ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 1976, p. 277-282

Vol. 10, No. 2
Printed in U.S.A.

Renal Extraction of Gentamicin in Anesthetized Dogs

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Received for publication 25 February 1976

The tubular handling of gentamicin (G) and its intrarenal distribution were determined to elucidate the mechanism of G accumulation in the kidney. At a serum level of 11.1 ± 0.5 μg/ml (10 animals), as maintained by constant infusion for 5 h, serum Na^+ and K^+, arterial pressure, effective renal plasma flow and glomerular filtration rate remained undisturbed. The clearance values in milliliters per minute for G, inulin, and *p*-aminohippuric acid were 40.3 ± 1.8, 49.9 ± 2.8, and 132 ± 14, respectively. The ratio of clearance of G to clearance of inulin was 0.82 ± 0.04 ($P < 0.005$), suggesting net reabsorption of G by the renal tubules. The renal cortex/serum ratio for G was 11.9 ± 2.1, and the medulla/serum ratio was 2.7 ± 0.4, indicating greater uptake of G by the cortex. The extraction ratio of *p*-aminohippuric acid was 0.74 ± 0.03. In contrast, the extraction ratio of G was 0.20 ± 0.03, which was significantly lower than that of inulin (0.30 ± 0.04). It is concluded that the accumulation of G in the cortex was due to tubular reabsorption. Probably some of the reabsorbed G became trapped in the epithelial cells after crossing the luminal membrane, whereas some returned to the circulation.

Gentamicin, an aminoglycoside antibiotic, is potentially nephrotoxic, particularly with excessive blood levels or in subjects with preexistent renal insufficiency (16). Gentamicin-induced nephrotoxicity has been documented in man (10, 25, 37), as expressed by elevations in blood urea nitrogen and serum creatinine levels. In rats (11, 19) and dogs (3), histopathological studies have shown that gentamicin caused tubular necrosis in the proximal convoluted tubule. Renal biopsy in patients also revealed tubular damage (25). As the kidney is the major route of elimination of gentamicin, its functional status is important in the development of nephrotoxicity in human subjects (8, 12, 29).

The clearance value for gentamicin has been found similar to glomerular filtration rate in dogs (3, 32) and man (14). It has also been established that there is significant correlation between the serum half-life of gentamicin and the glomerular filtration rate (12). Prolonged serum half-life is usually seen in patients with severe renal insufficiency (14, 21) or in animals with partial nephrectomy (15). In animals and human subjects with normal kidney function, the bulk of gentamicin administered appeared in the urine within 24 h (3, 7, 14, 26, 30).

Gentamicin uptake by the renal tissue was found in animals (H. Whalig, Proc. Int. Congr. Chemother., 8th, Athens, Greece, Abstr. A-14, 1973) as well as in man (1). In addition, prolonged half-life of gentamicin has been observed in rat kidney (22). The presence of tubular transport of gentamicin coupled with its concentration in the renal tissue may be related to its nephrotoxicity and/or delayed excretion (24; H. Whalig, Proc. Int. Congr. Chemother., 8th, Athens, Greece, Abstr. A-74, 1973).

We studied the tubular handling of gentamicin and intrarenal distribution by clearance techniques and tissue analysis, respectively, in an attempt to elucidate the mechanism of gentamicin accumulation in the kidney. Further, the effects of gentamicin on rrenal hemodynamics and electrolyte excretion were determined.

(This work has been published in abstract form [Annu. Meet. Am. Soc. Nephrol., 8th, Washington, D.C., 1975, p. 75].)

MATERIALS AND METHODS

Mongrel dogs of either sex were fasted overnight and were anesthetized with Nembutal (30 mg/kg, intravenously [i.v.]) on the day of each experiment. The animals were breathing spontaneously during each experiment. A suprapubic incision was made, and both ureters were cannulated with polyethylene tubing for urine collection. The left femoral artery was cannulated for measurement of blood pressure. The spermatic or ovarian vein was cannulated for sampling renal venous blood. The animals were given 400 to 500 ml of physiological saline to replace fluid loss and to ensure adequate urinary flow. The animals were given a priming injection of inulin, *p*-aminohippuric acid (PAH) and, except in the control

