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Effects of Fosfomycin and Imipenem–Cilastatin on the Nephrotoxicity of Vancomycin and Cisplatin in Rats

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Abstract

The nephrotoxicity of vancomycin and cisplatin and the protective effects of fosfomycin and imipenem–cilastatin on renal function have been studied in rats. The renal clearance of vancomycin after the induction of renal dysfunction was also evaluated by calculating the glomerular filtration rate (GFR) and its secretory clearance.

Plasma concentrations of creatinine and urea nitrogen increased dose-dependently after vancomycin injection. No such increases were observed after co-treatment with fosfomycin or imipenem–cilastatin. Changes of *N*-acetyl-β-D-glucosaminidase activity in the urine of vancomycin-treated rats were not remarkable compared with those in cisplatin-treated animals. The reduced renal clearance of vancomycin in rats with acute renal failure induced by vancomycin was because of a decrease in both GFR and secretory clearance. However, the changes in GFR and secretory clearance were not proportional—the change in GFR was more pronounced than that of secretory clearance in the experimental groups. In addition, the renal clearance of vancomycin was maintained at the control level after co-administration of fosfomycin or imipenem–cilastatin with vancomycin.

These results suggest that vancomycin impairs glomerular filtration more markedly than renal tubular function as compared with cisplatin. Co-administration with fosfomycin or imipenem–cilastatin confers significant protection against the nephrotoxic effects of vancomycin.

Vancomycin hydrochloride, a glycopeptide antibiotic used clinically to treat infections with methicillin-resistant *Staphylococcus aureus*, can induce nephrotoxicity at high plasma concentrations (Cook & Farrar 1978), and therefore routine monitoring of its plasma concentration is recommended.

Because vancomycin is eliminated mainly by the kidneys, renal function significantly influences its pharmacokinetics (Lee et al 1956–1957). We have previously used an in-vivo clearance study to examine the renal excretion of vancomycin in normal rats and rats with acute renal failure; we showed that the antibiotic is secreted via the renal tubules. In addition, tubular secretion of vancomycin is reduced more markedly than its glomerular filtration in rats with acute renal failure induced by uranyl nitrate and cisplatin (Nakamura et al 1996, 1997). It has been reported that some antibiotics might reduce the nephrotoxicity of vancomycin (Toyoguchi & Nakagawa 1996). We have also reported previously that fosfomycin and imipenem–cilastatin reduced the nephrotoxicity of vancomycin (Nakamura et al 1998). However, the pharmacokinetics of vancomycin in vancomycin-induced renal dysfunction and the effects on it of fosfomycin and imipenem–cilastatin are not fully understood.

In this study we have evaluated the nephrotoxicity of vancomycin in rats by measuring gain in body weight and three markers for renal function (creatinine, urea nitrogen and *N*-acetyl-β-D-glucosaminidase (NAG) activity) and compared this with the nephrotoxicity of cisplatin, which predominantly impairs the proximal tubules of the kidney (Dobyan et al 1980; Jones et al 1985). The in-vivo renal clearance of vancomycin was also evaluated in vancomycin-treated rats.

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Materials and Methods

Materials

Vancomycin hydrochloride was obtained from Shionogi (Osaka, Japan). Cisplatin for injection was purchased from Bristol-Myers Squibb (Tokyo, Japan). Fosfomycin sodium was obtained from Meiji Seika Kaisha (Tokyo, Japan). Imipenem-cilastatin sodium was obtained from Banyu (Tokyo, Japan). Inulin was purchased from Nacalai Tesque (Kyoto, Japan). Other chemicals were of the highest purity available.

Animals

Experiments were performed on male Wistar albino rats, 200–250 g. Before the experiments the animals were maintained in metabolic cages with free access to food and water. The animal experiments were performed in accordance with the Guideline for Animal Experiments of Kyoto University.

