Practicalities of once-daily aminoglycoside dosing

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Sir,

Gram-negative sepsis continues to have a high mortality rate. Survival in Gram-negative septicemia is dependent upon the extent of underlying disease, neutrophil count and early use of appropriate antibiotics (Kreger, Craven & McCabe, 1980). Using the aminoglycosides in the currently recommended dosage regimens often leads to gross underdosing (Zaske, Cipolle & Strate, 1980; Summer, Michael & Lipsky, 1983; Li et al., 1989). Li et al. (1989) found that over 10% of measured concentrations for 179 patients courses were below 4 mg/L. Given that approximately half of all Gram-negative septicemic fatalities occur during the first 24 h, it is not surprising that underdosing is associated with treatment failure (Moore et al., 1987). A study by Moore et al. (1984) looked at the association of aminoglycoside plasma concentrations with therapeutic outcome of Gram-negative bacillary pneumonia. Of 37 patients, treatment failed in 17; 12 of these died during antibiotic therapy. It was found that patients with a maximal peak plasma level of 7.0 mg/L or greater for gentamicin and tobramycin or 28 mg/L or greater for amikacin had a significantly greater chance of a successful outcome ($P < 0.006$).

Moore et al. (1987) reported the results of treatment of Gram-negative infection with an aminoglycoside (gentamicin, tobramycin or amikacin) combined with methicillin, nafcillin or cephalothin. Clindamycin was used when the source of infection was suspected to be pelvic or gastrointestinal or the infecting organism was Bacteroides fragilis. Maximum clinical response rates occurred when the peak serum concentration of the aminoglycoside exceeded the in-vitro MIC by at least six-fold. Recently reported studies have demonstrated that the pharmacokinetic parameters of the critically-ill patient are in a highly dynamic state, the underlying pathology and subsequent resolution causing appreciable changes in the volume of distribution ($V_d$), clearance (CL), and half-life of the aminoglycoside agents (Ter Braak et al., 1990; Marik et al., 1991). It is under these conditions that it becomes difficult to achieve peaks > 8 mg/L with three times daily dosing.

In a review of the impact of dosage regimens on the efficacy of antibiotics in the immunocompromised host, Bakker-Woudenberg & Roosendaal (1988) emphasized important pharmacodynamic differences between the aminoglycosides and $\beta$-lactam agents. The therapeutic effect of the $\beta$-lactams in immunocompromised animals is not strongly peak-concentration dependent, but depends mainly upon the time the drug concentration is maintained above the MIC of the infecting pathogen. In contrast the therapeutic activity of the
aminoglycosides in the immunocompromised animal is dependent on peak serum concentration. The need for peak aminoglycoside concentrations to exceed rather than equal the MIC may be explained in part by higher serum concentrations allowing a greater penetration of the agent into infected tissues. However, that would affect β-lactams and aminoglycosides equally. Pharmacodynamic differences between aminoglycosides and β-lactams are more likely to be explained by differences in their access to and effects on bacterial target sites. For aminoglycosides in-vitro evidence favours high initial peak concentrations with prolonged washout before re-exposure (Daikos et al., 1990; Jackson, Lolans & Daikos, 1990; Daikos, Lolans & Jackson, 1991). Several reviews have examined the existing in vitro, experimental and clinical data, of once-daily aminoglycoside dosing (Chan, 1989; Kovarik, Hoepelman & Verhoeef, 1989; Gilbert, 1991; Nordström & Lerner, 1991). This review examines the recent theoretical evidence which endorses once-daily aminoglycoside dosing and addresses the practicalities of once-daily dosing at ward level.

In-vitro it has been shown that the bactericidal action of the aminoglycosides is biphasic. The primary phase is a rapid drug-concentration-dependent bactericidal action; during this initial phase killing-rate is directly related to the initial drug concentration. The second phase is independent of the drug concentration and the bactericidal rate is slow (Jackson et al., 1990). The post-antibiotic effect (PAE) of the aminoglycosides is prolonged, i.e. surviving bacteria may not begin to metabolize normally for up to 8 h after all the extracellular aminoglycoside has been washed away (Daikos et al., 1991). Exposure of surviving bacteria to a second dose of aminoglycoside before they have recovered from the first seriously impairs the bactericidal effect of the second dose (Daikos et al., 1990, 1991). Increased oxygen tensions have been found to prolong the PAE even further. Park et al. (1991) demonstrated in vitro that hyperoxia prolonged the PAE of tobramycin on Pseudomonas aeruginosa. These authors suggested that the therapeutic activity of aminoglycosides in patients exposed to increased concentrations or hyperbaric oxygen may be prolonged.

Toxicity is related to the duration of treatment. Transient exposure to high aminoglycoside concentrations in serum and the long washout period with low trough concentrations results in less accumulation in the fluids and tissues of the inner ear (Mattie, Craig & Pechère, 1989). Verpooten et al., (1989) carried out an elegant study comparing the renal cortical uptake kinetics in humans of once-daily dosing of the aminoglycosides. It was found that the once-daily dosing decreased the renal accumulation of these agents, i.e. the cortical uptake kinetics may be saturable. In the case of a single injection the momentary high drug concentrations achieved immediately after injection probably result in saturation of the uptake mechanism. In contrast, low drug concentrations obtained during continuous infusion leads to increased drug uptake as the concentrations may remain below those required for saturation of uptake. An additional important consideration is that rapid achievement of effective peak concentrations may limit the amount of time the patient is exposed to the aminoglycoside and therefore reduce the potential for toxicity to occur.

