Leading articles


Prescription of aminoglycosides by nomogram

Since the introduction of gentamicin in the early 1960's as the first highly active aminoglycoside its dosage has been the subject of more debate than any other antibacterial drug, excepting perhaps antituberculous agents. Early problems with ototoxicity, although largely in patients with impaired renal function, led to dosage recommendations of typically 1 mg/kg 8-hourly. These doses based on fear of toxicity were too small to give optimal serum concentrations for treating tissue infections. The last 10 years have witnessed increasing awareness of the role of pharmacokinetics in dosage prediction and, with an enormous expansion of the use of parenteral gentamicin in the face of nosocomial infection with penicillin- and cephalosporin-resistant agents, Gram-negative bacilli, prescribing aids for gentamicin have been designed by Jelliffe (1971), Chan, Benner & Hoeprich (1972), and the Manchester-based group of Mawer et al. (1974). These rely upon a one-compartment model in which the drug is assumed to be evenly distributed, and from which it is cleared almost entirely by the kidneys. To predict the concentration of the drug in the compartment at any one time, assumptions must be made as to its size (apparent distribution volume), and the rates of input from the site of injection (rate constant for absorption in the case of intramuscular administration) and of clearance. For example, Mawer et al. (1974) found the best results were obtained by assuming the apparent distribution volume (litres) to be 0.275 x body mass (kg), and the renal gentamicin clearance to be 0.75 x creatinine clearance (ml/min). Since the creatinine clearance is usually not known it is predicted from the age, sex, mass and serum creatinine concentration of the patient. The Manchester nomogram is designed to utilize these four parameters to give a loading and maintenance dose of gentamicin resulting in serum concentrations in the range 3 to 10 mg/l 2 h after a dose, based on the pharmacokinetic assumptions given above.

Using the same nomogram our own investigations showed that the large majority of 1-h post dose serum concentrations fell into the range 5 to 10 mg/l (Reeves, Bint, Burges, Elliot & Stocks, unpublished data). In both Mawer's and our studies doses prescribed by clinicians not using a nomogram gave a much wider scatter of concentrations, and in our experience they were usually lower than the desired therapeutic range. Using doses given by the Manchester nomogram Tobias, Wrigley, Korde & Shaw (1977) compared the serum concentrations of tobramycin measured with those given by a fixed dose. The nomogram-predicted concentrations were significantly higher although often below the range found by ourselves. This discrepancy is probably due to their use of intravenous bolus injection rather than intramuscular injection, since the pharmacokinetics of tobramycin are very similar to those of gentamicin. Certainly Mawer (1976) could see little use for a separate tobramycin nomogram (Benner, Krauhold & Bush, 1974). Thus in patients with normal renal function or a stable impairment of it, nomogram-predicted doses of gentamicin or tobramycin usually gave satisfactory serum concentrations in the range considered suitable for effective therapy (Noone, Parsons, Pattison & Slack, 1974), at least during the early days of treatment. The nomogram does not necessarily predict satisfactorily low pre-dose (trough) concentrations since they will inevitably be high (>3 mg/l) when the plasma half life is prolonged by renal impairment or if adequate post-dose concentrations are maintained at a reasonable frequency.

The value of designing dose to individual patients rather than using a fixed dose was investigated by Anderton, Hanson & Raeburn (1976). In patients with serious Gram-negative infections and poor renal function, gentamicin was prescribed as a fixed dose of 80 mg at a frequency regulated by renal
function, or by the nomogram of Chan, Benner & Hoeprich (1972). The latter gave fewer therapeutic failures. In patients with episodes of fever in blood dyscrasies Wilkinson, Gorst, Tooth & Delamore (1977) found an improved response rate to intravenous gentamicin given by the Manchester nomogram as opposed to a fixed dose of 80 mg 8-hourly, both regimens including clindamycin. In patients with proven sepsis the response rate was significantly greater.

Nomogram-predicted dosage in a limited number of studies has therefore shown an improvement in clinical and pharmacological response over fixed doses. These prescribing aids are therefore of value to the clinician who has no access to a rapid and reliable assay service. The doses given by the Manchester nomogram also make the nurse's task easier because they are expressed in whole units of injection volume and at practical time intervals. A nomogram for kanamycin has been described (Mawer, Lucas & McGough, 1972) and this could probably be extrapolated to amikacin in view of the similar activity, toxicity and pharmacokinetics of the two drugs (Clarke, Libke, Regamey & Kirby, 1974).

