Screening for aminoglycoside auditory toxicity in the old

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1 We have investigated 22 patients receiving gentamicin, mean (s.d.) age 78 (6) years for auditory toxicity, using a standard audiometric technique in a sound-treated room (Study 1).

2 Use of a portable audiometer might allow a larger and more representative proportion of patients treated with aminoglycosides to be screened for ototoxicity. A method for detecting high frequency loss suitable for use in the ward was evaluated in 12 volunteers aged 27 (4) years (Study 2).

3 The error inherent in taking hearing at the start of treatment as a reference point was measured in 16 patients, aged 81 (8) years, prescribed non-ototoxic antibacterials (Study 3).

4 A significant ($P = 0.05$) reduction in hearing threshold was detected in Study 1, although psychometric tests revealed unchanged or improved ability to co-operate. This occurred only at 4000 Hz, the highest frequency used. The magnitude of this loss, mean 2.5 dB, was similar to that of the improvement in threshold detected ($P = 0.0004$) early in the course of treatment in Study 3. Thus, underestimation of ototoxicity is likely.

5 If a change of threshold of 10 dB or more is taken arbitrarily to represent a real change in hearing, then there was a significant excess of patients in Study 1 with losses at 4000 Hz only ($P = 0.032$). The six with such losses at this frequency were older than the rest. However, there was a significant ($P < 0.02$) positive correlation between log mean pre-dose serum gentamicin concentration and age. Thus, it remains to be determined whether presbycusis sensitises those hair cells which it does not destroy to toxic damage.

6 The cumulative dose of gentamicin (for a course of the duration given) was calculated according to published prescribing aids. There was no systematic reduction in the ratio of the dose recommended by a given aid to the dose prescribed in the six with hearing losses as defined above.

7 In Study 2, thresholds obtained at 6000 Hz in the open ward were, on average, 0.9 dB higher than in the sound treated room, but the effect of venue did not reach statistical significance. In the morning thresholds were marginally, but significantly ($P = 0.04$), lower than in the afternoon. Precision, as measured by the standard deviation of replicate determination, was independent of test conditions. Using multiple (ten) threshold determinations appeared to improve resolution.

8 The difference in threshold which could be reliably detected in elderly patients on the ward in Study 3 was 36% higher than the mean difference attributed to ototoxicity in Study 1, where conventional audiometry was used. Resolution might be improved by making, at

a single high frequency, more than the five determinations used in Study 3. If so, audiometry performed on the ward may prove adequate for patients who cannot be moved.

9 There was no evidence that advancing years (65 to 93) had any detrimental effect on the results obtained on the ward (Study 3).

Keywords gentamicin ototoxicity audiometry presbycusis screening

Introduction

Advancing years (Wright, 1979) and aminoglycoside ototoxicity (Keene *et al.*, 1982; Nadol, 1981) are each associated with loss of hearing at high frequencies. Are, then, the elderly, at greater risk of sustaining hearing losses than younger patients given an equivalent exposure to aminoglycosides? We have studied the auditory toxicity of gentamicin in patients aged 65 years and over, using standard audiometric procedures in a sound-treated room. However, testing patients whose condition allows them to be moved to the sound-treated room will tend to exclude those who are sick; the latter, are, perhaps, particularly susceptible to ototoxicity because of altered pharmacokinetics and/or dynamics. Moreover, audiometric measurements taken at the start of treatment, when the patient's ability to cooperate with audiometry is impaired because of the illness, may underestimate the patient's normal level of hearing (Davey *et al.*, 1983) and, consequently, the auditory toxicity of the treatment. A method for detecting high frequency hearing loss, which is suitable for use on the ward, is evaluated and the error inherent in taking the measurement of hearing at the start of treatment as a reference point quantified.

Methods

The three studies, the first to determine the frequency of gentamicin ototoxicity in the elderly, according to a set criterion (Winkel *et al.*, 1978) and using standard audiometric methods, the second to evaluate an audiometric screening method and the third to appraise the practice of taking the hearing at the start of treatment as a reference point, had the approval of the local ethics committees. Informed consent was sought from the subjects.

