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Influence of infusion time on unchanged cisplatin disposition in patients with ovarian cancer*

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Summary. The disposition of unchanged cisplatin in ten patients with ovarian cancer receiving 2-h infusions of 100 mg/m^2 was compared with that of ten patients receiving 6-h infusions. A high-performance liquid chromatographic assay specific for the unchanged drug was used and all collected samples were rapidly processed. Patients were catheterized for urine collections. Cisplatin renal clearance was significantly lower after 6-hour infusions (52.8 ± 16.2 ml/min per m^2) than after 2-h infusions (87.1 ± 38.2 ml/min per m^2) ($P = 0.026$). Total clearance was also lower and less variable, although not significantly, in patients receiving the longer infusion. No differences in nonrenal clearance, volume of distribution, or half-life were observed between the two groups. There was only a poor relationship between cisplatin renal clearance and creatinine clearance after 2-h ($r^2 = 0.02$; $P = 0.66$) and 6-h infusions ($r^2 = 0.18$; $P = 0.23$). A single cisplatin plasma level obtained at the end of the infusion proved to be a good predictor of total cisplatin clearance after both 2-h ($r^2 = 0.70$; $P = 0.0096$) and 6-h infusions ($r^2 = 0.97$; $P = 0.0001$). This level was not significantly related to the relatively small changes in creatinine clearance that occurred after three courses of treatment.

Introduction

Cisplatin [*cis*-diamminedichloroplatinum(II)] is active in the treatment of ovarian, head and neck, bladder, lung, cervical, and germ cell cancers. The drug is normally administered i.v., with infusion times ranging from a few minutes to several days. Several studies have suggested that longer infusions or divided doses of cisplatin are associated with reduced toxicity [2, 3, 7, 8, 11, 12, 18, 20]. Reduced renal toxicity has been reported with 24-h infusions [2], and significantly fewer emesis episodes were reported when the drug was given over 8 h rather than 1 h [7]. Ototoxicity also appeared less frequently with longer infusions [20]. Continuous infusions over 5 days [4, 11, 12, 18] may allow the administration of higher cumulative doses of cisplatin.

Posner et al. [11] recently reported that the continuous infusion of 25 mg/m^2 cisplatin/day over 5 days resulted in responses in patients failing bolus cisplatin at high doses. The same group [1] reported the results of a preliminary study in five patients demonstrating that the area under the plasma level-time curve (AUC) of ultrafilterable platinum was approximately 2 times higher and urinary excretion of platinum, considerably lower with a 5-day infusion than with a 30-min infusion. A possible explanation for this difference was not discussed. We have previously reported [14] that the renal clearance of ultrafilterable platinum is concentration-dependent, with saturation of renal tubular reabsorption occurring in patients at high plasma concentrations soon after completion of the infusion. This mechanism of renal clearance may account for the difference in platinum excretion and AUCs previously reported by Belliveau et al. [1]. Longer infusion would result in lower levels of plasma ultrafiltrate and urinary platinum and avoid saturation of renal tubular reabsorption; hence, renal clearance would be expected to be lower and the plasma AUC of ultrafilterable platinum, higher with longer infusion.

The aim of the present study was to compare the disposition of cisplatin in patients with ovarian cancer receiving the drug by either 2-h or 6-h i.v. infusion. An analytical methodology specific for the unchanged drug was used for the determination of plasma ultrafiltrate and urinary levels [9, 16] to avoid potential interference by plasma and urinary metabolites of cisplatin. All specimens were rapidly collected and processed to avoid irreversible loss of drug from the biological fluids.

Materials and methods

Patients and drug administration. A total of 20 female patients with ovarian cancer were studied during their first course of treatment with cisplatin and were randomized to receive either a 2-h or 6-hour infusion of the drug. Ten patients received 100 mg/m^2 infused over 2 h into an arm vein and ten received the same dose over 6 h. Five patients receiving 2-h infusions and five receiving 6-h infusions were also studied during their third course of cisplatin treatment. All patients gave informed consent before proceeding with the study. The drug was given in 1 l 1.0 *N* saline and infused at a constant rate using an infusion pump. Patients did not receive other anti-cancer drugs at the time of the cisplatin studies and all received uniform

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hydration and anti-emetic therapy (40 mg maxalon every 2 h). Pre-infusion hydration consisted of 1 l 1.0 *N* saline containing 2 g KCl and 20 mmol $MgSO_4$ given over 1 h. The infusion was commenced if urinary output exceeded 100 ml/h. The standard post-infusion hydration schedule used at our institution was applied consisting of 500 ml 10% mannitol over 1 h followed by 1 l 4% dextrose–0.2 *N* saline and a further 1 l 4% dextrose–0.2 *N* saline over 12 h.

