ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1979, p. 635-641
0066-4804/79/05-0635-07$02.00/0
Vol. 15, No. 5

Influence of Single or Multiple Doses of Gentamicin and Netilmicin on Their Cortical, Medullary, and Papillary Distribution

MICHEL G. BERGERON* AND SYLVIE TROTTIER

Infectious Disease Section, Le Centre Hospitalier de l'Université Laval, Québec, Québec G1V 4G2, Canada

Received for publication 2 February 1979

In this study, the comparative intrarenal distribution and accumulation of both gentamicin and netilmicin were investigated in normal rats. The animals received 1, 3, or 14 injections of 10 mg of gentamicin or netilmicin per kg. A total of 324 animals and 648 kidneys were analyzed. These animals were sacrificed at from 1 h to 25 days after the intraperitoneal injections. At each timed interval, the serum, urine, cortex, medulla, and papilla were analyzed for antimicrobial content. The peak serum values of gentamicin (8 to 12 μg/ml) and netilmicin (9 to 14 μg/ml) were close to those found in humans. There was a progressive increase in the cortical concentrations of both antibiotics from a low of 53 μg/g to a high of 719 μg/g when the animals were given increasing doses of the agents. At most timed intervals, the concentrations of gentamicin within the cortex were slightly lower than those of netilmicin. The accumulation of the drugs was also demonstrated in the medulla, where therapeutic levels could be detected for up to 25 days after the cessation of therapy. Even though gentamicin and netilmicin were transiently present in the papilla after 1 or 3 injections, both drugs could still be detected in the papilla on day 25 after 14 doses. The urinary concentration closely paralleled the papillary concentration. If applicable to humans, the persistence of high levels of both drugs within the medulla and papilla may have therapeutic implications.

A better understanding of the intrarenal pharmacokinetics and distribution of antimicrobial agents might be of value in the proper choice of drugs for the treatment of pyelonephritis. Most people interested in the intrarenal distribution of aminoglycosides (6, 12, 13) have tried to correlate the cortical concentrations of these drugs with their toxicity (14). In pyelonephritis, bacterial growth is largely limited to the medulla and the papilla (20). The accumulation of aminoglycosides within these zones may be critical in the therapy of renal infections.

Netilmicin has been reported to be less nephrotoxic than gentamicin (3, 14). If this is true and if netilmicin can accumulate within all sections of the kidney without any apparent toxicity, the intrarenal kinetics of this antibiotic may provide information of therapeutic utility.

The purpose of this study was to compare the cortical, medullary, and papillary distribution of gentamicin and netilmicin after one and multiple injections, which were designed to obtain a therapeutic serum range comparable to that in humans.

MATERIALS AND METHODS

White female Sprague-Dawley rats weighing between 200 and 280 g were used for all experiments. The animals were allowed free access to food and water. They were fed with standard rat diet free of antibiotics.

Shortly before each experimental period, the rats were weighed, and the doses of antibiotics and anesthetics were determined accordingly. Each rat received 1 or 3 intraperitoneal doses of either gentamicin or netilmicin (10 mg/kg of body weight; the 3 doses were given 8 h apart) or 14 injections of either drug (10 mg/kg of body weight) administered every 12 h for 7 days. In this series of experiments, subgroups of six rats were sacrificed at 1, 2, 4, and 24 h and on days 4, 8, 12, 18, and 25 after the last injection of either drug. In this study, a total of 324 animals and 648 kidneys were analyzed.

The rats were anesthetized with pentobarbital, and the urine was collected by suprapubic puncture after surgical extrusion of the bladder. To collect sufficient amounts of urine for testing, the urine was sampled hourly. These urine samples were used to determine antibiotic concentrations, pH, density, and creatinine. Through a midline abdominal incision, both kidneys were removed. At the moment of sacrifice, the animals were exsanguinated by cardiac puncture. Before disposing of the rats, a large dose of pentobarbital was given to insure death.

Determination of concentrations of antibiotics. The concentrations of gentamicin and netilmicin were determined by a standard disk biological assay. All impregnations were done on TSA agar with *Bacillus subtilis* as the test organism. Urine samples

were diluted with physiological saline as required before being plated. After dilution, the urine pH varied between 6.4 and 6.6.

