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Pharmacokinetics of Netilmicin in Patients with Renal Impairment and in Patients on Dialysis

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The pharmacokinetics of netilmicin were examined in 25 adult subjects, 7 normal subjects, and 18 patients with renal impairment. Five were dialysis patients who were studied on and off dialysis. Netilmicin, 2 mg/kg, was infused intravenously over 1 h. The peak serum concentration ranged from 9 to 11 μg/ml. The mean biological half-life of netilmicin for subjects with a creatinine clearance (Ccr) > 70 ml/min was 2.7 h, for those with Ccr > 25 < 70 ml/min it was 10 h, for those with Ccr > 4 < 25 ml/min it was 32 h, and for those who were anephric it was 42 h. Ccr was correlated positively with the elimination constant and the drug's serum clearance. It was negatively correlated with the drug's volume of distribution. The dialyzer clearance of netilmicin was positively correlated with plasma flow rate and was similar to values previously reported for gentamicin. Netilmicin behaves in a fashion similar to other aminoglycosides. Therapeutic guidelines are suggested.

Netilmicin, the 1-*N*-ethyl derivative of sisomicin, is a new semisynthetic aminoglycoside antibiotic which is active against a large number of gram-negative bacteria, including many strains that are resistant to currently available aminoglycosides (9, 10, 14). As is characteristic for aminoglycosides, netilmicin appears to be excreted into the urine unchanged. Animal studies in rats and dogs with both labeled and nonlabeled netilmicin have failed to indicate that netilmicin is metabolized (J. A. Waitz, personal communication). Studies in experimental animals suggest that netilmicin may be less toxic than gentamicin (8). Recently, the pharmacokinetics of netilmicin in patients with normal renal function (10) and decreased renal function (17) have been reported. However, information on the elimination of netilmicin in patients with severe renal failure or in those requiring hemodialysis has not been reported. This study was performed to obtain data useful to clinicians caring for such patients. A dosage adjustment table providing therapeutic guidelines was developed.

MATERIALS AND METHODS

Subjects. Twenty-five adult subjects were studied. For purposes of analysis, the subjects were divided into four groups on the basis of their renal function: group 1, seven subjects, creatinine clearance (Ccr) ≥ 70 ml/min; group 2, seven subjects, Ccr ≥ 25 < 70 ml/min; group 3, six subjects, Ccr ≥ 4 < 25 ml/min; group 4, five subjects on hemodialysis, who were surgically anephric. The subjects with diminished renal function suffered from a variety of renal diseases including glomerulonephritis, interstitial nephritis, polycystic kidneys, and nephrosclerosis. The subjects on hemodialysis underwent thrice weekly 6-h hemodialyses. They were studied during a 48-h interdialytic period and again during a hemodialysis. A 2-week interval was allowed between the study periods for the hemodialysis patients. Blood specimens for complete blood count, calcium, phosphorus, bilirubin, total protein, albumin, uric acid, blood urea nitrogen, glucose, cholesterol, alkaline phosphatase, lactic acid dehydrogenase, and serum glutamic oxaloacetic acid transaminase were obtained in all subjects. Approval for these studies was obtained from the Indiana University Committee on the Use of Human Subjects in Research. Written informed consent was obtained from all participants.

Administration of netilmicin and specimen collection. Netilmicin, 2 mg/kg, was dissolved in 50 ml of normal saline and infused intravenously for 1 h via a Harvard pump. The drug was infused over 1 h rather than as a single bolus injection to provide more reproducible volume of distribution estimates. Serum specimens for netilmicin determinations were obtained from a vein in the contralateral arm at 15 min, 30 min, 60 min, 62 min, 65 min, 70 min, 2 h, 4 h, 6 h, 12 h, 24 h, 36 h, 48 h, and 72 h from the start of the infusion. Daily 24-h urine specimens were collected for 3 days from those subjects who made urine. The Ccr values used in the calculations were the means of three determinations. The five subjects studied during dialysis received netilmicin, 2 mg/kg, in the above fashion over 1 h. Thereafter, hemodialysis was conducted

for 5 h. Arterial and venous specimens for netilmicin and blood urea nitrogen determinations were obtained hourly for 5 h.