Specimen collection. Blood was collected during and after infusion and plasma ultrafiltrate was immediately prepared and stored at −70° C as previously described [16]. Urine was collected via a catheter every 30 min during and after infusion, the volume was noted, and a sample was rapidly frozen and stored at −70° C. The infusion solution was assayed for cisplatin to ensure the accuracy and stability of the dose. Creatinine clearance was determined using the same urine and plasma samples collected for cisplatin determinations during each course of treatment.

Assay methods. Cisplatin was quantitated by a specific high-performance liquid chromatographic method involving on-line, post-column derivatization, which has been described elsewhere [9, 16]. Seven standards over the concentration range of 0–2,500 ng/ml were used for plasma ultrafiltrate standard curves, and six standards over the concentration range of 0–100 μg/ml were used for urine standard curves. The mean slope of the plasma ultrafiltrate standard curve was 0.1786 ± 0.0021 (n = 7; 1.16% CV) and that of the urine standard curve was 7.364 ± 0.268 (n = 7; 3.64% CV). Intra-assay variability (n = 4) was 3.9% and 10.3% at plasma ultrafiltrate concentrations of 100 and 25 ng/ml, respectively, and 1.4% and 4.6% at urinary concentrations of 5 and 0.2 μg/ml, respectively. The detection limit of this assay was approximately 15 ng/ml cisplatin in plasma ultrafiltrate. The lowest concentration of cisplatin quantitated in a patient sample was 21 ng/ml.

Pharmacokinetic analyses. Both model (M) and model-independent or noncompartmental (MI) methods of analysis were used. Concentrations of cisplatin in plasma ultrafiltrate during and after infusion were simultaneously fitted to a one-compartment model as previously described [16]. Clearance [CL(M)], volume of distribution [V_{ss}(M)], and elimination half-life [$t_{½}$(M)] were estimated from the coefficients of the equation describing the model in each patient. CL(MI) was estimated from the AUC determined by the trapezoidal method. Renal clearance terms for cisplatin [CL_R(M), CL_R(MI)] were determined from the product of each total clearance term by the fraction of the cisplatin dose excreted unchanged in the urine. Nonrenal clearance of cisplatin [Cl_{NR}(M), CL_{NR}(MI)] was the difference between the corresponding total clearance and renal clearance terms. The ratio of renal clearance to creatinine clearance [CL_R(MI)/CL_{CR}] was determined for each patient. The elimination half-life of cisplatin [$t_{½}$(MI)] was determined by nonlinear regression analysis of post-infusion plasma level-time data and urinary excretion rate-time data ($t_{½}$u). The cumulative urinary excretion of cisplatin was plotted against the cumulative AUC determined for each urinary excretion interval from the coefficients of the model equation.

Statistical analysis. Comparisons between the two groups of patients receiving the 2-h and 6-h infusions of cisplatin were made using Student's unpaired *t*-test for two means (two-tailed). Comparisons within patients studied during their first and third courses of treatment were made using Student's paired *t*-test (two-tailed). Similarly, paired comparisons of compartmental vs noncompartmental methods of determination of cisplatin disposition were made using the paired *t*-test.

Results

Plasma ultrafiltrate concentrations of unchanged cisplatin in all patients during the first course of treatment are shown in Fig. 1. The half-life of the drug was sufficiently short (34.4 ± 12 min) that steady state was attained by the end of the 2-h infusions. Mean (± SD) steady-state levels of cisplatin in plasma ultrafiltrate were 2.56 ± 1.02 μg/ml with the 2-h infusions and 1.18 ± 0.32 μg/ml with the 6-h infusions. There was no change in cisplatin concentration in the infusion solution over the duration of the infusion. As discussed in our previous publication, urinary excretion rates of cisplatin tended to parallel the decline in plasma ultrafiltrate levels with time in each patient. An example is shown in Fig. 2 for one of the patients. Mean pharmacokinetic parameters (± SD) for the first course of treatment in patients receiving 2-h and 6-h infusions are summarized in Table 1. The two groups of patients were approximately matched for age, surface area, and creatinine clearance.

