ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 1996, p. 2494–2499 Vol. 40, No. 11
0066-4804/96/$04.00+0

Validation and Nephrotoxicity of a Simplified Once-Daily Aminoglycoside Dosing Schedule and Guidelines for Monitoring Therapy

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Received 12 February 1996/Returned for modification 8 May 1996/Accepted 4 August 1996

There is no established dosing schedule for once-daily aminoglycoside dosing regimens, and accepted guidelines for monitoring therapy are lacking. We derived a simplified schedule from the Hull and Sarubbi (J. H. Hull and F. A. Sarubbi, Ann. Intern. Med. 85:183–189, 1976) nomogram, for which efficacy and safety in a once-daily dosing regimen were previously demonstrated, and prospectively followed serum aminoglycoside levels in patients. The standard treatment was gentamicin or tobramycin at 4 mg/kg of body weight given intravenously once daily. When the renal function was decreased, the daily dose was reduced, as follows: for an estimated creatinine clearance of between 50 and 80 ml/min, the daily dose was 3.25 mg/kg, for an estimated creatinine clearance of between 30 and 50 ml/min, the daily dose was 2.5 mg/kg, and for an estimated creatinine clearance of below 30 ml/min, the daily dose was 2 mg/kg. A total of 221 patients were studied (184 received gentamicin and 37 received tobramycin). First trough levels above 2 mg/liter were recorded in 11% of the patients, and they all had a baseline creatinine clearance below 50 ml/min, or a substantial decrease in clearance between enrollment and the day that the trough level was obtained. A peak level below 6 mg/liter was recorded in 6% of the patients, and half of them received the lowest daily dose. Twenty-five of the 179 evaluable patients (14%; 95% confidence interval, 9 to 19%) fulfilled the criteria for nephrotoxicity. In a multiple regression analysis, the duration of treatment and the use of other nephrotoxic antibiotics or high-dose furosemide, but not trough levels, were significant risk factors. Since the meaning of low peak levels is unclear and since most studies with multiple daily regimens confirm the lack of an association between trough levels and toxicity, we believe that monitoring of serum drug levels can be restricted to monitoring of trough levels in patients with a creatinine clearance below 50 ml/min or with a deteriorating renal function.

Aminoglycosides remain a mainstay of therapy in the treatment of severe gram-negative infections, but they have a potential for nephro- and ototoxicity and a narrow therapeutic index (12). Another problem is the wide interpatient variation in the pharmacokinetics of aminoglycosides (33). Nomograms, which use body weight and estimated creatinine clearance, often result in elevated trough levels or subtherapeutic peak levels (13).

A recent development is the use of once-daily aminoglycoside regimens (9, 16). Arguments in favor of this regimen are the fact that the resulting high peak levels may maximize the bacterial killing rate, whereas the prolonged drug-free interval may lead to a lower incidence of toxicity (2). The postantibiotic effect prevents bacterial regrowth during the period of low serum drug levels. An additional advantage of once-daily dosing is the fact that serum drug levels are more predictable. By using a nomogram, 78% of patients on a conventional thrice-daily gentamicin schedule required dose adjustment because of inadequate serum drug levels, whereas for 94% of patients on a once-daily schedule first serum drug levels were in the desired range (25).

So far, there is no established dosing schedule for once-daily regimens, and accepted guidelines for monitoring therapy are lacking. Because the aminoglycosides are excreted by the kidneys (9), adjustment of the daily dose in the case of patients with decreased renal function remains necessary for once-daily regimens. Two strategies are possible: extension of the interval or a dose reduction while maintaining the interval of dosing once daily. Recently, the use of a fixed dose of 7 mg/kg of body weight was advocated, with the drug administration interval (range, 24 to 48 h) being based on estimated creatinine clearance (22). However, justification of once-daily dosing as opposed to multiple daily dosings with regard to both efficacy and toxicity is based on studies in which the daily dose was lowered for patients with renal dysfunction (8, 15, 23, 30, 31). The efficacy and safety of large doses (e.g., 7 mg/kg) given every 48 to 72 h in comparison with those of the former standard of treatment (multiple daily dosing) have not been demonstrated. In addition, especially for patients with decreased renal function, this regimen resulted in prolonged aminoglycoside levels in serum, which is opposite the desired levels on the basis of the rationale of once-daily dosing, i.e., the presence of a substantial drug-free interval every 24 h. We therefore favor administration of a dose every 24 h, with dose de-escalation for patients with renal dysfunction in order to achieve low serum drug levels at the end of the dosing interval. By doing so, we demonstrated in a previous study equal efficacy and reduced nephrotoxicity for the once-daily gentamicin regimen compared with those for the thrice-daily dosing regimen (23).