Netilmicin was measured in duplicate in serum and urine by an agar well diffusion assay, using *Staphylococcus epidermidis* (ATCC 27626) as the test organism (1). The mean percent difference between duplicate assays was less than 12. Even though the assay is not affected by clinically attainable concentrations of nonaminoglycoside antibiotics (1), none of the subjects in this study received antibiotics other than netilmicin. To obtain antibiotic concentrations within assay limits, sera were appropriately diluted with pooled serum, whereas urine samples were diluted in phosphate buffer (pH 8). Complete blood counts were obtained via Coulter Counter. Serum chemistries were performed by standard autoanalyzer techniques (Technicon).

Dialysis procedures. The dialysis patients were dialyzed with the use of a recirculating single-pass delivery system (Travenol Corp. Buena Park, Calif.) and the Ultraflow II (UF-2) model A (Travenol Corp.) artificial kidney. Blood flow rates were varied between 50 and 300 ml/min. The dialysate flow rate was maintained at 800 ml/min. The temperature of the dialysate was held at 37°C.

Calculations. Analysis of the data was carried out via model-independent methods. The biological half-life was estimated from the relation $t_{1/2}(\beta) = 0.693/\beta$, where β is the slope of the terminal phase of the ln (serum concentration)-versus-time plot. β was estimated by linear least-squares regression. The apparent volume of distribution for netilmicin (V_{Net}, milligrams per kilogram) for the 20 subjects who were not on hemodialysis was calculated from the formula V_{Net} = netilmicin dosage/β AUC$\{o,\infty\}$, where AUC$\{o,\infty\}$ is the area under the serum concentration – time curve (o,∞). AUC$\{o,\infty\}$ was estimated via the formula AUC$\{o,T\}$ + CT/β, where AUC$\{o,T\}$ is the area estimated by the trapezoidal rule to time T and CT is the estimated serum concentration at the last sampling time. The serum clearance of netilmicin (ml/min) for the same twenty subjects was calculated from the formula $C_{Net} = V_{Net} \cdot \beta$. Dialyzer clearances were calculated from the relationship $C_x = [(A_x - V_x)/A_x]\ Q$, where C_x is clearance of substance x in milliliters per minute, A_x and V_x are arterial (inflow) and venous (outflow) concentrations of x, respectively, and Q is flow in milliliters per minute. Urea clearances (C_u) were determined by means of blood flow rates (Q_b), whereas netilmicin clearances (C_{Net}) were calculated from plasma flow rates (Q_P), where $Q_P = (Q_b)$ (1 - hematocrit). Q_b was measured with an electronic flow meter (Ward Associates, San Diego, Calif.). Correction of the clearance measurements for ultrafiltration were not attempted since the total influence of ultrafiltration on clearance is minimal (7). Statistical analysis was conducted by means of least-squares linear regression. Ninety-five percent confidence limits were generated for the prediction equations defining best fit and are represented by dashed lines in the figures.

RESULTS

The distribution of patients according to age and sex is given in Table 1. The mean netilmicin serum concentrations at each sampling period for the four groups of subjects are shown in Table 2. Mean peak serum concentrations at the time the infusion was terminated were approximately 11.0 μg/ml for group 1 and approximately 9.0 μg/ml for the other three groups.

Table 3 summarizes the mean kinetic parameters determined in this study. The Ccr was correlated with the overall elimination rate constant (β), the serum clearance (C_{Net}), and the volume of distribution (V_{Net}). The regression lines outlined in Fig. 1, 2, and 3 illustrate the relationship between these parameters and the Ccr. The equations defining the lines of best fit are as follows:

$$\beta = -0.013 + 0.003(\text{Ccr}), \quad r = 0.85, \quad P < 0.0001 \qquad (1)$$

$$C_{Net} = 3.72 + 0.65(\text{Ccr}), \quad r = 0.90, \quad P < 0.0001 \qquad (2)$$

$$V_{Net}(\text{area}) = 353.7 + (-1.7)(\text{Ccr}), \quad r = -0.83, \quad P < 0.0001 \qquad (3)$$

Since the elimination constant can be approximated by β = 0.003 Ccr, it follows that the biological half-life can be estimated from the relationship $t_{1/2} = 230/\text{Ccr}$.

