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Vestibulo-toxicity of tobramycin

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GENTAMICIN, an aminoglycoside antibiotic, has achieved clinical importance because of its effectiveness against 'problem' organisms. Gentamicin's ototoxic effects are largely avoidable, but the drug's therapeutic range is narrow. This explains the growing interest in tobramycin, an antibiotic complex which was isolated from Streptomyces tenebrarius (Higgens and Kastner, 1967).

In a proper culture medium, streptomyces tenebrarius produces a group of eight chemically-related antibiotic factors. The different compounds of this complex have been isolated chromatographically and purified. After microbiological studies it was stated that factor 6, afterwards known as tobramycin, was the most active and showed a broad antimicrobial spectrum. It is reported to have antibacterial activity against most Enterobacteriacae and against Gram-negative organisms of increasing clinical importance, such as the Proteus species and Pseudomonas aeruginosa (Del Bene and Farrar, 1972). Tobramycin is more effective than gentamicin, particularly against proteus and pseudomonas, because tobramycin is unaffected by resistance-transfer factors which inactivate gentamicin (Brezezinska *et al.*, 1972). However, because tobramycin belongs to the aminoglycoside group of antibiotics it might be ototoxic at higher doses, as the aminoglycoside antibiotics have been shown to have a common inner ear toxicity.

There have been several publications about the cochleotoxic properties of tobramycin, but there are only a few reports about its vestibulo-toxicity. The first report was from Wick and Welles (1967), who gave five cats 200 mg of the nebramycin complex per kilogram daily for 35 days. All animals exhibited ataxia and a reduced duration of post-rotatory nystagmus by the 29th day of treatment. Conraux *et al.* (1975) reported some vestibulotoxic effects of tobramycin in a clinical study. They studied two groups of patients; the first group consisted of ten patients with normal renal function, and the second group of fifteen patients with renal failure. In the first group there were four patients with a temporary spontaneous nystagmus, but without caloric test abnormalities. They were treated with tobramycin 100 mg three times a day for fifteen days; in the second group were eight patients with decreased excitability on caloric stimulation. This was permanent in five cases, and one patient had total permanent absence of excitability in the caloric test after treatment (50 mg/day for fifteen days).

In 1976 Lehmann *et al.* reported on the vestibulotoxic effects of tobramycin in eighteen patients. They administered the antibiotic in a dosage of 2–3 mg/kg/day i.m. Three of the five patients with impaired renal function developed subjective and objective evidence of vestibular dysfunction, as demonstrated by caloric vestibulometry; however, these bilateral vestibular lesions proved to be reversible a few weeks after the cessation of therapy.

Because there have been no previous reports of permanent changes in vestibular function in patients with normal renal function treated with tobramycin, it appeared justified to publish our findings.

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Case reports

Case 1. A 64-year-old man received tobramycin for a pseudomonas infection following extirpation of a duodenal diverticulum. On the first day he received 1×80 mg and 2×60 mg. Thereafter he was treated for $4\frac{1}{2}$ days with 3×60 mg/day. The renal function tests were within normal limits. After a few weeks he started to complain about dizziness, unsteady gait and hearing loss. A few weeks later, there were no further complaints about his hearing but the unsteady gait persisted. This was the reason for his reference to the E.N.T. department about nine months later. Routine E.N.T.-examination disclosed no abnormalities. Audiometry showed a normal hearing level and speech discrimination score. Vestibular examination showed the following results: the stepping and walking tests showed unsteadiness; there was no spontaneous nystagmus; in the torsion chair test there was no sensation of rotation and there were no nystagmus beats; the bithermal caloric test showed no reaction; all central tests (e.g. the sinusoidal tracking test, the calibration test and the optokinetic nystagmus test) showed no abnormalities. It was concluded that there was a total loss of peripheral vestibular function.

Case 2. The second patient was a 68-year-old woman who received a Björck Shiley prosthesis for an aortic valve stenosis. Post-operatively the patient developed an endocarditis due to Klebsiella and Pseudomonas organisms. She was treated with tobramycin 3×80 mg i.v./day, for five weeks. After this time she started to complain about dizziness, for which she was sent to the E.N.T. department. The renal function was normal. Routine E.N.T.-examination showed no abnormalities, nor did audiometry. On vestibular examination the following results were obtained: there were unsteady stepping and walking tests; no spontaneous nystagmus was recorded; in the torsion chair test and the bithermal caloric test, no rotatory sensation or nystagmus beats were observed; with ice water irrigation also, the same result was obtained; the central vestibular tests were normal. A further examination $1\frac{1}{2}$ years later produced the same results, with a permanent loss of peripheral vestibular function.

Conclusion

Despite normal renal function, these two patients developed permanent vestibular functional loss during treatment with tobramycin in normal dosage. The ototoxicity of tobramycin appears to be primarily vestibular, as it is with gentamicin (Federspil, 1973). This is confirmed by the present case report and by the studies of Lehmann *et al.* (1976) and of Conraux *et al.* (1975). Although the ototoxicity of tobramycin is generally lower than that of gentamicin (Brummett *et al.*, 1972; Federspil, 1975), some caution must be exercised in prescribing it, and prophylactic measures for ototoxicity, as proposed by Wagner (1975) and by Federspil (1975), must be followed. It seems advisable to monitor patients on tobramycin therapy for signs of vestibular dysfunction and hearing loss, especially in cases of renal insufficiency.

Summary

The case histories are described of two patients with normal renal function who developed permanent complete bilateral loss of peripheral vestibular function during tobramycin therapy. Despite the low incidence of the cochleo-

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toxic and vestibulotoxic side-effects of tobramycin, it seems advisable to monitor patients on tobramycin therapy for signs of vestibular dysfunction and hearing loss.

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