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Review

Once-daily dosing of aminoglycosides: review and recommendations for clinical practice

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The use of higher-dose, extended interval (i.e., once-daily) aminoglycoside regimens to optimize bacterial killing is justified by a pharmacodynamic principle of aminoglycosides, namely concentration-dependent killing, and by the partial attribution of the toxicity of aminoglycosides to prolonged serum concentrations. Numerous in-vitro and animal studies have supported using once-daily aminoglycoside dosing. Clinical studies show at least equal effectiveness and no greater toxicity when compared with traditional regimens. A dose of 5–7 mg/kg of gentamicin, tobramycin, or netilmicin, with at least a 24 h dosing interval should be employed and a similar regimen can be applied to amikacin dosing. As yet, there are some patient populations that have not been adequately studied to determine whether or not once-daily aminoglycoside dosing would be a better choice than traditional dosing regimens.

Introduction

Aminoglycoside antibiotics still find frequent use in today's hospitalized patient population owing to their spectrum of activity and unique mode of bacterial killing. Although highly effective, reservations concerning potential otovestibular toxicity and nephrotoxicity have often limited the use of these agents. However, based on more recent efficacy and toxicity data, a new dosage strategy for administering this class of antibiotics has evolved, namely, extended-dosing intervals, or once-daily administration of aminoglycosides. The purpose of this review is to explain the rationale behind this dosing strategy and provide guidelines for the administration of aminoglycosides in larger and less frequent doses.

In-vitro studies

Based on in-vitro data from bacteria-kill studies,[1–4] and on a synopsis made from such data,[5] it is apparent that aminoglycosides exhibit concentration-dependent killing. Studies that have examined the ratios of aminoglycoside concentration to MIC and area under the curve (AUC) to MIC have established that aminoglycoside concentration is a more important factor than time above the MIC in determining the pharmacodynamic effect of bacterial killing with these agents. Although the optimum peak concentration:MIC or AUC:MIC ratios have not been clearly defined, based on experimental data it appears that a peak concentration:MIC ratio of at least 8:1 to 10:1 is necessary to optimize bactericidal activity and avoid bacterial regrowth.[3,6] Clinical studies have tended to support the theory that higher peak concentrations lead to better outcomes.[6,7] In addition, a peak:MIC ratio of at least 10:1 may prevent the emergence of aminoglycoside-resistant pathogens.[3,8] Therefore, it would seem prudent to evaluate this ratio further in the clinical setting.

Adaptive resistance and refractoriness to the bactericidal activity of aminoglycosides has been demonstrated *in vitro* and in a neutropenic murine model by exposing *Pseudomonas aeruginosa* to concentrations below or at the MIC for the organism.[4,9,10] Constant exposure to an aminoglycoside at these concentrations leads to decreased

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bacterial killing. Therefore, longer dosing intervals which allow for a drug-free period in which the bacteria are not exposed to an aminoglycoside may preserve the bactericidal activity of these agents with subsequent doses.

Post-antibiotic effect

Studies evaluating the post-antibiotic effect (PAE) have found that this phenomenon exists *in vitro* for aminoglycosides and susceptible bacteria.[1,4,11,12] The PAE of aminoglycosides has been connected to four primary factors: (i) the bacterial strain (and its MIC), (ii) the duration of exposure, (iii) the inherent antibacterial potency and (iv) the relative concentration of the aminoglycoside (the higher the concentration, the longer the duration of the PAE). The PAE duration for aminoglycosides ranges from 0.5 to 8 h depending on these factors.[1,4,8] Therefore, in addition to optimizing the bactericidal activity with a higher aminoglycoside concentration, such as that achieved from a once-daily aminoglycoside regimen, the PAE should also be longer than with conventional regimens. The in-vitro PAE has also been shown to decrease with time.[13] It should also be noted that the vast majority of PAE studies have been confined to in-vitro and animal experiments, and the question of what happens with regard to PAE in an infected patient still remains unanswered.

