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# Pharmacokinetics of Netilmicin in the Presence of Normal or Impaired Renal Function

G. HUMBERT,* A. LEROY, J. P. FILLASTRE, AND G. OKSENHENDLER

*Departments of Infectious Diseases and Nephrology, University of Rouen-School of Medicine, Charles Nicolle Hospital, F 76038, Rouen, France*

Received for publication 25 November 1977

A pharmacokinetic study of netilmicin was conducted in 12 healthy subjects and 24 subjects with chronic renal failure. After intramuscular administrations of 2 and 3 mg of netilmicin per kg in normal subjects, the mean peak serum concentrations were 5.46 and 8.83 μg/ml, respectively. After intravenous infusions of identical doses, the mean maximum serum levels, occurring at the end of the infusion, were 11.79 and 15.75 μg/ml, respectively. The pharmacokinetic data were very similar via the two routes of administration and for the two doses. The elimination half-life was 2.20 h, and 80 to 90% of the injected dose was recovered in urine during the first 24 h. After intramuscular administration of 2 mg/kg in subjects with chronic renal impairment, the elimination half-life increased to 29.48 h, and urinary elimination was inversely related to the degree of impairment. A study was conducted throughout hemodialysis sessions: serum concentrations decreased by 63.3%. The linear relationships between the elimination rate constant and creatinine clearance and the elimination half-life and serum creatinine allowed us to establish dosage schedules according to the degree of renal failure.

Netilmicin (1-*N*-ethylsisomicin) is a new semisynthetic aminoglycoside derived from the dehydrogenation of gentamicin $C_{1A}$. In vitro studies have shown that the spectrum of activity of netilmicin is similar to that of gentamicin, but it is effective against some strains resistant to gentamicin, including indole-negative *Proteus* and strains that produce aminoglycoside-adenylating enzymes (6, 12). In addition, subacute toxicity studies performed in animals reveal that it is distinctly less nephro- and ototoxic than gentamicin (10; *Information material for the investigation drug SCH 20569,* Schering Corp., Bloomfield, N. J., 1975).

This study was designed to define the pharmacokinetics of netilmicin in subjects with normal renal function and patients with varying degrees of chronic renal insufficiency.

## MATERIALS AND METHODS

Thirty-six subjects were selected for the study after informed consent was obtained; 12 had normal renal function, and 24 had chronic renal impairment of various etiologies.

**Subjects with normal renal function.** After an overnight fast, six subjects with normal renal function, ranging in age from 23 to 39 years (27.1 ± 5.1) and in weight from 65.0 to 70.0 kg (67.6 ± 2.2), were given a single intramuscular dose of netilmicin, 2 mg/kg, and, 1 week later, the same dose as a 30-min intravenous infusion. Six other subjects, ranging in age from 24 to 29 years (26.7 ± 1.9) and in weight from 68.0 to 82.0 kg (75.2 ± 4.9), received 3-mg/kg doses intramuscularly and by intravenous infusion under the conditions indicated above. Blood samples were obtained during the intramuscular test at 0, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 12 h and during the intravenous study at 0, 0.25, 0.50 (end of the infusion), 0.58, 0.67, 0.75, 0.83, 1, 1.25, 1.50, 2, 3, 4, 6, 8, and 12 h. Urine samples were collected at six time intervals: 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 12 to 24 h.

**Subjects with chronic renal insufficiency.** Twenty-four patients with chronic renal insufficiency, 27 to 85 years of age and weighing 48 to 95 kg, were given a single intramuscular injection of netilmicin, 2 mg/kg. Six of these subjects required hemodialysis. The subject's renal functions are outlined in Table 1. In the 18 subjects with creatinine clearances between 5 and 80 ml/min, blood specimens were taken at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h. Further samples (36, 48, and 72 h) were drawn according to the severity of renal insufficiency. Urine samples were collected at 0 to 2, 2 to 6, 6 to 12, 12 to 24, 24 to 48, and 48 to 72 h after dosage. The six subjects requiring hemodialysis received the intramuscular injection of netilmicin 12 h before the extrarenal purification. Blood samples were taken at 0 (beginning of hemodialysis), 0.5, and 1 h and at each hour thereafter throughout the hemodialysis session. Coil dialyzers (UF 140 and EX 01) and Gambro multilayered dialyzers with a single-pass dialysis system were used. Blood flow was within 180 and 250 ml/min, and dialysate flow was held constant at 750 to 1,000 ml/min.

