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Pharmacokinetic evaluation of zeniplatin in humans

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Abstract Zeniplatin, a more water-soluble organoplatinum than cisplatin, was evaluated for clinical pharmacology in the context of a phase II trial in previously treated patients with ovarian carcinoma. A total of 12 patients were given zeniplatin at 120 mg/m^2 by rapid intravenous infusion over 90 min, with both blood and urine being sampled. All platinum moieties were analyzed in whole blood, plasma, plasma ultrafiltrate, and urine by atomic absorption, and free zeniplatin was analyzed in plasma ultrafiltrate by specific high-performance liquid chromatography (HPLC). In a comparison of the platinum-time concentration curve, AUC (area under the curve) values indicated that approximately 90% of platinum moieties were bound to circulating plasma proteins. There was no evidence of drug accumulation after repetitive dosing. The terminal half-life ($t_{1/2}$) of this drug in plasma ultrafiltrate (3.7–7.2 h.) as measured by HPLC was slightly longer than that of carboplatin, whereas total platinum moieties in plasma displayed a long $t_{1/2}$ (124–154 h). Approximately 60% of platinum moieties could be recovered in the urine within 24 h. These findings suggest that zeniplatin has a pharmacokinetic profile similar to that of carboplatin.

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Introduction

Zeniplatin, a third-generation water-soluble platinum analogue, was selected for clinical trials because of an apparent difference during preclinical studies in its spectrum of activity as compared with cisplatin and carboplatin. Zeniplatin has demonstrated greater antitumor effect in vitro against B-16 melanoma and M5076 reticulum-cell sarcoma, equivalent activity against colon 26 adenocarcinoma, and lower activity against P388 and L1210 leukemias as compared with cisplatin or carboplatin. Xenografts of human breast, ovary, lung, colon, and pancreatic cancers in athymic mice showed zeniplatin to have significantly greater activity against COOG breast tumors and comparable activity against H207 ovarian tumors as compared with cisplatin and carboplatin [1].

Preclinical pharmacokinetic studies of zeniplatin in rodents and dogs have demonstrated that the drug circulates in the plasma in both free and protein-bound forms. Bioanalytical analysis performed by atomic absorption (AA) spectroscopy and high-performance liquid chromotography (HPLC) showed that the pharmacokinetic profiles of all measured drug-related moieties were qualitatively similar across species [1]. Additionally, the free unbound zeniplatin as well as free platinum had high systemic clearances, shorter half-lives, and smaller volumes of distribution than did total platinum [2]. These differences have previously been reported for both cisplatin and carboplatin and have been attributed in part to time-dependent binding of the aquated complex to plasma proteins [3].

Tissue-distribution studies in rats revealed a rapid and extensive distribution of total platinum into tissues following a single intravenous dose of zeniplatin. Kidney, spleen, and blood showed a prolonged elimination

half-life for total platinum. Preclinical results showed excretion of zeniplatin to occur primarily in the urine (86% of the dose), with very little being observed in the feces ($< 2\%$ of the dose). These preclinical findings suggested that the pharmacokinetics of zeniplatin were similar to that of carboplatin[1,3].

Toxicology studies in rats and dogs and, subsequently, in human phase I studies at one center [2] indicated that myelosuppression, particularly leukopenia, was the dose-limiting toxicity. As this toxicity commonly occurs in antineoplastic treatments and is managed much more easily than other organ-system toxicities, this platinum analogue was deemed attractive for further clinical studies [4]. In addition, tumor regression was also seen in two tumor types (melanoma and renal-cell cancer) in the phase I study [2]. Thus, zeniplatin was brought to phase II trial in the United States, Europe, and Australia.