Animal studies

Efficacy

Animal models evaluating efficacy have included endocarditis, subcutaneous abscesses, peritonitis and pneumonia.[2,11,12,14–21] Some of these studies have combined aminoglycosides with β-lactam antibiotics,[11,14,16,17,19–21] while others have studied aminoglycosides alone.[2,15,18] Most of these studies have demonstrated equal or greater effectiveness of once-daily aminoglycosides, alone or in combination, compared with conventional administration. Studies involving experimental endocarditis animal models have yielded conflicting results depending on the strain of bacteria used in the experiment, as well as the aminoglycoside and the β-lactam used.[16,17,19–21] Five studies have found high-dose, once-daily administration of an aminoglycoside to be equally, or more, effective than low-dose, more frequent administration,[14,16,19–21] although one study of enterococcal endocarditis found a better outcome when the aminoglycoside was given in lower dosages at greater frequency.[17] Possible reasons for failure in any animal experiment include the following: (i) the selection of resistant bacterial strains when using an aminoglycoside alone, (ii) altered growth characteristics of bacteria within an endocarditis vegetation and (iii) the rapid clearance and reduced serum half-lives of aminoglycosides in small animals. Even though the aminoglycoside concentration appears to be a more important factor than the duration of exposure of bacteria, the length of drug exposure may be an important pharmacodynamic parameter when the concentration:MIC ratio is not optimized. Given the faster elimination rates of aminoglycosides in these small animals, failures may have been avoided by using a dosing frequency (8–12 h) more analogous to a 24 h interval in humans. Despite these discrepancies with the endocarditis model, the majority of studies in animal infection models support the administration of aminoglycosides once daily.

Toxicity

Studies of nephrotoxicity involving animal models have found that once-daily administration of gentamicin or tobramycin was significantly less toxic than more frequent (i.e., twice or three times daily) dosages or continuous infusion.[22–25] Animal studies have further elucidated the probable mechanism involved in aminoglycoside nephrotoxicity, which involves an absorptive influx at proximal convoluted tubule cells and is mediated by a low-affinity, high-capacity mechanism that can be saturable, linear, or a mixture of the two.[26,27] The exact mechanism is not known, but speculation has led primarily to the following hypotheses: (i) a lysosomal mechanism, with aminoglycosides causing an accumulation of myeloid bodies within lysosomes and thereby inhibiting lysosomal phospholipases with a subsequent decrease in sphingomyelinase activity, or (ii) an extralysosomal mechanism, with inhibition of Na^+,K^+-ATPase and phospholipase C, leading to unopposed angiotensin II activity, or (iii) a combination of these mechanisms.

Animal studies that have examined ototoxicity show that the degree of cochlear damage is more related to the total daily dose of the aminoglycoside rather than the frequency with which the drug is administered.[27,28] Saturation of cochlear cells may play a role in determining ototoxicity.[27,29] Discontinuous administration, as opposed to constant infusion or more frequent administration, may lead to less saturation and accumulation of aminoglycosides.[29,30]

Studies in humans

Efficacy

Previous aminoglycoside studies that have evaluated the relationship between serum concentration and the MIC for the pathogen have supported the theory that higher concentrations lead to less morbidity and mortality in humans.[31,32] As a result of the in-vitro data and experience in animal models of infection and toxicity, once-daily aminoglycosides have been evaluated in a number of patient populations, including those with urinary tract infections, pelvic inflammatory disease, cystic fibrosis, appendicitis and other intra-abdominal infections, Gram-negative bacteraemia, bone and soft tissue infections,