Effects of fosfomycin and imipenem–cilastatin on vancomycin- and cisplatin-induced nephrotoxicity in rats

Nephrotoxicity was induced by administration of vancomycin or cisplatin to rats. Vancomycin was administered intravenously at doses of 500, 700 or 1000 mg kg^{-1} in normal saline solution (50 mg mL^{-1}). Cisplatin (0·5 mg mL^{-1}) was administered intravenously, at doses of 5 or 10 mg kg^{-1}. Normal healthy rats injected with saline served as the control group. Fosfomycin (300 mg kg^{-1}) or imipenem–cilastatin (150–150 mg kg^{-1}) was administered intravenously just before administration of vancomycin or cisplatin (Nakamura et al 1998).

Concentrations of creatinine, urea nitrogen and vancomycin were determined in plasma, and the activity of NAG was determined in the urine; blood and urine were obtained 2 days after vancomycin injection and 2 or 3 days after cisplatin injection. Thereafter, the kidneys were removed, blotted, weighed and homogenized in three volumes of saline for determination of vancomycin content.

In-vivo clearance of vancomycin in rats with renal dysfunction

The renal clearance of vancomycin was estimated in rats with acute renal failure induced by vancomycin 2 days after vancomycin injection. The in-vivo clearance study was performed as described previously (Nakamura et al 1997). Briefly, control rats and rats with acute renal failure were anaesthetized by intraperitoneal administration of 50 or 30 mg kg^{-1} pentobarbital, respectively. Catheters were inserted into the left femoral artery and the right femoral vein for blood sampling and drug administration, respectively. Urine was collected from the urinary bladder catheterized after a suprapubic incision. The loading dose of vancomycin (0·5 mg) required to give a plasma concentration equivalent to that at steady-state was administered with inulin (10 mg) and mannitol (40 mg) through the femoral vein. Thereafter, vancomycin was continuously infused (0·5 mg h^{-1}) concomitantly with inulin (20 mg h^{-1}) and mannitol (100 mg h^{-1}) at 2·2 mL h^{-1} over a period of 1 h for equilibration. Mannitol was administered to maintain a sufficient and constant rate of urine flow. After a 1-h infusion for equilibration, three consecutive 20-min clearance studies were performed. All blood samples for antibiotic and inulin assays were collected at the midpoint of each experimental period, and centrifuged for determination of plasma concentration. Urine samples obtained during the three periods were diluted 1 : 100 with saline. Plasma and urine samples were stored at −20°C until analysis.

Analytical methods

The concentrations of creatinine and urea nitrogen in plasma were measured by the Jaffé method and the urease-indophenol method, respectively, with kits obtained from Wako (Osaka, Japan). NAG activity in urine was evaluated in terms of the concentration of *p*-nitrophenol liberated, according to Kornfeld & Siemers (1974), using a reaction mixture containing 0·15% Triton X-100.

The concentrations of vancomycin in plasma and urine were determined by high-performance liquid chromatography as described previously (Nakamura et al 1998). Briefly, the chromatograph (LC-10A; Shimadzu, Kyoto, Japan) was equipped with an SPD-10AV variable-wavelength UV detector (Shimadzu) operated at 235 nm and an analytical column (Cosmosil 5Ph packed column, 15 cm × 4·6 mm, Nacalai Tesque, Kyoto, Japan). The mobile phase was 50 mM sodium phosphate buffer containing 1 mM sodium lauryl sulphate (pH 3·3)–acetonitrile, 79 : 21. The flow rate was 1·0 mL min^{-1} and the column temperature was maintained at 40°C. The protein binding of vancomycin was determined by ultrafiltration of plasma samples with a micropartition system (MPS-1; Amicon, Beverly, MA). The unbound fraction of vancomycin was expressed as the ratio of the vancomycin concentration in the ultrafiltrate to that in plasma. Inulin concentrations in plasma and urine were

analysed spectrophotometrically according to a modification of the method of Dische & Borenfreund (1951).

Data analysis

The pharmacokinetic parameters of vancomycin were calculated on the basis of standard procedures for each experimental period in clearance studies (Nakamura et al 1997). Renal clearance was determined as the urinary excretion rate divided by the steady-state plasma concentration. The renal clearance of unbound vancomycin was determined by dividing the renal clearance by the unbound fraction. The net renal secretory clearance of vancomycin was calculated by subtracting the glomerular filtration rate (assumed to be equivalent to the renal clearance of inulin) from the renal clearance of unbound vancomycin. In each experiment, vancomycin and inulin clearance were estimated as the means of the values measured during three experimental periods.