animals, gentamicin (2.0 mg/kg, i.v.). An i.v. infusion immediately followed which contained sustaining doses of PAH and inulin in physiological saline at a rate of 4.0 ml/min. Except in the control experiments, gentamicin (30 mg/ml) was given in this infusion at a dose of 3.0 mg/kg per h. At least 1 h was allowed for equilibration before sample collections so that a steady-state blood level of the compounds could be attained. Urine samples were then taken every 25 min. Blood samples were drawn at the beginning and the end of each urine collection period; plasma from heparinized portions was used to determine PAH and inulin levels, and serum from nonheparinized portions was used to determine electrolytes and gentamicin. At the end of each experiment, both kidneys were excised. Portions of cortex and inner medulla were analyzed for gentamicin. Urine and blood samples were analyzed for PAH (5) and inulin (9). Sodium and potassium concentrations were determined with flame photometry.

Gentamicin in serum and urine was assayed by the cylinder-plate method with *Bacillus subtilis* (ATCC 6633) as the test organism (28). Tissue samples were weighed, diluted 1:5 with 0.1 M phosphate buffer (pH 8), and homogenized in a Tissumax homogenizer. The homogenates were assayed microbiologically in a manner similar to the serum level determination, except that the standard curve was prepared from control tissue homogenates.

Calculations. (i) Clearances. The clearance values of each compound was obtained by the equation U_XV/P_X, where U_X and P_X are the urinary and total plasma concentrations of compound X, respectively. V represents the urinary flow rate in milliliters per minute. Clearance rates of PAH and inulin were used to measure effective renal plasma flow and glomerular filtration, respectively.

(ii) Extraction ratio. The renal extraction ratio was calculated by dividing the arteriovenous concentration difference by the arterial concentration, or $(Pa - Pv)/Pa$, where Pa and Pv are the concentrations in arterial and renal venous plasma, respectively.

(iii) Fractional excretion of Na^+ or K^+. The fractional excretion of Na^+ or K^+ was calculated by the equation $(U_X \cdot V/GFR \cdot P_X) \times 100$, where U_X and P_X are urinary and serum concentrations of the electrolytes, and GFR is glomerular filtration.

All data were subjected to statistical analyses. The Student t test for independent and dependent variables was used to make appropriate comparisons.

RESULTS

Effect of gentamicin on serum electrolytes and blood pressure. At a serum level of 11.1 ± 0.5 μg/ml (N=10), as maintained by constant infusion for 5 h (Fig. 1), all animals demonstrated stable arterial blood pressure. The concentrations of serum sodium and potassium remained undisturbed and were similar to untreated animals (data not shown).

Urine and electrolyte excretion. No differences were discerned between the gentamicin and saline groups with respect to urinary flow (Table 1) and excretion of sodium and potassium. Mild natriuresis and kaliuresis in these animals were indications of physiological responses to moderate extracellular fluid volume expansion associated with the saline infusion.

Inulin and PAH clearances. The inulin and PAH clearances were quite stable throughout the experiments in animals treated with gentamicin, as shown in Fig. 2. The mean values of the two parameters did not differ from those of the animals receiving only saline (Table 2). Thus, gentamicin did not seem to show any adverse effects on the renal hemodynamics under the conditions of the present study.

Renal clearance of gentamicin. The clearance values of gentamicin were consistently less than inulin clearance values in all animals (Fig. 3); the difference between the mean values of the two parameters was statistically sig-

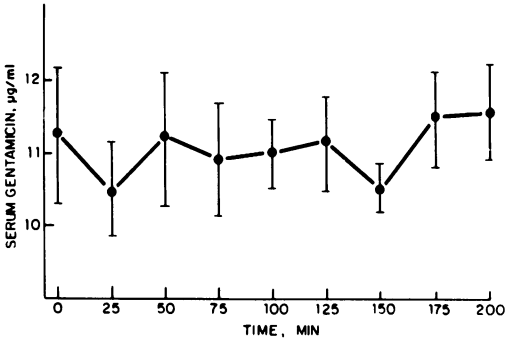

FIG. 1. *Serum levels of gentamicin during sustaining i.v. infusion in anesthetized dogs. Each point represents the mean of 10 animals; the vertical bars are standard errors. No significant alterations in serum concentrations were detected throughout the experiments.*

