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Pharmacokinetics of Tobramycin and Gentamicin in Abusers of Intravenous Drugs

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The kinetics of aminoglycoside elimination were determined in 18 hospitalized narcotics abusers receiving gentamicin or tobramycin for treatment of severe infection. Rapid aminoglycoside elimination (requiring doses of >5 mg/kg per day to maintain adequate drug levels) was noted in 12 of the 18 patients (18 of 27 clearance studies). Patients found to have rapid elimination were younger ($P < 0.01$) and had larger drug distribution volumes ($P < 0.005$), greater measured creatinine clearances ($P < 0.05$), and lower creatinine levels in serum ($P < 0.001$) than those with normal elimination. Nevertheless, by regression analysis, age, creatinine levels in serum, creatinine clearances, and drug distribution volumes proved to be unreliable predictors of individual aminoglycoside clearance. Measured drug half-life in serum appeared to be the only reliable predictor of drug clearance ($r = 0.93$). Patients with rapid drug elimination had aminoglycoside clearances 16 to 43% greater than measured creatinine clearances, suggesting an extraglomerular route of drug elimination. We conclude that in drug abuse patients a significant and clinically unpredictable interpatient variation occurs in aminoglycoside elimination and that accurate serum kinetics are needed to determine therapeutic dosing. In addicts younger than 35 years, with a creatinine level of <1.0 mg/100 ml in serum, the risk of inadequate therapy is high if standard dosing guidelines are followed. For this group, initial dosing of 8 mg/kg per day, with a drug half-life determination on the first dose, is recommended. Pharmacokinetic analysis is critical for all drug abusers treated with aminoglycosides for serious infection.

For heroin addicts, successful medical therapy of *Pseudomonas aeruginosa* endocarditis has required empirical use of gentamicin in doses of ≥8 mg/kg per day (21, 22). Although such doses are well above the maximum recommended daily regimen of 5 mg/kg (1, 11), it is not known why addicts require supranormal doses of aminoglycoside for therapy.

While reviewing several recent cases of severe *Pseudomonas* infection among Cleveland drug abusers, we noted that 60% of our addict patients required gentamicin or tobramycin therapy above 5 mg/kg per day to maintain therapeutic drug concentrations in serum. To define the pharmacokinetics of gentamicin and tobramycin elimination in a population of hospitalized addicts, we have undertaken this prospective study to determine the drug kinetics in a mixed group of addicts with *Pseudomonas* and non-*Pseudomonas* infections. We determined the prevalence of rapid drug elimination in a sequential group of hospitalized addicts with normal renal function and correlated individual kinetic data with clinical attributes previously postulated to affect aminoglycoside elimination (i.e., renal function, fluid balance, age, anemia, hypoproteinemia, and duration of aminoglycoside therapy [6, 8, 12, 15, 16, 17, 20, 25, 28]) to identify individuals at risk for undertreatment with standard therapy. We also tested the hypothesis that addicts, like burn patients and obstetrical patients (31, 32), require high aminoglycoside doses because of group-specific changes in pharmacokinetic parameters. Our results confirmed that many, but not all, addicts exhibit rapid aminoglycoside clearance (CL_{am}) and indicated that over 66% of hospitalized addicts require drug doses of >5 mg/kg per day to maintain therapeutic levels. No single patient feature was sufficiently predictive of rapid clearance to signal the need for high-dose therapy, although measured drug half-life ($t_{1/2}$) was found to effectively predict individual steady-state CL_{am}. Based on these findings, recommendations for aminoglycoside therapy in addict populations are discussed.

MATERIALS AND METHODS

Study population. A group of 18 hospitalized narcotics abusers were studied from September 1981 to August 1983. The patients eligible for this study were active abusers of intravenous drugs who were hospitalized at University Hospitals of Cleveland in the adult medical-surgical divisions and received either gentamicin or tobramycin for severe gram-negative, gram-positive, or mixed infections. Patients with abnormal renal function (as defined by a creatinine level in serum [S_{CR}] of >1.5 mg/100 ml) were excluded from the study.

