Gentamicin dosage in children

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Gentamicin dosage in children. The results of 49 serum gentamicin assays from children of 2 weeks to 11 years of age are presented. The dose of gentamicin given 8-hourly intramuscularly ranged from 0.7 mg/kg–4.9 mg/kg. Doses of 1.7 mg/kg or less did not give adequate serum concentrations. As a result of these observations it is suggested that an intramuscular dose of 2.5 mg/kg given 8-hourly is suitable for most children in the absence of renal failure, but that adjustment of the dose according to serum gentamicin concentration is necessary.

In recent years enteric Gram-negative infections have become an increasing problem. Gentamicin possesses the widest spectrum of activity of the currently available antibiotics, significantly including *Pseudomonas aeruginosa* (Garrod, Lambert, and O'Grady, 1973a). Shortly after its introduction fears were expressed that, as with other aminoglycosides, ototoxicity and nephrotoxicity would be a problem, though these dangers have been overemphasized (Reeves, 1974; McCracken and Eichenwald, 1974). The advent of a suitable method of assay has shown that with the earlier cautious therapy, undertreatment with gentamicin commonly occurred (Jackson and Arcieri, 1971), the fear of ototoxicity having been reflected in dosage schemes for children. We have found that low dosage regimens in children lead to unacceptably low serum concentrations of the antibiotic. While dosage regimens for adults (Mawer *et al.*, 1974), and for neonates and infants (Nelson and McCracken, 1972), are available in published reports, recommendations for children are scarce (McCracken and Eichenwald, 1974; McAllister, 1974). It is evident from these papers that the neonate and infant require a higher dose per kg to achieve therapeutic serum levels than does an adult. The dose suitable for a child is not clear. We present the results of gentamicin assays in children on a wide range of doses.

Materials and methods

The children were all inpatients at the National Children's Hospital, Dublin. Patients on antibiotics which might interfere with the gentamicin assay were excluded. As a further precaution β -lactamase I and

II (Whatman Biochemicals Ltd.) were added to all serum specimens to inactivate penicillins and cephalosporins. The presence of interfering antibiotics (such as clindamycin or lincomycin) was specifically considered in each case and assessed both by a history of previous drug therapy and by examination of the edge of the zone of inhibition on the assay plate (Garrod, Lambert, and O'Grady, 1973b). Gentamicin was given for established or suspected bacterial infection. Serum concentrations of gentamicin were measured as part of the patient's management. 49 specimens from 35 patients were assayed. The patients were aged from 2 weeks to 11 years (Fig. 1), with weight ranging from 3.0–38.9 kg. None of the children was suffering from established renal failure. Though some severely shocked children almost certainly had some degree of renal impairment, this did not persist once fluid and electrolyte abnormalities had been corrected.

Gentamicin was given by intramuscular injection into

FIG. 1.—Age distribution of the patients studied.

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the anterior thigh or by intravenous infusion over a period of one hour. The volume of the infusate varied with the fluid requirements of the patient. Doses were given every 8 hours. Blood specimens for estimation of gentamicin concentration were taken at least 24 hours after the start of therapy. The blood was taken one hour after intramuscular injection or within a few minutes of the completion of intravenous infusion of the drug.

The assay of gentamicin was made in quadruplicate using diffusion inhibition in an agar plate seeded with *Bacillus subtilis*. Some assays were performed using surface seeding with *Esch. coli* or a rapidly growing *Klebsiella* sp. Plating was carried out using a quasi-latin square format. A series of standard concentrations of gentamicin sulphate ranging from 20 μg -0.25 μg were tested in company with the patients' sera. A graph of the standards was prepared and the values for the patients' sera estimated from it. The results obtained using this test have been checked with those of other laboratories. Results in the range of 5-16 $\mu\text{g}/\text{ml}$ compared well. Results in the region of 2 $\mu\text{g}/\text{ml}$ were generally lower by about 0.6 $\mu\text{g}/\text{ml}$.

