

Netilmicin and Gentamicin: Comparative Pharmacology in Humans

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Thirteen male subjects received 1 mg of either gentamicin or netilmicin per kg, first intramuscularly and then intravenously. After the intramuscular dose, concentrations of gentamicin in the serum were more variable than those of netilmicin. After the intravenous dose, the distribution phase of netilmicin was twice as rapid as gentamicin. The average half-times of the elimination phase were similar, but there was marked variability among the subjects receiving gentamicin. Serum clearance of netilmicin was more rapid than that of gentamicin and could not be attributed to renal elimination. The data indicate that, after intramuscular administration, netilmicin may produce more predictable blood levels than gentamicin and suggest that the body distribution of netilmicin may differ from that of gentamicin.

Netilmicin is a new semisynthetic aminoglycoside (32). Netilmicin is *N*-ethyl sisomicin, with the substituent attached to 2-deoxystreptomine. Another aminoglycoside in clinical use with a substitution on 2-deoxystreptomine is amikacin, a hydroxyaminobutyric acid derivative of kanamycin A. In vitro testing in our laboratory and others (8-10, 20, 23, 27, 31) indicates that the activity of netilmicin against *Enterobacteriaceae*, *Pseudomonas*, and *Staphylococcus*, in general, approximates that of gentamicin. Serum concentrations in animals and humans are comparable to those of gentamicin (27).

Netilmicin appears to have two advantages. First, like amikacin, it is effective against some organisms resistant to gentamicin, including indole-negative proteus and strains that produce aminoglycoside-adenylating enzymes (16, 23). Second, animal studies indicate that netilmicin has significantly less oto- and nephrotoxicity than does gentamicin (19, 27; R. E. Brummett and K. E. Fox, Fed. Proc. 35:621, 1976). If reduced toxicity is also found in humans, it will strongly influence the relative usefulness of this agent.

Netilmicin is now in the early stages of therapeutic evaluation, and expanded information concerning its pharmacology will be of benefit to physician investigators and their patients. For this reason, we have investigated the disposition of netilmicin in humans.

MATERIALS AND METHODS

Thirteen adult male graduate students were used in our study. The subjects underwent a complete

medical history and psychological evaluation; physical examination; determination of base line blood chemistries (chloride, carbon dioxide, potassium, sodium, blood urea nitrogen and glucose, total protein, serum albumin, calcium, inorganic phosphorus, cholesterol, uric acid, creatinine, total bilirubin, alkaline phosphatase, creatine phosphokinase, lactic dehydrogenase, serum glutamic oxaloacetic transferase); complete blood count; urinalysis, including microscopic urinalysis and determination of creatinine clearance. All subjects were judged free from any recognizable illness by the above parameters. The experimental design of the project and the drugs used were explained, and informed consent was obtained from each individual. The study was approved by the Human Investigation Committee of the University.

With a preselected division of two groups, six gentamicin and seven netilmicin, the men were randomly assigned, single blind, to either group. The men receiving gentamicin had an average weight of 69.4 kg (range, 56 to 90 kg), and those receiving netilmicin had an average weight of 77.5 kg (range, 70 to 90 kg). None of the individuals was obviously under- or overweight. For the subjects receiving gentamicin the mean body surface area was 1.84 m², and for those receiving netilmicin it was 1.94 m². The mean age for both groups was 24 years (range, 22 to 27 years). Two of the men withdrew from the project after the intramuscular (i.m.) dose because of time pressures related to final examinations. Parenteral gentamicin, 40 mg/ml, and parental netilmicin, 100 mg/ml, were supplied specifically for this study by Schering Corp., Bloomfield, N.J. Each drug was given in a dose of 1 mg/kg of subject weight, first by i.m. injection into the deltoid and then by intravenous (i.v.) administration into a forearm vein, with a minimum of 1 week between doses (range, 7 to 41 days). The i.v. dose was given over 3 to 5 min in a side arm rider of 50 ml of normal

saline. Before and after each dose, a general symptom review, blood pressure, oral temperature, and complete urinalysis were obtained. The morning after a dose, the subject returned for urinalysis, evaluation of auditory and labyrinthine function, blood chemistries, and complete blood count. A 16-h overnight urine collection was used to determine creatinine clearance.