The results of the phase I trial of this agent involved a single institution's clinical pharmacologic experience in patients with diverse malignancies. In this study, patients had also received a variety of chemotherapeutic agents. For the above-mentioned reasons, the clinical pharmacology of this agent was restudied in a relatively homogeneous population of patients entered into a phase II trial who had previously received very similar chemotherapy, had excellent organ function, and were of the same sex. Patients with advanced ovarian cancer previously treated with organoplatinum compounds were entered into this study of the clinical efficacy of zeniplatin at North Shore University Hospital and at Memorial Sloan-Kettering Cancer Center (New York). A total of 31 patients entered the trial, and 27 were evaluated for efficacy. Toxicities and responses have previously been reported [4]. In all, 12 patients treated at North Shore University Hospital were also evaluated for pharmacokinetic parameters and serve as the basis of this report.

Materials and methods

Chemical formulation and preparation

Zeniplatin (CL 286,558) ([2, 2-bis(aminomethyl)-1, 3-propanediol-N,N^1] [1,1-cyclobutanedicarboxylato]-[(2-)-*0-0*^{1}]) platinum has a molecular weight of 471.38 KDa and the empirical formula of $C_{11}H_{20}N_2O_6$ platinum. The drug was supplied by the American Cyanamid Company as a lyophilized powder in 25- or 50-mg vials. For administration, the agent was reconstituted with sterile water to a concentration of 2.5 mg/ml, filtered, and transferred to a covered infusion bag containing 5% dextrose, as the mixed solution is light-sensitive. The maximal concentration of infused drug was 0.4 mg/ml.

Entry requirements

Women 18 years of age and older with signed, informed consent as per institutional guidelines, having histologically confirmed, measurable refractory or recurrent epithelial ovarian cancer were entered into this trial. Eligibility criteria included the absence of chemotherapy, radiation therapy, or surgery within the prior 4 weeks; a Cancer and Leukemia Group B (CALGB) performance status of 0–2; a life expectancy of > 3 months, and no prior malignancy other than in situ cervical or basal-cell carcinoma. Entry laboratory values included a white count of $\geq 4{,}000/mm^3$, a platelet count of $\geq 100{,}000/mm^3$, a hemoglobin (Hb) value of ≥ 9.5 g/dl, a serum creatinine level of ≤ 2.0 mg/dl, creatinine clearance of ≥ 60 ml/min, a total bilirubin value of ≤ 2.0 mg/dl, and serum transaminase levels of ≤ 2 times the upper limits of normal. Exclusion criteria were the presence of uncontrolled infection, concurrent medical conditions that could preclude aggressive intravenous hydration, the presence of brain metastasis, or a history of allergic reaction to platinum analogues or mannitol.

Treatment program

As previously reported [4], patients received 120 mg/m^2 of zeniplatin given as a continuous intravenous infusion by means of a calibrated pump over 90 min every 21 days. Initially, pretreatment hydration and first-cycle intensive antiemetic therapy were not required, but the protocol was subsequently modified to include at least 1.5 l of prehydration fluid and standard antiemetics because of the appearance of emesis and unexpected nephrotoxicity as reported in ongoing phase II trials in Europe. Patients participating in the pharmacokinetics studies were prohibited from receiving antiemetic treatment with metoclopramide, as this agent may perturb renal function [5]. Pharmacokinetic data were obtained for cycles 1 and 2 of all patients. Several patients had blood drawn beyond cycle 2 for evaluation of the drug's pharmacokinetics after multiple cycles.

Sample collection

Whole blood (10 ml) obtained from the arm contralateral to the site of infusion was collected into heparinized tubes at 0 (preinfusion), 0.75 (during the infusion), and 1.5 h (at the end of the infusion), with additional samples being obtained at 2.5, 3.5, 4.5, 5.5, 9.5, 13.5, 25.5, 27.5, 49.5, 169.5, and 337.5 h after the start of treatment. Duplicate aliquots of 0.15 ml of blood were pipetted into separate polypropylene tubes, temporarily stored on dry ice and frozen at -70°C. The remaining blood sample was immediately centrifuged (4°C at 1800 *g* for 10 min), and the plasma was separated and frozen at -70°C. Urine samples were collected on ice at time 0 (preinfusion) and at intervals of 0–2, 4–8, 8–12 and 12–24 h postinfusion, and were stored at -70°C. Plasma ultrafiltrate was obtained at the analytical site from previously frozen plasma. Patients underwent pharmacokinetic analysis of platinum in their whole blood, plasma, plasma ultrafiltrate (PUF), and urine during at least two cycles of chemotherapy. Total platinum concentrations were determined in whole blood for only the first five patients and in urine for only the last seven patients. Methodologic problems with whole-blood samples precluded the analysis of patients 6–12. These patients samples were analyzed at an analytical site different from that used for the first five patients.

