Pharm Res (2010) 27:1893–1899
DOI 10.1007/s11095-010-0189-4

RESEARCH PAPER

Pharmacokinetics and Toxicodynamics of Oxaliplatin in Rats: Application of a Toxicity Factor to Explain Differences in the Nephrotoxicity and Myelosuppression Induced by Oxaliplatin and the Other Platinum Antitumor Derivatives

Kazuhiko Hanada • Makoto Suda • Norihito Kanai • Hiroyasu Ogata

Received: 8 April 2010 / Accepted: 4 June 2010 / Published online: 15 June 2010

ABSTRACT

Purpose We previously reported that the product of the area under the plasma concentration–time curve (AUC_p) and a toxicity factor, which in turn was defined as the product of the apparent ratio of tissue to plasma concentration (Kp_{app}) and the apparent hydrolysis rate constant ($k_{hydrolysis}$), was a determinant of the different degrees of toxicities induced by platinum drugs, cisplatin, carboplatin and nedaplatin. We tested this model with oxaliplatin.

Methods Oxaliplatin was administered to rats by intravenous bolus or infusion, and the linearity of pharmacokinetics, total clearance and the Kp_{app} at steady state were determined. $k_{hydrolysis}$ was determined *in vitro*. Nephrotoxicity was estimated from blood urea nitrogen (BUN) level and myelosuppression from platelet count.

Results The platelet count decreased dose-dependently, but BUN did not increase significantly. The degree of decrease in platelet count caused by oxaliplatin and the other three platinum drugs was not explained by the differences of AUC_p and AUC for the bone marrow but was fitted by a combination of AUC_p and the toxicity factor ($r = 0.908$, $P < 0.001$).

Conclusion The product of AUC_p and the toxicity factor is a useful predictor of the degree of toxicity of oxaliplatin as has been observed with other platinum drugs.

KEY WORDS oxaliplatin · toxicity factor · nephrotoxicity · myelosuppression · hydrolysis rate constant

K. Hanada (✉) · M. Suda · N. Kanai · H. Ogata
Department of Biopharmaceutics, Meiji Pharmaceutical University
2-522-1 Noshio
Kiyose, Tokyo 204-8588, Japan
e-mail: hanada@my-pharm.ac.jp

ABBREVIATIONS

oxaliplatin	1R,2R-diaminocyclohexane-oxalatoplatinum(II)
cisplatin	*cis*-diamminedichloro-platinum (II)
carboplatin	*cis*-diammine 1-1 cyclobutane-dicarboxylato-platinum (II)
nedaplatin	*cis*-diammine glycolate-platinum (II)
CL_{tot}	total clearance
AUC_p	area under the concentration–time curve for plasma concentration of unchanged platinum drug
AUC_t	area under the concentration–time curve for concentration of unchanged platinum drug in the tissue
Kp_{app}	apparent ratio of tissue concentration of unchanged drug to plasma concentration under steady-state conditions
$k_{hydrolysis}$	apparent first-order rate constant of hydrolysis of unchanged platinum drug
Vd_t	volume of distribution of unchanged compound in the tissue

INTRODUCTION

In biological fluids, cisplatin is biotransformed through binding to low-molecular-mass substances (such as glutathione, methionine, and cysteine) and to high-molecular-mass substances (such as albumin and nucleotides). Many investigators have studied the pharmacokinetics of cisplatin by measuring the concentration of either total platinum or filterable platinum, which includes cisplatin and its mobile metabolites. However, it is difficult to estimate precisely the relationship between pharmacokinetics and pharmacodynamics on the basis of mixed concentration, because the

pharmacokinetics of these platinum species differ markedly (1–5).

