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Experience with a Once-Daily Aminoglycoside Program Administered to 2,184 Adult Patients

DAVID P. NICOLAU,[1,2,3]* COLLIN D. FREEMAN,[1,3]† PAUL P. BELLIVEAU,[1,3]‡ CHARLES H. NIGHTINGALE,[3,4] JACK W. ROSS,[2] AND RICHARD QUINTILIANI[2,5]

Department of Pharmacy,[1] Office for Research[4] and Department of Medicine,[2] Division of Infectious Diseases, Hartford Hospital, Hartford, Connecticut 06102; School of Pharmacy, University of Connecticut, Storrs, Connecticut 06268[3]; and School of Medicine, University of Connecticut, Farmington, Connecticut 06032[5]

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Once-daily aminoglycoside (ODA) regimens have been instituted to maximize bacterial killing by optimizing the peak concentration/MIC ratio and to reduce the potential for toxicity. We initiated an ODA program at our institution that utilizes a fixed 7-mg/kg intravenous dose with a drug administration interval based on estimated creatinine clearance: ≥60 ml/min every 24 h (q24h), 59 to 40 ml/min q36h, and 39 to 20 ml/min q48h. Subsequent interval adjustments are made by using a single concentration in serum and a nomogram designed for monitoring of ODA therapy. Since initiation of the program, 2,184 patients have received this ODA regimen. The median dose was 450 (range, 200 to 925) mg, while the median length of therapy was 3 (range, 1 to 26) days. The median age of the population was 46 (range, 13 to 97) years. Gentamicin accounted for 94% of the aminoglycoside use, and the majority (77%) of patients received the drug q24h. The 36-, 48-, and >48-h intervals were used for 15, 6, and 2% of this population, respectively. Three patients exhibited clinically apparent ototoxicity. Twenty-seven patients (1.2%) developed nephrotoxicity (the Hartford Hospital historical rate is approximately 3 to 5%) after a median of 7 (range, 3 to 19) days of therapy. On the basis of a prospective evaluation of 58 patients and follow-up of additional patients via clinician reports, we have noted no apparent alterations in clinical response with our ODA program. This ODA program appears to be clinically effective, reduces the incidence of nephrotoxicity, and provides a cost-effective method for administration of aminoglycosides by reducing ancillary service time and serum aminoglycoside determinations.

Although antibiotics have been available for decades, there has only recently been an emergence of adequate scientific data for determination of the best mode of drug administration to maximize bactericidal activity and minimize toxicity. The mode, however, is very different, depending on the antibacterial mechanism of the antimicrobial agent. For instance, β-lactams achieve maximum bacterial killing when the drug concentration remains constantly above the MIC. Since the intensity of killing is essentially the same once a concentration of four times the MIC has been achieved, β-lactams are considered to have time-dependent or concentration-independent killing, and as a result, the goal of therapy is to maintain the concentration above the MIC for the infecting pathogen for as long as possible during any drug administration interval (10). Unlike those of β-lactams, an aminoglycoside's rate and extent of bacterial killing are more a function of the concentration of the aminoglycoside. This type of killing is therefore referred to as concentration- or dose-dependent killing, and optimum bactericidal activity is achieved when the peak concentration is approximately 10 times the MIC (2, 8, 10, 15, 18).

These insights into the pharmacodynamic properties of antimicrobial agents allow clinicians to devise more efficient ways to administer antimicrobial agents for maximal bactericidal efficacy. Recently, considerable attention has centered on maximizing aminoglycoside bacterial killing, as these agents continue to have therapeutic utility in the treatment of serious gram-negative infections (11). By administering an aminoglycoside as a single daily dose, a clinician can take advantage not only of its concentration-dependent bacterial killing ability but also of two other important characteristics: time-dependent toxicity and a more prolonged postantibiotic effect (14, 30). This new approach to the administration of aminoglycoside antibiotics has been termed once-daily aminoglycosides (ODA). This methodology differs from the standard administration techniques in that the drug is administered in a single dose rather than in divided doses over a 24-h period. ODA regimens enhance concentration-dependent killing by maximizing the peak concentration/MIC ratio for the infecting organism(s). Owing to the concentration-dependent killing and the postantibiotic effect exhibited by aminoglycosides, ODA has been investigated in clinical practice. Many clinical studies have examined the efficacy and toxicity related to ODA regimens (1, 9, 14, 19, 22, 25, 26). Data from both animal models and clinical trials suggest that these regimens not only are as effective as conventional regimens but also reduce the ototoxicity and nephrotoxicity associated with aminoglycoside therapy (1, 3, 9, 14, 19, 20, 22, 25, 26). In addition, in an in vitro system, a peak/MIC ratio of at least 10:1 prevented the emergence of aminoglycoside-resistant pathogens (4).

