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Evaluation of the effect of furosemide on ultrafilterable platinum kinetics in patients treated with *cis*-diamminedichloroplatinum

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Summary. It has been reported that furosemide can prevent platinum nephrotoxicity by dilution of the toxic drug in the tubule or by another unknown mechanism. To evaluate its influence on ultrafilterable platinum pharmacokinetics, we undertook a randomized prospective trial of *cis*-diamminedichloroplatinum (CDDP) (80 mg/m^2 by a 20-min infusion) administered to 20 patients with hydration-induced diuresis. Ten patients received 20 mg/m^2 furosemide 1 h before CDDP administration, and 10 patients received no diuretic drug. Plasma and urinary pharmacokinetics of platinum and creatinine were compared in both groups of patients. Plasma total and ultrafilterable platinum was always higher in the furosemide group. However, protein binding, urinary concentrations, cumulative urinary excretion, renal clearance and creatinine clearance/renal clearance ratio (fractional clearance) were not statistically different. Moreover, the fractional clearance was successively lower, equal and higher than one in both groups. These results suggest that: (1) furosemide probably causes water depletion leading to a rise in plasma concentrations; (2) its protection by a pharmacokinetic interaction is doubtful, since all other parameters (especially urinary parameters) are not significantly modified; (3) renal clearance and fractional clearance suggest a bidirectional transport of platinum in the tubule not influenced by the diuretic drug.

Introduction

Despite its significant antitumor activity, the clinical use of cisplatin is limited by its renal toxicity. Various pretreatments have been proposed to reduce this side effect [5, 18]. Among them hyperhydration and diuretics are currently combined to dilute the antimitotic agent in urinary flow [10, 15, 16]. Comparative pharmacokinetic studies of different schedules are rare [1, 6, 15]. In a previous report [7], we indicated that furosemide had no influence on β_2 microglobulin excretion measured immediately after cisplatin infusion and that the total platinum pharmacokinetics were independent of combination with the diuretic. In this paper we present a randomized study on the influence of furosemide on filterable (non-protein-bound) cisplatin pharmacokinetics.

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Materials and methods

Cisplatin (80 mg/m^2) was administered as a 20-min i.v. infusion to 20 patients randomized to two groups. The first group did not receive diuretic and the second group received furosemide (20 mg/m^2) 1 h before CDDP infusion, as in Ostrow's study [15]. Selection conditions were: performance status with WHO score $\leqslant 2$ [19], normal blood urea, creatinine and hematological values. None of the patients had received CDDP treatment previously. We excluded patients who had received other nephrotoxic agents, such as methotrexate or aminoglycosides. The therapy was associated with hyperhydration: 2000 ml 5% glucose for 6 h before the CDDP infusion and 1500 ml glucose 5% up to 4 h after. Blood samples were drawn with a venous catheter and urine samples collected simultaneously, each sample being collected in less than 1 min with patients standing upright. They were taken for platinum and creatinine analysis before the start of infusion and 10, 20, 40, 60, 75, 90, 105, 135, 165, 195, 225, 255 and 285 min after starting infusion. Blood samples, kept in ice, were immediately centrifuged and the plasma removed. An aliquot was then centrifuged on Amicon Centriflo (CF 25) filters at 4° C for 30 min. Each urine sample was collected separately, the volume determined and an aliquot stored at −20° C until analysis (< 72 h).

The level of elemental platinum was determined by flameless atomic absorption using a Hitachi Z 7000 spectrophotometer. Biological samples (diluted or not) were injected into the furnace with the following conditions: drying 60–95° C/40 s, 95–105° C/40 s, 105–120° C/20 s, thermal decomposition 120–1300° C/30 s, 1300° C/30 s and atomization 2700° C/10 s. The absorption of the atomized platinum was measured at 265.9 nm. Each determination was performed in duplicate and the precision over the range 0.05–3 mg, l^{-1} was 6%. Creatinine was determined according to the method of Jaffé with dialysis.

All computations were carried out on an Olivetti M24 desktop computer using the TRIOMPHE software designed at the Département d'Informatique Médicale of the CHUR of Dijon. The terminal portion of the plasma concentration-time curve was fitted by standard log linear regression to obtain the slope, so that the elimination half-life of ultrafilterable platinum ($t_{1/2}$) was calculated as ln2/slope. The area under the curve ($AUCo^t$) was estimated by the trapezoidal rule and extrapolated to infinity ($AUCo^\alpha$) by exponential extrapolation beyond time of the

