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Renal failure and platinum pharmacokinetics in three patients treated with cis-diamminedichloroplatinum(II) and whole-body hyperthermia

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Summary. *Three patients with advanced refractory malignancies were treated with whole-body hyperthermia (WBH: 42–42.3° C) for 2 h during which time they also received an infusion of 60 or 80 mg/m² of cis-diamminedichloroplatinum II (DDP). Each patient developed an elevated serum creatinine (2.7–13.6 mg/dl), with maximum creatinine occurring between days 7 and 12 after treatment. WBH did not alter plasma or urinary pharmacokinetics of total or ultrafilterable platinum compared with pharmacokinetic data of the same or other patients given DDP euthermically. Although the mechanism of the renal damage is unclear, it appears that WBH can potentiate the nephrotoxic actions of DDP and that further study of this combination is not warranted.*

Introduction

Evidence suggesting that hyperthermia may be an effective anticancer therapy has accumulated in recent years. In vitro, temperatures of 41–43° C have shown a significantly greater lethal effect on many types of tumor cells than on non-tumor cells [7, 12, 13, 29, 30, 36]. Both in vitro and in vivo, an augmented antitumor effect has been found when hyperthermia has been combined with a number of chemotherapeutic agents [12, 16, 17], including DDP [1, 4, 16, 22, 24].

Whole-body hyperthermia (WBH) is a feasible therapeutic modality in selected patients with advanced cancer [3, 6, 34]. Antitumor synergy between DDP and local hyperthermia have suggested its potential use with WBH [4]. This study was begun to determine the therapeutic efficacy of WBH plus DDP in advanced refractory malignancies and to assess platinum pharmacokinetics in hyperthermic patients. The study had to be discontinued because renal toxicity occurred in the first three patients treated. The clinical and pharmacokinetic data from these three patients are reported here.

Materials and methods

Three patients with advanced refractory malignancies not amenable to surgery were selected for hyperthermia. All patients had measurable disease without evidence of central nervous system or hepatic metastasis. Cardiopulmonary fitness was determined by history, physical, electrocardiogram, chest roentgenogram, pulmonary function studies, and an exercise radionuclide scan of the heart. Additional tests included a cranial CT scan, serum electrolytes, blood urea nitrogen, creatinine, liver function studies, magnesium, coagulation profile, audiogram, urinalysis, and 24-h creatinine clearance. These tests were reviewed by a team of oncologists and anesthesiologists prior to a patient's acceptance for treatment. Written informed consent was obtained from all patients prior to entry on study.

Two patients first received one euthermic course of DDP, during which baseline pharmacokinetics were assessed. DDP 80 mg/m² in two patients and 60 mg/m² in the third patient, diluted in 1 l of 5% dextrose in 0.077 *M* NaCl, was infused over 2 h spanning the entire duration of Tmax (42.0–42.3° C). Mannitol 37.5 g as a 10% solution was infused over 6 h, starting 4 h prior to the administration of DDP. Additional IV fluid therapy was administered as 5% dextrose and 0.077 *M* NaCl with 10 mEq KCl/l. Initial hydration was begun at a rate of 150 ml/h, 8 h prior to the onset of heating. The rate of hydration was increased to 800 ml/h during heating and subsequently was increased if necessary to maintain a minimum systolic blood pressure of 90 mmHg and a minimum urine output of 50 ml/h. Patients received 800–1,200 ml/h during heating. After treatment, fluids were tapered over 8–12 h, to 150 ml/h so as to keep the urine output above 50 ml/h. Electrolyte replacement was adjusted based on serial determinations of serum electrolyte concentrations. Intravenous fluid was discontinued when the patients were awake and able to take fluid orally.

The heating technique began with gowining patients in cotton pajamas over which a vinyl plastic suit (Whittaker General Medical, Elliot City, MD, USA) was worn. The hands and feet were covered with vinyl plastic and sealed with tape. A Flexitherm nylon and vinyl mesh water-perfused suit (Acurex Corp., Mountainview, CA, USA) was put over this and connected by a hose to a thermal conditioning unit supplied the the National Aeronautics and Space Administration. Exclusive of the face, the head was covered with clear vinyl plastic whose edges were tucked into the sauna suit. The patient was then additionally covered by heating blankets.