Despite the growing clinical literature which supports the safety and efficacy of this new approach, several questions remain unanswered. First, can drug administration be standardized despite the variety of pathogens seen in clinical practice and the interpatient variability in aminoglycoside pharmacokinetics? Second, what approach should be used to monitor and adjust the dose for patients with diminished renal function to ensure adequate therapy and to minimize the potential for toxicity? We describe herein a method for dose determination,

* Corresponding author. Mailing address: Division of Infectious Diseases, Hartford Hospital, 80 Seymour Street, Hartford, CT 06102. Phone: (203) 545-3941. Fax: (203) 545-5112.

† Present address: College of Pharmacy, Butler University, Indianapolis, IN 46208.

‡ Present address: Department of Pharmacy, University of Massachusetts Medical Center, Worcester, MA 01655.

administration, and therapeutic monitoring of ODA together with our experience in using this program for nearly 2,200 patients.

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MATERIALS AND METHODS

Our ODA regimen was designed to enhance the bactericidal activity of aminoglycosides by maximizing the peak concentration/MIC ratio for the infecting organism(s). A recent review of the topic of ODA revealed a lack of standardization with this new approach, as evidenced by the wide range of dosages and resultant peak concentrations (14). Standardization is further complicated by the various pathogens and their aminoglycoside MICs. In actuality, the variance encountered in MICs is far greater than that observed in peak concentrations. To optimize the peak/MIC ratio, one generally targets the most troublesome pathogen with respect to the MIC. At our institution, this organism is *Pseudomonas aeruginosa* (median gentamicin MIC, ~2 μg/ml). As a result, we designed a drug administration regimen which would produce peak concentrations at 1 h of approximately 10 times the gentamicin MIC or 20 μg/ml. The chosen regimen should also allow a sufficient drug-free period; however, the optimal duration of the drug-free period with respect to the development of toxicity and its relationship to the length of the aminoglycoside-induced postantibiotic effect (7) and clinical outcome remains to be answered. In addition, the length of this drug-free period is dependent on the patient's renal function and the selected drug administration interval and is therefore variable from patient to patient. After evaluation of the available literature, we decided to convert our usual aminoglycoside administration to a once-daily schedule. This conversion was undertaken in four phases, the last of which was hospitalwide implementation of an ODA program.

Phase 1 of the ODA regimen design was done by computer simulation. Although much interpatient variation exists for the apparent volume of distribution (V) for aminoglycosides, average values of this parameter range from 0.2 to 0.3 liter/kg (28, 29). By using computer simulation with a one-compartment intravenous infusion model and a fixed V of 0.3 liter/kg, we tested different once-daily regimens by using various degrees of renal function to determine a dose and administration interval which produced the desired peak concentration/MIC ratio (10:1) and a drug-free period (concentration, <0.5 μg/ml) of at least 4 h (16). This model was used to determine not only the optimum dose needed to achieve the desired peak/MIC ratio but also the appropriate administration interval for patients with impaired renal function.

The validity of the model in our patient population was tested in phase 2. Pharmacokinetic data (i.e., V, elimination rate) for 35 patients receiving conventional aminoglycoside regimens (i.e., every 8 h [q8h]) in accordance with pharmacist determinations at our institution were reviewed. These data were then input into the model developed in phase 1 by using a 7-mg/kg once-daily regimen.