Study 1

Patients, aged 65 years and over, in whom the physician responsible for their care had made

the decision to start gentamicin treatment, were identified. Pure-tone audiometry was carried out in those, with no history of or evidence for middle ear damage, who were judged capable of co-operating. A Kamplex AC4 audiometer was used in a sound-treated room. The sequence in which the frequencies were tested and the procedure for threshold determination were those recommended by the British Society of Audiology (1981). In order to minimise demands on the patients, air conduction only was tested at frequencies of 500, 1000, 2000 and 4000 Hz. The frequency of 250 Hz was omitted because aminoglycoside ototoxicity initially affects higher frequencies. The presence of presbycusis often meant that the patient's hearing level at 8000 Hz was beyond the maximum sound intensity produced by the audiometer. The audiometry was repeated at the end of the course of gentamicin.

To assess any change in the patient's ability to co-operate over the course of treatment, two psychometric tests were carried out within 2 h of each audiometric session. The first was the Cognitive Assessment Scale (CAS), from the Clifton Assessment Procedures for the Elderly (Pattie & Gillear, 1979): this includes tests of information/orientation and mental ability. The second was adapted from the Kendrick battery of tests for the detection of dementia in the elderly (Gibson & Kendrick, 1979): one hundred random numbers containing ten 'sevens' were read out at a loudness which the patient could hear comfortably. The patient was asked to raise a hand whenever 'seven' was heard. The number of correct responses was counted. This was thought likely to be similarly demanding on the patient's ability to concentrate as audiometry.

Patients were questioned on, and observed for, signs of vestibular toxicity. Only incoordination of gait not explained by the patient's general condition was to be regarded as associated with treatment.

An initial dosage, selected according to the nomogram of Mawer *et al.* (1974) (using age, gender, bodyweight and serum creatinine con-

centration as entry data), was recommended to the doctor responsible for the patient's care, but patients who received other regimens were not excluded from the study. However, those who had received aminoglycoside therapy within the previous 6 months were excluded. Previous administration of other potentially ototoxic drugs was noted. Patients receiving these other drugs concurrently were excluded only if the dosage was changed in relation to the course of gentamicin.

Gentamicin was administered by intravenous bolus or intramuscular injection. Venous blood samples for gentamicin assay were collected into non-heparinised glass tubes (Yourassowsky *et al.*, 1972). Two pairs of samples were taken from each patient, the first sample of each pair being taken immediately before administration of a dose and the second 1 h after. The initial pair was taken within 24 h of the first dose of gentamicin, the other near the end of treatment. Where a course of 4 days or more was planned, another pair of samples was taken 2–3 days into that course. Maintenance doses were adjusted according to assay results, in an attempt both to achieve peak serum gentamicin concentrations adequate to kill the particular infecting organism and to maintain the pre-dose concentration below the $2.0 \mu\text{g ml}^{-1}$ recommended by local antibiotic policy. Samples were assayed by enzyme multiplied immunoassay technique (EMIT, Syva). The between assay coefficient of variation for a sample assayed in duplicate was 8.7% at $6.4 \mu\text{g ml}^{-1}$ and 7.4% at $3.0 \mu\text{g ml}^{-1}$.

Individual serum gentamicin concentration time profiles were simulated by entry of the patient's characteristics and the gentamicin concentration data into the commercially available OPT computer program (Kelman *et al.*, 1982). The exposure of each patient to gentamicin was expressed not only in terms of the mean measured pre-dose serum gentamicin concentration but also as the total area under the serum concentration/time profile and the 'baseline area', the area under a line joining the pre-dose serum concentrations. An alternative estimate of baseline area was made by multiplying the mean of the measured pre-dose gentamicin concentrations by the duration of treatment.

Study 2

Healthy, non-elderly, volunteers, were recruited. Audiometry was carried out in three different environments: a ward day room, a ward bay and a sound-treated room. Each subject was tested twice, once in the morning and once in the afternoon in each of the three venues

in the same assigned sequence. Two subjects were allocated to each of the six possible sequences of the three venues. During each test, ten consecutive threshold determinations at 6000 Hz were carried out for each ear, using a Maico MA41 portable audiometer. (This frequency was chosen with a view to avoiding the limitations imposed by presbycusis (see Study 1), whilst still working at a frequency sufficiently high to be very sensitive to aminoglycoside toxicity.) A table of random numbers was used to determine the order in which the ears (odd for right first, even for left) were tested.