Body temperature was elevated by the combination of water preheated to 46° C circulating through the vinyl mesh suit, warming blankets set at 46° C, and the metabolic heat of the patient. The patients' core cemperature was raised by 1–2.5 deg. °C/h until it reached 41.5° C, at which time the water-bath temperature was reduced to 34–36° C. The patients' temperature would then plateau between 42.0 and 42.3° C, and was maintained there by adjusting the water-bath temperature. Two hours after reaching 42° C, the patient was

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cooled by setting the water-bath temperature at 15° C, removing the blankets, and opening the plastic suit.

Core temperature was monitored with both rectal and esophageal probes attached to an electronic thermometer (model BAT-8, Baily Instruments, Saddlebrook, NJ, USA) which gave a continuous readout of core temperatures. Before each treatment, the temperature probes were calibrated against a mercury thermometer standard (sensitivity ± 0.05° C). Patient temperatures were recorded every 10 min.

Blood pressure was continuously monitored with an arterial catheter connected to a Gould Statham blood pressure monitor (Gould Inc., Medical Products Division, Oxnard, CA, USA). Vital signs were recorded every 5 min. The arterial catheter also served as an access for repeated determinations of blood gases, complete blood counts, electrolytes, blood urea nitrogen, creatinine, glucose, phosphate, calcium, magnesium, lactate dehydrogenase, hepatic transaminases, creatinine phosphokinase (CPK), alkaline phosphatase, bilirubin, uric acid, total protein, albumin, coagulation profiles, and drug levels. Urinary output was measured and collected hourly by a Foley catheter connected to a closed drainage system. Continuous electrocardiographic monitoring was displayed using a Gould-Statham ECG heart rate monitor (Gould Inc.).

Anesthesia was induced with 0.2 mg glycopyrrolate administered IV before heating. With heating, induction doses of 50–150 mg 2.5% thiamylal were administered IV over 5 min. A 0.5% thiamylal infusion was then begun and extra boluses of 25–50 mg were given if excessive movement occurred. Total doses of thiamylal were 2,000 mg, 3,100 mg, and 1,590 mg in patients 1, 2, and 3, respectively. Intravenous fentanyl citrate was also used for sedation to control hyperventilation.

Pharmacokinetics. At specified times after drug administration, blood samples were collected in heparinized tubes and centrifuged at 1,000 *g* for 10 min, after which the plasma was removed. An aliquot of plasma was frozen at −20° C until the time of assay. Protein-free ultrafiltrates were prepared by centrifuging 3 ml of the remaining plasma in Centriflo CF50A membranes (Amicon Corp., Lexington, MA, USA) at 1,000 *g* for 20 min at 4° C. Urine samples were collected at the time of voiding, measured, and stored at −20° C, either individually or as pooled 30-min or 4-h collections.

Plasma, plasma ultrafiltrates, and urine samples were analyzed for platinum by flameless atomic absorption spectrometry, employing the same instrumentation and methodology as previously reported [23]. Terminal half-lives of total and ultrafilterable platinum in plasma were calculated with a least-squares linear regression analysis. Urinary clearances of ultrafilterable platinum and creatinine were calculated according to the standard formula:

$$\frac{\text{Urinary concentration} \times \text{Urine volume}}{\text{Plasma concentration} \times \text{time}}.$$

Results

Characteristics of each patient and their WBH-associated renal toxicities are shown in Table 1. Urine output during WBH for patients 1, 2, and 3 averaged 300 ml/h, 155 ml/h, and 75 ml/h, respectively. During the 24 h after WBH the urine output averaged 350 ml/h, 250 ml/h, and 300 ml/h, respectively. No episodes of hypotension occurred during WBH, and no nephrotoxic drugs other than DDP were administered. Between 7 and 12 days after treatment, serum creatinine concentrations peaked at 2.7 mg/dl, 2.8 mg/dl, and 13.6 mg/dl in patients 1, 2, and 3, respectively. Subsequent serum creatinines in patiens 1, 2, and 3 were 1.1 mg/dl on day 114, 1.9 mg/dl at the time of death on day 82, and 4.8 mg/dl on day 40.