With the exception of one patient who was ultimately excluded because of the development of azotemia, all patients meeting these criteria participated in the study. In the latter half of the study a subgroup of eight patients agreed to undergo further testing, including urine collection for creatinine clearance (CL_{CR}) and repeat drug kinetic studies.

Patients included in this study gave written informed consent according to guidelines of the U.S. Department of Health and Human Services and were evaluated under a protocol approved by the Human Investigations Review Board of University Hospitals.

Data acquisition. Histories were obtained by patient interview, and diagnoses were confirmed by physical examination and review of laboratory and bacteriologic data. Hematocrit, serum protein, and CL_{CR} were determined by routine clinical testing. Aminoglycoside kinetics were determined under steady state conditions at least 3 days after the initiation of therapy. The aminoglycoside concentration in serum was obtained immediately before the study dose was

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TABLE 1. Aminoglycoside kinetics and clinical characteristics in drug abuse patients[a]

	All patients (% of total)	High-dose group (% of total)	Standard-dose group (% of total)
Men	11 (61)	6 (50)	5 (83)
Women	7 (39)	6 (50)	1 (17)
On tobramycin	15 (83)	10 (83)	5 (83)
On gentamicin	3 (17)	2 (17)	1 (17)
Type of infection			
Gram-negative endocarditis	7 (39)[b]	4 (33)	3 (50)
Gram-negative osteomyelitis	6 (33)	4 (33)	2 (33)
Gram-positive endocarditis	5 (28)[b]	4 (33)	1 (17)
Gram-positive abscess	2 (11)	2 (17)	
Mortality	2 (11)		2 (29)
Median duration (days) of symptoms before admission (range)	7 (1–100)	5 (1–100)	26 (5–60)
Reported drug use[c]			
Heroin	9 (50)	4 (33)	5 (83)
Pentazocine-pyribenzamine ("T's and blues")	8 (44)	5 (42)	3 (50)
Meperidine	5 (28)	5 (42)	
Hydromorphone (Dilaudid)	4 (22)	2 (17)	2 (33)
Methaqualone	1 (6)	1 (8)	
Amphetamines (not specified)	1 (6)	1 (17)	
Methadone	1 (6)		
Oxycodone-aspirin (Percodan)	1 (6)	1 (8)	
Median duration (yr) of drug abuse (range)	7 (1.5–15)	2 (1.5–15)	9 (5–15)
Renal function			
Prior history of renal disease, diabetes, hypertension, sickle cell anemia	4 (22)	3 (25)	1 (17)
Azotemia (S_{CR} > 2.0 mg/100 ml):			
Before therapy	—[d]	—	—
During therapy	2 (11)	1 (8)	1 (17)
Proteinuria	7 (39)	4 (33)	3 (50)
Hematuria	1 (6)	1 (8)	1 (17)

[a] All patients (n = 18): high-dose group (n = 12) received >5 mg/kg per day; standard-dose group (n = 12) received ≤5 mg/kg per day.
[b] Two patients had mixed gram-positive and gram-negative endocarditis.
[c] Of 18 patients, 13 patients reported multiple drug use.
[d] —, Not applicable.

administered. After a timed (20 to 30 min) infusion of drug, three to four aminoglycoside concentrations in serum were determined at 60 to 450 min after the end of infusion. All kinetic determinations were performed with a minimum of three and a maximum of five postdose determinations of drug concentrations in serum. The subgroup of eight patients who underwent CL_{CR} determinations had kinetic analyses performed on four determinations of drug concentrations in serum. Blood samples were drawn by venipuncture or by venous access different from that used to infuse the aminoglycoside. Concurrent therapy with beta-lactam drugs was withheld for 4 h before and during the kinetic studies to avoid in vitro inactivation of the aminoglycoside (19). Aminoglycoside concentrations in serum were determined within 4 h of sampling by using a quantitative enzyme immunoassay (EMIT; Syva Co., Palo Alto, Calif.).

