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Relationship between pharmacokinetics of unchanged cisplatin and nephrotoxicity after intravenous infusions of cisplatin to cancer patients

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Abstract *Purpose*: The relationships between pharmacokinetic parameters of unchanged cisplatin (CDDP) and several markers for nephrotoxicity after CDDP infusion (80 mg/m^2) over 2 and 4 h were quantitated in patients with various cancers (lung, stomach and colon cancers and mediastinal tumor). *Methods*: Plasma and urinary levels of unchanged CDDP were measured using a specific high-performance liquid chromatography method. Pharmacokinetic parameters were calculated according to the model-independent method. The nephrotoxicity markers, blood urea nitrogen (BUN), serum creatinine (SCr), plasma and urinary β_2-microglobulin (BMG_p and BMG_u), urinary *N*-acetyl-β-D-glucosaminidase (NAG) and creatinine clearance (CCR) were monitored for 30 days following CDDP administration. *Results*: The maximum plasma concentration (C_{max}), maximum urinary excretion rate (dAe/dt_{max}), area under the plasma concentration-time curve from time zero to infinity (AUC), cumulative amount excreted in urine from time zero to infinity (Ae), total clearance (Clt), renal clearance (Clr) and plasma half-life ($t_{1/2}$) of unchanged CDDP were not significantly different between the 2-h and 4-h infusion schedules. The values of the nephrotoxicity markers changed significantly following CDDP administration, suggesting that CDDP chemotherapy (80 mg/m^2) caused nephrotoxicity. The C_{max} of unchanged CDDP was the most informative pharmacokinetic parameter for nephrotoxicity. C_{max} was related to maximum BUN, maximum SCr and minimum CCR levels in 27 CDDP treatments according to an exponential model. *Conclusion*: In order to attain more effective CDDP chemotherapy with minimum nephrotoxicity, the present pharmacokinetic and pharmacodynamic studies suggest that the C_{max} or steady-state plasma level of unchanged CDDP should be maintained between 1.5 and 2 μg/ml in a standard continuous infusion schedule over 2 h and 4 h.

Key words Unchanged cisplatin · Nephrotoxicity · Pharmacokinetics · Pharmacodynamics · Maximum plasma concentration

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Introduction

Nephrotoxicity of cisplatin (CDDP) is the principle dose-limiting factor [22, 23], the primary site of acute kidney damage in animals being the S_3 segment of the proximal tubule [12, 28]. Acute tubular necrosis has also been observed in the human kidney, followed by chronic pathological damage, lasting for more than 12 months [11, 17].

The urinary excretions of β_2-microglobulin (BMG_u), alanine aminopeptidase (AAP), leucine aminopeptidase (LAP) and *N*-acetyl-β-D-glucosaminidase (NAG) have been used as more sensitive markers for acute kidney damage [4, 7, 10, 20]. A decrease in glomerular filtration rate (GFR), and increases in serum creatinine (SCr) and blood urea nitrogen (BUN) levels have been observed from a week to several months after CDDP

administration, suggesting that CDDP causes further chronic damage in both the glomerulus and distal tubule [14, 18, 24]. Hypomagnesemia, hypocalcemia and hypokalemia have also been noted after CDDP administration [5, 8, 13].

These nephrotoxicity markers have been studied extensively, and the relationship between the values of these markers and renal pathophysiology (as determined by microscopic examination) has been discussed in detail. However, few studies have linked nephrotoxicity markers to CDDP pharmacokinetics. Campbell et al. have reported that patients with nephrotoxicity show significantly higher total platinum levels than non-nephrotoxic patients [6]. Comparison of the pharmacokinetics of ultrafiltrable platinum by rapid and prolonged dosing schedules [2, 33], and the relationship between peak ultrafiltrable platinum and the decline in creatinine clearance (CCR) [26], suggest that maximum plasma concentration (C_{max}) could be an important parameter for nephrotoxicity. Additionally, several successful clinical trials in which marked amelioration of nephrotoxicity was observed with continuous infusion or fractional dosing schedules support the above suggestion [3, 15, 29]. However, no quantitative relationship between pharmacokinetics and nephrotoxicity has been obtained in humans because most of the previous studies have not been based on biologically active unchanged CDDP, but on the platinum level (total or ultrafiltrable platinum) including inactive high and low molecular-mass metabolites.