Statistical analysis

Data are expressed as means ± standard error of the means of results from 4–11 animals. If the variances of groups were similar the statistical significance of differences between mean values was calculated using the non-paired *t*-test, otherwise the Mann–Whitney *U*-test was used. If the variances of groups were similar, multiple comparisons were performed by analysis of variance then Sheffé's test for multiple comparisons, otherwise a Sheffé-type test was used after Kruskal–Wallis analysis. *P* values <0·05 (two-tailed) were considered to be indicative of significance.

Results and Discussion

We have previously reported that the relationship between glomerular filtration and the secretory clearance of vancomycin was curvilinear in experimental acute renal failure rat models (Nakamura et al 1997). In addition, we observed protective effects of fosfomycin and imipenem–cilastatin against vancomycin-induced nephrotoxicity (Nakamura et al 1998). In this study, we have evaluated and compared the nephrotoxicity of vancomycin and cisplatin in rats, and the effects of fosfomycin and imipenem–cilastatin were also examined. The renal clearance of vancomycin was estimated in rats treated with vancomycin alone or after co-injection with fosfomycin or imipenem–cilastatin.

Vancomycin treatment (500, 700 and 1000 mg kg^{-1}) resulted in an average body weight loss of 14, 24 and 36 g, respectively, compared with the control value (Table 1). In this study, the concentrations of creatinine and urea nitrogen in plasma and NAG activity in urine were selected as markers of dysfunction in glomeruli and proximal tubules in the kidney, respectively. Plasma concentrations of creatinine and urea nitrogen were dose-dependently increased by injection of vancomycin, suggesting that vancomycin impaired glomerular function (Table 1). Urinary NAG activity

Table 1. Effects of vancomycin on body weight, on creatinine and urea nitrogen in the plasma, on *N*-acetyl-*β*-D-glucosaminidase in the urine, and on plasma concentration of residual vancomycin and accumulation of vancomycin in the kidney.

	Body weight gain (g)	Plasma creatinine (mg/100 mL)	Plasma urea nitrogen (mg/100 mL)	Urinary *N*-acetyl-*β*-D-glucosaminidase activity (nmol mL^{-1})	Plasma residual vancomycin (μg mL^{-1})	Accumulation of vancomycin in the kidney (mg (g kidney)$^{-1}$)
Control	22 ± 1	0·521 ± 0·016	19·7 ± 0·8	215 ± 36	—	—
+imipenem–cilastatin	14 ± 2*	0·517 ± 0·048	14·7 ± 0·6*	215 ± 54	—	—
+fosfomycin	17 ± 4	0·617 ± 0·031	13·3 ± 1·2*	248 ± 49	—	—
Vancomycin (500 mg kg^{-1})	8 ± 3	0·753 ± 0·049	39·5 ± 3·9	301 ± 45	1·33 ± 0·41	1·98 ± 0·32
+imipenem–cilastatin	16 ± 3	0·615 ± 0·057	13·7 ± 1·4*	192 ± 44	0·36 ± 0·13	0·65 ± 0·06*
+fosfomycin	13 ± 6	0·580 ± 0·058	13·8 ± 1·0*	306 ± 91	0·25 ± 0·11*	0·58 ± 0·06*
Vancomycin (700 mg kg^{-1})	−2 ± 2	0·943 ± 0·064	61·5 ± 7·1	376 ± 63	4·44 ± 0·91	2·55 ± 0·05
+imipenem–cilastatin	17 ± 2*	0·663 ± 0·060*	22·4 ± 1·5*	376 ± 50	0·18 ± 0·04*	1·13 ± 0·21*
Vancomycin (1000 mg kg^{-1})	−14 ± 2	2·09 ± 0·34	118·2 ± 8·7	300 ± 65	62·4 ± 19·3	3·33 ± 0·07
+imipenem–cilastatin	−6 ± 4	1·16 ± 0·14	90·9 ± 10·3	330 ± 54	14·8 ± 4·8	2·81 ± 0·14*
+fosfomycin	17 ± 2*	0·509 ± 0·019*	17·9 ± 0·9*	272 ± 43	0·20 ± 0·03*	0·99 ± 0·07*

