Netilmicin Treatment of Complicated Urinary Tract Infection in Patients with Renal Function Impairment

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The efficacy and tolerance of netilmicin was studied in 28 elderly male patients with varying degrees of renal function impairment who suffered from complicated urinary tract infections. Doses of netilmicin, equivalent to 2 mg/kg divided by milligrams of creatinine per 100 ml, were administered every 12 h. A 62% cure rate, defined as negative urine culture at 1-week follow-up, was obtained. Treatment failure correlated with impaired renal function. Nephrotoxic reaction, defined as any significant increase in serum creatinine during treatment, was found in 6 of 28 patients (21%). The increase in serum creatinine was transient in all except one of these patients. Apart from the finding of a significant correlation between nephrotoxic reaction to netilmicin and postoperative urinary tract infection, no clinical or therapeutic features correlated with nephrotoxicity; trough concentrations correlated with serum creatinine.

In previous studies at this institution, netilmicin was shown to be clinically effective and relatively free from toxic side effects when given intramuscularly to elderly male patients in doses of 1 to 2 mg/kg every 8 to 12 h for 7 days (2, 11). The patients participating in these studies had normal renal function for their age (serum creatinine, ≤1.4 mg/100 ml). The purpose of this report was to study the efficacy and safety of netilmicin in the treatment of patients with relatively normal renal function and stable impairment of renal function.

Several formulas and nomograms have been proposed for adjustments in aminoglycoside dosage (4, 6, 12, 19). For the present study, we have used a clinically practical formula for estimation of reduced doses of netilmicin in azotemic patients, based solely on pretreatment serum creatinine. It takes into consideration that the maintenance dose for most drugs in continuous drug administration is inversely proportional to the half-life of the drug at reduced renal function (6). Since the half-life of netilmicin is directly proportional to the serum creatinine (18), it is postulated that dividing the normal daily dosage by the patient’s serum creatinine (in milligrams per 100 ml) will result in effective serum and urine concentrations in the treatment of urinary tract infections and not cause an accumulation of drug in the patient’s serum.

MATERIALS AND METHODS

Subjects were 28 elderly male patients, aged between 61 and 88 years (mean, 78) and weighing between 60 and 113 kg (mean, 78), in the urology ward of the William S. Middleton Memorial Veterans Hospital, Madison, Wis. These patients had urinary tract infections complicated by obstructions in the lower urinary passages, including benign hypertrophy of the prostate (10), cancer of the prostate (11), or urethral stricture (3). One patient had stones in the kidneys, two had indwelling catheters during part of the study, and one was infected with more than one microorganism. Five of the patients were considered to have relatively normal renal function (serum creatinine, ≤1.4 mg/100 ml). Fifteen patients had moderately impaired renal function (serum creatinine, 1.5 to 2.4 mg/100 ml), and eight patients had severe renal impairment (serum creatinine, ≥2.5 mg/100 ml). Netilmicin (2 mg/kg) was initially administered intramuscularly followed by a maintenance dose, equivalent to 2 mg/kg divided by milligrams of creatinine per 100 ml, every 12 h.

Before treatment, all patients had urine colony counts of ≥10^5 colonies per ml, and all microorganisms isolated from the urine were susceptible to netilmicin, as defined by the standardized disk susceptibility method (1). Urine cultures with colony counts were carried out on midstream clean-catch specimens before treatment, on day 3 of treatment, the last day of treatment, and 1 week after treatment.

Serum samples for bioassay of netilmicin were drawn 1 and 5 h after the first injection and 11.5 h after the second injection of netilmicin on days 1, 3 or 4, and 6 or 7 of treatment. Urine was collected from 0 to 6 and 6 to 12 h after treatment on days 1 or 2, 3 or 4, and 6 or 7.

Blood urea nitrogen, serum creatinine, and creatinine clearance were determined on each patient on days 1, 3 or 4, and 7 of treatment. Pure-tone audiograms were carried out before and within 1 week after treatment on as many patients as possible. In addition, hemoglobin, hematocrit, total leukocyte
count with differential count, alkaline phosphatase, lactate dehydrogenase, serum glutamic oxaloacetic transaminase, and serum bilirubin were determined in all patients before and after the study. The therapeutic results were assessed according to the urine cultures. The following standards were used: cure, negative culture at 1 week after treatment; persistence, $\geq 10^6$ colonies of the original organism per ml during treatment; relapse, negative culture during therapy and $\geq 10^6$ colonies of the original organism per ml at follow-up; reinfection, $\geq 10^6$ colonies of an organism different from the original organism per ml at follow-up; superinfection, $\geq 10^6$ colonies of an organism different from the original organism per ml during treatment. This assessment was based on routine bacteriological identification of the microorganisms since serotyping was not done.

