Pharmacokinetic Dosing of Aminoglycosides: A Controlled Trial

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PURPOSE: To evaluate whether individualized pharmacokinetic dosing of aminoglycosides can reduce nephrotoxicity and improve the outcome of patients with gram-negative sepsis.

METHODS: We conducted a prospective controlled trial at a tertiary care university hospital. Eighty-one patients with suspected or documented gram-negative infections were enrolled. All were treated with either gentamicin or amikacin, according to clinical judgement. Patients were allocated to one of two groups based on the last digit (odd/even) of their identification number. In the study group (pharmacokinetic dosing) of 43 patients, plasma aminoglycoside levels were determined 1 hour after initiation of drug infusion and 8 to 16 hours later to estimate the elimination half-life and volume of distribution, from which the subsequent dosage schedule was calculated. Target peak plasma levels were 20 μg/mL for gentamicin and 60 μg/mL for amikacin. Target trough levels were <1 μg/mL for both drugs. The control group (fixed once-daily dosing) consisted of 38 patients who were prescribed single daily doses of gentamicin or amikacin. The primary endpoints were renal toxicity (≥25% increase in serum creatinine level or a serum creatinine level ≥1.4 mg/dL) and 28-day mortality.

RESULTS: The two study groups were similar in age, sex, indications for therapy, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and clinical assessment at baseline. Although the pharmacokinetic group received significantly greater doses of aminoglycosides than did the once-daily group, the incidence of nephrotoxicity was significantly lower in the pharmacokinetic group (5% [2/43] vs. 21% [8/38], $P = 0.03$). There was no statistically significant difference in 28-day mortality (27% [12/43] vs. 22% [8/38], $P = 0.3$).

CONCLUSION: These results suggest that individualized pharmacokinetic dosing of aminoglycosides reduces the incidence of nephrotoxicity and allows the use of greater doses of aminoglycosides. **Am J Med. 2003;114:194–198.** ©2003 by Excerpta Medica Inc.

Aminoglycosides have been a major component of antibiotic treatment of gram-negative bacterial infections for half a century. They are effective against *Pseudomonas* and *Enterobacter* species that are usually resistant to cephalosporins and have a synergistic effect when used with β-lactam antibiotics (1). However, their inherent toxicity, combined with the introduction of alternative antibiotics, have limited their use (2).

Two major adverse effects are generally associated with use of aminoglycosides: nephrotoxicity, which occurs in about 15% to 17% of patients receiving the conventional divided-dose regimen, and injury to the eighth cranial nerve, which manifests as hearing loss (8%) and vestibular toxicity (3%) (3,4). Recently, a once-daily dose approach has been adopted to improve efficacy and possibly reduce toxicity. This regimen also offers an obvious cost advantage (5). A recent review that compared the once-daily dose with the traditional multiple-dose regimens suggests that the once-daily regimen has significantly greater clinical effectiveness (6). Although a reduction in the incidence of nephrotoxicity has never been shown clearly, the once-daily regimen has become the preferred mode of administration.

In the treatment of gram-negative infections, maximal clinical response occurs when peak serum aminoglycoside levels are greater than in vitro minimal inhibitory concentrations by a factor of at least six (7). Aminoglycosides are thought to have a two-phase mechanism of action. In the first phase, there is fast bactericidal activity that depends on peak drug concentration; in the second phase, the bactericidal activity is slower and independent of antibiotic concentration (8). This unique property of aminoglycosides, referred to as the postantibiotic effect, is the basis for the once-daily dosage recommendation (9). In this regimen, larger doses of gentamicin (5 mg/kg) and amikacin (15 mg/kg) are used to attain relatively high peak serum concentrations (20 μg/mL for gentamicin and 60 μg/mL for amikacin) (10,11).

