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Influence of hydration on ultrafilterable platinum kinetics and kidney function in patients treated with *cis*-diamminedichloroplatinum(II)

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Summary. It has been reported that hypertonic saline provides protection against the renal toxicity of cisplatin (CDDP). We therefore evaluated its influence on the plasma and urinary pharmacokinetics of ultrafilterable platinum and kidney function as estimated by creatinine, inulin and PAH clearance. We undertook a randomized trial including two groups of ten patients receiving 100 mg/m^2 CDDP in isotonic (group 1) or hypertonic saline (group 2) by a 20-min infusion. The hydration consisted of dextrose in group 1 and isotonic saline in group 2. Maximal concentration (C_{max}), protein binding and cumulative urinary excretion were significantly higher in the dextrose group. Urinary flow decreased in this group but not in the other one. Inulin clearance was higher in the dextrose group than in the saline group and *P*-aminohippuric acid (PAH) clearance was not significantly different in these groups of patients. Hyponatremia was observed in the dextrose group. These results suggest that hypertonic saline infusion and saline hydration may enhance the diffusion of CDDP into tissues, lowering C_{max} and renal excretion of platinum. The reduction of protein binding may indicate a diminution of aquation of CDDP in plasma. Our results suggest that the infusion of CDDP in hypertonic saline with salt hydration could exert a protective effect on the kidney. Moreover, there is a lessening of the risk of cellular hyperhydration. However, the better influence of dextrose hydration on glomerular filtration leads us to recommend a combination of the two methods of hydration for better tolerance and efficacy.

Introduction

Despite its significant antitumor activity, the clinical use of cisplatin (CDDP) is limited by its renal toxicity. In 1984 Ozols et al. [22] stated that high-dose CDDP could be given safely by using vigorous saline hydration and 3% saline as a vehicle for drug delivery. The "protective" effect of hypertonic saline was first described in a study on rats by Litterst [18]. Other investigators have also suggested an improvement in the therapeutic index of CDDP by increased urinary chloride excretion [8]. Salt should prevent cisplatin-induced nephrotoxicity by preventing renal ischaemia or by inhibiting renal uptake or transport of platinum [4]. The aim of the present study is to determine whether NaCl hydration might be expected to protect kidney function in the presence of cisplatin and whether salt hydration changes CDDP pharmacokinetics.

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Patients and methods

Cisplatin (CDDP; Cisplatyl Roger Bellon: one vial of 50 mg CDDP containing 450 mg NaCl and 500 mg mannitol) was given as a 20-min i.v. infusion containing 100 mg/m^2 drug to 20 patients randomized into 2 groups. In the first group hydration consisted of 4 l dextrose 5% with 20 mEq KCl/l per 12 h and CDDP was dissolved in 100 ml/m^2 water. In the second group hydration comprised 4 l NaCl 0.9% with 20 mEq KCl/l per 12 h and CDDP was dissolved in 100 ml/m^2 NaCl 3%. Selection conditions included a performance status with a WHO score of <2 [26] and normal blood urea, creatinine and hematological values. No patient had previously received CDDP therapy. Patients were excluded who had received other potentially nephrotoxic agents such as methotrexate or aminoglycosides.

At 45 min before CDDP administration, we started a rapid infusion of inulin (30 mg kg^{-1}) and *P*-aminohippuric acid (PAH) (10 mg kg^{-1}) in 120 ml dextrose 5% given over 10 min, followed by a slow infusion of inulin (80 mg kg^{-1}) and PAH (20 mg kg^{-1}) in 240 ml dextrose 5% given up to 4 h thereafter. Blood samples were drawn with a venous catheter; urine samples were collected simultaneously, each sample being collected in <1 min with patients standing upright. They were taken before the start of CDDP infusion and 10, 20, 40, 60, 75, 90, 105, 135, 165, 195, 225 and 255 min after the start of the infusion. Blood samples, kept in ice, were immediately centrifuged and the plasma was removed. An aliquot was then centrifuged on Amicon Centriflo (CF 25) filters at 4°C for 30 min. Each urine sample was collected separately and the volume was determined and an aliquot, stored at −20°C until analysis (<72 h)

Each sample was analysed for platinum, creatinine, inulin, PAH, Na, Cl and protein values. The level of elemental platinum was determined by flameless atomic absorption [7]. Creatinine, Na, Cl and pro-