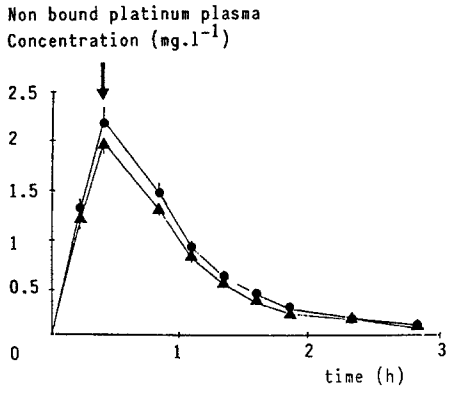

Fig. 1. Ultrafilterable platinum plasma concentration vs time in patients without (▲) and with (●) furosemide pretreatment. Each *point* represents mean ± SE of nine to ten determinations in the first group and eight to ten in the second group. The *arrow* indicates completion of the infusion

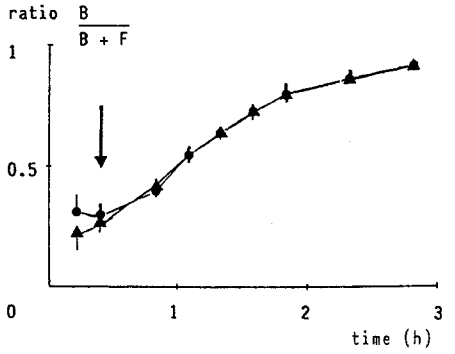

Fig. 2. B/B+F ratio vs time in patients without (▲) and with (●) furosemide pretreatment. [B, plasma bound platinum (total – ultrafilterable platinum); F, free platinum (ultrafilterable platinum). Each *point* represents mean ± SE of eight to ten determinations in each group. The *arrow* indicates completion of the infusion

last blood sample. Protein binding was estimated by the ratio B: (B+F), where B is bound platinum species (total platinum minus ultrafilterable platinum) and F is free (ultrafilterable) platinum. Renal clearance (Clr) of free platinum was calculated as the ratio of maximum cumulative urinary excretion (mg) to AUCo∞ (mg l^{-1} h^{-1}). Its fractional clearance (CL_F) was the ratio of renal clearance to creatinine clearance. All results are shown as means ± standard deviation. The two groups were compared for C_{max}, AUC, t½ and urinary flow with one-way analysis of variance; plasma concentration, ratio B: (B+F), urinary concentration, cumulative urinary excretion, renal clearance, ratio of renal clearance to creatinine clearance at time t with two-way analysis of variance; and the relationship between creatinine clearance and platinum clearance with linear one-way analysis of covariance.

Results

Plasma data

The decrease in plasma levels of ultrafilterable platinum is shown in Fig. 1. This decrease is observable from the end of infusion for up to 3 h. At this time, the plasma concentration is less than 0.05 mg l^{-1}. The curve of the second group is always above and significantly ($P < 0.001$) different from that of the other group. The difference is greatest at the end of infusion, where the C_{max} values are 2.0±0.4 and 2.2±0.4 mg l^{-1}. Areas under the concentration-time curve ($AUCo^t$) and the mean half-lives appear to be similar in both groups of patients (Table 1). Total platinum concentrations versus time are shown in Table 2. The mean concentrations in the second group are always higher than those in the first group, and there is a statistical difference ($P < 0.001$) between the two groups. All patients have a total platinum C_{max} less than 4.5 mg l^{-1}. The evolution of the ratio B: (B+F) (Fig. 2) shows no significant difference between the groups. The average ratio varies from 0.26 at 10 min to 0.91 in the last sample. Mean creatinine plasma concentrations (Table 2) are higher in group 2 ($P < 0.001$), though creatinine concentrations before furosemide administration do not differ significantly between the groups.

Urinary data

Mean values of urinary flow (Table 1) are higher in group 2. As shown in Fig. 3, the maximum urinary concentration of platinum is observed 1 h after infusion in both groups (65.9±57.3 versus 62.3±74.2 mg) and the two curves do not differ significantly. One patient in each group had a high maximum concentration: 185 mg l^{-1} (group 1) and

Table 1. Comparison of mean ± SD of area under curve (AUC_o^t), half-life (t½) of ultrafilterable platinum and urinary flow in patients without (group 1) and with (group 2) furosemide pretreatment

Group	AUC_o^t (mg l^{-1} h)	t½ (h)	Urinary flow (l h^{-1})
1	1.49±0.20	0.49±0.14	0.27±0.27
2	1.70±0.36	0.54±0.19	0.40±0.44
	NS	NS	$P < 0.001$

Table 2. Comparison of mean creatinine plasma concentrations (Crea), creatinine clearances (Crea Cl), total plasma platinum concentrations (Pt) and ultrafilterable platinum renal clearances (Cl_r) vs time in patients without furosemide (1st number) and with furosemide (2nd number)

