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Nonlinear renal clearance of ultrafilterable platinum in patients treated with *cis*-dichlorodiammineplatinum (II)

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Summary. Nonlinear renal clearance of ultrafilterable platinum was observed in 5 of 7 patients given *cis*-dichlorodiammineplatinum (II) in doses of 50–140 mg/m^2 by short-term infusion (2 h). Average renal clearance determined during and 24 h after infusion ranged from 100 to 543 ml/min and always exceeded creatinine clearance, suggesting that ultrafilterable platinum was renally secreted. Saturable tubular reabsorption was postulated on the basis that renal clearance was highest at peak plasma and urinary levels and fell as the levels declined. Although an overall relationship between dose and renal clearance was not apparent, one patient receiving the highest dose (140 mg/m^2) had elevated average renal clearance (485 ml/min), probably associated with saturation of reabsorption, whereas a patient receiving 50 mg/m^2 had the lowest average renal clearance (100 ml/min), indicating that either active secretion was lower, or tubular reabsorption was saturated. One patient also showed urine-flow-dependent changes in renal clearance. Four patients had transient rises in ultrafilterable platinum levels, which were attributed to changes in renal tubular reabsorption. The results suggest that renal clearance of ultrafilterable platinum is probably dependent on *cis*-DDP dose, urine flow rate, and individual variability in the extent of active secretion and tubular reabsorption. A sensitive HPLC method was applied and ultrafilterable platinum was detected in the plasma of all patients 24 h after infusion. Renal tubular reabsorption may result in prolonged plasma levels of ultrafilterable platinum, which could contribute to the drug's antitumour effect.

Introduction

Although there have been several reports indicating that the renal clearance of platinum following *cis*-dichlorodiammine platinum (II) (*cis*-DDP) may involve potentially saturable processes, such as tubular secretion and tubular reabsorption [4, 5, 8, 11, 14], none have demonstrated that the renal clearance of the drug is nonlinear in patients. This is clearly an important possibility, which could alter the disposition of the drug when it is given in different dosage regimens.

In the present study a range of *cis*-DDP doses were administered to patients with different tumour types. Simultaneous measurements of ultrafilterable plasma platinum and urinary platinum levels allowed detailed evaluation of changes in ultrafilterable platinum renal clearance following short-term *cis*-DDP infusion.

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Material and methods

Patients. All patients deemed suitable for *cis*-DDP therapy who were expected to survive for at least 2 months and able to give informed consent were eligible for the study. Seven patients were studied (Table 1) during their first course of *cis*-DDP therapy, with the exception of patient 2, who had received two previous courses. Six were male and one female, their ages ranging from 27 to 75 years. All had measurable disease. Patient 1 had adenocarcinoma of the lung and was receiving vinblastine 3.8 mg daily for 3 days, which was stopped the day before the *cis*-DDP study. Patient 2 had recurrent squamous cell cancer of the mandible, which was treated with a combination of methotrexate bolus (40 mg/m^2), bleomycin bolus (15 mg), and *cis*-DDP infusion. The methotrexate was given at the start of the *cis*-DDP infusion. Patient 3 had carcinoma of unknown primary origin and received vinblastine bolus (4 mg/m^2) and bleomycin bolus (15 mg) 30 min prior to the *cis*-DDP infusion. Patient 4 had carcinoma of unknown primary origin and received vinblastine bolus (6 mg/m^2) and bleomycin bolus (15 mg) 30 min prior to the *cis*-DDP infusion. Patient 5 had metastatic testicular teratoma and received vinblastine bolus (4 mg/m^2) and bleomycin bolus (30 mg). The vinblastine was administered immediately before the *cis*-DDP infusion, and bleomycin 5 h after completion. Patient 6 had adenocarcinoma of the lung and received vinblastine 3.8 mg daily for 3 days prior to the *cis*-DDP infusion. Patient 7 had metastatic testicular teratoma and received VP-16, 213 (120 mg/m^2) by a 1 h infusion immediately after completion of the *cis*-DDP infusion.

Patients 4, 5, and 7 had extensive pulmonary and intra-abdominal disease; patients 1 and 3 had intrapulmonary disease only; patient 6 had intrapulmonary and bone secondaries; and patient 2 had disease confined to the head and neck region. Patients 2, 4, 5, and 7 have had a documented response to therapy. Patient 3 died after two courses from progressive disease. Patients 1 and 6 have yet to be assessed. No patient had had previous radiotherapy or chemotherapy. Patients did not receive other agents which could have modified their renal function.