Analytical methods

The methodology has previously been reported in detail in the phase I study [2]. Modifications of this technique were employed as described below. Plasma ultrafiltrate was obtained by separation of plasma through an Amicon Centrifree Micropartition System (part 4104), centrifuged at 1,500 *g* for 20 min, and stored frozen prior to assay.

Atomic absorption spectroscopy

For subjects 1–5, total platinum concentrations in plasma, and whole blood as well as free (unbound) concentrations in PUF were determined by flameless AA spectrometry using a Perkin Elmer 2280 atomic absorption spectrometer fitted with an HGA 500 or 600 furnace controller. Samples were diluted as necessary for adjustment to the linear range of the assay. The sensitivity of the assay was 0.025 μg of platinum/ml (range, up to 1.0 μg of platinum/ml). PUF was injected directly, whereas plasma or whole blood was pretreated with Triton X-100. The injection volume was 20 μl . A quadratic equation using the peak height of platinum absorbance versus platinum concentration was used to determine the amount of total platinum in plasma, blood, and PUF (unbound). The interday coefficients of variation (CVs) for quality-control samples (prepared at different concentrations) for subjects 1–5 were $< 18\%$ in plasma, PUF, and blood, with relative errors (REs) being within $\pm 6\%$ ($n \geq 10$). Plasma, PUF, and urine from patients 6–12 (analyzed at a second analytic site) were analyzed by means of a Varian Zeeman Spectra-A 400 atomic absorption spectrometer. The biologic material was pretreated with Triton X-100 and an antifoaming solution prior to injection of 20 μl for AA analysis. Platinum concentrations were determined from two-tier (high- and low-range) calibration curves spanning the range of 0.050–10 μg platinum/ml using a natural log polynominal regression equation. For subjects 6–12, the interday CVs were $< 13\%$ in plasma, PUF, and urine, with REs being within $\pm 12\%$ ($n \geq 8$).

High-performance liquid chromatography

A sensitive and specific reverse-phase HPLC method with UV detection at 230 nm was developed for the determination of unchanged zeniplatin in PUF [6]. For subjects 1–5, the drug was analyzed by means of an HPLC system containing a Spectroflow 783 detector (Applied Biosystems, Ramsey, N.J.) using a Hypersil C_{18} (250- × 4.6-mm) analytical column (Keystone Scientific Co., Bella Fonte, Pa.), with the eluant being monitored by UV detection at 230 nm. Enloplatin, another organoplatinum compound, was used as an internal standard. The mobile phase was prepared with 0.01 *M* monobasic ammonium phosphate:acetonitrile:methanol (93:5:2, by vol.), which was pumped at a flow rate of 0.75 ml/min. Zeniplatin concentrations were determined by calibration curves using weighted (natural log) linear least-squares regression analysis of drug concentration versus the ratio of drug peak height to internal standard peak height. Additional patients on this study were analyzed at a different site using a different technique.

For patients 6–12, a column-switching technique was employed. A 50-μl aliquot of sample was injected through a CSC ODS-1 precolumn (150x4.6 mm). A portion of the eluant containing zeniplatin was diverted onto a Hypersil C_{18} analytical column, with the resulting eluant being monitored by UV detection at 230 nm. The retention time of zeniplatin was approximately 6.8 min at a flow rate of 1.2 ml/min. The mobile phase contained 0.01 *M* monobasic ammonium phosphate:methanol:2-propanol (98.5:1.0:0.5 by vol.). Zeniplatin concentrations were determined from standard curves using drug peak height with no internal standard. The assay's linear concentration range was 0.05–2.0 μg/ml for subjects 1–5 and 0.2–50.0 μg/ml for subjects 6–12. The interday CVs were $< 15\%$ for subjects 1–5, with REs being within $\pm 12\%$ ($n \geq 8$). For subjects 6–12, the interday CVs were $< 7\%$, with REs being within $\pm 9\%$ ($n \geq 4$).

