Effects of Disopyramide and Verapamil on Renal Disposition and Nephrotoxicity of Cisplatin in Rats

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Purpose. The purpose of this study was to determine the effects of disopyramide and verapamil on the renal handling of cisplatin (CDDP) and nephrotoxicity in rats. The stereoselective effect of verapamil was also studied.

Methods. CDDP was administered to rats by i.v. bolus injection or by infusion at a constant rate with or without concomitant administration of racemic disopyramide, racemic verapamil, or each verapamil enantiomer. The concentrations of CDDP in plasma and in the kidney and liver were determined by HPLC. In separate experiments, CDDP was administered as described above, and blood urea nitrogen (BUN) was monitored for 7 days.

Results. The BUN level after administration of CDDP was significantly reduced by coadministration of either disopyramide or verapamil. Renal accumulation of CDDP was significantly reduced by these drugs, whereas accumulation into the liver was not significantly changed. The relationship between the BUN levels and the area under the curve of CDDP concentration in the kidney versus time (AUC_k) was analyzed using a sigmoid E_{max} model; this showed that the reduced BUN levels were explained by the AUC_k. Furthermore, verapamil showed stereoselective inhibition of the renal accumulation of CDDP.

Conclusions. The renal accumulation of CDDP was inhibited by disopyramide and verapamil, and this inhibition resulted in the amelioration of nephrotoxicity.

KEY WORDS: unchanged cisplatin; renal accumulation; nephrotoxicity; verapamil; enantiomers.

INTRODUCTION

Cisplatin [*cis*-diamminedichloroplatinum (II), CDDP] is an effective antitumor agent that has been used extensively in the treatment of solid tumors of various types. However, CDDP causes several side effects, especially severe nephrotoxicity, which limit its use. CDDP undergoes ligand exchange reactions and the principal reaction associated with the antitumor activity of CDDP is the cross-linking of the N-7 atoms of proximate guanine nucleotides (1). In biological fluids, CDDP is extensively bio-transformed to mobile metabolites, through binding to low molecular mass substances (such as glutathione, methionine and cysteine), or to fixed metabolites, through binding to high molecular mass substances (such as albumin and nucleotides) (2,3) and these bindings are almost irreversible (3). Recently, we demonstrated that CDDP in plasma, but not its mobile or fixed metabolites, is the main determinant of nephrotoxicity induced by CDDP administration (4).

To reduce CDDP-induced nephrotoxicity, many investigators have coadministered protective agents such as diuretic agents, sodium thiosulfate and probenecid. Sodium thiosulfate reacts immediately with CDDP and reduces its antitumor and toxic effects (5). Probenecid reduces the nephrotoxicity of CDDP by inhibiting its renal secretion and accumulation (6). Both an organic anion (probenecid) and organic cations (quinidine, cimetidine, ranitidine) significantly decrease the renal clearance of filtered platinum in dogs (7). CDDP may be transported by multiple transport systems in renal tubular cells, and inhibition of the renal accumulation of CDDP may result in the amelioration of CDDP-induced nephrotoxicity. Safirstein *et al.* also suggested that the specific uptake of CDDP into the kidney may be a major factor in renal damage (8); however, they did not analyze the quantitative relationship between renal handling and accumulation of CDDP and nephrotoxicity.

Recently, we examined the mechanism of CDDP uptake into kidney using renal cortical slices. We found that CDDP was transported by the organic cation transport system but not by the organic anion transport system (9). The uptake of CDDP into rat renal cortical slices is significantly and competitively inhibited by verapamil. Disopyramide is also a basic drug that is transported by the organic cation transport system (10). Therefore, we studied the inhibitory effects of coadministration of either verapamil or disopyramide on CDDP-induced nephrotoxicity in rats *in vivo*. Disopyramide and verapamil exist as stereoisomers and show stereoselective pharmacokinetics and pharmacodynamics. In this study, we also examined the effects of verapamil enantiomers on the pharmacokinetics and toxicodynamics of CDDP in rats.

MATERIALS AND METHODS

Chemicals

CDDP was a kind gift from Nippon Kayaku (Tokyo, Japan). Disopyramide phosphate and verapamil hydrochloride were obtained from Sigma (St. Louis, MO).

Animals

Male Wistar rats (250–280 g) were maintained on a standard laboratory pellet diet with water *ad libitum* in a controlled environment. They were fasted for 16 hours prior to the experiment, but were allowed water *ad libitum*.