Phase 3 involved the confirmation of our model with patients actually given an intravenous dose of 7 mg of gentamicin or tobramycin per kg as a single daily injection. Initially, patients followed up by the infectious diseases consultation service and receiving aminoglycosides for documented or suspected gram-negative infections or as combination therapy for synergistic activity against gram-positive organisms were considered eligible for the ODA program. However, patients with highly variable or altered aminoglycoside pharmacokinetics, such as pediatric, pregnant, burn, ascites, and dialysis patients, were excluded. All patients received the 7-mg/kg dose with the administration interval based on the creatinine clearance (CL_{CR}), which was calculated by the Cockcroft-Gault method (5). Drug administration was based on actual body weight unless the patient was obese (i.e., 20% over ideal body weight). If the patient was obese, a dose-determining weight was calculated as follows: obese dose-determining weight = ideal body weight + 0.4 (actual body weight − ideal body weight). All aminoglycoside doses were diluted in 50 ml of a compatible intravenous fluid and were administered over 60 min. Initially, all patients enrolled in this pilot program had monitoring of the concentration of the administered aminoglycoside in serum. Patients had both determination of the peak concentration in serum (obtained at the end of the infusion) and at least one additional blood sample drawn at 8 to 12 h after the first dose was given. Subsequent administration interval adjustments were based on the pharmacokinetic parameters derived from concentrations in serum obtained after the initial 7-mg/kg dose was given (24). Since bedside audiometry was not the standard of practice at our institution when conventional aminoglycoside doses were prescribed, this test was not completed for the patients receiving ODA. Rather, the patients were followed up clinically and determination of ototoxicity was made on the basis of the patients' daily interviews and physical examinations. Nephrotoxicity was defined as a rise in serum creatinine of ≥0.5 mg/dl above the baseline value during aminoglycoside therapy.

RESULTS

In phase one, several different dosage regimens were examined to achieve the desired pharmacokinetic profile. This model suggested that a 7-mg/kg dose would be required to achieve the desired peak concentration in serum of 20 μg/ml. The model also provided drug administration interval adjustments for patients with impaired renal function receiving the fixed 7-mg/kg dose.

In phase two, the model was evaluated by using pharmacokinetic parameters obtained from patients who received conventional aminoglycoside regimens. Simulations were undertaken by using 7-mg/kg once-daily drug administration with the incorporation of our population pharmacokinetic parameters. The mean V in this population was 0.25 liter/kg (95% confidence interval, 0.22 to 0.29 liter/kg), while the half-life was 3.85 h. With this V value, the 7-mg/kg dose resulted in a mean peak (1-h) concentration in serum of 25.9 μg/ml (95% confidence interval, 23.0 to 28.8 μg/ml). This was anticipated because of the lower V in this group but was still consistent with our goal of approximately 20 μg/ml. Since this group of patients also had a large range of CL_{CR}s, this simulation allowed us to evaluate the 7-mg/kg dose and the resultant length of the drug-free period over a wide range of CL_{CR}s. The goal of interval adjustment was to provide a drug-free period of at least 4 h; however, it rapidly became apparent that patients with good renal function (e.g., CL_{CR} of ≥100 ml/min) would have drug-free periods that far exceed this value. On the other hand, patients with decreased renal function having CL_{CR} estimates near or at selected interval cutoff values would have shorter drug-free periods, often less than 2 h. Overall, this simulation using patient-specific pharmacokinetic parameters produced the desired peak concentrations and the concentration-versus-time profile. On the basis of data obtained from this patient sample and the estimations in phase 1, we designed an initial ODA protocol that utilized a fixed 7-mg/kg dose and a drug administration interval based on the patient's calculated CL_{CR} (e.g., ≥60 ml/min q24h, 59 to 40 ml/min q36h, 39 to 20 ml/min q48h, and a <20-ml/min dose and monitoring of serial levels to determine the time of next dose administration ([level, <1 μg/ml]).

During phase 3, 20 patients initially received the ODA regimen. Two patients received two courses of ODA each on two separate occasions. The mean age of the 20 patients was 43 (range, 20 to 80) years. Fourteen patients received 7 mg/kg q24h, and aminoglycosides were given to three patients q36h, one patient q48h, and two patients q72h. The mean duration of therapy was 6.9 (range, 2 to 14) days. The mean V in this population was 0.39 liter/kg (95% confidence interval, 0.34 to 0.45 liter/kg), which resulted in a mean peak concentration of 18.7 μg/ml (95% confidence interval, 16.4 to 21.0 μg/ml) at 1 h after administration of the 7-mg/kg dose. No patient appeared to exhibit clinical ototoxicity or nephrotoxicity (defined as a rise in serum creatinine of 0.5 mg/dl above the baseline), and no clinical failures were seen in this population. Since at least two concentrations in serum were obtained for each of these 20 patients, the concentrations in serum at 1, 8, 10, and 12 h were extrapolated as if samples had been obtained for a given patient at these specific time points. Once calculated, these data were input into a data set with the concentrations in serum obtained from the simulations in phases 1 and 2. The patients were then sorted into three groups according to their estimated CL_{CR}s (i.e., ≥60, 40 to 59, and 20 to 39 ml/min). The serum concentration-versus-time data were then plotted, and the regression line for each of the groups was used to develop a nomogram (Fig. 1) for monitoring of ODA regimens.