In the present study, plasma and urine concentrations of unchanged CDDP were measured in cancer patients infused with CDDP (80 mg/m^2) over 2 and 4 h. The relationships between pharmacokinetic parameters of unchanged CDDP and several nephrotoxicity markers were evaluated in a clinical setting.

Materials and Methods

Materials

CDDP (Randa) was a gift from Nippon Kayaku (Tokyo, Japan). All other chemicals and reagents were of analytical grade.

Pharmacokinetic study

A total of 12 patients hospitalized at St. Marianna University School of Medicine and Hospital participated in the study. This study was approved by the hospital Ethics Committee Board. All patients gave informed consent prior to the study. Patient characteristics and the methods of dosing are summarized in Table 1. The mean age and weight of the patients was 56.9 years (range 26–79 years) and 53.8 kg (range 34–67 kg). The total dose of CDDP (80 mg/m^2) ranged from 90 to 140 mg (mean 116.4 mg). Two patients received CDDP twice (first and second courses (no. 10 and no. 11) or second and third courses (no. 12 and no. 13) during the study. Seven patients received CDDP as a first course, two patients as a second course and one patient as a third course. After hydration for 2 h with 1000 ml Solita T_3 containing 35 mEq Na, 20 mEq K, 3 mEq Mg, 30 mEq Ca, 5 m*M* H_2PO_4 and 20 m*M* citrate (Shimizu Co., Tokyo, Japan), CDDP dissolved in 500 ml 0.9% sodium chloride solution was infused over 2 h (eight treatments), or 4 h (six treatments). During the infusion, the CDDP solution was shielded from light. For postinfusion hydration, 1000 ml Solita T_3 was given over 4 h after a 2-h infusion of CDDP, or 500 ml of Solita T_3 and 500 ml of mannitol was given over 2 h after a 4-h infusion of CDDP. In addition, all patients were infused with 1000 ml Solita T_3 on each of 3 consecutive days.

Blood (5 ml) was collected into heparinized dry test-tubes prior to CDDP infusion and at appropriate intervals during and after the infusion. Urine was collected via a catheter before and during the CDDP infusion, and up to 24 h after the completion of the CDDP infusion. The blood samples were immediately centrifuged (1000 *g*) for 10 min at 4 °C. The plasma was ultrafiltered (4000 *g*) for 30 min at 4 °C using a membrane with a molecular weight cut-off pore size of 10 000 Da (UFC 3GC; Japan Millipore, Tokyo, Japan). The ultrafiltered plasma and urine samples were immediately stored at −20 °C until assay.

Table 1 Patient characteristics and infusion schedules of CDDP for the pharmacokinetic and nephrotoxicity studies (*M* male, *F* female, *ADM* adriamycin, *5-FU* fluorouracil, *OK*-432 picibanil, *VP*-16 etoposide, *VDS* vindesin, *BLM* bleomycin, *MTX* methotrexate, *VCR* vincristine, *MMC* mitomycin-C, *CPA* cyclophosphamide

Patient no.	Age (years)	Sex	Weight (kg)	Dose (mg)	Course	Infusion time (h)	Tumor type	Other medication
1	79	F	53	110	1	2	Stomach	ADM, 5-FU, OK-432
2	55	M	57	130	3	2	Lung	VDS, OK-432
3	67	M	67	130	1	2	Lung	VDS, OK-432
4	72	F	34	90	1	2	Stomach	ADM
5	66	F	63	140	1	2	Lung	VP-16
6	26	M	58	120	1	4	Mediastinal tumor	BLM, MTX, CPA VCR, VP-16
7	51	F	63	130	2	4	Lung	VDS, MMC
8	63	M	41	100	1	4	Lung	VP-16, CPA, VCR, ADM
9	42	F	49	110	1	4	Stomach	ADM, 5-FU, MMC
10	65	M	55	110	1	4	Colon	5-FU, MMC
11	65	M	55	113	2	2	Colon	5-FU, MMC
12	49	M	64	113	2	4	Lung	MMC, VDS
13	49	M	64	116	3	2	Lung	MMC, VDS
14	56	M	51	120	2	2	Lung	ADM, CPA, VCR, VP-16