We have studied the pharmacokinetic and toxicodynamic relationships of cisplatin under various conditions, such as with coadministration of sodium thiosulfate, disopyramide, and glutathione, in order to elucidate the factors determining nephrotoxicity on the basis of pharmacokinetics. Sodium thiosulfate reacts immediately with cisplatin and reduces nephrotoxicity (1), indicating that unchanged cisplatin in plasma is an important platinum species in the plasma. Organic cations such as disopyramide and verapamil inhibit the uptake of cisplatin into the kidneys and reduce nephrotoxicity (2), indicating that nephrotoxicity is dependent on the renal concentration of unchanged cisplatin. Furthermore, we have found that the sulfhydryl concentration in the cytosol fraction of the kidney is markedly increased after glutathione administration and that, consequently, binding of cisplatin to the sulfhydryl compound is increased, whereas its binding to organelles is decreased (4). This decrease is correlated with amelioration of nephrotoxicity, suggesting that binding of unchanged cisplatin to intracellular organelles is an important factor in cisplatin-induced nephrotoxicity. The rate-limiting step for binding of cisplatin to intracellular organelles is thought to be the intracellular rate of hydrolysis (6–8). Therefore, the hydrolysis rate constants of platinum drugs should be taken into account when predicting toxicity.

Many platinum derivatives have been developed to improve the toxicity profile of this class of drugs and to enhance antitumor activity. (The chemical structures of these derivatives are shown in Fig. 1.) The antitumor mechanisms of these drugs are thought to be identical, but their dose-limiting toxicities are different. We previously reported that the product of the area under the plasma concentration–time curve for unchanged drug (AUC_p) and a toxicity factor, which was defined as the product of the apparent ratio of the tissue concentration of unchanged drug to plasma concentration (Kp_{app}) and the apparent hydrolysis rate constant of unchanged drug ($k_{hydrolysis}$), was a determinant of the differences in nephrotoxicity and myelosuppression induced by cisplatin, carboplatin, and nedaplatin in rats. In this study, we tested this model with oxaliplatin in rats.

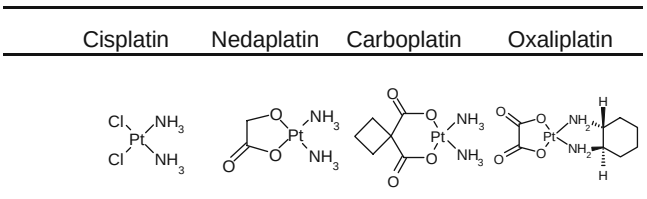

Fig. 1 Chemical structures of cisplatin, carboplatin, nedaplatin, and oxaliplatin.

MATERIALS AND METHODS

Chemicals

Oxaliplatin was kindly donated by Yakuruto Co. (Tokyo, Japan). All reagents and chemicals used were of analytical grade, except where stated otherwise. A blood urea nitrogen (BUN assay kit) was obtained from Wako Pure Chemical Industries (Tokyo, Japan).

Animals

Male Wistar rats (220 to 280 g) were purchased from Tokyo Laboratory Animal Science Co. (Tokyo, Japan) and were maintained on a standard laboratory pellet diet with water *ad libitum* in a controlled environment for at least 1 week. The rats used were handled in accordance with the *Guide for the Care and Use of Laboratory Animals* (National Academy Press, Washington, 1996), and the study protocol was approved by Meiji Pharmaceutical University.

In Vivo Pharmacokinetic Study

To derive the basic pharmacokinetic parameters, an *in vivo* renal clearance study was performed using methods reported previously (2–4,8). In brief, rats were anesthetized by intraperitoneal injection of sodium pentobarbital (50 mg/kg). Polyethylene cannulae (0.28 mm I.D.× 0.61 mm O.D.) were implanted into both the femoral vein and artery of one leg and into the ureters. Oxaliplatin in 5% glucose was infused via the femoral venous cannula at a constant rate of 0.037 mL/min (63 μg/min/kg). Blood samples were taken from the femoral artery at 60, 90, and 120 min. At 120 min after the start of drug infusion, the rats were sacrificed. The kidneys and bone marrow were excised quickly, blotted on filter paper, weighed, and homogenized with two to five volumes of 5% glucose. The tissue homogenate was ultracentrifuged at 105, 000*g* for 65 min at 4°C (Beckman L8-60 M). Blood samples were centrifuged at 1,000*g* for 5 min at 4°C, and the plasma and tissue supernatant were ultrafiltered at 4,000*g* for 30 min at 4°C with a membrane filter (Millipore filter UFC3GC, MW cut-off 10 000). These samples were stored at −80°C until analysis. The concentration of unchanged oxaliplatin was determined within 3 days. To confirm the linearity of the pharmacokinetics, an intravenous bolus administration study was also conducted. The rats were treated in the same manner as in the infusion study, and then oxaliplatin (5, 8, or 10 mg/kg in 5% glucose) was injected as a bolus via the jugular vein. Blood samples were taken from the femoral artery at 3.5, 10, 20, 30, 45, 60 and 90 min.