pneumonia, endocarditis, post-partum endometritis and febrile neutropenia.[30,33–57] Studies have also been conducted in paediatric patients,[30,36,41,50,56] neonates,[54] and pregnant[43] and postpartum women,[57] to determine serum concentrations as well as clinical efficacy. There are still disease states and patient populations in which once-daily aminoglycoside therapy has not been investigated or reported to an appreciable extent, if at all. These include certain Gram-positive infections (e.g., enterococcal infections), meningitis, osteomyelitis, dialysis patients, and burn patients. Most once-daily aminoglycoside studies have been conducted in Europe and have used netilimicin, alone, or in combination, in doses ranging from 4.5 to 6.6 mg/kg[20,33,34,37,38,39,44,47,52,53] or amikacin, alone or in combination with other antibiotics, in doses ranging from 11 mg/kg to 30 mg/kg.[41,48,50,51] To date there have been 13 studies or reports published that have evaluated antibacterial efficacy and have used gentamicin or tobramycin, alone or in combination therapy, in doses ranging from *ca.* 3 mg/kg to 7 mg/kg.[30,34–36,40,42,43,45,46,49,53,56,57] These studies have demonstrated that the efficacy of once-daily dosing with aminoglycosides was at least equal to that of multiple daily dosing: generally, however, aminoglycosides were administered in combination therapy with other antibiotics, e.g., β-lactams. Another criticism of these and other clinical studies that evaluate antibiotic efficacy is the lower percentage of positive cultures before, and even after, initiating therapy.[45,48] Many reasons for this may exist, including poor culturing technique, inadequate sampling or active human immune complexes in the specimen. Although this criticism is certainly valid, there does not seem to be any acceptable answer to this problem, since most clinical studies involving comparisons of antimicrobial agents fall short in this regard. Therefore, clinical efficacy for many trials of once-daily aminoglycosides continues to be based on other objective criteria (i.e., white blood cell count, temperature) or subjective criteria, since this also reflects what is routinely done in clinical practice to establish cure of infection.

Toxicity

Clinical studies of gentamicin, tobramycin, netilmicin and amikacin, alone and in combination with β-lactam antibiotics, have examined the potential for nephrotoxicity and ototoxicity when administered once daily. Different criteria have been used for assessing these toxicities. Nephrotoxicity has generally been defined in a more standard way (usually defined as either an increase of 0.5 mg/dL (44.2 μmol/L) or doubling of serum creatinine from baseline, although not all investigators have used these criteria),[58] as compared with otovestibular toxicity (defined in various ways). The available studies have found either no significant difference in the incidence of nephrotoxicity when comparing once-daily aminoglycosides with conventional dosage regimens[33,34,39,46,47,52,58–61] or a significant difference in favour of once-daily administration.[41,45,62] However, most of these clinical studies have had small sample sizes, making it difficult to assess adequately a comparatively uncommon outcome, such as aminoglycoside toxicity.

One study compared once-daily gentamicin (4 mg/kg; $n = 72$) with once-daily netilmicin (5.5 mg/kg; $n = 69$).[63] These authors found no statistically significant difference in the incidence of toxicity in the two groups of patients (gentamicin 6.9%, netilmicin 14.5%). Duration of treatment and higher trough serum concentrations were significant factors for the development of nephrotoxicity in the gentamicin group. Ototoxicity was discovered in three patients in both treatment groups, but only 15 patients in each group underwent audiometric testing. Tinnitus or dizziness occurred in six patients who received gentamicin and five patients who received netilmicin.

A delay in the development of toxicity has also been reported in patients given once-daily aminoglycosides.[39,48] This suggestion seems to be more plausible for studies that have observed a difference in the incidence of toxicities between once-daily and traditional aminoglycoside administration since one would surmise that length of therapy and/or total amount of drug administered, regardless of the dosage regimen, would lead to accumulation and toxicity given sufficient time.

Saturation of cochlear cells might occur after the use of high-dose, once-daily administration of aminoglycosides, although no studies to date have validated this theory. Other comparative studies of once-daily aminoglycosides have not all addressed the issue of ototoxicity, owing largely to the difficulty of this assessment. Furthermore, as with most studies that evaluate hearing loss, audiometric criteria have been conflicting.[35,39,48,50–52] Some investigators have merely used subjective criteria for the evaluation of hearing loss rather than audiometric testing.[41,49] The issue of acceptable criteria for assessing hearing loss remains open for debate.

Based upon results from animal and human studies, it appears that less frequent administration of aminoglycosides would be desirable in order to allow efflux of the aminoglycoside molecules from kidney tubule and cochlear cells.

Very few studies have measured any neuromuscular toxicity associated with once-daily aminoglycoside administration, and those that have addressed this issue have stated that none was observed.[41,47,49]

It would seem to be acceptable to say that based on the available data, once-daily aminoglycoside administration is associated with a no greater incidence of the usual aminoglycoside toxicities than administration of multiple-doses per day.