Results

Serum gentamicin levels after intravenous infusion were somewhat erratic (Fig. 2). Serum levels after intramuscular injection were more

FIG. 2.—Relationship between the intravenous dose of gentamicin (mg/kg body weight) and the peak serum level ($\mu\text{g}/\text{ml}$). The horizontal broken line indicates 5 $\mu\text{g}/\text{ml}$ and the vertical one 2.2 mg/kg per dose.

closely dose related (Fig. 3). Intramuscular doses of <1.8 mg/kg did not produce a peak serum concentration higher than 3 $\mu\text{g}/\text{ml}$. Once the intramuscular dose was increased to 2.2 mg/kg or above, the peak serum concentration reached or exceeded 5 $\mu\text{g}/\text{ml}$ on 12 out of 14 occasions. The two exceptions were levels of 4.5 and 4.6 $\mu\text{g}/\text{ml}$ with doses of 2.6 and 2.7 mg/kg, respectively. The results after intravenous injection were less satisfactory. Doses of up to 1.8 mg/kg resulted in peak concentrations of <5 $\mu\text{g}/\text{ml}$ on 5 out of 7

FIG. 3.—Relationship between the intramuscular dose of gentamicin (mg/kg body weight) and the peak serum levels ($\mu\text{g}/\text{ml}$). The horizontal broken line indicates 5 $\mu\text{g}/\text{ml}$ and the vertical one 2.2 mg/kg per dose.

occasions. Doses of 2.2 mg/kg and above produced levels of >5 $\mu\text{g}/\text{ml}$ on 9 out of 12 occasions. The three exceptions were levels of 1.0, 2.4, and 3.5 $\mu\text{g}/\text{ml}$ obtained with doses of 2.4, 2.3, and 2.5 mg/kg, respectively.

On two occasions after intramuscular injection the peak serum gentamicin concentration was unacceptably high. A dose of 2.1 mg/kg produced a level of 13 $\mu\text{g}/\text{ml}$ and a dose of 3.1 mg/kg produced a peak of 14 $\mu\text{g}/\text{ml}$. The first patient had been on co-trimoxazole up to 2 days before blood for gentamicin assay was taken and this may have affected the assay. The second patient had a urinary infection with a dilated ureter and renal pelvis on one side.

Discussion

Serum gentamicin concentrations after intravenous infusion were more erratic than those after intramuscular injection. Several factors may have been responsible for this. The infusions were powered by gravity and adjusted by humans and are unlikely to have run at a uniform rate throughout the hour over which the drug was given. The children who required intravenous fluids were, in general, more ill than those given intramuscular injections, and will have had more fluid, electrolyte, and tissue perfusion disturbances than those given the drug intramuscularly. All of these factors are likely to have affected the distribution and excretion of the antibiotic.

Paisley, Smith, and Smith (1974) found a closer correlation between dose and peak serum gentamicin

concentration when the drug was given intravenously than when it was given intramuscularly. Their studies were of infants in the first 23 days of life and the intravenous doses were given over 20–30 minutes by a constant infusion pump. The constant infusion may well account for the improved dose/serum level relation as compared with the present study. Studies in adults (Bailey and Lynn, 1974; Michel *et al.*, 1974) have shown that an intravenous injection of gentamicin given over a period of 10 seconds to 3 minutes may result in a potentially toxic serum concentration. It appears that an injection time of 20 minutes to one hour is to be preferred for intravenous administration of gentamicin.

While *in vitro* studies of gentamicin sensitivity are relatively easy to perform, there are few reports of therapeutic effectiveness in relation to peak serum concentrations. Noone *et al.* (1974) found in adults that the production of relatively high serum levels early in treatment was important in relation to the outcome of the illness. For urinary infections and Gram-negative septicaemia the important peak level was 5 µg/ml, reached within the first 3 days of treatment. The same peak level was important in wound infections, though the time factor seemed unimportant.

In Gram-negative pneumonia a peak serum level of 8 µg/ml or more was important in effecting a cure. If similar serum levels are necessary in children then relatively high doses of gentamicin will be required. Dosage schemes for children outside the neonatal period are scarce (McCracken and Echenwald, 1974; McAllister, 1974) and firm recommendations are not always given (Table). It is at times difficult to discover from reports exactly what dose was given and what serum level resulted. There has been a tendency to recommend higher doses over the past 3 years (Table). The

only figures of peak serum levels in children outside the neonatal period are those of McAllister (1974), who recommends a dose of 6 mg/kg per 24 hour (i.e. 2 mg/kg per dose 8-hourly). He suggests a therapeutic peak serum concentration of >2 µg/ml, based on minimum inhibitory concentrations. This is in contrast to the recommendations of Jackson and Riff (1971) (4 µg/ml) and Noone *et al.* (1974) (5–12 µg/ml). As the higher recommendations are based on therapeutic effect rather than on *in vitro* testing, it seems wise to accept them. The blood levels in the present paper are in general a little higher than those reported by McAllister (1974) for similar dosage regimens.

