ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 1977, p. 328-334

Vol. 12, No. 3
Printed in U.S.A.

Netilmicin Pharmacokinetics After Single Intravenous Doses to Elderly Male Patients

PETER G. WELLING,[1]* AXEL BAUMUELLER,[2] CURTIS C. LAU,[1] AND PAUL O. MADSEN[2]

School of Pharmacy[1] and Department of Medicine, University of Wisconsin Center for Health Sciences, and the Veterans Administration Hospital,[2] Madison, Wisconsin 53706*

Received for publication 10 May 1977

The pharmacokinetics of the new aminoglycoside antibiotic netilmicin were examined after single intravenous injections at two different dose levels to elderly male patients. The drug obeyed two-compartment model kinetics in serum, and elimination was monoexponential from 1 to 2 h after dosing. Netilmicin levels in serum were above minimum inhibitory concentration values for most susceptible organisms for up to 8 h after dosing in normal individuals and for at least 12 h in uremic patients. Urine levels of netilmicin were uniformly above minimum inhibitory concentration values throughout 24 h after dosing. Netilmicin distribution characteristics were largely independent of both dose level and renal function. Netilmicin elimination kinetics were independent of dose level but were markedly influenced by renal function. Relationships are described between netilmicin elimination and renal function indicators, which provide a basis for dosage adjustment in individuals with renal function impairment.

Netilmicin, the 1-*N*-ethyl derivative of sisomicin, is a new aminoglycoside which is effective against gram-negative bacteria, including strains resistant to gentamicin, sisomicin, and tobramycin (5, 6, 9).

In a previous study at this institution, netilmicin was shown to be clinically effective and free from toxic side effects when given intramuscularly to elderly male patients at doses of 1.0 to 2.5 mg/kg every 8 h for 7 days (A. Baumueller and P. O. Madsen, submitted for publication). A preliminary study in a similar patient population showed that after rapid intravenous injection, netilmicin had a serum half-life of about 4.5 h, and the half-life was linearly related to serum creatinine (Baumueller and Madsen, submitted for publication).

Here we report on the pharmacokinetics of netilmicin after single intravenous doses to elderly male patients with normal and impaired renal function.

MATERIALS AND METHODS

Subjects and protocols. Subjects were 42 patients in the urology ward of the Veterans Administration Hospital, Madison, Wis. Details of subjects' ages, weights, creatinine clearances, and serum creatinine values are described in Table 1. Almost all of the patients were suffering from lower urinary tract obstruction, infections associated with lower urinary tract obstruction, urethral stricture, carcinoma or hyperplasia of the prostate, or bladder tumor. Some patients had indwelling bladder catheters; most of them were not bedridden during the study.

For analysis, patients were divided into three groups based on creatinine clearances. Groups 1, 2 and 3 had creatinine clearances greater than 100 ml/min, between 50 and 100 ml/min, and less than 50 ml/min, respectively. Creatinine clearances were obtained from 12-h urine collections, except in the case of some severely uremic patients where 24-h urine clearances were obtained. Patients received netilmicin by rapid intravenous injection into a forearm vein at dose levels of 1 or 2 mg/kg. The injection was administered in 5 ml of physiological saline, and the injection time was 2 min.

Blood samples (5 ml) were taken for serum shortly before and at 0, 5, 15, 30, and 45 min and then at 1, 2, 4, 8, and 12 h after dosing. The sample obtained at 0 min was taken from a vein in the arm not being used for dosing immediately after the injection was complete. All other times are calculated from the time of completion of drug injection. Complete urine collections were obtained during 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 h after injection. Sera and also urine samples, were frozen until assayed. Assays were routinely done within 1 week of sampling.

Assay. Netilmicin in serum and urine was assayed by a disk diffusion method using *Bacillus subtilis* ATCC 6633 as test organism on streptomycin assay agar (BBL). To obtain antibiotic concentrations within assay limits, sera were appropriately diluted with pooled serum, whereas urine samples were diluted with pH 8 phosphate buffer.