Study 3

Hospital inpatients, aged 65 years or over, suffering from an infection, not requiring treatment with a potentially ototoxic antibacterial agent were recruited. The patients' hearing was monitored on the ward, using multiple threshold determination at 6000 Hz. Tests were carried out not later than 48 h after the start of a course of treatment, around the middle and at the end of it and at 1 week and 1 month after the end. Although only five threshold determinations in each ear were made per session (as compared with the ten in Study 2), there were three sessions on each test day. The first session was in the morning, the second in the late morning or early afternoon and the third in the late afternoon, with a minimum of 2 h rest between sessions. Two psychometric tests were carried out during a rest period on each test day. The test adapted from the Kendrick battery was used, as in Study 1, but a test more demanding on ability to concentrate, from the Wechsler Adult Intelligence Scale (Wechsler, 1955), was substituted for the CAS. In this test, patients were asked to repeat a series of numbers forward (progressing from a three to an eight digit number) and another series of numbers (of two to eight digits) backwards. Each exercise was terminated when an error was made, the maximum number of digits repeated correctly being recorded.

Statistical methods

Study 1 Two approaches were adopted to the detection of gentamicin auditory toxicity. Firstly, changes in hearing threshold in the patients studied (for each of the four frequencies and for each ear) were examined for significance using paired *t*-tests. Secondly, a change of 10 dB or more in threshold in either ear was considered to represent a real loss of or gain in hearing (Winkel *et al.*, 1978). The distribution of such losses and gains in our patients (at each of the four fre-

quencies) was tested for significance against the binomial distribution. Should a significant excess of losses be detected, exposure to gentamicin would be compared for patients with and without such losses, using unpaired *t*-tests.

Study 2 In the evaluation of an audiometric screening method for use on the ward, analysis of variance was used to elucidate the effect of the following independent variables: test environment, time of day of the session, order of the test within a session and ear being tested. The following dependent variables were used: the mean of the ten audiometric thresholds, the lowest of them, the first threshold obtained and the standard deviation of the ten.

Study 3 Comparison was made between audiometric results obtained 1 month after treatment and those obtained earlier: results obtained at 1 month, for different times of day and for each ear, were subtracted from the corresponding values at the beginning, the middle and the end of treatment, and at 1 week after its completion. Analysis of variance was used to assess the effect of the following independent variables on the change in threshold: timing of the earlier measurement with respect to the course of treatment, time of day of the test and ear being tested. The effect of the covariates, age and the results of serial psychometric tests were also considered. The following dependent variables were considered: change in the mean of the five thresholds determinations, change in the lowest, change in the first value obtained and change in the standard deviation of the five.

The time course of any change in threshold was investigated by an orthogonal contrast (Fleiss, 1986), comparing the change from the beginning of treatment with the average of those from the middle, end of treatment and one week after. This contrast was then compared between those with and without respiratory infections.

Results

1. Detection of gentamicin auditory toxicity in elderly patients using standard audiometric methods

The mean (s.d.) age of the 22 patients studied was 78 (6) years, body weight 67 (12) kg and serum creatinine concentration 108 (21) $\mu\text{mol l}^{-1}$. Fourteen were male and eight female. Gentamicin was prescribed for urinary tract infections in eleven patients, gram-negative bacteraemia in eight and soft tissue infections in

three. (Twelve had received an initial dosing recommendation according to the nomogram of Mawer *et al.* (1974)). Clinical assessment and appropriate haematological and bacteriological investigation demonstrated recovery in all. Psychological test scores improved in five patients and remained the same in the other 17.

No significant changes in hearing threshold were detected, except at the highest frequency studied, 4000 Hz. At this frequency, the change on the left side mean -2.50 (5.72) dB for the 22 patients reached statistical significance ($P = 0.05$), but that on the right, mean -0.46 (3.75), did not. At 4000 Hz, six patients had losses (Winkel *et al.*, 1978) of 10 dB or more: there were no gains (Table 1). The probability of obtaining this result by chance was 0.032. There was no statistically significant excess of hearing losses at lower frequencies: at 2000 Hz four patients had losses and three improvements, at 1000 and 500 Hz, the corresponding numbers being two and two, and five and four, respectively.