Separation of Verapamil Enantiomers

Verapamil enantiomers were separated using a Chiralpak AD column (250 × 20 mm I.D.; Daicel Chemical Industries, Tokyo, Japan) as reported previously (11). The HPLC system consisted of a Shimadzu (Kyoto, Japan) HPLC apparatus, an LC-6A HPLC pump, and an RF-535 fluorometric detector operated at excitation and emission wavelengths of 272 and 312

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ABBREVIATIONS: CDDP, cis-diamminedichloroplatinum (cisplatin); BUN, blood urea nitrogen; AUC_p, area under the curve of plasma CDDP concentration in plasma versus time; AUC_k, area under the curve of renal CDDP concentration in the kidney versus time; clearance ratio, renal clearance of CDDP divided by glomerular filtration rate.

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nm, respectively. The mobile phase was hexane-isopropanol-diethylamine (94:6:0.1, v/v/v) and the flow rate was kept constant at 6.0 ml/min. Peaks corresponding to the (+)- and (−)-enantiomers were identified by comparing their retention times with those of authentic standard enantiomers. The purities of each enantiomer were determined by HPLC [R-(+)-verapamil, 99.3%; S-(−)-verapamil, 98.6%].

CDDP Bolus Administration

Pharmacokinetic Study

The rats were anesthetized by i.p. injection of sodium pentobarbital (40 mg/kg). Polyethylene cannulae (0.28 mm I.D. × 0.61 mm O.D.) were inserted into both the femoral artery and vein of one leg, and into the ureters. Racemic disopyramide or verapamil were infused at a constant rate of 14 or 5.2 mg/h/kg through the femoral venous cannula for 30 min or 20 min, after which a maintenance dose of 3.6 or 0.8 mg/h/kg was infused (at 0.037 ml/min) throughout the experimental period, respectively. These concentrations of the drugs were chosen to be within the therapeutic plasma concentration range in humans. The control animals received 0.9% (w/v) sodium chloride at a rate of 0.037 ml/min. One hour after the start of the maintenance infusion, CDDP (2.5, 3.5, 4 or 5 mg/kg) was administered by bolus injection into the jugular vein. At 5, 15, 30 or 60 min after CDDP injection, the rats were sacrificed by withdrawing whole blood from the abdominal artery. The tissues were then treated according to the procedures described below.

Nephrotoxicity Study

CDDP was administered as described above except that infusion of disopyramide or verapamil was continued until 70 min after CDDP administration. Blood samples (0.3 ml) were taken from the contralateral jugular vein just before CDDP administration and 1, 2, 3, 5 and 7 days after administration. After drug administration, the rats were maintained on a standard laboratory pellet diet with water *ad libitum* in a temperature- and atmosphere-controlled room (12).

CDDP Infusion

The rats were treated as described above. Racemic verapamil, R-(+)-verapamil or S-(−)-verapamil containing 0.5% (w/v) inulin were infused at a constant rate (5.2, 12 or 3.9 mg/h/kg, respectively) through the femoral venous cannula for 20 min followed by maintenance infusions of 0.8, 1.8 or 0.6 mg/h/kg (0.037 ml/min), respectively. The control animals received 0.9% (w/v) sodium chloride at a rate of 0.037 ml/min. Twenty minutes after starting the maintenance infusion, CDDP was infused at a constant rate of 3.0 mg/h/kg through the jugular vein. Urine was collected at 90–120, 120–150 and 150–180 min after the start of the CDDP infusion and blood samples were taken from the femoral artery at the midpoint of each urine sampling interval. After CDDP infusion for 180 min, the rats were sacrificed by withdrawing whole blood from the abdominal artery. The tissues were treated according to the procedures described below.

Treatment of Liver and Kidneys

Ice-cold 0.9% (w/v) sodium chloride was injected quickly into the heart to remove the blood from the other organs. The kidneys and liver were excised, rinsed, blotted on filter paper, weighed and homogenized with ice-cold 0.9% (w/v) sodium chloride (1 g/4 ml) using a Potter-Elvehjem apparatus with a Teflon pestle. The tissue homogenate and blood samples were centrifuged at 105 000 g (Beckman L8-60 M) and 1 000 g for 65 and 5 min, respectively, and both the tissue cytosols and the plasma were ultrafiltered at 4 000 g for 30 min using a Millipore-filter with a molecular mass cut-off of 10 000 Da (UFC3GC; Nihon Millipore, Yonezawa, Japan). These samples were stored at −20°C until analysis. The concentrations of CDDP in these samples were determined within 3 days.