Physiological and biochemical changes that occurred during WBH were similar to those previously reported [28]. The most marked changes were reductions in mean serum phosphorus and magnesium concentrations to 0.9 mg/dl and 1.1 mg/dl, respectively, and elevations of mean serum glucose and creatinine concentrations to 369 mg/dl and 1.6 mg/dl, respectively. Within 24 h after WBH there were up to two-fold elevations in liver enzymes and up to three-fold elevations in CPK. These observations are consistent with the previous experience of Barlogie et al. [3]. The mean serum creatinine concentration at 24 h after WBH was 1.5 mg/dl, elevated from a mean baseline concentration of 0.9 mg/dl. The mean serum magnesium concentration remained low at 1.1 mg/dl, reduced from a mean baseline concentration of 1.8 mg/dl. The other plasma constituents had returned to baseline levels.

A 1.5 gm/dl decrease in mean hemoglobin was recorded at 24 h after WBH. The platelet count in two patients demonstrated a mean decrease of 177,000/μl and rose by 16,000/μl in the third patient at 24 h. Coagulation studies revealed no evidence of disseminated intravascular coagulation.

Clinical toxicities occurring in all patients included fatigue, nausea, and vomiting, diarrhea, and anasarca. One patient experienced one small second-degree burn and another developed perioral *Herpes simplex*. High-frequency hearing

Table 1. Patient characteristics

Pt	Sex/Age	Tumor	Prior therapy[a]	Pre-WBH: Creat. (mg/dl) / Creat. Cl (ml/min)	DDP (mg/m^2)	Peak Temp. (° C)	Peak Creat. (mg/dl)	Days post WBH	Follow-up: Creat./day post WBH + DDP
1	M/18	Malignant Fibrous Histiocytoma	Surgery RT,A,C DOX,DDP,V	0.9/104	80	42.2	2.7	7	1.1/114
2	M/66	Melanoma	DTIC,V	1.1/100	80	42.2	2.8	12	1.9/ 82 (death)
3	M/43	Mesothelioma	DOX	0.8/137	60	42.3	13.6	12	4.8/ 40

[a] A, actinomycin; C, cyclophosphamide; DOX, doxorubicin; DDP, *cis*-dichlorodiammineplatinum (II); DTIC, dacarbazine; RT, radiation; V, vincristine

loss as determined by audiogram was noted in two patients, being severe in one and mild in the other.

Disease progression after WBH and DDP was documented by CT scan in the patients with malignant fibrous histiocytoma and mesothelioma, and stabilization for 1 month was seen in the patient with melanoma.

Pharmacokinetics

WBH did not grossly alter the plasma or urinary pharmacokinetics of total or ultrafilterable platinum (Table 2). The peak plasma concentrations of total and ultrafilterable platinum achieved in these patients agree well with those from earlier reports of patients treated by ourselves [10, 25–27] and by others [9, 14, 15, 20, 32, 33, 35] with similar doses of DDP. Although patient 1 achieved greater concentrations of total plasma platinum when treated at 37° C than at 42.2° C, the peak concentrations of ultrafilterable platinum achieved in this patient at 37° C and 42.2° C were similar. In patient 3, WBH did not alter the peak concentrations of total or ultrafilterable

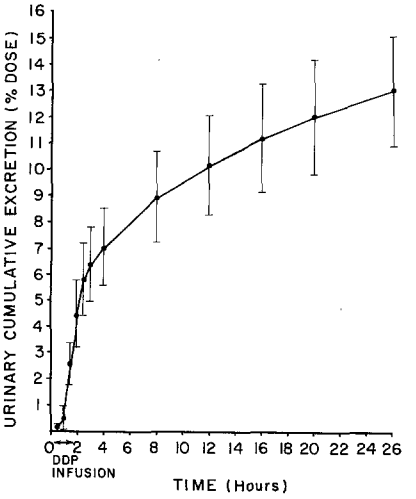

Fig. 2. Urinary excretion of platinum by three patients treated with DDP and WBH. *Points* and *bars* represent means ± SEM

