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MINIREVIEW

Once-Daily Aminoglycoside Therapy

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INTRODUCTION

With the availability of a plethora of highly active beta-lactam and fluorinated quinolone antimicrobial agents, the future of aminoglycoside antibiotics in the practice of infectious diseases is a frequent topic for speculation. Since their introduction into clinical practice, there has been recognition that this class of drug represented a two-edged sword. On the one hand, aminoglycosides are extremely active as antimicrobial agents. They demonstrate concentration-dependent killing (23, 35, 65, 68, 71), they are little influenced by the inoculum of bacteria (13), recognition of emergence of resistance during therapy is a rare event, and now, with the sequential expiration of patent protection, they are inexpensive. On the other hand, all the aminoglycosides share the potential for renal and otovestibular toxicity (33). Neuromuscular blockade can also occur but is sufficiently rare that clinical concern has focused on ototoxicity and nephrotoxicity (8, 37). A great deal of effort has been expended to sophisticate our understanding of aminoglycoside pharmacokinetics so as to ensure the achievement of therapeutic levels while avoiding toxic concentrations in serum at either the peak or the trough of an 8-h dosage interval for gentamicin, tobramycin, and netilmicin or a 12-h dosage interval for amikacin. Despite careful attention to dosage regimens designed to achieve targeted peak and trough levels in serum, the incidence of nephrotoxicity has not changed (41).

Over the years, a great deal of investigative effort has been expended in an attempt to devise clinically applicable measures which would preserve the potent antibacterial activity of aminoglycosides and simultaneously lessen the potential for nephrotoxicity and ototoxicity (5, 8, 27, 28, 33, 37, 40). In experimental animal models, a variety of maneuvers have been shown to attenuate the risk of nephrotoxicity, but the majority of these have little clinical applicability. For example, reduced fluid intake and the resulting dehydration amplify nephrotoxicity but excessive fluid administration does not attenuate nephrotoxicity (3, 17, 29). In the rat model, oral calcium supplements can attenuate the risk of nephrotoxicity but at the expense of causing nephrocalcinosis (53). Experimental diabetes mellitus attenuates aminoglycoside nephrotoxicity by mechanisms that are still debated (59). The concomitant administration of ticarcillin reduces the risk of nephrotoxicity, and this may have some clinical relevance (18, 57). On the other hand, there are many more drugs that amplify aminoglycoside nephrotoxicity, e.g., vancomycin, amphotericin B, and cyclosporine (4, 27, 28, 69). Recent experimental data have suggested that polyaspartic acid of sufficient molecular weight may protect animals from all manifestations of aminoglycoside nephrotoxicity and does not appear to block antibacterial activity (29). Whether this compound will prove to be safe for clinical testing is uncertain.

In experimental animals, the less frequent administration of the aminoglycosides has demonstrated the ability to lower the risk of nephro- and ototoxicities while preserving antibacterial activity (16, 40). This paper reviews the logic and available evidence that support the feasibility of administering a full day's dosage of aminoglycoside in a single dose rather than divided doses to patients with normal renal function.

EXPERIMENTAL NEPHROTOXICITY AND OTOTOXICITY

In 1978, our laboratory developed a standardized model of gentamicin nephrotoxicity in male Fischer 344 rats (4). To reproducibly cause sufficient renal injury to raise the serum creatinine concentration by the seventh day of drug administration, it was necessary to administer a gentamicin dosage of 40 mg/kg of body weight per day, which was arbitrarily divided into two equal doses. It was postulated that there were receptors for the aminoglycosides on the brush border of the proximal tubular cells and that these receptors had a threshold concentration for binding and internalization (34). We wondered what would happen to the tubular cell uptake of aminoglycosides if our purposefully toxic aminoglycoside dosage was given in a single daily dose of 40 mg/kg or as 13.3 mg/kg every 8 h, as opposed to two equal doses of 20 mg/kg. After 7, 10, and 14 days of therapy, the serum creatinine concentrations remained normal in the animals given one daily dose; they were highest in the animals that received the smaller individual dose three times a day (4). The degree of renal injury correlated with the concentration of gentamicin in the renal cortex; the highest renal concentrations were found in the animals that received three-times-a-day gentamicin. The animals given once-a-day aminoglycoside had undetectable serum gentamicin levels for the last 12 h of the 24-h dosage interval, whereas the animals receiving three-times-a-day aminoglycoside had lower peak concentrations in serum but detectable concentrations in serum for the entire dosage interval. These results were consistent with the postulate that the animals given once-a-day aminoglycoside had serum and glomerular filtrate aminoglycoside concentrations that fell below the necessary threshold level for binding to receptors with low affinity and high capacity on the brush border membrane with subsequent internalization for roughly 12 h of a 24-h dosage interval. Hence, the target cell would have a reduced drug burden per 24-h interval. In addition, the presence of myeloid bodies in the urine and prolonged posttreatment excretion of aminoglycoside are evidence that aminoglycoside taken up in the proximal tubular cell is processed and then returned to the lumen of