Study of Toxicity

Rats were anesthetized by intraperitoneal injection of sodium pentobarbital (50 mg/kg). Oxaliplatin (5 or 8 mg/kg in 5% glucose) or 5% glucose was injected as a bolus via the jugular vein (single dose). After the rats had regained consciousness, they were maintained on a standard laboratory pellet diet with water *ad libitum* in a temperature-controlled environment. Blood samples (0.2 mL) were taken from the other jugular vein just before administration and on days 1, 3, 5, 7, 10, and 17 after administration, and 100 μL of the sample was stored at 4°C until determination of platelet counts. An aliquot of the blood was centrifuged at 1,000×*g* for 5 min. The plasma was stored at −20°C until BUN analysis.

In Vitro Hydrolysis Reactions

This experiment was performed by using methods reported previously (Nagai *et al.* (1); Hanada *et al.* (8)). Phosphate buffer (0.067 M, pH 7.0) containing 14 mM sodium chloride (ionic strength was adjusted to 0.148 by sodium sulfate) and oxaliplatin (final concentration was 0.30 mM) was incubated at 37°C. One-hundred-twenty μL of the solution (total start volume was 3 mL) was withdrawn just before the start of incubation and again after 0, 1, 3, 6, 23, 29, 47, and 55 h. The concentration of unchanged oxaliplatin was determined.

Analytical Methods

The concentrations of unchanged oxaliplatin in the plasma and tissues were separated by HPLC (9), and the platinum in the eluted fraction that corresponded to unchanged oxaliplatin peak was quantified by ICP-MS. Briefly, the HPLC system consisted of a L-6200 Intelligent Pump (Hitachi, Tokyo, Japan), an L-4000 spectrometric detector (Hitachi), and a C-R6A Chromatopac integrator (Shimadzu, Kyoto, Japan). Unchanged oxaliplatin was separated with an L-column ODS (particle size: 5 mm, 12 nm; 250×4.6 mm I.D.; Chemical Evaluation and Research Institute, Tokyo, Japan) at room temperature. The mobile phase consisted of solvent A [0.02 M acetate buffer (pH 3.5) containing 5 mM sodium 1-heptanesulfonate] and solvent B (90% methanol in water) pumped at a constant rate of 1.0 mL/min under the following gradient conditions: solvent A 100% (0 to 20 min), 80% (20 to 25 min), 50% (25 to 30 min), and 0% (30 to 40 min). The unchanged oxaliplatin was eluted at 18 min, and the molecular mass of the eluted compound was confirmed by LC-MS. The platinum in the eluted fraction was determined by ICP-MS (Elan DRC II, Perkin Elmer, Germany) with nebulizer gas flow, 1.07 L/min; auxiliary gas flow, 1.10 L/min; plasma gas flow; 17.0 L/min; ion-lens voltage, 5.25 V; ICP RF power, 1,500 W; and scan mode, peak hopping. The recovery of oxaliplatin from plasma was higher than 90% (95.8±2.3%), and the within- and between-day coefficients of variation were less than 10%. BUN levels were determined with a BUN diagnostic kit. Platelet counts were determined by standard procedures.

Data Analysis

Data represent means±SD. The pharmacokinetic parameters of oxaliplatin after intravenous bolus administration were calculated by the following model-independent method. The values of the AUC (area under the curve) from time zero to the final sampling time were calculated by numerical integration of the plasma concentrations from time zero to the final sampling time, using the trapezoidal rule. The total clearance (CL_{tot}) and volume of distribution at steady state (Vdss) were estimated by the following equations:

$$\mathrm{CLtot} = \mathrm{Dose}/\mathrm{AUC}$$

$$\mathrm{Vdss} = \mathrm{Dose} \times \mathrm{AUMC}/\mathrm{AUC}^2$$

where AUMC is the area under the moment curve. For infusion study, CL_{tot} was also calculated as infusion rate divided by the mean plasma concentration of oxaliplatin at steady state. The Kp_{app} value was calculated as the ratio of the tissue concentration of oxaliplatin to the plasma concentration at steady state.