However, in that study we used the nomogram of Hull and Sarubbi (11), which discriminates more than eight levels of creatinine clearance, resulting in more than eight different percentages of reduction in the standard daily dose (23–25). This is not practical for routine use, and we therefore derived

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a simplified dosing schedule from this nomogram. In order to validate this schedule, we prospectively followed serum gentamicin and tobramycin levels in a large series of patients. We also examined the incidence of nephrotoxicity and searched for risk factors for nephrotoxicity with this once-daily dosing schedule.

MATERIALS AND METHODS

Patients. Consecutive patients over 16 years of age who were admitted to the general ward or the intensive care unit and who had a suspected or documented infection for which treatment with an aminoglycoside was indicated were eligible for participation in the study. Exclusion criteria were known allergies to aminoglycosides, granulocytopenia ($<1.0 \times 10^9$ granulocytes per liter), cystic fibrosis, or pregnancy.

The standard dosage was gentamicin at 4 mg/kg given intravenously once daily or, in the case of suspected or proven *Pseudomonas* infections, tobramycin at 4 mg/kg given intravenously once daily. For patients with decreased creatinine clearance (estimated by the formula of Cockroft and Gault [7]), the initial daily dose was reduced. When the estimated creatinine clearance was 80 ml/min or more, the daily dose was 4 mg/kg; when the estimated creatinine clearance was between 50 and 80 ml/min, the daily dose was 3.25 mg/kg (81%); when the estimated creatinine clearance was between 30 and 50 ml/min, the daily dose was 2.5 mg/kg (63%); and when the estimated creatinine clearance was below 30 ml/min, the daily dose was 2 mg/kg/day (50%). The lowest daily dose is similar to the recommended loading dose (irrespective of renal function) in the conventional thrice-daily schedule (9).

Gentamicin and tobramycin were administered over 30 min. After 24 to 48 h, trough and peak levels of drug in serum were determined immediately before and 30 min after the end of the infusion, respectively. Serum drug levels were measured by a fluorescence polarization assay (TDx; Abbott Laboratories, Abbott Park, Ill.). The daily doses were lowered when the trough level exceeded 2 mg/liter and were increased when the peak level was less than 6 mg/liter. After adjustment or for patients with deteriorating renal function, peak and trough levels were again determined 24 to 48 h later; otherwise, serum drug levels were determined weekly.

The attending physician calculated the initial dose and determined the duration of antibiotic therapy. Data for patients for whom initial dosing errors of greater than 30% were made were excluded from all analyses. The study protocol was approved by the Hospital Ethics Committee.

Evaluation of nephrotoxicity. The serum creatinine concentration was measured at the start of therapy and was subsequently measured thrice weekly until 1 week after the discontinuation of aminoglycoside therapy. Nephrotoxicity was defined as a rise in the serum creatinine concentration of 45 μmol/liter (0.5 mg/dl) or more during this period if the initial serum creatinine concentration was less than 270 μmol/liter (3.0 mg/dl) or a rise in the serum creatinine concentration of 90 μmol/liter (1.0 mg/dl) or more during this period if the initial serum creatinine concentration was 270 μmol/liter or more (29). Patients were not evaluable for nephrotoxicity if they had been treated with aminoglycosides in the previous week, if treatment with aminoglycosides was resumed within 1 week of stopping treatment, or if hemodialysis was started within 48 h after the start of treatment. Patients who met the criteria for nephrotoxicity within the first 24 h of therapy were also excluded from the study, because in that case the decline in renal function is unlikely to be the result of the aminoglycoside treatment.

Data on the following potential risk factors for nephrotoxicity were collected: age, gender, baseline creatinine clearance, initial daily dose, trough and peak levels of drug in serum, duration of treatment, admission to the intensive care unit during the study period, hypotension (defined as a systolic blood pressure of less than 90 mm Hg for 6 h or more), oliguria (defined as a daily urine production of less than 400 ml on 1 or more days), liver dysfunction (defined as an aspartate aminotransferase [serum glutamic oxalacetic transaminase] level more than two times the normal level, an alkaline phosphatase level more than 1.5 times the normal level, or a bilirubin concentration of ≥17 μmol/liter), the concomitant use of vancomycin or amphotericin B, and the use of ≥160 mg of furosemide daily on 1 or more days.

