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

PETER WILSON, R T RAMSDEN

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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 2] These aminoglycosides occasionally produce ototoxicity. Of the 1327 patients studied by Arcieri *et al*, 31 (2·3%) had significant ototoxicity attributable to gentamicin,[3] 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.

Transtympanic 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 DAV6 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.[8] 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.

The London Hospital, Whitechapel, London E1 1BB

PETER WILSON, MB, BCHIR, lecturer, department of clinical microbiology
R T RAMSDEN, FRCS, senior registrar, department of otolaryngology

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 (N_1) became very small and the second negative deflection (N_2) became relatively large. Fig 2 shows changes in the CM magnitude

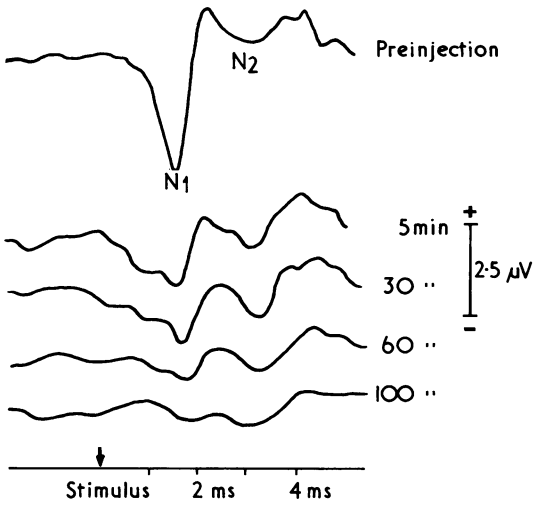

FIG 1—Case 1. Mid-treatment electrocochleography: changes in click-induced AP after intravenous injection of 80 mg tobramycin (wideband click 95 dB hearing level).

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.

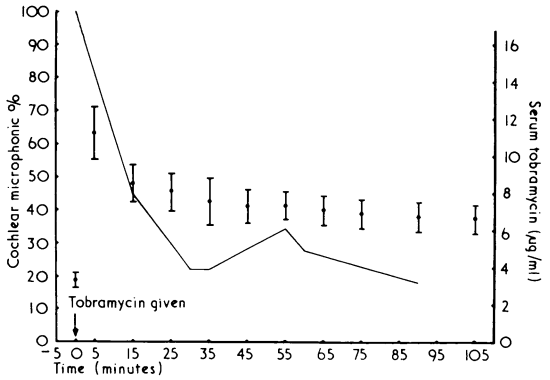

FIG 2—Case 1. Mid-treatment electrocochleography: serial tobramycin levels after intravenous injection of 80 mg tobramycin and concomitant reduction in CM amplitude (90 dB hearing level click stimuli). CM is expressed as percentage of the preinjection peak-to-peak amplitude. ——●—— = Serum tobramycin levels (mean of six estimations ± 1 SD). —— = CM percentage.

Case 2

A 59-year-old otologically normal housewife weighing 50 kg presented with an ulcerated primary carcinoma of the breast with secondary spread to the ribs and thoracic spine. Liver function was mildly impaired, but renal function was normal. She received fluoxymesterone 5 mg thrice daily and radiotherapy with twice-daily thiethylperazine maleate (10 mg). She developed a chest infection due to *Pseudomonas aeruginosa*, and antibiotic treatment was started using tobramycin 120 mg intravenously as a loading dose and thereafter 80 mg every eight hours. She initially responded well, but then developed appendicitis and peritonitis. She died six weeks after admission. She had remained free from otological symptoms, and renal function had remained normal.

The effects of the loading dose of tobramycin were monitored electrocochleographically. Within two minutes of injection the AP to the 4-kHz tone pips began to decrease in magnitude and continued to do so up to the end of the test (100 minutes). The AP rapidly assumed a dissociated waveform comparable with that seen in case 1. The CM also decreased (fig 3). Serum levels reached a peak of 15·6 μg/ml, and levels exceeding 8 μg/ml were maintained for 60 minutes (fig 3).

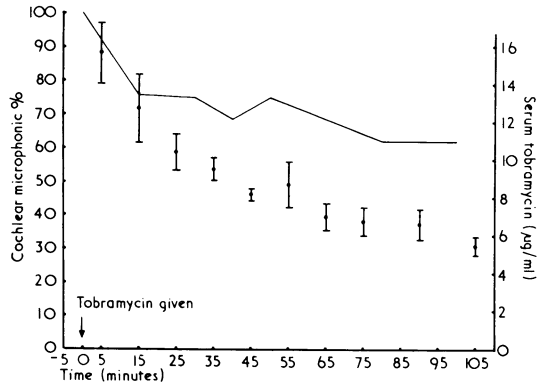

FIG 3—Case 2. Serial tobramycin levels after intravenous injection of 120 mg tobramycin (loading dose) and concomitant reduction in CM amplitude (4 kHz sine waves 100 dB hearing level). See legend to fig 2 for key to symbols.

Case 3

A 71-year-old otologically normal man weighing 60 kg had a sigmoid colectomy for adenocarcinoma. Postoperatively ampicillin 250 mg four times daily was started, but he developed evidence of a progressing chest infection due to *Pseudomonas aeruginosa*. Four days after operation tobramycin was given (120 mg intravenously followed 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 μg/ml (fig 4).

