Ototoxicity of Aminoglycoside Drugs in Tuberculosis Treatment

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ABSTRACT

The possible ototoxic effect of kanamycin, streptomycin and a standard anti-TB drug combination, used in the treatment of 92 TB patients (7-71 years old), was examined by measuring the highest audible electric bone conduction frequency before and after treatment, using an Audimax 500 audiometer. At the so-called "safe" levels of drug administration it was found that kanamycin was markedly ototoxic, streptomycin very slightly ototoxic and the standard anti-TB drug combination had practically no ototoxic effect. Furthermore, it was found that none of these drugs were gender specific. Lastly, the possible effects of ageing on highest audible bone conduction frequency is discussed.

OPSOMMING

Die moontlike ototoksiese effek van kanamisien, streptomisien en 'n standaard anti-tuberkulose kombinasiemiddel, soos gebruik in die behandeling van 92 tuberkuloselyers (7-71 jaar oud), is ondersoek deur die bepaling van die hoogste hoorbare elektriese beengeleidingsfrekwensie voor en na behandeling, deur middel van 'n Audimax 500 oudiometer. By die sogenaamde "veilige" toedieningsvlakke van hierdie middels is gevind dat kanamisien sterk ototoksies, streptomisien baie effens ototoksies en die standaard anti-tuberkulose kombinasiemiddel feitlik glad nie ototoksies was nie. Verder is gevind dat geen van hierdie middels geslagspesifiek is nie. Laastens word die moontlike effek van veroudering op die hoogste hoorbare beengeleidingsfrekwensie bespreek.

KEY WORDS: kanamycin, streptomycin, tuberculosis, high frequency hearing.

INTRODUCTION

One third of the world's population is infected with the tuberculosis mycobacterium and there are about 30 million cases of active tuberculous disease, with about 8 million new cases annually (Friedman & Bendinelli, 1988).

Due to the rising incidence of tuberculosis (TB) in recent years and the increasing bacterial resistance to the standard anti-tuberculosis (anti-TB) drugs (Frieden, Sterling, Pablos-Mendez, Kilburn, Cauthen & Dooley, 1993), medical treatment has to rely on an increasing diversity of drugs, like the aminoglycosides, which have accompanying adverse toxic reactions such as nephrotoxicity, ototoxicity, etc. These aminoglycosides include streptomycin and kanamycin. Streptomycin has a selective action on the eighth cranial nerve, vestibular damage being commoner than auditory damage. Kanamycin is even more toxic, causing mainly cochlear damage (Collins, 1989).

Aminoglycosides destroy hair cells in the organ of Corti, cristae or maculae of the ear. Once lost, the hair cells in these receptors never regenerate (Johnson & Kamerer, 1985). This places the physician in the dilemma of having to weigh the possibility of morbidity that could result from aminoglycoside administration against the probable ill-effects of the infection being treated.

Ototoxicity causes damage, 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 damaging process gradually and systematically progresses further into the cochlea (Schuknecht, 1974). By the time this damaging effect becomes visible on a conventional pure-tone audiogram (125 Hz to 8000 Hz), valuable time for preventative measures has been lost and permanent damage has been done to the high frequency region in the cochlea. This could be prevented by regularly monitoring the high frequency (>8000 Hz) hearing sensitivity of the individual being treated with aminoglycoside drugs (Tonndorf & Kurman, 1984).

Aminoglycoside drugs are administered to patients at so-called "ototoxically safe" dosages, as determined by standard audiometry ranging from 125 Hz up to only 8000 Hz, while the real and early damage occurs at frequencies higher than 8000 Hz. With the advent of newer generation audiometers capable of testing hearing up to 20 KHz, and with very good test-retest reliability (Fletcher, 1965), it has become possible to monitor the hearing acuity of these individuals to detect the very early stages of ototoxicity, long before it becomes visible on standard audiometry, thus enhancing any preventative actions taken to halt the ototoxic effect (Voogt, 1987). It has also been demon-

strated that cochlear toxicity is reversible in more than half of all cases, if detected early enough and appropriate steps taken (Fee, 1980).

Recently many researchers have done further studies on high frequency hearing and thresholds, with the main aim of eliminating some of the differences that existed amongst the findings of previous researchers. Okstad, Laukli & Mair (1988) compared high frequency air conduction (AC) and electric bone conduction (EBC) thresholds in adults; Schechter, Fausti, Rappaport & Frey (1986) and Stelmachowicz, Beauchaine, Kalberer & Jesteadt (1989) worked on age-related high frequency AC thresholds; Frank (1990) examined high frequency AC thresholds in adults; and Frank & Dreisbach (1991) tested for repeatability of high frequency AC thresholds in adults. The vast range of differences between testing equipment, subjects and methodology resulted in considerable difficulties when an attempt at direct comparison of their results was made. There was, however, found to be reasonable agreement on high frequency AC thresholds and norms, but less on bone conduction (BC). Therefore it would appear that many questions still need to be answered with regard to the exact stimulus pathways and precise components of the EBC sensation.