Statistical analysis. For comparison of the patients by means of discrete variables the χ^2 test or Fisher's exact test was used. For continuous variables, Student's *t* test or the Mann-Whitney test were applied when appropriate. In each instance, a two-tailed test was carried out and α was set at 0.05. Multivariate analysis was done by using logistic regression, entering only variables with a *P* value of <0.10 in the univariate analysis.

RESULTS

Serum drug levels. A total of 244 patients were enrolled in the study. In 23 patients (9.4%) initial dosing errors of greater than 30% were made, and data for those patients were excluded from the analysis. Of the remaining 221 patients, 184 received gentamicin and 37 received tobramycin. Trough levels were obtained for 204 patients, and peak levels were obtained for 185 patients. Trough levels were not evaluable in 17 patients, mainly because of sampling time errors; the main reason for not determining the peak level was the cessation of treatment within 24 to 48 h.

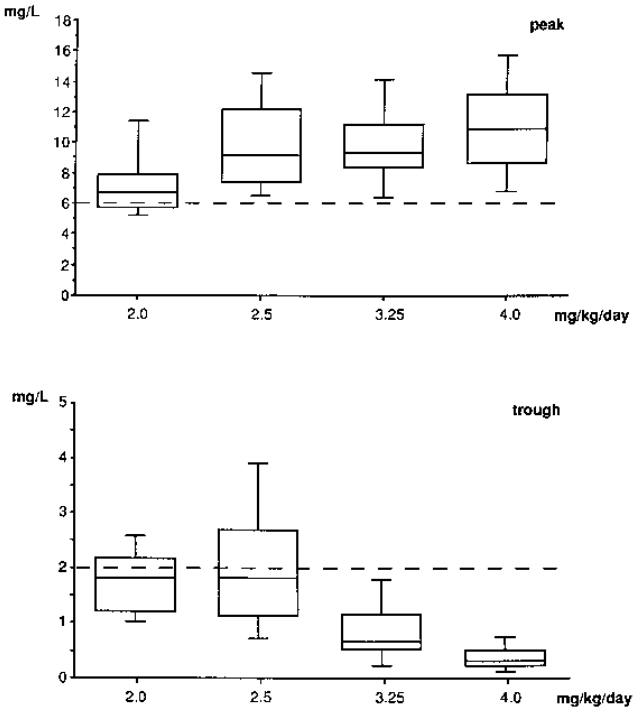

FIG. 1. First serum trough and peak aminoglycoside concentrations as a function of initial daily dose (estimated creatinine clearance above 80 ml/min, dose of 4 mg/kg; estimated creatinine clearance between 50 and 80 ml/min, dose of 3.25 mg/kg; estimated creatinine clearance between 30 and 50 ml/min, dose of 2.5 mg/kg; and estimated creatinine clearance below 30 ml/min, dose of 2 mg/kg). The horizontal lines inside the boxes indicate the median value; the boxes represent the 25th to 75th percentiles, and the bars represent the 10th to 90th percentiles. The dashed horizontal lines indicate the peak and trough levels initially aimed at.

Trough and peak concentrations of drug in serum did not differ significantly between gentamicin and tobramycin ($P > 0.50$ for all dosages; Mann-Whitney test); therefore, these data were combined. The drug concentrations in serum are presented in Fig. 1. First trough levels greater than 2 mg/liter were recorded for 1 of 112 (<1%) patients on the 4-mg/kg schedule, 4 of 48 (8%) patients on the 3.25-mg/kg schedule, 11 of 27 (41%) patients on the 2.5-mg/kg schedule, and 6 of 17 (35%) patients on the 2-mg/kg schedule. Hence, most patients with elevated trough levels were characterized by a baseline creatinine clearance of <50 ml/min; the patients with a creatinine clearance of ≥50 ml/min who had a trough level above 2 mg/liter all experienced a decrease in creatinine clearance (mean, 43%; range, 24 to 56%) between enrollment and the day that the trough level was determined. Peak levels of less than 6 mg/liter were recorded for 11 of 185 patients (6%), and 5 of them were patients in the group receiving the lowest daily dose (2 mg/kg).

According to the study protocol, trough levels of drug in serum were redetermined later during therapy for 90 patients. Eight of 81 patients who had first trough levels below 2 mg/liter later had trough levels above 2 mg/liter. Six of them were on the 3.25- or 4-mg/kg schedule. All six of these patients had experienced at that time a decrease in creatinine clearance

(range, 20 to 88%) compared with the baseline creatinine clearance.