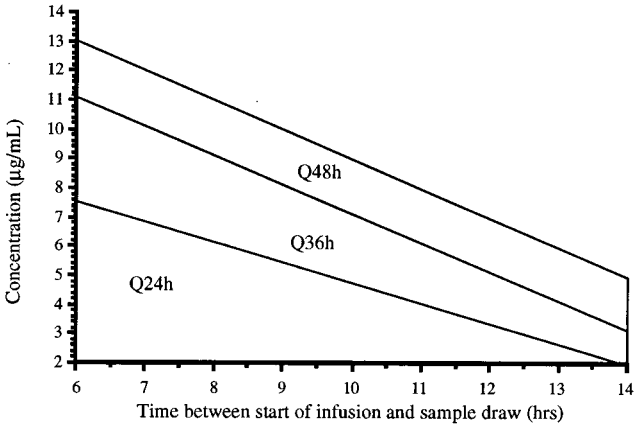

FIG. 1. ODA nomogram for gentamicin and tobramycin at 7 mg/kg.

TABLE 1. Distribution of nephrotoxicity for differing lengths of ODA therapy and age

Time period	No. of patients[a] with nephrotoxicity
Length of therapy (days)	
≤3	2
4–5	9
6–7	3
8–10	5
11–14	6
>14[b]	2
Age (yr)	
≤40	6
41–50	3
51–60	4
61–70	7
>70	7

[a] $n = 27$.
[b] Patients discontinued aminoglycoside therapy on days 15 and 19.

Following the three confirmatory phases described above, the ODA program was implemented hospitalwide at our institution in October 1992. All adult patients except those with ascites, burns of >20% of the total body surface area, pregnancy, end stage renal disease (e.g., requiring dialysis), and enterococcal endocarditis were considered eligible for the ODA program. A total of 2,184 patients (median age, 46 [range, 13 to 97] years) received our once-daily regimen. The age distribution of patients who received ODA therapy is as follows: ≤40 years, 40%; 41 to 50 years, 14%; 51 to 60 years, 7%; 61 to 70 years, 15%; >70 years, 24%. The 7-mg/kg dose was given to approximately 77% q24h, 15% q36h, and 6% q48h. The remaining 2% received this dose at intervals of greater than 48 h. Our patient population received 9,741 days of ODA therapy with a median length of therapy of 3 (mean, 4.5; range, 1 to 26) days. The percentage of patients receiving ODA according to the duration of therapy was as follows: ≤3 days, 50%; 4 to 5 days, 13%; 6 to 7 days, 17%; 8 to 10 days, 9%; 11 to 14 days, 6.5%; >14 days, 4.5%. Thirty-seven percent of the patients received 6 or more days of therapy.

We gave gentamicin to 94% of these patients, amikacin to less than 1% ($n = 5$), and tobramycin to the remainder. The median aminoglycoside dose (excluding amikacin [dose, 15 mg/kg]) was 450 (range, 200 to 925) mg. Patients received the ODA regimen for a variety of infections, including intra-abdominal (28%), pulmonary (26%), genitourinary (19%), skin and soft tissue (12%), staphylococcal or streptococcal endocarditis (3%), and other (12%) infections. Approximately 350 patients also received an aminoglycoside in this manner as part of a prophylactic regimen, most often for urologic procedures.