TABLE 1. *Urinary electrolyte excretion in dogs under constant infusion of saline and gentamicin*[a,b]

Electrolyte determination	Saline group (N = 7)	Gentamicin group (N = 10)
V (ml/min)[c]	1.6 ± 0.2	1.7 ± 0.2
$U_{Na}V$ (μeq/min)[c]	108 ± 18	127 ± 29
U_KV (μeq/min)[c]	37.1 ± 5.0	40.4 ± 5.4
FE_{Na} (%)[d]	1.8 ± 0.4	1.8 ± 0.4
FE_K (%)[d]	22.7 ± 2.8	23.1 ± 3.3

[a] All values represent means ± standard error.

[b] None of the differences between values was significant.

[c] $U_{Na}V$ and U_KV are absolute rate of urinary excretion of Na^+ and K^+, respectively. V is the urine flow rate.

[d] FE_{Na} and FE_K represent the percentage of filtered Na^+ and K^+ being excreted in the urine, respectively.

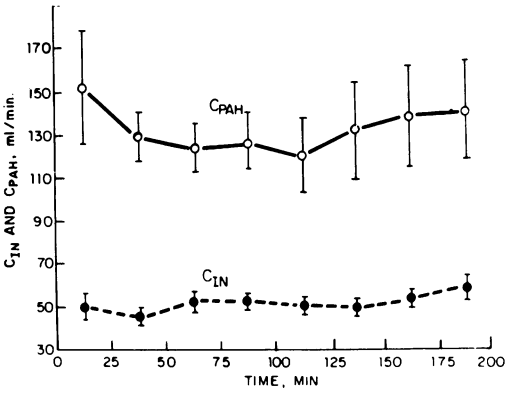

FIG. 2. *Effect of gentamicin on clearances of PAH (C_{PAH}) and inulin (C_{In}) in anesthetized dogs. C_{PAH} and C_{In} measure effective renal plasma flow and glomerular filtration rate, respectively. Each point represents the mean value of 10 animals; the vertical bars represent standard errors.*

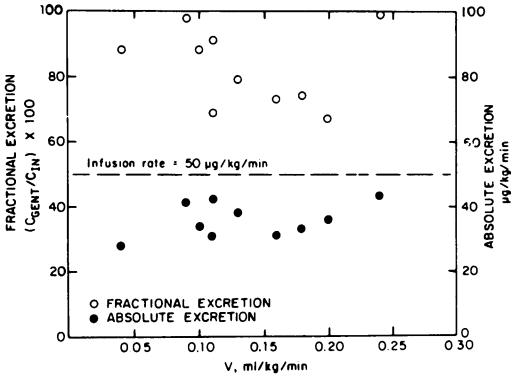

FIG. 3. *Urine flow rate versus urinary excretion of gentamicin in anesthetized dogs. Symbols: (○) fractional excretion of gentamicin; (●) absolute rate of excretion, of which all are less than the sustaining infusion rate (- - -). Each circle represents mean of eight consecutive clearance values per animal.*

nificant (Table 2). The ratio of clearance of gentamicin to clearance of inulin was 0.82 ± 0.04 ($P < 0.005$), significantly less than unity, suggesting that some gentamicin was reabsorbed by the renal tubule after being filtered (Table 2). The percentage of administered gentamicin that appeared in the urine was 71.2 ± 3.4; the fractional excretion and absolute excretion rate were independent of urine flow rate (Fig. 3).

Renal extraction ratios. The extraction ratios of PAH appeared unaffected by gentamicin (Table 3), since they were similar to control values obtained in this study and to values in the literature for dogs (27, 33). The normal extraction ratios and clearance values in drug-treated animals (Table 2), therefore, indicated that the presence of the drug did not interfere with the tubular secretion of PAH. On the other hand, the extraction ratio for gentamicin was significantly lower than the extraction ratio for inulin, presenting further evidence that the compound underwent tubular reabsorption.