Several monitoring strategies have been developed, primarily for the divided-dose regimens (4,10–13). However, because trough levels have been implicated in the nephrotoxic effect and are usually assumed to be low 24 hours after a dose, plasma concentration monitoring is often overlooked in the once-daily regimen. In addition, a fixed once-daily regimen ignores changes in volume of distribution and in creatinine clearance that may occur in patients with hemodynamic response to sepsis. Thus, a

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dosing method that relies on determination of the volume of distribution of the drug and its half-life may be more adequate and is probably safer (14–18).

It is not known whether once-daily aminoglycoside administration with doses based on monitoring of plasma levels is more effective and safer than using a fixed, single daily dose (19–22). We therefore tested the utility of pharmacokinetic monitoring of aminoglycoside levels in the context of once-daily treatment.

METHODS

Patients

Nonsurgical patients aged ≥18 years who were hospitalized at the Soroka University Medical Center with suspected or documented gram-negative sepsis were included if the house staff decided to prescribe gentamicin (Garamycin; Teva, Jerusalem, Israel) or amikacin (Amikin; Bristol-Myers Squibb, Anagni, Italy). A diagnosis of suspected gram-negative sepsis was made on the basis of conventional sepsis criteria and a clinical picture of infection (23). We excluded patients with allergy or hypersensitivity to aminoglycosides; pregnancy; life expectancy <48 hours; Acute Physiology and Chronic Health Evaluation (APACHE) II score >35; an underlying terminal illness with a life expectancy <28 days; nonsepsis-related neutropenia; human immunodeficiency virus infection; meningitis, osteomyelitis, or endocarditis; or an estimated creatinine clearance <10 mL/min. The study protocol was approved by the Ethics Committee of the Soroka University Medical Center. All patients provided signed informed consent.

Study Design

In this single-blind pseudorandomized study, patients were allocated to study groups by the last digit of their national identification card number. Patients with odd numbers were allocated to fixed, single daily doses, whereas patients with even numbers were assigned to the pharmacokinetic dosing group. The patients were enrolled in the study no later than 24 hours after receiving their initial aminoglycoside dose. The initial dose was determined by the ward physicians, usually gentamicin (3 mg/kg) or amikacin (15 mg/kg), and was identical for the two groups.

In the once-daily group, trough levels were determined every 2 to 3 days. However, no changes were made in dosage or dosing interval, unless the trough level (>2 μg/mL) indicated aminoglycoside accumulation and potential kidney damage. If the latter occurred, adjustment was made by prolongation of dosing intervals. No adjustments were made on the basis of peak levels.

In the pharmacokinetic group, aminoglycoside levels were determined daily by fluorescence polarization immunoassay (Cobas Integra 400; Hoffman-La Roche Ltd., Basel, Switzerland) 1 hour after the infusion was started as well as 8 to 16 hours later for the first 3 days of therapy, and then once every 3 days. The volume of distribution, elimination rate constant, and half-life were calculated by standard methods (14). Target peak levels were 20 μg/mL for gentamicin and 60 μg/mL for amikacin. Target trough levels were <1 μg/mL for both drugs. Dose adjustment was performed immediately based on the pharmacokinetic data generated for each patient.

Patients were removed from the study protocol in the event of serious deterioration in kidney function (a rise of serum creatinine level ≥25% above baseline) if aminoglycoside therapy was the suspected cause. Prolongation of the aminoglycoside half-life was a supporting criterion for withdrawal in the pharmacokinetic group.

Case report forms were filled on days 0, 2, 3, 7, and 28, and at completion of treatment. The study endpoints were nephrotoxicity and 28-day mortality. Nephrotoxicity was defined by either a rise in serum creatinine level ≥25% above baseline in at least two determinations, or an absolute serum creatinine level ≥1.4 mg/dL if baseline values were normal. The cure rate was also determined, defined as clinical improvement, defervescence, normalization of the white blood cell count, and sterile blood cultures.