Ototoxicity, in the form of vestibular manifestations, was observed in three patients. The first received 5 days of therapy before the onset of symptoms, the second received approximately 5 weeks of treatment as an outpatient prior to alerting his physician to the signs and symptoms of toxicity, and the third received a single dose. These symptoms resolved with the cessation of ODA therapy in patients 1 and 3; however, the patient 2 appeared to have some degree of residual toxicity. Nephrotoxicity, as previously defined at our institution (rise in serum creatinine of ≥0.5 mg/dl above the baseline value during aminoglycoside therapy), was detected in 27 patients (1.2%) during therapy. The median increase in serum creatinine was 1.0 (range, 0.5 to 6.5) mg/dl. The incidence of nephrotoxicity with the ODA was lower than the Hartford Hospital historical rate of approximately 3 to 5% in patients receiving an average of 4.5 days of conventional aminoglycoside therapy. Patients developing nephrotoxicity had a median age of 63 (range, 28 to 86) years and received aminoglycoside therapy for a median of 7 (range, 3 to 19) days. Thirteen of these patients required drug administration q24h, nine required a 36-h interval, four required a 48-h interval, and one required a greater-than-48-h interval. The distribution of patients experiencing nephrotoxicity in relation to the length of therapy and age is presented in Table 1. A comparison of patients who developed nephrotoxicity and those who did not revealed that there were no differences in age, daily dose, or dose in milligrams per kilogram; however, the length of therapy among the patients developing nephrotoxicity was significantly greater ($P < 0.05$). The fact that the criterion for nephrotoxicity at our institution does not differentiate between the likelihood of aminoglycoside-induced toxicity and the associated rise in creatinine but rather is based on a serum creatinine rise during aminoglycoside therapy indicates that this 1.2% incidence of toxicity accounts for other mechanisms besides that solely due to the ODA regimen. A review of 17 of the 27 patients with nephrotoxicity revealed that 6 had developed sepsis or had an episode of hypotension-hypovolemia prior to the increase in serum creatinine, 4 had recently started therapy with either naprosyn or bactrim, and 3 were receiving vancomycin, all of which can contribute to elevations in serum creatinine. Upon discontinuation of the ODA regimen, the serum creatinine declined to values observed prior to the initiation of therapy in all 27 patients and no patient required hemodialytic support. In addition, no patient experienced neuromuscular blockage with the ODA program.

Since our ODA methodology was implemented as a program and not as a clinical trial, clinical and microbiologic cure data are not available for comparison between the conventional drug administration strategies and our ODA approach. However, 58 of the first 500 patients in our program were prospectively followed up for a clinical cure, defined as resolution of the signs and symptoms of infection (e.g., normalization of temperature and leukocyte count), and a microbiologic cure, defined as eradication of a documented pathogen as determined by two consecutive culture specimens. For the 58 patients, 70 documented or suspected infection sites were identified. Infection sites (n, median length of therapy [range] in days) were as follows: skin and soft tissue, $n = 11$, 6 (4 to 10); genitourinary, $n = 9$, 6 (4 to 16); blood, $n = 7$, 13 (5 to 14), intraabdominal or other, $n = 14$, 5.5 (4 to 10); pulmonary, $n = 29$, 7 (4 to 16). Clinical and microbiologic cures were evident in

all patients with extrapulmonary infections. The clinical and microbiologic cure rates for those with pulmonary infections were 25 (86%) of 29 and 5 (40%) of 13, respectively. All of the four treatment failures occurred with ventilated patients; *P. aeruginosa* was the causative pathogen in two cases, while a *Citrobacter* sp. and an *Acinetobacter* isolate were involved with the other failures. In addition, since the conclusion of this prospective efficacy review, we have received no indication of an overtly high rate of therapeutic failures attributed to the ODA regimen by staff physicians.

Although our program initially required determination of only a single random concentration in serum for monitoring of ODA therapy, 57 patients had multiple determinations of concentrations in serum during therapy. As a result of these multiple determinations, we were able to evaluate the performance of the nomogram under typical use conditions. Patients with multiple concentration determinations had their glomerular filtration rates (i.e., CL_{CR}) determined from the calculated aminoglycoside clearance, since these agents are eliminated primarily via the renal route following glomerular filtration (27). The assignment of a patient to a specific drug administration interval on the basis of a single random level was compared to that suggested by the actual drug clearance of the patient. On the basis of the random aminoglycoside concentration, the distribution of patients for a given interval was as follows: q24h, $n = 25$; q36h, $n = 16$; q48h, $n = 10$; level off the nomogram, $n = 6$. The single random concentration predicted the appropriate interval for all patients assigned to the q24h regimen and for those falling off the nomogram. Of the 16 patients on the q36h regimen, 13 (81%) were assigned to the appropriate interval whereas 7 of 10 patients on the q48h regimen were assigned to the appropriate interval on the basis of the single random concentration. Patients on the q36h and q48h regimens not conforming to the interval as suggested by the nomogram were often borderline between intervals and were assigned to the longer of the two intervals. This approach was designed to minimize potential drug accumulation in these patients, a practice which subsequently produced longer drug-free periods than originally intended.