Table 1. Patient details and pharmacokinetic parameters

Patient no.	Sex	Age (year)	Surface area (m^2)	Dose (mg/m^2)	Other medication	Creat.[a] Cl (ml/min)	Cl_r[b] (ml/min)	Ratio $\frac{Cl_r}{Creat.\ Cl}$	$T^1/_2{}_{UF}$[c] (min)	$T^1/_2{}_r$[d] (min)	Percentage of dose excreted
1	M	48	1.9	80	–	123	437	3.55	35.1	40.7	29.2
2	M	75	1.7	50	MTX, BLEO	88.4	100	1.13	37.6	37.4	13.3
3	M	27	1.6	100	VINB, BLEO	81.7	543	6.65	33.7	33.7	24.0
4	F	37	1.3	120	VINB	55.3	108	1.95	29.0	27.5	10.7
5	M	23	1.8	120	VINB, BLEO	93.7	215	2.29	26.0	34.0	19.1
6	M	58	1.9	80	–	87.7	408	6.17	32.0	32.0	29.3
7	M	38	1.9	140	VP16, 213	167	485	7.23	29.9	35.3	28.2

[a] Creatinine clearance
[b] Average renal clearance of ultrafilterable platinum; for estimation see text
[c] Half-life of ultrafilterable plasma platinum estimated to 3 h after infusion
[d] Half-life estimated from urinary excretion rate-time plot to 4 h after infusion

All seven patients received uniform hydration and mannitol therapy. Prehydration was given as 2 l 4% dextrose and 20% normal saline over 2 h, with 200 mg 20% mannitol given in the last 30 min. *Cis*-DDP was given in 1 litre of normal saline over 2 h. Post-hydration fluids consisted of 3 litre of 4% dextrose-20% normal saline, given over 4, 6, and 8 h, respectively. Antiemetic therapy was also uniform, each patient receiving five doses of IV dexamethasone 10 mg 4-hourly, commencing 4 h before *cis*-DDP and seven doses of IV metoclopramide 1 mg/kg 2-hourly, commencing 30 min before *cis*-DDP infusion. All patients had nausea and vomiting as the only side effects, and all vomiting had ceased within 12 h. No decrease in expected urine flow occurred because of excessive vomiting.

A 6-ml blood sample was collected prior to commencing the *cis*-DDP infusion and then serial samples were collected 10, 20, 40 min and 1, 1.5, 2, 3, 4, 6, 12, and 24 h after completion of the infusion. Samples were collected into EDTA and immediately centrifuged at 4 °C. Plasma was immediately frozen (−20 °C) and then thawed when all collections were complete, to allow centrifugal ultrafiltration with Amicon cones (type C25, mol. wt. cut-off 25 000). Ultrafiltrate was stored at −20 °C until analysis (<2 days). Urine specimens were collected each time the patient voided. The volume was noted and a 10-ml aliquot stored at −20 °C until assayed (<4 days).

Assay methods. Ultrafilterable plasma platinum and urinary platinum levels were measured by published methods [1, 12]. The limit of detection for platinum in plasma ultrafiltrate was 2.5 ng/ml. Repeated analyses of samples from different patients showed that there was no significant decline in ultrafilterable plasma platinum levels when samples were stored at 20 °C for up to 2 days. However, after 1 week a significant loss (approx. 10%) was detectable. Serum and urinary creatinine determinations were performed using a Boehringer-Mannheim colorimetric test kit.

Pharmacokinetic analyses. The half-life of ultrafilterable plastma platinum ($Tl/2_{UF}$) was determined from levels obtained up to 3 h after infusion. Similarly, the half-life obtained from urinary excretion rate data ($Tl/2_r$) was estimated from data obtained up to 4 h after infusion. Estimates of rate constants were obtained by means of BMDP-AR, a nonlinear regression, least-squares analysis package. It should be noted that although ultrafilterable plasma levels of platinum were still detectable 24 h after the infusion and could be described by a second compartment, the half-life of this terminal phase could not be accurately determined without sampling for at least 1 week. This was not practical in the present study. Average renal clearance of ultrafilterable platinum (Cl_r) was calculated by dividing the amount of platinum excreted in urine during and 24 h after infusion over the corresponding area under the curve of ultrafilterable platinum estimated by the trapezoidal method for observed postinfusion data and predicted area under the curve during infusion assuming one-compartment kinetics. The cumulative area under the curve for ultrafilterable plasma platinum corresponding to the cumulative amount excreted was estimated by fitting data to a two-compartment model, interpolating to obtain plasma levels corresponding to the urine collection period, and then applying the trapezoidal method to each period.