Analytical Techniques

CDDP concentrations in the biological fluids were determined by an HPLC method as reported previously (13). Briefly, the HPLC system consisted of a Shimadzu HPLC apparatus, an LC-6A pump, an SPD-6A spectrophotometric detector operated at a wavelength of 290 nm with a range of 0.01 AUFS and a C-R6A Chromatopac integrator. CDDP was separated from other metabolites by an anionic exchange column (150 × 4.6 mm I.D.; 3013-N, Hitachi, Japan). The mobile phase was 10 mM sodium chloride-acetonitrile (85:15, v/v) and the flow rate was maintained at 0.9 ml/min. CDDP was detected after post-column derivatization with both 26 μM potassium dichromate and 6.6 mM sodium hydrogen sulfite, which were pumped at 0.6 and 0.3 ml/min, respectively. Atomic platinum concentrations were determined by an atomic absorption spectrophotometer (Hitachi Z-9000) (13). The concentration of inulin was determined by the method of White and Samson (14). Blood urea nitrogen (BUN) was determined by using a BUN assay kit (Wako Pure Chemical Industries, Japan). The enantiomer concentrations of disopyramide and verapamil in plasma were determined by enantioselective HPLC methods as reported previously (11).

Data Analysis

Data are expressed as means ± S.D. Platinum levels in the tissues are presented as micrograms of platinum per gram wet weight of tissue (μg Pt/g tissue). The CDDP concentration in the tissues was multiplied by a correction factor because CDDP was partly converted to fixed metabolites during ultracentrifugation (13). The concentrations of both types of metabolites were calculated as follows: fixed metabolites = total platinum—platinum in cytosolic filtrate; mobile metabolites = platinum in cytosolic filtrate—CDDP.

Pharmacokinetic Analysis

The pharmacokinetic parameters of CDDP were calculated using the model-independent method. The area-under the curve of CDDP concentration in plasma versus time curve (AUC_p) was calculated as previously reported (12). The AUC_{0-tl} was calculated by numerical integration, from time zero to the final sampling time, of the mean (n = 3) CDDP concentration in the kidney at 5, 15, 30 and 60 min, using the trapezoidal rule. The area under the curve of CDDP concentration in the kidney

versus time (AUC_k) and systemic clearance (CL_s) and renal clearance (CL_r) values based on the concentration of unchanged CDDP were calculated as follows (15):

$$AUC_k = AUC_{0-t_l} + C_l/k_{el}$$

$$CL_s = \text{infusion rate}/Cp^{ss}$$

$$CL_r = \text{urinary excretion rate}/Cp^{ss}$$

where C_l is the CDDP concentration in the kidney at the final sampling time (t_l); k_{el} is the terminal elimination rate constant in the kidney, which was calculated by linear regression using the program WinNonlin (Pharsight Co., CA); and Cp^{ss} is the plasma concentration of unchanged CDDP at steady state.

Toxicodynamic Analysis

The relationship between BUN levels at 5 days after CDDP administration and the AUC obtained from i.v. bolus injection of CDDP (2.5, 3.5, 4 and 5 mg/kg) was fitted using the following sigmoid E_{max} model using the nonlinear least square method program NLS (16);

$$\text{BUN level(mg / dl)} = BUN_0 + \frac{\text{BUN max}\cdot AUC^{\gamma}}{AUC_{50}^{\gamma} + AUC^{\gamma}}$$

where BUN_0 and BUN_{max} are the baseline and maximum BUN levels, respectively, AUC_{50} is 50% of the AUC corresponding to the maximum BUN level and γ is the slope factor. The NLS analysis was performed assuming that the error % of AUC_k was 20%.

Statistical Analysis

The effect of racemic verapamil on the pharmacokinetics of CDDP was analyzed using Student's unpaired t-test. Other statistical analyses were performed by one-way ANOVA, and Dunnett's test was used to compare the treatments when a significant difference among the means was indicated. Differences were considered to be statistically significant at $p < 0.05$.