The cumulative doses of gentamicin given to the six patients who sustained hearing losses of 10 dB or greater at 4000 Hz were at the upper end of the range used here (Figure 1). When comparing exposure to gentamicin in those with and without such losses, logarithmic transformation of mean pre-dose concentrations and areas was made in order to yield normal distributions. The log pre-dose concentration was significantly ($P < 0.02$) higher in patients with losses than in those without, the corresponding concentration having a mean of 2.3 (range 1.03–3.44) $\mu\text{g ml}^{-1}$ in those with and of 1.4 (0.70–2.56) $\mu\text{g ml}^{-1}$ in those without losses (Table 1). The log total area and the log baseline area (either the simple estimate or as calculated using the OPT program) were also significantly greater in the group with hearing loss ($P < 0.02$ in each case). The mean total area was 26.6 (14.2–46.6) $\mu\text{g ml}^{-1}$ days in those with loss and 17.1 (7.3–36.8) $\mu\text{g ml}^{-1}$ days in the rest, the corresponding values for baseline area, derived by the estimate and OPT method respectively, being 14.6 (7.3–26.6) and 7.0 (1.6–22.9), and 12.9 (7.4–22.1) and 7.5 (1.1–22.4) $\mu\text{g ml}^{-1}$ days.

Patients with hearing losses were significantly older, mean age 82 (4) years, than those without, 76 (6) years (unpaired *t*-test, $P < 0.05$). There was, however, a positive correlation between log pre-dose serum gentamicin concentration and age ($P < 0.02$).

There was concurrent administration of a potentially ototoxic drug (frusemide) (Brummett *et al.*, 1975) in four of the 22 patients, two of whom suffered hearing losses. Concurrent administration of frusemide did not appear to

Table 1 Incidence of hearing loss in relationship to the exposure to gentamicin in a group of 22 elderly patients

Patient	Age (years)	Sex	Weight (kg)	Serum creatinine concentration (mmol l ⁻¹)	Duration of treatment (days)	Mean pre-dose serum gentamicin concentration (µg ml ⁻¹)	Area under concentration time curve (µg ml ⁻¹ day) total	(a)	(b)	Hearing change at 4000 Hz*** (dB)
1	81	M	56.7	155	8.49	1.35	28.8	11.5	10.8	none
2	80	F	43.6	80	5.33	1.37	18.1	7.3	7.4	-10 R
3	83	M	81.2	100	5.74	1.56	17.8	9.0	8.5	none
4*	85	F	73.3	110	2.92	2.90	14.2	8.5	7.8	-10 L
5	83	M	71.2	110	7.15	2.77	31.6	19.8	18.2	-20 L
6*	84	F	54.0	108	6.63	2.35	22.2	15.6	12.5	-15 L
7	83	F	53.0	90	8.96	2.56	36.8	22.9	22.4	none
8	80	M	51.3	85	4.04	1.45	12.1	5.9	5.6	none
9	87	M	52.0	103	7.72	3.44	46.6	26.6	22.1	-10 L & R
10*	76	M	63.6	133	4.46	1.47	14.3	6.5	5.2	none
11	69	M	71.0	142	2.96	1.40	9.0	4.1	4.3	none
12	67	F	61.7	85	6.42	1.20	23.2	7.7	8.6	none
13	73	M	81.0	134	2.58	1.20	7.3	3.1	2.9	none
14	74	M	71.0	126	3.33	1.40	15.3	4.7	6.1	none
15	71	F	63.2	104	6.38	2.10	30.3	13.4	15.2	none
16	75	M	87.0	105	9.63	1.03	27.1	10.0	9.7	-10 R
17	72	M	78.0	80	3.08	1.40	9.0	4.3	3.2	none
18	70	M	84.0	119	1.83	1.20	7.9	2.2	1.1	none
19*	82	F	67.5	89	4.08	1.20	13.4	4.9	5.3	none
20	79	M	75.0	100	2.33	0.70	11.2	1.6	2.4	none
21	77	M	70.7	94	3.38	0.90	11.8	3.0	5.7	none
22	88	F	55.1	131	5.98	1.30	25.8	7.8	12.4	none

* concurrent ototoxic drug used

** (a) simple estimate; (b) calculated using OPT

*** classified as, none, that is no significant change by the criterion of Winkel *et al.* (1978), or a significant change of given magnitude in right, R, left, L, or both ears

Figure 1 Cumulative dose of gentamicin given (—), in ascending order, in patients with and without hearing losses of 10 dB or more at 4000 Hz. Cumulative doses which would have been given had the prescribing aids of other workers been followed for a course of the same duration are shown for comparison: Chan *et al.* (1972) (—), Cutler *et al.* (1972) (---), Mawer *et al.* (1974) (.....) and McHenry *et al.* (1971) (-.-.-).

increase the frequency of gentamicin ototoxicity (Fisher's exact probability test, $P = 0.29$).

