# Chapter 4

## Aminoglycosides

# a | Hearing loss and nephrotoxicity in long-term aminoglycoside treatment in patients with tuberculosis.

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P. de Jager,* R. van Altena†

* Faculty of Medical Sciences, University of Groningen, Groningen, † Tuberculosis Centre Haren, Haren, the Netherlands.

## SUMMARY

OBJECTIVE: To investigate the ototoxic and nephrotoxic effects of long-term use of aminoglycosides.

DESIGN: Patients treated for tuberculosis with aminoglycosides were evaluated for hearing loss and nephrotoxicity for a minimum of 14 days.

RESULTS: Hearing loss of 15 decibels (dB) at two or more frequencies, or at least 20 dB hearing loss at at least one frequency, was found in 18% of our total population treated with aminoglycosides (amikacin, kanamycin and/or streptomycin). In the group treated with kanamycin this percentage was 15.6. None of the factors sex, age, treatment duration, total aminoglycoside doses or first serum creatinine concentration, was found to be associated with hearing loss. Nephrotoxicity percentages at the end of treatment with aminoglycoside or kanamycin are 7.5% (1.9%) and 4.5% (2.3%) respectively, using the definition increase of serum creatinine ≥27 µmol/l (≥44 µmol/l). Patients developing nephrotoxicity had a longer duration of treatment and received larger total doses.

CONCLUSIONS: Patients developing nephrotoxicity had a significantly longer duration of treatment with aminoglycosides, and received a larger total dose. We did not find any factor significantly associated with the development of hearing loss. In the long-term treatment of tuberculosis with aminoglycosides, ototoxicity seems to be a greater problem than nephrotoxicity.

KEY WORDS: hearing loss; nephrotoxicity; aminoglycosides; kanamycin; tuberculosis

## INTRODUCTION

Both ototoxicity and nephrotoxicity are known to be major possible side-effects of treatment with aminoglycosides. In our Tuberculosis Centre patients are treated, often for many months, with aminoglycosides. Very little is known about the side-effects of long-term treatment with aminoglycosides.

The aim of this retrospective study was to investigate the overall auditory and nephrotoxic effects of aminoglycosides after long-term use. Aminoglycosides are known to have some degree of toxicity to the eighth cranial nerve; both vestibular and auditory divisions may become affected. In the case of cochlear damage, hearing loss occurs as a result of degeneration of the hair cells of the cochlea, beginning at the basal coil and progressing to the apex. High frequency hearing loss is followed by loss of lower frequencies. In the early stages of ototoxicity, damage is limited to the higher frequencies and does not usually affect frequencies utilised in conversational hearing. Vestibular disturbance is found predominantly in the vestibular sensory cells from the crista ampullaris, and causes ataxia and nystagmus. Neither cochlear nor ampullar cells can regenerate once they have been destroyed.[1–6]

Ototoxicity does not generally appear until 5 days after the start of aminoglycoside treatment.[3] It has been shown experimentally that toxicity in the cochlear and the vestibular portions may vary between different aminoglycosides. Streptomycin is predominantly vestibulotoxic, while amikacin appears to be exclusively cochleotoxic.[7] Amikacin and kanamycin were found to be similarly ototoxic in cats.[8]

Aminoglycoside antibiotics are nephrotoxic by inducing necrosis of the proximal tubules ranging from focal to diffuse lesions. Aminoglycosides are not metabolised, and they are excreted almost exclusively by glomerular filtration. The onset of glomerular dysfunction does not start until 5–7 days after initiation of treatment. Increase in serum creatinine is usually noted during the second week of treatment. The clinical threshold of aminoglycoside nephrotoxicity is determined by the rate of necrosis and the rate of regeneration of proximal tubular cells.[9–11]

