number of clinical adverse incident reports relating to gentamicin dosing errors. Investigation of these events showed that, with clearly written prescriptions showing benzyl penicillin to be given twice daily and gentamicin once daily, gentamicin was still being given more frequently or at the wrong time resulting in dosing levels exceeding the therapeutic range. This was despite double checking of doses and timings by two clinical staff members and perhaps highlights human fallibility even with standard systems in place. It was clear that the change to two different time regimens for the two antibiotics resulted in significant errors. To overcome this we have reverted to twice daily gentamicin given at the same time as the benzyl penicillin, the frequency of which cannot be reduced. The number of reported errors has since fallen dramatically.

This meta-analysis has focused predominantly on the reduction of serum drug concentrations outside the therapeutic range. Although this is clearly to be avoided in principle, there is little evidence that the increased number of both sub peak and elevated trough concentrations (which would normally be acted on) resulted in any significant adverse events in either group. Peak concentrations are notoriously unreliable, as the samples are often not taken at the correct time intervals, and this leads to a falsely increased number of sub peak threshold values. Most laboratories do not now routinely measure peak levels for this reason. The meta-analysis has not reported any nephrotoxic or ototoxic adverse effects that resulted in short or long term harm. Care should be taken over an assumption that laboratory or other changes such as the one raised creatinine concentration is meaningful. The authors themselves have counselled caution over interpreting the data as confirming that the extended dosing schedule is as effective.

Although this meta-analysis is interesting, it does raise the question as to whether a reduction in the number of measurements outside the defined range is the most important safety issue. We believe that a greater number of errors may occur, as in the clinical example above, if a wider risk assessment is not taken into consideration when considering a change to the dosing interval.

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Reference

- 1 **Nestaas E, Bangstad H-J, Sandvik L, et al.** Aminoglycoside extended interval dosing in neonates is safe and effective: a meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2005;**90**:F294-300.

Single daily dose aminoglycosides in the neonatal period appear to be effective: but are they safe?

A recent article by Nestaas *et al*¹ deserves comment. This meta-analysis attempts to evaluate the relative efficacy and toxicity of extended interval dosing (EID) compared with traditional dosing (TD) of aminoglycosides administered to newborn infants. The conclusion of the analysis was that "extended interval dosing of aminoglycosides in neonates is safe and effective, with a reduced risk of serum drug concentrations outside the therapeutic range".

This interpretation of the data presented can be questioned on several grounds. Even with meta-analysis, the number of reported treatment failures (two in the TD group, none in the EID group from a total of 555 patients) was too small to establish a statistically significant difference between the two regimens in relation to efficacy.¹

There were certainly more serum drug concentrations, both peak and trough, that were outside the defined therapeutic range using TD than using EID. However, this difference was only seen in trials that were aiming for a higher (usually 5-12 mg/l) peak serum drug concentration.¹ This observation is a self fulfilling prophecy. With EID, the drug is given at the same maintenance dose rate (mg/kg/day), but with higher single doses and longer dosage intervals than with TD. Basic pharmacokinetic principles indicate that during EID, peak serum drug concentrations will be higher and trough concentrations lower than when smaller drug doses are given at shorter dosage intervals (TD).²

The finding of increased numbers of serum drug concentrations outside the desired therapeutic range seems compelling, but is *per se* not necessarily a strong argument in favour of EID. The efficacy of aminoglycosides should not be based on this observation alone, even though there are theoretical and *in vitro* data to support the concept of "post antibiotic effect".^{1,3} Because treatment failures with TD are extremely rare,¹ the possible benefit in efficacy of EID becomes less important than establishing with confidence that this regimen has similar or less toxicity than TD.

Clinically significant renal impairment in neonates receiving aminoglycosides is extremely rare,^{3,4} and is nearly always transient.⁴

Of greater significance is the potential for ototoxicity, which can occur with excessively high serum drug concentrations.³ In 1979, Finitzo-Hieber *et al*⁵ published a comprehensive evaluation of ototoxicity in newborns receiving TD aminoglycosides (gentamicin or kanamycin). More than 100 infants in each of three groups (gentamicin treated, kanamycin treated, and controls) were followed annually for up to four years. Detailed audiological testing was performed together with measures of vestibular function and psychometric assessment. There were no significant differences between the three groups in any of these measures.

In contrast, only four of the 16 studies included in this meta-analysis provided any data on ototoxicity. Brain stem evoked responses were only measured during, or shortly after, a course of an aminoglycoside (gentamicin or amikacin).^{3,4,6,7} No adequate long term assessment of the incidence of hearing impairment has yet been reported in studies using EID. Until conclusive ototoxicity data are available in infants treated with EID, we will continue to use traditional dose aminoglycoside therapy.

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Book reviews in ADC this month

The following book reviews are published in this month's *Archives of Disease in Childhood*:

- Practical approach to pediatric intensive care
- Ethical dilemma in pediatrics: cases and commentaries
- Evidence paediatrics and child health, 2nd edition
- Antiepileptic drugs: combination therapy and interactions