RENAL DISTRIBUTION AND PHARMACOKINETICS OF DIBEKACIN IN RABBITS WITH ASCENDING RENAL INFECTION

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The pharmacokinetics of dibekacin concerning the renal accumulation were studied in the normal rabbits and infected rabbits whose right kidneys were caused dysfunction by the ascending infection with *Escherichia coli* O-124.

The elimination half-lives ($T_{1/2\beta}$) were 155 min. in the infected rabbits and 73.4 min. in the normal rabbits. There was no difference in the renal clearances, cumulative urinary excretion amounts, and renal levels of dibekacin between the right and the left kidneys in the normal rabbits. In the infected rabbits, however, the renal clearances, the cumulative urinary excretion amounts and the renal levels of dibekacin in the ipsilateral kidneys were about 80% of those in the contralateral kidneys. There was a good linear relationship between the ratio of the renal dibekacin levels of the right to the left kidneys and the ratio of the cumulative urinary excretion amounts of the right to the left kidneys. It is considered that the renal accumulation of dibekacin is proportional to the amounts of the drug excreted from the kidneys into urine.

Aminoglycoside antibiotics accumulate in high concentrations in the kidneys of experimental animals[1~5] and humans[6,7], especially in the renal proximal epithelium, as shown by autoradiography[8~10], and the accumulation and the persistence of aminoglycoside antibiotics in the kidneys is often associated with renal damage. Since these antibiotics are often used in patients with renal disease, studies about the accumulation of these antibiotics in impaired kidneys are clinically important.

In the present report, pharmacokinetics concerning the renal accumulation of dibekacin, one of aminoglycoside antibiotics, were studied in rabbits whose right kidneys were caused dysfunction by ascending infection with *Escherichia coli* O-124. The advantage of this animal model is that the accumulation of a drug in the impaired kidneys can be compared with that in the normal kidneys within the same individuals.

MATERIALS AND METHODS

Materials : Dibekacin sulfate prepared by Meiji Seika Kaisha, Ltd. was used in the present studies. All other chemicals were of reagent grade.

Procedures of animal experiments : Male albino rabbits, weighing 3.0 to 3.5 kg were cannulated into bilateral ureters and a femoral artery. Through the cannula into the right ureter, 10^5 cells of *E. coli* O-124 were infused backward into the kidney. The infection was developed in the right kidney for 3 hours, while the cannula into the right ureter was pinched and urine flow was stopped. After 3-hour development of the infection, dibekacin was administered into an ear vein by a bolus injection. Blood samples were collected through the cannula into the femoral artery and urine samples were collected separately through each cannula into the ureter. The bilateral kidneys were removed 24 hours after the administration of dibekacin in order to determine the concentration of dibekacin in the kidneys. Blood was centrifuged and serum was collected.

Analytical methods : The serum and urine samples were diluted adequately with control

rabbit serum and 1/35 M-veronal buffer (pH 8.8), respectively. The antibiotic in the kidneys was extracted with the buffer by the same method as previously reported[9]. The antibacterial concentration of dibekacin was determined by the paper disk method by use of *Bacillus subtilis* ATCC 6633 as the test organisms.

Pharmacokinetic analysis: A non-linear least square method was applied to the kinetic analysis of serum concentration data according to the two-compartment open model. Renal clearance of dibekacin, C_r, was obtained by the deconvolution method using Eq. (1).

$$E(t)=\int_0^t B(t-\theta)G(\theta)d\theta \qquad (1)$$

where $B(t)$ and $E(t)$ represent the serum dibekacin level and the cumulative amount of dibekacin excreted into urine, respectively, and $G(\theta)$ is the weight function which describes the transfer of the drug from serum into urine. The deconvolution was performed numerically according to the method proposed by UMEMURA et al.[11] in order to obtain $G(\theta)$. If the renal clearance of dibekacin is independent of time (i.e., renal function is

Fig. 1 Serum concentrations of dibekacin after intravenous bolus administration in the normal and infected rabbits. Each value is expressed as the mean±S.D.

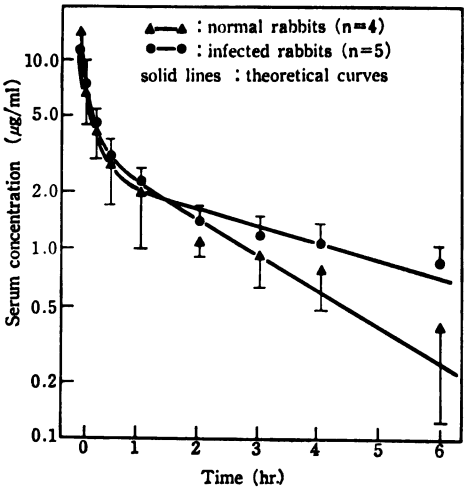


Fig. 2 Urinary excretion of dibekacin after intravenous bolus administration in the normal and infected rabbits. Each value is expressed as the mean±S.D.