Although many comparative studies of aminoglycoside nephrotoxicity in humans are available, there is no consensus about the differences in nephrotoxicity of the aminoglycosides.[7,11,12] Streptomycin was found to be the least nephrotoxic in a study comparing the effects of aminoglycosides on renal function and structure in the rat, while amikacin was found to be as toxic as kanamycin. The relevance of these findings to the situation in humans remains unclear.[13] The number of free amino groups seems to correlate with the relative nephrotoxicity of these compounds. Both amikacin and kanamycin have four free amino groups, while streptomycin has three, and therefore streptomycin is considered to be the least toxic.[14]

## MATERIALS AND METHODS

### Patients and aminoglycosides

All patients hospitalised in the Tuberculosis Centre Beatrixoord in the period January 1995 to July 2000 and treated for a minimum period of 14 days with streptomycin, amikacin or kanamycin, were included in this retrospective chart study. Diagnoses were multidrug-resistant tuberculosis, tuberculosis with intolerance or resistance to isoniazid or rifampicin, or infections with environmental mycobacteria. Hearing loss and nephrotoxicity were determined for all patients receiving these aminoglycosides.

Consecutive audiograms were evaluated for hearing loss for each patient. The first audiogram of each patient was considered as the baseline audiogram. All audiograms were obtained in a sound-proof auditory test chamber with an audiometer at 250, 500, 1000, 2000, 4000 and 8000 Hz. If necessary, translators were available.

An audiogram is considered to be normal with a maximum of one value between 20 and 30 decibels (dB), not involving conversational hearing ability, and the rest between 0 and 20 dB. Hearing loss was defined as a loss of 15 dB at two or more frequencies, or a minimum of 20 dB hearing loss of at least one frequency between 0.25 and 8.0 kHz. The time between the audiograms was variable. In our retrospective study, not enough data were available to be able to reach conclusions regarding signs or symptoms of vestibular dysfunction.

Serum creatinine levels were determined at the start of aminoglycoside treatment, with normal values between 60 and 110 µmol/l, and were evaluated throughout the whole period of treatment. Aminoglycoside-related nephrotoxicity was defined as a rise in the serum creatinine concentration of 27 µmol/l (0.3 mg/ml) and 44 µmol/l (0.5 mg/ml) at any time during treatment. The reversibility was determined by the creatinine level at the end of treatment. Serum creatinine tests were obtained very frequently, almost daily at the start of treatment. When the patient's situation improved, the tests were performed less frequently.

Age, sex, total duration of aminoglycoside treatment, total aminoglycoside doses and serum creatinine level were determined before treatment commenced.

For continuous variables, differences between groups were compared using the Mann-Whitney rank sum test. The $X^2$ test was used for analysing categorical data. A P value of less than 0.05 was accepted as indicating statistical significance.

## RESULTS

One hundred and ten patients treated with kanamycin, amikacin, streptomycin, or a combination of these, were included in this study. There were 81 (73.6%) men and 29 (26.4%) women, with a mean age of 35.7 years (range 10–83, standard deviation [SD] 16.0). The total number of weeks for which patients received aminoglycosides was 11.8 (SD 8.1), during which they received 53.2 g of any aminoglycoside (range 8–191 g, SD 32.2).

At the start of treatment, the aminoglycosides were given daily because of the high bacterial load; after a certain period a switch was made to a dosage schedule of five or three times a week, in order to be able to treat for a longer period. The hypothetical reasons for this were to minimise the toxic effects and to achieve optimal results. In general the average dose varied between 750 and 1000 mg by intravenous infusion, depending on serum drug and creatinine levels and body mass. The choice between the three different aminoglycosides was based on sensitivity tests and cost. The preferred choice was kanamycin. No patient received more than one aminoglycoside at a time.

Ninety patients were treated with kanamycin (K), seven with streptomycin (S), and two with amikacin (A). Two aminoglycosides were used in 10 patients (5 KS, 4 KA, 1 AS) and one patient received all three aminoglycosides during the period of treatment.
Treatment was changed for reasons of cost, availability of drugs, and problems of drug resistance.

