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Clinical pharmacology of high-dose cisplatin

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Summary. *Although nephrotoxicity has frequently limited conventional treatment with cisplatin to doses of 100–120 mg/m² per cycle, vigorous chloruresis can permit the administration of high-dose cisplatin (200 mg/m² per cycle) with minimal nephrotoxicity. Systemic toxicities are worsened, but therapeutic response seems to be enhanced. The pharmacokinetics of cisplatin in plasma and urine were examined to assess the causes of these effects. Plasma disappearance of ultrafiltrable platinum was well-described by a single exponential for each patient. The mean $t_{1/2}$ was 50% longer for patients receiving high-dose cisplatin than for patients receiving conventional doses. The total systemic exposure was three times greater in the high-dose group, which tends to explain the systemic toxicity and improved tumor efficacy, but not the lack of nephrotoxicity. It is suggested that the kidneys of patients in the high-dose group were relatively protected by dilution of active Pt species in the urine in the tubule lumen as well as by high chloride ion concentrations in the urine.*

Introduction

Cisplatin is a coordination compound with substantial activity in several human malignancies, including testicular and ovarian carcinoma [3, 15]. Administration of cisplatin is accompanied by myelosuppression, gastrointestinal toxicity, ototoxicity, and peripheral neuropathy. While these toxicities can be severe, the dose-limiting toxicity of cisplatin has been nephrotoxicity [10]. Mannitol and/or furosemide diuresis is commonly used, but nephrotoxicity has generally set an upper dose limit of 100–120 mg/m² per cycle [10].

Recently, we have reported that high-dose cisplatin (HDP, 40 mg/m² daily for 5 days) can be given safely in conjunction with extensive chloruresis [11]. While transient elevations in serum creatinine were observed, this regimen produced no residual nephrotoxicity and was accompanied by responses in several patients who were resistant to conventional-dose cisplatin (CDP, 20 mg/m² daily for 5 days). Although nephrotoxicity is minimal with HDP, systemic side-effects are worse than with CDP. However, therapeutic benefit also appears to be enhanced. Recently, another group has reported on the use of a similar regimen [12].

In this report, we have examined the plasma pharmacokinetics of HDP compared with CDP in an effort to understand the increased efficacy of our regimen. In addition, we have measured urinary chloride ion and Pt concentrations in three patients receiving HDP to ascertain the mechanism of the renal protective effect of our regimen.

Methods

Treatment. HDP (40 mg/m²) was dissolved in 250 ml 3% NaCl and infused over approximately 30 min. Hydration and chloride loading consisted of 0.9% NaCl 6 l/day (250 ml/h) with 20 mEq KCl/l, beginning 12 h before the infusion, continuing throughout the 5 days of therapy, and ending 12–24 h after the last infusion. Furosemide (20 mg) was given 1 h before each dose of cisplatin.

Patient characteristics in the CDP and the HDP groups are shown in Table 1.

CDP (20 mg/m²) was dissolved in 150–250 ml 0.9% NaCl and infused over approximately 30 min. For patients 8 and 11 (testicular cancer), 0.9% saline 150 ml was infused, beginning 12 h before the first daily dose and continuing until 12–24 h after the fifth daily dose. Patients 9 and 10 (ovarian cancer) received 1,000 ml 5% dextrose in 0.45% NaCl, infused 1 h before the cisplatin was administered, and 125 ml 15% mannitol after the drug was given. For 8–12 h after the cisplatin infusion, 0.9% NaCl 150 ml/h was given. Patients 8 and 11 received 20 mg furosemide immediately before each cisplatin dose. Patients 9 and 10 received no furosemide.