With the initial implementation of the program, all patients were required to have a random aminoglycoside concentration determination after the first or second dose. Once a concentration had been reported, it was evaluated with our nomogram by a pharmacist and interval adjustments were completed as required. Approximately 5% of these patients required interval adjustments on the basis of the first concentration in serum, and 3% required interval adjustments as a result of subsequent aminoglycoside concentration determinations. An evaluation of our ODA database with 500 and again with 1,400 patients revealed that drugs were given to 74% of the patients q24h, 17% of the patients q36h, and 7% of the patients q48h. In addition, the median length of ODA therapy was 3 days and the incidence of nephrotoxicity remained 1.2%. As a result of the low toxicity, its presence at 7 days, the short duration of therapy, and the fact that most patients had good renal function (i.e., received drugs q24h), a modification was made in the determination of the previously mandated random concentrations. Criteria were developed and approved by our institutional therapeutics committee to withhold the random concentration for patients (i) receiving ODA q24h, (ii) without concurrently administered nephrotoxic agents (e.g., amphotericin, cyclosporine, vancomycin), (iii) without exposure to contrast media, (iv) not quadriplegics nor amputees (v) not in the intensive care unit, and (vi) less than 60 years of age. Although the initial random concentration is withheld for eligible patients, monitoring of serum creatinine continues to occur at 2- to 3-day intervals, as it has throughout the entire period of the ODA program. For patients who continue in the ODA program for ≥5 days, a random concentration is determined on day 5 and weekly thereafter. Since this modification has been implemented with ODA therapeutic drug monitoring, approximately 600 patients have received ODA and the incidence of nephrotoxicity is unchanged ($n = 8$ [1.3%]), while the number of requests for serum gentamicin concentration determinations has dropped by approximately 40%.

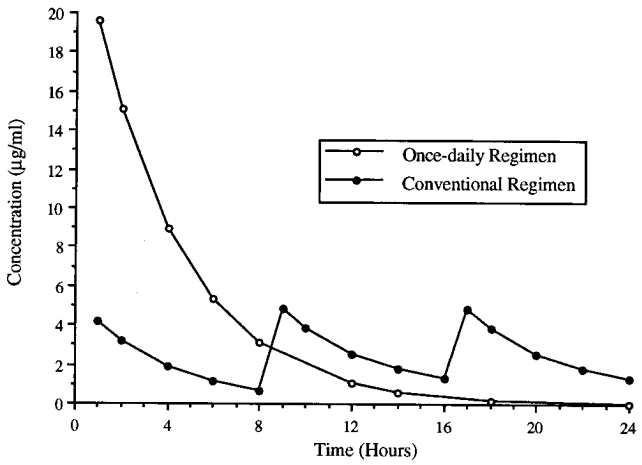

FIG. 2. Simulated concentration-versus-time profile of once-daily (7 mg/kg q24h) and conventional (1.5 mg/kg q8h) regimens for patients with normal renal function.

DISCUSSION

Although the literature suggests that subtherapeutic drug concentrations in serum are often obtained with conventional aminoglycoside administration schedules, these methods continue to be frequently utilized for the treatment of serious infections (13, 21, 23). This stems from the widely published data that emphasize aminoglycoside toxicity. Recent evidence, however, suggests that some of these accepted concepts relating to aminoglycoside toxicity are incorrect.