Meta-analyses

To date there have been three major published meta-analyses of data comparing the clinical effectiveness and

toxicity of once-daily aminoglycosides with conventional dosing strategies.[64–66]

The meta-analysis by Hatala *et al.*[64] focused on five outcome assessments, namely bacteriological cure, clinical cure, mortality, nephrotoxicity and ototoxicity. They included an assessment of methodological quality and rated the various studies according to completeness, randomization, explicit criteria and intervention with other antibiotics. In addition, the authors also performed a test of heterogeneity to confirm that variation between individual study relative risk ratios were due to chance and not to true variation differences. A total of 14 studies met their criteria: these did not include studies in immunodeficient patients and not all studies were used in each analysis. The pooled risk ratio for bacteriological cure was 1.02 (95% CI: 0.99, 1.05), indicating no difference between once-daily and other dosage regimens. The meta-analysis for clinical effectiveness was not performed due to heterogeneity. The relative risks for mortality, nephrotoxicity, and ototoxicity (with their corresponding confidence intervals) were: 0.91 (0.63, 1.31); 0.87 (0.60, 1.26); and 0.67 (0.35, 1.28), respectively. All analyses displayed a trend towards more favourable results with once-daily aminoglycosides but none of them were significant.

Munckhof *et al.*[65] used a similar strategy and criteria for performing their meta-analyses, including their definitions of nephrotoxicity and ototoxicity and testing for heterogeneity. These authors included studies that involved comparisons in immunodeficient and paediatric patients, and analysed 19 comparative studies that met their criteria. Comparisons were performed with a random effects model as opposed to estimating a common odds ratio or relative risk. A statistically significant difference was found in favour of once-daily aminoglycoside administration for clinical efficacy (3.5% difference, CI 0.5%, 6.5%, $P = 0.027$), but not for bacteriological effectiveness, nephrotoxicity, ototoxicity or vestibular toxicity.

Finally, Ferriols-Lisart and Alós-Alimiñana[66] performed a meta-analysis of clinical effectiveness using inclusion/exclusion criteria that were very similar to those of Munckhof *et al.*[65] and Hatala *et al.*[64] Their definition of nephrotoxicity was more liberal than in the other studies (an increase of serum creatinine of at least 30 μmol/L). To analyse the possible differences in clinical efficacy, nephrotoxicity and ototoxicity between once-daily and standard aminoglycoside dosing regimens, the authors used the Mantel-Haenszel odds ratio (OR) method. Their search found 18 studies that met their criteria for inclusion, which apparently excluded paediatric but included immunodeficient patients. These authors also found a statistically significant difference in favour of once-daily aminoglycosides for clinical efficacy (OR = 1.47; CI: 1.13, 1.94). Ototoxicity showed a difference in favour of once-daily administration but this was not statistically significant (OR = 0.56; CI: 0.26, 1.16). There was a statistically significant difference in favour of the multiple-daily-dosed aminoglycoside regimens with respect to nephrotoxicity (OR = 0.60; CI: 0.40, 0.89).

There are numerous criticisms of these and other meta-analyses. These comments include: (i) inherent bias when establishing criteria and performing a meta-analysis, (ii) heterogeneity of patients, even though tests are performed to compensate, (iii) heterogeneity of disease states (e.g., pneumonia, bacteraemia, pelvic inflammatory disease, etc.), (iv) heterogeneity of doses used of the medications of interest (i.e., doses of 3–7 mg/kg/day of netilmicin or gentamicin have been used in these clinical studies), (v) inherent problems with retrospective data collection, (vi) inherent problems with establishing clinical efficacy with regard to infections (i.e., resolution of subjective symptoms, nonspecific indicators (temperatures, white blood cell count), etc.) and (vii) inherent problems with criteria used in establishing an outcome (e.g., definition and assessment of ototoxicity). Superficially, the question of whether or not high-dose, extended-interval aminoglycoside dosing is more effective and less toxic than standard aminoglycoside dosing regimens would seem ideal for meta-analysis. However, as D. B. Petitti has stated, 'Meta-analysis will not compensate for deficiencies in these (clinical) studies'.[67] Discrepancies between these three meta-analysis papers only serve to prove this point. Combining incomplete or faulty data in a meta-analysis does not make the data or conclusions any more robust.