Rats were injected intravenously with saline or vancomycin (500, 700 or 1000 mg kg^{-1}). After two days plasma and urine were collected for measurements. Each value is the mean ± standard error of the mean of results from four to eleven rats. *$P < 0·05$ compared with the results from corresponding control or vancomycin (500, 700 or 1000 mg kg^{-1})-injected groups.

in control and vancomycin-injected groups was not significantly different. Fosfomycin afforded significant protection against vancomycin-induced nephrotoxicity—body weight gain was comparable with that in controls, and the concentrations of creatinine and urea nitrogen in plasma and the activity of NAG in urine were also maintained at the control levels (Table 1). The protective effects of imipenem–cilastatin on these four markers were similar to those of fosfomycin.

We further evaluated the plasma concentration of residual vancomycin and its accumulation in the kidney after administration of vancomycin (Table 1). After vancomycin treatment, the concentration of residual vancomycin in the plasma increased dose-dependently and accumulation of vancomycin in the kidney also tended to increase dose-dependently. The protective effects of fosfomycin and imipenem–cilastatin against the nephrotoxicity of vancomycin were highly associated with the decrease in accumulation of vancomycin in the kidney. When fosfomycin and imipenem–cilastatin were co-administered the plasma and renal concentrations of vancomycin were significantly reduced, although the suppressive effect of fosfomycin was more marked than that of imipenem–cilastatin (Table 1).

Table 2 shows the four markers examined in rats after administration of cisplatin. In all animals, marked weight loss was observed after treatment with cisplatin (5 and 10 mg kg^{-1}), and the concentrations of creatinine and urea nitrogen in the plasma increased dose- and time-dependently, indicating that glomerular filtration was impaired. A dose-dependent increase in urinary NAG activity was observed, confirming impairment of the renal tubules. Urinary NAG activity 3 days after 10 mg kg^{-1} cisplatin injection was reduced compared with that 2 days after cisplatin injection; this might be attributable to the markedly damaged tubules by this time. NAG activity 2 days after injection of 10 mg kg^{-1} cisplatin tended to be reduced by co-administration with fosfomycin or imipenem–cilastatin, but the effect was not significant (Table 2).

The clearance study was performed in rats with vancomycin-induced renal dysfunction and in the animals which were most effectively protected by fosfomycin or imipenem–cilastatin against vancomycin-induced nephrotoxicity. Table 3 shows the plasma markers of renal dysfunction and the pharmacokinetic parameters of vancomycin in vancomycin-treated rats. NAG excretion corrected by urine volume during the clearance studies was increased dose-dependently (Table 3). Vancomycin, therefore, seemed to impair renal tubule function similarly to cisplatin. In all experiments, we confirmed that the plasma concentration and urinary excretion of vancomycin were in a steady-state during the three experimental periods. The plasma concentrations of vancomycin in acute renal failure rats were significantly greater than those in the controls, and reached a 10-fold increase 2 days after vancomycin treatment (1000 mg kg^{-1}). The renal clearance of vancomycin decreased significantly with increases in vancomycin dose. The unbound fraction of vancomycin was reduced, but this was not significant (Table 3).

We have previously reported that two important processes, glomerular filtration and tubular secretion, were involved in the renal excretion of vancomycin and that the magnitudes of the decreases

Table 2. Effects of cisplatin on body weight, on creatinine and urea nitrogen in plasma and on *N*-acetyl-β-D-glucosaminidase in urine.

