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Acute effects of *cis*-diamminedichloroplatinum (CDDP) on renal function

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Summary. *Ten previously untreated patients with metastatic non-seminomatous testicular carcinoma received cis-diamminedichloroplatinum (CDDP). Renal function studies were performed before and following the first CDDP infusion. A decrease in effective renal plasma flow (ERPF) and an increase in filtration fraction (FF) was found in all patients. These findings suggest primary changes in renal hemodynamics during CDDP infusion.*

Introduction

cis-Diamminedichloroplatinum (CDDP or *cis*-platinum) is an antineoplastic drug applied particularly in the treatment of testicular and ovarian malignancy [4, 14]. It is also used, as a single agent or in combination with other cytostatic drugs, in the treatment of head and neck cancer, bladder cancer, cervical and prostate cancer, and lung cancer [10, 13]. The major dose-limiting toxicity of CDDP is its effect on the kidney. This toxicity is thought to be mediated by effects of CDDP on renal perfusion, tubular function, or both.

Recently, we described the effect of CDDP on renal function in patients treated for disseminated testicular carcinoma [8, 9]. We found a reduction in glomerular filtration rate (GFR) and effective renal plasma flow (ERPF). On the basis of the changes in ERPF and filtration fraction (FF), we postulated a hemodynamically induced nephrotoxic effect of CDDP.

In the patients treated subsequent to these reports we determined the immediate, short-term effects of *cis*-platinum infusion on GFR and ERPF.

Patients and methods

Ten previously untreated patients with histologically proven disseminated nonseminomatous testicular carcinoma were studied. Their ages ranged from 21 to 48 (mean 31 years). Patients were all treated with *cis*-platinum, vinblastine, and bleomycin according the Einhorn regimen [4]. All patients were normotensive. Renal function was studied before, during, and after the administration of *cis*-platinum on the first day of therapy, before other chemotherapeutic agents were given. To ensure a steady state of hydration during the whole study period, all patients were hydrated IV with 0.9% saline 333 ml each hour. This hydration scheme started 12 h before renal function studies were performed. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured twice over a period of 2 h. *cis*-Platinum was infused in a dose of 20 mg/m^2 over a period of 4 h, from 12 a.m. till 4 p.m. After the end of *cis*-platinum infusion hydration was maintained as stated before. GFR and ERPF also were measured frequently during and after CDDP infusion, urine collection periods being 2, 1, 1, 1, and 2 h.

GFR and ERPF were measured simultaneously, with the patients in the supine position, by means of radioisotopes. ERPF was determined by measuring the clearance of ^{131}I-hippuran (I × V/P) and GFR by measuring the clearance of ^{125}I-iothalmate (U × V/P). (I, counts per minute of 1 ml sustaining solution; V, infusion or urine volume in milliliters per minute; P, counts per minute in 1 ml plasma; U, counts per minute in 1 ml urine.) Errors in GFR caused by incomplete collection of urine were corrected according to a method previously described [2]. The filtration fraction (FF) was calculated as the quotient of GFR and ERPF (FF = GFR/ERPF).

Results

The pretreatment values of ERPF, GFR, and FF of all patients are listed in Table 1. Values are not corrected for body surface area. Also shown are the nadir values of ERPF, and the

Table 1. Acute effects of *cis*-platinum on renal function

Patient no.	ERPF (ml/min)		GFR (ml/min)		FF	
1	748[a]	565 (5)[b]	139[a]	133[c]	0.19[a]	0.24[c]
2	365	330 (5)	102	100	0.27	0.30
3	888	786 (1)	224	203	0.25	0.26
4	793	727 (3)	170	185	0.21	0.25
5	829	663 (3)	152	136	0.18	0.21
6	511	416 (4)	123	107	0.24	0.26
7	983	732 (5)	185	196	0.19	0.27
8	937	790 (3)	190	178	0.20	0.23
9	705	682 (4)	182	194	0.26	0.28
10	688	604 (5)	128	128	0.19	0.21
Mean	744	629	159	156	0.22	0.25

[a] Values before CDDP infusion
[b] Nadir values of effective renal plasma flow during CDDP infusion. Figures in parentheses give hours from start of CDDP infusion to nadir values
[c] Values of glomerular filtration rate and filtration fraction at the time of the nadir values of ERPF

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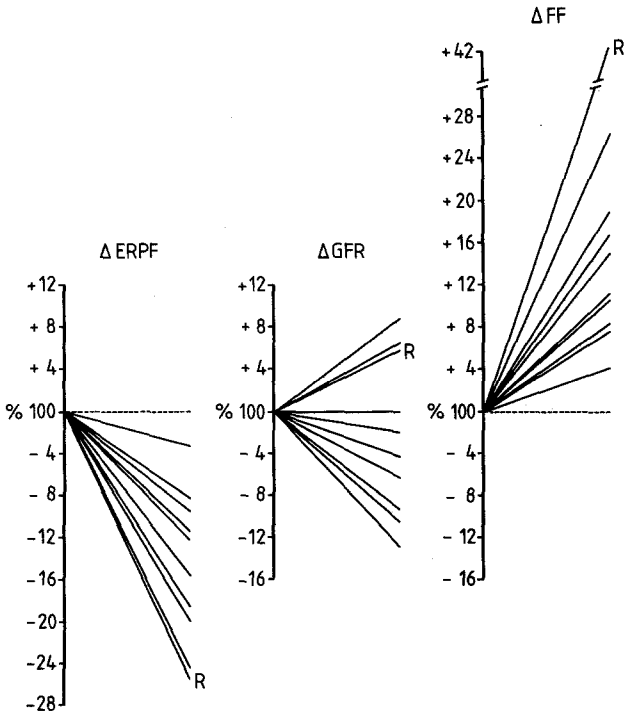