CL_{CR} was determined by standard 24-h urine collection with concurrent determination of fasting S_{CR}. All collections were supervised by us. Results were rejected and the urine collection was repeated if the measured creatinine excretion in urine was less than 15 mg/kg per day or if the total volume of urine collected was less than 1,250 ml. All reported CL_{CR}s were determined within 48 h of the aminoglycoside kinetic determinations. Estimated CL_{CR} was also calculated for all patients by the method of Cockcroft and Gault (8).

Data analysis. Aminoglycoside kinetics were determined by least-squares regression analysis of the natural logarithm of drug concentration plotted against time. This analysis is based on a single-compartment model of drug elimination with all drug concentrations obtained during β-phase elimination after distribution. For clinical analysis, this model has been shown to closely approximate aminoglycoside elimination (24). The drug elimination constant (k_{el}) was determined by the slope of the line of best fit for ln(drug) versus time and, by derivation, $t_{1/2} = \ln 2/k_{el}$. The volume of distribution (V) was calculated from the formula of Sawchuk and Zaske (24) and, as described earlier (10), normalized for patient ideal body weight as liters per kilogram. Aminoglycoside clearance (CL_{am}) was calculated as $k_{el} \cdot V$.

Statistical analysis. In this study, gentamicin and tobramycin kinetics were assumed to be equivalent, as previously demonstrated by Regamey et al. (20). Analysis of patient groups was performed by two-tailed chi-square test (with Yates' correction) and Fisher's exact test for nominative data and by Student's t-test for unpaired continuous data. Correlation of clinical and kinetic data was determined by linear regression analysis with calculation of Pearson's correlation coefficient (27) or (for nonlinear associations) by Spearman's nonparametric correlation of ranks (9). The significance of correlations was determined by standard t test methods (27).

RESULTS

A total of 27 aminoglycoside kinetic determinations were performed on 18 patients. The clinical presentations of the patients and their treatments are summarized in Table 1. Clinical and laboratory results and drug kinetic data are summarized in Tables 2 and 3.

Aminoglycoside kinetic parameters were extremely variable in this population; although individual patients had reproducible kinetics (r = 0.90, correlation for repeat kinetics [$P < 0.001$]), there was wide interpatient variation. Determinations of drug $t_{1/2}$s ranged from 1.0 to 4.8 h, with a mean (± standard deviation) of 2.3 ± 0.9 h. The k_{el} ranged from 0.14 to 0.68 h^{-1}, with a mean of 0.34 ± 0.15 h^{-1}. The V ranged from 0.19 to 0.41 liters/kg, with a mean of 0.30 ± 0.06 liters/kg, and the total CL_{am} varied from 40 to 193 ml/min, with a mean of 111 ± 50 ml/min.

For further analysis, the addict patients were assigned to one of two groups for comparison: (i) a high-dose group of 12 patients, who were determined by kinetic analysis to require >5 mg/kg per day to maintain recommended peak and trough drug concentrations (peak, 6 mg/ml [18]; trough, 1 mg/ml [14] and (ii) a standard-dose group of 6 patients, who required ≤5 mg/kg per day to maintain these drug concentrations in serum.

Data for these two groups are summarized in the tables. The high-dose and standard-dose groups were not significantly different in terms of multiple characteristics: sites and agents of infection, choice of aminoglycoside therapy, reported drugs of abuse, duration of therapy, pre-existing disease affecting renal function, hematocrit, serum protein and albumin, weight, and urinalysis findings. The high-dose group was significantly younger (mean age, 31 versus 40

TABLE 2. Aminoglycoside kinetics and clinical and laboratory data in drug abuse patients[a]

Patients (n = 18)	Age (yr)	Wt (kg)	S_{CR} (mg/100 ml)	CL_{CR} (ml/min)		Hematocrit (%)	Serum protein (g/100 ml)	
				Estimated[b]	Measured		Total	Albumin
High-dose group (n = 12)	31 ± 4	67 ± 16	0.9 ± 0.2	96 ± 18	120 ± 21 (n = 4)	31 ± 9	7.3 ± 0.8	2.8 ± 0.5
Standard-dose group (n = 6)	40 ± 7[c]	74 ± 8	1.3 ± 0.1[c]	78 ± 12[d]	84 ± 20[d] (n = 4)	33 ± 5	7.4 ± 1.4	3.2 ± 0.8
All patients (n = 18)	34 ± 7	66 ± 12	1.0 ± 0.3	91 ± 18	104 ± 27 (n = 8)	33 ± 6	7.3 ± 1.1	2.9 ± 0.6

