# Early Detection of Ototoxicity by High-Frequency Audiometry — A Case Study

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*ABSTRACT*

*The effect of an ototoxic aminoglycoside antibiotic (tobramycin) on the hearing acuity of an adult Black female cardiac patient was evaluated with a new type of high-frequency audiometer. Results indicated the effectivity of this audiometer for the early detection of ototoxicity. The possibility of higher susceptibility to ototoxic damage in Blacks due to a higher concentration of melanin in the inner ear is discussed.*

*OPSOMMING*

*Die effek van 'n ototoksiese aminoglikosied antibiotikum (tobramycin) op die gehoorsensiwiteit van 'n volwasse Swart vroulike hartpasiënt is geëvalueer met behulp van 'n nuwe tipe hoëfrekwensieoudiometer. Resultate dui op die effektiwiteit van hierdie oudiometer vir die vroeë opsporing van ototoksisiteit. Die moontlikheid van 'n hoër vatbaarheid vir otoksiese skade by Swartes as gevolg van 'n hoër konsentrasie van melamien in die binneoor word bespreek.*

Conventional diagnostic audiometry generally deals with assessment of auditory sensitivity for frequencies of 8 kHz and below, even though humans can hear tones as high as 16 to 20 kHz. It has also been proven that ototoxic substances first cause a decline in the high-frequency hearing, i.e., above 10 kHz (Schuknecht, 1974).

Various drugs are known to be ototoxic. Of these, tobramycin is rated as highly ototoxic (Lane and Routledge, 1983). In these reports the ototoxic effects were determined by histologic examinations of the hair cell damage occurring in the cochlea and by measuring the resultant decline in hearing sensitivity as measured by conventional pure tone audiometry (Fee, 1980; Smith, Lipsky, Laskin, Hellmann, Mellits, Longstreth and Lietman, 1980; Matz, 1986). Ototoxic agents cause hair cells to begin to degenerate first at the very basal end of the organ of Corti, that part of the cochlea which is used to detect the highest frequencies the living animal can hear. This is a process that gradually and systematically progresses farther into the cochlea (Schuknecht, 1974). By the time this damaging effect becomes visible on a conventional pure tone audiogram valuable time for prevention has passed and permanent damage has been done to the high frequency region in the cochlea. Thus, by measuring high-frequency hearing, drug-induced ototoxic damage can be detected at a much earlier stage (Tonndorf and Kurman, 1984).

This preoccupation with testing may be explained by various mechanoacoustic problems encountered when trying to test for the higher frequency auditory thresholds. The biggest problem appears to be in calibration as the quarter and half wavelengths of the higher frequency sound approach ear canal width and length, causing transversal resonances and standing waves to occur. This means that the sound front impinging on the tympanic membrane no longer resembles the sound being fed into the external ear canal (Stinson, 1984; Tonndorf and Kurman, 1984). Logically this also leads to immense problems when trying to mask the contralateral ear. A further problem seems to be to find audiometers and transducers capable of producing these high-frequency stimuli at the necessary amplitude and fidelity but still maintaining a reasonably flat response curve. Then there are also a vast number of smaller aspects which still need clarification, e.g., high-frequency interaural attenuation, inter subject variability in responding to high-frequency sounds, etc. Quite a number of large-scale studies of high-frequency hearing can be found in the literature (Rosen, Plester, El-Mofty, and Rosen, 1964; Zislis and Fletcher, 1966; Harris and Myers, 1971; Northern, Downs, Rudmose, Glorig and Fletcher, 1971). It is, however, practically impossible to compare results due to differences in audiometer, transducer, ear coupling, calibration methods and equipment, testing method and environment, population characteristics, selection criteria and very high inter- and intra-individual variability. As such, no normative audiometric threshold values exist for high-frequency audiometry (Fausti, Frey, Erickson and Rappaport, 1979; Fletcher, 1965; De Seta, Bertoli and Filipo, 1985; Gauz and Smith, 1985; Henry, East, Nguyen, Paolinelli and Ayors, 1985).

Furthermore it has been found that certain drugs like the polycyclic amines, especially the aminoglycocide antibiotic tobramycin, has a very high melanin affinity (Potts, 1962a; 1962b; 1964a; 1964b; Potts and Au, 1971; 1976; Lindquist, 1973). Add to this the fact that melanin is present in quite large quantities in the cochlea, as first reported by the Italian anatomist Alfonso Corti as far back as 1851. This may be an important factor in the etiology of drug induced ototoxicity (Dencker and Lindquist, 1975; Dencker, Lindquist and Ullberg, 1975; Wästerström, 1984; Wästerström, Brendberg, Lindquist, Lyttkens and Rask-Anderson, 1986).

