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Comparison of Netilmicin and Amikacin in Treatment of Complicated Urinary Tract Infections

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Netilmicin and amikacin, two recently developed aminoglycosides, were compared in a prospective, randomized study of 57 male patients with complicated urinary tract infections. Both drugs were administered intramuscularly every 12 h for 7 to 10 days, netilmicin at 2 mg/kg and amikacin at 7.5 mg/kg. The two groups were comparable as to infecting bacteria and underlying pathology of the urinary tract. No patients had indwelling catheters. All microorganisms isolated were sensitive to both antibiotics. A total of 69% of the patients treated with netilmicin and 57% of the patients treated with amikacin were cured of the infection, as defined by a negative culture at 7 days after discontinuation of treatment. No major side effects were recorded, and no significant changes were noted in parameters of renal function. Of the patients treated with amikacin, 21% experienced temporary local pain at the injection site; no such effect was noted in the netilmicin-treated group. Therefore, netilmicin appeared to be as effective and better tolerated than did amikacin in the treatment of complicated urinary tract infection.

Netilmicin, a semisynthetic aminoglycoside, is the 1-*N*-ethyl derivative of sisomicin. In vitro studies have shown that the activity of netilmicin is similar to that of gentamicin against most gram-negative bacteria, including *Pseudomonas aeruginosa* and *Staphylococcus aureus* (5, 11, 12). Netilmicin has also been shown to be active against many gentamicin-resistant organisms (5, 11). Preliminary toxicity studies indicate that netilmicin has less ototoxic and nephrotoxic potential than gentamicin in various laboratory animals (13).

In previous studies at this institution, netilmicin was shown to be clinically effective and free from toxic side effects when given intramuscularly to elderly male patients in doses of 1.0 to 2.5 mg/kg every 8 h for 7 days (2). Pharmacokinetic studies have confirmed that netilmicin, like other aminoglycosides, is mainly eliminated by urinary excretion (16).

Amikacin, another recently developed semisynthetic aminoglycoside, has proven effective in treatment of various infections, and its toxicity seems to be similar to that of gentamicin (3, 6, 10).

The present study was designed to compare the safety and efficacy of netilmicin and amikacin in treatment of complicated urinary tract infections caused by susceptible organisms.

MATERIALS AND METHODS

A total of 63 male patients in the urology ward of the W. S. Middleton Memorial Veterans Administration Hospital, who were between the ages of 27 and 87 years (mean age, 69 years), were prospectively assigned at random to one of two groups. The patients received intramuscular injections of 2 mg of netilmicin per kg (group I) or 7.5 mg of amikacin per kg (group II) every 12 h for 7 to 10 days. All patients had complicated urinary tract infections, mainly due to obstruction of the lower urinary tract from benign hyperplasia, prostate or bladder carcinoma, or urethral stricture. All patients, except three, had normal renal function, as defined by serum creatinine at $\leq$1.5 mg/100 ml and/or blood urea nitrogen (BUN) at $\leq$25 mg/100 ml. Of the three abnormal patients, two had normal serum creatinine, but BUN was at 26 and 30 mg/100 ml, respectively; the third patient had normal BUN but serum creatinine was at 1.8 mg/100 ml. No patients had indwelling catheters.

Before treatment, all patients had urine colony counts of $\geq 10^5$ colonies per ml, and all microorganisms isolated from the urine were susceptible to netilmicin and amikacin, 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 and the last day of treatment, and 1 week and 4 to 6 weeks after treatment.

BUN, serum creatinine, and creatinine clearance were determined before, during, and after treatment. Pure tone audiograms were also carried out before and within 1 week after treatment. In addition, plasma hemoglobin, total white cell 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, $\geq 10^5$ colonies of the original organism per ml during treatment; relapse, negative culture during therapy and $\geq 10^5$ colonies of the original organism per ml at follow-up; reinfection, $\geq 10^5$ colonies of an organism different from the original organism per ml at follow-up; and superinfection, $\geq 10^5$ colonies of an organism different from the original organism per ml during treatment.

Microorganisms were identified by routine bacteriological methods without serotyping. The minimum inhibitory concentration (MIC), performed by a two-fold 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°C. Serum and urine concentrations were determined by a disk diffusion method on streptomycin assay agar with *Bacillus subtilis* ATCC 6333 as test organism.

RESULTS

Of the 57 patients selected for the study on the basis of susceptible organisms, 29 belonged to group I and 28 belonged to group II. The two groups were comparable as to infecting microorganisms (Table 1), age, and pathology of the urinary tract. Six patients in group I and five patients in group II were infected with two microorganisms.