Our ODA regimen was designed to optimize efficacy and minimize the potential for toxicity on the basis of recent aminoglycoside pharmacodynamic data. This approach is, however, a radical change from standard aminoglycoside administration schedules (Fig. 2). This regimen consists of a fixed 7-mg/kg dose of either gentamicin or tobramycin. We selected a dose that is higher than that of both standard therapy and the previously noted ODA studies. This dosage was selected on the basis of the pharmacokinetics and pharmacodynamics of aminoglycosides and was intended to optimize the peak/MIC ratio in most clinical situations. Therefore, our dose was not simply based on conversion of the conventional dosage (1.5 mg/kg per dose) to 4.5 mg/kg given once daily. It is evident from both our data and the references cited that large variations in V values for aminoglycosides in hospitalized patients exist. Utilizing this larger dose will maximize the percentage of patients in whom the desired peak will be achieved. This is especially important for those patients infected with organisms for which the MICs are higher, such as *P. aeruginosa*. On the other hand, if this dose produces a peak/MIC ratio or peak serum concentration for a given patient that is above the target values, there appear to be no untoward alterations in the pharmacodynamic effect or the incidence of toxicity. The issue concerning the appro-

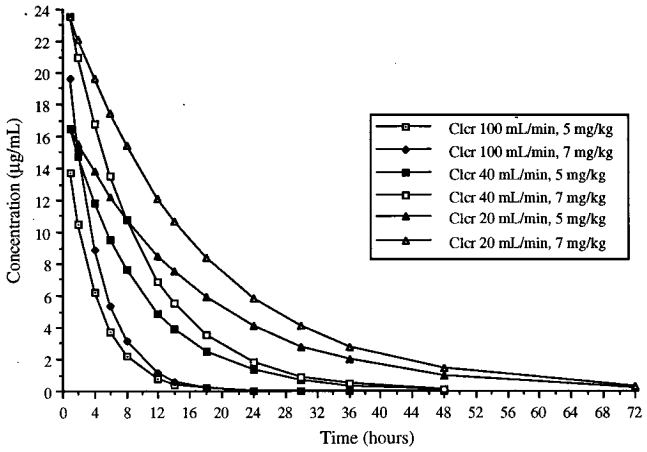

FIG. 3. Simulated concentration-versus-time profile of once-daily 7- and 5-mg/kg regimens for patients with various CL_{CR}s.

priateness of the selected once-daily dose (milligrams per kilogram per day) is illustrated in a recently reported trial of ODA versus thrice-daily aminoglycosides (22). In this prospective randomized trial, 59 patients received the once-daily regimen of 4 mg of gentamicin per kg. In this group, the mean ± the standard deviation for the first and maximum peak concentrations were 10.3 ± 3.3 and 14.2 ± 7.7 μg/ml, respectively. Not only was there a wide variation in the resultant peak concentrations, as anticipated, but the 4-mg/kg dose produced concentrations that we feel would not optimize the peak/MIC ratio for many difficult pathogens. Although the investigators demonstrated that there was no statistical difference in efficacy between the regimens, 40% of the patients in both groups had no microorganism cultured. This apparent variation in the resultant peak concentration, the variability of MICs for the infecting pathogen, the concentration-dependent postantibiotic effect, the rationale for optimization of the peak/MIC ratio, and the lack of apparent toxicity of our ODA regimen argue for the use of the 7-mg/kg dose. In addition, during the initial pharmacokinetic modeling of ODA regimens, we demonstrated that although the peak concentrations obtained with a dose of 7 mg/kg were greater than those obtained with 5 mg/kg, the estimated concentrations at the end of the drug administration interval were quite similar (Fig. 3). Therefore, we selected the higher dose to optimize the peak/MIC ratio for more-resistant organisms. We also did not alter the ODA methodology for treatment of infections caused by more-susceptible pathogens. Although this dose will result in a much higher peak/MIC ratio for more-susceptible pathogens, Craig and Ebert have demonstrated that such concentrations continue to improve bactericidal activity compared with exposures to lower multiples of the MIC (6).

We also chose an approach which uses a fixed dose, with drug administration interval adjustments for patients with impaired renal function. The previously cited studies either employed dosage de-escalation corresponding to reductions in renal function or excluded patients with altered renal function. Although dosage de-escalation would allow a fixed 24-h drug administration interval for most patients, this methodology would not achieve the desired peak concentration to optimize the peak/MIC ratio. If reductions in the dose are made as a result of poor renal function, the subsequent drug concentrations in serum would also be lower, ultimately resulting in a peak/MIC ratio that is less than optimal and quite possibly no better than those achieved with conventional regimens. Additionally, if the ODA regimen were used only for patients with CL_{CR}s of >80 ml/min, a large percentage of our hospitalized population would be excluded because of the age-related decline in renal function.