The kidneys were removed of their capsule and slit by a longitudinal incision. Under a dissecting microscope, the kidneys were separated into cortical, medullary (outer medulla), and papillary (inner medulla and papillary tip) components. Light microscopy was performed on the specimens of cortex, medulla, and papilla to verify the accuracy of the dissection. Each entire cortex, medulla, and papilla was weighed, placed in phosphate buffer solution (pH 7.4), and homogenized with a VirTis homogenizer (Fisher Scientific Co.).

The concentrations of antibiotics in serum were assayed from curves prepared with rat serum, and urine antibiotic concentrations were determined from standard curves prepared in physiological saline solution. Renal tissue concentrations were analyzed by using standard curves prepared in cortex, medulla, or papilla homogenate.

All disks containing standards and urine, serum, and tissue samples were plated in triplicate and incubated for 18 h at 37°C. The size of the clear zone of inhibition adjacent to the disk was proportional to the concentration of antibiotic in the disk. From the size of the zones of inhibition, a standard curve was plotted. By projecting the size of the zone of inhibition caused by serum, urine, or tissue onto the standard curve, the concentration of antibiotic in micrograms per milliliter or micrograms per gram could be determined. Recovery of either gentamicin or netilmicin after the addition of known amounts to drug-free homogenates of cortex, medulla, and papilla was almost 100%.

Protein binding. The degree of protein binding of the antimicrobial agents by rat serum and renal tissue (cortex, medulla, papilla) was determined in the following manner. Dialysis chambers were prepared by using a single thickness of dialysis tubing. Phosphate buffer (pH 7.4) and pooled serum or renal tissue diluted in this buffer were placed on opposite sides of the membrane. The drugs were initially present in either the buffer or the rat serum in concentrations of 10 μg/ml. In the cortex, medulla, and papilla, the concentration was 50 μg/g. The chambers were then rotated for 18 h at 37°C, after which the content of each compartment was assayed for antibiotic by using standards prepared in the same diluent.

The half-lives (8), the area under the curve (AUC)(2, 15, 16), the total volume of distribution (8), the volume of distribution in the papilla (24), and the total and the urinary clearance (18) of both antibiotics were determined by standard methods.

Statistical analyses of the results were performed by the Student *t* test.

RESULTS

Table 1 shows the concentrations of gentamicin and netilmicin in the serum after 1, 3, or 14 10-mg/kg injections of either drug. The serum levels of both aminoglycosides were identical and similar to those found in humans (9, 17). The half-lives of the two antibiotics in serum were not clinically different (Table 2). At 4 h after the injections, we could not detect any antibiotic in the serum. The levels of both drugs in the cortex are compared in Fig. 1. After a single dose, gentamicin and netilmicin exhibited respective peak cortical values of 53 and 241 μg/g at 2 and 4 h after the injections ($P < 0.001$). The concentration of netilmicin decreased rapidly in the first 24 h, reaching a value of 95 μg/g. In contrast to the results with netilmicin, the level of gentamicin was more stable in the first 24 h of the experiment. After day 4, the cortical levels of both drugs were almost identical. The two antibiotics were still detectable within the cortex on day 25 of the experiment. The levels of gentamicin and netilmicin were 3.7 and 2.9 μg/g, respectively.

TABLE 1. *Average concentration of gentamicin and netilmicin in the serum at from 1 to 4 h after 1, 3, or 14 10-mg/kg doses of either drug*

Time (h)	No. of injections	Concn (μg/ml)	
		Gentamicin	Netilmicin
1	1	12.1 (0.8)[a]	14.5 (2.5)
	3	12.4 (1.7)	10.0 (2.0)
	14	8.8 (0.9)	9.9 (3.2)
2	1	2.3 (0.5)	2.8 (0.4)
	3	3.8 (1.2)	3.3 (0.6)
	14	0.5 (0.5)	1.6 (0.5)
4	1	<0.4	<0.4
	3	<0.4	<0.4
	14	<0.4	<0.4

[a] Numbers in parentheses are standard errors of the mean.

It is evident that there was a progressive increase in the cortical concentrations of both antibtiotics when the animals were given multiple doses (Fig. 1). The highest peak cortical concentrations were seen within the first 4 h after the last injection. After 14 injections, the concentration of netilmicin was 719 μg/g, whereas the maximal level reached with gentamicin was 633 μg/g. At most timed intervals, the concentrations of gentamicin within the cortex were slightly but not significantly lower than those of netilmicin. At 25 days after the last injection of 14 doses of either antibiotic, the levels of gentamicin and netilmicin were 28 and 24 μg/g, respectively. At all timed intervals, the cortical concentrations associated with multiple injections were significantly different than those seen after a single injection of either drug ($P < 0.01$).