Platinum levels in the tissues were expressed as micrograms of platinum per gram wet weight of tissue (μg Pt/g tissue). $k_{hydrolysis}$ in phosphate buffer was calculated by log-linear least-squares regression (7,8).

Pharmacokinetic parameters among doses and the three drugs were compared by one-way analysis of variance at a significance level of $P<0.05$. The linear relationships between pharmacokinetic parameters and toxicity grade were analyzed by Pearson's correlation test. These statistical analyses were performed with the computer program SPSS (SPSS Inc., Chicago, IL). The relationships between pharmacokinetic parameters and maximum BUN level and platelet counts were analyzed with a sigmoid Emax model and linear model, respectively, using the computer program WinNonlin (Pharsight, Mountain View, CA, USA).

Derivation of Toxicity Factor

We have already reported the theoretical background for derivation of the toxicity factor (8). Briefly, the amount of complex formed in the tissue is expressed as formation clearance×AUC_t=kf×Vd_t×AUC_t, where AUC_t is AUC in the tissue, kf is the formation rate constant of the platinum–organelle complex, and Vd_t is the volume of distribution of

Table I Tissue Distributions and Apparent Hydrolysis Rate Constants of Oxaliplatin and Other Platinum Derivatives in Rats

	Oxaliplatin	Cisplatin[a]	Carboplatin[a]	Nedaplatin[a]
Dose range studied (mg/kg)	5–10	1–10	20–60	3–10
CL_{tot} (mL/min/kg)	44.6 ± 12.1	25.9 ± 3.66	15.2 ± 3.23	8.48 ± 3.34
Distribution into tissues				
Kp_{app} (kidney)	2.11 ± 0.50	3.12 ± 0.47	3.04 ± 0.18	3.89 ± 0.68
Kp_{app} (bone marrow)	0.94 ± 0.28	0.065 ± 0.014	0.49 ± 0.02	0.29 ± 0.15
Apparent hydrolysis rate constant				
$k_{hydrolysis}$ (min^{-1})	6.00×10^{-4}	3.60×10^{-3}	3.35×10^{-5}	1.89×10^{-4}
Toxicity factor (mL/g tissue/min)				
Kidney	1.27×10^{-3}	1.12×10^{-2}	1.02×10^{-4}	7.35×10^{-4}
Bone marrow	5.64×10^{-4}	2.34×10^{-4}	1.63×10^{-5}	5.52×10^{-5}

[a] These data are cited from a previous study by Hanada *et al.* (8).

CL_{tot} total clearance, Kp_{app} apparent ratio of tissue concentration of unchanged drug to plasma concentration under steady-state conditions, $k_{hydrolysis}$ apparent first-order rate constant of hydrolysis of unchanged platinum drug, Toxicity factor values are calculated as $Kp_{app} \times k_{hydrolysis}$

unchanged compounds in the tissue. AUC_t was calculated by the following equation, assuming that the concentration of platinum compounds rapidly reaches a state of equilibrium between the plasma and the intracellular fluid in the tissue: $AUC_t = Kp_{app} \times AUC_p = Kp_{app} \times dose/CL_{tot}$. kf can be replaced by $k_{hydrolysis}$, because the hydrolysis of these compounds is the rate-limiting step for complex formation with intracellular high-molecular-mass substances. As the compounds studied have similar physicochemical characteristics, their Vd_t values are assumed to be the same. The toxicity factor represented the product of AUC_t and $k_{hydrolysis}$.

RESULTS AND DISCUSSION

We examined pharmacokinetics and toxicodynamics of oxaliplatin and whether the toxicity factor we had previously established could be applied to oxaliplatin in rats.

