Gentamicin dosage schedules

Sir,

The paper by Yoshioka et al. (Archives, 1978, 53, 334), gives a guide to gentamicin dosage for an age group missed by the popular adult nomograms. Such a guide is necessary when choosing initial dosage, but we believe that subsequent maintenance therapy should be monitored by determining serum gentamicin levels in all patients rather than just in "difficult" cases as suggested by the authors. The disadvantage of determining the half-life of gentamicin from creatinine clearance is that the latter should be corrected to the patient's lean body mass (Hull and Sarubbi, 1976). The lean body mass of an acutely-ill oedematous child with chronic renal disease is difficult to estimate.

Gentamicin clearance is a sensitive indicator of renal function, and is logically best predicted by measuring serum levels of the drug itself. Sawchuck and Zaske (1976) described a method of calculating the half-life and distribution volume of gentamicin. We have adapted this method for a programmable calculator instead of the computer. Our experience suggests that the one-compartment model used in this method is perhaps too simple: the half-life derived from serum levels of gentamicin in the first 4 hours after a dose overestimates the subsequent rate of clearance and slightly underestimates the interval between doses. A better model could be made by fitting a 2- or 3-term exponential function to later serum levels (Kahlmeter et al., 1978) but the one-compartment model does provide useful insight into the effects of varying dosage regimens.

We question whether a dosage of 1 mg/kg is enough to treat serious infections, especially by IM injection. The peak serum levels achieved in the 3 patients treated by the schedule were all below 5 µg/ml. The longer the dose takes to enter the circulation, the lower the interstitial fluid levels will be (Kozak et al., 1977).

There appears to be no alternative to repeated measurement of serum gentamicin levels, and our efforts should be directed towards improving the accuracy and availability of our assays. Micromethods using small quantities of blood would be particularly valuable for very young children for whom venepuncture is often difficult or impossible. There is one factor in our favour: the interval between doses for many patients with renal failure is longer than our slowest bio-assay.

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References


Dr Yoshioka and co-workers comment:

We welcome the comments from Dr Mayon-White and Miss Perks. Their opinion is acceptable as a principle that serum levels should be monitored in all patients receiving gentamicin treatment. But unfortunately many hospitals do not provide antibiotic assay systems, and even in hospitals in which this service is available, the reproducibility of measured levels is reported to be poor (Reeves and Bywater, 1975). In such a situation we believe proposed nomograms or other pharmacokinetic data are still a useful guide in planning gentamicin treatment.

The statement about correcting the creatinine clearance value to the patient's lean body mass seems misleading. Obviously, endogenous creatinine clearance is a value which is determined on the basis of the serum level and the amount of creatinine excreted in urine in a unit of time. Rapid evaluations of creatinine clearance or glomerular filtration rate are proposed on the basis of age, body weight, and serum creatinine level for adults (Hull and Sarubbi, 1976), and of body length and plasma creatinine level for children (Schwartz et al., 1976). However, we do not agree with the use of values obtained by these expedients until it is otherwise proved that these values actually correlate with serum half-life of gentamicin. Only values determined in individual patients should be used for our dosage schedules at the present time.

As far as the serum half-life determination of gentamicin is concerned, we do not argue with their statement that it should be done after 4 hours of dosing. However, absorption of gentamicin from the injected site is rapid even in patients with renal insufficiency. Peak levels were attained within 2 hours in all our patients (Table 1) after intramuscular dosing, and therefore we do not believe the lower blood level in the 3 patients was due to delayed absorption.

The serum concentration of gentamicin was once reported to be unpredictable (Kaye et al., 1974). But recently it became evident that a series of factors affect the serum concentration. These include obesity of the patient, unstable renal function, haematocrit values, administration of other drugs, or certain disease states of the patient. The accuracy of prediction of gentamicin level was reported to have markedly improved by taking account of these factors (Hull and Sarubbi, 1976). We believe that satisfactory treatment can be achieved, with few exceptions, by using dosage schedules; however, it
would surely be convenient if reliable micromethods of gentamicin assay which are accurate and applicable to clinical practice could be developed.

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References

Sweat testing for cystic fibrosis

Sir, Bray et al. (Archives, 1978, 53, 483) conclude that the mass screening of newborn babies with chloride ion-selective electrodes is a feasible method for the diagnosis of cystic fibrosis; they also suggest that this procedure might be used in conjunction with meconium analysis to reduce the incidence of false positive results.

In 1972 we reported the details of a child with proved cystic fibrosis in whom raised sweat sodium but normal sweat chloride levels were obtained during treatment with cloxacillin (Griffiths and Bull, 1972). Attention was drawn to the implication of the finding with regard to screening procedures, and the suggestion was made that, in at least some children with cystic fibrosis, the cloxacillin radical might replace the chloride ion in the sweat.

Infants might also be exposed to drugs administered to their mothers (either by transplacental passage or excretion in the breast milk). Although Beechams Ltd have no direct information on cloxacillin, after an oral dose of 250 mg of flucloxacillin, anamnestic fluid concentrations of less than 2.5 µg/ml, and breast milk concentrations of less than 0.1 µg/ml were obtained (personal communication).

When mass screening for cystic fibrosis is to be undertaken using methods based on the estimation of sweat chloride levels, it is therefore prudent to inquire whether the infant is receiving medication from any source and, if so, to interpret the results with caution.

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Reference

Dr Bray and co-workers comment:

We welcome the opportunity of commenting on the letter from Drs Griffiths and Bull. The instance mentioned of a child with proved cystic fibrosis in whom normal sweat chloride was obtained together with raised sweat sodium (Griffiths and Bull, 1972) is known to us (Bray et al., 1975). One of us (P. T. B.) came across a similar case about 2 years ago, giving credence to the view that ionised penicillinate displaces the chloride in excreted sweat.

These are instances of false-negative sweat chloride readings, but there is no evidence yet from our 1205 tests of any false-negative cystic fibrosis sweat chloride (Bray et al., 1978); the statistical chance of this is in any case small. Nevertheless, the two cases cited above do give the cause for concern that must arise for false negative results of any screening programme. The aim must be to recognise their cause and eliminate them.

The above two cases may be related to the observation (di Sant'Agnese, 1975) that IM injection of aldosterone lowers sweat electrolyte levels in patients with cystic fibrosis to the normal range. These several cases suggest a need for a systematic investigation of the effect of medication on sweat ion levels in general as well as in cystic fibrosis cases.

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