RESULTS

The concentrations of disopyramide and verapamil in plasma were maintained at almost constant values (2.02 ± 0.33 and 0.38 ± 0.07 μg/ml, respectively) 60 min after the start of the maintenance infusion of each drug. The BUN level was significantly increased 3 days after CDDP administration and reached a maximum level at 5 days. When CDDP was administered concomitantly with disopyramide or verapamil, the BUN level was reduced significantly at 3 and 5 days after administration compared to the levels observed after administration of CDDP (5 mg/kg) alone (Fig. 1). Similarly, the plasma concentration of creatinine was significantly reduced (data not shown).

When disopyramide and CDDP were administered concomitantly, the concentrations in the kidney of both CDDP and its fixed metabolites were significantly reduced to 33.3% and 26.9% of the control values, respectively, but their concentrations in the liver were not changed significantly (Table 1). Similarly, when racemic verapamil and CDDP were coadministered, the kidney concentrations of CDDP and its fixed metabolites were reduced significantly to 51.7% and 34.8% of the control values, respectively, but they were not changed significantly in the liver (Table 1).

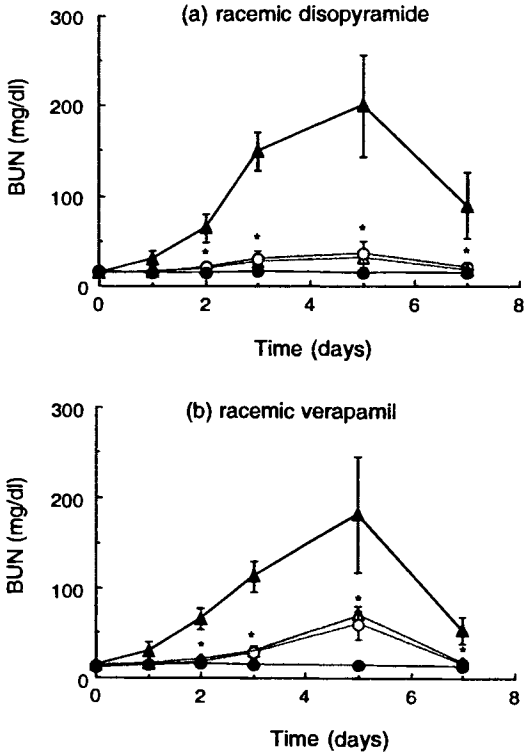

Fig. 1. Time-courses of blood urea nitrogen (BUN) level after i.v. bolus administration of cisplatin with or without concomitant administration of disopyramide (a) or verapamil (b). Each point represents the mean ± S.D. (n = 4). * Significantly different from 5 mg/kg cisplatin alone ($p < 0.05$). (a) ▲, 5 mg/kg cisplatin; △, 2.5 mg/kg cisplatin; ○, 5 mg/kg cisplatin + disopyramide; ●, 0.9% sodium chloride. (b) ▲, 5 mg/kg cisplatin; △, 3.5 mg/kg cisplatin; ○, 5 mg/kg cisplatin + verapamil; ●, 0.9% sodium chloride.

The values of AUC_k were dose-dependent. The elimination constant of CDDP in the kidney was dose-independent and was not affected by either disopyramide or verapamil (Table 2). To quantify the relationship between the renal accumulation of CDDP and the extent of reduction of nephrotoxicity, AUC_k values were plotted against BUN levels at 5 days after CDDP administration using the sigmoid E_{max} model (Fig. 2). The data obtained for concomitant administration of CDDP and either disopyramide or verapamil were fitted on the curve. The results suggested that both disopyramide and verapamil inhibit the accumulation of CDDP into the kidney, but not into the liver, and that this inhibition may result in the amelioration of CDDP-induced nephrotoxicity.