Of the 90 patients treated with kanamycin only, there were 67 (74.4%) men and 23 (25.6%) women, with a mean age of 36.9 years (range 14–83, SD 16,5). They received 46.3 g of kanamycin (SD 24.6), over 10.2 weeks (SD 6.2).

**TABLE 1** Hearing loss observed during and at the end of treatment

| Aminoglycoside | Patients *n* | Hearing loss during treatment *n* (%) | Hearing loss last audiogram *n* (%) |
|---|---|---|---|
| Kanamycin (K) | 45 | 9 (20.0) | 7 (15.6) |
| Streptomycin (S) | 5 | 3 (60.0) | 3 (60.0) |
| Amikacin (A) | 2 | 1 (50.0) | 1 (50.0) |
| K + S | 3 | 0 | 0 |
| K + A | 4 | 0 | 0 |
| S + A | 1 | 0 | 0 |
| K + S + A | 1 | 0 | 0 |
| Total | 61 | 13 (21.3) | 11 (18.0) |

*Audiograms*

Only one audiogram was available for 49 patients. The audiograms of 18 of these were considered normal. Of the 31 abnormal audiograms, 12 did not interfere with conversational hearing ability, and 19 did. One patient complained of loss of conversational hearing ability after 5 weeks of treatment. The audiogram confirmed this result, but unfortunately there was no earlier audiogram.

Two or more audiograms were available for the remaining 61 patients, who received 62.9 g aminoglycosides (range 15–181, SD 34.8), over 11.9 weeks (range 3–46, SD 8.0). Hearing loss was observed in 13 (21.3%) patients; it was bilateral in seven (53.9%) and unilateral in six (46.1%). Recovery of hearing loss occurred in three patients. At the last audiogram, four (6.6%) showed bilateral and seven (11.5%) showed unilateral hearing loss (Table 1). In five patients only the high frequencies (4000 and 8000 Hz) were involved, and in one patient only the low frequencies (250, 500, 1000 Hz) were involved. In seven patients there was a loss of conversational hearing ability: in five cases there was already conversational hearing loss at the start of treatment, while in the other two patients only the highest frequency of conversational hearing ability (4000 Hz) was involved.

Improvement of hearing of 15 dB or more during treatment was found in at least 22 of all patients

(36.1%), and an improvement of 20 dB or more in 10 patients (16.4%). In the group of patients with hearing loss an improvement of 15 dB was found in four (30.8%), and one of 20 dB or more in three (23.1%) patients.

In the group of patients receiving kanamycin, two or more audiograms were available from 45 patients. They received 42.6 g aminoglycosides (range 14–97, SD 22.9) over 9.4 weeks (range 3–25, SD 5.0). Hearing loss was shown in nine (20.0%) of the patients, three (6.7%) bilateral and six (13.3%) unilateral. Recovery of hearing loss developed in two patients. Unilateral hearing loss was observed at the last audiogram in five patients (11.1%) and bilateral in two (4.4%) (Table 1). We did not find any factor significantly associated with the development of hearing loss (Table 2).

**TABLE 2** Univariate associations of independent factors related to hearing loss at any time during treatment

| Factors | Hearing loss | Without hearing loss | *P* value |
|---|---|---|---|
| Aminoglycoside treatment | | | |
| Sex (%) | | | |
| Male | 83.3 | 73.5 | |
| Female | 16.7 | 26.5 | 0.477 |
| Age (years) | 41.5 ± 23.5 | 33.2 ± 13.0 | 0.591 |
| Duration of AG | | | |
| treatment (weeks) | 10.1 ± 5.8 | 12.4 ± 8.4 | 0.437 |
| Total dose of AG (g) | 75.4 ± 40.7 | 59.5 ± 32.7 | 0.252 |
| T0 creatinine level (µmol/l) | 70.4 ± 9.5 | 68.9 ± 16.4 | 0.721 |
| | | | |
| Kanamycin treatment | | | |
| Sex (%) | | | |
| Male | 88.9 | 77.1 | |
| Female | 11.1 | 22.9 | 0.436 |
| Age (years) | 41.9 ± 24.2 | 35.5 ± 14.0 | 0.771 |
| Duration of AG | | | |
| treatment (weeks) | 7.9 ± 3.4 | 9.9 ± 5.3 | 0.405 |
| Total dose of AG (g) | 66.4 ± 36.4 | 49.0 ± 22.1 | 0.211 |
| T0 creatinine level (µmol/l) | 70.7 ± 11.2 | 71.4 ± 13.8 | 0.940 |

AG = aminoglycoside; T0 = time zero.