With respect to these presently unanswered problem areas in EBC audiometry it would appear that the only truly reliable method of measuring the effect of ototoxic drugs on high frequency hearing using EBC, would be to compare each patient's post-treatment highest audible frequency test results with his own pre-treatment baseline results. As ototoxicity usually occurs bilaterally and given the fact that EBC cannot at the present time be effectively masked, the test results would indicate the BC hearing sensitivity of the "best" ear. This suits the purpose of this study as the only interest is determining the ototoxic effect of different anti-TB drug treatments on the highest frequency the subject can hear.

METHODOLOGY

From patients having to undergo treatment for TB in a TB hospital, all 172 admitted to this hospital in one month were included in this study and followed up over a six month period. These included newly diagnosed TB patients receiving the standard TB medication (a standardised four drug combination of rifampicin, isoniazid, pyrazinamide and ethambutol), patients with resistant TB receiving kanamycin (15 mg/kg/day) and patients with resistant TB receiving streptomycin (15mg/kg/day). This group of patients consisted of 106 males and 66 females, ranging in age from 7 to 71 years old.

From the test results of the original 172 subjects, 80 were excluded because they did not have measurable hearing above 8 KHz, developed middle ear problems, did not show up for follow-up audiometry, absconded from the treatment regimen, had renal failure, their drug treatment was altered/stopped, or they were discharged from hospital. Thus only data from 92 subjects was included in the analysis of the results.

All of them had their normal hearing (7 8 KHz) and their high frequency hearing (8 8 KHz) tested twice in the week prior to commencement of any treatment, and thereafter once a month over a period of six months. The average thresholds of the first two of each type of audiogram of each patient were used as the baseline audiograms for each patient against which any later changes in hearing was compared. As no effective masking was available for the high frequency tests, the test results indicated the "best ear" high frequency hearing for each patient. Consequently, the results of standard audiometry of each patient's left and right ears were also reworked to give a "best ear" test result, in order to be able to compare these results with those from the high frequency tests. A Maico MA-41 audiometer was used for the standard audiometry and an Audimax 500 for the high frequency tests.

The Audimax 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. Numerous studies have identified electrostimulation as a means of audio-transmission of electromechanical vibration in the bone and tissue structures surrounding the inner ear and the cochlea. It would therefore appear that the subject's BC hearing is being tested (Sommers & 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 sound pressure level (SPL) (Voogt, 1987).

Even though the full frequency range audiograms were recorded every time for the high frequency tests, for the purpose of this study only the highest frequency that the subject was able to hear at the maximum stimulus intensity of the Audimax audiometer, was taken into account. All test results for each patient were compared to their baseline test results to determine if any high frequency hearing loss (HFHL) had occurred.

The hospital is built on a vast expanse of open field, resulting in very quiet surroundings. The hearing tests were performed in a large and unused dental examination room which is situated a considerable distance away from the main hospital buildings, resulting in an extremely quiet test environment.

The treatment regimen for each subject was withheld from the audiologist until completion of the six month treatment period, and the information on the type of medication was given only as standard, streptomycin or kanamycin. Therefore the test results were grouped into a kanamycin group (K-group), a streptomycin group (S-group) and a standard anti-TB drug group (N-group). The test results of these groups were then statistically compared as were the results of males and females within each treatment group.

RESULTS

Using standard audiometry, it would appear that none of the subjects in these treatment groups experienced any resultant loss of hearing, as no differences could be found between their final audiograms and their baseline audiograms. This, however, was not the case when considering their high frequency audiograms. In this case very clear resultant losses of hearing could be seen. Therefore, only the high frequency audiometric data was statistically analysed.

Table 1 shows that the mean ages for the three groups were reasonably evenly matched, so the possible effect that age differences amongst the three groups could have had on the results, were negligible.

Table 2 reflects the characteristics of HFHL between

the three treatment groups.

From Table 3 it can be seen that in all three treatment groups there were no clinically significant differences in average HFHL between males and females, indicating that aminoglycoside ototoxicity is not gender specific.

Statistical analysis was comprised of a comparison of the three treatment groups (K, S and N) in respect of HFHL by the Kruskal-Wallis test, which revealed a highly significant difference amongst the groups (Chi-squared = 42,53 and p = 0,0001). Pairwise comparisons by the rank sum test showed that the mean HFHL value in the K-group differs significantly from the means in the S-group and N-group ($p < 0,01$). Clinically the means in the S- and N-groups did not differ. The K-group, however, suffered a marked HFHL as a result of the medication they received.

TABLE 1: Age characteristics of subjects.

Treatment group	n	Age (Yrs)			
		Mean	Std. dev.	Min.	Max.
K	23	35,22	10,60	7	50
S	12	30,92	8,12	19	41
N	57	35,58	12,11	16	71

TABLE 2: Comparison of HFHL between the three treatment groups.

Treatment group	n	Age (Yrs)			
		Mean	Std. dev.	Min.	Max.
K	23	2,17	1,76	0,20	7,60
S	12	0,65	0,28	0,20	1,20
N	57	0,32	0,20	0,00	0,80

TABLE 3: Comparison of HFHL between males and females within the three treatment groups.