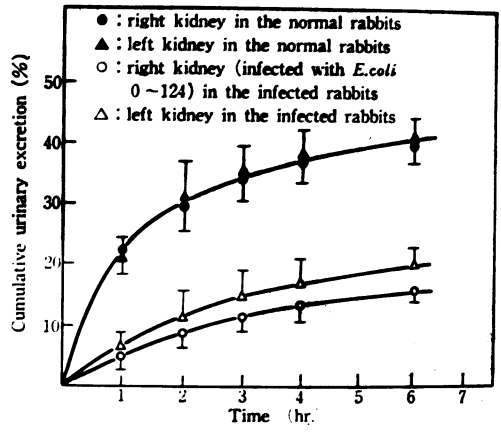


Table 1 Cumulative urinary excretion of dibekacin 24 hours after intravenous bolus administration in the normal and infected rabbits

	Rabbit No.	Excretion % from the right kidney	Excretion % from the left kidney	Total excretion %	Right/Left (Ru)
Infected rabbit	1	18.8	27.3	46.1	0.69
	2	23.4	28.6	52.0	0.82
	3	23.6	29.2	52.8	0.81
	4	22.7	28.9	51.6	0.79
	5	18.4	22.1	40.5	0.83
	Mean±S.D.	21.4±2.6	27.2±3.0	48.6±5.2	0.79±0.06
Normal rabbit	11	44.0	45.9	89.9	0.96
	12	44.5	45.7	90.2	0.97
	13	46.4	43.9	90.3	1.06
	14	38.2	37.7	75.9	1.01
	Mean±S.D.	43.3±3.5	43.3±3.8	86.6±7.1	1.00±0.05

Ru: urinary excretion ratio.

Table 2 Renal cortical level of dibekacin 24 hours after intravenous bolus administration in the normal and infected rabbits

	Rabbit No.	Renal cortical level (μg/g·tissue)		Right/Left (Rc)
		Right kidney	Left kidney	
Infected rabbit	1	36.3	53.6	0.68
	2	53.9	69.2	0.78
	3	38.6	43.7	0.88
	4	48.1	63.5	0.76
	5	32.5	42.3	0.77
	Mean±S.D.	41.9±8.8	54.5±11.9	0.77±0.07
Normal rabbit	11	44.2	46.6	0.95
	12	30.7	28.9	1.06
	13	31.9	31.8	1.00
	14	26.5	23.6	1.12
	Mean±S.D.	33.3±7.6	32.7±9.9	1.03±0.09

Rc: renal cortical concentration ratio.

Table 3 Pharmacokinetic parameters of dibekacin after intravenous bolus administration in the normal and infected rabbits

	Rabbit No.	$C_{tot.}$ (ml/min./kg)	C_r (ml/min./kg)			$T_{1/2\beta}$ (min.)
			Right kidney	Left kidney	Total	
Infected rabbit	1	0.969	0.191	0.297	0.488	170.5
	2	1.204	0.266	0.354	0.620	202.6
	3	1.280	0.254	0.301	0.555	178.4
	4	1.852	0.416	0.516	0.932	127.6
	5	2.350	0.375	0.455	0.830	96.6
	Mean±S.D.	1.531±0.561	0.300±0.093	0.385±0.097	0.685±0.188	155.1±42.5
Normal rabbit	11	2.802	0.923	1.008	1.931	50.4
	12	2.928	1.068	1.139	2.207	69.1
	13	2.112	1.050	0.989	2.039	72.3
	14	1.421	0.512	0.513	1.025	101.9
	Mean±S.D.	2.316±0.696	0.888±0.259	0.912±0.297	1.798±0.534	73.4±21.3

$C_{tot.}$: the apparent total serum clearance, C_r: renal clearance, $T_{1/2\beta}$: elimination half time.

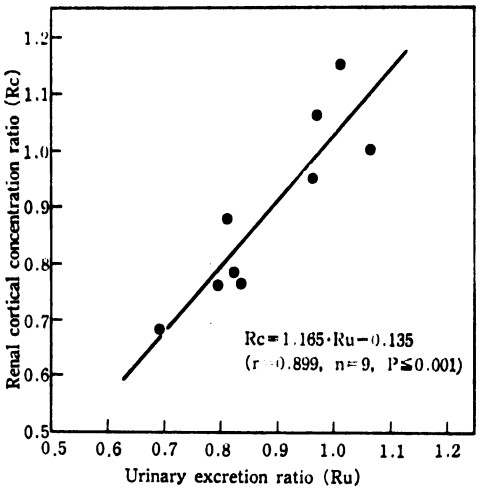
stable throughout the experiments), $G(\theta)$ will be a step function. The renal clearance, C_r, was obtained from the hight of the step function.

RESULTS

Figure 1 represents the average serum concentration of dibekacin in normal and infected rabbits after the bolus intravenous administration of 1 mg/kg of dibekacin. The mean elimination half-lives, $T_{1/2\beta}$, were 73.4 min. in the normal rabbits and 155 min. in the infected rabbits.

