Single or multiple daily doses of aminoglycosides

More details needed of treatment in neonates and young children

EDITOR,—I welcome Michael Barza and colleagues' paper comparing the use of single or multiple daily doses of gentamicin.[1] This issue has considerable practical importance in developing countries because gentamicin is relatively cheap; it is thus typically the first line antibiotic used to treat (with benzylpenicillin) neonatal sepsis and neonatal meningitis and (with cloxacillin) staphylococcal pneumonia in young children.[2] The paper, however, does not discuss how the findings should be interpreted for neonates or young children. The authors mention that two trials studied "a substantial number of children" but give no further details. They also report a risk ratio for the failure of treatment in a subgroup analysis of "paediatric patients."

I would be interested to know more details of the data relating specifically to neonates and young children. As the pharmacokinetics of gentamicin varies substantially with age (particularly in the neonatal period),[3-5] the validity of extrapolating findings to young children, and in particular to neonates, is questionable. Given the importance of this issue, I would ask the authors to clarify whether they consider that the data support their general conclusions being applied to young children and specifically to neonates.

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1 Barza M, Ioannidis JPA, Cappelleri JC, Lau J. Single or multiple daily doses of aminoglycosides: a meta-analysis. *BMJ* 1996;312:338-5. [With commentary by F Smaill.] (10 February.)
2 Programme for the Control of Acute Respiratory Infections. *Antibiotics in the treatment of acute respiratory infections in young children.* Geneva: World Health Organisation, 1990. (WHO/ARI/90.10.)
3 Weber W, Kewitz G, Rost KL, Looby M, Mitz M, Harnisch L. Population kinetics of gentamicin in neonates. *Eur J Clin Pharmacol* 1993;44(suppl 1):S23-5.
4 De Cos MA, Gomez-Ullate J, Gomez F, Armijou JA. Time course of trough serum gentamicin concentrations in preterm and term neonates (review). *Clin Pharmacokinet* 1992;23:391-401.
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Giving gentamicin once daily for neutropenic fever has proved to be simple

EDITOR,—Michael Barza and colleagues' meta-analysis of single versus multiple daily doses of aminoglycosides[1] confirms the view that once daily dosing is safe and clinically effective.[2] However, specific experience with gentamicin (the most commonly prescribed aminoglycoside in Britain) is extremely limited because most trials have compared either netilmicin or amikacin.[1] Only three trials of aminoglycosides in the management of febrile neutropenic patients were referenced, none of which used gentamicin. Haematology units that treat neutropenic fever with gentamicin may therefore be reluctant to move to the once daily regimen. Furthermore, uncertainties over the practical application of a once daily regimen, highlighted in Fiona Smaill's commentary on the paper,[1] may be an added deterrent to change.

Nevertheless, giving gentamicin once daily remains an attractive option since it will result in more standardised dosing, less frequent use of the central venous line, better use of nursing time, and a reduction in laboratory costs. For these reasons we have incorporated once daily dosing with gentamicin into our management protocol for neutropenic fever; we report here our experience with this regimen.

During a 12 month study 42 adults with febrile neutropenia (mean age 63 (range 17-89)) were treated with gentamicin once daily. Exclusion criteria included an initial serum creatinine concentration >300 mmol/l[3] and previous treatment with cisplatin. Gentamicin (5 mg/kg, maximum dose 400 mg) was infused over 30 minutes and a trough value measured about 24 hours later. Peak serum concentrations were not measured. If the trough concentration proved satisfactory (<1 mg/l)[4] then twice weekly monitoring was performed. If the trough concentration was 1-2 mg/l the dose was halved and the measurement repeated 24 hours later. If the trough concentration was >2 mg/l gentamicin was usually stopped and replaced by ciprofloxacin. Nephrotoxicity was defined as either an increase of >45 mmol/l or a >50% rise from the baseline serum creatinine concentration.[1]

Altogether 160 trough samples were assayed. The concentration was <1 mg/l in 122, 1-2 mg/l in 27, and >2 mg/l in 11. All concentrations of 1-2 mg/l reverted to normal values after a reduction in the dose. Only three patients had evidence of nephrotoxicity, which was reversible in two. The third patient, an 89 year old man with myelodysplasia, died of multiple complications of the disease.

The protocol proved simple and easy to follow. No deaths due to sepsis or unexpected deaths occurred during the study. Haematology units that use gentamicin for neutropenic fever should consider moving to the once daily regimen.

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1 Barza M, Ioannidis JPA, Cappelleri JC, Lau J. Single or multiple daily doses of aminoglycosides: a meta-analysis. *BMJ* 1996;312:338-45. [With commentary by F Smaill.] (10 February.)
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3 European Organisation for Research and Treatment of Cancer, International Antimicrobial Co-operative Group. Efficacy and toxicity of single daily doses of amikacin versus multiple daily doses of amikacin and ceftazidime for infections in patients with cancer and granulocytopenia. *Ann Intern Med* 1993;119:584-93.
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Authors' reply

EDITOR,—Harry Campbell asks for an interpretation of the findings of our meta-analysis in young children, particularly neonates. None of the data we found apply specifically to the neonatal period, although there are some data for older infants. Marik *et al* studied 132 patients under 1 year of age, the mean (SD) age being 0.35 (0.26) years in the group given once daily doses and 0.41 (0.31) years in the group given twice daily doses.[1] The authors do not state how many, if any, of the patients were neonates. Adult patients were included in the same trial. There was a higher clinical and bacteriological rate of cure with once daily rather than twice daily dosing for all age groups, and the benefit was greater in the paediatric than the adult patients. Vigano *et al* studied children ranging in age from 1 month to 12 years who had pyelonephritis.[2] There was no significant difference in efficacy or the incidence of nephrotoxicity between a once daily and a thrice daily regimen of netilmicin. Two children, both in the group given the once daily regimen, had mild impairments on audiometry. Elhanan *et al* studied patients aged from 3 months to 16 years; their report was published after our meta-analysis had been accepted for publication.[3] They found no significant difference in efficacy, ototoxicity, or nephrotoxicity between children receiving gentamicin once daily and those receiving it thrice daily.

There are pharmacokinetic differences in the handling of aminoglycosides between adults, children from 6-12 months of age, and children aged less than 6 months: in the youngest patients the volume of distribution and clearance are greater and the β phase half life of the drugs is longer.[4] In rabbits, sexually immature animals were less susceptible than mature animals to the nephrotoxic effects of gentamicin. Lacking data from randomised clinical trials in humans, we are not able to make any statement about the relative efficacy and toxicity of single or multiple daily doses of aminoglycosides in neonates.

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