It would be wrong however to assume that the published nomograms provide a complete answer for the prescription of aminoglycosides, and their originators accept certain limitations. The first of these is a failure of the pharmacokinetic assumptions to match individual patient characteristics. The apparent distribution volume may not be a fixed proportion of the body mass, and it is probable that this discrepancy assumes clinical significance in obesity, disturbances of hydrations, and in neonates. The discrepancy in obesity may be overcome by using lean body mass calculated by a formula. The serum creatinine concentration may not accurately reflect renal function when the latter is changing rapidly, and measurements of the actual creatinine clearance are time-consuming, often impracticable and frequently inaccurate. Furthermore, aminoglycoside clearance may not always be a fixed proportion of creatinine clearance. Certainly some authors have found the plasma half-life of gentamicin to correlate poorly with serum creatinine (Barza, Brown, Shen, Gibaldi & Weinstein, 1975; Kaye, Levison & Labovitz, 1974). Discrepancies between predicted and actual concentrations may arise because of the inadequacy of the single compartment model. In patients treated with a long (≥ 10 days) course an unexpected rise in serum concentrations may become detectable. This may be due to decreased renal function (Hewitt, 1974) or to slow accumulation in a deep compartment (Schentag & Jusko, 1977). Schentag et al. (1977) have claimed that a two-compartment model accurately predicts accumulation and tissue concentrations. Finally, we have all encountered the rare 'odd-ball' patient in whom gentamicin serum concentrations seem quite unrelated to dosage, and for which no explanation can be found. Besides the group of patients known as damped responders (Riff & Jackson, 1971), such deviations may be quite gross and the patient is thus put at serious risk from under- or over-dosage.

The second major limitation is the quality or availability of data used in the nomogram. While the age and sex of the patient are rarely in doubt, an accurate body mass can be surprisingly difficult to obtain, particularly in patients admitted as an emergency. The most frequent problem, however, is the lack of a reliable serum creatinine value, and the generation of one may well take longer than an assay. In view of the limitations of nomograms and other means of predicting dosage it is hardly surprising that many centres still continue to use assays for controlling aminoglycoside therapy. The initial dosage can be written up on the basis of the Manchester nomogram as this rarely results in underdosing, and is subsequently modified where necessary according to assay results. Groups of patients for whom assays are virtually indispensable are (i) those in whom renal function is changing rapidly, (ii) those where very high concentrations (≥ 8 mg/l) are needed, such as for the treatment of Gram-negative pneumonia (Noone & Rogers, 1976), (iii) those who have had previous courses of aminoglycosides or other ototoxic drugs and are therefore at risk from cumulative toxicity, (iv) those being treated with a prolonged course at full dosage.

Another approach to the individualization of dosage is to give the first dose of gentamicin and to follow the decline in serum concentrations. Using a minimum of 3 blood samples Sawchuk et al. (1977) used the assay results to calculate individual pharmacokinetic parameters based on a one-compartment model for each patient on which subsequent doses were based. While this method should eliminate one disadvantage of a nomogram, that is making pharmacokinetic assumptions about distribution and clearance which do not necessarily hold for individual patients, it cannot obviate the need for further concentration monitoring should the patient's
condition change. Furthermore, an intravenous dose would be necessary as data based on a single intramuscular dose might be unreliable.

In summary it seems that a pharmacokinetic approach to dosage of aminoglycosides, whether by nomogram or calculation, can give the clinician more confidence in the resulting serum concentrations, and is certainly superior to giving fixed doses. For some patients this is all that is needed, but for the groups of patients mentioned above, initial dosage by nomogram must be followed by assays of serum concentrations.

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References

Ampicillin resistance in Haemophilus influenzae
In 1972, an ampicillin resistant type B Haemophilus influenzae was isolated from the CSF of a child with meningitis who subsequently died (Gunn, Woodall, Jones & Thornberry, 1974). In 1974 Thomas, McReynolds, Mock & Bailey reported the occurrence of two more fatal cases of H. influenzae meningitis associated with the isolation of ampicillin-resistant organisms. All three of these patients were treated with ampicillin, the results of sensitivity testing not becoming available until after their death. Following this latter report further ampicillin-resistant strains were soon recorded by a number of centres both in the U.S.A. (Tomeh, Starr, McGowan, Terry & Nahmias, 1974; Khan, Ross, Rodriguez, Conroni & Szaz, 1974; Thornberry & Kirven, 1974a) and Great Britain (Turk, 1974; Clymo & Harper, 1974; Williams & Cavanagh, 1974; Mackintosh & Dadwell, 1974).

It was soon established that the resistance exhibited by these organisms was mediated by a penicillinase enzyme (Williams, Kattan &