In the medullary region of the kidney (Fig. 2), the peak concentrations of both drugs were reached within the first 4 h after the injection. After 3 and 14 injections, the concentrations of the two antibiotics in the medulla were always lower than those found in the cortex ($P < 0.01$).

TABLE 2. *Half-lives of gentamicin and netilmicin in the serum, cortex, medulla, papilla, and urine of normal rats at from 1 h to 25 days after 1, 3, or 14 injections*

No. of injections	Antibiotic	Half-life (h) in the:				
		Serum	Cortex	Medulla	Papilla	Urine
1	Gentamicin	0.29 (0.6)[a]	174 (32)	79.2 (20.3)	4.2 (1.3)	40.3 (6.2)
	Netilmicin	0.42 (0.15)	121 (17)	138 (23)	47.1 (39.2)	46.9 (7.2)
3	Gentamicin	0.59 (0.42)	111 (12)	100 (13)	50.8 (12.1)	63.3 (9.5)
	Netilmicin	0.48 (0.07)	113 (12)	102 (14)	0.9 (0.3)	63.4 (9.2)
14	Gentamicin	0.24 (0.20)	144 (17)	133 (16)	38.2 (4.7)	76.8 (15.6)
	Netilmicin	0.38 (0.24)	134 (16)	124 (16)	218 (65)	74.3 (11.2)

[a] Numbers in parentheses are standard errors of the mean.

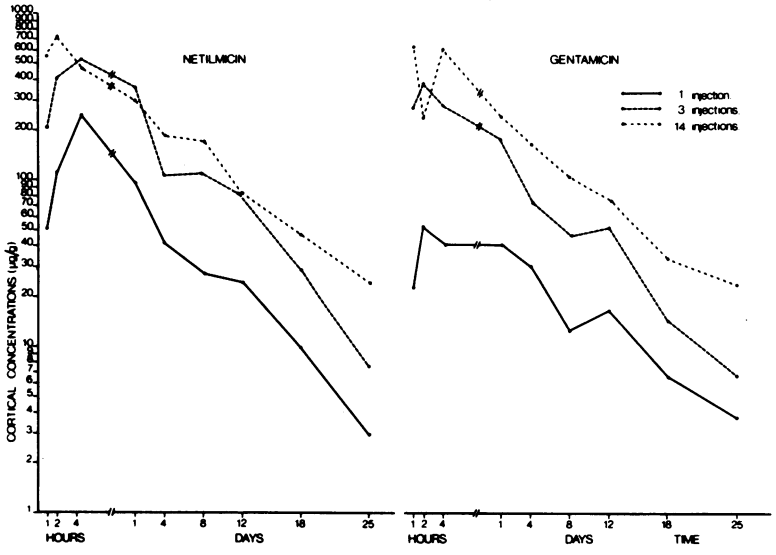

FIG. 1. *Cortical concentrations of netilmicin and gentamicin at from 1 h to 25 days after 1, 3, or 14 10-mg/kg injections of either drug.*

The levels of both antibiotics within the medulla were almost identical after a single injection, but netilmicin could still be detected on day 25, whereas gentamicin was undetectable on day 18 (Fig. 2). After three injections of the aminoglycosides, the mean medullary concentration of netilmicin in the first 12 days was above that of gentamicin. Thereafter they were identical. After 14 injections of the two drugs, the medullary levels were not significantly different.

The administration of 3 and 14 injections of the drugs resulted in a noticeable accumulation of antibiotics in the medulla. This intrarenal accumulation was proportional to the total dose given, so that there was a significant difference between the tissue levels after 1, 3, and 14 injections ($P < 0.01$). Therapeutic concentrations of netilmicin could be detected in the medulla for up to 25 days after single or multiple doses. In contrast, multiple injections were necessary to obtain reasonable levels of gentamicin up to 25 days after the last dose.