For the i.m. injection, blood samples for serum drug concentration were obtained predose and at 10, 20, 30, 40, 60, and 90 min and 2, 3, 4, 5 or 6, and 7.5 h after drug administration. For the i.v. dose, blood samples were obtained predose, at 10-min intervals for h 1, 20-min intervals for h 2, at hourly intervals until 6 h, and at 7.5 h. Blood samples were collected in red-top Vacutainer-brand tubes, which are silicon coated, but do not contain anticoagulant. Urine was collected immediately prior to the dose, and the total urinary output from each subject was collected in timed portions; urinary concentrations of drug were measured at 1, 2, 4, 6, 8, 16, and 24 h after each dose.

Laboratory. Serum samples were separated, frozen at -20°C , and assayed within 1 to 6 days. Portions of urine collections were treated similarly. Assays were performed by the agar well diffusion technique (18, 26), using Mueller-Hinton agar (Difco) seeded with *Bacillus subtilis* spores. Standards for either gentamicin or netilmicin were used on each assay plate in concentrations of 1.2, 2.5, 5, 10, and 20 $\mu\text{g}/\text{ml}$. Portions of a stock solution of laboratory standard assay powder (gentamicin and netilmicin, supplied by Schering Corp., Bloomfield, N.J.) at 2,000 $\mu\text{g}/\text{ml}$ of water were stored at -20°C . The standard solutions were freshly diluted in 100% human serum (Grand Island Biological Co., Grand Island, N.Y.) immediately prior to assay. Each urine assay plate contained standards of 3.1, 6.2, 12.5, 25, and 50 μg of the appropriate drug per ml, prepared by diluting stock solution in phosphate buffer, pH 8.0, that had previously been determined to give the same diffusion characteristics as human urine. Each serum and urine sample was determined in triplicate.

Analysis. The formulas and methods of Wagner (30) and Greenblatt and Koch-Weser (14) were used for the pharmacokinetic analyses. The "stripping" technique was used to determine the rate constants for the serum concentration curves after i.v. administration. The statistical analyses used are those of Batson (3).

RESULTS

i.m. administration. Figure 1 shows the average and range of observed serum concentrations for 8 h after i.m. administration of a 1-mg/kg dose. For most of the time points, the subjects given gentamicin exhibited a broader range of serum concentrations than did those receiving netilmicin.

The average peak serum concentration was identical for both drugs, 3.76 $\mu\text{g}/\text{ml}$. However, the time to achieve peak serum concentration

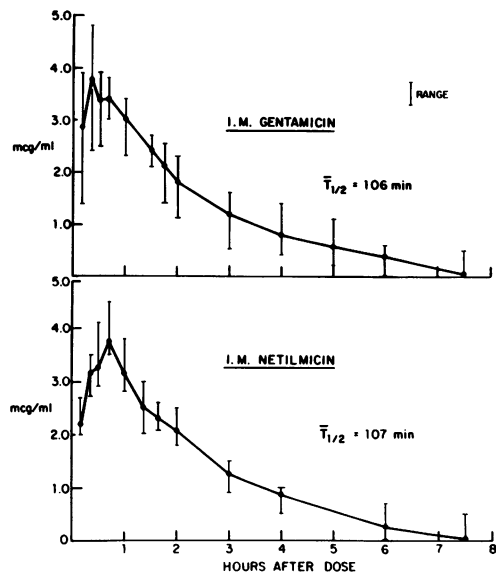


FIG. 1. Average and range of serum concentrations after i.m. administration of netilmicin (seven subjects) and gentamicin (six subjects). The dose for each drug was 1 mg/kg of body weight.

was different for the two drugs. For four of the six subjects receiving gentamicin, the peak serum concentration occurred at 20 min, one occurred at 10 min, and one occurred at 40 min. Of the seven subjects who received netilmicin, one occurred at 30 min, and six had peak serum concentrations at 40 min.