the nephron (27, 34). Less frequent dosing would, in theory at least, allow a period for cellular processing of internalized aminoglycoside before the next exposure of the cell to additional drug.

Both before and after the publication of our data in 1979, other authors duplicated the results (22, 48, 51, 54). Despite minor variation in the study design, the more frequently the aminoglycoside was administered to rabbits, dogs, guinea pigs, and rats, the greater the degree of renal injury as long as the total daily dose was held constant.

The impact of reduced aminoglycoside dosage frequency on experimental ototoxicity has not been studied as often. To date, the reported experiments focus on hearing loss rather than vestibular injury. In a guinea pig model of ototoxicity, the results with gentamicin and tobramycin paralleled the results for nephrotoxicity (7). If the total daily dose was held constant, there was less anatomic and functional evidence of cochlear injury in the animals that received once-a-day aminoglycoside than in the animals that received the same total dose divided into several increments equally spaced. Of interest, when kanamycin or amikacin was studied with a similar experimental design, reduced frequency of administration had no impact on the severity of ototoxicity (2, 14). There is no clear explanation for this discrepancy. Additional recent animal studies demonstrate that, for a given total dose of gentamicin, discontinuous administration led to far less drug accumulation in the organ of Corti than continuous administration (61, 62).

At the time, the experiments on dosage frequency and oto- and nephrotoxicities were considered something of an oddity. The conventional wisdom was that it was necessary to maintain the level of antimicrobial agents in serum above the MIC, and perhaps the MBC, for the infecting organism for an entire dosage interval. For a period, this concept was extended to exploration of the desirability of the continuous infusion of aminoglycoside antibiotics with the hope of maximizing efficacy and simplifying the dosage regimen. Enthusiasm for this approach decreased when a high incidence of nephrotoxicity was encountered (20, 21).

PAE

The postantibiotic effect, or persistent antibiotic effect (PAE), is simply stated as that period of suppression of bacterial growth after cessation of exposure of the bacteria to an active antibiotic. Since there are several recent reviews of PAE, only the data pertinent to once-daily aminoglycoside therapy are discussed here (1, 10, 12, 16, 23, 40, 66, 68).

PAE is not new. A PAE of penicillin against streptococci was described early in the investigation of penicillin G (68). Kunin revived interest in the PAE when studying the interaction of beta-lactam antibiotics and aminoglycosides with aerobic gram-negative rods (36). In vitro there was no demonstrable PAE of a variety of beta-lactam antibiotics against aerobic gram-negative rods, whereas the aminoglycosides consistently demonstrated a 1- to 3-h PAE in both broth and human serum (12). Subsequently, Vogelman et al. expanded these studies (66, 68). Depending on the organism, carbapenems demonstrate either no PAE or a PAE of up to 3 h (11). Susceptible organisms exposed to tetracycline have a mean PAE of approximately 3 h. With quinolones, PAE can range from 1 to 4 h; with rifampin, it can range from 1 to 5 h. Demonstration of an in vitro PAE for aminoglycosides raised the possibility of less frequent dosing since maintenance of concentrations in serum above the MIC for an entire dosage interval might not be necessary for antibacterial efficacy.