The cumulative urinary excretion in the infected rabbits was compared with that in the normal rabbits (Fig. 2), and the individual urinary excretion data are shown in Table 1. The total urinary recoveries (sum of the urinary recoveries from right and left kidneys) 24 hours after the administration were 48.6% and 86.6% of the dose in the infected rabbits and the normal rabbits, respectively. In the infected rabbits, the urinary excretion amount of dibekacin from the infected kidney (right kidney) was 79% of that from the contralateral kidney 24 hours after the administration. On the other hand, in the normal rabbits, there was no difference in the urinary excretion amounts

Fig. 3 Relationship between the urinary excretion rabbits (Ru) and renal cortical concentration ratio(Rc) of dibekacin of the right to the left kideny



between right and left kidneys (Fig. 2 and Table 1).

Table 2 represents the renal cortical concentration of dibekacin 24 hours after the intravenous administration. In the infected rabbits, the ratio of the dibekacin concentration in the infected kidney to the contralateral kidney was 0.77±0.07 (mean± S.D., n=5), while it was 1.04±0.09 (mean±S.D., n=4) in the normal rabbits.

Table 3 summarizes the pharmacokinetic parameters, i.e. the apparent total serum clearance (C_{tot}), the renal clearance (C_r), and the elimination half-life ($T_{1/2\beta}$) of dibekacin. The apparent total serum clearance of dibekacin in the infected rabbits was 1.531±0.561 ml/min./kg (mean±S.D., n=5), which was 66% of that in the normal rabbits. The total renal clearances (sum of the renal clearances from right and left kidneys) were 0.830 in the infected rabbits and 1.798 in the normal and the ratio between the two values was 0.462. In the infected rabbits, the renal clearance of dibekacin from the infected kidney was 78% of that from the contralateral kidney, whereas in the normal rabbits, the renal clearances from bilateral kidneys were almost the same.

Figure 3 depicts the relationship between the urinary excretion ratio (Ru) and renal cortical concentration (Rc) of the right to the left kidney. A considerably good linear correlation was obtained ($r=0.899$, $n=9$, $P<0.001$), and the slope was about unity. This means that the renal accumulation of dibekacin is proportional to the amount of the drug which was excreted from the kidney.

DISCUSSION

The remarkable side effect of aminoglycoside antibiotics are nephrotoxicity and neurotoxicity. That these antibiotics cause proximal tubular cell dysfunction and necrosis[5,12~15] suggests a causal relationship between the accumulation of these antibiotics in the proximal tubular cells and the subsequent development of their nephrotoxicity.

WHELTON et al.[16] reported that the accumulation of gentamicin in human diseased kidneys was less than that in healthy dog kidneys. However, since species of animals are different in their studies, it is difficult to compare directly the accumulation of the antibiotic in diseased kidneys with that in healthy ones. In the present study, one kidney was infected with *E. coli* O-124 via a cannula into a ureter, and the other was used as a control. Hence, it is possible to compare the accumulation of a drug in the infected kidneys with that in the healthy ones in the same individuals (under the same serum levels).

In the infected rabbits, the renal clearance of dibekacin was considerably smaller even in the contralateral kidney (left kidney which was not infected with the bacteria directly) than that in the kidneys of the normal rabbits. This implies that there is some systemic effects by the ascending infection to the kidney, and this smaller renal clearance in the contralateral kidney of the infected rabbits is probably caused by the systemic effects. The ratio of the total renal clearance to the total serum clearance were 0.447 in the infected rabbits, and this was smaller than that in the normal (0.776). Other elimination routes than the renal excretion may be enhanced relatively in the infected rabbits, because of the decrease of the renal function.

A good linear correlation was obtained between urinary excretion ratio and renal cortical concentration ratio of the ipsilateral to the contralateral kidneys (Fig. 3). Furthermore, the slope and the intercept of the regression line was almost unity and zero, respectively. From this result, therefore, it can be concluded that the renal ac-

cumulation of dibekacin is proportional to the amount of the drug excreted from the kidneys into urine.

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上行性腎盂腎炎家兎によるジベカシンの腎分布と薬動力学的検討

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健常家兎および右側腎を大腸菌にて上行性感染させた家兎を用い，ジベカシンの腎蓄積に関する薬動力学的検討を行なった。

感染家兎におけるジベカシンの血中濃度の半減期は 155 分であり，健常家兎のそれは 73.4 分であった。健常家兎ではジベカシンの腎クリアランス，累積尿中排泄量，腎濃度は左右の腎の間に差異は認められなかった。感染家兎では感染腎（右腎）における腎クリアランス，累積尿中排泄量，腎濃度は左側腎の約 80% であった。右側腎と左側腎の各々のジベカシンの腎濃度の比と右側腎からの累積尿中排泄量と左側腎からの累積尿中排泄量の比との間には，直線関係が認められた。

このことから，ジベカシンの腎蓄積はその腎臓から尿中に排泄された薬剤量に比例するものと考えられる。