	Body weight gain (g)	Plasma creatinine (mg/100 mL)	Plasma urea nitrogen (mg/100 mL)	Urinary *N*-acetyl-β-D-glucosaminidase activity (nmol mL^{-1})
Control	14 ± 1	0·468 ± 0·007	21·3 ± 0·8	286 ± 36
+imipenem–cilastatin	11 ± 6	0·478 ± 0·016	15·1 ± 1·2*	272 ± 69
+fosfomycin	10 ± 8	0·464 ± 0·048	17·9 ± 1·6	382 ± 142
Cisplatin (5 mg kg^{-1}, day 2)	−7 ± 4	0·606 ± 0·037	26·4 ± 1·6	519 ± 66
+imipenem–cilastatin	−5 ± 3	0·563 ± 0·026	21·8 ± 1·6	429 ± 39
+fosfomycin	2 ± 4	0·828 ± 0·099	21·1 ± 1·7	308 ± 68
Cisplatin (10 mg kg^{-1}, day 2)	−17 ± 3	0·891 ± 0·052	47·2 ± 3·3	708 ± 84
+imipenem–cilastatin	−23 ± 1	0·799 ± 0·038	40·9 ± 2·5	409 ± 93
+fosfomycin	−21 ± 2	0·980 ± 0·196	34·3 ± 4·6	406 ± 29
Cisplatin (10 mg kg^{-1}, day 3)	−27 ± 4	1·57 ± 0·14	127 ± 17	463 ± 109
+imipenem–cilastatin	−27 ± 1	1·35 ± 0·04	117 ± 6	440 ± 128
+fosfomycin	−29 ± 2	1·31 ± 0·16	103 ± 22	295 ± 39

Rats were injected intravenously with saline or cisplatin (5 or 10 mg kg^{-1}). After 2 or 3 days plasma and urine were collected for measurements. Each value represents the mean ± standard error of the mean of results from 4–9 rats. *$P < 0·05$, significantly different from the result from the cisplatin (5 mg kg^{-1}, day 2)-injected group.

Table 3. Urinary excretion of vancomycin and the effects of fosfomycin and imipenem–cilastatin.

	Control	Vancomycin treatment ($mg\,kg^{-1}$)			Vancomycin 700 + imipenem–cilastatin	Vancomycin 1000 + fosfomycin
		500	700	1000		
Plasma creatinine (mg/100 mL)	0·558 ± 0·076	0·819 ± 0·018	1·12 ± 0·04	1·63 ± 0·15	0·552 ± 0·020	0·520 ± 0·036
Plasma urea nitrogen (mg/100 mL)	15·7 ± 1·7	35·1 ± 5·1	63·7 ± 14·3	100·2 ± 10·8*	19·1 ± 2·8	14·4 ± 0·9
Urinary excretion of *N*-acetyl-β-D-glucosaminidase ($nmol\,min^{-1}$)	3·13 ± 0·78	7·50 ± 1·32	8·74 ± 1·03	10·9 ± 2·8	6·79 ± 1·08	4·62 ± 0·69
Steady-state plasma vancomycin concentration ($\mu g\,mL^{-1}$)	4·63 ± 0·34	8·62 ± 0·93	16·4 ± 3·2	48·4 ± 8·3*	4·83 ± 0·27	4·46 ± 0·25
Renal clearance ($mL\,min^{-1}$)	1·86 ± 0·19	1·39 ± 0·12	0·74 ± 0·26	0·29 ± 0·04*	1·97 ± 0·11	2·18 ± 0·09
Unbound fraction	0·475 ± 0·043	0·448 ± 0·010	0·435 ± 0·025	0·380 ± 0·030	0·434 ± 0·018	0·421 ± 0·022
Renal clearance of unbound vancomycin ($mL\,min^{-1}$)	4·03 ± 0·52	3·10 ± 0·24	1·62 ± 0·45	0·75 ± 0·06	4·56 ± 0·30	5·24 ± 0·49
n	6	4	4	6	4	4

Vancomycin was infused intravenously at $0·5\,mg\,h^{-1}$ two days after the injection of vancomycin (500, 700 and $1000\,mg\,kg^{-1}$). Each value is the mean ± standard error of the mean. $*P < 0·05$ compared with the control value.