[a] All values are means ± standard deviations.
[b] CL_{CR} was estimated by the formula of Cockcroft and Gault (8): CL_{CR} = [140 − age (yr) × ideal body weight (kg)]/[72 × S_{CR} (mg/100 ml)]. (See Table 3, footnote b, for determination of ideal body weight.)
[c] Significant at $P < 0.01$ level.
[d] Significant differences between high- and standard-dose groups ($P < 0.05$) by Student's t test.

years [$P < 0.01$]) and reported fewer years of drug abuse (median, 2 versus 9 years). All patients in the high-dose group were younger than 39 years, and 92% were 35 years or younger.

During therapy, two patients developed azotemia (S_{CR}, >2.0 mg/100 ml), one each from the high-dose and standard-dose groups. Two patients died during therapy; both were in the standard-dose group. With regard to renal function, patients in the high-dose group had significantly lower S_{CR}s (mean S_{CR}, 0.9 versus 1.3 mg/100 ml; $P < 0.001$), and all high-dose patients had S_{CR}s of <1.3 mg/100 ml. When CL_{CR} was measured (n = 8), patients in the high-dose group (n = 4) had significantly greater CL_{CR}s than those in the standard-dose group (n = 4) (mean CL_{CR}, 120 versus 84 ml/min; $P < 0.05$). It was noted that in this study subgroup, all high-dose addicts had CL_{am}s that were 16 to 43% greater than measured CL_{CR} but that no standard-dose patients demonstrated this phenomenon ($P < 0.01$ by Fisher's exact test).

In terms of kinetic parameters, the high-dose group had significantly larger Vs (mean V, 0.33 versus 0.25 liters/kg; $P < 0.005$), shorter $t_{1/2}$s (mean $t_{1/2}$, 2.0 versus 3.3 h; $P < 0.001$), and significantly greater CL_{am}s than those in the standard-dose group (mean CL_{am}, 122 versus 64 ml/min; $P < 0.001$).

Correlation analysis. To evaluate the association of clinical data with aminoglycoside kinetics, linear regression analysis or rank correlation analysis was performed. This confirmed the association of CL_{am} with age (r = 0.58; $P < 0.05$), S_{CR} (r = −0.70; $P < 0.001$), and CL_{CR} (estimated, r = 0.60; $P < 0.01$; measured, r = 0.86; $P < 0.01$) (Fig. 1 and 2).

The correlation of measured CL_{CR} to CL_{am} improved with data distributed along two correlation lines instead of one: for line A (high-dose group), r = 0.99; for line B (standard-dose group), r = 0.99 ($P < 0.01$) (Fig. 2). Lines A and B differed significantly in their intercepts but not in their slopes, suggesting that a nonglomerular elimination process may have been augmenting drug clearance for patients on line A (high-dose group).

An excellent correlation was found between $t_{1/2}$ and CL_{am} (r = 0.93; $P < 0.001$) (Fig. 3); however, no correlation was found between CL_{am} and V (r = 0.10; not significant) or between CL_{am} and hematocrit, serum protein, or weight (r < 0.26; not significant).