Principles and goals

The use of a once-daily aminoglycoside regimen in the treatment of infection in humans is founded on two distinct principles: first, optimal bactericidal activity can be achieved with these agents if the peak concentration:MIC (or AUC:MIC) ratio is maximized; second, aminoglycoside toxicity (both anatomical and functional changes) appears no greater when the same total dose of the aminoglycoside is administered less frequently.

The application of these principles, and therefore the goals of once-daily aminoglycoside therapy, are to improve the microbiological and clinical cure rates of infected patients, while producing no greater incidence of aminoglycoside-associated toxicities. These recommendations are not to be taken to suggest that all patients who receive a once-daily aminoglycoside regimen will have a better outcome and less chance of drug-related toxicities as opposed to a standard dosing regimen.

Clinical application of once-daily aminoglycoside therapy in the treatment of infection

Patient populations

The clinical efficacy and toxicity of once-daily aminoglycosides have been reported in a variety of patient popula-

Table. Recommendations for patient populations suitable for high-dose, extended-interval aminoglycoside therapy

Category	Definition	Patients
A	moderate to strong evidence of probable clinical benefit	Gram-negative infections, e.g. pneumonia, urinary tract infections, pelvic inflammatory disease, bacteraemia
B	moderate evidence of a possible limited benefit, or no difference in efficacy and/or toxicity compared with conventional dosage regimens	Gram-positive infections, as listed for Gram-negative infections in category A, and abdominal infections,
C	little or no evidence for benefit of once-daily aminoglycoside use	paediatric, geriatric, pregnant, obese, burn, or cystic fibrosis patients; creatinine clearance <20 mL/min; ascites >20% actual body weight; meningitis; skin and soft tissue infections; mycobacterial infections; osteomyelitis
D	once-daily aminoglycoside may be inappropriate	enterococcal infections

tions, but certain patient populations have not yet been adequately studied. These populations include patients with significant alterations in the pharmacokinetic parameters of volume of distribution and/or drug clearance (e.g., neonates/paediatrics, pregnant women, patients with burns, gross ascites and renal failure). Although, theoretically, the principles and the goals of once-daily aminoglycoside therapy would apply to patients with these alterations in pharmacokinetics, sufficient data are not yet available to suggest an optimal regimen (e.g., modifying the dose and/or dosing interval) for these subpopulations of patients.

Recent data on the use of once-daily aminoglycosides in the treatment of neutropenic patients suggests that these regimens are as efficacious as conventional dosing approaches.[47,48,50,68] Consequently, it would seem unnecessary to exclude the neutropenic patient from possible outcome benefits offered by once-daily aminoglycoside regimens. The Table shows which patient populations/infections the authors consider would be suitable candidates for once-daily aminoglycoside therapy.

Selection of dosing regimens

At present, the dosage of aminoglycoside to use in a once-daily aminoglycoside strategy has not been clearly determined. Dosages for gentamicin, tobramycin and netilmicin have ranged from 3 to 7 mg/kg, and amikacin dosages have ranged from 11 to 30 mg/kg. Those regimens which utilize dosages ⩽ 6 mg/kg for gentamicin and tobramycin have calculated this dose based on the total daily dose given in the conventional regimen (1.5–2.0 mg/kg tds). Another approach to dosage selection has been based on the pharmacokinetic and pharmacodynamic parameters of the aminoglycosides and is intended to optimize the peak:MIC ratio in the majority of clinical situations; it suggests a 7 mg/kg dosage of either gentamicin or tobramycin.[49] The rationale for this dosage was based on achieving a target peak concentration of ten times the usual MIC of gentamicin for susceptible *P. aeruginosa*, which are usually 0.5–4.0 mg/L. A similar dosage regimen (i.e., one based on a 10:1 ratio) for amikacin could also be devised based upon the typical MIC of this antibiotic for *P. aeruginosa.*

In patients who are infected with organisms that typically have higher gentamicin MICs, such as *P. aeruginosa*, it would be more prudent to use an aminoglycoside that typically has a lower MIC, such as tobramycin. However, much of clinical antimicrobial usage is based upon empirical treatment, and the identification of the infecting bacteria, let alone its gentamicin MIC, will often not be known before initiating therapy. Therefore, one way to approach this problem would be simply to use a large enough dose (5–7 mg/kg) of gentamicin or tobramcyin in any patient who would potentially benefit from once-daily aminoglycoside therapy.