There was no evidence of vestibular toxicity.

2. Evaluation of an audiometric screening method for use on the ward

Twelve healthy volunteers of mean age 27 (4) years were studied. Figure 2 illustrates the magnitude of the differences in audiometric results obtained between venues, times of day and order of test with respect to the mean and the standard deviation of the ten threshold determinations. The statistical significance of the effect of the test conditions on the mean, lowest, first and s.d. of the ten determinations is given in Table 2a. The means obtained in the ward bay appeared to be higher than those from other venues, but the difference between venues did not reach statistical significance ($P = 0.09$). The mean thresholds obtained in the morning, however, were significantly different ($P = 0.04$) from those obtained in the afternoon. The magnitude of this difference was small, the mean thresholds of the morning session being, on average, just 0.8 (95% confidence limits: 0.1, 1.5) dB lower

than those of the afternoon. No significant effect of order of test was detected, nor were there any significant interactions between venue, time of day and order of test, with respect to this measure of threshold. The trend towards lower values for threshold determinations made in the mornings than in the afternoon was also seen with respect to the lowest and first values of the samples of ten threshold determinations, but this did not reach statistical significance in either case.

The s.d. of the samples of ten thresholds was not affected significantly by any of the test conditions studied, nor by interactions between them. In other words, precision appeared to be independent of the test conditions.

The smallest difference between two values of a given measure of threshold which could be detected reliably was calculated for each of the three measures (the mean, lowest and first of ten determinations), using the variance estimate derived from the mean square error in the corresponding analysis of variance, and assuming, for the purpose of comparison with Study 1, a sample size of 22 'independent' ears. (The criteria adopted for reliability were a probability of 0.05 of a type 1 error and of 0.1 of a type 2, that is a

Figure 2 Effect of venue, time of day and order of test on audiometric results with respect to the mean and the s.d. of the samples of ten determinations of hearing threshold. For both dependent variables, mean values ($\square$) for all samples from 12 healthy volunteers under the given conditions are shown, together with the 95% confidence intervals. Interrupted lines indicate the corresponding grand mean values.

Figure 3 Changes between observations on auditory threshold made one month after a course of a non-ototoxic antibacterial agent and those made earlier in sixteen elderly inpatients. The mean change is expressed in terms of the following measures of threshold: a) the mean ($\square$), b) the lowest ($\triangle$) and c) the first ($\circ$) of five determinations. 95% confidence intervals are shown. (N.B. A mean change of zero (interrupted line) is well within the 95% confidence limits when the earlier observation is at the middle of, end of, or one week after treatment, but not when it is at the beginning of treatment, that is observations one month after appear to be significantly different only from those at the beginning.)

Table 2 Factors affecting hearing threshold

a) Analysis of variance on threshold determinations for each ear of 12 healthy volunteers								
Test condition	Samples of ten threshold determinations (dB)							
	F*	Mean P	F lowest P	F first P	F s.d. P			
Venue	2.44	0.09	1.93	0.15	0.85	0.43	1.71	0.19
Time of day	4.54	0.04	3.16	0.08	3.14	0.08	0.35	0.56
Ear tested**	56.80	< 0.0001	45.68	< 0.0001	38.43	< 0.0001	2.04	0.16
Order of test	0.33	0.72	0.41	0.66	1.05	0.35	0.70	0.50
b) Analysis of variance and co-variance on changes in threshold determinations for each ear of 16 elderly patients								
Test condition	Change in samples of five determinations (dB)							
	F*	Mean P	F lowest P	F first P	F s.d. P			
Timing of earlier measurement	3.02	0.04	3.00	0.04	2.94	0.04	0.26	0.86
Time of day	0.06	0.95	1.53	0.23	0.54	0.59	1.97	0.16
Ear tested	0.35	0.56	0.30	0.59	0.71	0.41	0.00	0.97
Covariate								
Age (years)	0.00	0.95	0.28	0.60	0.07	0.80	0.23	0.64
Psychometric tests*** a)	0.00	0.97	0.19	0.67	0.11	0.75	1.52	0.24
b)	0.21	0.65	0.15	0.71	0.85	0.38	0.36	0.56
c)	0.55	0.47	1.11	0.31	1.17	0.30	0.19	0.67