The bacteriological results of the treatments are listed in Table 2. At follow-up (1 week after discontinuation of treatment), cure rates, rates of relapse and/or persistence, and rates of su-

TABLE 1. *Distribution and MIC of the bacteria isolated from the urine*

Strain	No. in treatment group		MIC (μg/ml, geometric mean ± 1 SE)[a] with:	
	Netilmicin (n = 29)	Amikacin (n = 28)	Netilmicin	Amikacin
S. aureus	1	2	0.68 ± 0.31 (0.18–1.25)[b]	0.45 ± 0.16 (0.12–0.62)
S. epidermidis	4	4	0.11 ± 0.02 (0.07–0.31)	0.55 ± 0.28 (0.15–2.5)
Escherichia coli	13	10	0.60 ± 0.06 (0.31–1.25)	1.25 ± 0.20 (0.31–5.0)
Citrobacter freundii	1	2	0.51 ± 0.10 (0.31–0.62)	1.04 ± 0.21 (0.62–1.25)
Klebsiella pneumoniae	2	4	0.45 ± 0.15 (0.16–1.25)	0.98 ± 0.33 (0.19–2.5
Enterobacter cloacae	1	1	0.83 ± 0.25 (0.62–1.25)	1.56 ± 0.94 (0.62–2.5)
Proteus (indole negative)	7	4	1.16 ± 0.22 (0.31–2.5)	2.10 ± 0.48 (0.62–5.0)
Proteus (indole positive)	2	3	1.24 ± 0.34 (0.62–2.5)	1.15 ± 0.30 (0.62–2.5)
P. aeruginosa	4	4	1.52 ± 0.55 (0.62–5.0)	1.95 ± 0.53 (0.62–5.0)

[a] SE, Standard error.
[b] Numbers in parentheses represent range of values.

TABLE 2. *Results of treatment of complicated urinary tract infections with netilmicin or amikacin administered intramuscularly twice daily in 57 patients*

Time of assessment	Treatment group	No. with a negative culture	No. with relapse or persistence	No. with reinfection or superinfection
Day 3 of treatment	Netilmicin (n = 29)	29 (100)[a]	0	0
	Amikacin (n = 28)	27 (96)	1 (4)	0
Last day of treatment	Netilmicin	28 (97)	1 (3)	0
	Amikacin	25 (89)	2 (7)	1 (4)
1-week follow-up	Netilmicin	20 (69)	5 (17)	4 (14)
	Amikacin	16 (57)	3 (11)	9 (32)
Chi-square test with Yates correction		$P > 0.5$	$P > 0.5$	$0.1 < P < 10.2$

[a] Numbers in parentheses are percentage of total.

perinfection and/or reinfection were comparable. A total of 33 patients could be reevaluated at 4 to 6 weeks after treatment. Of 18 patients in group I, 16 had negative urine cultures and 2 had reinfection. Of the 15 patients in group II, 12 still had sterile urine, whereas relapse was found in 2 patients, and reinfection was found in 1 patient. There was no statistical difference between the two groups.

Serum and urine concentrations, together with urinary excretion percentages of the two antibiotics, are shown in Table 3. The urine concentrations were many times higher than the MIC for the pathogens and most gram-negative organisms commonly found in urinary tract infections.

Six patients in the amikacin group complained of moderate to severe pain at the injection site, whereas no local reaction or pain was observed in the netilmicin group. The difference is statistically significant ($P < 0.05$, chi-square test with Yates correction). No changes in audiograms (>5 decibels) were observed in either group.

The effect of these two drugs on renal function is outlined in Table 4. No significant changes were found in the parameters of renal function in the two groups. There were no changes in plasma hemoglobin, leukocyte count with differential, alkaline phosphatase, serum glutamic oxalacetic transaminase, lactate dehydrogenase, or serum bilirubin.

DISCUSSION

The therapeutic results would be expected to be poor in these patients with complicated infections. Both antibiotics, however, eradicated practically all primary pathogens from the urine, and cure rates of 69 and 57% in the netilmicin and amikacin groups, respectively, were accomplished. There was no statistical difference between these figures. The results were comparable to other similar studies with these and other aminoglycosides (8, 9, 14).

The two antibiotics were comparable with regard to cure rates, rates for reinfection and/or superinfection, and rates for relapse and/or persistence both at the 1-week follow-up and during the 4- to 6-week follow-up. The microorganisms isolated before and after treatment from patients with relapse or persistence demonstrated no change in MIC values, indicating no development of resistance to either netilmicin or amikacin. Only two strains resistant to both antibiotics (MIC > 10 μg/ml), both pseudomonas species, were encountered at the same time in a group II patient with reinfection.