Creatinine clearance was estimated by pooling a measured aliquot proportional to the collected volume of each urine sample obtained over the period of study, quantitating the urinary creatinine level and excretion rate, and then dividing by the plasma creatinine level obtained 12 h after *cis*-DDP infusion.

Results

Average renal clearance of ultrafilterable platinum determined over the period of study (26 h) ranged from 100 to 543 ml/min and always exceeded creatinine clearance (Table 1). A plot of the cumulative amount of platinum excreted versus cumulative area under the plasma level–time curve for each patient is shown in Fig. 1. The slope of this plot at any point represents renal clearance. Only two patients (2 and 4) had linear plots consistent with constant renal clearance over the period of study. All other patients had plots with changing slopes, indicating that renal clearance was changing, initially reaching a very high value and then declining. This was particularly evident in patient 7, who had received 140 mg/m^2 *cis*-DDP. Renal clearance, which averaged 485 ml/min, never reached linearity in this patient. In patients 1, 3, 5, and 6 renal clearance appeared to approach linearity as the plasma concentration of ultrafilterable platinum declined. The amount of drug excreted over 26 h in those patients (2 and 4) showing line-

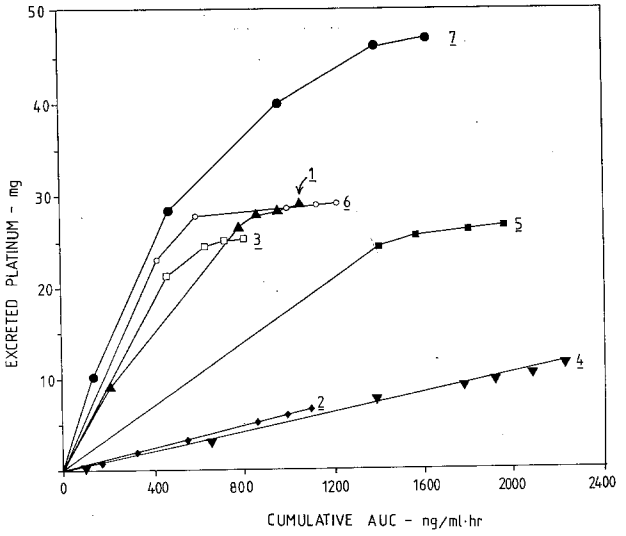

Fig. 1. Cumulative amount of platinum excreted in urine versus corresponding cumulative area under plasma level–time curve. The number on each graph corresponds to the patient number in Table 1. The *slope* of the line at any point corresponds to renal clearance

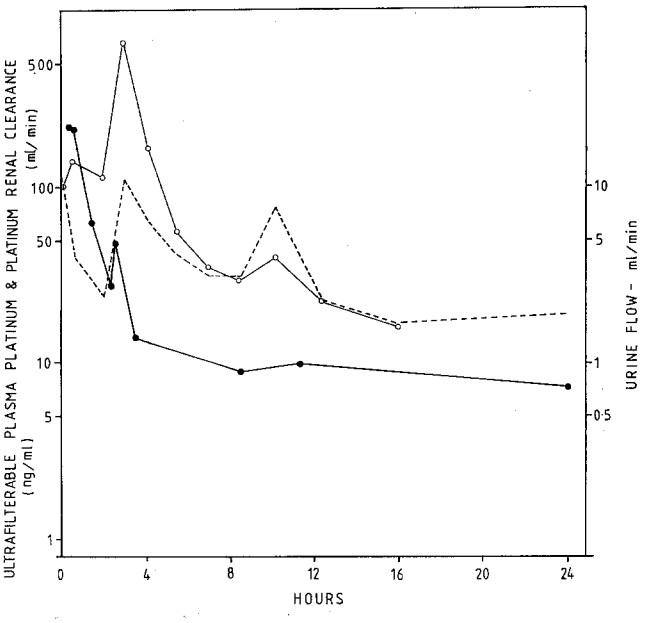

Fig. 3. Time course of ultrafilterable platinum plasma levels (●–●), renal clearance of ultrafilterable platinum (O–O), and urine flow (-----) in patient 2

ar plots was 13.3% and 10.7% of the dose administered, compared with 19.1%–29.3% in patients demonstrating nonlinear renal clearance.