TABLE 1. *Distribution of patients by age, sex, and creatinine clearance*

Group	No.	Age (yr)		Sex	
		Mean	Range	M	F
1, Ccr ≥ 70	7	41	25–78	7	0
2, Ccr < 70 ≥ 25	7	62	19–90	6	1
3, Ccr < 25 ≥ 4	6	61	42–83	5	1
Group 4[a]	5	44	37–55	1	4

[a] Anephric hemodialysis patients.

TABLE 2. *Mean serum concentrations of netilmicin (2 mg/kg)*

Time	Mean serum concn (μg/ml, ± standard deviation)			
	Group 1	Group 2	Group 3	Group 4
15 min	4.5 ± 1.1	2.5 ± 1.2	2.8 ± 0.7	4.3 ± 0.4
30 min	8.0 ± 1.6	4.4 ± 1.6	4.8 ± 1.2	6.9 ± 0.6
60 min	10.8 ± 1.6	8.7 ± 3.3	8.6 ± 1.2	9.2 ± 1.0
62 min	10.7 ± 1.8	7.4 ± 2.8	8.1 ± 1.5	9.0 ± 1.4
65 min	10.2 ± 2.7	6.8 ± 3.6	7.9 ± 0.7	9.2 ± 0.9
70 min	10.7 ± 2.1	6.8 ± 2.2	7.4 ± 0.3	8.6 ± 0.8
90 min	9.0 ± 2.7	6.4 ± 3.2	7.0 ± 0.7	8.2 ± 1.5
2 h	6.9 ± 2.1	6.1 ± 1.0	5.8 ± 1.0	7.3 ± 0.8
4 h	3.2 ± .4	4.9 ± 1.2	5.3 ± 1.0	6.4 ± 0.4
6 h	1.7 ± 0.5	3.8 ± 1.2	4.7 ± 0.9	6.5 ± 0.8
8 h	1.2 ± 0.6	3.4 ± 1.2	4.9 ± 0.8	6.3 ± 0.6
12 h	0.5 ± 0.5	2.5 ± 1.9	4.6 ± 0.9	5.8 ± 0.7
24 h		1.1 ± 0.8	3.2 ± 0.9	5.3 ± 0.6
36 h		0.5 ± 0.5	2.8 ± 0.4	4.4 ± 0.4
48 h		0.4 ± 0.3	2.2 ± 0.3	4.5 ± 1.1
72 h			1.0 ± 0.3	—[a]

[a] —, Interdialytic interval comprised 48 h.

TABLE 3. *Mean kinetic parameters (± standard deviation) for 20 non-dialysis subjects*

Group	β (h^{-1})	$T_{1/2}$ (h)	V_{Net} (area) (ml/kg)	C_{Net} (ml/min)
1	0.29 ± 0.10	2.7 ± 1.2	192 ± 52	68 ± 14
2	0.08 ± 0.04	10.0 ± 4.8	322 ± 90	28 ± 10
3	0.02 ± 0.01	31.9 ± 7.2	340 ± 51	9 ± 2

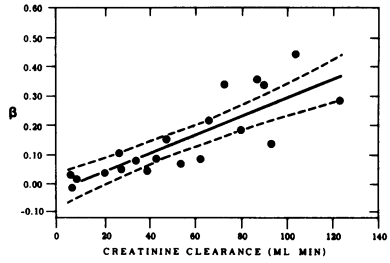

FIG. 1. *Positive correlation between the elimination constant β and Ccr.*

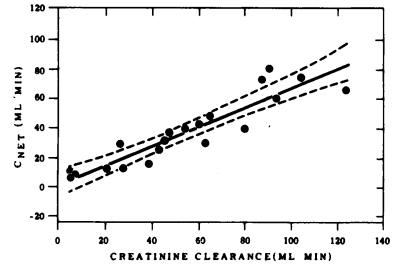

FIG. 2. *Positive correlation between the serum clearance (C_{Net}) and Ccr.*

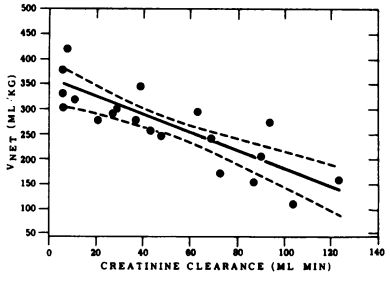

FIG. 3. *Inverse correlation between the volume of distribution (V_{Net}) and Ccr.*

The volume of distribution decreased with increasing Ccr. Design of a dosage regimen requires adjustments in the design to allow for this phenomenon. A dosage nomogram was constructed with this consideration and is presented in Table 4 (17). After an appropriate initial loading dose based on body weight, a patient with renal impairment would be dosed at the same interval as for normal subjects (e.g., 8 h) at the reduced dose indicated. The criterion used in constructing the dosing guide was that the average steady-state serum concentration in patients with renal impairment be equal to the average steady-state rate concentration in normal patients.