Statistical Analysis

Statistical analyses were performed using the Epi Info, Version 6.04 (Centers for Disease Control and Prevention, Atlanta, Georgia) and the Quatropro, Version 6 (Corel/Novell, Ottawa, Ontario, Canada) software. The chi-squared tests or Fisher exact test were used for categorical variables. Analysis of variance was used for continuous variables with a normal homogenous distribution. The nonparametric Wilcoxon test was used for nonhomogenous distributions.

RESULTS

Eighty-one patients were enrolled between November 1999 and May 2000. Two patients declined to participate. There were 38 patients in the fixed once-daily dose group and 43 in the pharmacokinetic group. The baseline characteristics of the patients in the two groups were generally similar (Table 1). Fifty-one patients (63%) were treated with gentamicin, and 30 patients (37%) were treated with amikacin. The most common indication for treatment was continued fever despite treatment with another antibiotic.

Endpoints

Of the 43 patients in the pharmacokinetic group, 2 (5%) developed nephrotoxicity compared with 8 (21%) of the 38 patients in the fixed-dose group ($P = 0.03$; Table 2). Similarly, the incidence of nephrotoxicity was lower in

Table 1. Characteristics of the Patients by Study Group

Characteristic	Pharmacokinetic Group (n = 43)	Single Daily Dose Group (n = 38)	*P* Value
	Number (%) or Mean ± SD		
Male sex	23 (53)	24 (63)	0.8
Age distribution (years)			0.7
17–40	6 (14)	5 (13)	
41–60	8 (19)	10 (26)	
61–90	29 (67)	23 (61)	
Aminoglycoside used			0.6
Gentamicin	26 (61)	25 (66)	
Amikacin	17 (40)	13 (34)	
Baseline creatinine (mg/dL)	0.9 ± 0.2	1.0 ± 0.3	0.3
Chronic renal insufficiency*	3 (7)	2 (5)	0.6
Use of nonsteroidal anti-inflammatory drugs	2 (5)	3 (4)	0.3
Hypertension or diabetes mellitus	3 (7)	4 (10)	0.4
Cumulative gentamicin dose (mg)	1845 ± 318	1450 ± 180	<0.001
Cumulative amikacin dose (mg)	7650 ± 460	4850 ± 340	<0.001
Gentamicin peak (μg/mL)	16 ± 4		
Amikacin peak (μg/mL)	46 ± 8		
Gentamicin trough (μg/mL)	2 ± 2		
Amikacin trough (μg/mL)	9 ± 2		
High trough levels†		15 (40)	
APACHE II score			
Amikacin-treated patients	20 ± 3	18 ± 3	0.6
Gentamicin-treated patients	10 ± 2	11 ± 3	0.5
Indications for therapy			
Nosocomial pneumonia	7 (16)	5 (13)	0.9
Other nosocomial infection	7 (16)	7 (18)	0.8
Urinary tract infection	8 (19)	12 (32)	0.2
Unexplained fever during antibiotic treatment	5 (12)	3 (8)	0.4

* Serum creatinine ≥1.4 mg/dL.
† Patients in whom there was a need to change the dose or the dosing interval.
APACHE = Acute Physiology and Chronic Health Evaluation.

the pharmacokinetic group when nephrotoxicity was defined by final serum creatinine level ($P = 0.02$). Twenty percent (5/25) of the patients who received once-daily gentamicin developed nephrotoxicity, as did 23% (3/13) of the patients in this group who were treated with amikacin. The range of serum creatinine levels in the patients who developed renal failure was 1.3 to 3.0 mg/dL; none required hemodialysis. The mean (± SD) frequency of dose adjustment in the pharmacokinetic group was 3 ± 1 per course. Fifteen (39%) of the patients in the once-daily group required dose adjustment because of high aminoglycoside trough levels.

Greater cumulative doses of both gentamicin and amikacin were administrated in the pharmacokinetic group, as compared with the once-daily group (Table 1). These greater doses in the pharmacokinetic group are consistent with the upward dose adjustments made on the basis of peak level determinations.