The papillary and urinary concentrations of both drugs are presented in Table 3. The concentrations in the papilla were much lower ($P < 0.01$) than those detected in the cortex and the medulla. On day 12 of the experiment, we could not detect any antibiotic in the animals which had received one or three injections. After 14 injections therapeutic levels persisted up to 25 days. Maximal urinary concentrations of both antibiotics were obtained in the first 2 h after the last injection. With the exception of single-dose therapy, both antibiotics were present in the urine up to the last day of the experiment.

From 50 to 60% of the aminoglycoside injected was eliminated within the first hour after the intraperitoneal injection. Table 4 shows the quantities of antibiotics in whole kidneys, which were estimated by adding the amount recovered in the different portions of the kidney. More netilmicin than gentamicin was usually present in the kidney. There was also an increase in the total amount of drug recovered in the kidney

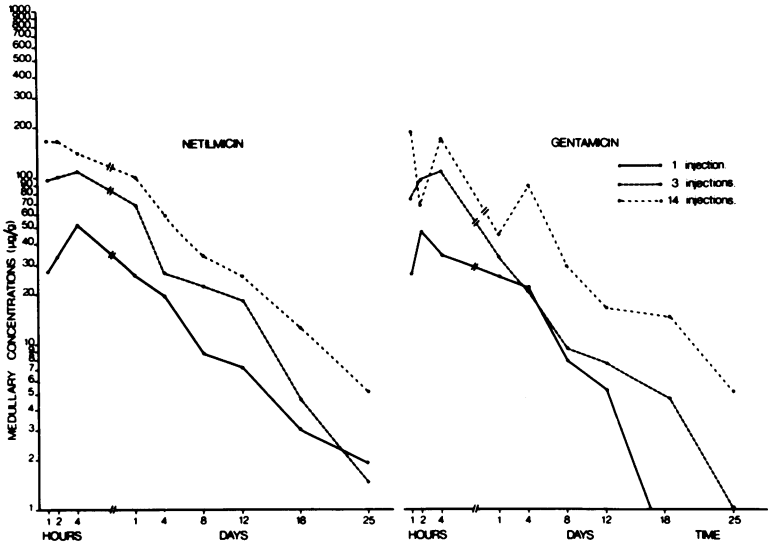

FIG. 2. *Medullary concentrations of netilmicin and gentamicin at from 1 h to 25 days after 1, 3, or 14 10-mg/kg injections of either drug.*

TABLE 3. *Average concentration of gentamicin and netilmicin in the papilla and urine of rats at from 1 h to 25 days after 1, 3, and 14 injections*

Time	No. of injections	Concn (μg/g) in papilla		Concn (μg/ml) in urine	
		Gentamicin	Netilmicin	Gentamicin	Netilmicin
1 h	1	109 (13)[a]	67.6 (15.0)	7373 (1581)	5454 (1302)
	3	92.7 (43.6)	84.7 (14.9)	7945 (2087)	4516 (511)
	14	106 (15)	47.3 (12.5)	3978 (851)	1519 (436)
2 h	1	73.3 (18.2)	42.7 (4.6)	4125 (937)	2800 (191)
	3	40.5 (11.7)	44.2 (8.2)	7050 (800)	5614 (920)
	14	12.6 (2.1)	28.1 (2.2)	869 (869)	984 (197)
4 h	1	110 (77)	1.7 (1.1)	208 (78)	153 (54)
	3	18.9 (2.5)	8.2 (2.4)	212 (21)	273 (54)
	14	29.8 (4.1)	13.2 (3.3)	125 (23)	2710 (369)
1 day	1	2.4 (1.5)	5.7 (2.0)	8.2 (3.6)	15.5 (2.3)
	3	1.5 (0.5)	Nil	30.4 (5.6)	42.2 (9.5)
	14	4.0 (0.7)	5.8 (1.3)	33.6 (9.4)	24.1 (2.1)
4 days	1	Nil	4.7 (1.5)	9.8 (2.5)	11.0 (1.0)
	3	3.7 (0.9)	Nil	22.3 (2.2)	19.9 (3.4)
	14	5.4 (1.0)	10.9 (2.1)	15.9 (3.1)	27.8 (2.2)
8 days	1	Nil	Nil	4.1 (1.0)	6.2 (1.5)
	3	0.8 (0.5)	Nil	8.0 (0.8)	21.8 (3.1)
	14	5.4 (1.2)	8.8 (2.4)	8.7 (1.9)	12.9 (2.2)
12 days	1	Nil	Nil	2.6 (1.0)	3.4 (0.6)
	3	Nil	Nil	4.1 (0.7)	14.0 (2.9)
	14	5.9 (2.0)	4.5 (0.9)	5.0 (1.2)	7.3 (2.1)
18 days	1	Nil	Nil	0.8 (0.3)	0.13 (0.13)
	3	1.7 (0.4)	Nil	2.8 (0.6)	3.3 (1.3)
	14	Nil	4.8 (0.8)	6.8 (0.8)	6.8 (1.2)
25 days	1	Nil	Nil	Nil	0.18 (0.18)
	3	0.5 (0.5)	Nil	2.2 (1.5)	1.80 (1.28)
	14	2.2 (0.9)	2.9 (0.3)	1.1 (0.5)	3.0 (1.8)

