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PRESCRIBING AIDS FOR GENTAMICIN

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1 A nomogram and a digital computer program have been developed to calculate dosage schedules of gentamicin for individual patients. The minimum input data consist of the patients' age, sex, body weight and serum creatinine concentration.

2 These prescribing aids have been evaluated in 36 patients with severe Gram negative infections. Renal function ranged from normal to complete anuria. Nomogram dosage schedules gave serum concentrations of gentamicin within the chosen therapeutic limits. Physician dosage schedules gave serum concentrations which sometimes exceeded and sometimes fell below these limits. The validity of the computer program was demonstrated by its ability to predict serum concentrations of gentamicin whatever the dosage schedule.

3 Half the patients recovered from the bacterial infection but seven remained infected and eleven died. *Pseudomonas aeruginosa* was the most difficult organism to eradicate.

4 Four of the patients who survived developed ataxia and two developed hearing loss at high frequencies. The risk of ototoxicity was a function of mean trough serum gentamicin concentration and duration of treatment. Ototoxicity was only detected in patients with serum creatinine concentrations above 3 mg/100 ml who tended to have higher trough concentrations. When treatment was prolonged beyond 8-10 days the risk of ototoxicity was increased without evidence of further substantial therapeutic benefit.

Introduction

Gentamicin is an effective antibiotic in the treatment of severe Gram negative infections but its use in patients with renal insufficiency is limited by the risk of accumulation and ototoxicity. This is most commonly manifested as vestibular damage.

A nomogram for gentamicin dosage has been developed by Jelliffe (1971) in Los Angeles. The principle developed by Dettli, Spring & Habersang (1970), has been used as the basis for an alternative nomogram (Chan, Benner & Hoeprich, 1972) and we have developed a third which closely resembles that previously described for kanamycin (Mawer, Knowles, Lucas, Stirland & Tooth, 1972; Mawer, Lucas & McGough, 1972).

We report here the results of clinical experience with our nomogram.

Methods

Patients

Thirty-six patients were studied. Most had serious Gram negative infections of the respiratory or renal tract. The decision to prescribe gentamicin was made on clinical or bacteriological grounds. Seventeen patients had creatinine clearances below 20 ml/min and five of these were anuric. The different infecting organisms treated are listed in Table 1.

Samples of venous blood were taken for assay 2 h after a dose and immediately before a dose. Whenever possible blood was taken from each patient on at least four occasions.

Nomogram

Recommended dose schedules were based on the nomogram shown in Figure 1. The method of use is as follows:

A. Patient not receiving dialysis treatment

(1) Join with a straight line the serum creatinine concentration appropriate to the sex on scale A and the age on scale B. Mark the point at which the straight line cuts line C.

(2) Join with a straight line the mark on line C and the body weight on scale D. Mark the points

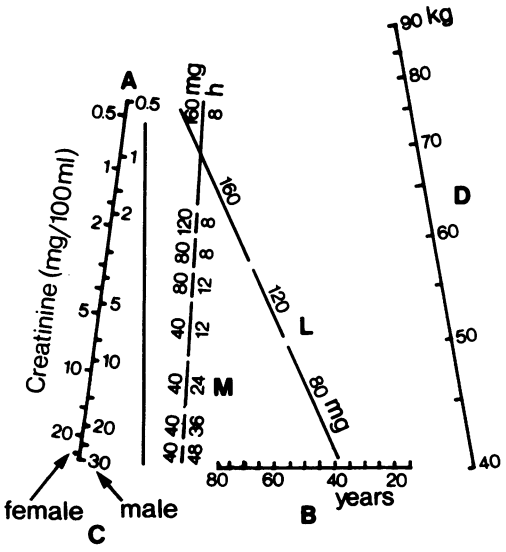

Fig. 1 Nomogram for gentamicin dosage. The nomogram provides a loading dose (L), a maintenance dose (M) and a suitable interval between doses for a patient whose serum creatinine concentration (A), age (B) and body weight (D) are known. To use, join A to B with a line which cuts C, then join C to D with a line which cuts L and M. A more detailed description is given in the text.

at which this line cuts the dosage lines L and M.

(3) The loading dose (mg) is written against the marked part of line L. The maintenance dose (mg) and the appropriate interval (h) between doses are written against the marked part of line M.