Pharmacokinetic analysis

Noncompartmental pharmacokinetic parameters were estimated for the 12 subjects using previously described methods [6, 7]. A two-compartment open model could also describe the data. Drug disposition was evaluated in whole blood, plasma, and PUF. The area under the concentration versus time curve (AUC) extrapolated to infinity (AUC_{0-inf}), was calculated by trapezoidal summations with extrapolation from zero to infinity. The terminal log-linear phase of the concentration-time curve was identified by least-squares linear regression analysis of at least three data points, which yielded a minimal mean square error. The terminal elimination rate constant, K, was the slope of the final log-linear phase. The terminal elimination half-life, $t_{1/2}$, was determined by the relationship $t_{1/2} = 0.693/K$. The maximal plasma concentration, C_{max}, the time to maximal concentration, T_{max}, and the percentage of dose excreted in the urine, Ae%, were observed values from the tabulated data. Total systemic clearance, CL_T, was determined by $CL_T = Dose/AUC_{0-inf}$. The steady-state volume of distribution, V_{ss}, was derived from $V_{ss} = CL_T \times MRT$, where $MRT = MRT_{iv} + T/2$, MRT being the mean residence time; MRT_{iv}, the mean residence time of the short infusion, and T, the infusion time [7].

Results

A total of 12 patients from North Shore University Hospital underwent pharmacokinetic evaluation. The median age of the patients was 57 years (range, 37–75 years). Five patients were classified as having primary refractory disease (non-platinum-sensitive) and seven patients, as having recurrent disease. All patients had been heavily pretreated with either carboplatin- or cisplatin-based regimens, having received a median of 2 (range, 1–4) prior treatment courses. Table 1 shows pertinent laboratory data obtained prior to each cycle of the pharmacokinetics study. Of note was that all patients had an uncorrected creatinine clearance of > 60 ml/min as required by the protocol for entry. Overall, the median number of cycles completed in this group of patients before documentation of disease progression was 4 (range, 2–10 cycles).

Only 5 of the 12 patients had their whole blood analyzed for total platinum because of technical bioanalytical difficulties. Table 2 lists the pharmacokinetic parameters for whole-blood sampling in these 5 patients. C_{MAX} occurred at the end of the infusion of zeniplatin. Within the bounds of the limited number of patients evaluated, peak concentrations of platinum moeities showed substantial variation as shown in

Table 1 Pretreatment laboratory parameters

	Median	Range
24-h Creatinine clearance	72.5 ml/min	61–88 ml/min
Pretreatment serum creatinine:		
Cycle 1	1.15 mg/dL	0.7–1.5 ml/dl
Cycle 2	1.10 mg/dL	0.8–1.5 mg/dl
Pretreatment Hb:		
Cycle 1	10.5 mg/dL	9.1–12.2 mg/dl[a]
Cycle 2	10.2 mg/dL	8.8–11.6 mg/dl[a]

[a] One patient in cycle 1 and two patients in cycle 2 received at least 1 unit PRBC transfusion each prior to zeniplatin administration; no repeat Hb value was obtained immediately posttransfusion

Table 2 (range, 6.2–15.9 μg/ml) in the first cycle and in the second treatment cycle (range, 6.4–19.4 μg/ml).The terminal half-life, $t_{1/2}$, and clearance, CL_T, remained constant through both cycles of treatment (Table 2).