**Antibiotic assay.** Serum and urine concentrations

of netilmicin were determined by the agar diffusion method, using *Bacillus subtilis* ATCC 6633 as the test strain (2, 5). Assays were performed in triplicate. The confidence limits of the method were within 4 and 6% for all samples.

**Creatinine measurements.** Creatinine measurements in urine and serum were determined by the colorimetric method of Jaffe (1).

**Pharmacokinetic analysis.** Programs written for a Hewlett-Packard (HP 65) programmable digital calculator (50326, 50327, 50330, and 0417) were used to analyze the pharmacokinetic data. The data were fitted to two regression lines, and the following pharmacokinetic parameters, based on a two-compartment, open-body model (9), were calculated: half-life ($T_{1/2}$) of the distribution phase ($\alpha$) and $T_{1/2}$ of the elimination phase ($\beta$), total apparent volume of distribution, renal clearance, and bioavailability of netilmicin (percentage, calculated by comparison between total areas under the serum concentrations versus time curve in the two routes of administration).

## RESULTS

**Subjects with normal renal function.** In subjects with normal renal function, after intramuscular or intravenous injection of netilmicin the pharmacokinetic data were quite similar. After 2- and 3-mg/kg doses, in the intramuscular study, the mean peak serum levels were 5.46 ± 0.55 (mean ± standard deviation) and 8.83 ± 0.73 μg/ml, respectively, and occurred at 0.5 or 1 h after injection; in the intravenous study, the average maximum serum concentrations were 11.79 ± 1.27 and 15.75 ± 1.80 μg/ml, and the mean $T_{1/2}\alpha$'s were 0.26 ± 0.05 and 0.33 ± 0.16 h, respectively. In both studies, $T_{1/2}\beta$ was within 2.14 ± 0.06 and 2.40 ± 0.32 h; the apparent volume of distribution was about 0.250 liter/kg. Of the injected dose, 60 to 70 and 80 to 90% were recovered in urine during the first 6 and 24 h, respectively; renal clearance of netilmicin was about 80 ml/min per 1.73 $m^2$, i.e., 60% of the creatinine clearance; bioavailability of netilmicin was within 83 and 92%.

**Subjects with chronic renal insufficiency.** Subjects with chronic renal insufficiency received a single intramuscular dose of 2 mg/kg, and the results are given in Table 1 and Fig. 1. Peak serum levels increased with greater renal impairment (9.60 μg/ml in subject 19), but this difference was not statistically significant ($0.10 < P < 0.20$). The increase in $T_{1/2}\beta$ from 1.94 to 29.48 h was particularly pronounced when the creatinine clearance fell below 30 ml/min per 1.73 $m^2$ (Fig. 2). Renal insufficiency did not significantly modify the apparent volume of dis-

TABLE 1. *Renal function, serum, and urine data of normal (1 through 7) subjects and uremic (8 through 24) subjects after a single intramuscular dose of 2 mg of netilmicin per kg*