Analyses

Unchanged CDDP was determined using a specific high-performance liquid chromatography (HPLC) method with online post-column derivatization [21]. Briefly, ultrafiltered plasma and urine samples were thawed just before analysis. The urine samples were centrifuged at 4 °C and the supernatant diluted (1:10 v/v) with water. A 100-μl aliquot of the ultrafiltered plasma or diluted urine was injected into the analytical column (Hitachi No. 3013-N, Chromato Research, Tokyo, Japan). The column was eluted with acetonitrile/10 m*M* sodium chloride (15:85 v/v) at a constant flow rate of 0.9 ml/min. The unchanged CDDP was detected at 290 nm after derivatization with 26 μ*M* potassium dichromate and 6.6 m*M* sodium hydrogen sulfite. The detection limit of this HPLC assay for a 100-μl injection volume was 80 ng/ml in human plasma, and the coefficient of variation for the plasma concentration between 0.5 and 2 μg/ml was less than 8% [21].

Nephrotoxicity study

The same plasma and urine concentrations of unchanged CDDP from the patients for the pharmacokinetic study (Table 1) were used. Further plasma samples (three or four per patient) were obtained to determine the C_{max} of unchanged CDDP from 13 CDDP treatments at both St. Marianna University School of Medicine and Hospital and the Niigata Cancer Center Hospital (Table 2). The study was approved by the Ethics Committee Boards of both hospitals. In order to determine nephrotoxicity markers, blood samples were collected before CDDP dosing and at appropriate intervals after dosing, and urine specimens were collected as a 24-h pooled sample or as a fractional sample up to 30 days after CDDP administration. The levels of BUN, serum and urinary creatinine, urinary NAG, and BMG_p and BMG_u were determined using the Urea *N*-HA test (Wako Chemical Co., Osaka, Japan), the Creatinine-HA test (Wako), the NAG test (Shionogi Pharmaceutical Co., Osaka, Japan) and the Phadebas β_2-micro test RIA kit (Pharmacia Diagnostics Co., Tokyo, Japan), respectively. CCR was calculated as follows: CCR (ml/min) = U/P·(V/24·60), where U/P denotes the ratio of urinary to serum concentration of creatinine and V (ml) is the urine volume for 24 h.

Pharmacokinetics

The AUC_{0-t1}, Ae_{0-t2} and $AUMC_{0-t1}$ were calculated by numerical integration of the plasma concentration- and urinary excretion rate-time data from time zero to the final sampling time using the trapezoidal rule. The area under the plasma concentration-time curve from time zero to infinity (AUC), the cumulative amount excreted in urine from time zero to infinity (Ae), the mean residence time (MRT), the total clearance (Clt), the renal clearance (Clr) and the plasma hal-life ($t_{1/2}$) values were calculated from the following equations [16]:

$$AUC = AUC_{0-t1} + Cp_{t1}/kel_p$$

$$Ae = Ae_{0-t2} + (dAe/dt)_{t2}/kel_u$$

$$Ae(\%) = Ae/D \cdot 100$$

$$AUMC = AUMC_{0-t1} + Cp_{t1}/kel_p \cdot (1/kel_p + t1)$$

$$MRT = AUMC/AUC - T/2$$

$$Clt = D/AUC$$

$$Clr = Ae/AUC$$

$$t_{1/2} = 0.693/kel_p$$

in which Cpt_1 is the plasma concentration at the final sampling time (t1), kel_p is the plasma terminal elimination rate constant, $(dAe/dt)_{t2}$ is the urinary excretion rate at the final sampling interval, t2 is the midpoint of the final sampling interval, kel_u is the terminal elimination rate constant calculated from the urinary excretion rate-time profile, Ae(%) is the cumulative percentage of unchanged CDDP excreted in urine from time zero to infinity, and D and AUMC are the dose of CDDP and the area under the first moment curve from time zero to infinity. *T* is the infusion time.