[a] Numbers in parentheses are standard errors of the mean.

after 3 and 14 successive injections (Table 4). The weights of the kidneys of the animals receiving the two drugs were identical. In the first hour after a single injection, the medullary and papillary regions contributed up to 45% of the antibiotic found in the kidney. After 24 h, more than 75% of the antibiotic was located in the cortex, whereas 15 to 25% of the drug was found

TABLE 4. *Amount of gentamicin and netilmicin in the kidney and relative proportions found in the cortex, medulla, and papilla at various times after 1, 3, and 14 10-mg/kg injections of the drugs*

Time	No. of injections	Amt (μg) in kidney		% In cortex		% In medulla		% In papilla	
		Gentamicin	Netilmicin	Gentamicin	Netilmicin	Gentamicin	Netilmicin	Gentamicin	Netilmicin
1 h	1	15.8 (1.5)[a]	31.3 (4.1)	53.7 (2.1)	63.0 (1.2)	30.0 (1.9)	31.4 (1.1)	16.3 (2.3)	5.6 (0.7)
	3	132 (27)	117 (17)	79.6 (2.6)	67.0 (1.1)	18.6 (2.2)	30.8 (0.9)	1.8 (0.5)	2.2 (0.5)
	14	322 (32)	272 (24)	77.0 (2.5)	81.1 (2.3)	22.1 (2.5)	18.5 (2.3)	0.9 (0.2)	0.4 (0.1)
2 h	1	35.5 (4.0)	55.7 (4.2)	68.0 (2.9)	75.0 (3.4)	27.7 (2.6)	23.2 (3.4)	4.3 (0.8)	1.8 (0.2)
	3	167 (31)	192 (34)	84.4 (0.9)	80.8 (1.2)	14.9 (0.8)	18.3 (1.2)	0.7 (0.3)	0.9 (0.3)
	14	123 (14)	338 (42)	81.7 (1.1)	87.7 (1.4)	18.0 (1.1)	12.1 (1.4)	0.3 (0.0)	0.2 (0.1)
4 h	1	25.7 (2.0)	113.9 (11.8)	70.8 (4.1)	83.8 (1.6)	25.2 (5.7)	16.2 (1.5)	3.9 (2.3)	Nil
	3	127 (13)	237 (31)	78.5 (1.2)	84.4 (3.2)	21.1 (1.2)	15.5 (3.2)	0.4 (0.0)	0.1 (0.0)
	14	287 (32)	246 (34)	81.8 (1.7)	83.6 (2.5)	17.9 (1.7)	16.3 (2.5)	0.3 (0.0)	0.1 (0.0)
1 day	1	22.4 (3.2)	43.2 (16.9)	77.2 (2.0)	82.1 (4.7)	22.6 (1.9)	17.7 (4.7)	0.2 (0.1)	0.2 (0.1)
	3	67.8 (9.6)	158 (25)	83.8 (0.4)	89.1 (7.1)	16.1 (0.4)	10.9 (1.1)	0.1 (0.0)	Nil
	14	109 (16)	154 (21)	84.6 (2.2)	74.7 (1.3)	15.3 (2.1)	25.2 (1.3)	0.1 (0.0)	0.1 (0.0)
4 days	1	15.0 (1.2)	22.3 (1.9)	76.6 (2.3)	79.4 (2.9)	23.4 (2.3)	20.0 (2.7)	Nil	0.6 (0.2)
	3	40.3 (5.4)	56.4 (9.6)	83.7 (1.3)	87.0 (3.0)	16.1 (1.3)	13.0 (3.0)	0.2 (0.1)	Nil
	14	116 (16)	100 (9)	73.9 (1.6)	77.2 (0.6)	26.0 (1.6)	22.5 (0.6)	0.1 (0.0)	0.4 (0.1)
8 days	1	7.1 (0.5)	13.8 (1.4)	72.6 (2.1)	77.3 (0.4)	27.4 (2.1)	22.7 (0.4)	Nil	Nil
	3	18.9 (2.1)	53.7 (5.7)	83.5 (2.1)	85.3 (1.7)	16.5 (2.0)	14.7 (1.7)	0.1 (0.1)	Nil
	14	52.7 (6.7)	76.8 (15.9)	80.9 (1.7)	83.0 (1.0)	18.7 (1.6)	16.7 (1.0)	0.3 (0.1)	0.3 (0.1)
12 days	1	8.5 (0.5)	13.4 (2.4)	84.3 (3.1)	77.2 (2.6)	15.7 (3.1)	22.8 (2.6)	Nil	Nil
	3	24.1 (3.3)	34.0 (3.6)	87.2 (1.5)	81.2 (3.2)	12.8 (1.5)	18.8 (3.2)	Nil	Nil
	14	35.6 (6.8)	45.0 (5.2)	82.4 (1.7)	83.2 (0.9)	16.9 (1.8)	16.5 (0.9)	0.7 (0.4)	0.3 (0.1)
18 days	1	3.1 (1.0)	4.9 (1.1)	82.0 (1.0)	75.2 (2.9)	18.0 (1.0)	24.8 (2.9)	Nil	Nil
	3	6.8 (1.1)	14.3 (3.7)	73.6 (1.7)	84.6 (2.4)	25.8 (1.6)	15.4 (2.4)	0.7 (0.2)	Nil
	14	17.2 (1.5)	23.3 (5.5)	71.0 (2.4)	81.2 (1.2)	29.0 (2.4)	18.1 (1.2)	Nil	0.7 (0.1)
25 days	1	1.6 (0.6)	1.7 (0.6)	100 (1.0)	68.2 (4.2)	Nil	31.8 (4.2)	Nil	Nil
	3	3.2 (0.9)	3.5 (0.9)	86.0 (1.0)	73.8 (8.0)	13.5 (0.9)	26.2 (8.0)	0.5 (0.5)	Nil
	14	14.2 (1.9)	12.5 (2.3)	87.5 (1.4)	85.1 (1.3)	12.2 (1.4)	14.2 (1.4)	0.3 (0.1)	0.7 (0.1)