Time (h)	Crea (mg dl^{-1})	Crea Cl (l h^{-1})	Pt (mg l^{-1})	Cl_r (l h^{-1})
[a]	0.82 : 0.86 NS	–	–	–
0	0.83 : 0.98	11.9 : 14.1	0 : 0	–
0.18	0.80 : 0.96	11.0 : 6.5	1.5 : 2	4.4 : 3.4
0.33	0.85 : 0.93	7.4 : 7.8	2.6 : 3.2	7.7 : 6.0
0.66	0.81 : 0.94	8.5 : 6.1	2.2 : 2.4	8.2 : 9.0
1.	0.81 : 0.94	8.6 : 8.4	1.7 : 1.9	9.6 : 8.3
1.25	0.79 : 0.97	9.2 : 7.0	1.4 : 1.6	10.1 : 13.7
1.5	0.84 : 0.95	8.6 : 7.9	1.2 : 1.5	10.2 : 10.0
1.75	0.79 : 0.96	8.3 : 6.9	1.0 : 1.3	10.4 : 10.1
2.25	0.80 : 0.97	9.3 : 7.1	1.0 : 1.2	11.9 : 10.6
2.75	0.81 : 0.92	6.1 : 6.4	1.0 : 1.1	12.8 : 10.9
3.25	0.80 : 0.94	5.5 : 6.4	1.0 : 1.2	–
3.75	0.78 : 0.90	7.5 : 6.1	1.0 : 1	–
4.25	0.79 : 0.94	7.3 : 6.8	1.0 : 1	–
4.75	0.76 : 0.95	6.2 : 7.9	0.9 : 1	–
	$P < 0.001$	NS	$P < 0.001$	NS

[a] Before hydration and furosemide administration

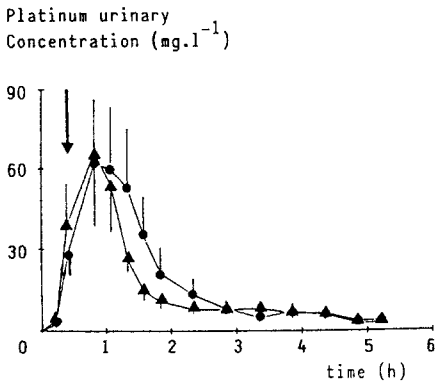

Fig. 3. Platinum urinary concentration vs time in patients without (▲) and with (●) furosemide pretreatment. Each *point* represents mean ± SE of eight to ten determinations in the first group and six to ten determinations in the second group. The *arrow* indicates completion of the infusion

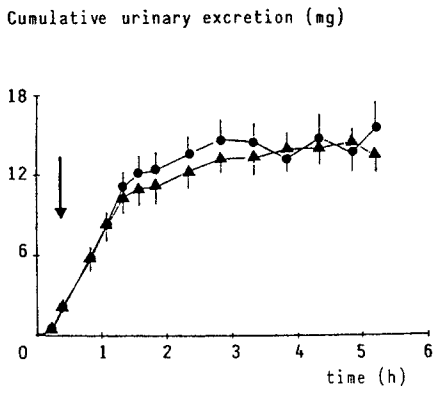

Fig. 4. Platinum cumulative urinary excretion vs time in patients without (▲) and with (●) furosemide pretreatment. Each *point* represents mean ± SE of eight to ten determinations in the first group and six to ten determinations in the second group. The *arrow* indicates completion of the infusion

245 mg l^{-1} (group 2). Cumulative urinary excretion is similar in both groups (Fig. 4). The excretion is 13.3±3.4 versus 15.4±4.8 mg at the end of the study and is only 16% of the dose. However, half the excretion measured occurs during the first hour following the start of infusion.

Clearance data

Free platinum mean renal clearances are correlated significantly with mean creatinine clearances of patients (r = 0.82 in the first group and 0.89 in the second group). The slopes of the two straight lines are identical (1.45). The time-courses of renal clearance of free platinum (Table 2) do not differ significantly between groups of patients, but the clearance rise during infusion, to become steady from 30 min after the end of infusion (from 3.9±4.9 to 11.3±5.7 l h^{-1}), while creatinine clearance (Table 2) decreases from 13.1±6.7 to 6.9±2.5 l h^{-1}. The fall essentially appears during infusion and the clearance becomes steady after the end of platinum administration (Table 2). The mean fractional renal clearance of ultrafilterable platinum species (renal clearance/creatinine clearance) versus time is shown in Fig. 5. There is no significant difference between both groups of patients. The initial fractional clearance is 0.26±0.31, and it rises to 1.54±0.70; it is 1 at