(4) The nomogram is designed to give serum concentrations of gentamicin within the range 3-10 μg/ml 2 h after each dose. In patients with renal insufficiency it is still desirable to perform check assays and to make appropriate dose adjustment.

Example: male, serum creatinine 5.0 mg/100 ml, 45 years, 55 kg; loading dose 120 mg, maintenance dose 40 mg, interval between doses 12 hours.

B. Patient receiving dialysis treatment

(5) When the patient is severely oliguric or anuric do not use the serum creatinine and age scales. To determine the dose schedule join with a straight line the bottom end of line C and body weight on scale D. Then proceed as in (2) and (3) above.

(6) Peritoneal dialysis. In addition to the dose schedule add gentamicin to the dialysis fluid. A concentration of 5 μg/ml is suitable.

(7) Haemodialysis. In addition to the dose schedule give a booster dose after dialysis. Half the loading dose is suitable after a 10 h Kiil dialysis.

The doses are all given in multiples of 40 mg (1.0 ml gentamicin sulphate solution for injection; Cidomycin, Roussel or Genticin, Nicholas). The intervals between doses are all given in multiples of 8 or 12 hours. No calculation is required and no rounding off is necessary.

Eleven patients received nomogram based dosage regimes throughout their gentamicin course. Seventeen received a physician prescribed regime for the first part of the course and a nomogram regime later. Eight received a physician prescribed regime throughout the course.

Serum gentamicin concentration

Serum concentrations of gentamicin were assayed by the method described previously (Mawer *et al.*, 1972). The range of therapeutic concentration was considered to be 3-10 μg/ml. Other workers have used a similar range (Chan *et al.*, 1972).

Table 1 Bacteriological response to gentamicin therapy.

	Number of patients			
Infection	*Cleared*	*Persistent*	*Died*	*Total*
Pseudomonas	5	4	2	11
Klebsiella	4	1	2	7
Gram negative septicaemia*	2**	0	5	7
Eschericia coli	3	0	0	3
Mixed Gram-negative	4	1	1	6
Proteus	0	1	1	2
Total	18	7	11	36

*Positive blood cultures were obtained in two cases only. Both died.
**Survived.

Computer program

The computer program was as described previously for kanamycin (Mawer *et al.*, 1972) with the following modifications. Gentamicin doses ranged from 40-160 mg in increments of 40 mg. Doses yielding 2 h serum concentrations above 10 μg/ml were rejected by the computer. The interval between successive doses was prolonged in accordance with the calculated serum concentration half time.

The program was based upon the one compartment model used for kanamycin. The best results were obtained assuming a gentamicin distribution volume (litres) of 0.275 x body weight (kg) and a renal gentamicin clearance (ml/min) of 0.75 x calculated creatinine clearance (ml/min).

The nomogram is based upon the computer program and thus the two give consistent dosage recommendations. The program is more flexible, however, for it can deal with situations where serum creatinine concentration is changing and it can take account of a measured serum gentamicin concentration. The program was used retrospectively for each of the patients studied in order to test the agreement between calculated and assayed serum concentrations of gentamicin. By this means it was possible to reconstruct the entire serum concentration/time profile for each patient.

Warning

Correct dosage schedules can only be obtained from these prescribing aids if the input data are correct. The patient must be weighed and the serum creatinine concentration measured at the start of therapy. If the patient has been recently dialysed, the pre-dialysis serum creatinine concentration should be used. When deterioration of renal function is expected it is wise to prescribe only one or two doses and to enter the nomogram again with each successive measurement of serum creatinine concentration. If the input data are guessed, the resulting dosage schedule is no better than the guess.

Therapeutic response

Before starting gentamicin therapy a bacteriological diagnosis was made. Most of the patients were regular attenders at the out-patient clinic and the Renal Unit and recent culture reports were available. In other cases, specimens of blood, pus, sputum or urine were cultured and antibiotic sensitivity was determined on three successive days. In a few cases the gentamicin therapy was given on clinical grounds without awaiting results of culture. In these cases two specimens were taken before the start of therapy.

After a course of gentamicin lasting 4-20 days cultures were repeated. An infection was considered to be cleared when the pathogenic organism failed to grow in two or more cultures. The organism was described as persistent when one or more of these cultures was positive.

Two patients with suspected Gram negative septicaemia survived. The infection was considered cleared even though blood cultures taken before treatment had been negative.