### *Creatinine serum concentrations*

There was no initial serum concentration available for three patients; none of these patients had any serum creatinine concentration suggesting nephrotoxicity.

The initial and subsequent serum creatinine concentrations were available for the remaining 107 patients, 33 of whom had a serum creatinine concentration of 59 µmol/l or lower, and none of whom had a higher concentration than 110 µmol/l. They received 53.5 g aminoglycosides (range 8–191, SD 32.5), over 11.9 weeks (range 2–46, SD 8.1). An increase in serum creatinine concentration of at least 27 µmol/l (0.3 mg/ml), and 44 µmol/l (0.5 mg/ml) throughout treatment was observed in respectively 18 (16.8%) and 10 (9.3%) of the

patients. In respectively 10 and eight cases, the increased serum creatinine concentration returned to normal values, and the increased serum creatinine concentration was still detectable in respectively eight (7.5%) and two (1.9 %) patients at the end of treatment (Table 3). Only one patient had a serum creatinine concentration (140 µmol/l) higher than the normal values (60–110 µmol/l).

All serum creatinine concentrations were available for the 88 patients receiving kanamycin. They received 46.6 g aminoglycosides (range 8–143, SD 24.8) over 10.2 weeks (range 2–44, SD 6.3). Nephrotoxicity during treatment, with increases of at least 27 µmol/l and 44 µmol/l, was observed in respectively 13 (14.8%) and six (6.8%) of these patients. In respectively nine and four cases the serum creatinine concentration returned to normal values, and an increase in serum creatinine concentration was still detectable in respectively four (4.5%) and two (2.3%) patients at the end of kanamycin treatment (Table 3).

In the univariate analysis, patients developing nephrotoxicity had a significantly longer duration of treatment with aminoglycosides and received a larger total dose (Table 4).

**TABLE 3** Nephrotoxicity observed during and at the end of treatment

| Aminoglycoside | Patients *n* | Increase ≥27 µmol/l during treatment n (%) | Increase ≥27 µmol/l end of treatment n (%) | Increase ≥44 µmol/l during treatment n (%) | Increase ≥44 µmol/l end of treatment n (%) |
|---|---|---|---|---|---|
| Kanamycin (K) | 88 | 13 (14.8) | 4 (4.5) | 6 (6.8) | 2 (2.3) |
| Streptomycin (S) | 7 | 2 (28.6) | 1 (14.3) | 2 (28.6) | 0 |
| Amikacin (A) | 2 | 1 (100) | 1 (100) | 1 (100) | 0 |
| K + S | 4 | 1 (25) | 1 (25) | 0 | 0 |
| K + A | 4 | 0 | 0 | 0 | 0 |
| S + A | 1 | 0 | 0 | 0 | 0 |
| K + S + A | 1 | 1 (100) | 1 (100) | 1 (100) | 0 |
| Total | 107 | 18 (16.8) | 8 (7.5) | 10 (9.3) | 2 (1.9) |