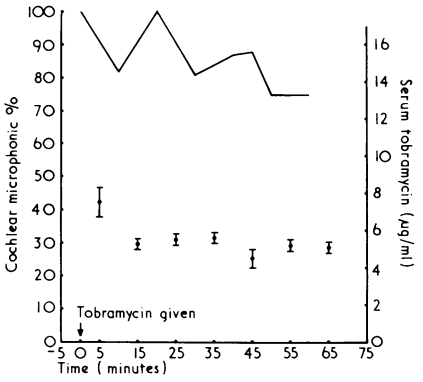

FIG 4—Case 3. Serial tobramycin levels after intravenous injection of 120 mg tobramycin (loading dose) and concomitant reduction in CM amplitude (100 dB hearing level click stimuli). See legend to fig 2 for key to symbols.

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 μg/ml (fig 5).

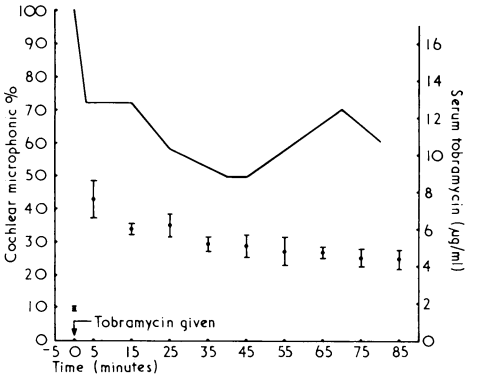

FIG 5—Case 3. Mid-treatment electrochleography: serial tobramycin levels after intravenous injection of 80 mg tobramycin and concomitant reduction in CM amplitude (100 dB hearing level click stimuli). See legend to fig 2 for key to symbols.

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.[9] Certain features of this immediate effect are similar to those of delayed aminoglycoside ototoxicity. Delayed outer hair cell loss usually occurs in association with

prolonged serum levels exceeding 8-10 μg/ml. In cases 1 and 2 the immediate and dramatic changes occurred with levels greater than this. In case 3 lesser changes occurred even though the serum levels were in the "safe" range. The basal turn of the cochlea seems most vulnerable to both immediate and delayed effects, both of which may produce the dissociated pattern of AP response that is well recognised in high-tone sensory deafness of whatever cause.[10]

The speed of onset of the observed effect suggests a direct action at a site in the cochlea, involving a temporary metabolic block—for example, interference with an energy requiring process or blocking of transport of cations across cell membranes. There is experimental and clinical evidence to show that aminoglycosides interfere with calcium metabolism (probably by binding).[11-14] In the lateral line organ of the fish they may block potassium transport.[15] Both these effects are rapid and may be reversed by administering the appropriate cation in solution. Other metabolic effects follow intoxication with aminoglycosides, although their speed of onset is not clearly established. Guinea-pigs treated with tobramycin sustain most outer hair cell damage in areas of the cochlea where there is the least amount and smallest granule size of glycogen—namely, the basal turn. The greatest oxygen consumption of the cochlea occurs in the basal turn, and is decreased by kanamycin.[17] The adenosine triphosphatase hydrolysing system has been shown to be modified within the microstructures of the cochlea after the administration of aminoglycosides.[18] This may have an important effect on the function of the stria vascularis, which uses adenosine triphosphatase to support a sodium-potassium ion pump to maintain endolymphatic homoeostasis. The possibility that interference with protein synthesis caused of our observed changes is ruled out by their speed of onset.

How our findings relate to long-term ototoxicity is not clear. 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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Falls in the elderly related to postural imbalance

P W OVERSTALL, A N EXTON-SMITH, F J IMMS, A L JOHNSON

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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, drop attacks, turning the head, and rising from bed or a chair. This suggests that there is a physiological decline in postural control with advancing age and also a decline due to disease of the central nervous system.

University College Hospital Medical School, London WC1

P W OVERSTALL, MB, MRCP, senior registrar, department of geriatric medicine

A N EXTON-SMITH, MD, FRCP, Barlow professor of geriatric medicine

A L JOHNSON, PHD, MIS, scientific officer, MRC statistical research and services unit

London School of Hygiene and Tropical Medicine, London WC1

F J IMMS, MB, PHD, scientific officer, MRC environmental physiology unit

Introduction

Although falls in the elderly are common and are associated with appreciable morbidity and mortality, there have been few investigations of their causes. In a random survey of the elderly population Sheldon[1] found that 21% of men and 43% of women were affected. More recently, in a random sample of people over the age of 65 living at home, a history of falls was obtained in 24% of the men and 44% of the women.[2] In both sexes the proportion who fell increased with age.

Describing the pattern of falls in the elderly, Sheldon[3] commented on the many accidental falls that were apparently caused by impaired balance. Although both young and old may trip over a kerb stone or lose their balance while descending stairs, the ability of the young to regain balance rapidly and avoid an actual fall is in strong contrast to what happens to the elderly. Not only are the elderly unable to correct their balance once they have stumbled but also there is probably a change in gait with age, resulting in the feet not being lifted as high as they used to be.[3]