Accurate estimations of total plasma clearance of ultrafilterable platinum were not possible owing to the large potential error in estimation of the area under the curve beyond 24 h after infusion. This estimate relies heavily on accurate determinations of terminal half-life, which were not possible without extended sampling probably for at least a week. It was therefore not possible to express average renal clearance as a fraction of total clearance or to directly determine metabolic clearance.

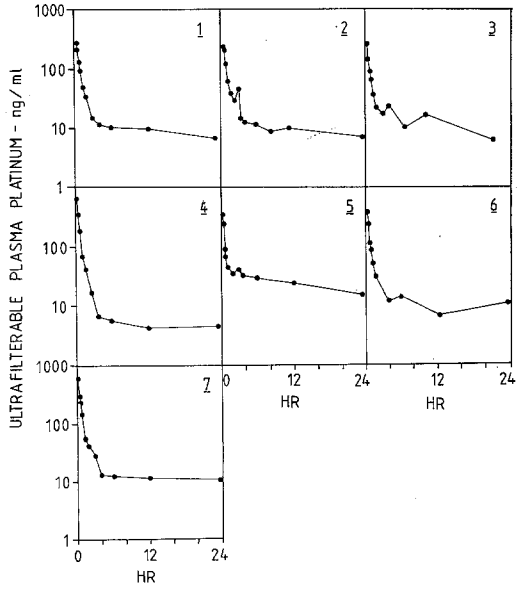

Fig. 2. Ultrafilterable platinum plasma levels in each patient following IV infusion of CDDP. Patient numbers shown on each graph correspond to those in Table 1

The half-life of ultrafilterable platinum determined from plasma data obtained up to 3 h after infusion ranged from 26.0 to 37.6 min and was in close agreement with that determined using urinary excretion data (Table 1). There were insufficient data points to justify a more complex, two-compartment description of the data during the first 3 h after the infusion. The time-courses of ultrafilterable platinum plasma levels in each patient are shown in Fig. 2. In all cases ultrafilterable platinum was still detectable in plasma 24 h after infusion. In patients 2, 3, 5, and 6 secondary rises in ultrafilterable platinum levels were observed between 2.5 and 10 h after administration. In patient 2 these fluctuations corresponded closely to fluctuations in renal clearance and urine flow (Fig. 3). Close correlations between urine flow and platinum renal clearance could not be demonstrated in the other patients. Mean urine flow in all patients immediately after completion of the infusion was 4.7 ± 2.2 ml/min and was not significantly different from that at the midpoint of the collections (3.8 ± 1.9 ml/min) or at the end of the study (3.2 ± 3.7 ml/min).

Discussion

Nonlinear renal clearance of ultrafilterable platinum was observed in five of seven patients treated with *cis*-DDP in doses of 50–140 mg/m^2. The major changes in renal clearance were observed at times during and up to 4 h after the infusion, when ultrafilterable platinum consisted primarily [2, 10, 15], and possibly entirely [13], of unchanged drug. Bannister et al. [2] have shown that *cis*-DDP may account for 55% of the total platinum level in urine up to 25.5 h after administration. It was therefore reasonable to assume that the changes observed were attributable mainly to alterations in the handling of parent drug. Eventually the availability of more sensitive and convenient assays for *cis*-DDP may allow this possibility to be examined more rigorously.

A number of reports have indicated that the renal clearance of platinum following *cis*-DDP administration involves glomerular filtration, tubular secretion [4, 5, 8, 11, 14] and possibly tubular reabsorption [5]. A mechanism was proposed in rabbits, with a suggestion that ultrafilterable platinum was secreted by the kidney's anionic transport system [4]. There have been no reports of tubular reabsorption accompanying secretion of the drug in patients. However, the observation by Le Roy et al. [9] that platinum clearance declined rapidly for 1 to 2 h immediately after infusion of 1 mg/kg *cis*-DDP to dogs suggested saturation of a reabsorption process. A change in total ultrafilterable platinum clearance through a change in the proportion of parent drug to metabolite levels was unlikely in view of recently published data [10, 15] which have demonstrated that this ratio remains constant in patients for at least 2 h after infusion. Gormley et al. [6] also found evidence of nonlinear changes in platinum renal clearance in patients given 70 mg/m^2 by 1-h infusion, although in this case total plasma platinum levels were measured. Total platinum clearance equalled creatinine clearance initially but fell to a small fraction of this within 4 h. Unfortunately, interpretation of these results was difficult, since total platinum levels declined slowly compared with ultrafilterable platinum levels. Jacobs et al. [8] found that average free platinum clearance was 156% of creatinine clearance in patients given 50–80 mg/m^2 *cis*-DDP by 24-h infusion, indicating secretion of the drug or a metabolite. In two patients given 30-min infusions of 100 mg/m^2, free platinum clearance reached a peak of 658 ml/min and then declined by 8 h to 117 ml/min. The implications of this observation were not discussed by the authors. These results all contrast with those obtained in rabbits [4], in which ultrafilterable platinum renal clearance was highest at low plasma concentrations, when saturation of tubular secretion was presumed to occur.