| Subject | Creatinine | | | Netilmicin | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Clearance[a] (ml/min per 1.73 $m^2$) | Serum (mg/%) | Peak serum level (μg/ml) | $T_{1/2}\beta$ (h) | $\beta$Ln2 ($h^{-1}$) $T_{1/2}\beta$ | Vol of distribution (liter/kg) | % Excreted in urine | | Renal clearance[a] (ml/min per 1.73 $m^2$) |
| | | | | | | | 0 to 24 h | 0 to 48 h | |
| 1 | 155.6 | 0.70 | 6.40 | 2.40 | 0.284 | 0.358 | 62.6 | | 64.5 |
| 2 | 102.8 | 1.00 | 5.40 | 2.43 | 0.286 | 0.285 | 68.3 | | 64.0 |
| 3 | 164.1 | 0.70 | 5.20 | 1.94 | 0.357 | 0.201 | 80.3 | | 116.3 |
| 4 | 135.8 | 0.80 | 5.52 | 2.16 | 0.321 | 0.258 | 90.0 | | 103.3 |
| 5 | 139.8 | 0.80 | 5.52 | 2.32 | 0.299 | 0.245 | 70.4 | | 61.7 |
| 6 | 180.6 | 0.70 | 4.72 | 2.10 | 0.330 | 0.195 | 83.3 | | 90.8 |
| 7 | 81.8 | 0.95 | 5.12 | 3.35 | 0.207 | 0.341 | 44.3 | | 32.9 |
| 8 | 77.1 | 1.85 | 6.40 | 7.30 | 0.095 | 0.349 | 61.9 | | 22.8 |
| 9 | 53.3 | 1.20 | 6.64 | 4.43 | 0.156 | 0.300 | 66.2 | | 28.3 |
| 10 | 48.9 | 1.25 | 8.00 | 5.17 | 0.134 | 0.282 | 44.4 | | 20.7 |
| 11 | 39.5 | 1.45 | 5.48 | 7.59 | 0.091 | 0.338 | 54.8 | | 24.2 |
| 12 | 32.1 | 1.90 | 6.40 | 6.33 | 0.109 | 0.274 | 54.9 | | 20.8 |
| 13 | 27.4 | 3.30 | 7.97 | 14.64 | 0.047 | 0.257 | 25.9 | 35.7 | 6.0 |
| 14 | 19.6 | 8.25 | 7.76 | 17.58 | 0.039 | 0.277 | 30.5 | 44.7 | 6.7 |
| 15 | 18.5 | 2.50 | 3.68 | 15.07 | 0.046 | 0.588 | 29.5 | 45.4 | 10.3 |
| 16 | 16.4 | 4.55 | 8.00 | 14.00 | 0.050 | 0.306 | 27.7 | 50.3 | 9.4 |
| 17 | 11.8 | 6.85 | 5.52 | 24.61 | 0.028 | 0.371 | | | |
| 18 | 11.7 | 7.35 | 8.00 | 26.09 | 0.027 | 0.328 | 21.2 | 33.5 | 4.6 |
| 19 | 8.5 | 6.45 | 9.60 | 16.22 | 0.043 | 0.202 | 27.6 | 41.3 | 3.8 |
| 20 | 7.4 | 7.75 | 5.64 | 28.96 | 0.024 | 0.338 | 14.7 | 26.5 | 3.2 |
| 21 | 6.5 | 13.20 | 6.32 | 29.48 | 0.023 | 0.357 | 15.7 | 27.7 | 4.1 |
| 22 | 5.5 | 10.00 | 5.04 | 24.97 | 0.028 | 0.395 | 7.1 | 15.8 | 1.9 |
| 23 | 4.6 | 12.75 | 7.60 | 24.80 | 0.028 | 0.318 | 11.5 | 17.2 | 2.0 |
| 24 | 4.6 | 9.05 | 8.16 | 24.37 | 0.028 | 0.238 | 11.2 | 17.8 | 2.7 |

[a] Creatinine clearance and renal clearance were calculated during the same time intervals of the study.

tribution ($P < 0.20$). Urinary elimination was inversely related to the degree of impairment, since 62.6 to 90.0% of the injected dose in normal subjects and 7.1 to 15.7% in severely uremic patients (subjects 20 through 24) were recovered in urine during the first 24 h. However, urinary concentrations were above the minimum inhibitory concentration of netilmicin-susceptible bacteria in patients with creatinine clearances higher than 10 ml/min. In patients requiring hemodialysis, pharmacokinetics study during a 7- to 8-h dialysis session showed a mean serum concentration decrease of 63.3 ± 9.0% and a mean $T_{1/2}\beta$ of 5.49 ± 0.72 h (Fig. 3). Various dialysis systems were used (UF 140, EX 01, and Gambro multilayered dialyzers), and significant differences were observed according to the dialyzer used. For the UF 140 coil dialyzers, $T_{1/2}\beta$'s were shorter than those found for the other dialyzers. Since, like other aminoglycosides, netilmicin is a "middle molecule" and since blood and dialysate flow were held constant for all patients, membrane surface area may play an important role in the elimination of netilmicin during the session (3).

## DISCUSSION

**Subjects with normal renal function.** Our pharmacokinetics data are quite similar to those found by other authors (4, 11, 13, 15; F. C. Luft, D. E. Brannon, L. L. Stropes, R. S. Sloan, and D. R. Maxwell, Program 10th Int. Cong. Chemother., Zurich, Switzerland, Abstr. no. 333, 1977; J. C. Pechere and R. Dugal, Program 10th Int. Cong. Chemother., Zurich, Switzerland, Abstr. no. 332, 1977). Thus, netilmicin behaves in a fashion similar to other aminoglycosides already in clinical use (7, 8).

**Patients with chronic renal insufficiency.** In patients with chronic renal insufficiency, the increase in the $T_{1/2}\beta$ of netilmicin seemed to be less than those of other aminoglycosides we have so far studied. In patients with creatinine clearances lower than 10 ml/min, we found the $T_{1/2}\beta$'s of lividomycin, amikacin, and sisomicin to be 40.20, 58.09, and 56.98 h, respectively (7). In our patients, renal insufficiency did not significantly modify the apparent volume of distribution. However, Luft et al. (Program 10th Int. Cong. Chemother., Zurich, Switzerland, Abstr. no. 333, 1977) found that the volume of distribution was inversely related to the creatinine clearance and was 30% greater in subjects with very severe renal impairment as compared with normal subjects.