Table 1. Comparison of means ± SD of the AUC_0^∞, half-life ($t_{1/2}$) and maximal urinary concentrations (U_{max}) of ultrafilterable platinum, plasma creatinine concentrations before (BH) and during hydration (DH) and creatinine clearance in patients receiving dextrose (group 1) and salt hydration (group 2)

Group	AUC_0^∞ (mg l^{-1} h)	$t_{1/2}$ (h)	U_{max} (mg l^{-1})	Creatinine (mg l^{-1})		Creatinine clearance (l h^{-1})
				BH	DH	
1	1.51 ± 0.44	0.48 ± 0.12	49.86 ± 23.12	8.5 ± 1.9	7.4 ± 1.7	8.69 ± 4.84
2	1.52 ± 0.32	0.55 ± 0.17	49.19 ± 24.10	8.5 ± 0.9	7.9 ± 0.8	8.04 ± 3.92
	NS	NS	NS	NS	$P < 0.01$	NS

NS, not significant

Table 2. Comparison of means ± SD of sodium (Na), chlorine (Cl) and protein (Pt) plasma concentrations before (BH) and during hydration (DH) and urinary concentrations of sodium (Na_u) and chlorine (Cl_u) during hydration, respectively, in patients receiving dextrose (group 1) and salt hydration (group 2)

Group	Na (mmol l^{-1})		Cl (mmol l^{-1})		Pt (g l^{-1})		Na_u (mmol l^{-1})	Cl_u (mmol l^{-1})
	BH	DH	BH	DH	BH	DH	DH	DH
1	139 ± 5	130 ± 6	100 ± 5	97 ± 6	73 ± 9	65 ± 7	37 ± 31	53 ± 45
2	138 ± 3	138 ± 3	100 ± 5	105 ± 3	68 ± 9	59 ± 1	133 ± 55	138 ± 58
	NS	$P < 0.001$	NS	$P < 0.001$	NS	$P < 0.001$	$P < 0.001$	$P < 0.001$

NS, not significat

teins were analysed with an SMA 2 (Technicon). Inulin and PAH were determined according to the method of Heyrouski [14] and Hamburger et al. [12].

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). Pharmacokinetic parameters of ultrafilterable platinum such as elimination half-life ($t_{1/2}$), area under the curve (AUC_0^t) and that extrapolated to infinity (AUC_0^∞) were calculated as previously described [7]. Protein binding was estimated by the ratio B/(B+F), where B represents bound platinum species (total plasma platinum minus ultrafilterable plasma platinum) and F represents free (ultrafilterable) platinum. Renal clearance of ultrafilterable platinum, creatinine, inulin or PAH was calculated for each interval (t,t') according to the formula:

$$Cl_r = \frac{\Delta u}{\int_t^{t'} cdh},$$

where c represents the platinum, creatinine, inulin or PAH plasma concentration at time t and u indicates the amount excreted in urine from t to t' (h standing for any time between t and t'). The fractional clearance of free platinum (Cl_F) is the ratio of renal clearance to inulin clearance. Glomerular filtration was estimated by inulin clearance and renal plasma flow, by PAH clearance. All results are shown as means ± standard deviation.

The two groups were compared for C_{max}, AUC and $t_{1/2}$ by one-way analysis of variance and for plasma concentration, ratio B/(B+F), urinary concentration, cumulative urinary excretion, clearances and fractional clearances at time t by two-way analysis of variance.

Results

Plasma data

The study of the decrease in plasma levels of filterable platinum exhibited no statistical difference between the groups from (1.98 ± 0.59 mg l^{-1} at the end of the infusion to 0.11 ± 0.06 mg l^{-1} in the first group and from 1.60 ± 0.51 to 0.13 ± 0.05 mg l^{-1} in the second group). The analysis of C_{max} independently of the curves showed a significantly higher value for the group 1 ($P < 0.05$). AUCs and $t_{1/2}$ appeared to be similar in both groups (Table 1). The plasma total platinum levels were significantly higher in the dextrose group (from 3.09 ± 0.77 mg l^{-1} at the end of the infusion to 0.85 ± 0.23 mg l^{-1} 255 min later in the group 1 and from 2.2 ± 0.45 to 0.78 ± 0.20 mg l^{-1} in group 2; $P < 0.05$). All patients had a total platinum C_{max} of <4.5 mg l^{-1}.