In order to elucidate the effect of verapamil on the renal disposition of CDDP, a study of renal clearance *in vivo* was performed. The glomerular filtration rate (GFR) was not changed significantly by a constant rate infusion of CDDP or 0.9 (w/v) sodium chloride during the experimental period. When the plasma concentration of racemic verapamil wasmaintained at a steady state, GFR was significantly increased in comparison with that observed in the absence of racemic verapamil (Table 3). This increase in the GFR may be the result of the pharmacological effect of verapamil (17). The value of the ratio of CL_r to GFR (clearance ratio) and the CDDP concentration in the

Table 1. Effects of Disopyramide and Verapamil on Platinum Concentrations in the Kidney, Liver, and Plasma at 60 min After i.v. Bolus Injection of Cisplatin (5 mg/kg)

	Cisplatin	Mobile metabolites	Fixed metabolites
Kidney (μg Pt/g tissue)			
cisplatin alone	2.34 ± 0.26	3.02 ± 0.39	14.7 ± 2.66
with disopyramide	0.78 ± 0.21**	2.45 ± 1.47	3.96 ± 2.66**
with verapamil	1.21 ± 0.71*	2.46 ± 0.98	5.11 ± 2.63**
Liver (μg Pt/g tissue)			
cisplatin alone	0.14 ± 0.06	1.03 ± 0.70	1.94 ± 0.97
with disopyramide	0.23 ± 0.24	0.95 ± 0.69	1.91 ± 0.56
with verapamil	0.48 ± 0.67	0.48 ± 0.31	2.15 ± 1.20
Plasma (μg Pt/ml)			
cisplatin alone	0.33 ± 0.04		
with disopyramide	0.48 ± 0.29		
with verapamil	0.59 ± 0.33		

Note: Values are means ± S.D. (n = 4).
* $p < 0.05$; ** $p < 0.01$ (significantly different from cisplatin alone).

kidney both decreased during infusion of racemic verapamil. On the other hand, the clearance ratio of CDDP and the GFR did not change when the concentration of R-(+)-verapamil in plasma was maintained at 0.90 ± 0.20 μg/ml (Table 4). When the plasma concentration of S-(−)-verapamil was maintained at 0.34 ± 0.17 μg/ml, the GFR increased significantly, and both the clearance ratio and accumulation of CDDP into the kidney were reduced to levels similar to those seen after administration of racemic verapamil (Table 4).

DISCUSSION

We studied the relationship between the accumulation of CDDP in the kidney and CDDP-induced nephrotoxicity in rats after concomitant administration of CDDP and each of the basic drugs disopyramide and verapamil.

The observed CDDP concentration ratios for the kidney and liver compared to the plasma at steady state were about 3 and 0.3, respectively, suggesting that a specific mechanism controls the renal uptake of CDDP. The uptake of CDDP into the kidney may be associated partially with the organic cation transport systems (8,18). We have shown that verapamil competitively inhibits CDDP uptake by rat renal cortical slices (9). Our present *in vivo* results show that both racemic disopyramide and racemic verapamil inhibited the accumulation of CDDP in the kidney. In contrast, the CDDP concentration in the liver was slightly but not significantly increased by both disopyramide and verapamil; this may result from the slight but not significant increases of the CDDP concentration in plasma. These results suggest that disopyramide and verapamil specifically affect the accumulation of CDDP in the kidney and result in amelioration of nephrotoxicity.

In clinical investigations, coadministration of verapamil has been shown to provide slight protection against CDDP-induced nephrotoxicity (19,20), and it has been suggested that this protective effect is the result of increased renal blood flow caused by the renal vasodilative action of verapamil. The reason why the protective effect of verapamil against CDDP-induced nephrotoxicity was relatively weak in these clinical studies may be related to the route of administration and to the plasma concentration of verapamil required to produce effective inhibition. In humans, the bioavailability of verapamil is low and shows stereoselectivity, and the inter-individual variation in the plasma concentration is large (21).

Nagai and Ogata recently showed that the area under the plasma concentration-time curve of CDDP (AUC_p), calculated from plasma concentrations greater than the threshold level, is an important pharmacokinetic parameter related to nephrotoxicity (12). We analyzed the effect of the basic drugs disopyramide and verapamil on the pharmacokinetics and nephrotoxicity of CDDP using the same sigmoid E_{max} model. Significant changes of CLs of CDDP were not detected after coadministration of verapamil (Tables 3 and 4). The renal excretion of CDDP was only 30% of the dose, and therefore it was difficult to detect changes in the plasma CDDP concentration during the coadministration of these drugs. Furthermore, when BUN levels at 5 days after CDDP administration were plotted with AUC_p, all of the data obtained after coadministration of CDDP and either disopyramide or verapamil shifted from a curve (Fig. 2), suggesting that AUC_p was not related to nephrotoxicity on this condition. Therefore, we used the CDDP concentration in the kidney rather than that in plasma to analyze the effects of disopyramide and verapamil on the relationship between the pharmacokinetics of CDDP and nephrotoxicity. The sigmoid E_{max} model using AUC_k and BUN level at 5 days after CDDP