Nephrotoxicity was defined as any significant increase in serum creatinine during therapy with netilmicin. We based our definition on the findings of Brochner-Mortensen and Rødbro (3; J. Brochner-Mortensen, Ph.D. thesis, University of Copenhagen, Denmark, 1978) that serum creatinine is the most reliable of the routine clinical methods for the determination of renal function and that changes in serum creatinine of $31\%$ in patients with glomerular filtration rates $\geq 30$ ml/min and $18\%$ for glomerular filtration rates $\leq 30$ ml/min are necessary to demonstrate a significant change in a patient's renal function ($95\%$ significance limits). The glomerular filtration rate was determined as creatinine clearance from the nomogram of Siersbaek-Nielsen et al. (16). Nephrotoxic reaction was excluded when the following conditions and were involved: (i) a nephrourological explanation for the change in renal function, and (ii) a major operation performed within 3 days before change in serum creatinine. Ototoxic reaction to netilmicin was defined as a decrease $\geq 20$ dB in any frequency on pure-tone audiograms after treatment.

Serum and urine concentrations of netilmicin were determined by a disk diffusion method on streptomycin assay agar with Bacillus subtilis ATCC 6333 as the test organism. The minimal inhibitory concentration, performed by a twofold dilution procedure on streptomycin assay agar, was considered to be the lowest concentration of antibiotic suppressing $99\%$ of bacterial growth after $24$ h of incubation at $37^\circ$C. Statistical methods used were the $\chi^2$ test and the $t$-test for paired or independent observations, both with Yates correction, as well as regression analysis. $P$ values $<0.05$ were considered significant.

**RESULTS**

Twelve-hour creatinine clearances correlated well with estimated values for that age group using the nomogram of Siersbaek-Nielsen et al. (16) ($0.01 > P > 0.001$). The peak serum concentrations of netilmicin on days 1, 3 or 4, and 6 or 7 of treatment (mean $\pm$ standard deviation) were $10.8 \pm 4.7$, $10.3 \pm 4.4$, and $9.4 \pm 4.3$ $\mu$g/ml. There were no significant differences among these; there were also no significant differences among the corresponding trough serum concentrations (mean $\pm$ standard deviation), which were $3.9 \pm 1.8$, $4.5 \pm 3.3$, and $4.6 \pm 3.3$ $\mu$g/ml. This indicates that no accumulation occurred in the patients' sera during treatment for 7 to 8 days. Figure 1 shows the positive, significant correlation between trough serum concentrations of netilmicin and serum creatinine as determined on days 3 or 4 and 6 or 7 of treatment. Blood samples for determination of netilmicin concentrations were lost in eight patients on day 3 or 4 and in five patients on day 6 or 7, respectively. This positive correlation could be expected when a variable dosage regimen was used for dosage adjustment (19). There was no significant correlation between peak serum concentrations and serum creatinine on day 3 or 4 or day 7 of treatment. As expected, urine concentrations of netilmicin decreased with decreasing renal function (Fig. 2). Urine samples from six patients were lost. Urine concentrations of netilmicin were always

**FIG. 1.** Correlation between serum creatinine and trough serum concentrations on days 3 or 4 and 7 or 8, respectively, of treatment with netilmicin.

$y = -24.7x + 61.66$
$r = -0.42$
$0.05 > P > 0.005$

**FIG. 2.** Correlation between pretreatment serum creatinine and urine concentration (0 to 6 h) of netilmicin. Urine concentrations are means of determinations on days 1, 3 or 4, and 7 or 8 of treatment.
several times higher than the minimal inhibitory concentrations for the infecting organisms, even in patients with severe renal impairment.

Of the 28 patients in this study, 1-week follow-up urine cultures were missed in 2 patients. Causative organisms isolated from urine cultures before treatment in 26 patients were (with number of strains in parentheses): Pseudomonas aeruginosa (7), Escherichia coli (6), Klebsiella pneumoniae (5), Proteus mirabilis (2), Staphylococcus epidermidis (2), and one each for Staphylococcus aureus, Proteus morganii, Citrobacter freundii, Enterobacter aerogenes, and Providencia rettgeri. One patient was infected with two organisms.

Table 1 shows the bacteriological results of netilmicin treatment in 26 patients. Netilmicin eradicated the primary pathogen in 74% of the patients at the 1-week follow-up. The microorganisms isolated before and after treatment from patients with relapse or persistence demonstrated no change in minimal inhibitory concentrations, indicating no development of resistance to netilmicin.