Nephrotoxicity. Nephrotoxicity could be evaluated for 179 of the 221 patients. Reasons for exclusion from the study were the use of aminoglycosides within 1 week before or after the study period (10 patients), the start of hemodialysis within 48 h (2 patients), the criteria for nephrotoxicity were met within 24 h after the start of treatment (16 patients), and the lack of complete follow-up (14 patients). None of the patients had also been treated with *cis*-platinum.

Twenty-five of the 179 evaluable patients (14%; 95% confidence interval, 9 to 19%) fulfilled the criteria for nephrotoxicity. Because risk factors for nephrotoxicity were equally distributed between patients treated with gentamicin and those treated with tobramycin ($P > 0.05$; Mann-Whitney test or χ^2 test), the data for these patients were pooled. The only exception was the median duration of treatment, which was 5 days for gentamicin and 9 days for tobramycin ($P < 0.001$; Mann-Whitney test). Therefore, for this risk factor data for patients receiving gentamicin and those receiving tobramycin were analyzed separately. Eighteen patients also used other nephrotoxic antibiotics: 13 patients received vancomycin, 1 patient received amphotericin B, and 4 patients were treated with both drugs. In a univariate analysis, statistically significant risk factors for toxicity were a low baseline creatinine clearance, a daily dose of <4 mg/kg, a high trough concentration in serum or a low peak concentration in serum, admission to the intensive care unit, the concomitant use of other nephrotoxic antibiotics or a high dose of furosemide, and, only for gentamicin, the duration of treatment (Table 1).

In a multiple regression analysis, only a longer duration of treatment and the concomitant use of other potentially nephrotoxic antibiotics or a high dose of furosemide remained significant risk factors for nephrotoxicity (Table 2).

DISCUSSION

Once-daily aminoglycoside regimens are gradually accepted as the preferred aminoglycoside administration schedule, but there is no established dosing schedule, and changes in the current practice of monitoring concentrations in serum might also be necessary. We derived a simplified dosing schedule from the nomogram of Hull and Sarubbi (11) for which efficacy and safety in a once-daily dosing regimen were demonstrated previously (23) and prospectively followed drug levels in the sera of 221 patients from the general ward as well as from the intensive care unit.

The minimal peak and maximal trough levels that we wanted to achieve in the patients were initially set at 6 and 2 mg/liter, respectively, which are the same as those for the conventional regimens in which multiple daily doses are administered. Whether these levels are indeed desirable in once-daily regimens will be discussed below.

The desired serum drug levels were achieved in the majority of patients. Elevated trough levels were recorded for only 22 of the 204 evaluable patients (11%), and all of these patients were characterized by a baseline creatinine clearance of less than 50 ml/min or a substantial decrease in creatinine clearance between enrollment and the day that the trough level was determined. This confirms earlier reports that in once-daily regimens elevated trough levels occur especially for patients with a deterioration of renal function (6, 8, 25, 31). A peak level of less than 6 mg/liter was observed for 11 of the 185 evaluable patients (6%). Five of them were patients in the group receiving the lowest daily dose (2 mg/kg).

Nephrotoxicity was recorded in 14% of the patients. This is more than the 5 to 7% in our previous study of once-daily dosing regimens (23, 24), in which the dosing schedule was based on the dosing chart of Hull and Sarubbi (11). However, in that study patients who were concurrently using other potentially nephrotoxic antibiotics or high-dose furosemide were excluded. If we exclude data for those patients from the present study, nephrotoxicity occurred in 9 of 148 patients (6%; 95% confidence interval, 2 to 10%). Because serum drug levels were also comparable to the levels in the previous study (24), the simplification of the dosing schedule of Hull and Sarubbi (11) seems justified.

The incidence of nephrotoxicity was also higher than the incidence of 1.2% found in a recent large series (22), in which a fixed dose (7 mg/kg) was administered to all patients, with a variable dosing interval depending on estimated renal function. However, in that study the median duration of therapy was 3 days, as opposed to 5 days in the present study. In both studies the duration of therapy was found to be a risk factor for nephrotoxicity. In addition, in that study nephrotoxicity was defined as a rise in the creatinine level during therapy. It is well known that aminoglycoside-associated nephrotoxicity may become evident after the drug has been discontinued. In our study, in only 7 of the 25 patients who experienced nephrotoxicity were the criteria met before the last day of therapy, which yields a proportion of patients in whom nephrotoxicity develops during the course of therapy of only 3.9% (7 of 179 patients).