If the aminoglycoside dose produces a peak:MIC ratio for a given patient that is greater than the target ratio of 10:1, it is unknown whether there would be unfavourable alterations in the pharmacodynamics and the incidence of toxicity. At this point, one can only surmise, based upon pharmacodynamic principles, that there is a point at which the added efficacy of a high aminoglycoside concentration would be offset by an enhanced risk for toxicity, but that dose and subsequent concentration is unknown at present.

Another dosage nomogram has been used by Vreede which is more complex and was designed to achieve peak concentrations between 6 and 12 mg/L and trough concentrations of <2mg/L.[33]

In addition to deviations in the selected dose, there also have been disputes as to how to alter the dosing regimen in patients with decreased drug clearances. Some investigators have used dosage de-escalation methodologies which correspond to reductions in renal function, thereby allowing the patient to be maintained on a 24 h dosing

regimen.[34,45,69] Others have chosen a fixed dose and altered the dosing interval in response to variations in renal function.[33,49] If one is to adhere to the principles of high-dose, less frequent aminoglycoside dosing therapy, it would seem more logical to maintain a fixed dose and lengthen the interval for patients with decreased renal function. This second method would continue to optimize the peak:MIC ratio while allowing for the necessary drug-free period which is postulated to lead to a lower incidence of aminoglycoside toxicity and adaptive resistance. Dosage reduction would potentially sacrifice the higher peak concentration while at the same time potentially allow greater opportunity for aminoglycoside accumulation and subsequent toxicity. The optimal time for a patient to be technically 'drug-free' of aminoglycosides has not been ascertained, although the vast majority of patients who receive aminoglycosides will also be given other antibiotics (e.g., β-lactams; glycopeptides) that should be present throughout the 24 h period. Many of these questions also revolve around the issue of concentration of antibiotic at the actual site of

Method one[69]

Reduction of initial daily dose in case of decreased renal function

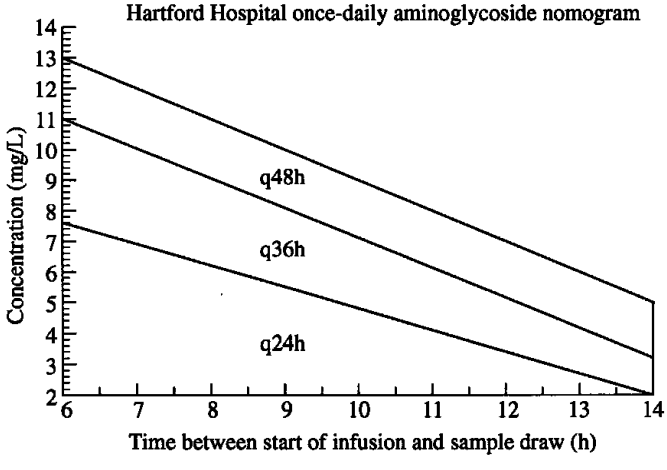
Estimated creatinine clearance rate (mL/min)	Percentage of standard dose
<90	100
90	90
80	88
70	84
60	79
50	74
40	66
30	57

Method two[49]

Hartford Hospital once-daily aminoglycoside programme.

Initial dosing regimen—Determine the patient's creatinine clearance

Creatinine clearance (mL/min)	Dose and interval
⩾60	7 mg/kg every 24 h
60–40	7 mg/kg every 36 h
40–20	7 mg/kg every 48 h
<20	7 mg/kg, then follow serial levels to determine time of next dose (level <1)



Dosing will be based on actual body weight unless the patient is morbidly obese (i.e. 20% over ideal body weight [IBW]). Obese dosing weight = IBW + 0.4 (actual body weight − IBW).

Monitoring. Obtain a single random serum level after the first dose between 6–14 h after the start of the infusion. Evaluate on the nomogram. If the level falls in the area designated q24h, q36h or q48h, the interval should be every 24, 36 or 48 h, respectively; however, if the point is on the line one should choose the longer interval. If the random level is off the nomogram at the given time, the scheduled therapy should be stopped and the serial levels followed to determine the appropriate time of the next dose (level, 1).