The group of 10 patients with no cure had an overall decreased renal function as compared with the group of 16 cured patients, as expressed by significant differences in serum creatinine (mean ± 1 standard deviation) (no cure, 2.6 ± 1.4 mg/100 ml; cure, 1.7 ± 0.8 mg/100 ml; 0.05 > P > 0.02 and creatinine clearance (no cure, 24 ± 17 ml/min; cure, 46 ± 18 ml/min; 0.05 > P > 0.02). Peak serum concentrations of netilmicin were similar in the two groups of patients, but trough serum concentrations were significantly higher in the patients who were not cured (no cure, 6.4 ± 2.6 μg/ml; cure, 3.5 ± 2.6 μg/ml; P = 0.01). This can be explained by the reduced renal function in the latter group (Fig. 1). We found no significant differences between the two groups regarding therapeutic outcome when comparing total dose of netilmicin, duration of treatment, minimal inhibitory concentration for infecting organisms, percent urine excretion, or urine concentration of netilmicin.

 Twelve patients were evaluated by pure-tone audiograms before and after netilmicin treatment. Most of these patients had moderate age-dependent hearing loss before treatment. Two of the 12 patients developed a unilateral 15-dB decrease in one of six tested thresholds, but none exceeded the defined limit of 20 dB for ototoxicity. Seven patients demonstrated significant increases in serum creatinine. Increased renal impairment was attributed solely to underlying disease (hydronephrosis) in one patient, leaving six patients with possible nephrotoxic reaction to netilmicin. The changes in serum creatinine and blood urea nitrogen are depicted in Table 2. One patient (no. 5 in Table 2) had received gentamicin for 2 days, 3 weeks before netilmicin treatment. No one received other antibiotics during treatment, but two patients received small doses of diuretics. All of the six patients demonstrated increases in serum creatinine on both days 3 or 4 and 6 or 7 of treatment. The mean increase from pretreatment to days 3 or 4 and 6 or 7 of treatment showed much larger variation for blood urea nitrogen than for serum creatinine (Table 2). The renal impairment progressed to total renal failure and death in one of these patients 3 weeks after treatment (patient no. 5 in Table 2). Dialysis was not attempted due to the general clinical condition and the underlying malignant disease of this patient. Serum creatinine values had improved in the other five patients at 2- to 4-week follow-up. There were no significant differences with regard to age, total dose, duration of treatment, or cure of infection between the two groups of patients showing nephrotoxic reaction or no toxic action to netilmicin. Furthermore, we found no differences in pretreatment renal function between the two groups and neither peak nor trough serum concentrations correlated with nephrotoxicity.

 Four of the 6 (67%) patients with nephrotoxic reaction to netilmicin underwent surgery (transurethral prostatectomies), whereas only 9 of 22 (41%) patients with no toxic reaction did (P = 0.28) (transurethral prostatectomies and one suprapubic prostatectomy). The four patients in the group showing nephrotoxic reaction who were operated on during admission were all treated for a postoperative urinary tract infection (mean, 8.8 days after operation; range, 3 to 19 days), whereas postoperative urinary tract infections were found only in three of the oper-

<table>
<thead>
<tr>
<th>Time of assessment</th>
<th>No. of patients with:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative culture</td>
<td>Relapse or persist</td>
<td>Reinfec</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ence</td>
<td>tion or superinfe</td>
</tr>
<tr>
<td>Day 3 of treatment</td>
<td>24 (92)*</td>
<td>2 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Last day of treatment</td>
<td>21 (81)</td>
<td>4 (15)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>1-week follow-up</td>
<td>16 (62)</td>
<td>7 (27)*</td>
<td>3 (12)*</td>
</tr>
</tbody>
</table>

* Number in parentheses is percentage of total.

1 The microorganisms responsible for relapse or persistence were: P. aeruginosa (3), C. freundii, P. mirabilis, K. pneumoniae, and E. coli, one each.

2 The microorganisms responsible for reinfection or superinfection were: P. stuarti, S. aureus, and C. albicans.

Table 1. Results of treatment of complicated urinary tract infections with netilmicin administered intramuscularly twice daily in 26 patients
ated patients from the group with no toxic reaction ($P = 0.03$). This could indicate that the trauma of an operation, including general anesthesia, might in some way predispose a patient to nephrotoxicity from netilmicin. Methoxyflurane was not used as an anesthetic in any of these patients. No changes during treatment were observed in hemoglobin, leukocyte count with differential, alkaline phosphatase, serum glutamic oxaloacetic transaminase, lactate dehydrogenase, or serum bilirubin.

**DISCUSSION**

The therapeutic results are expected to be poor in these patients with complicated infections. Yet netilmicin eradicated most of the primary pathogens from the urine, and a cure rate of $62\%$ at the 1-week follow-up was accomplished. This result is comparable to those of other similar studies with this and other aminoglycosides (2, 11, 14, 20). The main factor governing a poor outcome of treatment for these patients seems to be impaired renal function, whereas serum concentrations per se do not appear to have any importance in predicting the effect of netilmicin in these infections.

