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.

R. T. MAYON-WHITE and ELIZABETH M. PERKS
Regional Public Health Laboratory and Department of Bacteriology, Radcliffe Infirmary, Oxford

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 schedule 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.

Hajime Yoshioka, Masatoshi Takimoto,
Ichiro Matsuda, and Shinzaburo Hattori
Department of Paediatrics, Asahikawa Medical College,
and Kumamoto University School of Medicine,
Japan

References
concentrations: pharmacokinetic predictions. Annals of
Internal Medicine, 85, 183-189.

unpredictability of serum concentrations of gentamicin:
pharmacokinetics of gentamicin in patients with normal
and abnormal renal function. Journal of Infectious Diseases,
130, 150-154.

Reeves, D. S., and Bywater, M. J. (1975). Quality control of
serum gentamicin assays—experience of national surveys.
Journal of Antimicrobial Agents and Chemotherapy, 1,
103-116.

Schwartz, G. J., Haycock, G. B., Edelmann, C. M., Jr, and
Spitzer, A. (1976). A simple estimate of glomerular filtration
rate in children derived from body length and plasma creatinine. Pediatrics, 58, 259-263.

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, amniotic fluid concentra-
tions of less than 2.5 µg/ml, and breast milk concentra-
tions of less than 0.1 µg/ml were obtained (personal
communication).

When mass screening for cystic fibrosis is to be under-
taken 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.

A. D. Griffiths and F. E. Bull
Departments of Paediatrics and Biochemistry,
Nevill Hall Hospital,
Abergavenny, Gwent NP7 7EG

Reference
Griffiths, A. D., and Bull, F. E. (1972). Anomalous sweat
chloride levels in cystic fibrosis during antibiotic therapy.
Archives of Disease in Childhood, 47, 132-134.

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
lower 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.

P. T. Bray
Department of Paediatrics,
University of Wales Institute of
Science and Technology,
King Edward VII Avenue,
Cardiff CF1 3NU

References
Bray, P. T., Clark, G. C. F., Moody, G. J., and Thomas,
J. D. R. (1975). A Perspective of Sodium and Chloride Ion-
sensitive Electrode Sweat Tests for Screening in Cystic
Fibrosis. University of Wales Institute of Science and
Technology: Cardiff.

Bray, P. T., Clark, G. C. F., Moody, G. J., Thomas, G., and
Diagnostic screening with a combination chloride ion-
selective electrode. Archives of Disease in Childhood, 53,
483-486.

test. In GAP Conference on Problems in Sweat Testing,
Hilton Head, South Carolina, February 1975, p. 9.

Griffiths, A. D., and Bull, F. E. (1972). Anomalous sweat
chloride levels in cystic fibrosis during antibiotic therapy.
Archives of Disease in Childhood, 47, 132-143.

Correspondence to Dr J. D. R. Thomas.