* *F* statistic

** There was right sided predominance in hearing in this small group

*** Test a) involved reciting a series of numbers forward, b) reciting a series backwards, and c) responding to the number 'seven'

Figure 4 Effect of the nature of the infection on the time course of the changes in hearing threshold observed in relation to treatment with a non-toxic antibacterial agent. The mean changes (in the means of samples of five determinations) and the corresponding 95% confidence intervals are given for those with urinary (○) and respiratory (□) tract infections. (N.B. A mean change of zero at the beginning of treatment is just within the 95% confidence limits for patients with urinary infections, but well outside those for patients with respiratory infections.)

significance level of 5% and a power of 90%.) As might be expected, the resolution increased with the amount of information on which the measure was based. It is estimated that within-subject differences of 2.3 and 2.5 dB could have been detected using the mean and the lowest of ten threshold determinations respectively, as compared with a difference of 3.0 dB using the first.

3. Error inherent in using the threshold measured at the start of treatment

Sixteen inpatients, of mean (s.d.) age 81 (8) years, prescribed non-ototoxic antibacterials were studied. The difference between the measurement of threshold made 1 month post treatment and a measurement made earlier in relation to the course of treatment was significantly ($P = 0.04$) affected by the timing of that earlier measurement (Table 2b). It can be seen from Figure 3 that the difference from the observation at 1 month was greater at the beginning of treatment than at its middle, its end and 1 week after; a statistically significant difference ($P = 0.0004$) was found on orthogonal contrast of the change from the beginning with the average of those from the other times.

Nine of the 16 patients studied had respiratory infections, the rest had urinary tract infections. Figure 4 shows that the mean change in hearing threshold, between the beginning of treatment and 1 month after it, appeared to be greater in those with respiratory infections. Analysis of variance revealed no significant effect of the nature of infection on the change in threshold observed ($P = 0.54$), nor on the time relationship of the change ($P = 0.20$). However, a significant ($P = 0.04$) difference between types of infection was detected with respect to the orthogonal contrast of the change from the beginning of treatment with the average of those from the other times.

In this group of elderly inpatients, the time of day when the tests were carried out had no significant effect on the change observed in the three measures of threshold (Table 2b). The change in s.d. of the five threshold determinations was unaffected by either timing with respect to treatment or the time of day. There was no significant interaction between these independent variables.

Table 2b also shows that the magnitude of the changes in the three measures of threshold and in the s.d. of the five determinations appeared not to be influenced significantly by the age of the patient (65 to 93 years). The individual changes in hearing did not reflect changes in the results of the psychometric tests. Indeed, no

significant changes in the scores of these tests were detected.

The resolution of this type of audiometric testing in such a group of elderly inpatients was estimated (assuming a sample size of 22 as before) as 3.4, 3.6 and 3.4 dB in the case of the mean, lowest and first of five threshold determinations, respectively.

Discussion

Hearing loss, in relation to courses of gentamicin, was detected in a group of 22 elderly patients, despite their maintained or increased ability over the course of treatment to perform psychometric tests. The latter, along with possible learning effects, resulting from repetition of the hearing test, and any transient physical effect of the infection on the hearing mechanism, may even have masked the extent of the hearing loss. Indeed, in another group of elderly inpatients, the magnitude of the improvement in hearing threshold observed during treatment with antibacterials not associated with ototoxicity was similar (Figure 3) to that of the loss (mean 2.5 dB) seen in the left ears of those exposed to the ototoxic drug. Underestimation of ototoxic effects was thus a distinct possibility.

Interestingly, in the group exposed to non-ototoxic drugs, the results of a more exacting psychometric test proved stable, and the precision of the threshold measurements, as monitored by their standard deviation, did not vary significantly over the course of recovery. Moreover, there was a tendency for the dip in hearing at the beginning of treatment to be associated with respiratory rather than urinary infections. A larger, specially designed study would be necessary to elucidate whether this dip had a local physical cause (e.g. blockage of the Eustachian tube) rather than being due to a change in mental state.