The low creatinine clearances (Table 4), which correlated well with estimated values for that

TABLE 3. *Urine and serum concentrations and urinary excretion of netilmicin and amikacin*

Day of treatment	Collection period (h)	Netilmicin (n = 29)				Amikacin (n = 28)			
		Urine concn (μg/ml)	Urine excretion (%)	Serum concn (μg/ml) at:		Urine concn (μg/ml)	Urine excretion (%)	Serum concn (μg/ml) at:	
				1 h	12 h			1 h	12 h
Day 1	0–12	121 ± 2.3[a] (31–260)[b]	57.4 ± 4.6 (10.9–91)	8.9 ± 0.7 (2.9–16)	1.5 ± 0.2 (0.29–3.7)	480 ± 65 (104–1338)	71.7 ± 5.8 (18.8–100)	29.0 ± 2.0 (17–51)	4.4 ± 0.7 (1.4–8.7)
	12–24	141 ± 15.1 (9–445)	81.5 ± 6.4 (5.8–129.9)			488 ± 47.8 (138–965)	85.2 ± 3.8 (138.2–111.9)		
Day 3	0–12	180 ± 20.0 (64–436)	83.5 ± 3.6 (44.8–12.0)	10.4 ± 0.7 (2.6–17)	2.2 ± 0.4 (0.3–9.2)	530 ± 74.1 (70–1157)	72.7 ± 5.8 (30.6–112.8)	31.2 ± 3.3 (14–72)	4.8 ± 0.6 (2.1–10.5)
	12–24	177 ± 18.3 (60–518)	84.4 ± 4.2 (11.7–123.7)			494 ± 72.6 (118–1156)	71.0 ± 6.0 (15.6–96.9)		
Last day	0–12	167 ± 16.8 (50–336)	85.3 ± 3.7 (42.3–141.4)	10.8 ± 0.5 (3.8–19.0)	2.1 ± 0.4 (0.1–6.4)	581 ± 62.0 (138–1156)	79.8 ± 5.9 (23.7–111.2)	32.6 ± 3.1 (12–81)	5.1 ± 0.5 (1.8–8.2)
	12–24	190 ± 18.0 (58–447)	88.6 ± 5.0 (53.6–170.9)			447 ± 40 (162–813)	80.6 ± 3.7 (55.1–99.7)		

[a] Mean ± 1, standard error.
[b] Numbers in parentheses represent range of values.

TABLE 4. *BUN, serum creatinine, and creatinine clearance before and after treatment*

Patient group	BUN (mg/100 ml)			Serum creatinine (mg/100 ml)			Creatinine clearance (ml/min)		
	Pretreatment	Posttreatment		Pretreatment	Posttreatment		Pretreatment	Posttreatment	
Netilmicin (n = 29)	17.7 ± 0.8 (8–30)[a]	19.0 ± 1.1 (9–32)		1.14 ± 0.04 (0.8–1.8)	1.2 ± 0.04 (0.7–1.6)		74.6 ± 4.8 (41–128)	76.2 ± 4.3 (46–124)	
		$0.05 < P < 0.1$[b]			$0.05 < P < 0.1$			$0.4 < P < 0.5$	
Amikacin (n = 28)	16.8 ± 0.8 (8–25)	18.1 ± 1.1 (8–30)		1.12 ± 0.04 (0.8–1.5)	1.17 ± 0.05 (0.8–1.7)		81.5 ± 6.7 (31–149)	78.6 ± 5.1 (38–129)	
		$0.1 < P < 0.2$			$0.1 < P < 0.2$			$0.3 < P < 0.4$	

[a] Numbers in parentheses represent range of values.
[b] Probability values were determined by the paired *t* test.

age group using the nomogram of Siersbaek-Nielsen et al. (15), could explain the observation that the serum concentrations for both antibiotics were slightly higher than those reported in other studies (6, 7).

Gooding et al. (4), in a review of 1,098 patients treated with amikacin, recorded nephrotoxic side effects in 2% and signs of ototoxicity in only 3%. Schmidt et al. (14) reported that 6% of patients treated with amikacin developed signs of nephrotoxicity, as evidenced by a rise in levels of BUN and/or serum creatinine, whereas 6% showed changes in auditory function. Baumueller and Madsen (2) found a statistically but not clinically significant increase in serum creatinine and BUN in treatment of patients having complicated urinary tract infections with netilmicin.

Whereas no major side effects were found in the present study, the slight changes in renal function parameters illustrate the nephrotoxic potential of both aminoglycosides.

It appears from this study that netilmicin and amikacin are equally effective in treatment of complicated urinary tract infections caused by susceptible organisms.

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