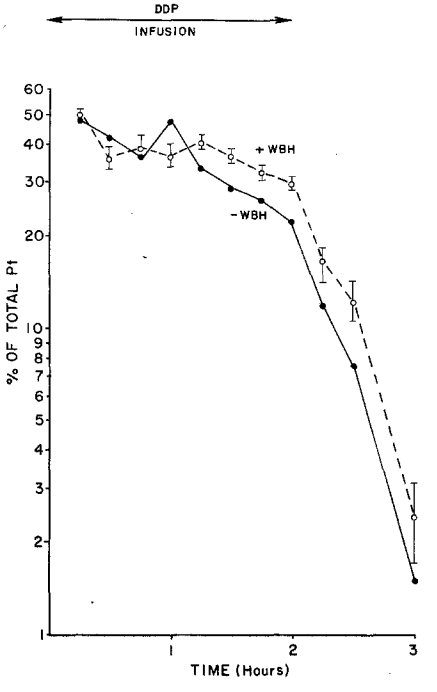

Fig. 1. Ultrafilterable platinum in plasma of two patients treated with DDP without WBH (●– – –●) and the same two patients and one other treated with DDP and WBH (○– – –○). *Points* represent mean values, in the case of WBH *bars* indicate SEM

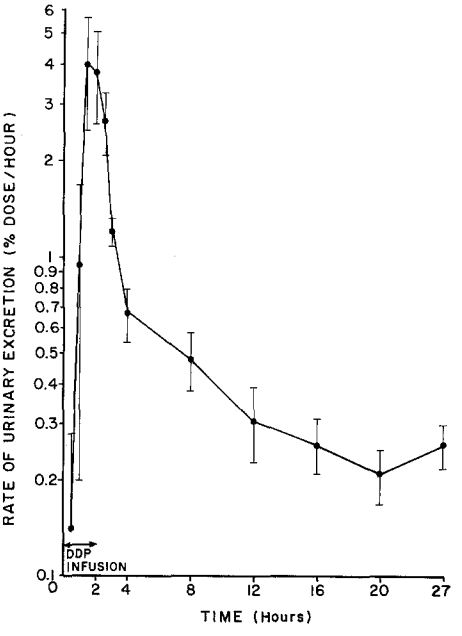

Fig. 3. Rate of urinary excretion of platinum by three patients treated with DDP and WBH. *Points* and *bars* represent means ± SEM

Table 2. Pharmacokinetic characteristics of DDP in patients treated with DDP and whole-body hyperthermia

Patient	Peak Temp. (° C)	Total Pt peak (plasma)	Terminal $t_{1/2}$	24-h urinary excretion	Ultrafilterable Pt	
					peak (plasma)	$t_{1/2}$
1	37	5.87 μg/μl	ND	ND	1.35 μg/μl	13 min
	42.2	3.65 μg/μl	242 h	17.2%	1.24 μg/μl	14 min
2	42.2	2.95 μg/μl	107 h	1%–4%	0.92 μg/μl	14 min
3	37	2.62 μg/μl	ND	ND	0.78 μg/μl	26 min
	42.3	2.51 μg/μl	385 h	11.5%	0.87 μg/μl	17 min