Data analysis. Individual serum netilmicin levels declined in a biphasic manner when plotted against time on semilogarithmic graph paper. This type of profile is consistent with two-compartment, open-

TABLE 1. *Subject details*

Subject and parameter	Dose									
	1 mg/kg					2 mg/kg				
	n[a]	Age (yrs)	Wt (kg)	CL_{CR}[b] (ml/min)	C_{CR}[c] (mg/100 ml)	n	Age (yrs)	Wt (kg)	CL_{CR} (ml/min)	C_{CR} (mg/100 ml)
Group 1										
Mean	3	54	62	124	1.0	6	66	78	125	1.0
SD[d]		5	6	17	0.1		13	13	10	0.2
Range		48–58	58–69	104–134	0.9–1.1		50–84	58–92	112–140	0.8–1.2
Group 2										
Mean	11	74	70	73	1.5	7	80	71	63	1.7
SD		9	11	19	0.6		4	17	11	0.2
Range		61–83	52–91	50–100	0.8–2.6		74–84	50–97	50–82	1.5–2.2
Group 3										
Mean	9	73	80	32	2.5	6	74	70	25	3.0
SD		13	17	12	0.9		9	10	15	1.3
Range		55–85	60–120	20–46	1.3–4.2		62–81	55–85	5–46	1.4–5.1

[a] n, Number of subjects.
[b] CL_{CR}, Creatinine clearance.
[c] C_{CR}, Serum creatinine.
[d] SD, Standard deviation.

model kinetics, with drug elimination occurring from the central compartment (11). With this model, serum levels of netilmicin, C, at any time, t, after dosing are described by equation 1, where D is the dose and V_1 is the apparent distribution volume of the central compartment.

$$C = \frac{D}{V_1(\alpha - \beta)}[(k_{21} - \beta)e^{-\beta t} - (k_{21} - \alpha)e^{-\alpha t}] \quad (1)$$

The complex rate constants α and β are given by equation 2, where k_{12} and k_{21} are first-order rate constants for drug distribution from the central to the tissue compartment and from the tissue to the central compartment, respectively, k_{el} is the first-order rate constant for drug elimination from the central compartment, $\alpha > \beta$, and the elimination half-life of netilmicin in serum is given by $0.693/\beta$.

$$\begin{matrix}\alpha \\ \beta\end{matrix} = 0.5[(k_{12} + k_{21} + k_{el}) \pm \sqrt{(k_{12} + k_{21} + k_{el})^2 - 4k_{21}k_{el}}] \quad (2)$$

Individual serum levels were fitted to equation 1 using the digital computer program NREG (15).

Although serial urine collections were obtained, the combined effects of rapid elimination and also bladder holdup caused considerable variation in calculated renal clearances both between subjects and at different urine collection times in the same individual. These values were therefore not included in our calculations. Differences in various values between groups were compared using Student's two-tailed t test.

RESULTS

Serum levels of netilmicin are summarized in Table 2. The levels are clearly dose related, being approximately twice as high after the 2-mg/kg dose compared to the 1-mg/kg dose at most sampling times in groups 1 and 2. In group 3, netilmicin serum levels were increased about 1.5-fold after the higher dose. In group 1, netilmicin serum levels had fallen to values below the minimum inhibitory concentration values for most susceptible organisms by h 8 after both the high and low doses (5). In group 3, netilmicin serum levels exceeded minimum inhibitory concentration values for most organisms at 12 h after dosing. Group 2 yielded intermediate values.

The biphasic nature of serum netilmicin levels is indicated by the semilogarithmic plots of averaged data in Fig. 1 and 2. The drug appears to equilibrate between the serum and extravascular tissues and fluids within 1 to 2 h of dosing. After that time, clearance of drug is monoexponential.

Urinary excretion data are summarized in Table 3. In all groups, and at both dose levels, urine concentrations of netilmicin far exceeded minimum inhibitory concentration values of susceptible organisms during 24 h after dosing. The percentage of dose excreted in 24-h urine tended to be greater in patients with normal renal function, although differences in this value between groups were not significant ($P > 0.05$). Urinary recovery of antibiotic was considerably less than 100% of the dose in all groups.

Results of a pharmacokinetic analysis are summarized in Table 4. Pharmacokinetic constants were generally not influenced by the different dose levels used and are similar to those reported for other aminoglycosides (1, 7, 8, 16).