Table 1. Patient characteristics

Patient	Age	Sex	Diagnosis	Prior Pt therapy
High-dose cisplatin				
1	53	F	Ovarian	CDDP
2	19	F	Dysgerminoma	CDDP
3	35	F	Ovarian	CBDCA
4	58	F	Ovarian	CDDP, CBDCA
5	67	F	Ovarian	CDDP, CBDCA
6	44	F	Ovarian	CDDP
7	26	M	Testicular	None
Conventional-dose cisplatin				
8	20	M	Testicular	None
9	52	F	Ovarian	None
10	75	F	Ovarian	None
11	21	M	Testicular	None

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Plasma pharmacokinetics. The pharmacokinetics of HDP were evaluated in six patients during one cycle and in an additional patient during three cycles. For comparison, we studied the pharmacokinetics of CDP in four patients receiving this drug as part of multimodal therapy for either testicular or ovarian cancer. For both HDP and CDP, each cycle consisted of cisplatin given in five daily doses as a single agent or in combination. Blood was drawn before and at 0, 15, 30, 45, 60, and 90 min after the drug infusion on days 1 and 5. Blood samples were also obtained immediately before the infusion on days 2, 3, and 4. Blood samples were immediately placed on ice. Blood was centrifuged and plasma was further separated using Amicon membrane C-25 ultrafiltration cones (25,000 daltons cut-off). All separations were completed within 60 min after the blood sample was taken. The Pt concentration was determined by flameless atomic absorption spectroscopy [9] and standard techniques.

Urine. Pt and chloride ion concentrations were determined in urine collected from patients 1 and 2 on days 1 and 5. Patient 3 had a uterostomy tube in place due to tumor obstructive uropathy. For this patient the Pt and chloride ion concentrations were determined on day 1 in both urine and the effluent from the uterostomy tube.

The Pt concentration was determined in an aliquot of untreated urine by flameless atomic absorption. The urinary chloride ion concentration was determined on filtered urine using a chloride ion electrode (Orion Research, Model 94-17B) vs a standard reference electrode.

Results

Plasma pharmacokinetics

The time course of total and ultrafiltrable Pt for a representative patient receiving HDP is shown in Fig. 1. This patient was sampled on the third cycle of HDP, 4 weeks after the previous cycle. There was no detectable ultrafiltrable Pt prior to treatment on day 1, but there was residual bound Pt (0.47 μg/ml). After cessation of the drug infusion, ultrafiltrable Pt decayed with first-order kinetics on both days 1 and 5. On days 2 through 5, total Pt increased prior to therapy (1.5, 2.4, 3.1, 3.6 μg/ml). There was a minimal amount of ultrafiltrable Pt (0, 0.06, 0.10, 0.11 μg/ml).

The disappearance of ultrafiltrable Pt after the drug infusion was well described by a single exponential for each patient. Results for the seven HDP patients and the four CDP patients are displayed in Table 2. There was no consistent variation in $t_{1/2}$ between day 1 and day 5. The mean $t_{1/2}$ for HDP (31 min) was 50% longer than the mean $t_{1/2}$ for CDP (19 min). This difference was statistically significant ($P < 0.001$).

Urine

The cumulative urinary excretion of Pt is shown in Fig. 2 for patients 1, 2, and 3. Urine voided during the infusion is included in the zero-time value. For patient 3, 0.3 mg Pt was removed in the first 11 h via the uterostomy tube, as against 6 mg collected from the voided urine. Peak urinary Pt concentrations were 6–10 μg/ml.

Chloride ion concentrations for the urine samples are shown in Fig. 3. These chloride values are generally greater than 134 mEq/l, which is the value for normal urine. The urine volume was greater than 5 l/day in all patients receiving HDP.