Renal clearance determined by either the compartmental or noncompartmental method was significantly lower with the longer infusion. The difference in mean renal clearance determined by the noncompartmental method for the 2-h and 6-h infusions was 39.4%. The percentage of the cisplatin dose excreted unchanged in the urine was significantly lower with the longer infusion. No differences were observed in the volume of distribution, nonrenal clearance, total clearance or elimination half-life of cisplatin determined from either plasma or urinary data, and there were no differences in estimates made by the compartmental or noncompartmental methods. There was

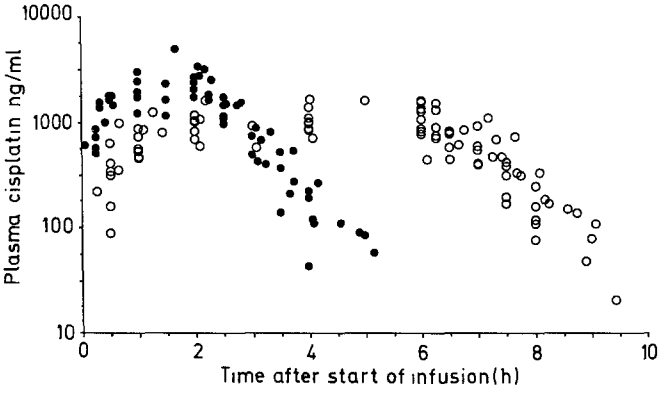

Fig. 1. Concentrations of unchanged cisplatin in plasma ultrafiltrate after the first course of treatment in 10 patients receiving 2-h i.v. infusions (●) and 10 patients receiving 6-h i.v. infusions (○) of cisplatin (100 mg/m²). Cisplatin levels were determined by a specific on-line, post-column derivatization method

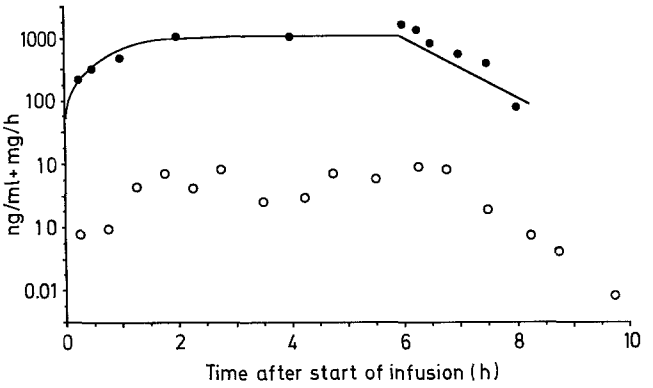

Fig. 2. Plasma concentrations (●), predicted plasma concentrations (−), and urinary excretion rates (○) of cisplatin after the first course of treatment in a patient receiving a 6-h infusion of cisplatin (100 mg/m^2)

only a poor relationship between cisplatin renal clearance and creatinine clearance in patients receiving the 2-h ($r^2 = 0.02$; $P = 0.66$) and 6-h infusions ($r^2 = 0.18$; $P = 0.23$).

A comparison of parameters of cisplatin disposition and creatinine clearance is shown in Table 2 for ten patients who were studied during their first and third courses of treatment. Five patients received the drug by 2-h infusion and five, by 6-h infusion. There were no significant differences between course 1 and course 3 for any of the parameters, although both renal and total cisplatin clearance tended to be lower in the third course of treatment.

The steady-state plasma level at the end of each first-course infusion (C_{ss}) was correlated with CL(MI) estimated from the total AUC for both the 2-h ($r^2 = 0.70$; $P = 0.0096$) and 6-h infusions ($r^2 = 0.97$; $P = 0.0001$). Possible relationships between C_{ss} and the change in creatinine clearance between courses 1 and 3 were also examined. No relationship was found between the percentage of change in creatinine clearance and C_{ss} for all patients considered as a group; there were too few patients for separate consideration of the two infusion subgroups. However, the mean difference in creatinine clearance between the courses was relatively small (16%).