The concentration-dependent bactericidal activity of aminoglycosides is also relevant. In vitro, the higher the aminoglycoside concentration the more rapid the kill of high inocula of susceptible organisms (23, 35, 66, 68). This statement is true at least for the first few hours. MacArthur et al. found two phases of netilmicin activity versus *Pseudomonas aeruginosa*: an early concentration-dependent phase and a later concentration-independent phase (38). The relevance of this finding to the results of in vivo experiments is uncertain.

The higher the aminoglycoside concentration, the longer the PAE (35). Less frequent dosage administration results in higher peak concentrations in serum relative to the MICs for infecting pathogens and thereby enhances antibacterial efficacy with a longer PAE. The longer the PAE, the less frequently one would have to administer aminoglycosides and, in theory, the lower the risk of aminoglycoside nephrotoxicity and ototoxicity.

Blaser and colleagues tested part of this hypothesis in vitro (6). To duplicate the pharmacokinetics of aminoglycosides in intact animals, an in vitro two-compartment system was generated. The rate of bacterial killing and simultaneous drug concentrations were studied. When single-dose kinetic curves were compared with curves for the same total dosage given in smaller increments, the single large dose demonstrated the greatest degree of antibacterial activity.

Only a few studies have focused on the in vivo suppression of bacterial growth after drug levels at the site of infection fall below the MIC (25, 67). Most of these studies address the activity of beta-lactam antibiotics. Recently, Vogelman et al. described aminoglycoside in vivo PAEs of 2 to 7.5 h in neutropenic mice with thigh infections due to *Escherichia coli*, *Klebsiella pneumoniae*, and *P. aeruginosa* (67). Animals were rendered neutropenic so as to avoid interactions between infecting bacteria and neutrophils or residual tissue antibiotic, either of which would amplify the PAE.

The longer in vivo aminoglycoside PAE despite the absence of neutrophils is not understood. Perhaps some of the organisms were susceptible to the serum complement system or underwent phagocytosis by fixed phagocytic cells. The presence of an in vivo aminoglycoside PAE stimulated further animal studies to determine the feasibility of once-daily aminoglycoside dosing in infected animals.

ONCE-DAILY AMINOGLYCOSIDES IN ANIMAL MODELS OF INFECTION

A number of variables are inherent to animal model studies. The justification of human-adapted small animal models was reviewed recently (23). Reported animal experiments differ as to whether there was concomitant administration of a beta-lactam antibiotic and as to the presence or absence of neutropenia. Other variables include the animal studied, infecting organism, total daily aminoglycoside dose, and route of administration.

In nonneutropenic rats, guinea pigs, and rabbits with *P. aeruginosa* subcutaneous abscesses, pneumonia, or endocarditis, once-daily tobramycin was equivalent in antibacterial activity to the same total daily dose divided into smaller more frequent increments (31, 51, 70). There was no systematic attempt to ascertain an in vivo PAE, but a long interval of sub-MICs in serum is predictable in the animals given once-daily doses due to the measured peak level data

provided and the known short serum half-lives of aminoglycosides in small animals. In only two studies has there been a concomitant study of toxicity and efficacy (51, 70). In rats with subcutaneous abscesses, once-daily dosing was as efficacious and less toxic than dosing every 4 h (which mimicked human pharmacokinetics) or every 8 h (70). The results were more dramatic with *E. coli* pyelonephritis. Greater efficacy and less nephrotoxicity was observed in the group of animals dosed once daily (31). There was no evidence of emergence of resistant organisms in any of these animal model studies.

Four studies have addressed the issue of aminoglycoside dosage frequency in neutropenic animals with and without a concomitant beta-lactam antibiotic (24, 35, 45, 55). In thigh infections in mice, hourly gentamicin had less antibacterial activity than the same cumulative dose given every 3 h (24). In rats with peritonitis, the two regimens studied were of equal efficacies (45). Rats with pneumonia due to *K. pneumoniae* did as well with every-6-h gentamicin as with the same dose given by continuous infusion (55). Only one study has compared once-daily dosing and dosing at 4-h increments in a neutropenic animal (35). In guinea pigs with pneumonia due to *P. aeruginosa*, an every-24-h regimen of tobramycin was less effective due to bacterial regrowth late in the dosage interval. The organisms remained aminoglycoside susceptible. When tobramycin was combined with mezlocillin, once-daily and every-4-h regimens had equal antibacterial efficacies.