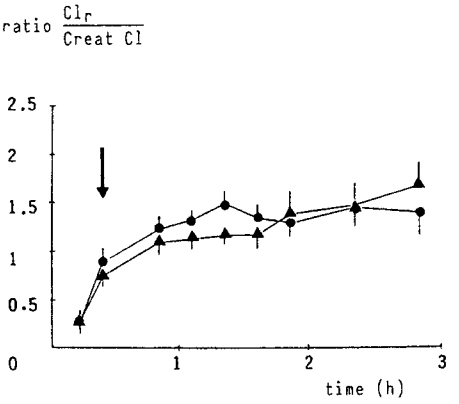

Fig. 5. Ratio of renal clearance (Clr) to creatinine clearance (Creat Cl) ratio vs time in patients without (▲) and (●) furosemide pretreatment. Each *point* represents mean ± SE of eight to ten determinations in each group. The *arrow* indicates complication of the infusion

30 min and 1 h after the start of the infusion, and subsequently the ratio is > 1.

Clinical data

Acute gastrointestinal toxicity was similar for both groups. No patient exhibited early nephrotoxicity. Delayed toxicity was observed once in the first group and four times in the second group (rise of plasma creatinine greater than 50% of their reference value). Creatinine plasma concentration was never over 2 mg dl^{-1}.

Discussion

There are few randomized studies evaluating the influence of diuretics on cisplatin administration [1, 15]. In our study, the high number of plasma and urinary samples taken immediately after infusion and the number of patients included in the protocol allow evaluation of the real influence of furosemide on ultrafilterable platinum species (which are thought to be predominant in transfers) kinetics when transports are maximal (from plasma to tissues and particularly through the kidney).

Plasma decays of ultrafilterable and total platinum are similar to those shown by other studies [1, 4, 9]. Mean half-lives of ultrafilterable platinum in both groups of patients are similar to those determined in Gullo's and Reece's studies [9, 17]. Maximal concentrations of free platinum are similar to those of Belt's study [1]. Moreover, concentrations in the diuretic group are higher than in the other group. Belt et al. [1] observed exactly the same for patients treated with mannitol. They concluded that it was probably the consequence of modification of protein binding by the diuretic. In our case, it is unlikely because similar data are obtained with total platinum plasma concentrations and with clearance plasma concentrations. The reason is probably dehydration with a decrease of extracellular volume. Nevertheless, it does not seem to be sufficient to increase the efficacy of the antimitotic agent; the area under the curve is not significantly influenced by furosemide. Despite a short infusion time, total platinum C_{max} never exceeds 6 μg ml^{-1}. If this value is predictive of renal disease [11], this may explain the absence of early nephrotoxicity. Protein binding of platinum is 25% at the beginning

of the study, becoming more than 90% 3 h later. These values confirm the findings of a previous report [15]. Furosemide has no influence on binding and, as mentionned above, its administration cannot explain the increase in the plasma concentrations of free platinum, as was suggested by Belt et al. [1] for mannitol.

The percentage of platinum excreted in the urine is low; this is in keeping with observations recorded in other studies [9, 15]. Despite an effect on urinary flow, the influence of furosemide on platinum urinary concentration is not significant, in contrast to a previous study in the rat [16].

However, the doses used in this experimental work was not comparable with those used when CDDP and furosemide are given to human patients (doses respectively $\times 4$ and $\times 20$ in the rat). No patient had a urinary concentration over 200 mg l^{-1} (which is an index of nephrotoxicity) for several hours [8, 13]. This may also explain why no patient presented acute nephrotoxicity. It seems unusual to observe such concentrations over a long time with hyperhydration.

As in previous work, we again found an important decrease in creatinine clearance during the first 5 h after the administration of cisplatin [4, 7]. This could be in accordance with an observation concluding that the drug may alter the filtration by vascular changes [14]. The study of the fractional clearance indicates that the reabsorption process is predominant during perfusion, followed by a predominant secretion process. All these data suggest a bidirectional transport of platinum, as has been described elsewhere [2, 3]. Furosemide apparently does not affect this transport. Daley-Yates et al. [3] found that furosemide has an effect on platinum clearance in the isolated rat kidney only at very high doses, when it increases the reabsorption of platinum. To observe the same phenomenon we would probably have to considerably increase the dose of the diuretic. In this case the risk of a higher tissue concentration of platinum and of nephrotoxicity would increase [3]. Ward et al. [18] observed a protective effect of furosemide in the rat with 8 mg/kg of the diuretic (our dose $\times 15$) and not with 5 mg/kg (our dose $\times 10$). We therefore remain doubtful about kidney protection by furosemide. It cannot be explained by pharmacokinetic modifications. A previous study did not show any protection against the tubular injury caused by the antimitotic agent [7]. Moreover, it could potentiate platinum toxicity, as suggested by Lehane et al. [12], by analogy with the potentiation of aminoside nephrotoxicity and otoxicity.

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