ND, not done

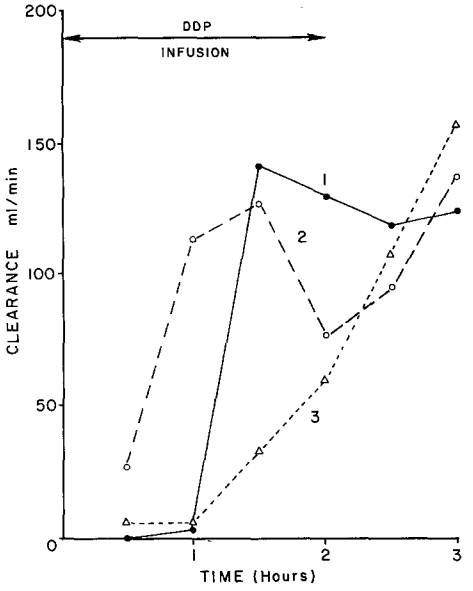

Fig. 4. Urinary clearance of ultrafilterable platinum by three patients treated with DDP and WBH

platinum. Elevated temperature did not alter the rapid disappearance from plasma of non-protein-bound platinum (Table 2). This rapid $t_{1/2}$ agrees well with values previously reported by ourselves [10, 25–27] and by others [9, 14, 15, 20, 32, 33] for patients treated euthermically with similar doses of DDP. In addition, elevated body temperature did not alter the percentage of total plasma platinum that was non-protein-bound (Fig. 1). The final aspect of plasma platinum pharmacokinetics not altered by WBH was the long $t_{1/2}$ observed for total plasma platinum (Table 2). WBH did not alter the renal excretion of platinum (Table 2 and Fig. 2), the 24-h excretion agreeing well with earlier reports released by ourselves [10, 25, 27] and others [14, 15] on patients treated at 37° C. The presence of Foley catheters in patients treated with WBH allowed us to examine in more detail the renal excretion of platinum by these individuals (Figs. 3 and 4). The rate of platinum excretion increased during the infusion, but decreased rapidly after cessation of the infusion, corresponding to the rapid disappearance of ultrafilterable platinum in plasma (Figs. 1 and 3). This is similar to the behavior of platinum administered to euthermic patients as reported previously [9, 10, 14, 15, 27]. The urinary clearance of ultrafilterable platinum increased during the infusion and by 3 h was greater than or equal to the concomitant creatinine clearance in all patients (Fig. 4).

Discussion

WBH alone [6] or in combination with cyclophosphamide [28, 34], melphalan [3, 34] 5-fluorouracil and vincristine [34], carmustine [31], and doxorubicin [31] does not produce a change in creatinine or creatinine clearance. DDP when given with vigorous hydration and mannitol-induced diuresis is reported to produce less severe nephrotoxicity, although this adverse reaction can still occur in up to one third of patients [2, 18]. In the three patients discussed here, the significant increase in serum creatinine observed at 24 h after WBH suggested synergistic nephrotoxicity ($P = 0.026$, paired t-test) between DDP and WBH, despite the use of hydration and mannitol.

The pharmacokinetic data in this study reveal no obvious effects of WBH on the plasma or urinary pharmacokinetics of DDP. Moreover, these data offer no obvious explanation for the severe nephrotoxicity encountered in these patients. There were no elevations in the amount of ultrafilterable platinum, which has been implicated as the nephrotoxic as well as active antineoplastic form of DDP [8]. In addition, the percentage of the DDP dose excreted in 24 h by hyperthermic patients was neither increased nor decreased. One could hypothesize that the low renal clearances of ultrafilterable platinum observed during the first 30–60 min of infusion might be related to the renal damage observed, but similar measurements have never been made in patients treated with DDP under euthermic conditions. Of interest is the fact that with time all three patients achieved urinary ultrafilterable platinum clearances greater then concomitant creatinine clearances, agreeing with the studies of Jacobs [21] and our center [10] in euthermic patients receiving DDP.

Our clinical results are in contrast with experience in an animal study, in which hyperthermia (42.5° C) did not potentiate DDP nephrotoxicity [11]. Additionally, we cannot readily explain the discrepancy between the uniform renal toxicity observed here and the apparent lack of renal toxicity in similarly treated patients reported by Herman et al. [19] and Beckley et al. [5]. In view of the apparent augmentation of the effect of WBH upon DDP renal toxicity, further trials of this combination do not appear warranted until the eitology and prevention of this adverse effect can be established.

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