Fig. 1. Percentage change in effective renal plasma flow (ERPF), glomerular filtration rate (GFR) and filtration fraction (FF) in 10 patients during or within 3 h after CDDP infusion. R = patient in Fig. 2

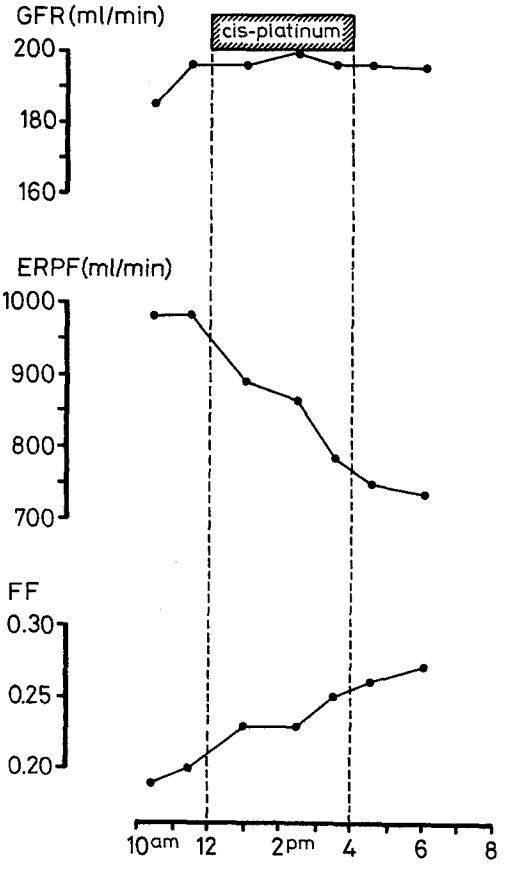

Fig. 2. Glomerular filtration rate (GFR), effective renal plasma flow (ERPF), and filtration fraction (FF) in a patient during and after CDDP infusion

corresponding values of GFR and FF. In all patients there was a decrease in ERPF during or within 3 h after CDDP infusion. The decrease varied from 3.3% to 25.5% (mean 15.5%) compared with the pretreatment values (Fig. 1). At the moment when ERPF values were at the nadir, GFR estimations varied between an increase of 8.8% and a decrease of 13% (mean decrease 1.7%). The corresponding filtration fraction was increased in all patients, the increase varying from 4.0% to 42.1% (mean 13.6%). This implies that the decrease in ERPF was always more pronounced than the change (decrease or increase) in GFR. Blood pressure remained constant in all patients.

The decrease in ERPF started in the first 2 of the 4 h of CDDP infusion. In one patient the nadir ERPF was reached within these 2 h. In all other patients the nadir ERPF was reached later.

Comparing the moment of decrease in ERPF and a change in GFR, we observed an ERPF decrease initially, and afterwards a change in GFR. In two patients a simultaneous decrease in ERPF and GFR was found, but in these patients the FF also increased, implying that ERPF decreased more than the GFR.

Figure 2 shows the changes in ERPF, GFR, and FF in one of the patients during and after *cis*-platinum infusion.

Discussion

This study has shown that the first change induced during *cis*-platinum infusion was a fall in effective renal plasma flow, which occurred prior to any change in GFR. This observation means that CDDP infusion increases renal vascular resistance. It suggests that CDDP has hemodynamic effects in the kidney, occurring during the first administration of CDDP. Afterwards secondary changes in glomerular and/or tubular function can develop [8, 9]. Winston et al. [15] in studies on CDDP nephrotoxicity in rats, also concluded that the initial fall observed in GFR was caused by renal vasoconstriction, a reduced renal perfusion, and a reduced glomerular hydrostatic pressure. The vascular changes occurred without evidence of tubular obstruction. Furthermore, in experimental studies on intoxication with various heavy metals, a fall in renal blood flow was noticed before other nephrotoxic manifestations were observed [1, 5, 11].

The occurrence of vascular changes during CDDP therapy was further suggested by Vogelzang et al. [12], who observed Raynaud's phenomenon after combination chemotherapy with CDDP for testicular cancer. Edwards et al. [3] described an association between long-term treatment with CDDP and severe coronary artery disease. Kletzel et al. [7] reported systemic hypertension during intra-arterial infusion of CDDP. Finally, Harrell et al. [6] have described a patient with systemic hypertension after treatment with CDDP-containing therapy.

The finding of vascular effects of CDDP may have practical consequences, as vasoactive pharmacological agents might be able to prevent the initial changes in ERPF and possibly to guard against long-term effects of CDDP on renal function.

In conclusion, we have found early changes in renal function during treatment with *cis*-platinum, consisting of a decrease in effective renal plasma flow and an increase in filtration fraction, which suggest primary changes in renal hemodynamics. It might be that these changes play a role in CDDP-induced nephrotoxicity.

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