Pharmacodynamics

The relationships between the pharmacokinetic parameters of unchanged CDDP (C_{max}, dAe/dt_{max}, AUC, Ae(%), Clt, Clr, MRT) and the values of the nephrotoxicity markers (maximum BUN, maximum SCr, minimum CCR and maximum BMG_p) were tested statistically by the calculation of Pearson's correlation coefficient (*r*) for 14 CDDP treatments. The final pharmacodynamic analysis was carried out using C_{max} and the nephrotoxicity markers (BUN, SCr and CCR) for 27 treatments according to linear, exponential and sigmoid maximum response (E_{max}) models [19]. The pharmacodynamic analysis was performed using the program NLS [32] and Akaike's Information Criterion (AIC) [34].

Statistics

Data are expressed as means ± SD. Pharmacokinetic parameters of unchanged CDDP after 2- and 4-h infusions of CDDP were

Table 2 Characteristics of additional patients and infusion schedules for the nephrotoxicity study. For an explanation of the abbreviations, see Table 1

Patient no.	Age (years)	Sex	Weight (kg)	Dose (mg)	Course	Infusion time (h)	Tumor type	Other medication
15	50	M	53	120	1	2	Lung	VDS, MMC,
16	74	M	70	120	5	2	Lung	VP-16, ADM
17	77	M	60	120	6	4	Lung	VDS, MMC
18	69	M	51	110	1	4	Lung	ADM, VP-16
19	64	M	53	135	3	2	Lung	VDS
20	49	M	53	147	1	4	Lung	VDS
21	67	M	50	101	3	4	Lung	VP-16
22	70	M	56	115	4	2	Lung	VP-16, ADM
23	60	M	59	120	2	3.5	Lung	VDS
24	77	M	60	120	7	2	Lung	VDS, MMC
25	67	M	50	101	4	4	Lung	VP-16
26	49	M	53	147	2	4	Lung	VDS
27	59	M	59	120	1	2	Lung	VDS

compared statistically using Student's *t*-test for unpaired data, at the 0.05 level of significance. The individual maximum levels of BUN, SCr, NAG, BMG_p and BMG_u, and the minimum level of CCR after CDDP administration were compared with those obtained before CDDP administration using Student's *t*-test for paired data, at the 0.05 level of significance.

Results

The time courses of the mean plasma concentration and mean urinary excretion rate of unchanged CDDP after 2- and 4-h infusions of CDDP are shown in Fig. 1. The steady-state levels of unchanged CDDP in plasma were attained by 2 h in most patients. Unchanged CDDP was eliminated monoexponentially after completion of the infusion.

The mean pharmacokinetic parameters of unchanged CDDP are summarized in Table 3. Only the MRT showed a significant difference ($P < 0.05$) between the 2- and 4-h infusion schedules. No significant difference was found in other pharmacokinetic parameters. Mean Clr was 110.5 ± 56.5 ml/min, corresponding to $18.4 \pm 8.1\%$ of the Clt. The ratio of Clr to CCR exceeded unity (1.72 and 2.02 for the 2- and 4-h infusions). The mean C_{max} was 2.22 ± 0.90 μg/ml after the 2-h infusion and 1.39 ± 0.79 μg/ml after the 4-h infusion. The biological half-life of unchanged CDDP was very short (24.8 ± 6.7 and 35.2 ± 15.7 min, respectively).

The nephrotoxicity markers (BUN, SCr, CCR and BMGp) showed maximum or minimum values at 5.3 ± 4.2, 4.0 ± 3.4, 9.1 ± 7.5 and 2.0 ± 0.5 days after CDDP administration, respectively. These values gradually returned to the levels obtained before CDDP administration within 30 days of CDDP therapy. Figure 2 shows the maximum differences for those values that changed significantly ($P < 0.01$ or $P < 0.001$) after CDDP administration, suggesting that various stages of nephrotoxicity were induced by CDDP administration (80 mg/m^2 infused over 2 h and 4 h). More sensitive nephrotoxicity markers (NAG and BMG_u) were also monitored as urinary concentrations in the present study. These concentrations were markedly increased after CDDP administration (Fig. 2).