[a] Numbers in parentheses are standard errors of the mean.

in the medulla and less than 1% of either aminoglycoside was distributed in the papilla.

The half-lives of the two drugs in the serum, cortex, medulla, and papilla of the kidney are shown in Table 2. The rate of elimination from the cortex and medulla or the apparent half-life of each drug was evaluated between the first hour and day 25 after the last dose. The half-lives of gentamicin and netilmicin were different when 1 and 14 injections were given ($P < 0.01$).

The AUC of both antibiotics in the serum were identical, but the AUC (in micrograms per minute per milliliter) of netilmicin within the cortex was significantly higher than that of gentamicin after 1 (778 versus 428 μg/min per ml), 3 (2,450 versus 1,354 μg/min per ml) or 14 injections (3,138 versus 2,642 μg/min per ml) ($P < 0.01$). The total volume of distribution of netilmicin (102 ml) was not significantly different from that of gentamicin (89 ml). After 14 days of treatment, the apparent volumes of distribution of gentamicin (11.3 μl) and netilmicin (14.1 μl) in the papilla were identical. The clearance of both aminoglycosides (0.9 ml/min) was identical to that of the creatinine clearance (0.9 ml/min). We did not detect any change in the creatinine clearance after multiple doses of antibiotics. The blood urea nitrogen was also stable.

As Table 5 shows, gentamicin and netilmicin were weakly bound to serum, but both antibiotics were highly bound to the different parts of the kidney. The binding of gentamicin to the cortex was 49%, whereas netilmicin exhibited a higher binding (65.8%).