**TABLE 4** Univariate associations of independent factors related to the development of nephrotoxicity

| Factors | Nephrotoxicity | Without nephrotoxicity | *P* value |
|---|---|---|---|
| Aminoglycoside treatment | | | |
| Sex (%) | | | |
| Male | 72.2 | 73.5 | |
| Female | 27.8 | 27.0 | 0.944 |
| Age (years) | 34.7 ± 18.3 | 36.2 ± 15.8 | 0.342 |
| Duration of AG | | | |
| treatment (weeks) | 19.9 ± 11.7 | 10.3 ± 6.1 | 0.000* |
| Total dose of AG (g) | 86.1 ± 44.2 | 46.8 ± 25.1 | 0.000* |
| T0 creatinine level (µmol/l) | 67.7 ± 14.9 | 70.0 ± 16.4 | 0.588 |
| | | | |
| Kanamycin treatment | | | |
| Sex (%) | | | |
| Male | 69.2 | 74.7 | |
| Female | 30.8 | 25.3 | 0.680 |
| Age (years) | 37.1 ± 20.2 | 37.3 ± 16.0 | 0.609 |
| Duration of AG | | | |
| treatment (weeks) | 17.6 ± 10.2 | 9.0 ± 4.2 | 0.001* |
| Total dose of AG (g) | 76.6 ± 30.6 | 41.4 ± 19.6 | 0.000* |
| T0 creatinine level (µmol/l) | 70.3 ± 15.4 | 70.8 ± 15.8 | 0.888 |

* Statistical significance.
AG = aminoglycoside; T0 = time zero.

## DISCUSSION

In this retrospective study, we examined the toxic effects of long-term intravenous aminoglycoside treatment. In most studies, the length of aminoglycoside treatment had a maximum of 2–3 weeks. In our study, patients had a minimum treatment of 2 weeks, with a mean of 11.8 (SD 8.1) and a maximum of 46 weeks. They received an average of 53.2 g of aminoglycosides (range 8–191 g, SD 32.2).

In our centre, 21.3% developed hearing loss during treatment with aminoglycosides, 20.0% with kanamycin, 18.0% at the last audiogram of patients treated with aminoglycosides, and 15.6% at the last audiogram of patients treated with kanamycin

(Table 1). These incidences are higher than the average percentages of hearing loss for amikacin (13.9%) found by Kahlmeter and Dahlager in clinical studies published between 1975 and 1982.15 More recent studies about the toxicity of kanamycin are not available. In the literature, there is a discrepancy between on the one hand the clinical observations that very few patients receiving aminoglycosides complain of developing hearing loss, and on the other hand the reported incidence of hearing loss of up to 41% in studies in which auditory thresholds were obtained. Reasons for this discrepancy could be diverse: patients are unlikely to complain of hearing loss until considerable damage has been done, and there is no universally agreed upon standard for the definition of drug-induced hearing loss.[16]

Hearing loss does not generally appear until at least 5 days after the start of aminoglycoside treatment. Not all cases of hearing loss may be due to the ototoxic effects of aminoglycosides: patients receiving no ototoxic drugs can have auditory changes considered to represent the established criteria of ototoxicity.[16]

Brummett found test-retest differences suggestive of 20–30% hearing loss in a group of healthy volunteers who were not taking any known ototoxic drugs.[17] We found an improvement in hearing of 15 dB or more in 22 patients (36.1%) and an improvement of 20 dB or more in 10 patients (16.4%). In the group with hearing loss, at least one improvement of 15 dB was seen in four patients (30.8%), and an improvement of 20 dB in three (23.1%) patients. There may be more than one explanation for this: inaccurately obtained audiograms, fluctuating conductive hearing losses (allergies, middle ear and atmospheric pressure changes, collapsed external auditory canals, the common cold, and other sources), use of other ototoxic drugs, attentiveness, learning effects and motivation of the test subjects.[17] Due to the lack of many baseline audiograms, we are unable to say anything about hearing loss over the total period of treatment. The reasons for missing audiograms made at the start of treatment include the fact that critically ill patients very frequently cannot undergo baseline auditory testing before receiving aminoglycosides, and some patients started their aminoglycoside treatment in other hospitals where such tests were not being performed.

In many cases we could not determine which abnormalities in baseline audiograms were pre-existent, and which were the result of cochlear damage induced by aminoglycosides. Pre-existing high frequency hearing loss may be related to advancing age, congenital defects, previous ear infections or noise exposure.