TABLE 2. *Mean serum levels of netilmicin (±1 standard deviation) after single 1- and 2-mg/kg bolus injections*

Dose (mg/kg)	Group	Netilmicin concn in serum (μg/ml)								
		0 min	5 min	15 min	30 min	45 min	1 h	2 h	4 h	8 h	12 h
1	1	13.4 ± 3.7	9.3 ± 0.3	7.2 ± 1.4	5.1 ± 1.4	4.5 ± 0.3	3.7 ± 0.8	2.0 ± 0.7	1.1 ± 0.3	0.6 ± 0.3	0.2 ± 0.2
	2	11.2 ± 5.5	8.7 ± 3.7	6.1 ± 2.5	5.3 ± 4.0	4.1 ± 1.8	3.2 ± 1.1	2.5 ± 1.0	1.7 ± 0.7	1.2 ± 0.7	0.7 ± 0.5
	3	12.8 ± 4.2	10.9 ± 6.3	8.9 ± 4.2	6.2 ± 2.1	5.5 ± 2.1	5.2 ± 2.1	3.9 ± 1.5	3.4 ± 0.9	2.4 ± 0.7	2.0 ± 0.6
2	1	28.2 ± 9.6	20.3 ± 5.0	13.8 ± 3.6	11.2 ± 2.9	9.3 ± 1.9	8.0 ± 1.8	5.0 ± 1.3	2.6 ± 0.8	1.1 ± 0.4	0.5 ± 0.3
	2	16.3 ± 4.2	18.2 ± 3.0	12.9 ± 3.0	10.8 ± 2.6	9.5 ± 2.2	8.4 ± 1.5	6.7 ± 1.4	4.7 ± 1.2	3.0 ± 0.9	2.3 ± 0.8
	3	19.6 ± 7.4	14.0 ± 1.9	11.8 ± 2.5	10.1 ± 0.7	8.9 ± 1.7	7.5 ± 0.6	6.4 ± 0.7	5.0 ± 1.2	4.2 ± 0.8	3.2 ± 1.1

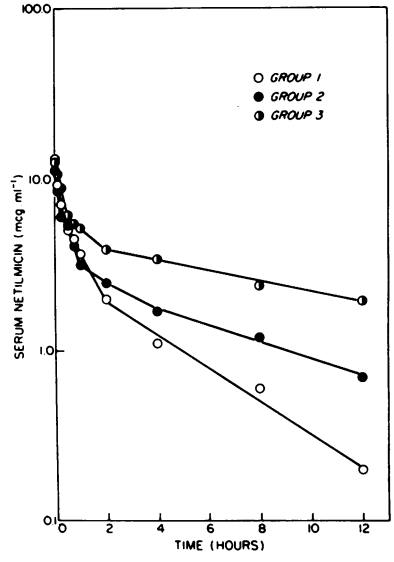

FIG. 1. *Average serum levels of netilmicin in patients receiving 1 mg of netilmicin per kg of body weight by intravenous injection.*

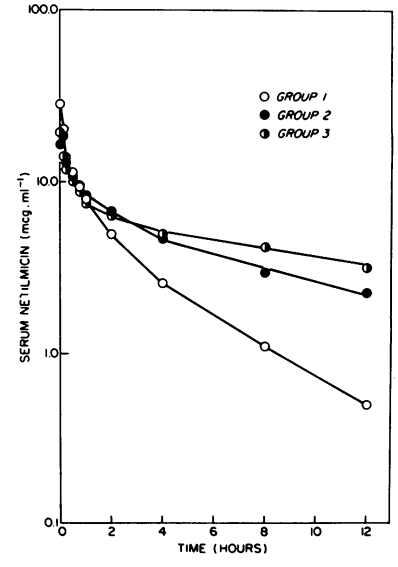

FIG. 2. *Average serum levels of netilmicin in patients receiving 2 mg of netilmicin per kg of body weight by intravenous injection.*

Pharmacokinetic constants associated primarily with drug distribution (α, k_{12}, k_{21}, T/P, V_1, V_d) were not significantly altered by changing renal function in patients receiving the smaller dose of netilmicin. In patients receiving the larger dose, there was a tendency for distribution volumes to increase with declining renal function.