When the inoculum of organisms is large, there is the potential for selection of aminoglycoside-resistant mutants. In the in vitro two-compartment model of Blaser et al., it was observed that once-daily netilmicin was superior to continuous infusion in the reduction of *P. aeruginosa* in the inocula; however, in three instances regrowth occurred due to selection of resistant strains (6). No experiments with concomitant netilmicin and beta-lactam were reported. Gerber et al. documented a similar phenomenon in neutropenic mice with *P. aeruginosa* thigh infection (24–26). Treatment with an aminoglycoside selected resistant variants; this problem was not observed with concomitant ticarcillin therapy. The postulated mechanism of concomitant ticarcillin is of interest. The efficacy of aminoglycosides correlates with the magnitude of the inside-negative transmembrane potential, which serves as the driving force for the internalization of the polycationic aminoglycosides (9). Bryan demonstrated that aminoglycoside-selected small-colony resistant mutants had respiratory transport enzyme changes that resulted in a marked reduction in the transmembrane potential (9). In a manner not yet understood, in the presence of an active beta-lactam there is a preservation of the high transmembrane potential in small-colony variants of *P. aeruginosa* (42).

In conclusion, aminoglycoside antibacterial efficacy in animal models is greatest with treatment regimens that result in the highest peak concentration in serum and the largest area under the serum time-concentration curve (16). These results suggest that aminoglycosides need not be given frequently to maintain drug concentrations above the MIC.

DOSAGE REGIMEN, RENAL ACCUMULATION OF AMINOGLYCOSIDE, AND PREDICTIVE VALUE OF LEVELS IN SERUM

Barring modifying factors, it seems reasonable to postulate that the more and/or faster an aminoglycoside is accumulated in the renal cortex or the inner ear tissues, the greater the toxic potential. The influence of dosage regimen on renal accumulation has been tested in both rats and human beings. In rats, the renal cortical concentrations were greater after continuous infusion than after three injections 8 h apart (70). The smallest concentrations were observed after a single daily dose.

Similar experiments were performed in patients with tumors in one kidney, normal renal function, and planned elective nephrectomy (15, 30, 64). Patients were administered identical total doses of gentamicin or netilmicin either as a single 30-min infusion or as a 24-h continuous infusion. Renal tissue was collected at surgery, and drug concentrations were determined. For each drug, the cortical concentration was roughly 50% higher after continuous infusion than after a single daily dose. These results, along with those presented above, have stimulated clinical studies of the safety and efficacy of once-daily aminoglycoside therapy.

The cumulative data from the nephrotoxicity experiments, the PAE data, results of the treatment of infected animals, and analysis of clinical trials provide a clearer perspective of the meaning of serum aminoglycoside concentrations. In addition to the animal data, analysis of levels in serum in clinical trials indicates that the higher the peak concentration in serum in relation to the MIC for the infecting pathogen, the greater the antibacterial efficacy (43, 44, 46, 56). In animals, the higher the trough concentration the greater the area under the time-concentration curve, the greater the renal accumulation of drug, and the more severe the renal (and probably auditory nerve end-organ) injury. Hence, the desirable profile of peak and trough levels in serum changes. No longer is the intent to maintain levels in serum above the MIC for an entire dosage interval. The current hypothesis is that high peak levels in serum (and concomitant large areas under the time-concentration curve) and low-to-undetectable trough levels in serum maintain efficacy and attenuate the risk of toxicity.