Several risk factors for nephrotoxicity were identified, but after multivariate analysis only the duration of treatment and the use of other nephrotoxic antibiotics or a high dose of furosemide were significant risk factors. The risk of nephrotoxicity increased 1.7-fold with an increase in the duration of treatment of 4 days. Three studies with more than 200 treated patients have systematically assessed risk factors for nephrotoxicity with a multiple daily gentamicin or tobramycin dosing regimen (5, 27, 28). Only the duration of treatment was consistently found to be a risk factor, as it was in our study.

Trough levels of drug in serum were not a risk factor for toxicity, in contrast to what is usually thought (17). However, it has always been a question of whether elevated serum drug levels are the cause or the result of a decline in renal function (14, 23). Little evidence supports a direct or causal relation between a specific serum aminoglycoside concentration and the development of nephrotoxicity (17). In addition, and perhaps even more important, monitoring of serum drug levels also did not prevent nephrotoxicity (17). Trough levels were not a risk factor in two of the three studies mentioned above in which risk factors for nephrotoxicity in patients receiving drug on multiple daily dosing schedules were evaluated (27, 28). Only in the last study (5) trough levels were identified as being an independent risk factor. However, mean trough levels in the patients experiencing nephrotoxicity were 1.2 mg/liter, whereas they were 0.8 mg/liter in the patients not experiencing nephrotoxicity. Because 1.2 mg/liter is still in the therapeutic range, it is not clear why the maximum acceptable trough level should be 2 mg/liter. In our own study, the first one in which risk factors for nephrotoxicity were systematically looked for in a once-daily regimen, trough levels were not a risk factor for nephrotoxicity. In our study the daily dose was lowered when trough levels exceeded 2 mg/liter, and this may have influenced the incidence of nephrotoxicity in these patients. When multivariate analysis was restricted to patients with a trough level of ≤2 mg/liter, in whom no dose adjustment was performed, the trough level still was not an independent risk factor.

The main purpose of monitoring trough levels is therefore to identify patients in whom aminoglycosides accumulate. The

TABLE 1. Risk factors for nephrotoxicity: univariate analysis[a]

Parameter	All patients (n = 179)	Nonnephrotoxic patients (n = 154)	Nephrotoxic patients (n = 25)	P
Age (yr [range])	61 (17–92)	60	65	0.82[b]
Baseline creatinine clearance (ml/min [range])	88 (15–318)	91	68	0.03[b]
Daily dosage (mg/kg/day [range])	4 (2–4)	4	3.25	0.11[b]
Trough level (mg/liter [range])	0.5 (0–4.2)	0.4	0.8	0.02[b]
Peak level (mg/liter [range])	9.8 (3.6–26.8)	9.9	7.9	0.01[b]
Duration of treatment (days [range])				
Gentamicin	5 (1–20)	5	7	0.03[b]
Tobramycin	9 (2–23)	9	6	0.59[b]
No. (%) of patients receiving:				
Gentamicin	144	123	21 (15)	0.63[c]
Tobramycin	35	31	4 (11)	
Gender (no. [%])				
Male	116	96	20 (17)	0.09[c]
Female	63	58	5 (8)	
Daily dose (no. [%] of patients)				
4 mg	100	91	9 (9)	0.03[c]
<4 mg/day	79	63	16 (20)	
Admission to intensive care (no. [%] of patients)				
Yes	74	59	15 (20)	0.04[c]
No	105	95	10 (10)	
Hypotension (no. [%] of patients)				
Yes	8	6	2 (25)	0.31[d]
No	171	148	23 (13)	
Oliguria (no. [%] of patients)				
Yes	3	2	1 (33)	0.36[d]
No	176	152	24 (14)	
Liver dysfunction (no. [%] of patients)				
Yes	90	75	15 (17)	0.35[c]
No	62	55	7 (11)	
Unknown	27			
Toxic antibiotics (no. [%] of patients)				
Yes	18	10	8 (44)	<0.001[c]
No	161	144	17 (11)	
High-dose furosemide (no. [%] of patients)				
Yes	21	9	12 (57)	<0.001[c]
No	158	145	13 (8)	

[a] For continuous variables, the median (range) is given; for dichotomous variables, the absolute number of patients (percentage of patients with nephrotoxicity) is given.
[b] Mann-Whitney test.
[c] χ^2 test.
[d] Fisher's exact test.

accumulation of aminoglycosides is undesirable with regard to ototoxicity, because in animals the total dose and the total area under the curve in plasma are predictive of ototoxicity (3). Whether collecting blood for determination of trough levels 8 or 12 h after administration of the last dose or 24 h after administration of the last dose is the best way to detect the accumulation of aminoglycosides remains to be defined, and this could be the subject of subsequent studies.