TABLE 3. *Urinary concentration of netilmicin (±1 standard deviation) and cumulative percentage of dose (±1 standard deviation) excreted in 24 h*

Dose (mg/kg)	Group	Netilmicin concn in urine (μg/ml)					% of dose excreted in 24 h	24-h urine vol (liters)
		0-2 h	2-4 h	4-8 h	8-12 h	12-24 h		
1	1	101 ± 89	20 ± 4	44 ± 53	9 ± 9	2 ± 1	54.3 ± 17.8	1.8 ± 0.3
	2	67 ± 55	36 ± 16	34 ± 31	19 ± 12	8 ± 4	52.3 ± 15.6	1.8 ± 1.1
	3	45 ± 40	40 ± 31	32 ± 26	25 ± 15	16 ± 17	43.4 ± 24.5	2.0 ± 1.0
2	1	429 ± 203	210 ± 164	101 ± 75	42 ± 37	22 ± 21	88.0 ± 13.9	1.5 ± 0.5
	2	155 ± 90	139 ± 74	104 ± 56	58 ± 26	17 ± 7	58.3 ± 22.5	1.7 ± 1.4
	3	45 ± 38	48 ± 50	35 ± 26	31 ± 25	22 ± 19	41.2 ± 15.8	1.8 ± 0.4

Pharmacokinetic constants associated primarily with drug elimination (β, $t_{1/2}$, k_{el}) were influenced by renal function, although differences in these values between groups were not always significant. The serum half-life of netilmicin increased from approximately 2 to 3 h in "normal" individuals to approximately 10 to 14 h in severe uremia. The individual with greatest impairment of renal function (CL_{CR} = 5 ml/min) had a netilmicin half-life of 22 h.

The relationships between some pharmacokinetic constants and kidney function are described in the form of linear regressions in Table 5. Good correlations were obtained between netilmicin β values and half-lives, and also serum clearances and appropriate kidney function indicators. Correlations between drug distribution characteristics and renal function were poor.

DISCUSSION

Results obtained in this study indicate that netilmicin has pharmacokinetic characteristics similar to those of the other aminoglycosides. Serum levels of antibiotic are greater than the minimum inhibitory concentrations for susceptible organisms for at least 8 h after dosing, and, from our data, there appears to be little advantage to using the higher dose, except perhaps for more resistant organisms. A large proportion of antibiotic is cleared unchanged through the kidneys, although part of the dose is eliminated by other mechanisms. This urinary recovery pattern, particularly in group 1, is very similar to recoveries of gentamicin, gentamicin C_1 (7), sisomicin (8), and tobramycin (16) in similar patient populations and lends support to our previous suggestion that extrarenal elimination may account for 10 to 40% of dosed aminoglycosides in these elderly individuals.

The drug distributes in the body in a fashion consistent with a central compartment approximately 10% of body weight and a total distribution volume approximately 20 to 30% of body weight. In Table 4, the overall distribution volumes were calculated by two different methods to give $V_{d(ss)}$ and $V_{d(\beta)}$. The methods of calculating these values are given as footnotes to the table, and their significance has been discussed elsewhere (2, 10).

A major criticism of the use of $V_{d(\beta)}$ to describe the total apparent distribution volume of a drug obeying two-compartment model kinetics is that the method tends to yield a biased overestimate of the equilibrium volume as calculated by $V_{d(ss)}$ (10). The values of $V_{d(\beta)}$ calculated from our data do not overestimate but rather agree extremely well with $V_{d(ss)}$ values. Although netilmicin, like other aminoglycosides, has a fairly short biological half-life, the value of k_{el} is small compared to k_{12} and k_{21} in all groups. The similarity of the volumes calculated by the two methods is therefore consistent with the observation by Riegelman et al. (10) that $V_{d(\beta)}$ will overestimate the true equilibrium distribution volume only when k_{el} is large compared to k_{12} and k_{21}.

The reason for the increase in netilmicin distribution volumes with decreasing renal function is not clear. Aminoglycosides bind to serum proteins to only a small extent (1). Thus, if any displacement of drug from circulating proteins were to occur in renal failure, this should not cause a detectable change in the apparent drug distribution volume (14). Other possible mechanisms for the increase in distribution volume in uremia after the high dose, i.e., changes in circulatory characteristics or membrane permeability, were not investigated in this study.

There is evidence from experimental animals that netilmicin is somewhat less ototoxic and nephrotoxic than gentamicin (4, 6). Nevertheless, dosage adjustment is necessary in patients with impaired renal function. As relationships between netilmicin elimination and renal function were similar at both dose levels used, regressions of netilmicin serum half-life versus serum creatinine and of netilmicin β values versus creatinine clearance were calculated using data from the 42 patients.