Monitoring for ototoxicity

An otological history was taken at the beginning of each gentamicin course. Clinical examinations were carried out with special reference to auditory and vestibular function. As most of the patients were severely ill, only limited pre-treatment investigations of auditory and vestibular function were practicable. Any impacted wax in the external auditory meatus was removed.

Pure tone audiometry was performed. The standard audiometer was a Peter's Clinic Audiometer AP5 in a sound-proofed room. Measurements on patients too ill to be taken to the sound-proofed room were made with a Madsen Electronics TBN60 portable audiometer, in the quietest surroundings obtainable. The calibration of each audiometer was checked (British Standard 2497, Part 2, 1969). At the frequencies (2,000 Hz and above) where early aminoglycoside toxicity occurs (Ballantyne, 1970), the maximum error produced by lack of sound-proofing was 10 decibels.

Patients were repeatedly questioned about tinnitus, hearing loss, dizziness and ataxia, and the examinations of auditory and vestibular function were repeated at weekly intervals during therapy. In assessing the vestibular response to gentamicin, only a degree of incoordination of gait, which could not be attributed to the patient's general condition, was regarded as ataxia resulting from the therapy.

The follow up period was as long as practical in each case, to a maximum of nine months.

Results

Serum concentrations

Serum concentrations of gentamicin in samples taken 2 h after doses are shown in Figure 2. Thirty-nine values obtained from patients during nomogram based treatment lay within the chosen therapeutic range. Twenty-nine values were

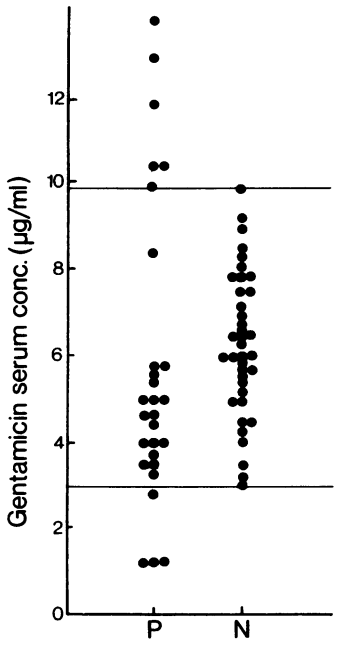

Fig. 2 Concentrations of gentamicin in serum samples taken 2 h after a dose. Patients treated in accordance with the nomogram (N) had serum concentrations within the chosen therapeutic range (between dotted horizontal lines). Patients treated according to physician (P) dosage schedules showed a wider scatter of concentrations.

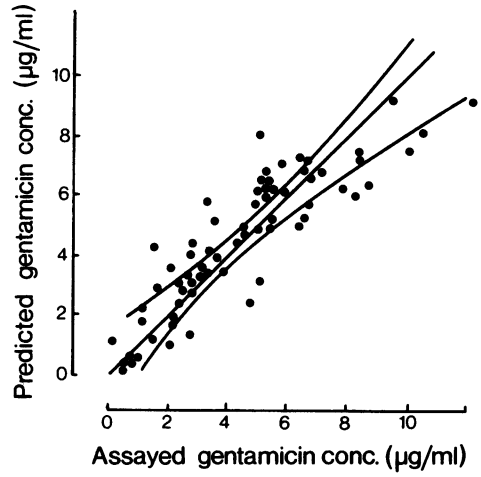

Fig. 3 Agreement between serum concentrations of gentamicin predicted by the computer and measured by bioassay. Each patient contributed two points; one was the mean of serum samples taken before a dose and the other was the mean of samples taken 2 h after a dose. The straight line representing perfect agreement lay between the curved lines representing the 95% confidence limits of the best fitting line.

obtained from patients during treatment with doses prescribed by the physician. Nine of these values lay outside the chosen range. This difference was significant ($X^2 = 13$, $P < 0.001$; $F = 4.5, P < 0.01$).

The mean predicted concentration and the mean assayed concentration were compared in each patient for samples taken 2 h after doses and for samples taken before doses. There was a strong ($r = 0.88$) and significant ($P < 0.001$) positive correlation between mean predicted concentrations and mean assayed concentrations (Figure 3). The mean difference between predicted concentrations and measured concentrations (0.30 ± 0.30, μg/ml ± S.E.M.) was not significant.