There was evidence of active secretion of ultrafilterable platinum in all patients in the present study, since the average renal clearance determined over the 26-h period of the study always exceeded creatinine clearance. A probable explanation for the change in renal clearance of ultrafilterable platinum with time was that active tubular reabsorption occurred in parallel with active secretion. That is, immediately after infusion, when plasma and urinary levels were high, reabsorption was saturated, resulting in high renal clearance of platinum. As the levels dropped reabsorption was no longer saturated and proportionally more tubular uptake occurred, with a consequent decline in renal clearance. Since urine flow did not drop significantly over the period 0–24 h after infusion, it could not have contributed substantially to the change in tubular reabsorption seen with time. The level at which saturation occurred appeared to vary between patients and was not necessarily dose-related. Nevertheless, patient 7, who received a dose of 140 mg/m^2, had an average renal clearance of 485 ml/min, whereas patient 2, who received 50 mg/m^2, had an average renal clearance of 100 ml/min. The ratio of cumulative area under the curves for ultrafilterable platinum in patients 7 and 2 was 1.5, as against a dose ratio of 2.8, indicating that proportionally higher plasma levels of drug were attained in the patient who had lower, linear renal clearance and no evidence of saturation of tubular reabsorption. Figure 1 shows that a similar trend was apparent in the other patients studied. The highest cumulative area under the curve was observed in patient 4, who received 120 mg/m^2 without saturation of reabsoption.

Renal clearance of ultrafilterable platinum might be expected to be urine-flow-dependent if tubular reabsorption occurs. This was apparent in patient 2, in whom increased urine flow was accompanied by increased platinum renal clearance (Fig. 3). It also appeared that the change in reabsorption of drug was reflected in the plasma level profile of ultrafilterable platinum. A secondary peak rise of approximately 50 ng/ml in ultrafilterable platinum occurred 2.5 h after infusion, followed by a much smaller rise 12 h after infusion. In this patient an approximate estimation of volume of distribution equal to 56 l was determined for ultrafilterable platinum assuming one-compartment kinetics. A rise of 50 ng/ml in plasma platinum would therefore be associated with an input into the systemic circulation of approximately 2.8 mg platinum or 5% of the dose. Similar transient rises in ultrafilterable platinum were seen in patients 3, 5, and 6. Such peaks have been observed by other workers [16] and attributed to enterohepatic recycling [3, 9, 16]. However, the present data suggest that fluctuations in tubular reabsorptions may provide an alternative explanation. That is, a rise in renal clearance through increased urine flow would be accompanied by a fall in the plasma level and vice versa. The peak renal clearance in Fig. 3 may therefore correspond to the trough in plasma levels seen 2 h after administration.

Nonlinear renal elimination kinetics associated with saturation of renal tubular reabsorption has also been reported for methotrexate [7]. In this case, renal clearance was linear at low plasma concentrations, increased as concentrations increased above 500–800 ng/ml owing to saturation of tubular reabsorption, and then fell at still higher plasma levels owing to saturation of active secretion. In the case of *cis*-DDP, saturation of active secretion has only been observed in rabbits, although at plasma concentrations comparable to those seen in patients [4].

Tubular reabsorption may contribute to prolonged plasma levels of ultrafilterable platinum. If, as appears likely, a substantial proportion of this platinum consists of unchanged drug, then an effective concentration of cytotoxic material may be maintained in the body longer than previously expected. The data also susggest that *cis*-DDP clearance may be dose and urine-flow-dependent, and that for the same dose quite different plasma levels of active drug may be obtained, depending on the extent of active renal secretion and tubular reabsorption in a particular patient. Coadministration of other anticancer drugs may also alter renal clearance, although the present study has not addressed this question. It may therefore be rational to tailor *cis*-DDP dose requirements for subsequent courses of therapy on the basis of the renal clearance determined during the first course of treatment.

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