DISCUSSION

This investigation has clearly established the intrarenal accumulation of netilmicin and gentamicin. Both antibiotics were recovered in therapeutic concentrations for up to 25 days after one or multiple injections. Although most investigators (1, 3, 7, 14) have studied the concentration of aminoglycosides in the whole kidney or in the cortex after multiple toxic doses of these drugs, only a few people (6, 22, 23) have tried to define the pharmacological behaviors of these antimicrobial agents in the cortex, medulla (outer medulla), and papilla (inner medulla and papillary tip) after therapeutic doses.

In our studies, the levels of gentamicin and netilmicin in the serum were comparable to those obtained in humans receiving standard doses of these antimicrobial agents (9, 17). The half-lives of these drugs were shorter in rats than in humans, but the urinary excretion described here closely paralleled the rate of urinary elimination seen in humans (9).

The results show that netilmicin behaved differently than gentamicin in the first 24 h of the experiment. The high peak cortical concentrations of netilmicin obtained after a single 10-mg/kg dose were followed by a rapid decline in these levels. In contrast, the concentration of gentamicin reached a much lower peak cortical value, which was stable for 24 h. These data suggest that the affinities of the two aminoglycosides for receptor sites within or on the surface of renal cells might be different.

Our investigation also suggests that both gentamicin and netilmicin might have a limited capacity to accumulate in the cortex and the medulla. Luft et al. have estimated this capacity to be around 500 μg/g (13, 14). It is interesting to note that in our study the maximal value obtained after multiple dosages of the aminoglycoside was around 700 μg/g. This cellular accumulation appeared to be maximal after 14 injections of the aminoglycosides.

Our findings are in agreement with those of other investigators, who have demonstrated similar persistence of aminoglycosides for several weeks after antibiotic treatment has been stopped (6, 11, 13, 19). Several explanations have been proposed for the persistence and accumulation of those antibiotics within the renal parenchyma (4, 5, 7, 10, 21–23).

The most likely mechanism by which these aminoglycosides concentrate in the kidney is their binding to renal cells. Many authors have suggested that this binding of aminoglycosides might be localized on the cell membranes, organelles, or intracellular protein (10, 12, 22). This could explain why the antibiotics persisted for many days in the kidney and accumulated in the tissue after multiple doses (11, 19). The link between the antibiotics and the renal cells is transient. This allows the aminoglycosides to be liberated slowly and recovered in the urine.

An important finding was the presence of sig-

TABLE 5. *Protein binding of gentamicin and netilmicin to serum and homogenates of cortex, medulla, and papilla of rats*

Antibiotic	% Protein binding to:			
	Serum	Cortex	Medulla	Papilla
Gentamicin	1.5	49.1	63.7	45.2
Netilmicin	1.1	65.8	56.8	50.7

nificant concentrations of both aminoglycosides in the papilla (inner medulla and papillary tip) and medulla (outer medulla) up to 25 days after the cessation of the drug treatments in the animals which were treated for 7 days. Bacterial growth being largely limited to the medulla and papilla in pyelonephritis, the accumulation of these aminoglycosides within the medulla and papilla may be critical in the therapy of renal infections (22). These drugs can be of therapeutic value as long as their binding to the kidney cells does not limit their biological activity.

ACKNOWLEDGMENTS

We are deeply grateful to Nicole Poisson and Céline Lessard for their technical assistance.

This study was supported by grants DG-132 and MA-5527 from the Medical Research Council of Canada and by a grant from Schering Corp.