Although concerns about the extended intervals and possible risk of increased toxicity for patients with reduced drug clearance should be mentioned, the incidence of toxicity should be no greater than that commonly encountered in this population with conventional drug administration. Since the implementation of this program, nearly 2,200 patients have received our ODA regimen. The incidence of toxicity has been very low compared with both our institutional rate and that of previously published ODA reports. In this study, 37% of our patients received greater than 6 days of therapy with an incidence of nephrotoxicity of 2.0%, while those receiving greater than 11 days of therapy had a 3.3% nephrotoxicity rate. Despite the use of this ODA program for patients of all ages, the rate of nephrotoxicity is quite low, while even for patients greater than 61 years old (39% of the total population) the incidence of nephrotoxicity was only 1.6%. Interim analysis of nephrotoxicity data after 100, 250, 500, 1,021, 1,400, and 2,200 patients revealed that the overall incidence remained stable at 1%. Additionally, questions have been raised concerning the prolonged drug-free period of some patients and the potential for bacterial regrowth. Bacterial regrowth was not clinically evident from the apparent response of our patient population, nor was it evident in the 79 neutropenic patients included in this group who received ODA as part of their antimicrobial regimen. Although the drug-free period was prolonged for many patients, it did not appear to result in modification of their antibiotic therapy, possibly because of the common concomitant use of combination therapy for all patients with extrarenal infections.

Our ODA regimen and nomogram offer clinicians an opportunity to monitor aminoglycoside therapy and avoid potential problems for patients with actual CL_{CR}s that differ from estimated clearance values. As a result of the high peak concentrations obtained with this approach and the drug-free period at the end of the drug administration interval, it is no longer necessary to draw standard peak and trough samples. In fact, several recent reviews have questioned the validity of conventional therapeutic drug monitoring protocols and the presently accepted therapeutic range (12, 17). Monitoring of the ODA regimen can be completed by obtaining a single random blood sample between 6 and 14 h after the start of an aminoglycoside infusion. This single concentration will be evaluated on the nomogram for once-daily drug administration (Fig. 1). If the level falls in the area designated q24h, the dosing interval is q24h (the same applies for the areas of q36h and q48h). If the point is near the line, the longer interval is chosen to avoid drug accumulation and provide a sufficient drug-free period. If the random drug concentration in serum is off (i.e., above) the nomogram between the 6- and 14-h time points, the scheduled therapy is stopped and the drug concentration in serum is monitored to determine the appropriate time for administration of the next dose (i.e., concentration of <1 μg/ml). Although determination of even a single random concentration may no longer be necessary for many patients, it will be necessary to obtain several samples for patients with changing CL_{CR}s or those whose CL_{CR}s are significantly reduced. When ODA therapy is continued for ≥5 days, random drug concentrations in serum should be determined weekly to monitor therapy.

At our institution, we use very little amikacin therapy and although the nomogram and our ODA regimen were designed

for gentamicin and tobramycin, this approach can be utilized with amikacin. With amikacin, one should administer a single daily dose of 15 mg/kg and the initial interval should be determined by the estimated CL_{CR} as previously noted in this report. Since aminoglycosides exhibit linear pharmacokinetics, the resultant amikacin concentration obtained by the protocol (at 6 to 14 h) can be evaluated on the nomogram by simply halving the concentration and applying it to the nomogram. Since a linear profile is observed with aminoglycosides, peak concentrations from the 15-mg/kg amikacin dose will approximate 40 μg/ml, thus resulting in a sufficient peak/MIC ratio (median MIC for *P. aeruginosa*, 4 μg/ml at our institution).

Overall, our ODA regimen appears to be a safe and effective alternative to conventional aminoglycoside administration practices, while the nomogram offers clinicians a method of monitoring therapy. This regimen also allows a workload reduction for pharmacists, nurses, and laboratory workers. In addition to the reduction in aminoglycoside concentrations, this methodology reduces the need for multiple blood samples while increasing the interpretability of the concentrations reported. As a result, our ODA approach promotes maximal efficacy, reduces toxicity, and promotes a cost-effective alternative for the administration and monitoring of patients requiring aminoglycoside therapy.

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