Table 3 Mean pharmacokinetic parameters of unchanged CDDP in cancer patients after continuous infusion of CDDP (80 mg/m^2) over 2 and 4 h. Values are means ± SD (Cl_t total clearance, Cl_r renal clearance, CCR creatinine clearance, AUC area under plasma concentration-time curve from zero to infinity, Ae cumulative excretion of unchanged CDDP in urine, C_{max} maximum plasma concentration, dAe/dt_{max} maximum urinary excretion rate, $t_{1/2}$ plasma half-life, MRT mean residence time)

Pharmacokinetic parameter	2 h ($n = 8$)	4 h ($n = 6$)
Cl_t (ml/min)	726.3 ± 410.7	533.2 ± 193.6
Cl_r(ml/min)	110.6 ± 69.3	110.4 ± 39.7
Cl_r/CCR	1.72 ± 0.58	2.02 ± 0.84
AUC(μg/ml.h)	3.28 ± 1.44	4.08 ± 1.89
Ae(%)	15.3 ± 5.3	22.5 ± 9.7
C_{max} (μg/ml)	2.22 ± 0.90	1.39 ± 0.79
dAe/dt_{max} (mg/h)	11.6 ± 5.3	8.8 ± 2.5
$t_{1/2}$ (min)	24.8 ± 6.7	35.2 ± 15.7
MRT(h)	0.78 ± 0.36	1.38 ± 0.57*

* $P < 0.05$

The correlation coefficients between the pharmacokinetic parameters of unchanged CDDP (C_{max}, dAe/dt_{max}, AUC, Ae(%), Clt, Clr, MRT) and the values of the nephrotoxicity markers (BUN, SCr, CCR and BMG_p) after CDDP administration are summarized in Table 4. The C_{max} and AUC showed significant positive correlations with BUN ($r = 0.740$, $P < 0.01$ and $r = 0.701$, $P < 0.01$), and Clr negative correlations with SCr ($r = -0.563$, $P < 0.05$) in the data from 14 CDDP treatments. However, dAe/dt_{max}, Ae(%), and MRT did not correlate significantly with the markers monitored. In the data from 27 CDDP treatments, the C_{max} of unchanged CDDP correlated with BUN ($r = 0.649$, $P < 0.001$), SCr ($r = 0.408$, $P < 0.05$) and CCR ($r = -0.596$, $P < 0.01$). The final pharmacodynamic

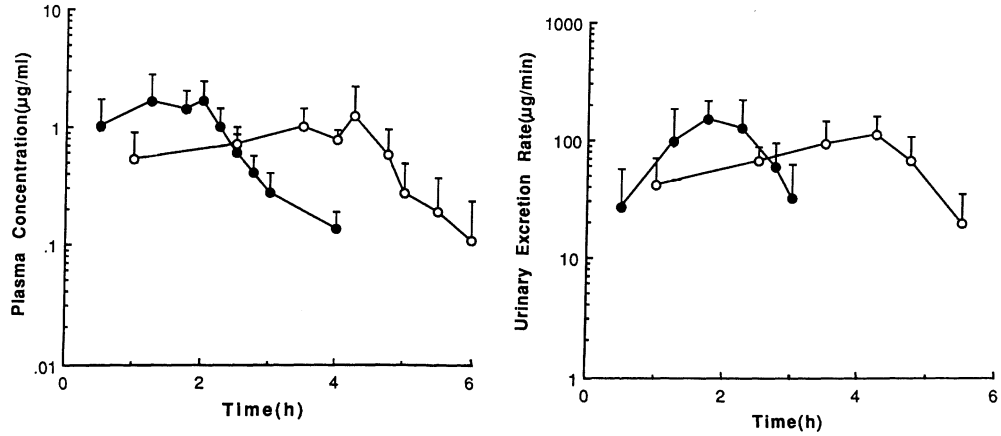

Fig. 1 Mean plasma concentration (*left*) and urinary excretion rate (*right*) time courses of unchanged CDDP in cancer patients receiving CDDP (80 mg/m^2) over 2 h (●) and 4 h (○)