Due to the earlier-mentioned problems encountered when trying to measure high-frequency thresholds, a new type of

high-frequency audiometer, the Tonndorf Audimax Model 500, has recently been developed which could possibly bypass most of these problems (Tonndorf and Kurman, 1984). This audiometer works on the principle of electrostimulation. The test signal is superimposed on a modulated carrier frequency and is delivered via mylar-coated electrodes into the skin over each mastoid (fig. 1.). As the subject is then capacitatively coupled to the electrodes, no real current flows between the electrodes and the subject. Numerous studies have identified electrostimulation as a

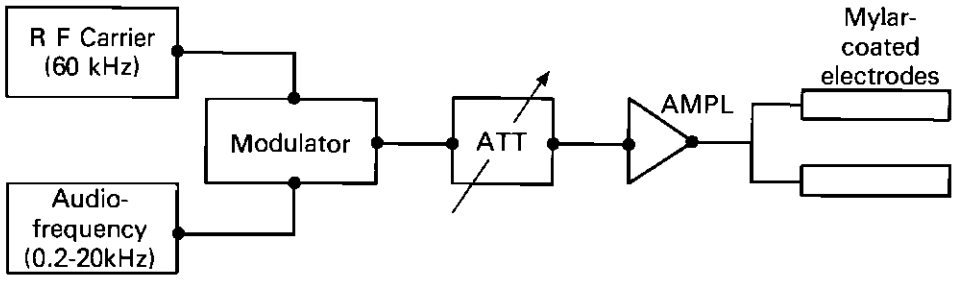


**Fig 1: Schematic of high-frequency audiometer (From: Tonndorf and Kurman, 1984)**

means of audio-transmission of electromechanical vibration in the bone and tissue structures surrounding the inner ear and the cochlea. Thus it would appear that the subject's bone-conduction hearing is being tested (Sommers and Von Gierke, 1964). This audiometer tests frequencies from 200 Hz right up to 20 kHz in 200 Hz steps. The stimulus intensities can be adjusted from 0 to 120 electrostimulation hearing threshold levels (ESHTL) in 1 ESHTL step sizes. Zero to 120 ESHTL corresponds with zero to 60 dB SPL.

It was therefore decided to use this new audiometer to monitor the very early ototoxic effect of tobramycin on the high-frequency hearing of a Black cardiac surgery patient in Ga-Rankuwa Hospital, near Pretoria.

## METHODOLOGY

The subject for this case report is a 25 year old Black woman who required open-heart surgery. She had to use tobramycin prophylactically for a period starting immediately after the operation. Before the operation her hearing was tested on two consecutive days by impedance audiometry, conventional pure tone audiometry and high-frequency audiometry. Seeing that both ears tested almost identically the test results for left and right ears were combined. As no standardized norms for high-frequency thresholds exist, it was decided to use the first two high-frequency test results as the biological baseline.

On the day of the operation she received 40 mg tobramycin and thereafter the consecutive doses were altered so that the tobramycin serum levels were maintained between a trough of not less than 2 μg/ml and a peak not exceeding 10 μg/ml. This range is considered ototoxically safe (Matz, 1986). The tobramycin regimen was continued for 72 hours. Throughout this period, the tobramycin blood serum levels were carefully monitored, as well as the renal functioning, in order to guard against possible renal failure. Any renal failure during this period would have resulted in very high serum levels due to the accumulation of tobramycin in the bloodstream.

The hearing test battery as mentioned above was repeated post-operatively on day 3, day 6, day 13 and day 20. On post-operation (PO) day 21 she was discharged from hospital. Three months later when she came to hospital for a follow-up examination her hearing was tested again according to the above test battery. The initial two tests before the operation served to check on test-retest reliability and also served as the control test against which all further test results were to be compared.

## RESULTS

On impedance audiometry no differences could be detected for consecutive tests except for very small variations in middle-ear pressure. All the other impedance test results (maximum compliance, acoustic reflex thresholds) remained essentially the same throughout the test period.

Conventional pure tone audiometry test results also remained essentially unchanged, with only about 5 dB total differences in thresholds between tests.

High-frequency audiometry, on the other hand, showed marked changes (fig. 2). The first two pre-operation test results were decidedly identical, indicating very good test-retest reliability. On PO day 3 there was a very clear decrease in high-frequency sensitivity, especially at the high end of the hearing range. This decrease continued as is shown on the PO day 6 test. On PO day 13 there was a marked recovery, but not back to the original pre-operation hearing levels. The last test before the patient was discharged on PO day 20 indicated that the recovery process had ceased and the test results were similar to those of PO day 13. The follow-up test done 3 months after discharge from hospital matched that of PO days 13 and 20, thus indicating that there was no further recovery whatsoever. It is to be noted that this patient did not suffer from any renal dysfunction during the entire period. Thus there was no possibility of tobramycin accumulation due to renal failure which could have led to the tobramycin exceeding the ototoxically safe upper serum level of 10 μg/ml.