Patient exclusion. Paediatrics, pregnancy, burns (>20%), ascites, dialysis, enterococcal endocarditis.

Figure. The published methods for adjustment of aminoglycoside dosing using high-dose, extended interval regimens.[49,69]

the infection, which is another problem not well studied for any antimicrobial therapy.

Monitoring

The issue of optimal serum aminoglycoside concentrations after once-daily administration for the purpose of therapeutic drug monitoring has not been addressed to a great extent. Most studies have continued to monitor a peak concentration and at least one other sample concentration, either a midpoint or trough concentration.[69,70] Others have chosen multiple samples to describe the elimination rate more accurately[68] or a midpoint concentration based upon population pharmacokinetics and extrapolation[49,71] (see Figure). Finally, some investigators have chosen to target a particular AUC and subsequently extrapolate data from two or more serum concentrations with the assistance of computer pharmacokinetic modelling.[72,73] These investigators chose target peak and trough gentamicin concentrations of 10 and 2 mg/L, respectively, to create their desired AUC.[72] They then conducted a study which involved administering gentamicin at doses of 2.9–13.8 mg/kg based upon lean body weight (mean initial dose of 5.68 mg/kg).[71] The target AUCs the investigators attempted to achieve with 5, 6 and 7 mg/kg were 72, 86 and 101 mg/L/h, respectively. AUCs in these patients were calculated based upon two serum concentrations: a peak and a 6–14 h midpoint concentration. They evaluated 90 courses of once-daily gentamicin. The gentamicin dose was adjusted in 72 of these courses, resulting in a final AUC of 93.2 mg/L/h.

We offer the guidelines found in the Table regarding patients who might or might not be appropriate candidates for a once-daily aminoglycoside regimen, whether used alone or in combination with other antibiotics, based upon literature published to date. The recommended regimen should employ an optimal individualized dose (e.g., 5–7 mg/kg for gentamicin, tobramycin or netilmicin) every 24 h. We also advocate that the dosing interval should be lengthened (e.g., 36, 48 h, etc.) in patients with decreased renal function (creatinine clearance $\leqslant$ 60 mL/min). It should be noted that the nomogram developed by Nicolau *et al.*,[74] or any nomogram, only pertains to the particular initial dosage of aminoglycoside used in that protocol and the patient population in which it was used. Extrapolation of published nomograms to other doses, frequencies and populations would be inappropriate.

Pharmacoeconomics of once-daily aminoglycosides

Another advantage of once-daily aminoglycoside therapy, given what is known about aminoglycoside pharmacokinetics, may be that routine monitoring of serum aminoglycoside concentrations is not necessary. We know that a larger dose administered on a 24 h or longer frequency will result in higher than usual peak concentrations and lower than normal trough concentrations; therefore it would be reasonable not to follow serum aminoglycoside concentrations in all patients, at least not in the first few days of therapy. This would produce a pharmacoeconomic advantage for once-daily aminoglycoside administration.

Nicolau *et al.*[74] reported a 40% decrease in the number of requests for gentamicin and tobramcyin serum concentration determinations, as well as a historic reduction in nephrotoxicity (1.3%, down from 3 to 5%) with the implementation of their once-daily aminoglycoside programme. These reductions, using their programme in a 850-bed institution, were estimated to result in a cost savings of US$40,000 to >US$100,000/year.

In a related study, Belliveau *et al*.[57] focused on 118 patients in the same institution who were diagnosed with postpartum endometritis. In comparing the cost of their 7 mg/kg/24 h dosing regimen with a traditional 2 mg/kg/8 h dosing strategy, they found that the average cost per patient was 48% less for the 7 mg/kg/24 h regimen (US$18.06 compared with US$34.60). These cost comparisons included the drug acquisition cost, preparation and administration but not serum concentration monitoring.

Parker and Davey[75] provided an excellent review of the pharmaco-economic advantages of once-daily aminoglycoside administration. In addition to drug acquisition, preparation and administration costs, they noted wastage, monitoring costs, direct and indirect toxicities and treatment failures as factors that need to be considered when comparing once-daily and conventional dosing strategies, and all of which support the use of once-daily aminoglycoside administration when prudent.

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