DISCUSSION

Altered aminoglycoside kinetics have been noted previously in selected patient groups, e.g., obstetrical patients and burn victims (31, 32). In such patients, the failure of routine doses to provide adequate drug levels is accounted for by changes in the following recognized pharmacokinetic factors: increased V, increased glomerular filtration rate, or significant extrarenal loss. By contrast, multiple factors appear to be involved in the apparent need for supranormal doses of aminoglycosides in drug addict populations. First, addicts are significantly younger and have better renal function than the average hospitalized adult (8). Second, addicts develop infections (such as endocarditis) which predispose them to pathologic or iatrogenic fluid overload and consequently to an increased V (7, 13). Third, the types of infections seen in addicts require higher doses of aminoglycosides for control of infection (13, 14). Lastly, our data suggest that recreational drug use may induce an alternate, extraglomerular means of aminoglycoside elimination not previously noted in other hospitalized subjects or normal volunteers; because gentamicin has been detected in the bile of test animals (5) and treated patients (26) and because radiotracer drug elimination studies have indicated that inactive metabolites may also be excreted in the urine (29), it is possible that chronic drug abuse activates or accelerates alternate means of aminoglycoside elimination, leading to an increase in drug clearance.

Renal CL_{am} was not measured in this study. It is possible, therefore, that the increases in CL_{am} noted in our patients were due to increased renal drug clearance, either by enhanced glomerular filtration or by tubular loss. In the clinical

TABLE 3. Aminoglycoside kinetics and CL_{am} data in drug abuse patients[a]

Patients (n = 18)	CL_{am} (ml/min)	$-k_{el}$	$t_{1/2}$ (h)	V (liter/kg of IDB[b])	Final aminoglycoside dose (mg/kg of IDB)
High-dose group (n = 12)	122 ± 40	0.37 ± 0.12	2.0 ± 0.6	0.33 ± 0.05	8.2 ± 3.8
Standard-dose group (n = 6)	64 ± 13[c]	0.21 ± 0.04[c]	3.3 ± 0.6[c]	0.25 ± 0.04[c]	4.5 ± 1.9[d]
All patients (n = 18)	111 ± 50	0.34 ± 0.15	2.3 ± 0.9	0.30 ± 0.06	7.0 ± 3.7

[a] All values are means ± standard deviations.
[b] Ideal body weight (IDB) was calculated as follows (10): for men, IDB = 50 + 2.3 × [height (in) − 60]kg; for women, IDB = 45 + 2.3 × [height (in) − 60]kg.
[c] Significant at $P < 0.005$ level.
[d] Significant differences between values for high- and standard-dose groups ($P < 0.025$) by student's t test.

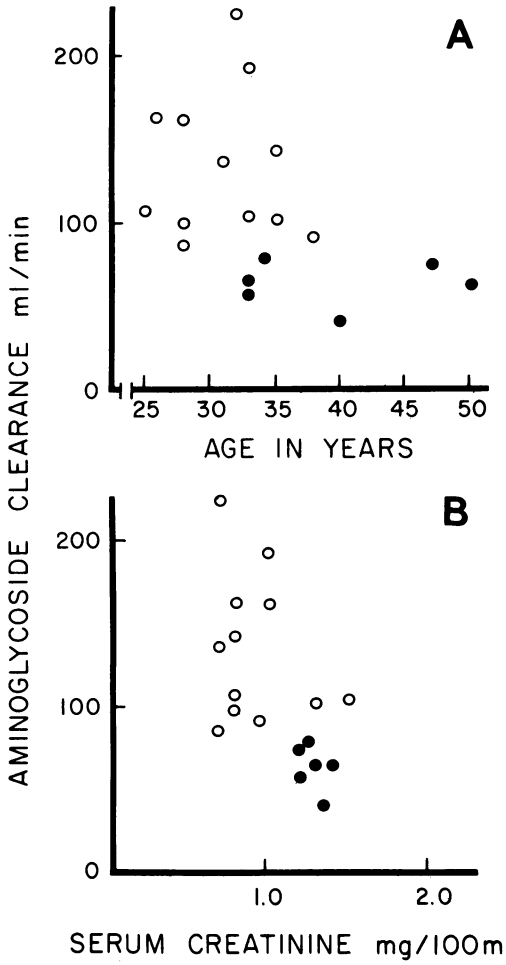

FIG. 1. Aminoglycoside elimination by addicts: association of age and S_{CR} with CL_{am}. (A) CL_{am} plotted by age for 18 hospitalized narcotics addicts treated with gentamicin or tobramycin. (B) CL_{am} plotted against S_{CR} at the time of the pharmacokinetic study. Significant inverse correlation exists between CL_{am} and age ($r = -0.58$, Spearman method; $P < 0.05$, Student's t test) and between CL_{am} and S_{CR} ($r = -0.70$, Spearman method; $P < 0.001$). Symbols: ○, patients requiring high-dose therapy; ●, patients requiring standard-dose therapy (see text).

