attributable to gentamicin,4 19 had vestibular impairment, four had permanent high-tone hearing loss, and eight had both.

The "safe" upper limit for serum levels of gentamicin and tobramycin is thought to be 10 μg/ml, judged primarily from clinical experience of undesirable side effects.3-7

This paper demonstrates an immediate reversible change in human cochlear function following the administration of tobramycin and examines possible correlation with serum levels.

Patients and methods

Three patients who required tobramycin and were sufficiently fit for transtympanic electrocochleography were studied. The patients' informed consent was obtained.

Transstympanic electrocochleography provided exact objective indications of the functioning of the cochlea and primary eighth nerve neurones. The compound eighth nerve action potential (AP) and the remote cochlear microphonic (CM) were recorded through an active electrode placed through the tympanic membrane on to the promontory under local anaesthesia. Stimuli were generated by the Amplaid III Research Audiometer delivering tone pips (two sine waves at 4 kHz) and wideband clicks (centered on 3 kHz). The responses were averaged in a Medelec DA-V6 averager.

These functions were recorded at intervals for up to two hours after intravenous tobramycin was given in a bolus injection over three minutes. Blood samples for tobramycin assay were taken from a site away from the injection site. Tobramycin assays were carried out in triplicate using the plate assay method.4 Klebsiella NCTC 10896 was flooded on to DST agar, and wells cut into the agar were filled with the serum samples in a coded randomised pattern. After overnight incubation zone sizes were measured in duplicate using a zone reader (Leebrook Instrument Co Ltd) and then decoded.

All patients had the effects of their first tobramycin dose monitored, and two had further electrocochleograms performed during the course of treatment.

Case 1

A 69-year-old otologically normal woman weighing 70 kg underwent abdominoperineal excision of the rectum for carcinoma. By the 37th day after operation the abdominal wound had become infected with Pseudomonas aeruginosa and Staphylococcus aureus, and tobramycin 120 mg intravenously was given, followed by 80 mg every eight hours plus flucloxacillin 500 mg every six hours. When tobramycin was started she was also receiving heparin 10 000 units every six hours and warfarin 2 mg twice daily for leg thrombosis. The wound subsequently healed well and she was discharged home.

Before tobramycin was given AP and CM recordings were normal both to wideband clicks and to 4-kHz tone pips. By 85 minutes after the tobramycin injection there had been a 30% reduction in the amplitude of AP and CM to click and tone pip stimuli. The shape of the click-induced AP had also widened.

Electrocochleography performed on the 12th day of treatment showed that the preinjection AP and CM waveforms had reverted to normal. Fig 1 shows the rapid changes in the click-induced AP that followed the tobramycin injection. It decreased considerably in magnitude and assumed a dissociated waveform—that is, the first negative deflection (N1) became very small and the second negative deflection (N2) became relatively large. Fig 2 shows changes in the CM magnitude correlated with serum tobramycin levels. The CM fell to under half the preinjection level in 15 minutes. The peak serum level of tobramycin was 11.2 μg/ml, and levels exceeding 8 μg/ml were maintained for 30 minutes.

Five days after treatment ended a final electrocochleogram showed that the AP and CM had again reverted to normal forms. The patient never had vestibular or auditory symptoms, and conventional pure-tone audiometry conducted before, during, and after treatment showed no changes. Serum urea and creatinine concentrations remained normal throughout.
by 80 mg every eight hours). Ampicillin was stopped on the ninth day after operation. His chest infection responded to tobramycin, but progress was marred by cardiac failure and a pulmonary embolus. This patient had no otological symptoms and his renal function was normal.

Electrocochleographical monitoring was carried out with the loading dose of tobramycin and again on the sixth day of treatment. After the loading dose the AP and CM decreased to 70% of their original values by one hour, and the AP became slightly dissociated. Serum tobramycin levels reached a peak of 7-4 \mu g/ml (fig 4).

The mid-treatment electrocochleogram showed normal waveforms before the tobramycin injection, but the post-injection changes were greater than those of the initial test. A decrease in the size of AP and CM started immediately and was still progressing at 80 minutes. Again the peak serum level of tobramycin did not exceed 8 \mu g/ml (fig 5).

Discussion

Tobramycin produced an immediate and reversible depression of cochlear function without any otological symptoms in our three patients. Reports on the ototoxicity of aminoglycosides have concentrated on their delayed effects—deafness or vertigo. Our observations suggest that asymptomatic changes might occur undetected in many patients receiving aminoglycosides. Why these changes in cochlear function should be asymptomatic has been discussed elsewhere. Certain features of this immediate effect are similar to those of delayed aminoglycoside ototoxicity. Delayed outer hair cell loss usually occurs in association with...
Falls in the elderly related to postural imbalance

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Summary

Two hundred and forty-three elderly people aged 60 to 96 years were questioned about their falls, and their sway was measured. For comparison sway was also measured in 63 younger subjects. Sway increased with age and was higher in women at all ages. There was no difference in sway between those with no history of falls and those who fell only because of tripping. In both sexes sway was significantly increased in people who fell because of loss of balance and in women whose falls were due to giddiness.

Doses of aminoglycosides are often therapeutically insufficient, however, and monitoring of the serum levels is required not only for ototoxicity but to ensure that adequate doses are administered.

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References

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