There were no significant differences between the study groups in mortality or cure rates (Table 2). The slightly greater mortality in the pharmacokinetic group was not statistically significant. Mortality was greater in patients treated with amikacin (46% [14/30]) than in patients treated with gentamicin (12% [6/51]), consistent with the higher APACHE II scores in amikacin-treated patients ($P = 0.01$; Table 1).

DISCUSSION

Pharmacokinetic dosing of aminoglycosides is based on sound microbiologic and pharmacologic rationale. Our results indicate that it is also a safe regimen, leading to a significantly reduced incidence of nephrotoxicity of only 5%. A similar reduction in nephrotoxicity to 5% was also observed in a study of pharmacokinetic monitoring in patients in a surgical intensive care unit (13).

Table 2. Clinical Outcomes by Study Group

Outcome	Pharmacokinetic Group (n = 43)	Single Daily Dose Group (n = 38)	*P* Value
	Number (%)		
Nephrotoxicity			
≥25% rise in serum creatinine or serum creatinine ≥1.4 mg/dL	2 (5)	8 (21)	0.03
Serum creatinine ≥1.4 mg/dL*	1/40 (2)	7/36 (19)	0.02
Cure of infection	32 (74)	26 (68)	0.3
28-day mortality	12 (27)	8 (22)	0.3

* Among patients with baseline serum creatinine <1.4 mg/dL.

Several studies have shown the utility of monitoring peak and trough aminoglycoside levels in enhancing efficacy and reducing toxicity when using multiple-dose regimens (4,7). However, there are no clear guidelines for monitoring once-daily administration of aminoglycosides. It is generally believed that trough levels with once-daily regimens are low enough to obviate the need for monitoring plasma level. Moreover, many practitioners tend to prescribe lower than recommended doses of aminoglycosides for gram-negative infections, and consequently few consider regular monitoring of aminoglycoside levels. Thus, the accepted approach is to measure trough levels every 3 days, at best.

We found that 40% of patients treated with the once-daily regimen, and 34% treated with the pharmacokinetic regimen, had trough levels above target, necessitating dose reduction or prolongation of the dosing interval. These potentially nephrotoxic levels were often observed within 48 hours of the initiation of therapy. Based on these observations, we believe that a change in the monitoring strategy for patients receiving aminoglycosides on a once-daily dosing regimen is warranted. Trough levels should be determined before every administration, starting as early as possible.

Mortality was greater among patients treated with amikacin than among those treated with gentamicin, consistent with their significantly higher mean APACHE II scores. Physicians in our institution tended to treat more seriously ill patients with amikacin. Moreover, five of the deaths in the amikacin group occurred after completion of treatment, primarily due to recurrent nosocomial infections.

Mortality was greater in the pharmacokinetic group than in the once-daily group, but the difference was not statistically significant. Although this may be a result of chance, our results do not rule out the possibility that a single daily dose may lead to better outcomes.

Our study has several limitations. It was not a true randomized trial, as physicians could have known in advance the group to which patients were assigned. In addition, we used an indirect measure of renal function, namely serum creatinine levels, to determine nephrotoxicity; this parameter may underestimate renal deterioration in severely ill patients. Conversely, ascribing a deterioration in renal function to antibiotic toxicity in critically ill patients may overestimate the incidence of aminoglycoside-induced renal damage. Moreover, we used a relatively liberal definition of nephrotoxicity to minimize patients' risk. A recent trial of critically ill patients used a stricter definition of renal failure: a rise in serum creatinine level of more than 2 mg/dL or double the baseline value in patients with pre-existing renal dysfunction (24).

In conclusion, pharmacokinetic dosing reduced aminoglycoside nephrotoxicity among patients with gram-negative sepsis. Pharmacokinetic monitoring also allowed administration of a significantly greater cumulative dose. Further study with larger groups of patients and a true randomized design is warranted.

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