After the peak concentration was achieved, the elimination half-life ($T_{1/2}$) was the same for both drugs. The individual $T_{1/2}$ values, based on $n = 7$ to 11 points for each subject, demonstrated more variability for gentamicin than for netilmicin. For gentamicin, the $T_{1/2}$ ranged from 64 to 131 min; for netilmicin, the $T_{1/2}$ ranged from 79 to 117 min. The average time from the injection of dose to 50% of the peak level was approximately 2 h (126 min) for gentamicin and 2.5 h (147 min) for netilmicin.

i.v. administration. Figure 2 shows representative subjects who received gentamicin and netilmicin by i.v. "slow bolus" over 3 to 5 min, with actual (not "stripped") values plotted on semilog graph paper. Although not shown in the figure, serum concentrations were sampled until 450 min (7.5 h). The individual serum concentration curves were based on 14 to 17 determination points for each subject. Table 1 shows the mean values and range of serum concentrations at representative time points for the subjects in each group.

When the serum concentration plots were

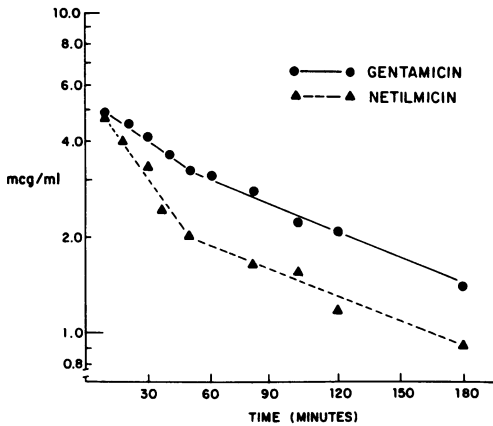


FIG. 2. Serum concentrations after i.v. slow bolus in a subject receiving gentamicin as compared with one receiving netilmicin. The dose for each drug was 1 mg/kg.

TABLE 1. Average (and range) serum concentrations after i.v. slow-bolus administration of gentamicin and netilmicin (1 mg/kg)

Time (min.)	Serum concn ($\mu\text{g/ml}$)	
	Gentamicin	Netilmicin
10	5.0 (4.2-6.0) ^a	4.8 (4.1-6.3)
20	4.5 (3.8-5.8)	3.9 (2.8-5.0)
30	4.0 (3.4-5.3)	3.4 (2.6-4.2)
40	3.6 (2.9-4.5)	2.9 (2.3-3.5)
60	3.0 (2.2-4.1)	2.3 (1.7-2.9)
80	2.5 (1.9-3.3)	1.9 (1.6-2.2)
100	2.2 (1.7-3.2)	1.7 (1.3-1.9)
120	1.9 (1.1-2.5)	1.5 (1.1-1.7)
180	1.2 (0.6-1.9)	0.9 (0-1.1)
240	0.8 (0.5-1.1)	0.4 (0-0.8)
360	0.3 (0-0.8)	0

^a Numbers in parentheses indicate ranges.

examined individually, all subjects evidenced a biphasic curve, as illustrated by the subjects shown in Fig. 2. The initial portion of the curve, the α segment, or distribution phase, was markedly and consistently distinctive for the individuals receiving netilmicin as compared with those receiving gentamicin. For the group receiving gentamicin, the $T_{1/2\alpha}$ averaged 23.8 min (range, 20.6 to 27.4 min). The $T_{1/2\alpha}$ for the netilmicin group averaged 9.2 min (range, 6.4 to 10.4 min). The differences in $T_{1/2}$ values for the α phase are significant ($P = <0.01$).