Mean values for the cumulative amount (percentage of dose administered) of netilmicin recovered in the urine are given in Table 5. One subject in the first group failed to collect a 24-h urine specimen on day 3, accounting for the apparent decrease in the cumulative urinary excretion. The degree of renal impairment was reflected by the percentage of dose recovered in the urine. By day 1, 70% was recovered in the urine for group 1; for group 2, 70% was recovered by day 3 (last day of collection); and for group 3, 36% of the dose administered was recovered in the urine by day 3.

The clearance of netilmicin during hemodialysis, C_{Net}, with the UF-2 dialyzer was correlated with the plasma flow rate (Q_P). The relationship between C_{Net} and Q_P is shown in Fig. 4. By least-squares regression, the relationship between the two variables is as follows: $C_{Net} = 17.10 + 0.12\ (Q_P)$, $r = 0.65$, $P < 0.0002$. The relationship between the clearance of blood urea nitrogen (C_{BUN}) and blood flow through the

TABLE 4. *Dosage adjustment guide for patients with renal impairment*[a]

Ccr	$t_{1/2}$ (h)	% of initial dose
>100		100
70–100	2.9	86
55–70	4.0	65
45–70	5.1	53
40–55	6.1	46
35–40	7.0	41
30–35	8.2	36
25–30	10.0	31
20–25	12.7	27
15–20	17.5	22
10–15	28.3	17
<10	42.0	10

[a] Adjusted doses were calculated from the relation

$$D_r = \frac{(V_d \text{ area})r \cdot \beta_r}{(V_d \text{ area})n \cdot \beta_n} \cdot D_n = \frac{(\text{serum clearance})r}{(\text{serum clearance})n} \cdot D_n$$

where D_r and D_n = doses in impaired and normal subjects, respectively. To estimate (serum clearance)n, a creatinine clearance of 100 ml/min was used (16).

TABLE 5. *Mean (± standard deviation) cumulative percentage of dose recovered in urine*

Group	Day 1	Day 2	Day 3
1	70.3 ± 37.1	75.5 ± 34.3	72.2 ± 35.2[a]
2	41.2 ± 10.8	58.8 ± 13.3	70.6 ± 11.2
3	15.0 ± 8.1	26.8 ± 14.0	35.7 ± 15.6

[a] One subject failed to collect urine specimen on day 3.

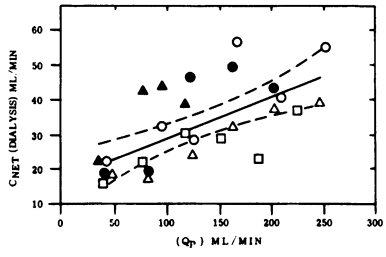

FIG. 4. *Dialyzer clearance (C_{Net}) was positively correlated with plasma flow (Q_P). The symbols correspond to each individual patient.*

dialyzer (Q_b), measured at the same time, was also highly correlated and is defined by the expression: $C_{BUN} = 11.6 + 0.497\ (Q_b)$, $r = 0.95$, $P < 0.0001$. The clearance of blood urea nitrogen and netilmicin were correlated according to the expression: $C_{Net} = 17.6 + 0.160\ (C_{BUN})$, $r = 0.57$, $P < 0.002$.

The complete blood counts and serum chemistries obtained yielded values commensurate with the degree of renal dysfunction. No differences were observed in these measurements after the netilmicin infusions. Netilmicin caused no measurable effects or reactions in any of the subjects.