Treatment group	HFHL (KHz)	
	Male	Female
K-group:		
n	11	12
Mean	2,18	2,15
Std. Dev.	1,37	2,11
S-group:		
n	5	7
Mean	0,68	0,63
Std. Dev.	0,23	0,34
N-group:		
n	35	22
Mean	0,32	0,32
Std. Dev.	0,20	0,21

DISCUSSION

An unfortunate aspect of this study was that almost 47% of the original subjects had to be excluded from the final set of data acquired. Nevertheless, the remaining 53% of subjects yielded some interesting data.

It was very clear that although all the subjects had their hearing tested regularly by standard audiometry (0-8 KHz) to detect any ototoxic effect (and if found positive treatment was ceased/altered), ototoxicity still occurred. But as this ototoxicity had an effect only on the very high frequencies, standard audiometry was not able to detect it, whilst high frequency audiometry showed the effect very clearly. Thus it would appear that the practice of using standard audiometry to monitor ototoxicity and to determine so-called "safe" aminoglycoside dosage levels is of doubtful clinical use.

None of the subjects in this study suffered any renal failure, so there was no abnormally high accumulation of treatment drug (which can also cause ototoxicity) in the blood serum. At the "safe" drug levels administered to the subjects, kanamycin was proved to have an ototoxic effect about three times that of streptomycin. Clearly, the ototoxically "safe" levels of kanamycin administration requires more attention and probably some readjustment. It would appear that these levels are really not "safe" at all. The administration of aminoglycosides at these "safe" levels are also being questioned by De Vaal (1994), who found very wide intrapatient variation in aminoglycoside pharmacokinetics when using the currently recommended dosages.

With respect to gender, it could be seen that both kanamycin and streptomycin showed no gender specificity in terms of ototoxic effects. Males and females were almost equally affected by the ototoxicity of these two aminoglycoside drugs.

An interesting finding was that the group of subjects who received no kanamycin or streptomycin (N-group), but only the standard anti-TB drug treatment (rifampicin, isoniazid, pyrazinamide and ethambutol, administered for a six month period), also showed a very small but real decrease (0,32 KHz) in high frequency hearing acuity during this six month period. It could be that the standard anti-TB treatment also has a very mild ototoxic effect, but according to Teale, Goldman & Pearson (1994), this standard treatment regimen has no ototoxic effect whatsoever. It is also possible that this mild deterioration in high frequency acuity simply reflected the normal reduction which occurs as a part of the natural ageing process. This would be in agreement with Stelmachowicz et al. (1989) who found a monotical increase in high frequency threshold as a function of age.

The N-group reduction of 0,32 KHz in high frequency acuity over a six month period, if extrapolated, reflects a reduction of 12,8 KHz over 20 years. What is not so clear is whether this reduction truly occurs linearly with increasing age. As the average age of subjects in the N-group was about 35 years, this would then give a highest audible frequency of about 8 KHz by age 55, which appears to fit in well with the fact that most people start showing a high frequency hearing loss on standard audiometry from this age onwards. Stelmachowicz et al. (1989) found that the loss in high frequency hearing begins at approximately 40 years old, while Schechter et al. (1986) determined this age to be approximately 30 years old.

If this ageing factor is taken into consideration, then it can be deduced that in the S-group, the streptomycin treatment regimen actually had a fairly minor ototoxic effect, as the average HFHL of 0,65 KHz should then be reduced by 0,32 KHz, giving a 0,33 KHz HFHL as a result of the streptomycin treatment.

This may then also mean that the average high frequency hearing loss of 2,17 KHz that occurred in the K-group should be decreased by 0,32 KHz to 1,85 KHz, if the effect of ageing is to be taken into account.

It therefore becomes clear that the kanamycin treatment regimen is more than three times more ototoxic than the streptomycin regimen (average HFHL of 2,17 KHz vs. 0,65 KHz). If the above-mentioned correction for the effect of ageing is taken into consideration, then it means that the kanamycin regimen is almost six times more ototoxic than the streptomycin regimen (average HFHL of 1,85 KHz vs. 0,33 KHz).

CONCLUSION

This study showed that high frequency audiometry is superior to standard audiometry with regard to the early detection of ototoxicity and that the use of standard audiometry for detecting ototoxicity is really of no clinical value.

Furthermore it was found that the so-called "safe" levels presently used in anti-TB treatment still lead to ototoxic damage. These levels will most probably have to be revised. The kanamycin treatment regimen was found to be three times more ototoxic than that of streptomycin. Ageing was also found to have a possible effect on the HFHL measured. If a correction was made for HFHL occurring as a result of ageing, then kanamycin was found to be almost six times more ototoxic than streptomycin.

It was also found that kanamycin and streptomycin ototoxicity were not gender specific as males and females were equally affected.

Lastly it became quite clear that the specific effects of ageing on the high frequency hearing will require further long-term studies.

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