The evolution of the ratio B/(B+F) (Fig. 1) exhibited a significantly higher ratio in the first group of patients. Despite similar values before hydration, sodium, chlorine and creatinine plasma concentrations were higher in group 2 and protein plasma concentrations were significantly higher in the group 1 (Tables 1, 2). Sodium plasma concentrations were under the normal range (135–145 mmol l^{-1}) in group 1.

Urinary data

Urinary flow (Fig. 2) showed no significant difference between the two groups, but it decreased from 0.42 ± 0.19 (at the beginning of the infusion) to 0.10 ± 0.08 l h^{-1} 4.5 h later in patients who received dextrose hyperhydration ($P < 0.05$). In those receiving saline hyperhydration, urinary flow remained uniform: from 0.36 ± 0.12 to 0.33 ± 0.23 l h^{-1} at the same times.

The maximal urinary platinum concentration (Table 1) was observed 20 min after the end of the infusion. There was no significant difference between the two groups of patients. No patient had a urinary concentration higher than 200 mg l^{-1}. The study of the cumulative urinary excretion

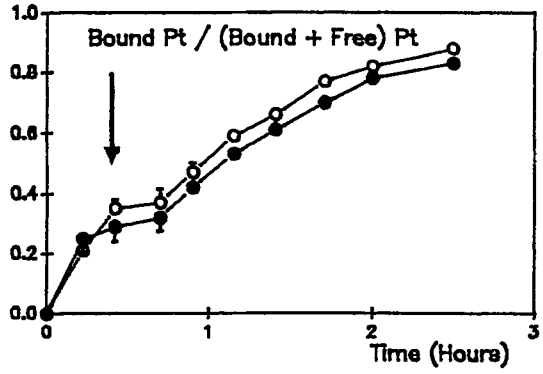

Fig. 1. B/B+F ratio vs time in patients receiving dextrose (O) or saline (●) hydration. Each point represents the mean ± SE of 9–10 determinations in each group. The *arrow* indicates completion of the infusion

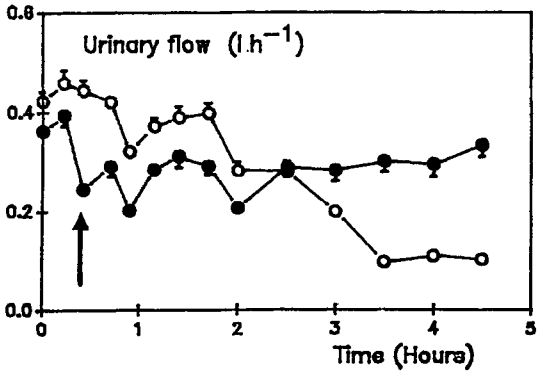

Fig. 2. Urinary flow vs time in patients receiving dextrose (O) or saline (●) hydration. Each point represents the mean ± SE of 7–10 determinations in both groups. The *arrow* indicates completion of the infusion

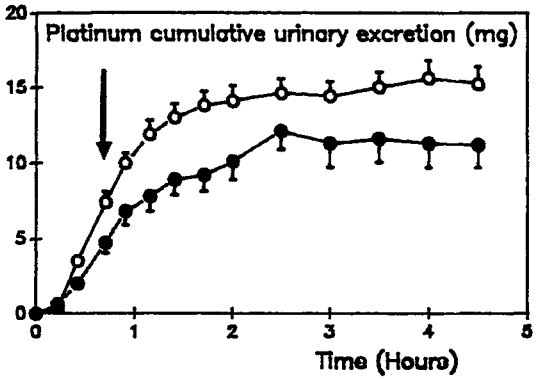

Fig. 3. Cumulative urinary platinum excretion in patients receiving dextrose (O) or saline (●) hydration. Each point represents the mean ± SE of 7–10 determinations in each group. The *arrow* indicates completion of the infusion