Renal tissue and urine antibiotic levels. The concentration of gentamicin in the renal cortex was 12 times as much as the serum level (Table 4). In contrast, the medullary concentration of gentamicin was less than 3 times the serum level. The mean urinary concentration of gentamicin was 310 ± 74 µg/ml and was over 10 times as much as the medullary concentration.

DISCUSSION

The present finding that gentamicin clearance was 82.5% of inulin clearance suggested the existence of tubular reabsorption. Since at concentrations of up to 5 mg/ml about 30% gen-

TABLE 2. *Renal handling of gentamicin in anesthetized dogs*[a]

Determination	Saline group ($N = 7$)	Gentamicin group ($N = 10$)
C_G (ml/min)[b]		40.3 ± 1.8
C_{In} (ml/min)[b]	46.7 ± 4.4	49.9 ± 2.8
C_{PAH} (ml/min)[b]	108 ± 6	132 ± 14
FE_G (%)[c]		82.5 ± 3.7[d]
U_GV (µg/kg per min)[e]		35.6 ± 1.7
V (ml/kg per min)[e]	0.14 ± 0.03	0.14 ± 0.02

[a] All values represent means ± standard error.
[b] C_G, C_{In}, and C_{PAH}, Clearance values for gentamicin, inulin, and PAH, respectively.
[c] FE_G, Percentage of filtered gentamicin being excreted in the urine.
[d] Mean value is significantly ($P < 0.005$) less than 100%.
[e] U_GV, Absolute rate of urinary excretion of gentamicin. V is the urine flow rate.

TABLE 3. *Extraction ratios of gentamicin, inulin, and PAH in anesthetized dogs*[a,b]

Determination	Saline group ($N = 7$)	Gentamicin group ($N = 7$)
Inulin	0.29 ± 0.05[c]	0.30 ± 0.04
PAH	0.69 ± 0.03	0.74 ± 0.03
Gentamicin		0.20 ± 0.03[d]

[a] Extraction ratio = $(Pa - Pv)/Pa$, where Pa and Pv are the femoral arterial and renal venous concentrations of the individual compounds, respectively.
[b] All values represent means ± standard error.
[c] Mean value of four animals; measurements of venous inulin in the other three animals were not done.
[d] Significantly different from the mean exctraction ratio for inulin ($P < 0.05$).

TABLE 4. *Gentamicin in serum, kidney, and urine of anesthetized dogs*[a]

Tissue examined	Gentamicin concn[b]	Ratio[c]
Serum (μg/ml)	10.4 ± 0.3	(C/S) 11.9 ± 2.1
Cortex (μg/g)[d]	122.8 ± 22.1	(M/S) 2.7 ± 0.4
Medulla (μg/g)[d]	28.2 ± 4.0	(C/M) 4.8 ± 0.8
Urine (μg/ml)	310 ± 74	

[a] All values represent means ± standard error of seven dogs.

[b] Gentamicin (2 mg/kg, i.v.) was given and followed by sustaining infusion at a rate of 3.0 mg/kg per h, the total dose administered being approximately 200 mg per animal over a period of 5 h.

[c] C/S and M/S, Cortex to serum and medulla to serum concentration ratios, respectively. C/M is cortex to medulla ratio. Serum concentrations of gentamicin are shown on Fig. 1.

[d] Tissue concentration is based on the wet weight of tissues.

tamicin was reported to be protein bound in human sera (6, 31), some authors suggested tubular secretion of gentamicin (8, 14), because in their experiments gentamicin clearance exceeded inulin clearance, after corrections were made for presumed serum protein binding. Since only the free form is available for filtration, the clearance value of gentamicin may be underestimated by using the total serum concentration in our calculations. However, a recent report (13) showed that at a concentration close to therapeutic level (5 μg/ml) and measured under physiological conditions of temperature and pH, serum protein binding of gentamicin was absent. Naumann and Auwärter (26) also found no evidence of serum protein binding of gentamicin with concentrations of 2.5 and 5.0 μg/ml. It is probable that protein binding was negligible at serum levels around 10 μg/ml, as existed in the present experiments.