Discussion

The present study shows that cisplatin disposition in patients is dependent on infusion duration; longer infusion resulted in lower and less variable urinary excretion of the drug. These differences were seen with only a 3-fold difference in infusion time. The underlying mechanism probably involves the avoidance of saturable renal tubular reabsorption of cisplatin at the lower plasma and urinary levels resulting from the longer infusion. This is consistent with our previous observations [14], where ultrafilterable plasma platinum and total urinary platinum were quantitated in patients receiving 2-h infusions of cisplatin. The renal clearance of cisplatin was highest near the end of the infusion, when plasma steady-state levels were reached and urinary concentrations of cisplatin were the greatest, but then fell as the concentrations in plasma and urine decreased. We recently reported similar results in seven patients in whom unchanged cisplatin concentrations were

Table 1. Patient characteristics and mean pharmacokinetic parameters for cisplatin after the first course of treatment

Characteristic/parameter	2-h Infusion (n = 10)		6-h Infusion (n = 10)		P
	Mean	SD	Mean	SD	
Age (years)	56	8	63	10	0.08
Surface area (m^2)	1.68	0.18	1.60	0.15	0.33
Infusion time (h)	2.13	0.20	6.35	0.53	0.0001
Creatinine clearance (ml/min per m^2)	42	12	35	14	0.28
C_{ss}[1] (μg/ml)	2.56	1.02	1.18	0.32	0.0007
CL(M)[2] (ml/min per m^2)	299	80.7	254	46.3	0.17
CL(MI)[3] (ml/min per m^2)	299	72.7	250	49.7	0.12
V_{ss}(M)[4] (l/m^2)	13.2	5.6	19.1	14.7	0.30
$t_{1/2}$(M)[5] (min)	30.5	9.0	39.9	14.1	0.12
$t_{1/2}$(MI)[6] (min)	29.7	5.4	38.7	14.7	0.12
$t_{1/2}u$[7] (min)	32.0	9.9	34.3	9.2	0.61
Percentage excreted in the urine	27.6	8.3	20.4	4.6	0.029
CL_R(M)[8] (ml/min per m^2)	85.8	33.8	53.8	16.5	0.023
CL_R(MI)[8] (ml/min per m^2)	87.1	38.2	52.8	16.2	0.026
CL_{NR}(M)[9] (ml/min per m^2)	212	66.6	200	37.8	0.62
CL_{NR}(MI)[9] (ml/min per m^2)	212	54.8	197	42.0	0.53
CL_R(MI)/CL_{CR}[10]	2.22	0.95	1.72	0.86	0.27

[1] Steady-state plasma level
[2] Total clearance determined from one-compartment model parameters
[3] Total clearance determined from the AUC calculated by the trapezoidal method
[4] Volume of distribution determined from one-compartment model parameters
[5] Elimination half-life determined from one-compartment model parameters
[6] Elimination half-life determined by regression analysis of post-infusion plasma data
[7] Elimination half-life determined by regression analysis of urinary excretion rate – time data
[8] Renal clearance corresponding to respective total clearance terms
[9] Nonrenal clearance corresponding to respective total clearance terms
[10] Ratio of renal clearance to creatinine clearance determined by the model-independent method

Table 2. Mean pharmacokinetic parameters for cisplatin after the first and third courses of treatment in patients receiving 2-h and 6-h infusions of 100 mg/m^2

Characteristic/parameter	2-h Infusion (n = 5)		6-h Infusion (n = 5)	
	Course 1	Course 3	Course 1	Course 3
Age (years)	58	58	65	65
Surface area (m^2)	1.63	1.63	1.58	1.58
Infusion time (h)	2.01	2.75	6.50	7.15
Creatinine clearance (ml/min per m^2)	44	35	29	30
C_{ss}[1] (μg/ml)	2.32	2.26	1.10	1.32
CL(M)[2] (ml/min per m^2)	341	287	266	229
CL(MI)[3] (ml/min per m^2)	343	278	256	218
V_{ss}(M)[4] (l/m^2)	16.2	15.6	12.8	13.5
$t_{1/2}$(M)[5] (min)	33.3	29.2	33.4	40.9
$t_{1/2}$(MI)[6] (min)	27.6	33.3	31.9	38.5
$t_{1/2}u$[7] (min)	31.4	34.7	28.8	22.1
Percentage excreted in the urine	29.0	22.4	20.1	18.5
CL_R(M)[8] (ml/min per m^2)	99.3	66.9	53.0	44.7
CL_R(MI)[8] (ml/min per m^2)	102	65.3	50.4	43.7
CL_{NR}(M)[9] (ml/min per m^2)	242	220	213	185
CL_{NR}(MI)[9] (ml/min per m^2)	241	213	205	174
CL_R(MI)/CL_{CR}[10]	1.7	1.8	2.2	1.6

See footnotes to Table 1 for definitions of symbols

specifically measured [16]. Renal clearance would be expected to be lower at lower plasma and urinary concentrations during longer infusions due to greater renal tubular reabsorption, although we did not have sufficient patients in our earlier study [16] to examine this question. Altered protein binding with different infusion durations cannot be excluded.