DISCUSSION

The complexities of aminoglycoside pharmacokinetics have recently been emphasized by Schentag et al. (16), who identified a second half-life for tobramycin and gentamicin that did not correlate with renal function. Their patients were studied after multiple doses, by means of a highly sensitive radioimmunoassay which was capable of detecting very low "washout" serum concentrations (<0.25 μg/ml). They were able to explain both the increasing peak and trough concentrations observed during treatment and the detection of the drug in serum and urine long after the last dose, by means of a two-compartment model. The purpose of the present study was to describe the half-life of netilmicin dependent upon renal function so that therapeutic guidelines could be formulated. We found the model independent methods of analysis were best suited for our data.

The results of the present study suggest that the elimination of netilmicin resembles that of other aminoglycoside antibiotics in that it is a function of the glomerular filtration rate (2, 5, 12, 13). Similar results were obtained by Welling et al. (18) who gave netilmicin to elderly men with normal and impaired Ccr's as low as 20 ml/min. Our results correspond very closely to theirs. The relationship they obtained between β and the Ccr after a 2-mg/kg intravenous injection was $\beta = -0.01 + 0.003$(Ccr), almost identical to our own calculation (Fig. 1).

The serum clearance of netilmicin in normal subjects was 68 ml/min, approximately 60% of the Ccr. This value is similar to clearances reported for amikacin (13) and kanamycin; however, it is greater than that reported for sisomicin (12). The gentamicin clearance, measured directly in a group of normal subjects, was 61 ml/min, also approximately 60% of the Ccr (11). Since the non-renal clearance of aminoglycosides is extremely low (Table 4) and since protein binding is minimal or absent (4), it is likely that tubular reabsorption occurs.

The apparent volume of distribution of netilmicin, 20 to 30% of body weight, is similar to those reported for sisomicin (12), gentamicin, and tobramycin (14). We observed an inverse relationship between the volume of distribution and the Ccr. The same phenomenon was reported by Welling et al. (18). The reason for the increase in netilmicin distribution volumes with decreasing renal function is not clear. Although aminoglycosides accumulate in tissue, primarily in renal cortex (5), the renal accumulation of the aminoglycoside gentamicin is sharply reduced in patients with chronic renal failure (3). An increase in the tissue distribution of netilmicin in patients with chronic renal failure therefore appears unlikely. Although few of the patients with renal insufficiency who participated in the present study were frankly edematous, attempts were made to expand extracellular fluid volume and hence circulating fluid volume in order to maximize renal function. It is possible that the increased volume of distribution of netilmicin observed in these patients was a result of therapeutic measures used in the course of their renal failure management.

The linear relationship between the elimination constant and the Ccr allowed for the construction of a useful monogram. We have recommended altering the dose rather than the interval of administration; however, the relationship $t_{1/2} = 230/\text{Ccr}$ provides a convenient method of altering the interval instead. Netilmicin is given approximately every third half-life. The new half-life may be estimated from the formula and the new dosage interval calculated accordingly.

In normal subjects, 70% of the administered netilmicin was recovered in the urine during the first 24 h. In a similar study, the recovery of gentamicin after a single intramuscular injection was 74% in 24 h (5). Seventy percent of the netilmicin was recovered from those with moderate renal impairment in 3 days, whereas only

36% could be recovered during that time from subjects with severe renal failure. The low urine recovery rate is a consequence of the long serum half-life and the limited amount of timed urine data collected.

The clearance of netilmicin during hemodialysis was examined with only one type of dialyzer, the UF-2. Although there was considerable variability, the results were comparable to those reported for gentamicin with the UF-2 dialyzer (6), suggesting that the characteristics of the two drugs, with respect to dialysis, are similar. The clearance of netilmicin varies directly with the plasma flow rate in a linear fashion over the flow range clinically used. The amount of netilmicin removed by dialysis is not only a function of the plasma flow rate, but also of the length of the procedure. Therapeutic adjustments will be required with respect to both of these parameters. Assuming a volume of distribution approximating 340 ml/kg, a 70-kg patient undergoing a 5-h dialysis at a plasma flow rate of 200 ml/min would have a netilmicin clearance approaching 12 liters for that time interval. Therefore, with a standardized dialysis, 50% of the netilmicin may be lost. If the dialysis patient is initially given a 2-mg/kg loading dose of netilmicin, and subsequently receives the drug in "anephric" doses during the interdialytic period, at least one-half of the initial loading dose of 1 mg/kg would be required after dialysis. In such circumstances, as with any drug with a fairly narrow therapeutic margin of safety, serum concentrations should be monitored.

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