CLINICAL STUDIES OF ONCE-DAILY AMINOGLYCOSIDES

Volunteers. Two studies have evaluated full-dose once-daily aminoglycoside exposure in healthy volunteers. Petty et al. administered tobramycin at 5.1 mg/kg/day as either 1.7 mg/kg every 8 h or 5.1 mg/kg in a single dose in a double-blind fashion to 20 volunteers for 9 days (49a, 52). No evidence of renal or vestibular toxicity was detected in any recipient. Pierre et al. exposed 30 volunteers to once-daily netilmicin, 4.5 mg/kg, alone or in combination with teicoplanin, 6 mg/kg, for 7 days (50). Vestibular testing and audiograms were unchanged in all participants. The netilmicin recipients demonstrated mild enzymuria without any change in creatinine clearance; without an every-8- or 12-h comparison group, the importance of the enzymuria is unclear.

U.S. clinical studies. The retrospective evaluation of clinical trials of patients with gram-negative bacillary infections supports the need for high peak serum aminoglycoside concentrations to maximize the chance for bacteriologic cure (43, 44, 46, 56). Peak levels in serum have been correlated with therapeutic success. However, none of these studies was designed to assess the question of dosage frequency with a constant total daily dose.

Only one U.S. study in young adults with cystic fibrosis has addressed the role of dosage regimen (Table 1) (51). A tobramycin constant infusion of 11 mg/kg/day was compared to a single daily dose of 9 mg/kg in a small number of

TABLE 1. Summary of clinical trials which compare standard dosage regimens and once-daily aminoglycoside therapy and maintain a constant total daily dose

Patient population (reference; location)	Aminoglycoside (concomitant antibiotic)	Regimen[a] (mg/kg/day) (no. of patients)		Peak level in serum (μg/ml)[b]		Result[a]	
		Comparison	Once daily	Comparison	Once daily	Efficacy	Toxicity
Young adults with cystic fibrosis (51; United States)	Tobramycin (none)	11, Constant infusion (16)	9 (15)	5.6 ± 0.3	52 ± 5	No difference	None
Teenagers and adults with gangrenous and perforated appendicitis (19; Hong Kong)	Netilmicin (metronidazole)	1.5, q8h (20)	4.5, q24h (20)	4.2–7.9 (day 7)	8.2–20.6 (day 7)	Two wound infections, each group	None
Adults with appendicitis and other intra-abdominal infections (32; collaborative international)	Netilmicin (metronidazole)	1.5, q8h (55)	4.5, q24h (57)	1.5–16.3 (mean, 5.1)	3.2–26.9 (mean, 12.5)	No significant difference	None
Adults with gram-negative bacteremia (60; The Netherlands)	Netilmicin (ceftriaxone)	1.3, q8h (72)	3.9, q24h (69)	8 ± 2	15 ± 6	Clinical cure: 76% of q8h patients	Delayed onset of nephrotoxicity in q24h patients
Adults with serious infections (39; Sweden)	Amikacin (not stated)	7.5, q12h	15, q24h	33	55	Not stated	No significant differences
Intra-abdominal infection (15a; The Netherlands)	Netilmicin (tinidazole)	1.8, q8h (99)	5.6, q24h (98)	10 ± 0.4	21 ± 1.0	No difference	No difference
Adults with severe infection (47; Sweden)	Netilmicin or gentamicin	1.5, q8h (27)	4.5, q24h (29)	Not provided	Not provided	No difference	No difference
Pelvic inflammatory disease (63; Belgium)	Netilmicin (tinidazole and ampicillin)	2.2, q8h (14)	6.6, q24h (14)	6.6 ± 1	22 ± 4	No difference	No difference
Gram-negative bacteremia (58; The Netherlands)	Netilmicin (not stated)	2, q8h (35)	6, q24h (35)	7.5 ± 2	19.2 ± 4.5	No difference	No difference

[a] q8h, q12h, and q24h, Every 8, 12, and 24 h, respectively.
[b] Values are presented as means, means ± standard deviations, or ranges.

patients. Improvements in symptom scores were roughly equivalent, and no toxicity was detected.