By least-squares regression, linear relationships between the elimination rate constant ($\beta$) and creatinine clearance (Ccr)—$\beta$ ($h^{-1}$) = 0.002

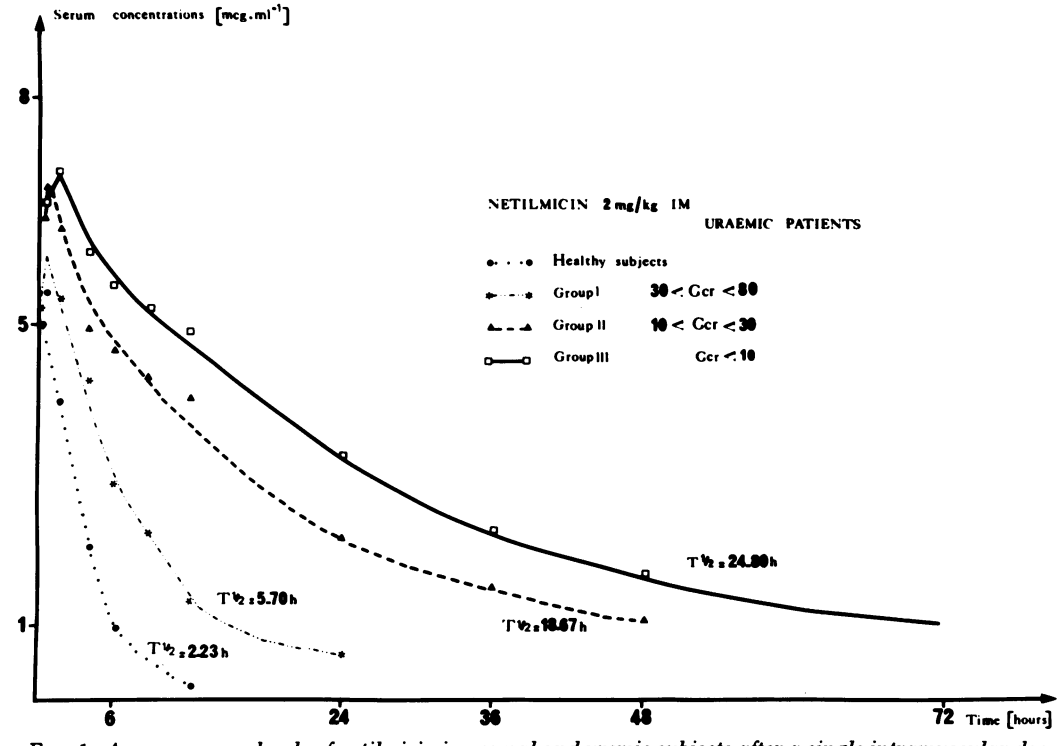


FIG. 1. *Average serum levels of netilmicin in normal and uremic subjects after a single intramuscular dose of 2 mg/kg. Uremic groups' creatinine clearances (Ccr) are given in milliliters per minute per 1.73 $m^2$.*