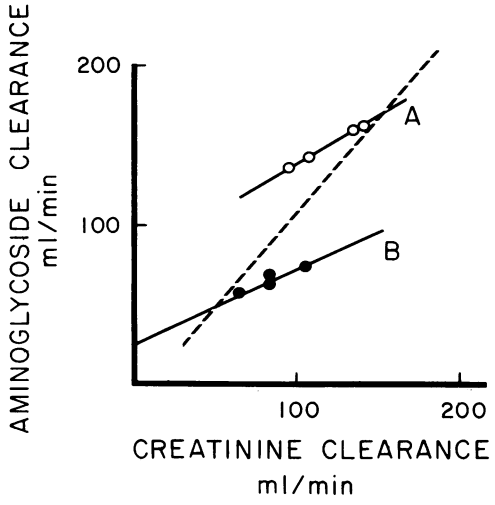

FIG. 2. Aminoglycoside kinetics in drug abusers: correlation of CL_{am} with measured CL_{CR}. Data from eight drug abusers are plotted (CL_{am} versus CL_{CR}). For all data, a significant ($P < 0.01$, Student's t test) correlation of these two parameters was found ($CL_{am} = 1.55 \cdot CL_{CR} - 49$; $r = 0.862$; dashed line). Correlation was markedly improved when data were distributed along two lines. Line A, $CL_{am} = 0.612\ CL_{CR} + 78$ ($r = 0.994$, $P < 0.01$); line B, $CL_{am} = 0.425\ CL_{CR} + 30$ ($r = 0.998$, $P < 0.01$). Line A and line B differ significantly ($P < 0.02$) from the dashed line in terms of slope. The intercepts of line A and line B are significantly different ($P < 0.05$), although their slopes are not. Symbols: ○, high-dose patients; ●, standard-dose patients.

setting of this study, it appeared that continued excretion of beta-lactam drugs made urinary aminoglycoside determinations unreliable. In practice, the distinction between accelerated renal versus extrarenal aminoglycoside elimination in addicts will require precise measurements of CL_{am} and renal CL_{am} under defined, single-therapy conditions.

As might be expected, the group of addicts requiring high-dose therapy was on the average younger, with relatively larger Vs and greater CL_{CR}s than those requiring only standard-dose therapy. Our regression analysis confirms that a significant correlation exists between CL_{am} and the three clinical factors of age, CL_{CR}, and S_{CR}. Yet, although these associations are statistically significant, as others have noted (16), the data distribution is such that no clinically reliable predictions can be drawn from these values. In terms of pharmacokinetic parameters, only drug $t_{1/2}$ (and not V) proved to be predictive of CL_{am}. Currently, our sample size is insufficient to isolate the effects of confounding variables (specifically age for these data) or to determine the specific contributions of individual kinetic factors to rapid drug clearance in this patient group.

No control group of nonaddict patients was studied concurrently. This prevents any specific discussion of differences in pharmacokinetics between addict and nonaddict populations. However, in several earlier studies of CL_{am} in hospitalized patients, similar techniques for kinetic analysis were used, and we examined our data, albeit with caution, using these studies as historical controls. The individual