Cisplatin renal clearance exceeded creatinine clearance for both infusion durations (Table 1), confirming previous suggestions from ultrafilterable platinum plasma data that cisplatin renal clearance involves active renal tubular secretion [6, 14]. The lack of correlation between cisplatin renal clearance and creatinine clearance was also consistent with a complex mechanism of renal excretion involving renal tubular secretion and reabsorption. We have previously described the poor correlation between either renal or total ultrafilterable platinum clearance and creatinine clearance [17]. The present study also provides confirmation of a correlation between a single plasma concentration, in this case C_{ss}, and the total clearance of the drug.

The lack of a significant difference in cisplatin disposition between the first and third courses of treatment in this study contrasts with our previous results for ultrafilterable platinum disposition after four courses of treatment [15]. However, only five patients in each infusion group were available for the present comparison. Nevertheless, there was a trend towards lower renal and total cisplatin clearance in the third course (Table 2). The difference between these studies may be attributed to differences in the cumulative cisplatin dose, which was 300 mg/m^2 in the present study and 320–400 mg/m^2 in the earlier study [15]; this may also account for the relatively small difference in creatinine clearance between courses 1 and 3 in the present study. Cisplatin courses were repeated with the same frequency in both studies. The accumulation of cisplatin metabolites that may contribute to ultrafilterable platinum plasma levels could also have contributed in part to the changes observed in the previous study; the analytical methodology used in that study [13] quantitated the combined cisplatin and reactive metabolite levels.

Several studies comparing the pharmacokinetics of various platinum species have been reported after long- and short-term infusions, although the information provided has been limited. Gullo et al. [4] studied seven patients, four of whom received a 1-hour infusion and three, a 20-h infusion. Ultrafilterable platinum levels were not detectable in patients receiving the longer infusion, although urinary excretion appeared lower with the longer infusion. Vermorken et al. [19] studied only three patients and found similar AUCs for each infusion. Von Heyden et al. [5] infused cisplatin over 24, 8, and 1 h, in that order, to the same patients at 3-week intervals. Interpretation of the results was difficult since only four patients received all three infusions and the previous cisplatin courses may have affected the pharmacokinetics in subsequent courses [15]. Patton et al. [10] compared plasma levels of intact cisplatin in four patients given 20 mg/m^2 by i.v. bolus followed immediately by 80 mg/m^2 by a 6-h infusion with those from a previous study in which 100 mg/m^2 cisplatin was given by i.v. bolus to six patients. The AUC of cisplatin appeared to be higher, although the design of the study did not allow meaningful statistical analyses to be undertaken; patients had also received previous courses of cisplatin. Jacobs et al. [6] briefly reported results from eight patients, six of whom received a cisplatin dose of 50–80 mg/m^2 given over 24 h and two, 100 mg/m^2 over 30 min. Although the implications of their findings were not discussed by these authors, the average renal clearance of ultrafilterable platinum in patients receiving the 24-h infusion was 156% of creatinine clearance, compared with a peak of 362% after the 30-min infusion, which rapidly declined to 111% of creatinine clearance. This result was consistent with the observations in the present study.

If peak cisplatin levels prove to be an important determinant of toxicity, longer infusions could be expected to

be associated with reduced toxicity. We recently reported that the change in creatinine clearance with repeated courses of cisplatin was related to peak plasma levels of ultrafilterable platinum [17]. However, the AUCs of ultrafilterable platinum and cisplatin dose were also related to the change in creatinine clearance, and longer infusions could not necessarily be associated with reduced nephrotoxicity. Changes in creatinine clearance between courses 1 and 3 were too small in the present study for the examination of possible relationships between steady-state plasma levels of cisplatin and changes in creatinine clearance. There were also an insufficient number of patients to enable a conclusion as to whether renal or emetic toxicity was less frequent with the 6-h infusion. Further controlled studies are required to establish this. Clearly, some toxicities of cisplatin may be related to peak plasma levels and others, to the AUC or both. The therapeutic effect is probably related to the AUC, since tumors appear to respond to 5-day infusions of cisplatin [11] despite the fact that plasma levels are approximately 60 times lower than those recorded after 2-h infusions. The relative AUC of unchanged cisplatin is expected to be higher and less variable with longer infusions due to the avoidance of saturable renal tubular reabsorption. This should be taken into consideration in clinical trials where infusion duration is a variable.

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