For the second portion of the curve, the β segment or elimination phase, the average half-times were not different for gentamicin and netilmicin. The subjects receiving gentamicin displayed more variability in the half-time of the β phase than did those receiving netilmi-

cin. The $T_{1/2\beta}$ for the subjects receiving gentamicin averaged 119.5 min (range, 94 to 160 min), and the $T_{1/2\beta}$ for the netilmicin group averaged 103.4 min (range, 91 to 119 min).

Urine recovery of drug. Figure 3 shows the average and range of urine recovery of both drugs after i.m. and i.v. administration at three representative time points, 2, 8, and 24 h. When the two routes of administration were compared for each drug individually, the i.v. dose resulted in greater urine recovery of both drugs at all time periods.

At 2 h after the administration of gentamicin, an average of 51% of the dose appeared in the urine when the drug was given i.v., as compared with 24% when the same dose was given to the same subject by the i.m. route. This difference is statistically significant ($P = <0.05$). The urine recovery of drug progressively increased after both i.m. and i.v. doses, and a differential of approximately 30% greater recovery after i.v. administration of gentamicin persisted for all time points. The urine recoveries after i.m. versus i.v. administration of gentamicin were significantly different at 8 and 24 h (for both time periods, $P = <0.05$). As shown in Fig. 3, the ranges of urine recovery for gentamicin were mutually exclusive for each method of administration.

When the two routes of administration for netilmicin were examined, the urine recovery at 2 h after an i.v. dose was approximately 13% greater than after an i.m. dose. This difference progressively diminished until, at 24 h after a dose, there was very little difference in urine recovery of netilmicin, regardless of the route of administration.

At 2 h after an i.m. dose, slightly more netilmicin was recovered than gentamicin (29 versus 24%). The average urinary netilmicin re-

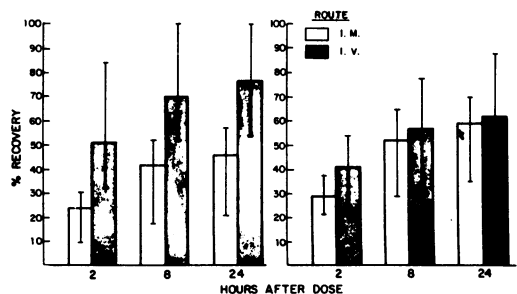


FIG. 3. Cumulative urine recovery of aminoglycosides expressed as a percentage of the administered dose. (Left) Average of five subjects given 1 mg of gentamicin per kg by the i.m. and i.v. routes; (Right) six subjects given 1 mg of netilmicin per kg. I, Range of subjects.

covery after i.m. administration showed a progressively greater increase as compared with gentamicin at 8 h (52 versus 42%) and 24 h (59 versus 46%). None of these values was significantly different. After i.v. administration, the average gentamicin recovery was greater than netilmicin recovery at all time periods. At 2 h after the i.v. dose, the average recovery of gentamicin was 51% of the administered dose; at 8 and 12 h, gentamicin recovery averaged 70 and 76% of the dose given. After i.v. administration of netilmicin, urine recovery at 2, 8, and 12 h averaged 41, 57, and 62% of the administered dose.

During the first 2 h after the i.m. dose of both drugs, urinary concentrations of the antibiotic ranged from approximately 15 to 60 $\mu\text{g/ml}$. During the first 2 h after the i.v. dose, urine concentrations of both drugs ranged from approximately 20 to 150 $\mu\text{g/ml}$. For both drugs, the urinary concentrations varied inversely with urinary output.

Distribution and clearance. The total volume of distribution (V_d) of drug for each individual was calculated by the formula: $V_d = [\text{Dose}(\text{mg})]/[\beta (\text{area under serum concentration curve from } T = 0 \text{ to } T = \infty = [\text{Dose}(\text{mg})]/[\beta(A/\alpha + B/\beta)]]$. The total V_d was divided by the weight of the subject to convert the value to V_d per kilogram of body weight. The average V_d per kilogram of body weight for gentamicin was 222 ml, and for netilmicin it was 267 ml. These values are significantly different ($P = <0.05$).