The basic principle of gentamicin therapy should be to reach an effective serum level early in treatment. From the work of Noone *et al.* (1974) it appears that for most infections the aim should be to produce a peak serum level of at least 5 µg/ml in the first 3 days of treatment. If a low starting dose is used and there is a long delay between taking blood for gentamicin assay and receiving the result, this delay may produce a therapeutic failure. From the present results it appears that 2.5 mg/kg 8-hourly should be the initial dose. In the absence of renal failure, serum gentamicin levels should be checked after 24 hours' therapy and the dose adjusted if necessary. In the presence of renal failure smaller maintenance doses will be required after a first dose of 2.5 mg/kg. Repeated serum gentamicin assays will be required to adjust the maintenance dose.

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TABLE
Recommended gentamicin doses for children from 1971 to the present

Dose	Frequency of administration	Source	Comment
2 mg/kg per 24 h 0.4 to >6 mg/kg per dose	Not stated 8-hourly	Holt and Newman (1971) Riley <i>et al.</i> (1971)	Urinary infections Wide range of infections; no dose recommended
2.5 mg/kg per dose	„	Nelson and McCracken (1972)	Neonate and young infant
0.8–1.7 mg/kg per dose	„	Manufacturers pre 1974	Children
2 mg/kg per dose	„	McAllister (1974)	5 days–13 years
2 mg/kg per dose	„	Manufacturers 1974	Children
2.5 mg/kg per dose	„	Present study	Children

REFERENCES

- Bailey, R. R., and Lynn, K. L. (1974). Serum levels of gentamicin after intravenous bolus injection. *Lancet*, **1**, 730.
- Garrod, L. P., Lambert, H. P., and O'Grady, F. (1973a). *Antibiotic and Chemotherapy*, p. 124. Churchill Livingstone, Edinburgh.
- Garrod, L. P., Lambert, H. P., and O'Grady, F. (1973b). *Antibiotic and Chemotherapy*, p. 527. Churchill Livingstone, Edinburgh.
- Holt, R. J., and Newman, R. L. (1971). Gentamicin in pediatrics. II. Treatment of severe urinary-tract infections caused by gram-negative bacilli and of staphylococcal infections. *Journal of Infectious Diseases*, **124**, S257.
- Jackson, G. G., and Arcieri, G. (1971). Ototoxicity of gentamicin in man: a survey and controlled analysis of clinical experience in the United States. *Journal of Infectious Diseases*, **124**, S130.
- Jackson, G. G., and Riff, L. J. (1971). *Pseudomonas* bacteremia: pharmacologic and other bases for failure of treatment with gentamicin. *Journal of Infectious Diseases*, **124**, S185.
- McAllister, T. A. (1974). Gentamicin in paediatrics. *Postgraduate Medical Journal*, **50** (Suppl. 7), 45.
- McCracken, G. H., and Echenwald, H. F. (1974). Antimicrobial therapy: therapeutic recommendations and a review of the newer drugs. *Journal of Pediatrics*, **85**, 451.
- Mawer, G. E., Ahmad, R., Dobbs, S. M., McGough, J. G., Lucas, S. B., and Tooth, J. A. (1974). Prescribing aids for gentamicin. *British Journal of Clinical Pharmacology*, **1**, 45.
- Michel, J., Sacks, T., Stessman, J., and Licht, A. (1974). Serum-gentamicin levels after intravenous bolus injection. *Lancet*, **2**, 525.
- Nelson, J. D., and McCracken, G. H. (1972). The current status of gentamicin for the neonate and young infant. *American Journal of Diseases of Children*, **124**, 13.
- Noone, P., Parsons, T. M. C., Pattison, J. R., Slack, R. C. B., Garfield-Davies, D., and Hughes, K. (1974). Experience in monitoring gentamicin therapy during treatment of serious gram-negative sepsis. *British Medical Journal*, **1**, 477.
- Paisley, J. W., Smith, A. L., and Smith, D. H. (1973). Gentamicin in newborn infants. *American Journal of Diseases of Children*, **126**, 473.
- Reeves, D. S. (1974). Gentamicin therapy. *British Journal of Hospital Medicine*, **12**, 837.
- Riley, H. D., Rubio, T., Hinz, W., Nunnery, A., and Englund, J. (1971). Clinical and laboratory evaluation of gentamicin in infants and children. *Journal of Infectious Diseases*, **124**, S236.

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