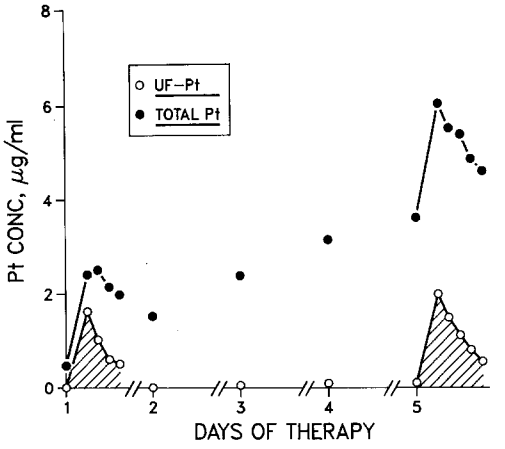

Fig. 1. Total Pt *(closed circles)* and ultrafiltrable Pt *(open circles)* in the plasma of patient 1 over the 5-day course of therapy

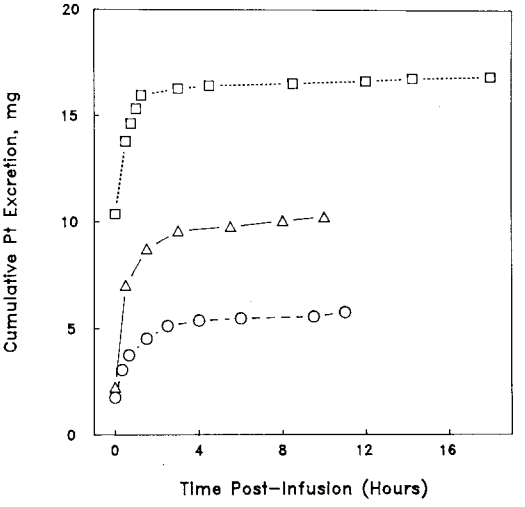

Fig. 2. Cumulative urinary excretion of Pt on day 1 for three patients receiving high-dose cisplatin: Patient 1 *(solid line, triangles);* patient 2 *(dotted line, squares);* and patient 3 *(dashed line, circles)*

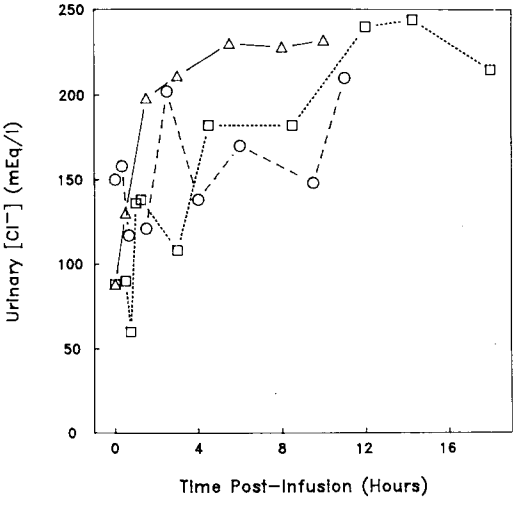

Fig. 3. Chloride ion concentrations in the urine of three patients receiving high-dose cisplatin: Patient 1 *(solid line, triangles);* patient 2 *(dotted line, squares);* and patient 3 *(dashed line, circles)*

Table 2. Plasma half-lives

Patient	Cycle no.	Serum creatinine (mg/ml)	Creatinine clearance (ml/min/m²)	Day 1 $t_{1/2}$ (min)	Day 5 $t_{1/2}$ (min)
High-dose cisplantin					
1	3	0.9	77	26	33
2	1	0.8	62	22	21
3	1	1.4	43	31	–
4	2	0.9	63	45	41
5	1	1.4	59	33	38
6	1	1.1	72	31	36
7	1	1.1	–	21	23
	2	1.0	82	16	–
	3	0.9	–	46	34
Daily $t_{1/2}$ (mean ± SE)				30 ± 3.4	32 ± 2.8
Overall $t_{1/2}$ (mean ± SE)				31 ± 2.2	
Conventional-dose cisplatin					
8	1	12.1	[a]	19	–
	2	0.9	84	19	–
9	1	1.0	75	26	–
10	3	1.0	87	14	19
11	1	0.9	76	19	–
Daily $t_{1/2}$ (mean ± SE)				19 ± 1.9	–
Overall $t_{1/2}$ (mean ± SE)				19 ± 1.6	

[a] No urine output

Discussion

The HDP regimen has three biological effects which we sought to explain: (1) antitumor efficacy is improved over that of CDP; (2) systemic toxicities (bone marrow, gastrointestinal system, ears, and nervous system) are at least as severe or worse with HDP; (3) despite a doubling of the dose, nephrotoxicity is minimal [11].