Comparison between nomograms

The nomograms of Jelliffe (1971) and Chan *et al.* (1972) were used to derive alternative dosage schedules for each of the patients we have studied. The total dose of gentamicin for the first six days of treatment was used as the basis for comparison. Six days was a convenient multiple of the different dosage intervals used. The six day doses from the two alternative nomograms each correlated strongly ($r = 0.97$) with our nomogram doses. The ratio of our doses to the average doses from the other centres was 1.24 ± 0.03 (S.E.M.).

Response to gentamicin therapy

The bacteriological response is described in Table 1. The two groups showing the poorest response were the patients with *Pseudomonas* infections which often persisted and the patients with suspected Gram negative septicaemia who had a high mortality. Persistence of the infection was observed in two patients who received nomogram dose schedules, two who received mixed dose schedules and two who received only physician prescribed dose schedules.

Clinical evidence of ototoxicity was obtained in five of the 25 patients who survived their illness (Table 2). Ototoxicity was never observed in patients with a serum creatinine concentration below 3 mg/100 ml. In several patients ataxia did not develop until after the course of gentamicin treatment had been completed and was only obvious at out-patient assessment. The hearing loss was restricted to high frequencies, did not affect the ability to hear speech and was not recognized by the patients.

Table 2 Otological response to gentamicin therapy.

Patient Sex	Age (years)	Serum creatinine concentration (mg/100 ml)	Maximum serum gentamicin level (μg/ml)	Duration of treatment (days)	Baseline area (μg days/ml)	Symptoms of vestibular toxicity	Hearing loss decibels at 8,000 Hz Right ear	Left ear
F	28	3.5	6.7	8	25	Ataxia	<10	<10
F	68	5.0	20.9*	15	66	Ataxia	<10	<10
M	47	9.0	14.0	6	47	Ataxia	<10	<10
F	43	13.0	8.0	18	81	Ataxia	20	25
F	31	14.4	6.9*	11	47	Dizziness	25	<10

*Estimated retrospectively by computation.

Fig. 4 Relationship between gentamicin ototoxicity and baseline area (mean trough serum concentration x duration of treatment). When the trough concentration exceeded 4 μg/ml and the duration of treatment exceeded 10 days there was a high likelihood of ototoxicity.

Discussion

It has been clearly demonstrated that the nomogram provides dosage schedules which will give serum gentamicin concentrations within the chosen therapeutic range. The two alternative nomograms would have provided slightly smaller doses. Patients with normal renal function will often accept doses of 120 or 160 mg without the serum concentration, 2 h later, exceeding 10 μg/ml (Figure 1). Other authors have made similar recommendations (Wise & Reeves, 1972; Ingham & Emslie, 1972).

The close agreement between the serum gentamicin concentrations predicted by the computer and the concentrations measured by bioassay demonstrates the validity of the one compartment model which is the basis of the computer program and the nomogram.

Patient numbers were not large enough for a comparison of the relative therapeutic effectiveness of nomogram and physician dosage schedules. The patients whose infections persisted did not differ from those whose infections were eradicated with respect to duration of treatment ($P > 0.10$, Wilcoxan rank order test).

Ototoxicity developed in two patients who received excessive doses which produced serum concentrations above 10 μg/ml. There was no

evidence of excessive concentrations in the other three patients however (Table 2).

The one measurement in all patients which was most strongly associated with ototoxicity ($P < 0.01$, Wilcoxan rank order test) was the baseline area (mean trough serum gentamicin concentration μg/ml x duration of treatment in days). This is illustrated in Figure 4. Four out of five patients with baseline areas above 45 μg days/ml developed ototoxicity, whereas only one out of twenty with a lower area developed toxicity. The importance of a high trough concentration has already been recognized in relation to streptomycin ototoxicity (Line, Poole & Waterworth, 1970).

When the patient who is being treated according to the nomogram has a serum creatinine concentration above 3 mg/100 ml or a trough serum gentamicin concentration above 4 μg/ml it is suggested that the course should not usually exceed 8-10 days. If the nature or site of the infection demands more prolonged treatment some degree of ototoxicity may be unavoidable.

Availability

Copies of the nomogram are available from the authors who are also willing to train physicians to use the computer program and to provide them with the necessary software.

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