Patients frequently present for treatment of septicemia when senior members of staff are not readily available and it is recently qualified medical staff who are responsible for initiation of therapy. Individualization of dosage regimens requires an estimation of creatinine clearance (CLcr) corrected for age, sex and weight and an estimation of a volume of distribution (Vd) for the aminoglycoside, and calculation of dosage intervals to achieve peak concentrations equivalent to > 7 mg/L gentamicin (Moore et al., 1984) and trough concentrations below 2 mg/L before the next dose is given. These calculations demand a level of background knowledge and expertise that is often lacking. Consequently due to fear of inducing toxicity patients are often subjected to subtherapeutic doses.

A study by Dunagan et al. (1989) examined antibiotic regimens on a daily basis. Appropriateness of antibiotic use was judged according to the availability of information such as culture and sensitivity results and serum drug concentrations. For 88 patients, these authors considered 10-2% of aminoglycoside antibiotic days to be inappropriate. Three-quarters of the inappropriate use was accounted for by dosing errors (54-7%) and the failure to check serum concentrations (21-4%). In the multiple dosing regimens where dosage adjustment and individualization is reliant on assay results, variation in dosage administration and variation in specimen collection time complicates the interpretation of assay results and it can be many days before appropriate serum concentrations are achieved (Li et al., 1989).

An audit of iv antibiotic administration by
Aminoglycoside dosage selection and associated clinical parameters

1. First dose to be within the range of 4–5 mg/kg regardless of sex, age or renal function.
2. Renal function to be measured in the following 24 h—amend dosage if necessary.
3. Trough level to be measured before the next dose:
   (i) if level < 2 mg/L—maintain selected dose
   (ii) if level > 2 mg/L—extend dosing intervals beyond 24 h or reduce dosage.

Davey et al. (1990) showed that between 16–45% of administrations differed from the prescribed time by more than an hour. This phenomenon of inaccurate administration times for iv injections has been described elsewhere (Clark et al., 1986; Cousins et al., 1989). Inaccurate administration times are particularly important for the aminoglycosides because they may lead to inappropriate dosage adjustment.

A prospective audit of aminoglycoside usage by Li et al. (1989) showed that specimen collection time post-dose varied by up to 5 h. Distribution is considered to be complete 30 min after a 30 min infusion or 60 min after bolus administration; it is at this point that a post-dose specimen is ideally taken and unless information is supplied to the contrary it is assumed that this is when a sample has been taken. Dosage adjustments are therefore made based on these assumptions and the actual results of drug assays. Inaccurate timing of night time doses also affects serum concentrations. Serum monitoring tends to be carried out in the morning. If a dose is administered late the previous evening then the time interval between successive doses will be much reduced. A dose administered 2 h late within an 8-h dosing interval reduces the interval by 25%. Should a trough serum concentration be taken at the end of this interval then a misleadingly high concentration will be measured. This problem has been detected by others. Davey et al. (1983) reporting on a study of gentamicin clearance in 26 patients noted four patients whose serum concentration measured 4–6 h after a dose were less than the trough level measured immediately before that dose was given. These patients were prescribed a three times daily regimen i.e. the dosage interval was intended to be 8 h, but the data collected suggested that previous doses had been given 4–6 h before the morning dose was due.

A single daily dose of an aminoglycoside calculated on a mg/kg basis could overcome the problem of suboptimal dosing (Table). A high peak concentration would be obtained much in excess of the infecting organism's MIC. During the following 24 h serum drug concentrations would decay to below 2 mg/L before administration of the next dose, assuming adequate renal function. Where renal function is compromised an extension of the dosing interval beyond 24 h may prove to be necessary. However, the initial dose (4–5 mg/kg) would be the same irrespective of age, sex or renal function, and the following 24 h would allow time for renal assessment and dose calculation by experienced staff whilst ensuring adequate antibiotic cover; this may increase survival rates for those critically-ill patients (Jackson & Riff, 1971). The effect on trough serum concentrations of an inaccurately timed once-daily dose would be proportionally less than occurs in multiple daily regimens. For example, a dose administered 2 h late within 24 h reduces the interval by only 8% compared to the 25% reduction in time interval should a dose be administered 2 h late in a three times daily regimen. It is more likely that single daily doses will be administered at the correct time, being given during normal working hours when senior staff supervision is available. Quality control of preparation, administration and monitoring of aminoglycosides is therefore easier for once-daily dosing regimens than for three times daily regimens.

As early as 1974 once-daily doses of aminoglycosides were shown to be efficacious (Labovitz, Levison & Kaye, 1974). This and other studies (Powell et al., 1983; Kapusnik et al., 1988; Hollender et al., 1989; Nordström et al., 1990; Pechère, Craig & Meunier, 1991; Tulkens, 1991) suggest that less frequent administration is associated with less toxicity whilst efficacy remains unaltered. Animal and human data suggest that the most effective and safe dosing regimen is the one that produces a high peak serum concentration with a low trough concentration (Powell et al., 1983).

With once-daily dosing it may be reasonable to monitor only trough concentrations, to ensure < 2 mg/L of aminoglycoside is present before administration of the next dose. This would release personnel time in that the post-dose serum sample would not need to be taken, and would lead to more patient acceptability due to less venepuncture.

In summary, the practical advantages of once-daily dosage calculation are: (i) a straightforward dosage calculation, (ii) a guaranteed peak...
serum concentration in the therapeutic range, (iii) a potential reduction in treatment period, (iv) easier quality control of preparation and administration, (v) a decrease in personnel time, (vi) fewer assays required and (vii) lower costs (e.g. consumables).

As suggested by Davey (1991), concerns about breakthrough infection with extended dosing intervals can be met by combination with a β-lactam drug.

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References