A creatinine clearance was obtained for each subject on the day the i.v. dose was given. The serum clearance of administered drug was calculated by using the formula: $\text{Cl} = \beta \times V_d$ (14, 30).

The relationship of creatinine clearance and drug clearance for the two groups is shown in Table 2. There was no difference in creatinine clearance for the group receiving gentamicin as compared with netilmicin, nor was there any difference between creatinine clearance and the clearance of gentamicin. However, netilmicin

was cleared from serum at a substantially higher rate than creatinine ($P = <0.01$). This was observed for each subject who received netilmicin. When the range of clearance of netilmicin was compared with the range of clearance of gentamicin, there was no overlap. For the subjects who received gentamicin, the range of drug clearance was 60 to 127 ml/min, and for netilmicin it was 122 to 162 ml/min. When the t test for unequal sample sizes is used, the differences between the clearance of netilmicin and gentamicin are significant ($P = <0.01$).

Tolerance and toxicity. Both drugs were tolerated very well. None of the subjects experienced pain or discomfort from the i.m. or the i.v. administration of either drug. None of the physical parameters or symptoms that were checked before and after drug administration showed a meaningful change. Fluctuations in creatinine clearance, blood counts, and chemistries were all within normal limits and showed no consistent upward or downward trends.

During the second portion of the study (i.v. administration), it was noted that the 4- to 6-h postdose blood samples from three subjects appeared to have abnormal clotting (clotting did not appear to proceed as usual and did not have the customary morphology when complete). One of the subjects received gentamicin, and the other two received netilmicin. Evaluation of clotting parameters was performed by our special coagulation laboratory. One of these subjects, who received netilmicin, was discovered to have a mild deficiency of factor VIII (36 to 40% of normal). On repeated evaluations over the next 3 months, his partial thromboplastin time varied between normal and slightly prolonged. An explanation was not found for the other two subjects. It was the opinion of the coagulation specialist that we were viewing excessive erythrocyte "fallout," and not incomplete clotting. No other individuals in the study had an unusual appearance of blood clots or showed evidence of any coagulation abnormality.

DISCUSSION

The behavior of netilmicin in humans appears to differ from gentamicin in several respects. After i.m. administration, the average peak concentrations of netilmicin and gentamicin in the serum were the same, but the times from injection to peak serum concentration were notably different. The rapidity of peak levels of gentamicin in the serum differs from earlier observations (6, 12, 25). The rapidity may be due to the evaluation of lean, healthy,

TABLE 2. Relationships of creatinine clearance and drug clearance for the groups receiving either gentamicin or netilmicin

Subjects receiving:	Mean creatinine clearance (ml/min)	Mean drug clearance (ml/min)
Gentamicin	108.2	98.6 (± 12.4) ^a
Netilmicin	95.8	140.0 (± 6.4)

^a Numbers in parentheses indicate mean standard deviations.

young subjects, who have neither diminished blood supply to muscles concurrent with aging nor other factors (intercurrent disease, prolonged bed rest, etc.) that may decrease muscle perfusion.

The time difference between peak levels may be either the effect of differences in the concentration of injected material, a characteristic of the compounds themselves, or a distortion due to small sample size. The latter seems unlikely because of the consistency of the differences between the drugs. Although medications given by i.m. injection generally follow a concentration gradient in diffusion from the i.m. site, at least one drug in clinical use does not: atropine has been reported to be more rapidly absorbed when given in a dilute solution and a larger volume (29).