Table 3 shows the pharmacokinetic parameters for total platinum found in plasma and blood as measured by the AA method. As mentioned above, the use of AA measures all platinum moeities (parent drug, degradation products, and/or metabolites) and, therefore, the pharmacokinetic parameters derived from these data may not reflect the disposition of the parent drug. For these reasons, unbound, unchanged zeniplatin in PUF was measured by HPLC methods. The apparent mean half-life $t_{1/2}$ of total platinum in plasma as measured by AA in both cycles of zeniplatin treatment was 124–154 h (the range in all patients, both cycles, was 32–376 h), whereas the $t_{1/2}$ of unbound, unchanged zeniplatin in PUF was much shorter at 3.8–7.2 h (range, 1.2–34 h in all patients, both cycles; Table 4).

Table 2 Mean pharmacokinetic results obtained for total platinum[a] in human whole blood by AA spectroscopy

	C_{MAX}(μg/ml)	T_{MAX}(h)	AUC_{0-inf} (μg h/ml^{-1})	$t_{1/2}$(h)	CL_T(ml/h)
Cycle 1:					
Mean	9.06	1.35	152.6	51.9	24.3
SE	1.83	0.15	26	12.5	4.86
Cycle 2:					
Mean	11.38	1.5	125.2	39.6	32.2
SE	2.99	0	29.9	11.2	7

[a] Representing all platinum moieties

Table 3 Pharmacokinetic findings in plasma and PUF for total platinum[a] as determined by AA analysis

	C_{MAX}(μg/ml)	T_{MAX}(h)	AUC_{0-inf} (μg h/ml^{-1})	$t_{1/2}$(h)	CL_T (ml/min)
Plasma:					
Cycle 1:					
Mean	12.25	1.3	258.88	153.8	15.4
SE	2.15	0.3	32.17	40	1.8
Cycle 2:					
Mean	10.21	1.5	232.92	123.6	19
SE	0.82	0	37.8	28.5	3.3
PUF:					
Cycle 1:					
Mean	7.25	1.4	27.32	17	142.1
SE	1.18	0.1	2.89	4.5	17.5
Cycle 2:					
Mean	6.45	1.4	25.9	14.8	178.4
SE	0.9	0.1	4.2	4.3	31.1

[a] Representing all platinum moieties

Table 4 Pharmacokinetics of zeniplatin in PUF determined by HPLC

	C_{MAX} (μg/ml)	T_{MAX}(h)	AUC_{0-inf} (μg h/ml^{-1})	$t_{1/2}$(h)	CL_T (ml/min)
Cycle 1:					
Mean	6.49	1.5	20.24	3.8	204.2
SE	1.27	0.1	2.33	1.67	43.2
Cycle 2:					
Mean	5.26	1.5	20.76	7.21	207
SE	0.46	0	3.76	3.2	37.1