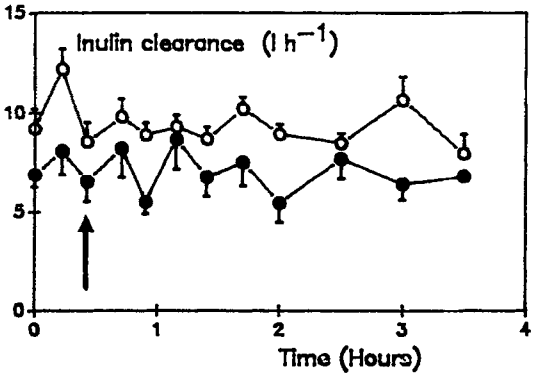

Fig. 4. Inulin clearance vs time in patients receiving dextrose (O) or saline (●) hydration. Each point represents the mean ± SE of 7–10 determinations in each group. The *arrow* indicates completion of CDDP infusion

of platinum (Fig. 3) exhibited a significant difference between the groups (P <0.001), with platinum excretion being higher in the first group. The urinary excretion of sodium and chlorine was statistically higher in the group receiving saline hyperhydration (Table 2).

Clearance data

The time courses of the renal clearance of free platinum showed no significant difference between the two groups of patients. The clearance was 4.46 ± 2.74 vs 6.04 ± 4.47 l h^{-1} during infusion and rose to become steady 50 min after the infusion (8.92 ± 2.07 l h^{-1} in group 1 vs 10.39 ± 6.28 l h^{-1} in group 2). In group 1, creatinine clearance was higher but not significantly different from that in the second group (Table 1).

Despite the lack of a significant difference in urinary and plasma inulin concentrations, inulin clearance was always higher in group 1 (Fig. 4), even before platinum infusion (9.23 ± 3.47 l h^{-1} vs 6.89 ± 1.99 l h^{-1}). Although PAH clearance showed no statistical difference between the two groups of patients, a constant albeit non-significant decrease in PAH clearance could be seen in the first group of patients (from 31.39 ± 12.69 to 20.91 ± 6.17 l h^{-1}) but not in the second (28.86 ± 12.53 and 27.28 ± 17.70 l h^{-1}).

The mean fractional clearance of ultrafilterable platinum (renal clearance over inulin clearance ratio) vs time showed no significant difference between the two groups of patients. The mean initial fraction was 0.57 ± 0.32 and it rose to 1.29 ± 0.52.

Clinical data

Acute gastrointestinal toxicity was the same in both groups. The volume of vomiting was 138.5 ± 114 and 150 ± 197 ml in the first and second groups, respectively. No patient exhibited acute nephrotoxicity. Delayed toxicity was observed in two patients in each group (plasma creatinine increase of >50% of the reference value).

Discussion

To our knowledge no randomized study has evaluated the simultaneous effect of hydration on free platinum kinetics, electrolyte equilibrium and kidney function. A high number of plasma and urinary samples enables a good evaluation of these parameters when platinum transport is maximal.

In the present study, the plasma kinetics of total and ultrafilterable platinum were similar to those obtained in other studies [1, 6, 7, 11]; $t_{1/2}$ values were similar to those for unchanged cisplatin obtained by Reece et al. [23]. Our results can be compared with those from an animal study by Litterst [18], who had given CDDP in water or salt to rats. As with our data, total platinum concentrations were lower in the salt-loaded group. But Litterst did not observe any change in free platinum concentrations, and he concluded that protein binding was lower in the NaCl group. We could have reached the same conclusions as of 45 min after the start of the infusion since total platinum concentrations were lower, free platinum concentrations were higher and protein binding was lower in the salt-loaded group. However, this finding did not seem to be verified during the time of infusion: total and free platinum were lower in the NaCl group and protein binding was similar in both groups. Therefore, NaCl may have increased platinum diffusion into tissues.

This may have been the consequence of a diminution of the aquation of CDDP in the infusion flask, as has been suggested by Greene et al. [10] for the stability of CDDP in aqueous solution. The diffusion of CDDP in saline solution may be higher than that of the aquated form, as is the affinity for proteins. This could have been responsible for an increase in efficacy and toxicity (if they are dependent on C_{max} and not on AUC, which were similar in both groups). On the other hand, the higher plasma chlorine and lower plasma protein concentrations observed in the second group favour a diminution of aquated compound formation and protein binding; the latter process has been demonstrated by Nanji et al. [19]. Nevertheless, patients in both groups had total plasma platinum concentrations of $<6\ \mu g\ l^{-1}$, which may be considered to be an index of toxicity [15].