Table 2. Area-Under the Curve of Cisplatin Concentration in the Kidney Versus Time (AUCk) and Elimination Rate Constant (k_{el}) of Cisplatin in the Kidney After i.v. Bolus Injection of Cisplatin

Dose (mg/kg)	$AUC_{0\text{-}t}$ μg Pt/ml hr	k_{el} hr^{-1}	AUC_k μg Pt/ml hr
2.5	4.68	2.69	5.04
3.5	6.44	2.41	7.06
4	7.34	2.44	8.07
5	9.18	2.50	10.1
with disopyramide	4.85	2.33	5.18
with verapamil	6.66	2.47	7.15

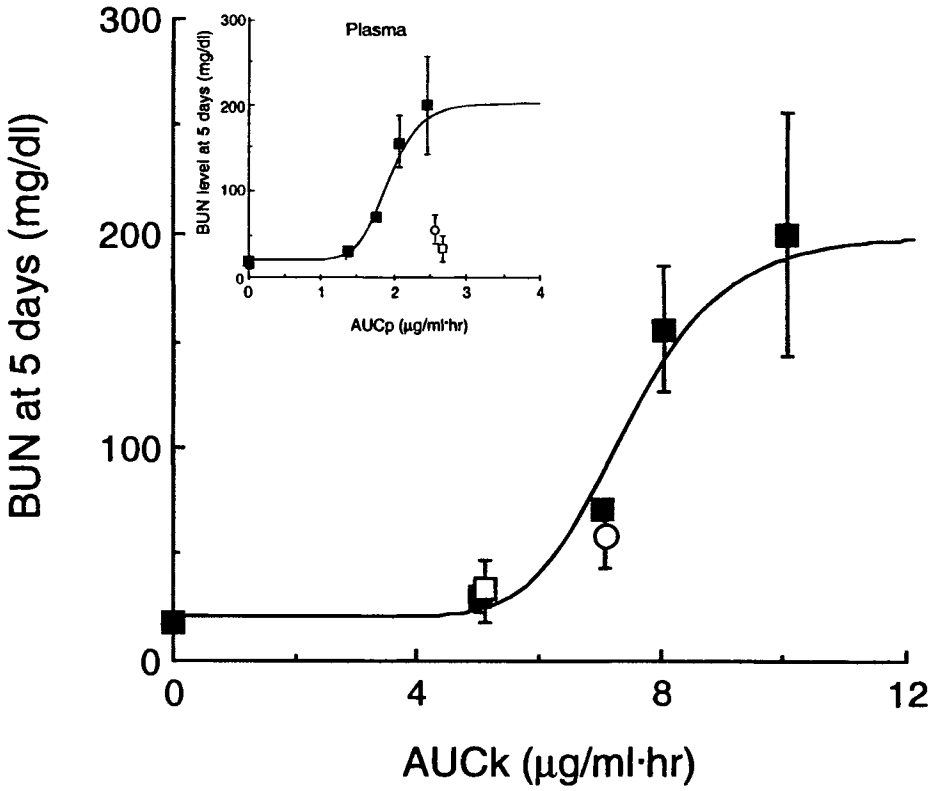

Fig. 2. Effects of disopyramide and verapamil on the relationships between the area under the curves of cisplatin concentration in plasma and kidney versus time (AUC_p and AUC_k) and the BUN level at 5 days after administration of cisplatin. The simulation curve was obtained using the following sigmoid E_{max} model equation:

$$\text{plasma:BUN level(mg/dl)} = BUN_0 + \frac{BUN\ max \cdot AUC^{\gamma}}{AUC_{50}^{\gamma} + AUC^{\gamma}}$$

$$= 19.6 + \frac{201 \cdot AUC_p^{8.01}}{2.02^{8.01} + (AUC_p)^{8.01}}$$

$$\text{kidney: BUN level(mg/dl)} = 20.0 + \frac{200 \cdot AUC_k^{7.49}}{7.54^{7.49} + (AUC_k)^{7.49}}$$

Each point represents the mean ± S.D. (n = 4). ■, cisplatin injection alone (dose: 2.5, 3.5, 4 or 5 mg/kg); □, 5 mg/kg cisplatin + disopyramide; ○, 5 mg/kg cisplatin + verapamil.