In contrast with PAH, which is profusely secreted by the proximal tubule and has a high extraction ratio (33), gentamicin has a very low extraction ratio. This value is even less than that for inulin, which is neither reabsorbed nor secreted (Table 2). It appeared that some of the filtered gentamicin was reabsorbed by the renal tubule and returned to the peritubular capillary network; the low extraction ratio was due to a smaller arteriovenous concentration difference relative to the arterial concentration. The finding provides additional evidence that gentamicin reabsorption occurs in the proximal tubule. The possibility of net tubular secretion can be ruled out at this point.

Although there are active transport systems in the proximal tubule of the nephron for exogenous organic compounds, passive reabsorption of many of these compounds occurs in the distal nephron and is influenced by the lipid solubility and pKa of the specific organic acid or base under consideration, in addition to urine flow and urine pH. Alterations in urine pH (23) and urine flow (17) did not influence urinary excretion of gentamicin in human subjects. In the present study the excretion of gentamicin was found to be independent of urine flow rate as well. The findings are suggestive of minimal nonionic back-diffusion of gentamicin in the distall nephron in spite of the great differences between the urinary and medullary concentrations (Table 4).

Gentamicin demonstrated preferential accumulation in the renal cortex (Table 4). Based on the whole-kidney weight of the dog (approximately 60 g), it is estimated that the cortex contained about 4 mg of the compound, less than 2% of the administered dose. It seems evident that there is a reabsorptive mechanism for gentamicin in the proximal tubule, the major portions of which are situated in the cortex. High affinity of gentamicin for kidney cell particulates has been reported (20), and the filtered compound was probably bound to the intracellular substances after crossing the luminal membrane, and concentration buildup ensued. Accumulation of gentamicin in the renal tissue occurs in animals (H. Whalig, Proc. Int. Congr. Chemother., 8th, Athens, Greece, Abstr. A-74, 1973) and man (1). Furthermore, Luft and Kleit (22) observed a half-life of 109 h in the kidney of rats after a single subcutaneous injection of gentamicin, 10 mg/kg (cf. serum half-life: 0.5 h). In addition, the drug was found in serum and in urine for more than a week after the last dose in uremic patients (24). Delayed excretion of gentamicin also occurred in mice and dogs (H. Whalig, Proc. Int. Congr. Chemother., 8th, Athens, Greece, Abstr. A-74, 1973). Bergan et al. (2) found that the clearance of gentamicin, even after correction was made for 30% protein binding, was markedly below the creatinine clearance in eight patients with chronic pyelonephritis. The authors suggested that the apparent enhancement of gentamicin reabsorption might provide a physiological correlate to the possibly increased incidence of nephrotoxicity in these patients with reduced kidney function. Although the relationship between the intracellular existence of this aminoglycoside antibiotic and its nephrotoxicity remains unclear, it is of interest to note that cephaloridine, a cephalosporin an-

tibiotic, resembles gentamicin in that it accumulates in the renal cortex and also causes acute necrosis of the proximal tubule (35). In contrast to gentamicin, cephaloridine is transported into the proximal tubular cell at the peritubular membrane, but does not move readily across the luminal membrane into the tubular fluid. Further studies did suggest that the nephrotoxicity of cephaloridine was related to its renal cortical transport, with high intracellular concentrations of drug (34).

Under the conditions of the present study, gentamicin did not appear to interfere with kidney function, as the animals had normal glomerular filtration and effective renal plasma flow (Table 2) in addition to slight natriuresis in response to the moderate extracellular fluid volume expansion with saline (Table 1). Serum levels as high as 30 to 40 μg/ml have been tested previously (32). It appears that the nephrotoxicity of gentamicin cannot be demonstrated in short-term experiments on anesthetized dogs with apparent normal kidney function, although dogs are known to be markedly sensitive to the nephrotoxic effects of aminoglycoside antibiotics (3).

In conclusion, the present data have provided evidence that gentamicin undergoes filtration and reabsorption in the kidney. That the bulk of filtered drug is excreted in the urine indicates that the renal clearance of gentamicin mainly depends on filtration rate (Fig. 3). Only a small fraction of filtered drug is reabsorbed by the proximal tubule. A portion of reabsorbate might have returned to the circulation, as shown by the low extraction ratio of the compound, whereas some was trapped in the epithelial cells, leading to cortical accumulation.

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