TABLE 4. *Summary of pharmacokinetic values (±1 standard deviation)*

Dose (mg/kg)	Group	α (per h)	β (per h)	k_{12} (per h)	k_{21} (per h)	k_{el} (per h)	$t_{1/2}(\beta)$ (h)	T/P[a]	V_1 (%)[b]	$V_{d(ss)}$ (%)[c]	$V_{d(\beta)}$ (%)[d]	$V_1 k_{el}$[e] (ml/min)	r^2[f]
1	1	4.1 ± 3.4	0.25 ± 0.07	2.3 ± 2.3	1.2 ± 0.8	0.82 ± 0.39	2.3 ± 0.7	1.9 ± 1.1	8.2 ± 2.2	20.0 ± 1.8	24.8 ± 1.7	64 ± 14	0.994
	2	5.7 ± 3.6	0.17 ± 0.08	3.6 ± 3.0	1.6 ± 1.1	0.66 ± 0.52	5.0 ± 2.6	2.9 ± 2.7	9.6 ± 5.0	25.0 ± 7.2	27.0 ± 6.8	54 ± 27	0.992
	3	4.1 ± 3.3	0.08 ± 0.03	2.5 ± 2.2	1.5 ± 1.1	0.21 ± 0.11	10.3 ± 4.0	1.7 ± 0.6	9.5 ± 5.3	23.4 ± 11.9	23.8 ± 11.6	21 ± 6	0.959
t test[g]		NSD[h]	1,2 > 3	NSD	NSD	1,2 > 3	3 > 1,2	NSD	NSD	NSD	NSD	1,2 > 3	
2	1	7.6 ± 3.8	0.34 ± 0.08	3.9 ± 2.4	3.3 ± 1.5	0.81 ± 0.23	2.1 ± 0.5	1.3 ± 0.6	7.6 ± 2.6	16.1 ± 2.9	17.2 ± 3.3	77 ± 32	0.995
	2	4.6 ± 3.8	0.13 ± 0.05	2.6 ± 2.6	1.7 ± 1.2	0.30 ± 0.12	6.2 ± 2.3	1.5 ± 0.4	9.5 ± 1.8	22.4 ± 2.6	22.6 ± 4.2	34 ± 15	0.995
	3	3.2 ± 2.0	0.06 ± 0.02	1.9 ± 1.3	1.3 ± 0.8	0.18 ± 0.09	12.9 ± 5.6	1.8 ± 0.4	11.4 ± 2.6	27.8 ± 5.6	29.3 ± 6.1	21 ± 8	0.993
t test		NSD	1 > 2 > 3	NSD	NSD	1 > 2,3	3 > 2 > 1	NSD	3 > 1	3 > 1	3 > 1	1 > 2,3	

[a] T/P, Ratio of amount of drug in tissue compartment to amount of drug in central compartment during the β phase $[k_{12}/(k_{21} - \beta)]$.
[b] Volume of central compartment expressed as percentage of body weight.
[c] $V_{d(ss)} = V_1(k_{12} + k_{el})k_{21}$.
[d] $V_{d(\beta)} = V_1(k_{el})/\beta$.
[e] Serum clearance.
[f] Coefficient of determination $(\sum obs^2 - \sum dev^2)/\sum obs^2$.
[g] Significant when $P < 0.05$.
[h] NSD, No significant differences.

TABLE 5. *Regression equations, correlation coefficients, and significance levels after single intravenous injections of netilmicin*

Correlation	Linear equation of best fit	r^a	P
Dose = 1 mg/kg; n = 23			
Beta vs creatinine clearance	$y = 0.02 + 0.002x$	+0.79	<0.01
$V_{d(ss)}$ vs creatinine clearance	$y = 21.8 - 0.07x$	−0.34	NS
Serum clearance vs creatinine clearance	$y = 8.3 + 0.55x$	+0.75	<0.01
T/P vs creatinine clearance	$y = 1.52 + 0.01x$	+0.22	NS
$t_{1/2}$ (β) vs serum creatinine	$y = 0.18 + 3.53x$	+0.75	<0.01
Dose = 2 mg/kg; n = 19			
Beta vs creatinine clearance	$y = -0.01 + 0.003x$	+0.86	<0.01
$V_{d(ss)}$ vs creatinine clearance	$y = 19.0 - 0.046x$	−0.53	<0.05
Serum clearance vs creatinine clearance	$y = 5.51 + 0.53x$	+0.74	<0.01
T/P vs creatinine clearance	$y = 1.76 - 0.004x$	−0.33	NS
$t_{1/2}$ (β) vs serum creatinine	$y = -1.22 + 4.32x$	+0.85	<0.01

[a] r, Correlation coefficient.