Table 3. Effects of Racemic Verapamil on the Pharmacokinetics of Cisplatin

	Cisplatin alone	With racemic verapamil
CL_s (ml/min/kg)	19.6 ± 2.77	20.2 ± 3.05
CL_r (ml/min/kg)	9.29 ± 2.64	11.1 ± 1.68
GFR (ml/min/kg)	5.42 ± 1.42	9.34 ± 0.69**
Clearance ratio[a]	1.72 ± 0.36	1.19 ± 0.13*
Concentration ratio[b]	2.63 ± 0.36	1.64 ± 0.22**

Note: Values are means ± S.D. (n = 4).
* $p < 0.05$; ** $p < 0.001$ (significantly different from cisplatin alone).
[a] CLr/GFR.
[b] Kidney-to-plasma cisplatin concentration ratio at steady state.

Table 4. Effects of Verapamil Enantiomers on the Pharmacokinetics of Cisplatin

	Cisplatin alone	With R-(+)-verapamil	With S-(−)-verapamil
CL_s (ml/min/kg)	21.8 ± 1.66	19.3 ± 3.75	24.4 ± 1.31
CL_r (ml/min/kg)	7.06 ± 2.53	8.12 ± 1.34	8.26 ± 0.77
GFR (ml/min/kg)	5.01 ± 1.61	4.11 ± 1.05	8.20 ± 0.85*
Clearance ratio[a]	1.56 ± 0.41	2.05 ± 0.45	1.02 ± 0.20*
Concentration ratio[b]	3.12 ± 0.25	2.43 ± 0.29*	1.72 ± 0.33**

Note: Values are means ± S.D. (n = 4).
* $p < 0.05$; ** $p < 0.001$ (significantly different from cisplatin alone).
[a] CLr/GFR.
[b] Kidney-to-plasma cisplatin concentration ratio at steady state.

administration demonstrated that reduced renal CDDP accumulation resulted in amelioration of CDDP-induced nephrotoxicity in rats.

Some drugs show stereoselective pharmacokinetics and pharmacodynamics *in vivo* and *in vitro*, as demonstrated by their hepatic metabolism, plasma protein binding and pharmacological effects (22). Some drugs show stereoselectivity of brush-border membrane transport. Recently, Ott and Giacomini studied the enantiomeric effects of basic drugs on tetraethylammonium uptake into an opossum kidney cell line (23). The inhibitory effect of S-(−)-verapamil was about 18 times higher than that of R-(+)-verapamil. In the current study, however, the clearance ratio of CDDP was reduced by either racemic or S-(−)-verapamil. The reduced clearance ratio induced by S-(−)-verapamil (to 65% of the control level) was consistent with the reduced renal accumulation (kidney-to-plasma concentration ratio) of CDDP (to 55% of the control level), suggesting that the inhibitory effect of verapamil on the renal uptake of CDDP may result from competitive inhibition via the basolateral membrane transport system (9). Unfortunately, few studies have reported on the stereoselectivity of cationic drugs with the basolateral membrane transport system.

CDDP concentrations in the kidney were decreased by coadministration of R-(+)-verapamil (Table 4). On the other hand, the clearance ratio was slightly but not significantly increased by R-(+)-verapamil. These results suggest that accumulation of CDDP into the renal tubular cells may occur through both tubule secretion and reabsorption. Safirstein *et al.* used a microinjection technique with early segments of superficial proximal tubules to show that only 10% of CDDP undergoes tubule absorption in the rat (24). By contrast, a study using isolated perfused kidney showed that the renal excretion of CDDP involves tubule secretion and tubule reabsorption (25). The uptake of CDDP into rat renal brush-border membrane vesicles was not associated with the proton/cation exchange transport system but was partially inhibited by verapamil (unpublished data). Further studies are required to determine the contribution and the mechanism of the renal tubular transport of CDDP.

In summary, we have demonstrated that concomitant administration of CDDP and a basic drug, disopyramide or verapamil, reduced the accumulation of CDDP in the kidney and ameliorated CDDP-induced nephrotoxicity. Furthermore, verapamil enantiomers had different effects on the renal handling of CDDP. These results showed that it is possible to ameliorate CDDP-induced nephrotoxicity by inhibiting the accumulation of CDDP into the kidney.

NOTATION

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