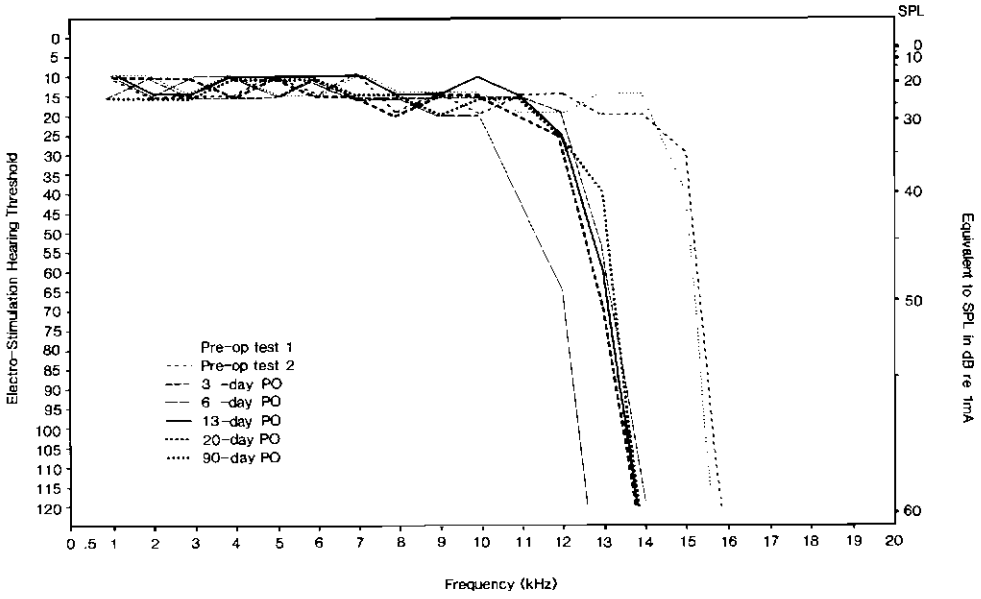


**Fig 2: High-frequency threshold changes over time**

## DISCUSSION

It would appear that high-frequency audiometry by electrostimulation shows very good test-retest reliability, seeing that the average difference in thresholds between the first two tests was no larger than 5 ESHTL units, corresponding to about 2,0 to 2,5 dB SPL.

High-frequency audiometry could detect ototoxicity at a very early stage, as well as the severity of damage and recovery from damage, whilst standard audiometry and impedance tests were still showing no effects whatsoever of ototoxicity on hearing sensitivity.

It is clear from fig. 2 that the otoxic effect continued long after cessation of drug administration and long after the serum levels indicated no drug residue in the bloodstream. This might be further proof of the possible accumulation of this drug on the melanin of the inner ear. This accumulation could, however, not be proved in this case study as no biopsies could be taken from or histological examinations done on the patient's inner ear. On the other hand, if the drug really accumulates in the inner ear, the monitoring of drug/serum levels would be of no use, since it would not represent the actual level of tobramycin in the inner ears. It may also be possible that Blacks have more melanin in the inner ear than Whites (Dencker and Lindquist, 1975; Dencker et al. 1975) and are thus more susceptible to ototoxic damage, but this is only speculative as no human experimental data on this aspect could be found in the literature. This possibility has, however, been proven in a study done on albino and pigmented guinea pigs (Wästerström, 1984; Wästerström et al. 1986).

Thus it would appear that the "safe" serum levels for ototoxic drugs were based on hearing tests for frequencies up to 8 kHz only and may really not be safe at all. It would appear that the monitoring of patients for drug-induced ototoxicity should rather be done by high-frequency audiometry or a combination of measuring blood/serum levels and high-frequency audiometry.

## CONCLUSION

High-frequency electrostimulation audiometry seems to show good test-retest reliability. It is also very effective in the early detection of ototoxicity, compared to standard audiometry. Ototoxic drug accumulation, possibly on the melanin in the inner ear will have to be investigated further. Also the possibility of Blacks having more melanin in the inner ear and thus a higher susceptibility to drug-induced ototoxicity needs further research. Lastly, a thorough investigation of present ototoxically "safe" serum levels is required.

## ACKNOWLEDGEMENTS

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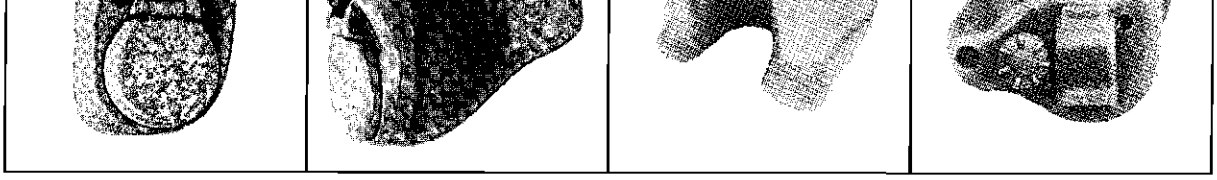

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