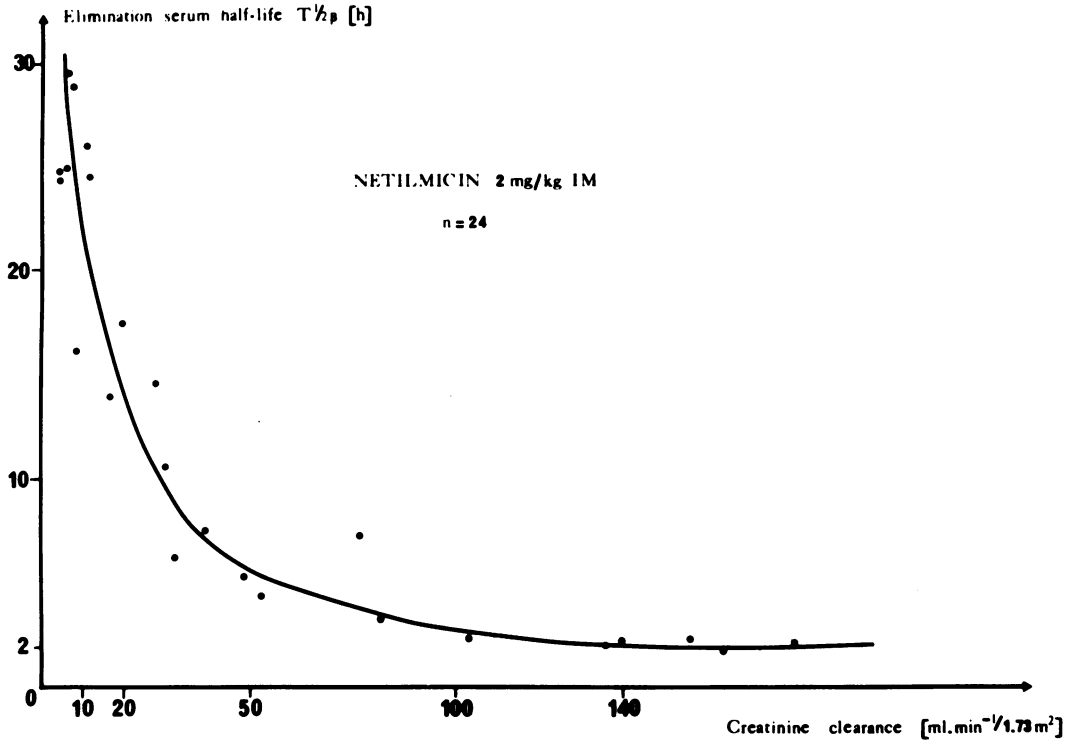


FIG. 2. *Relationship between netilmicin $T_{1/2}\beta$ and creatinine clearance in normal and uremic subjects.*

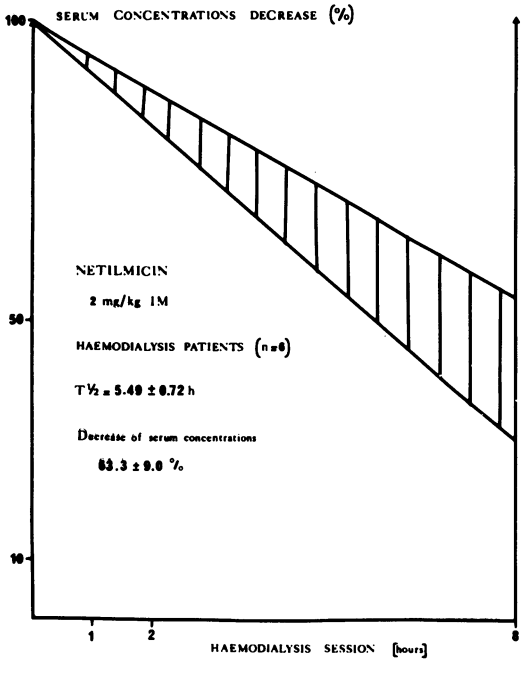


FIG. 3. *Netilmicin serum concentration decrease during hemodialysis sessions after a single intramuscular dose of 2 mg/kg.*

Ccr (ml/min) + 0.017, ($n$ = 24, $r$ = 0.970, $P <$ 0.001)—and $T_{1/2}\beta$ and serum creatinine $T_{1/2}\beta$ (h) = 2.275 creat (mg/%) + 2.865 ($n$ = 24, $r$ = 0.924, $P < 0.001$)—C(creat)— provided a basis for dosage adjustment in subjects with renal function impairment.

In subjects with normal renal function, we suggest an intramuscular or intravenous dose (over 30- or 60-min infusion) of 2 mg/kg every 8 or 12 h, according to the minimum inhibitory concentrations for most susceptible gram-negative bacilli. In the treatment of urinary infections, since drug concentrations were adequate until the 12-h sample after a 2-mg/kg injection (20 μg/ml), a dose of 2 mg/kg intramuscularly every 12 h seems to be sufficient. In subjects with chronic renal insufficiency, to avoid accumulation of the antibiotic it is necessary to extend the interval between doses and so to inject a dose of 2 mg/kg intramuscularly every three $T_{1/2}$s (14); the $T_{1/2}$ is calculated by using the correlations earlier described. Last, concerning patients undergoing chronic hemodialysis, a dose of 2 mg/kg at the end of each extrarenal purification session should be sufficient to maintain effective antibiotic concentrations between sessions, i.e., generally twice weekly.

All these suggestions are tentative, however,

pending their verification in clinical trials. But in the case of extended administration of netilmicin, serum concentrations must be regularly checked to maintain effective and nontoxic serum levels during the treatment. This is all the more true because of the predisposition of uremic patients to dehydration, severe infections, and hypertension, as well as possible previous extended treatment by aminoglycosides and preexisting damage to the cochlea and vestibule.

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