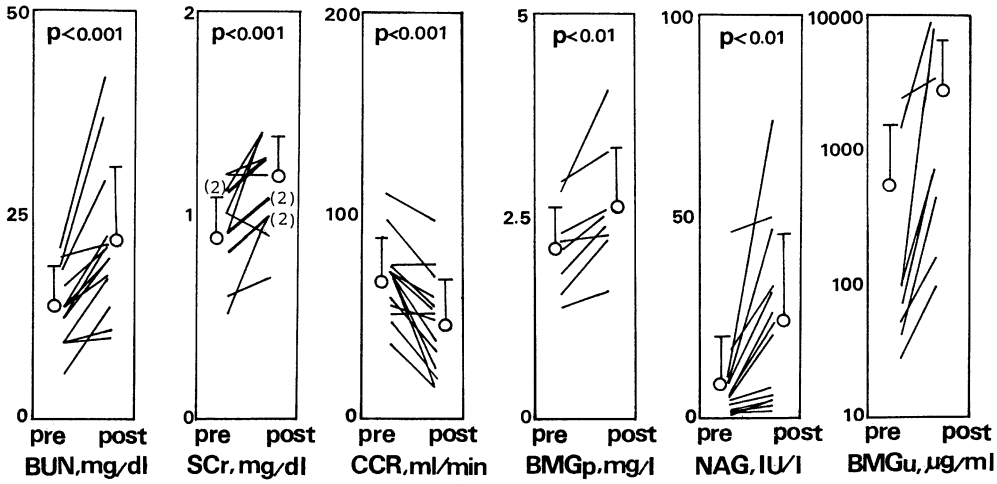

Fig. 2 Comparison of blood urea nitrogen (BUN), serum creatinine (SCr), creatinine clearance (CCR), *N*-acetyl-β-D-glucosaminidase (NAG), plasma and urine β_2-microglobulin (BMG_p and BMG_u) in cancer patients before and after CDDP administration (80 mg/m^2). The *solid lines* connect the values from the same individual. Mean values (○) are also shown (± SD). Parentheses indicate that the data are from two patients

relationships which most successfully estimated nephrotoxicity markers were as follows; $BUN = 5.022 \cdot (C_{max})^{1.124} + 10.595$, $SCr = 0.029 \cdot (C_{max})^{2.260} + 0.841$, $CCR = 94.409 - 26.575 \cdot (C_{max})^{0.791}$, respectively (Fig. 3). The plasma concentrations of unchanged CDDP corresponding to the boundary of the normal range of these markers were 1.75 μg/ml for BUN (20 mg/dl) and 1.91 μg/ml for CCR (50 ml/min), respectively.

Discussion

The main aim of the present study was to investigate and quantitate the relationships between pharmacokinetic parameters of unchanged CDDP and the values of nephrotoxicity markers in cancer patients after CDDP therapy.

The urinary concentrations of NAG, BMG, LAP and AAP increased rapidly in the immediate period after CDDP administration, and this was consistent with pathophysiological changes in the kidney (acute tubular necrosis) caused by CDDP [8, 13, 28]. Therefore, these substances have been used as highly sensitive markers for detection of acute renal tubular damage caused by CDDP. However, measurements of these proteins and enzymes in urine have been reported to be of little value in predicting chronic renal tubular damage or progressive nephrotoxicity [8, 31]. In the present study, no significant relationship between the pharmacokinetics of unchanged CDDP and the urinary excretion of BMG or NAG was observed. Among BUN, SCr and CCR, the change in SCr was generally so small that it was difficult to precisely detect SCr change following CDDP administration in a clinical setting. The limitation of creatinine as a renal function marker has already been suggested [8, 9, 30]. Although BUN can be increased by nonrenal factors such as high protein intake, bleeding or catabolism of tissue [1, 25], renal damage is the most important factor involved in BUN increases. Furthermore, the dose-related nature of tubular necrosis caused by CDDP, which has been observed by microscopic examination, is consistent with BUN levels in rats [13, 23]. Therefore, we monitored all three markers and evaluated their relationships with unchanged CDDP pharmacokinetics in cancer patients.