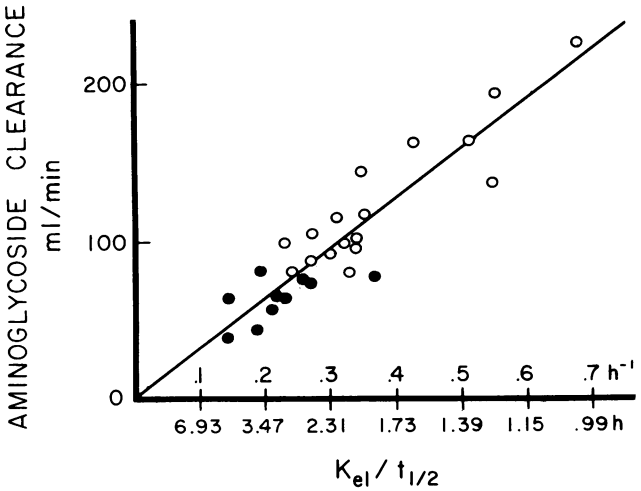

FIG. 3. Aminoglycoside pharmacokinetics in addicts: correlation of CL_{am} with k_{el} or $t_{1/2}$. For these data, a significant linear correlation was found ($CL_{am} = 308\ k_{el} + 4.6$; $r = 0.92$; $P < 0.001$, Student's t test). Symbols: ○, high-dose patients; ●, standard-dose patients.

kinetic values for our 18 patients were not outside the ranges reported by Zaske et al. for 1,640 hospitalized patients (30). However, Kaye et al. have determined the correlation between estimated CL_{CR} and k_{el} in 64 hospitalized patients, and the results for 6 of our 18 patients fell above the 95% confidence limits of their data (16). This appears to confirm the premise that certain addicts demonstrate abnormally rapid CL_{am}. In a study of tobramycin kinetics in nonaddict patients with normal renal function, Bauer and Blouin (4) have reported an average $t_{1/2}$ of 2.2 to 2.3 h for patients aged 20 to 79 years, which was comparable to the mean $t_{1/2}$ (2.3 h) noted for the total addict population in our study. Although their ranges of kinetic data were not reported, they did note that 35 of 77 patients required doses of >5 mg/kg per day to maintain therapeutic drug levels (peak, >6 μg/ml; trough, 1 μg/ml). Our observed high-dose rate for a younger addict population was 66%, a rate significantly higher than theirs (45%; $P < 0.025$, chi-square test). Taken together, these data suggest that wide and clinically unpredictable interpatient variation in aminoglycoside elimination occurs among all hospitalized patients and that addicts, particularly younger addicts, represent a subset of patients likely to require higher aminoglycoside doses and more careful monitoring of drug levels during therapy.

Intravenous-narcotics addicts have an estimated mortality rate of 0.7% per year (7). Of these deaths, 15 to 33% are infection related (7, 23). It is apparent from our data that narcotics abusers are at significant risk for undertreatment with aminoglycoside drugs and are consequently at increased risk for treatment failure. Manufacturer recommendations and rules of thumb consistently underestimate the doses required to maintain therapeutic drug levels in addicts, and although nomograms (6) and estimated CL_{CR}s (16) may work well in predicting doses in renal failure, we have found them to underestimate clearance in patients with CL_{CR}s of >100 ml/min. As we have shown, this may be particularly important in addicts, where CL_{CR}s may be significantly less than CL_{am}s, making an estimation based on CL_{CR} invalid.

Because rapid drug elimination is unpredictable by routine clinical data, it is imperative that drug kinetics be determined in every addict receiving aminoglycosides for severe infection. As shown in Fig. 3, CL_{am} is well correlated with drug $t_{1/2}$, a kinetic parameter which may be determined on the first dose (30). By this method, first-dose pharmacokinetic evaluation permits early identification of patients with rapid CL_{am}. In consideration of initial empirical dosing, Archer and Fekety (3) and Reyes et al. (21, 22) have shown that 8 mg/kg per day is effective and relatively safe in treating *Pseudomonas* endocarditis, and it is known that delay in instituting effective aminoglycoside therapy has been associated with failure of antibiotic treatment (2, 14, 18). Therefore, pending the results of kinetic studies, initial doses of 8 mg/kg per day should be administered to addicts who are younger than 35 years and who have S_{CR}s of ≤1.0 mg/100 ml (in our study, all 10 of our patients in this category required high-dose therapy). It is these addict patients who appear to be at specific risk for undertreatment with standard aminoglycoside therapy.

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