Whilst detection of aminoglycoside ototoxicity will depend on the accuracy and precision of the screening method (see below) and the relative magnitude of masking influences, its determinants are likely to be exposure to the drug (Barza & Lauermann, 1978) and the susceptibility of the population studied. Those who developed hearing losses in relation to gentamicin treatment were the older members of our elderly group. However, their exposure to gentamicin had been greater than that of the younger members. It is well recognised that, in the elderly, renal function can be overestimated from the serum creatinine concentration because of re-

duced creatinine production, consequent on reduced muscle bulk.

Can the routine use of prescribing aids protect against ototoxicity in the aged? The cumulative dosages of gentamicin which would have been received by each of the patients in Study 1 had the recommendations of such aids (Chan *et al.*, 1972; Cutler *et al.*, 1972; Mawer *et al.*, 1974; McHenry *et al.*, 1971) been followed for a course of the same duration are shown in Figure 1. There appears to be no systematic reduction in the ratio of the dose recommended by a given aid to the dose given in the six patients with hearing losses of 10 dB or more at 4000 Hz compared with the 16 without. (The doses recommended by one prescribing aid (McHenry *et al.*, 1971) were smaller than those given for all patients: following these recommendations might be at the expense of efficacy.) Furthermore, since there appeared to be considerable overlap in the parameters of safe and unsafe concentration/time profiles in our patients standardisation of exposure to gentamicin in terms of the concentration/time profile, even were it possible, may not suffice to protect against ototoxicity.

The consensus of opinion seems to be that high pre-dose concentrations are more important than high peak concentrations with respect to the risk of toxicity, and that a pre-dose concentration above $2 \mu\text{g l}^{-1}$ is too high (Reeves, 1978). However two of our six elderly patients with hearing loss at 4000 Hz had mean pre-dose concentrations well below 1.5 mg l^{-1} . It may be that presbycusis, in addition to destroying some hair cells, may sensitise others to the toxic damage, but it has yet to be established whether or not the elderly do have increased endorgan sensitivity to aminoglycosides.

Although much has been written about the pharmacokinetics of gentamicin, there is relatively little in the literature to document the relationship between the serum concentration achieved and its efficacy and toxicity. Imposing the use of a sound-treated room severely limits the number of patients, otherwise capable of co-operating, to whom audiometry can be offered. Use of a portable audiometer on the ward would allow a much larger and more representative proportion of patients receiving gentamicin to be screened. In patients with a limited attention span, due for example to age and/or illness, it

might be best to make multiple determinations of hearing threshold at one relevant frequency, a frequency sensitive to ototoxicity yet within the limitations set by presbycusis.

When the mean of ten determinations at 6000 Hz was taken as the measure of threshold, it was, on average, only 0.9 dB higher in the open ward than in the sound-treated room: no significant difference between the three venues studied was detected when the comparison was made, in the morning and in the afternoon, in each of 12 healthy volunteers. There was a marginally significant reduction, on average 0.8 dB, in accuracy in the afternoon. Whether this resulted from more ambient noise, poorer concentration or genuine diurnal variation in hearing is not known. Precision, as measured by the s.d. of the samples of ten determinations, appeared to be unaffected by test conditions.

The benefit of using multiple threshold determinations, rather than just one, was apparent in the normal volunteers, but not in the elderly patients: this may simply have reflected the use of samples of ten determinations in the former but only five in the latter. It was calculated that, using samples of five threshold determinations in the ward at 6000 Hz (and assuming a sample size of 22 independent ears, as in Study 1), the difference which could reliably be detected in elderly patients, such as those of Study 3, was 3.4 dB. This is 36% higher than the mean difference attributed to ototoxicity in Study 1, where conventional audiometry was used. When patients cannot be transferred to a sound-treated room to be screened for ototoxicity, audiometry performed on the ward may provide a useful alternative to conventional audiometry, and may even approach a similar resolution, when effort is concentrated on making more than five determinations of threshold at a single high frequency. Moreover, and encouragingly, age had no effect either on the magnitude of error inherent in taking the measurement of hearing at the start of treatment as a reference point, or on the precision of threshold measurement, in a group of patients, aged 65 to 93 years, who were able to co-operate with audiometry on the ward.

We wish to thank Mrs C. Doré, Head of the Section of Medical Statistics, CRC, for her advice and support.

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(Received 22 November 1989,
accepted 21 February 1990)