Although both C_{max} and AUC showed significant correlations with BUN levels in cancer patients (Table 4), C_{max} showed the best correlation with nephrotoxicity markers. Belliveau et al. [2] and Vermorken et al. [33] have speculated that the peak concentration of ultrafiltrable platinum might play an important role in CDDP-induced nephrotoxicity. Reece et al. showed that the peak plasma level of ultrafiltrable platinum correlated significantly ($P < 0.005$) with the decline in CCR in 12 patients after four courses of CDDP therapy [26]. In the same study, it was found that the AUC of ultrafiltrable platinum also correlated with the change in CCR, but was a less satisfactory predictor than C_{max}. The peak urine levels of platinum have been shown not to correlate with CCR levels [26], and our findings substantiate this result.

We examined the quantitative relationship between the pharmacokinetics of unchanged CDDP and nephrotoxicity in rats given CDDP at various doses and in various schedules. AUC calculated using plasma concentrations of unchanged CDDP greater than the threshold level, $AUC_{>Cmin}$ was found to be an important pharmacokinetic parameter predicting nephrotoxicity, irrespective of dose and schedule. Furthermore, BUN increase was dependent upon C_{max} and AUC for CDDP administered according to the same dosing schedule. In the present study, since the total dose administered to cancer patients was kept constant (80 mg/m^2) and the infusion rate was set within the comparatively narrow range between 20 and 40 mg/m^2

Table 4 Correlation coefficients between pharmacokinetic parameters of unchanged CDDP and nephrotoxicity markers in cancer patients after continuous infusion of CDDP (80 mg/m^2) over 2 and 4 h (*BUN* maximum blood urea nitrogen level, *SCr* maximum serum creatinine level, *CCR* minimum creatinine clearance level, BMG_p maximum plasma β_2-microglobulin level, C_{max} maximum plasma concentration, dAe/dt_{max} maximum urinary excretion rate, *AUC* area under plasma concentration-time curve from time zero to infinity, *Ae* cumulative percentage of unchanged CDDP excreted in urine from time zero to infinity, Cl_t total clearance, Cl_r renal clearance, *MRT* mean residence time *NS* not significant)

		BUN (mg/dl)	SCr (mg/dl)	CCR (ml/min)	BMGp (mg/l)
C_{max}	*r*	0.740	0.359	− 0.487	0.455
(μg/ml)	*P*	< 0.01	NS	NS	NS
	n	14	14	14	8
C_{max}	*r*	0.649	0.408	− 0.596	
(μg/ml)	*P*	< 0.001	< 0.05	< 0.01	
	n	27	27	20	
dAe/dt_{max}	*r*	0.095	− 0.081	− 0.001	− 0.186
(mg/h)	*P*	NS	NS	NS	NS
	n	14	14	14	8
AUC	*r*	0.701	0.235	− 0.410	0.744
(μg/ml · h)	*P*	< 0.01	NS	NS	< 0.05
	n	14	14	14	8
Ae	*r*	0.210	− 0.173	− 0.137	− 0.397
(%)	*P*	NS	NS	NS	NS
	n	14	14	14	8
Clt	*r*	− 0.539	− 0.453	0.428	− 0.651
(ml/min)	*P*	< 0.05	NS	NS	NS
	n	14	14	14	8
Clr	*r*	− 0.457	− 0.563	0.422	− 0.178
(ml/min)	*P*	NS	< 0.05	NS	NS
	n	14	14	14	8
MRT	*r*	− 0.165	− 0.334	0.181	0.582
(h)	*P*	NS	NS	NS	NS
	n	14	14	14	8

per h, C_{max} was thought to be correlated with $AUC_{>Cmin}$. The C_{max} values showed a wide range (0.672 to 3.758 μg/ml) in the present study. CDDP was probably infused to some patients at a slightly faster rate near the completion of the infusion because an automatic infusion pump was not used for these patients. Nonlinear pharmacokinetics of unchanged CDDP have been suggested in a previous study [27]. Both of these factors may have contributed to unexpectedly high C_{max} values in some patients who showed severe nephrotoxicity. Therefore, it is possible that C_{max} might be a rather clearer and more useful pharmacokinetic parameter for nephrotoxicity in patients when the dosing rate is limited to a narrow range.