The rate of nephro- and ototoxic reaction to netilmicin found in this study corresponded with the findings of others (17), but comparison among studies concerning this and other aminoglycosides is complicated by widely varying definitions or lack of definitions of these conditions. Nephrotoxicity rates are usually based upon changes in one or more of the routine clinical methods for estimation of renal function, i.e., creatinine clearance, blood urea nitrogen, or serum creatinine. Of these, creatinine clearance and blood urea nitrogen are the most unreliable due to inaccuracy in urine collection or dependence on unrelated factors such as nitrogen metabolism (Brøchner-Mortensen, Ph.D. thesis) (Table 2). With certain exceptions, serum creatinine is the most precise and reliable for detection of changes in renal function (3; Brøchner-Mortensen, Ph.D. thesis). One exception concerns conditions which involve acute changes in renal function (Brøchner-Mortensen, Ph.D. thesis). In addition, the creatinine excretion rate varies in the first days after major surgery, decreasing on the first postoperative day and increasing the following 2 to 3 days (9). Apart from the first postoperative days, an increase in serum creatinine should, therefore, indicate that other factors are involved postoperatively, such as the nephrotoxic reactions considered in the four patients showing steady increase in serum creatinine. Our definition of nephrotoxic reaction may be more sensitive than that of others, and it should be emphasized that interpretation of changes in renal function is difficult in patients with uronephrological disorders. As observed after treatment with other aminoglycosides (5, 15), the nephrotoxic reaction to netilmicin is usually reversible. Netilmicin seems to produce the same toxic reactions as gentamicin, but further studies with larger populations are needed to show if the lower oto- and nephrotoxic potential for netilmicin than for gentamicin seen in laboratory animals can be reproduced in humans (10).

A correlation between high trough serum concentrations and nephrotoxicity has been reported for gentamicin (5, 15). The doses in these studies were administered by adjusting the dos-

### Table 2. Serum creatinine and blood urea nitrogen values in six patients with nephrotoxic reaction during treatment with netilmicin

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Creatinine clearance pretreatment¹ (ml/min)</th>
<th>Serum creatinine (mg/100 ml) Day 3–4 of treatment (¹% increase from pretreatment)</th>
<th>Blood urea nitrogen (mg/100 ml) Day 3–4 of treatment (¹% increase from pretreatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>2.0 (33)</td>
<td>42 (56)</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>2.4 (50)</td>
<td>28 (−)</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>2.0 (33)</td>
<td>28 (27)</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>1.9 (46)</td>
<td>52 (53)</td>
</tr>
<tr>
<td>5</td>
<td>22</td>
<td>2.2 (22)</td>
<td>132 (74)</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>3.1 (7)</td>
<td>67 (56)</td>
</tr>
</tbody>
</table>

Mean ± 1 SD of % increase from pretreatment values:

<table>
<thead>
<tr>
<th>Serum creatinine (mg/100 ml) Day 3–4</th>
<th>Blood urea nitrogen (mg/100 ml) Day 3–4</th>
</tr>
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<tbody>
<tr>
<td>23 ± 10</td>
<td>19 ± 19</td>
</tr>
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</table>

¹ Estimated from nomogram of Siersbæk-Nielsen et al. (17).

² SD, Standard deviation.
age interval, in contrast to this study where the doses were adjusted while administered in fixed intervals. Trough concentrations theoretically do not change in patients with reduced renal function as compared to normal patients when the fixed-dose regimen is used, but these concentrations increase in the fixed-interval regimen (Fig. 1) (19). Rising trough concentrations in a patient during treatment with the fixed-interval regimen, therefore, do not necessarily imply the development of a nephrotoxic reaction. This explains why trough concentrations did not correlate with nephrotoxicity with the regimen used in our study. No differences in toxicity or efficacy were found in a study comparing the two regimens (8), but the fixed-dose regimen appears more appropriate to predict nephrotoxicity by monitoring serum trough concentrations.

By applying the formula for dose adjustment proposed here, we succeeded in avoiding drug accumulation in the patient's serum and in obtaining effective concentrations in the urine. Tissue accumulation, however, is bound to occur when the aminoglycosides are administered in intervals shorter than the slow excretion-phase half-life (18). Administration of gentamicin once daily is equally as effective as three times a day in treatment of complicated urinary tract infections (13). Further increases in dosage intervals or shorter periods of treatment should theoretically result in less toxicity, but probably also reduce effectiveness. Prospective studies comparing dosage regimens with regard to these factors are required.

ACKNOWLEDGMENTS

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LITERATURE CITED