First, we examined the effect of our chloruresis treatment upon the plasma pharmacokinetics of ultrafiltrable Pt. It was found that the mean $t_{1/2}$ for clearance of ultrafiltrable Pt was prolonged by about 50% in the HDP group. This finding is relevant for the first two biological effects. The exposure of all systemic tissues (including both the tumor and normal tissues such as the bone marrow, gastrointestinal system, ears, and nervous system) should be proportional to plasma exposure. For the HDP patients, the combination of a doubling of the dose and a 50% increase in plasma $t_{1/2}$ produces a three-fold increase in plasma concentration and, thus, in systemic exposure.

The mechanism that causes the increase in plasma $t_{1/2}$ remains unknown. Plasma concentrations of chloride ion do not change, so the hydrolysis rate of cisplatin in plasma should also not change. Even if the chloride loading did change plasma chloride concentrations, the rate of hydrolysis is relatively slow [5] compared with the plasma $t_{1/2}$. The difference was also unrelated to creatinine clearance. In any event, urinary excretion accounts for only 20%–30% of the total-body clearance of cisplatin [4]. Other groups report plasma $t_{1/2}$ values for ultrafiltrable Pt in the range of 20–40 min [1, 5].

Since the plasma pharmacokinetics did not provide an explanation for the minimal renal toxicity observed with the HDP regimen, the renal dynamics were examined for an explanation of the lack of nephrotoxicity. The brush border of the proximal tubule is the principal site of the deleterious effects of heavy metals such as Pt [10, 13]. There is substantial evidence that increasing the volume of fluid traversing the renal tubules can decrease nephrotoxicity. This is usually accomplished by moderate hydration and the use of mannitol and furosemide [2].

If renal tubular toxicity is directly related to the concentration of active cisplatin-derived species in the tubular lumen, then the protective effect of increased urine output is straightforward. Renal tubular resorption of water is suppressed, and therefore the active Pt species in the lumen of the renal tubule is not as concentrated. While the same amount of active Pt species will be filtered at the glomerulus and the concentration at the entrance to the proximal tubule will be unchanged, the inhibition of water resorption will produce a more dilute urine at the distal end of the proximal tubule. Similarly, any active Pt species secreted into the tubule [8] will also be more dilute. Increased output of urine was ensured in the HDP regimen by the administration of 6 l normal saline per day. Urine production was consistently greater than 5 l/day. In the HDP regimen, peak urinary Pt concentrations of 6–10 μg/ml were observed. Peak urinary Pt concentrations of 25–40 μg/ml have been reported for CDP [7].

In addition to a dilution of Pt concentrations in the tubular fluid, our use of large volumes of 0.9% saline with supplemental KCl maintains high concentrations of chloride ion in tubular fluid and urine. High chloride ion concentrations may help to protect the abluminal cells from damage by lowering the reaction rate of cisplatin hydrolysis or reactions with tubular sulfhydryl-containing enzymes. Evidence is accumulating which suggests that the key reaction for cisplatin is nucleophilic substitution with sulfhydryl groups [13]. Renal tubular cells are rich in sulfhydryl-containing enzymes, including metallothionein. Preliminary studies in our laboratory (BJ Corden, unpublished data) suggest that sodium chloride can suppress the reaction of cysteine with cisplatin. Other possibilities include inhibition of cisplatin transport into the cell by high chloride ion concentrations.

Thus, it is possible that a diuresis induced by 5% dextrose in 0.3%–0.45% saline, as used in some protocols [2, 14], may be less desirable. Lower concentrations of chloride ion would be produced in the tubular lumen, and the propensity for cisplatin to damage abluminal cells would be increased. This could offset the advantage of the lowered Pt concentration in the tubular fluid.

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