in these processes were not proportional in experimental-acute renal failure rats (Nakamura et al 1996, 1997). In the current study the renal excretion of vancomycin was evaluated in rats with acute renal failure induced by vancomycin. Figure 1 shows the relationship between the glomerular filtration and tubular secretion of vancomycin in such rats. Two days after vancomycin injection (500, 700 and $1000\,mg\,kg^{-1}$), the values of GFR were 56, 32 and 15% of the control value whereas values for the secretory clearance of vancomycin were 107, 52 and 23%, respectively. These results suggested that the kidney was impaired primarily in the glomeruli, and thereafter renal dysfunction in the glomeruli and tubules seemed to progress in parallel. This imbalance in the changes in these functions was, however, quite different from that observed in our previous study, i.e. the renal tubular secretion of vancomycin was reduced more markedly than glomerular filtration in cisplatin- and uranyl nitrate-induced acute renal failure models (Nakamura et al 1997). Taken together with these findings, the mechanism of vancomycin toxicity might be different from those of cisplatin and uranyl nitrate in the kidney (Toyoguchi et al 1997).

In our previous study the interaction of fosfomycin and imipenem–cilastatin with renal tubular secretion of vancomycin might have been partially related to reduction of the accumulation of vancomycin in the kidney, resulting in a protective effect against the nephrotoxicity of vancomycin (Nakamura et al 1998). In this study when fosfomycin or imipenem–cilastatin was administered concomitantly with vancomycin, GFR and the secretory clearance of vancomycin were maintained at control levels (Figure 1). This suggested that fosfomycin and imipenem–cilastatin protected against both types of renal dysfunction induced by vancomycin, and that their protective effects against vancomycin-induced nephrotoxicity were not restricted to the renal tubules. Although vancomycin-induced nephrotoxicity has been reported, the mechanisms of glomerular impairment remain unclear (Toyoguchi et al 1997). Therefore, further study is needed of the mechanism of vancomycin toxicity not only in renal tubules but also in

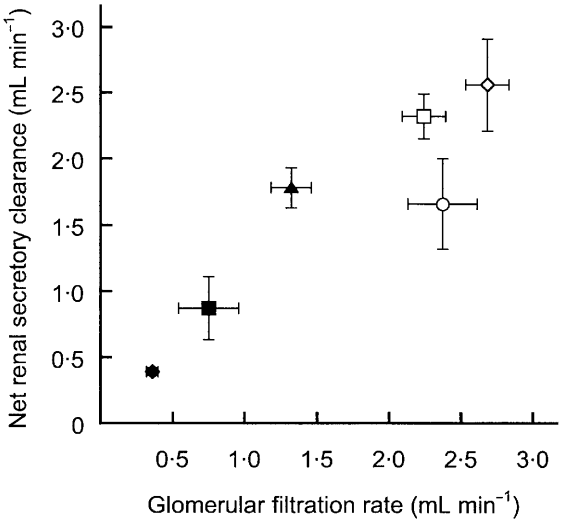

Figure 1. Relationship between glomerular filtration rate and the secretory clearance of vancomycin in rats with acute renal failure induced by vancomycin. Control (○) and vancomycin-treated rats were examined two days after the injection of vancomycin 500 (▲), 700 (■) or 1000 (◆) $mg\,kg^{-1}$. Fosfomycin ($300\,mg\,kg^{-1}$) (◇) and imipenem–cilastatin ($150–150\,mg\,kg^{-1}$) (□) were co-administered with 1000 and $700\,mg\,kg^{-1}$ vancomycin, respectively.

glomeruli, to clarify the effects of this antibiotic in the whole kidney.

In conclusion, we have investigated vancomycin- and cisplatin-induced nephrotoxicity, and the effects on this of fosfomycin and imipenem–cilastatin, and evaluated the renal excretion of vancomycin in vancomycin-treated rats. Our results suggested that the effect of vancomycin nephrotoxicity is to reduce glomerular filtration of vancomycin more markedly than renal tubular secretion, in contrast with the effect of cisplatin. Furthermore, fosfomycin and imipenem–cilastatin protect these two renal functions against vancomycin-induced nephrotoxicity. These findings provide new insight for the clinical use of vancomycin in renal failure and co-treatment with fosfomycin or imipenem–cilastatin with vancomycin.

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