[a] Representing all platinum moieties

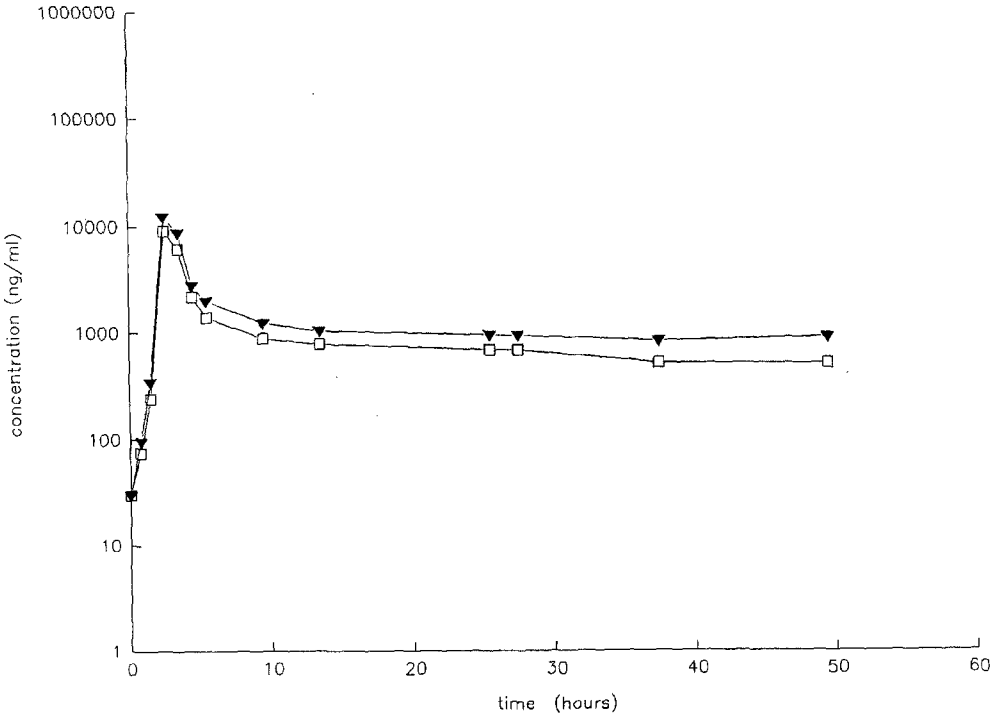

Fig. 1. Determination of circulating platinum moieties in (▼) plasma (atomic absorption) and (□) blood (atomic absorption) over time as measured by AA spectroscopy

The mean AUC_{0-inf} for total platinum in the blood was about 60% of that seen in plasma (Tables 2, 3), suggesting that platinum does not distribute extensively in red blood cells (RBC), even after accounting for the minor hemoglobin differences from patient to patient and cycle to cycle. The AUC_{0-inf} determined in PUF by AA was only about 10% of that seen in plasma, suggesting that 90% of the circulating platinum is bound to circulating plasma proteins. In the PUF, approximately 75% of the circulating total platinum could be accounted for by unchanged drug (Tables 3, 4). A representative plot of platinum concentration (measured by AA) or unchanged zeniplatin (measured by HPLC) versus time for cycle 1 in an individual patient is shown in Figs. 1 and 2.

During and immediately following the intravenous infusion of zeniplatin, the fraction of unbound, unchanged drug as measured by HPLC in PUF was about 60–80% of the total platinum, and it decreased to $< 25\%$ at 25 h posttreatment, thereby suggesting that there is a time/concentration-dependent binding. Comparison of AUCs between cycles 1 and 2 suggests no drug accumulation. There appeared to be no correlation between the AUC_{0-inf} for total and PUF platinum with renal function within the small range of creatinine clearance studied (61–88 ml/min.). All 12 patients had urine samples submitted, and 7 underwent analysis of total platinum via AA spectroscopy. The mean Ae% (percentage of the dose excreted in 24 h) was found to be 57.6% (SE, 7.11%) after the cycle-1 infusion and 58.2% (SE, 4.97%) after the cycle-2 infusion.

Discussion

Zeniplatin, a third-generation platinum compound with water solubility greater than that of cisplatin, was studied in this relatively homogeneous group of 12 patients with ovarian cancer to confirm and amplify the pharmacologic parameters seen in the previous phase I trial of 5 patients subjected to limited sampling [2]. In the previous study the drug was infused over 60–90 min. In the original phase I study, ten sampling points per patient were obtained, with only four patients being evaluated at the suggested phase II dose and schedule [2]. In contrast, the present study evaluated 12 patients for 2 cycles of treatment with 14 sampling time points in each cycle. All patients received the drug via a calibrated pump over 90 min. In this trial, the disposition of platinum was evaluated in whole blood, plasma, PUF, and urine by AA spectroscopy and that of unchanged drug in PUF, by HPLC.

When the drug was given as a 90-min infusion at the 120-mg/m^2 dose, the $t_{1/2}$ of unchanged, unbound zeniplatin was shorter (3.7–7.2 h) than that of total plasma platinum (124–154 h). The $t_{1/2}$ of total platinum in PUF was 14–17 h and is probably an underestimate due to limitations of analytical sensitivity and low levels of total platinum in PUF. These values recorded for the parent drug are similar but slightly lower than the result (9.8 h) of the previous study [2]. The outcome is consistent with unbound drug removal and is similar to results obtained for carboplatin, with an