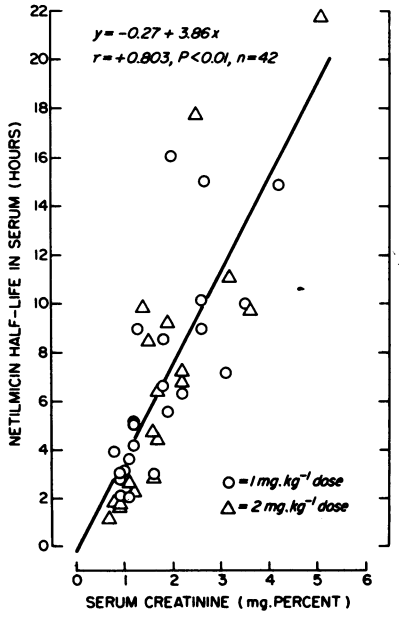

FIG. 3. *Relationship between netilmicin half-life in serum and serum creatinine.*

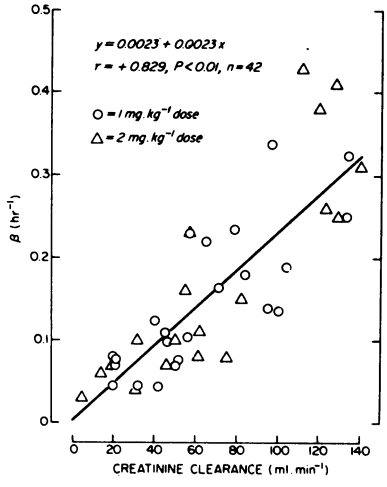

FIG. 4. *Relationship between the netilmicin elimination rate constant β and creatinine clearance.*

These combined regressions are illustrated in Fig. 3 and 4. Both regressions had large correlation coefficients and were highly significant.

According to Wagner et al. (12), mean circulating drug levels at the steady state during repeated dosing are described by equations 3 and 4 for the one-compartment and two-compartment models, respectively.

$$\bar{C}^{ss} = \frac{D}{VK\tau} = \frac{(1.44)t_{1/2} \cdot D}{V\tau} \quad (3)$$

$$\bar{C}^{ss} = \frac{D}{V_1 k_{el} \tau} = \frac{D}{V_{d(\beta)} \cdot \beta \cdot \tau} = \frac{(1.44)t_{1/2} \cdot D}{V_{d(\beta)} \cdot \tau} \quad (4)$$

Several methods of dose adjustment in uremic patients are available to achieve desired steady-state circulating drug levels (13). The simplest and most commonly used methods comprise adjusting the dose or the dosage interval.

The regression in Fig. 3 can be closely approximated by the expression $y = 4x$. Thus the netilmicin half-life can be calculated by multiplying serum creatinine by a factor of 4, and the dose or dosage interval can be appropriately adjusted by means of equation 4, assuming the distribution volume to be reasonably constant. Alternatively, if the dosage interval is 8 h in normal individuals, the interval can be adjusted directly by multiplying the serum creatinine by a factor of 8.

Similarly, the regression in Fig. 4 can be reasonably approximated by $y = 0.002x$. Thus,

the value of β is obtained by multiplying the creatinine clearance by a factor of 0.002, or the drug half-life can be calculated from the relationship $t_{1/2} = 350/CL_{CR}$. The serum creatinine and creatinine clearance methods yield comparable results. Using the approximations described above, a patient with normal renal function (C_{CR} = 1.0 mg/100 ml; CL_{CR} = 100 ml/min) has calculated netilmicin half-lives of 4 and 3.5 h using C_{CR} and CL_{CR}, respectively. A patient with impaired renal function (C_{CR} = 2.6 mg/100 ml; CL_{CR} = 30 ml/min) has calculated netilmicin half-lives of 11.2 and 11.6 h using C_{CR} and CL_{CR}, respectively.