During the pharmacodynamic analysis of C_{max} with BUN and SCr, because of the clinical setting, it was impossible to incorporate the maximum effect in the sigmoid E_{max} model. The relationships were analyzed according to both linear and exponential models.

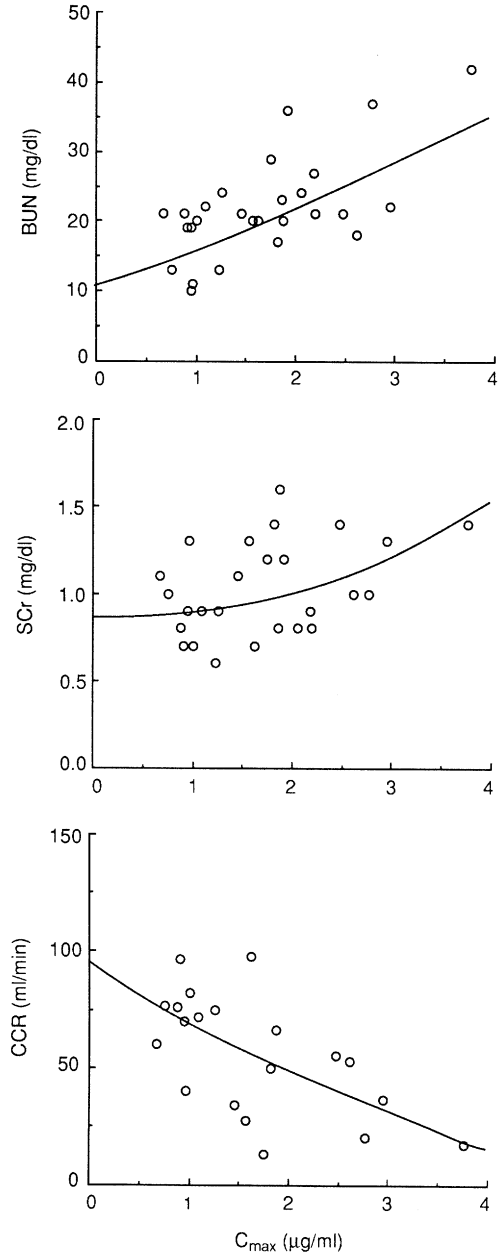

Fig. 3 Relationships between C_{max} of unchanged CDDP and maximum BUN (*top*), maximum SCr (*center*) and minimum CCR (*bottom*) levels in cancer patients after CDDP administration (80 mg/m^2). The pharmacodynamic relationships were as follows: $BUN = 5.022 \cdot (C_{max})^{1.124} + 10.595$, $SCr = 0.029 \cdot (C_{max})^{2.260} + 0.841$, $CCR = 94.409 - 26.575 \cdot (C_{max})^{0.791}$

Meanwhile, the relationship between C_{max} and CCR was evaluated according to linear, exponential and sigmoid E_{max} models. It was concluded that an exponential model gave the most successful estimations, because the AIC was small and reasonable baseline values were obtained within normal ranges of these nephrotoxicity markers.

In conclusion, the C_{max} of unchanged CDDP was quantitatively correlated with the maximum and min-

imum levels of nephrotoxicity markers in cancer patients receiving CDDP over 2 h and 4 h. From these pharmacokinetic and pharmacodynamic analyses, we suggest that severe nephrotoxicity can be avoided if the C_{max} of unchanged CDDP is strictly maintained between 1.5 and 2.0 μg/ml in a dosing schedule in which CDDP is administered within 4 h. This will provide useful quantitative information for establishing effective CDDP dosage regimens.

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