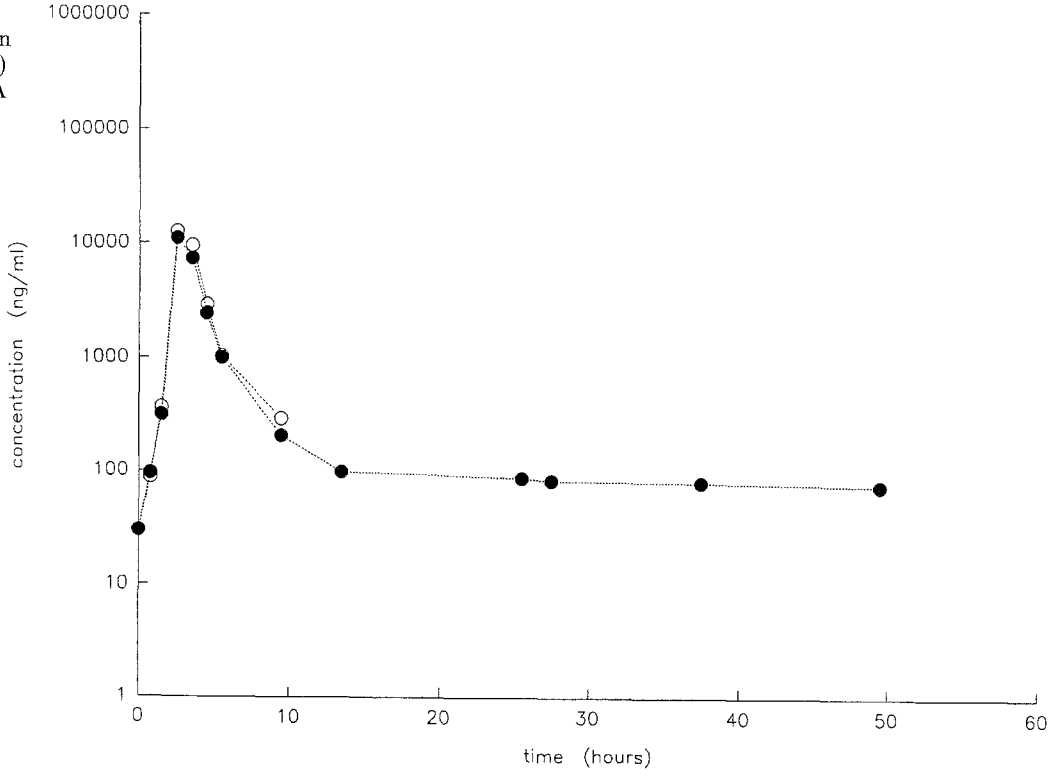

Fig. 2. Determination of unbound platinum moieties in (○) PUF (atomic absorption) over time as measured by AA spectroscopy and (●) HPLC

unbound-drug $t_{1/2}$ of 1.75 h when given as a 60-min 100-mg/m^2 intravenous infusion [9]. As zeniplatin is water-soluble, it is not unexpected to find the majority (58%) of platinum moieties identified by AA in the urine by 24 h in both the first and the second cycle of therapy. Again, this result is similar to those reported for carboplatin[8–11]. However, unlike carboplatin, zeniplatin was found to produce nephrotoxicity in the phase II trials [4].

The AUC_{0-inf} found for platinum in plasma as compared with PUF by AA analysis suggests that only 10% of the circulating platinum is not bound to plasma proteins. This result was also noted in the phase I study, with the magnitude of binding of platinum to plasma proteins being time-dependent [2]. The time-dependent binding of platinum moieties to plasma was also noted in this study. This result, however, is a composite of total platinum compounds as measured by AA spectroscopy and therefore does not reflect the binding of individual moeities (unchanged zeniplatin, degradation products, or metabolites). The amount of free drug in PUF was therefore determined by HPLC methods. About 75% of the circulating levels of platinum in PUF represents unchanged zeniplatin.

The rapid disposition and short PUF half-life of the parent drug and the high-affinity protein binding of this third-generation organoplatinum compound can thus be confirmed, with the predominant mode of excretion being renal. Cumulative dosing was not found to change the pharmacokinetic parameters in this study.

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