The calculated zero intercept of the regression in Fig. 4 appears to be inconsistent with the less than quantitative excretion of antibiotic in urine. Although the overall elimination rate constant of a drug cleared partially by nonrenal mechanisms is expected to decline in renal insufficiency, a residual clearance should remain in severe renal failure depending on the extent of nonrenal elimination. The reason for this inconsistency is not clear, but it may be due to reduced extrarenal elimination in these elderly patients or to data noise preventing the description of a more precise relationship between renal function and drug clearance.

As the production of, and also circulating levels of, creatinine are influenced to a far greater extent than creatinine clearance by body weight, muscle mass, age, and sex, the relationship between creatinine clearance and netilmicin excretion may be the method of more general application (3). However, from a practical standpoint, either method may be used as a guide for netilmicin dose adjustment in patients with chronic renal impairment.

LITERATURE CITED

1. **Gyselynck, A-M., A. Forrey, and R. Cutler.** 1971. Pharmacokinetics of gentamicin: distribution and plasma and renal clearance. J. Infect. Dis. 124(Suppl):S70–S76.
2. **Jusko, W. J., and M. Gibaldi.** 1972. Effects of change in elimination on various parameters of the two-compartment open model. J. Pharm. Sci. 61:1270–1273.
3. **Kampmann, J., J. M. Hansen, K. Siersbaek-Nielson, and M. Kristensen.** 1973. Serum creatinine and drug half-lives. J. Am. Med. Assoc. 223:193.
4. **Luft, F. S., N. Yum, and S. A. Kleit.** 1976. Comparative nephrotoxicities of netilmicin and gentamicin in rats. Antimicrob. Agents Chemother. 10:845–849.
5. **Meyers, B. R., and S. Z. Hirschman.** 1977. Antimicrobial activity in vitro of netilmicin and comparison with sisomicin, gentamicin, and tobramycin. Antimicrob. Agents Chemother. 11:118–121.
6. **Miller, G., G. Arcieri, M. J. Weinstein, and J. A. Waitz.** 1976. Biological activity of netilmicin, a broad-spectrum semisynthetic aminoglycoside antibiotic. Antimicrob. Agents Chemother. 10:827–836.
7. **Mosegaard, A., P. G. Welling, and P. O. Madsen.** 1975. Gentamicin and gentamicin C_1 in the treatment of complicated urinary tract infections: comparative study of efficacy, tolerance, and pharmacokinetics. Antimicrob. Agents Chemother. 7:328–332.
8. **Mosegaard, A., P. G. Welling, F. L. S. Tse, and P. O. Madsen.** 1975. Treatment with sisomicin of complicated urinary tract infections in patients with varying degrees of renal function impairment. Infection 3:143–147.
9. **Rahal, J. J., Jr., M. S. Simberkoff, K. Kagan, and N. J. Moldover.** 1976. Bactericidal efficacy of Sch 20569 and amikacin against gentamicin-sensitive and -resistant organisms. Antimicrob. Agents Chemother. 9:595–599.
10. **Riegelman, S., J. Loo, and M. Rowland.** 1968. Concept of a volume of distribution and possible errors in evaluation of this parameter. J. Pharm. Sci. 57:128–133.
11. **Wagner, J. G.** 1975. Fundamentals of clinical pharmacokinetics, p. 82–84. Drug Intelligence Publications, Hamilton, Ill.
12. **Wagner, J. G., J. I. Northam, C. D. Alway, and O. S. Carpenter.** 1965. Blood levels of drug at the equilibrium state after multiple dosing. Nature (London) 207:1301–1302.
13. **Welling, P. G., and W. A. Craig.** 1976. Pharmacokinetics in disease state modifying renal function, p. 173. *In* L. Z. Benet (ed.), The effect of disease states on drug pharmacokinetics. Academy of Pharmaceutical Sciences, American Pharmaceutical Association, Washington, D.C.
14. **Welling, P. G., W. A. Craig, G. L. Amidon, and C. M. Kunin.** 1974. Pharmacokinetics of cefazolin in normal and uremic subjects. Clin. Pharmacol. Ther. 15:344–353.
15. **Welling, P. G., W. R. Shaw, S. J. Uman, F. L. S. Tse, and W. A. Craig.** 1975. Pharmacokinetics of minocycline in renal failure. Antimicrob. Agents Chemother. 8:532–537.