Total clearance obtained from the intravenous bolus administration at the dose of 5, 8 and 10 mg/kg were 46.6 ± 12.9, 43.9 ± 9.6 and 43.6 ± 15.5 mL/min/kg, respectively. The respective volume of distribution at steady state was 490 ± 149, 374 ± 124 and 514 ± 179 mL/kg. These pharmacokinetic parameters were linear within the dose range studied. Total clearance of oxaliplatin was highest among the platinum drugs studied (Table I). The steady state was attained within 60 min after the start of infusion (data not shown). With regard to tissue distribution, Kp_{app} for the kidney was similar among the platinum drugs, whereas distribution of oxaliplatin into the bone marrow was much higher than for the other drugs (Table I).

The concentration of oxaliplatin in phosphate buffer showed a two-phase exponential decay (data not shown), as has been observed by Jerremalm *et al.* (10). They reported

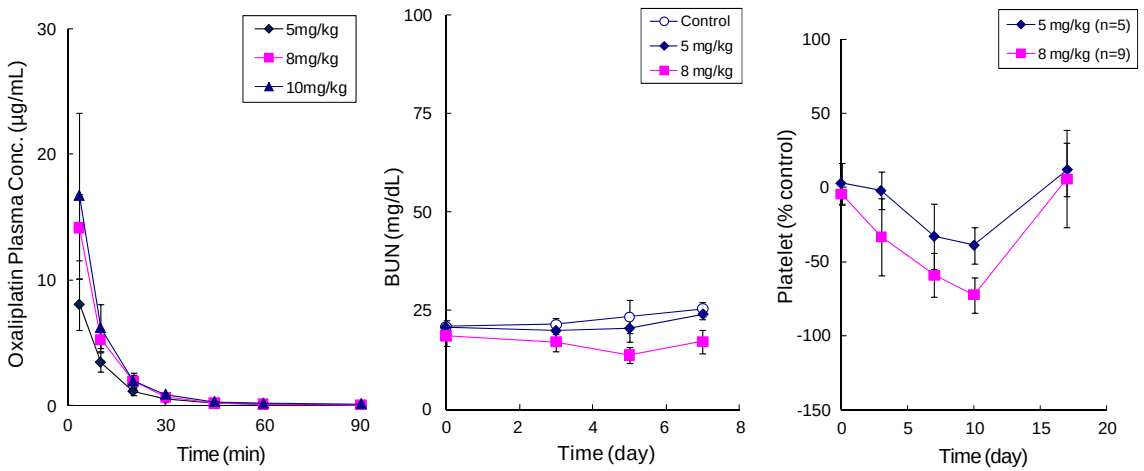

Fig. 2 Time courses of oxaliplatin concentration in plasma (**a**) and of blood urea nitrogen (**b**) and platelet count (% of control value) (**c**) after intravenous bolus administration of oxaliplatin in rats.