Risk factors in the development of auditory toxicity are still a matter of discussion. Moore et al. identified risk factors that included duration of aminoglycoside use, bacteraemia, fever, liver dysfunction and hypovolaemia. Age did not reach statistical significance.[18] Conversely, Gatell et al. found that only age was retained as an independent factor in the development of auditory toxicity.[19] In our study, age, sex, total duration of

aminoglycoside treatment, total aminoglycoside dose and serum creatinine level before the start of treatment were not significantly associated with the development of hearing loss (Table 2). Because of the lack of data about vestibular dysfunction, we can not draw any conclusions about vestibular toxicity.

The incidence of nephrotoxicity of aminoglycosides or kanamycin only was 16.8% or 14.8%, using the increase of serum creatinine levels ≥27 µmol/l over the total period of treatment as the definition.

Incidences at the end of treatment were respectively 7.5% and 4.5%. Using the definition of serum creatinine increase ≥44 mol/l, the incidence decreases to 1.9% overall, and to 2.3% for kanamycin, at the end of treatment (Table 3). Incidences in the literature vary between 2% and 50%. Kahlmeter and Dahlager, in a review of aminoglycoside toxicity of clinical studies published between 1975 and 1982, found a 9.4% average incidence of nephrotoxicity for amikacin.[12,15] As far as we know, no investigations have been done recently on the nephrotoxicity of kanamycin.

One reason for the relatively low rate of nephrotoxicity found in our centre could be the understanding that a once-daily aminoglycoside regimen reduces the potential for toxicity.[20] Second, many different definitions of nephrotoxicity are used. Third, the study of different patient populations may produce very different incidences of nephrotoxicity. A complex combination of drug- and patient-related factors, such as dose duration, dose regimen, prior aminoglycoside treatment, choice of drug, associated drugs, patient age, prior renal or hepatic insufficiency, patient illness and hypovolaemia are involved in the development of nephrotoxicity. It has been noted before that the highest incidence of renal damage has occurred in severely ill populations.[7,12,14,18,21] In our study we did not include data on other medications that patients received, patient illness, volume depletion or prior hepatic insufficiency, so it is not possible to determine whether there were any interactions.

It is of note that only one of our patients had a serum creatinine value at the end of treatment that was higher than the normal values. Increased creatinine values can also be the result of increasing muscle mass. At the start of treatment, many patients are severely ill and often improve physically during treatment.

We found that patients who developed nephrotoxicity had a significantly longer duration of treatment with aminoglycosides, and received larger total doses. None of the patients had a creatinine level above the normal values suggestive of pre-existing renal failure (Table 4).

As there was no follow-up of most patients after the end of treatment, we cannot say anything about the long-term reversibility of damage to the kidneys.

Both hearing loss and nephrotoxicity (increase of serum creatinine ≥27 µmol/l) developed in five patients and was seen at the end of treatment in two patients.

There are some limitations to this retrospective study: the lack of many baseline audiograms, the variability in the frequency of obtaining audiograms and serum creatinine tests, the lack of data about vestibular dysfunction, other medications the patients received, the patients' illnesses, volume depletion and prior hepatic insufficiency, and the different aminoglycosides and schedules used. A prospective study based on the frequency of serum creatinine levels and of obtaining audiograms may clarify the frequency of evaluations, while a prospective study based on dosing schedules and serum aminoglycoside levels may clarify the differences in toxicity.

## CONCLUSIONS

In our study, age, sex, total duration of aminoglycoside treatment, total aminoglycoside dose and serum creatinine level before the start of treatment were not significantly associated with the development of hearing loss. Patients developing nephrotoxicity had a significantly longer duration of treatment with aminoglycosides and received larger total doses, a significance we did not find in hearing loss. In the long-term treatment of tuberculosis with aminoglycosides, hearing loss seems to be a greater problem than nephrotoxicity.

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