LITERATURE CITED

1. **Barza, M., Y. Pinn, P. Tanguay, and T. Murray.** 1978. Nephrotoxicity of newer cephalosporins and aminoglycosides alone and in combination in a rat model. J. Antimicrob. Chemother. 4(Suppl.):59–68.
2. **Bergan, T., and E. K. Brodwall.** 1972. Human pharmacokinetics of a sulfamethoxazole-trimethoprim combination. Acta Med. Scand. **192**:483–492.
3. **Bowman, R. L., F. J. Silverblatt, and G. J. Kaloyanides.** 1977. Comparison of the nephrotoxicity of netilmicin and gentamicin in rats. Antimicrob. Agents Chemother. **12**:474–478.
4. **Chiu, P. J. S., A. Brown, G. Miller, and J. F. Long.** 1976. Renal extraction of gentamicin in anaesthetized dogs. Antimicrob. Agents Chemother. **10**:277–282.
5. **Chiu, P. J. S., G. H. Miller, A. D. Brown, J. F. Long, and J. A. Waitz.** 1977. Renal pharmacology of netilmicin. Antimicrob. Agents Chemother. **11**: 821–825.
6. **Fabre, J., M. Rudhardt, P. Blanchard, and C. Regamey.** 1976. Persistence of sisomicin and gentamicin in renal cortex and medulla compared with other organs and serum of rats. Kidney Int. **10**:444–449.
7. **Gilbert, D. N., C. Plamp, P. Starr, W. M. Bennett, D. C. Houghton, and G. Porter.** 1978. Comparative nephrotoxicity of gentamicin and tobramycin in rats. Antimicrob. Agents Chemother. **13**:34–40.
8. **Greenblatt, D. J., and J. Koch-Weser.** 1975. Clinical pharmacokinetics. N. Engl. J. Med. **293**:702–705, 964–970.
9. **Gyselynck, A. M., A. Forrey, and R. Cutler.** 1971. Pharmacokinetics of gentamicin: distribution and plasma and renal clearance. J. Infect. Dis. **124**(Suppl.): 70–76.
10. **Hsu, C. H., T. W. Kurtz, and J. M. Weller.** 1977. In vitro uptake of gentamicin by rat renal cortical tissue. Antimicrob. Agents Chemother. **12**:192–194.
11. **Kahlmeter, G., and C. Kamme.** 1975. Prolonged excretion of gentamicin in a patient with unimpaired renal function. Lancet **i**:286.
12. **Kornguth, M. L., and C. M. Kunin.** 1977. Distribution of gentamicin and amikacin in rabbit tissues. Antimicrob. Agents Chemother. **11**:974–977.
13. **Luft, F. C., and S. A. Kleit.** 1974. Renal parenchymal accumulation of aminoglycoside antibiotics in rats. J. Infect. Dis. **130**:656–659.
14. **Luft, F. C., M. N. Yum, and S. A. Kleit.** 1976. Comparative nephrotoxicities of netilmicin and gentamicin in rats. Antimicrob. Agents Chemother. **10**:845–849.
15. **Normand, M.** 1972. APL computer program for the analytical and numerical integration of hormonal disappearance data. Can. J. Physiol. Pharmacol. **50**:845–852.
16. **Normand, M., and C. Fortier.** 1970. Numerical versus analytical integration of hormonal disappearance data. Can. J. Physiol. Pharmacol. **48**:274–281.
17. **Panwalker, A. P., J. B. Malow, V. M. Zimelis, and G. G. Jackson.** 1978. Netilmicin: clinical efficacy, tolerance, and toxicity. Antimicrob. Agents Chemother. **13**: 170–176.
18. **Ritschel, W. A.** 1976. Handbook of basic pharmacokinetics, 1st ed. Drug Intelligence Publications, Inc., Hamilton, Ill.
19. **Shentag, J. J., W. J. Jusko, J. W. Vance, T. J. Cumbo, E. Abrutyn, M. Delattre, and L. M. Gerbracht.** 1977. Gentamicin disposition and tissue accumulation on multiple dosing. J. Pharmacokinet. Biopharm. **5**:559–577.
20. **Stamey, T. A., E. D. Govan, and J. M. Palmer.** 1965. The localization and treatment of urinary tract infection: the role of bactericidal urine levels as opposed to serum levels. Medicine (Baltimore) **44**:1–36.
21. **Szweb, J. J., F. C. Luft, H. R. Black, R. A. Elliott, and S. A. Kleit.** 1974. Comparison of the distribution of tobramycin and gentamicin in body fluids of dogs. Antimicrob. Agents Chemother. **5**:444–446.
22. **Whelton, A., G. G. Carter, T. J. Craig, H. H. Bryant, D. V. Herbst, and W. G. Walker.** 1978. Comparison of the intrarenal disposition of tobramycin and gentamicin: therapeutic and toxicologic answers. J. Antimicrob. Chemother. 4(Suppl.):13–22.
23. **Whelton, A., D. G. Sapir, G. G. Carter, J. Kramer, and W. G. Walker.** 1971. Intrarenal distribution of penicillin, cephalothin, ampicillin and oxytetracycline during varied states of hydration. J. Pharmacol. Exp. Ther. **179**:419–428.
24. **Whelton, A., and W. G. Walker.** 1974. Intrarenal antibiotic distribution in health and disease. Kidney Int. **6**: 131–137.