In the comparison of amikacin and kanamycin (formulated as 260 and 250 mg/ml, respectively), Clarke et al. (7) found that, after i.m. injection, antibiotic concentration reached peak levels between 45 min and 2 h (J. T. Clarke, personal communication). Categorization of peak times according to drug was not given; however, from the data presented, it appears that kanamycin levels peaked approximately 30 min earlier than did amikacin levels and then sustained a plateau. If netilmicin and amikacin, both of which possess side chains on 2-deoxystreptamine, are absorbed from an i.m. site at a different rate (i.e., slower) than the analogous compounds gentamicin and kanamycin, then the alteration in the 2-deoxystreptamine moiety may confer pharmacological differences as well as microbiological ones. Whether apparent differences in absorption of gentamicin and netilmicin are due to structural differences in the two compounds or whether aminoglycosides as a class behave differently from other i.m. medications and mimic the behavior of atropine is unknown. If the differences are related to concentration of injected material, then the phenomenon may well be observed in patients: for clinical use, gentamicin is formulated as 40 mg/ml, and netilmicin is formulated as 100 mg/ml. The observation may be worthy of further investigation.

Even in a young, healthy population, gentamicin continues to display marked variability in peak serum concentration after i.m. injection (2, 11, 13, 15, 17, 24, 28). The variability in the peak level of gentamicin was almost twice that of netilmicin. In addition, there was a twofold range of variability in the $T_{1/2}$ among subjects who received gentamicin. These observations emphasize the need for monitoring the blood levels of gentamicin, even in patients with normal renal function (2, 22, 24, 25).

The i.v. dose of both drugs, given over 3 to 5 min, resulted in serum concentrations that were in an acceptable range and not excessively high. This is consistent with the observations of Mendelson et al. (21), who used higher doses of gentamicin in patients than our subjects received. Although the i.v. slow bolus appears to be relatively safe, it may have a major disadvantage as a routine method of administration to patients. An average of half the administered dose of gentamicin appeared in the urine within 2 h after the rapid i.v. dose. Obviously, a drug that is rapidly excreted is not available for tissue distribution.

The serial blood levels after the i.v. slow-bolus dose demonstrated a biphasic curve for both drugs. Although the average β phase was similar for both drugs, the α phase of netilmicin was considerably more rapid than gentamicin. The rapid plasma disappearance of netilmicin could be due to several causes, such as: metabolism of the drug, very rapid urinary excretion, or movement out of the vascular compartment to elsewhere in the body. Although metabolism is possible, it is unlikely in view of the knowledge of other aminoglycosides. The urinary recovery of netilmicin after the i.v. dose was less than the urinary recovery of gentamicin administered i.v., and the urine recovery of netilmicin was almost the same regardless of the route of administration. These observations, combined with the fact that the α phase of netilmicin exceeds that of gentamicin, suggest that the extravascular distribution of netilmicin appears independent of the route of administration. The converse appears true for gentamicin. That is, a large urinary output and a slow α phase after an i.v. dose suggest less extravascular distribution than with netilmicin.

There were no adverse reactions directly attributable to either of the drugs; however, an unusual observation regarding the blood clots in the samples from three subjects was noted. One subject was discovered to have a factor VIII deficiency, a congenital defect that was previously unsuspected (1; F. Rodriguez-Erdmann, submitted for publication). Other than for this individual, we have no explanation for the abnormal appearance of the clots in some samples after the i.v. doses. The phenomenon was observed with gentamicin as well as with netilmicin. Although it is entirely possible that some extraneous factor (such as excess silicon coating of the sample tubes) caused the phenomenon, unusual effects have been observed with drugs that have been in use for long periods of time (4, 5). The occurrence is reported here to inform other investigators of the possibility.

In summary, a comparison of gentamicin with netilmicin showed that netilmicin had a slower onset to peak concentration in serum and less variance in peak level after i.m. administration, a faster disappearance from serum after i.v. administration, a greater V_d , less variability in the $T_{1/2}$ phase, and a lesser recovery in urine than gentamicin. Our observations suggest that therapeutic levels of netilmicin may be more easily predicted in patients than levels of gentamicin. The rate differences and the urinary recovery data suggest that netilmicin may have a greater extravascular distribution than gentamicin. Future studies should also be directed toward determining the tissue distribution of netilmicin.

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