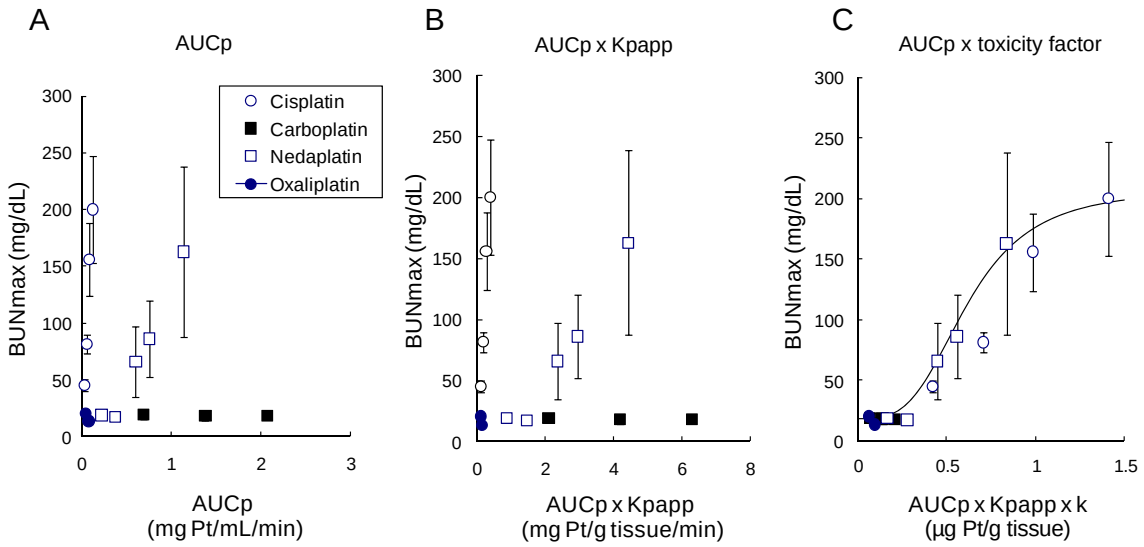

Fig. 3 Relationships between pharmacokinetic parameters, AUC_p (**a**), AUCt in the kidneys (**b**), AUC_p × toxicity factor (**c**), and maximum blood urea nitrogen (BUN_{max}). The simulation curve was obtained by using the following sigmoid Emax model equation: $BUN\ max = 18.18 + \frac{190.2\times\left(AUCp\times Kpapp\times k_{hydrolysis}\right)^{3.33}}{0.619^{3.33}+\left(AUCp\times Kpapp\times k_{hydrolysis}\right)^{3.33}}$ [○, cisplatin (*); ■, carboplatin (*); □, nedaplatin (*);●, oxaliplatin ($n = 5$ to 9)]. * These data are cited from a previous study by Hanada *et al*. (8).

that the fast initial degradation of oxaliplatin can be coupled to the fast formation of [Pt(dach)oxOH]– and the final product, the diaquo complex (Pt(dach)OH2). Oxaliplatin and [Pt(dach)oxOH]– rapidly reach an equilibrium state, especially in the presence of low chloride concentration, and the [Pt(dach)oxOH]– is slowly converted to (Pt (dach)OH2) (10,11). Therefore, we decided that the latter reaction was a rate-limiting step for oxaliplatin binding to biological substances. This rate constant value was comparable to that reported (10).

BUN was not significantly increased after oxaliplatin administration within the dose range studied, indicating that oxaliplatin does not cause obvious nephrotoxicity in rats within this dose range (Fig. 2). However, oxaliplatin caused dose-dependent depression of the platelet count, as has been observed with the other platinum drugs (8).

We previously defined a toxicity factor that was the product of the extent of drug distribution into the affected tissue and the reactivity of the distributed drug with intracellular organelles, and we showed that the differences