Finally, the administration of a high dose of furosemide or other potentially nephrotoxic antibiotics was an independent risk factor. Their use also predisposes patients to a rise in the serum creatinine level independent of the use of aminoglycosides. High-dose furosemide is often used in situations when diuresis cannot be stimulated with lower dosages. In addition, furosemide enhances the nephrotoxicity of gentamicin in an experimental model because of the enhanced uptake of gentamicin by renal tubule cells (1, 21). Amphotericin B usually decreases the glomerular filtration rate (4). The risk of nephrotoxicity from the use of vancomycin in combination with aminoglycosides is probably only slightly greater than the risk

TABLE 2. Risk factors for nephrotoxicity: multiple regression analysis

Variable	Odds ratio (95% CI[a])	*P*
High-dose furosemide	15.2 (3.2–71.8)	0.001
Nephrotoxic antibiotics	7.9 (1.8–33.9)	0.006
Duration of treatment[b]	1.7 (1.0–2.9)	0.043
Baseline creatinine clearance	0.8 (0.3–2.2)	0.64
Trough level	0.8 (0.4–1.7)	0.62
Peak level	0.6 (0.3–1.4)	0.25
Female gender	0.4 (0.1–1.4)	0.14
Daily dose of 4 vs <4 mg/kg	0.5 (0.1–3.4)	0.49
Admission to intensive care	1.0 (0.3–3.4)	0.95

[a] CI, confidence interval.
[b] Odds ratio of every 4-day increase in duration of treatment.

of nephrotoxicity from the use of vancomycin monotherapy (10). Nonetheless, it is clear that the chance of a decreased renal function and subsequent elevated trough levels is increased in patients also treated with a high dose of furosemide or other nephrotoxic antibiotics.

The following question remains: What peak levels should be the goal for patients receiving once-daily regimens? In animal models, in the case of aminoglycosides the most important parameter determining the efficacy of bacterial killing was the $\log_{10}$ area under the concentration-versus-time curve (32). The prevailing view that low peak levels are associated with therapeutic failure is mainly based on the studies by Moore et al. (18–20). However, those studies have been scrutinized by McCormack and Jewesson (17). They concluded that the evidence was insufficient to support a causal relationship between low peak levels and poor treatment outcome. Their objections against the studies of Moore et al. (18–20) were the fact that the breakpoint levels in serum were determined retrospectively, and were therefore liable to bias, and that much of the evidence was conflicting. For instance, in one study the maximal peak level was identified as the most important factor associated with therapeutic outcome (19), whereas this was not found in the other two studies (18, 20). In addition, in very ill patients the volume of distribution increases, resulting in lower peak levels, which may explain why patients with low peak levels seem to do worse. Finally, in two recent studies of once-daily aminoglycoside treatment, no association was found between peak levels of drug in serum and treatment outcome (8, 26). So, the value of peak levels is unclear, and because low peak levels are found in only a very small percentage of patients, it is questionable if it is useful to follow these levels at all.

What guidelines for monitoring therapy can be derived from these observations? As discussed above, it is questionable if it is useful to follow peak levels at all. Elevated trough levels were only found in the patients with an estimated creatinine clearance of less than 50 ml/min and in patients who developed a significant decline in renal function during therapy. Therefore, the measurement of trough levels can be restricted to these groups of patients. Independent factors predisposing patients to a decline in renal function (and therefore elevated trough levels) were the duration of treatment and the concomitant use of other nephrotoxic antibiotics and a high dose of furosemide. Given the broad range of trough levels found in the patients with a clearance below 50 ml/min, it is not likely that any standard nomogram will yield satisfactory levels in this group of patients.

Restricting monitoring of serum drug levels to trough levels in the groups mentioned above would imply an important simplification of therapeutic monitoring compared with current practices, because only 23% of patients had creatinine clearances of less than 50 ml/min. Whether the daily dose should be lowered or the dosage interval increased in patients with elevated trough levels remains to be established.

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