International studies. Seven published papers and one abstract attest to the international interest in once-daily therapy (Table 1) (15a, 19, 32, 39, 47, 58, 60, 63). Thus far, all studies have excluded neutropenic patients. Netilmicin has been used most often with once-daily doses ranging from 4.5 to 6.6 mg/kg with resulting peak levels in serum as high as 18 to 26 μg/ml. Despite the high peak levels in serum, none of the reports indicate any differences in the observed incidence of toxicity. However, there was a relationship between nephrotoxicity and treatment duration in one study (60). The 50% cumulative nephrotoxicity occurred at 9 days in patients receiving multiple daily doses for 9 days versus 12 days for patients receiving a once-daily dose, $P = 0.03$ (60). Similarly, there were no statistical differences in clinical or bacteriologic cures or responses between patients receiving standard or once-daily dosage regimens. The numbers of enrolled patients are modest; only one trial had over 90 evaluable patients in each arm. Because of the small numbers of patients, a real difference in efficacy or toxicity might have been missed.

Clinical practice. Encouraged by the animal studies showing no reduction in efficacy and reduced risk of toxicity, safety in human volunteers and patients with cystic fibrosis, and controlled international trials, we cautiously initiated once-daily gentamicin or tobramycin therapy in 1988. Initially, education and discussion sessions were conducted with house officers and other physician colleagues and pharmacists. It was agreed that once-daily therapy would be given only to patients identified by the infectious diseases consultant. To be considered, patients had to have a measured or estimated creatinine clearance of ≥90 ml/min. Neutropenic patients were excluded. As a precaution against potential neuromuscular blockade, the 5-mg/kg daily dose was infused over 60 min rather than the customary 15 to 30 min. Patients receiving concomitant calcium channel blockers may be at increased risk of neuromuscular blockade (49). Peak levels in serum were measured only for academic interest and, when ordered, were almost always in the 16- to 24-μg/ml range. It was decided, arbitrarily, to measure the level in serum at 18 h postdose both to ensure adequate renal clearance and to document a concentration in serum of ≤1 μg/ml with the attendant theoretical reduction in nephro- and ototoxicities. This approach deletes the concept of a loading dose and maintenance dose; every dose is a loading dose. Occasionally, 12-h postdose serum drug levels were determined if there was concern that a patient's slow clinical response might be due to a more rapid renal clearance of aminoglycoside resulting in concentrations in serum below the MIC for the infecting organism for up to 12 h. Over the first year, approximately 100 patients were given once-daily gentamicin or tobramycin with no apparent problems with respect to clinical response or toxicity.

What about patients with creatinine clearances of less than 90 ml/min? The majority of patients in our institution, due to their age and non-infectious-associated disease processes, have various degrees of impaired renal function. To date, there are no animal model studies or clinical trials which address the influence of aminoglycoside efficacy or toxicity in the presence of various degrees of renal impairment. Because of the apparent success of once-daily therapy in patients with normal renal function, standard pharmacokinetic formulas were used to generate guidelines for the once-daily or once-every-other-day administration of aminoglycosides in the presence of various degrees of renal impairment (28). Again, caution is in order. It is anticipated that there is a maximum duration of PAE. In patients with an endogenous creatinine clearance of 20 ml/min or less, an every-48-h aminoglycoside dosage regimen could result, especially with *P. aeruginosa*, in a protracted period when the concentration in serum is below the MIC and the PAE is no longer operative. In addition, the metabolic derangement of renal failure may influence once-daily aminoglycoside therapy in some unforeseen way. There is a clear need for more data for infected animals and clinical trials of human beings with impaired renal function.

SUMMARY

The once-daily administration of aminoglycosides is an attractive concept. In animal experiments and clinical trials, there is either a reduction in or no influence on the risk of toxicity. Less frequent dosing reduces the contact time between host tissue binding sites and drug. Thanks to the PAE and perhaps other as-yet-unrecognized factors, the fall in the level in serum below the MIC does not appear to impair antibacterial efficacy; in fact, the higher peak level in serum may enhance drug efficacy early in a dosage interval. In neutropenic patients, the in vivo PAE may be lost or small-colony variants with a shorter PAE may be selected unless a concomitant beta-lactam is administered. Because it will be some time before data from clinical trials in the United States are available, because the results from the international trials are encouraging, and because there is potential benefit to patients, it seems reasonable for infectious diseases consultants to cautiously initiate the educational process necessary to implement once-daily aminoglycoside therapy in their institutions.

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