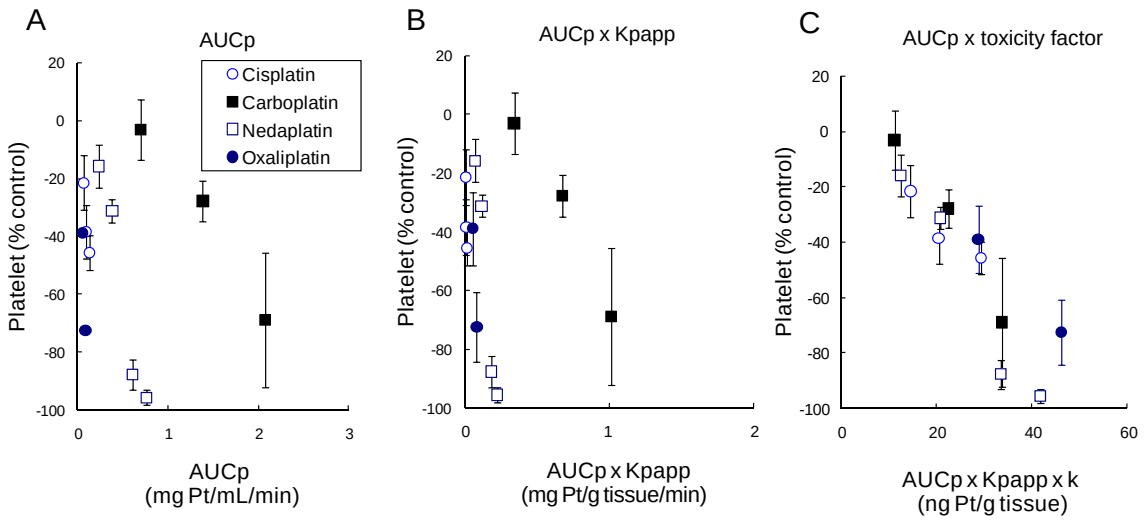

Fig. 4 Relationships between pharmacokinetic parameters, AUC_p (**a**), AUC_t in the bone marrow (**b**), AUC_p × toxicity factor (**c**), and maximum platelet depression (% of control values). [○, cisplatin (*); ■, carboplatin (*); □, nedaplatin (*);●, oxaliplatin ($n = 5$ to 9)]. * These data are cited from a previous study by Hanada *et al*. (8).

Table II Pharmacokinetic Parameters and Calculated the Products of AUC_p × Toxicity Factor in the Kidneys and Bone Marrow in Humans

	Cisplatin	Carboplatin	Nedaplatin	Oxaliplatin
Dose (mg/m^2)	90	400	100	85
CL_{tot} ($mL/min/m^2$)	592	105	94	535
AUC_p (mg/min/mL)	0.152	3.81	1.07	0.161
AUC_p × toxicity factor in the kidneys	1.70	0.39	0.79	0.20
AUC_p × toxicity factor in bone marrow	0.036	0.063	0.059	0.091

Total clearances of cisplatin, carboplatin, nedaplatin, and oxaliplatin are from the work of Hanada *et al*. (5), Reece *et al*. (12), Hirabayashi *et al*. (13), and Ehrsson *et al*. (14), respectively.

Toxicity factors in the kidneys and bone marrow were derived from the data in Table II, assuming that the tissue distributions into the kidney and bone marrow were the same in both the rat and human

in the degrees of nephrotoxicity and decrease in platelet count caused by the cisplatin, carboplatin and nedaplatin could be fitted by a combination of AUC_p and toxicity factor (8). Here, we therefore analyzed the relationships among pharmacokinetic exposure parameters and extent of toxicity (Figs. 3 and 4). Maximum BUN level was plotted against AUC_p (Fig. 3a), which was calculated from dose and total clearance, against AUC_t in the kidney (Fig. 3b), which was calculated from AUCp and Kp_{app}, and against AUC_p × toxicity factor (Fig. 3c). The differences in degree of nephrotoxicity caused by the platinum drugs studied were not explained by the differences in drug exposure in the plasma (AUC_p) or AUC in the kidney, but were fitted by a combination of AUCp and toxicity factor with a simulated curve derived from Emax model (Fig. 3c). Similar relationships were observed between myelosuppression and kinetic parameters, and the percentage platelet count was significantly correlated with AUC_p × toxicity factor ($r=0.908$, $P<0.001$) but not with AUC_p or AUC_t (Fig. 4). Although all of these parameters were required to explain the degree of toxicity, in particular, carboplatin was highly affected by the slow reactivity of carboplatin in the tissues, and other platinum drugs were highly affected by the tissue distribution (Figs. 3 and 4). These results indicate that the toxicity factor, $Kp_{app} \times k_{hydrolysis}$, is a useful kinetic parameter for predicting the toxicities of new platinum antitumor compounds, provided that the rate-limiting step of platinum binding to intracellular organelles is the hydrolysis rate. Confirmation of the rate-limiting step for formation of platinum complexes in tissues is a critical issue for validating the use of this toxicity factor with other platinum antitumor drugs.

Finally, we tried to expand this concept to the prediction of human data. We calculated the products of AUC_p × toxicity factor in the kidneys and bone marrow in humans by using reported doses and total clearances of unchanged platinum drugs (5,12–14), assuming that the extent of tissue distribution was the same in rats and humans (Table II). AUC_p × toxicity factor for the kidneys for cisplatin was much higher than for the other drugs, and that for nedaplatin was the second highest. On the other hand, AUC_p × toxicity factor for the bone marrow values were comparable among the platinum drugs, with the exception of cisplatin, which had a low value. The toxicity orders of these drugs corresponded roughly to clinical data.