Results of urinary platinum excretion indicate that there is probably also an effect of the nature of infusion on urinary kinetics. Tubular transport in the kidney was probably similar in both groups since fractional clearances were not different. Moreover, the invariability of PAH clearance in the salt-loaded group attests to the lack of competition with anion system transport with this infusion [24]. The higher platinum excretion observed in the dextrose group may have been the consequence of higher plasma concentrations observed during the infusion, with a higher glomerular filtration rate of this compound.

In contrast, Earhart et al. [8] showed an increase in intact CDDP excretion in the salt-treated rat (199 vs 130 μg in chlorine-deprived rats), with a decrease in other species. In the study by Kirshbaum et al. [16], salt loading was responsible for a more significant increase in the urinary excretion of mercury (4.3-fold that of controls). On the other hand, Daley-Yates et al. [4] did not observe any change in the urinary excretion of CDDP in the salt-loaded rat, despite an improvement in the tolerance. If we consider urinary platinum concentrations to be an index of toxicity [17], salt loading produced no improvement in our study, unless the ratio of intact CDDP to the aquated form was not similar in both groups, as suggested by Earhart et al. [8].

The study of urinary concentrations of electrolytes exhibited of course, a great difference between the two groups of patients, since the chlorine level was 2.5 times higher in the salt-loaded group. However, it was 3.4 times lower than that in the study by Earhart et al. [8] and 2.5 times lower than that obtained by Daley-Yates and McBrien [4] in the salt-loaded rat. In contrast, it was similar to the concentration previously determined in patients receiving the same hydration [3, 9]. If we study the ratio of the urinary concentration of chlorine to the concentration of platinum, it is higher in man, whose drug excretion is much lower. It is therefore possible to obtain a decrease in aquated products in salt-loaded urine, as previously suggested [22].

In the present study, CDDP infusion was not responsible for proximate alterations in glomerular function as attested by a decrease in inulin clearance. On the other hand, the study of PAH clearance demonstrated a propensity to decrease in the dextrose group. Other studies have shown various results on the proximate influence of CDDP on glomerular filtration and hemodynamics: a reduction in renal blood flow is observed 72 h after the administration of 5 mg/kg CDDP in the rat [25] and during and after the infusion of 20 mg/m^2 CDDP in man [20]. However, the results of the latter study were observed with saline hydration. Daugaard et al. [5] did not find any change in kidney function after the administration of 5 mg/kg CDDP in the dog. Heidemann et al. [13] observed a better influence of salt hydration displayed by the suppression of a creatinine elevation 5 days after a dose of 5 mg/kg CDDP in the rat.

Another alteration that we could attribute to platinum infusion was a progressive decrease in urinary flow in the dextrose group. However, this may also have been due to progressive cellular hyperhydration with extracellular dehydration, since dextrose and water without ions penetrate very quickly into the cells. This risk is evidenced by the sodium plasma concentration's being under the normal range in the dextrose group, with protein plasma concentrations being higher than in the salt group.

We also observed a significantly higher inulin clearance, with significantly lower creatinine plasma concentrations and a non-significantly higher creatinine clearance, in the dextrose-loaded group. These results are surprising, since one of the objectives of saline infusion is to protect renal hemodynamics by the suppression of the renin-angiotensin system [2, 4]. It seems to be the case in this study, since we observed a propensity to a decrease in plasma renal flow in the dextrose group but not in salt-loaded patients. On the other hand, the higher inulin clearance observed with dextrose infusion cannot be explained by osmotic diuresis, since urinary flow showed no significant difference between the two groups of patients.

In conclusion, we can say that the decreases in C_{max} and renal excretion of CDDP in the salt hydration group may have been the consequence of a better diffusion of CDDP into tissues. The lower protein binding evokes a probable diminution of the aquation of CDDP in plasma. Moreover, salt infusion avoids the risk of cellular hyperhydration and the propensity to a decrease in urinary flow and renal plasma flow. On the other hand, dextrose-induced diuresis is responsible for a higher glomerular filtration. These results favour a combination of these two methods of hydration for better tolerance and efficacy; for example,

dissolution of CDDP in 3% NaCl and hydration with dextrose supplemented by KCl and 4.5 g/l NaCl [1, 21].

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