The dose-limiting toxicity of oxaliplatin is peripheral neuropathy; therefore, the differences of this toxicity also should be studied in future.

CONCLUSION

The pharmacokinetics of unchanged oxaliplatin were linear within the dose range studied. The degree of decrease in platelet count caused by oxaliplatin was not explained by the differences of AUC_p and AUC for the bone marrow but was fitted by a combination of AUC_p and the toxicity factor. This toxicity factor may be a useful parameter for predicting the degree of toxicity of platinum antitumor compounds.

REFERENCES

1. Nagai N, Ogata H. Quantitative relationship between pharmacokinetics of unchanged cisplatin and nephrotoxicity in rats—importance of area under the concentration-time curve (AUC) as the major toxicodynamic determination in vivo. Cancer Chemother Pharmacol. 1997;40:11–8.
2. Hanada K, Odaka K, Kudo A, Ogata H. Effects of disopyramide and verapamil on renal disposition and nephrotoxicity of cisplatin in rats. Pharm Res. 1999;16:1589–95.
3. Hanada K, Ninomiya K, Ogata H. Pharmacokinetics and toxicodynamics of cisplatin and its metabolites in rats: relationship between renal handling and nephrotoxicity of cisplatin. J Pharm Pharmacol. 2000;52:1345–53.
4. Hanada K, Mukasa Y, Nomizo Y, Ogata H. Effect of buthioninesulfoximine, glutathione and methimazole on the renal disposition of cisplatin and on cisplatin-induced nephrotoxicity in

rats: pharmacokinetic-toxicodynamic analysis. J Pharm Pharmacol. 2000;52:1483–90.
5. Hanada K, Nishijima K, Ogata H, Atagi S, Kawahara M. Population pharmacokinetic analysis of cisplatin and its metabolites in cancer patients: possible misinterpretation of covariates for pharmacokinetic parameters calculated from the concentrations of unchanged cisplatin, ultrafiltered platinum and total platinum. Jpn J Clin Oncol. 2001;31:179–84.
6. Dedon PC, Borch RF. Characterization of the reactions of platinum antitumor agents with biologic and nonbiologic sulfur-containing nucleophiles. Biochem Pharmacol. 1987;36:1955–64.
7. Nagai N, Okuda R, Kinoshita M, Ogata H. Decomposition kinetics of cisplatin in human biological fluids. J Pharm Pharmacol. 1996;48:918–24.
8. Hanada K, Asano K, Nishimura T, Chimata T, Matsuo Y, Tsuchiya M, *et al.* Use of a toxicity factor to explain differences in nephrotoxicity and myelosuppression among the platinum antitumour derivatives cisplatin, carboplatin and nedaplatin in rats. J Pharm Pharmacol. 2008;60:317–22.
9. Luo FR, Yen TY, Wyrick SD, Chaney SG. High-performance liquid chromatographic separation of the biotransformation products of oxaliplatin. J Chromatogr B Biomed Sci Appl. 1999;724:345–56.
10. Jerremalm E, Hedeland M, Wallin I, Bondesson U, Ehrsson H. Oxaliplatin degradation in the presence of chloride: identification and cytotoxicity of the monochloro monooxalato complex. Pharm Res. 2004;21:891–4.
11. Jerremalm E, Wallin I, Ehrsson H. New insights into the biotransformation and pharmacokinetics of oxaliplatin. J Pharm Sci. 2009;98:3879–85.
12. Reece PA, Bishop JF, Olver IN, Stafford I, Hillcoat BL, Morstyn G. Pharmacokinetics of unchanged carboplatin (CBDCA) in patients with small cell lung carcinoma. Cancer Chemother Pharmacol. 1987;19:326–30.
13. Hirabayashi K, Okada E, Oguma T, Shimamura K. Pharmacokinetics of cis-diammine (glycolato) platinum (254-S), a new platinum antitumor agent, following an intravenous and intraperitoneal infusion bioactive platinum concentration profile. Gan To Kagaku Ryoho. 1990;17:2221–7. in Japanese.
14. Ehrsson H, Wallin I, Yachnin J. Pharmacokinetics of oxaliplatin in humans. Med Oncol. 2002;19:261–5.