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# Nephrotoxicity of cis-Diamminedichloride Platinum (CDDP) During Remission-induction and Maintenance Chemotherapy of Testicular Carcinoma

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***Summary.*** *We studied renal function in nine patients with disseminated testicular carcinoma before and after remission-induction and maintenance therapy with a drug combination containing cis-platinum. The median glomerular filtration rate (GFR) decreased during remission-induction therapy from 146 to 118 ml/min. No effect of cumulative toxicity on the median GFR was found during maintenance therapy, nor did the median GFR improve. The median effective renal plasma flow (ERPF) decreased during the total period from 705 to 514 ml/min. No significant changes in median filtration fraction (FF) and serum creatinine were observed. It is suggested that intrarenal hemodynamic effects are important in the nephrotoxicity of cis-diamminedichloride platinum (CDDP).*

## Introduction

The heavy metal derivative *cis*-diamminedichloride platinum (CDDP) is a new anticancer agent with an established role in the treatment of various tumor types, including testicular carcinoma [6, 9]. Among the toxic effects renal toxicity is the dose-limiting factor. Characteristically CDDP toxicity manifests itself in a rise of BUN or serum creatinine concentration. Histopathologically focal tubular necrosis has been found, but no signs of glomerular pathology. No consistent tubular dysfunction has been described [3, 4, 8, 11, 12, 14].

However, in some studies serum creatinine concentration was reported to remain normal, while a transient fall in the glomerular filtration rate (GFR) measured as $^{125}$I-iothalamate clearance was observed [14]. Uncertainty also persists concerning cumulative toxicity when CDDP is administered for a prolonged period. We performed a prospective study of the renal function of nine patients treated with combination therapy including CDDP for disseminated testicular carcinoma during remission-induction and maintenance therapy.

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## Patients and Methods

Nine previously untreated men, ranging in age from 20–39 years (mean 27) and with biopsy-documented disseminated nonseminomatous testicular carcinoma, were studied. Remission-induction therapy consisted of four cycles of 21 days of the combination CDDP, bleomycin and vinblastine [6]. After prehydration with 1 l saline, CDDP 20 mg/m$^2$ in 300 ml 15% mannitol was infused over 2 h on each of 5 consecutive days. Diuresis was maintained with 4 l saline/24 h. On days 1 and 2 of each cycle vinblastine 0.2 mg/kg daily was given. On day 2 and also at weekly intervals thereafter for 12 weeks bleomycin 30 mg was given in a 15-min infusion. After successful remission-induction all patients received maintenance chemotherapy. This consisted of vinblastine alternating with vinblastine plus CDDP 50mg/m$^2$ at 3-week intervals for 1 year. This maintenance therapy started 6 weeks after the completion of remission-induction therapy [15]. For maintenance treatment patients were admitted to hospital for 1 day every 6 weeks for the CDDP-vinblastine combination. No other nephrotoxic drugs were administered. Before induction therapy all patients received an A-V fistula to ascertain blood access. Obstruction of the urinary tract was excluded by intravenous urography and repetitive isotope studies. All patients were normotensive. All patients were studied before the start of the remission-induction therapy (A); 6 weeks after the last cycle of remission-induction therapy (B); and 1 year later, at the end of maintenance therapy (C). At times A, B, and C, blood samples were collected for estimation of creatinine and albumin. Glomerular filtration rate (GFR), effective renal plasma flow (ERPF), and body weight were also determined. Serum creatinine and albumin were measured by standard automatic analysis. GFR and ERPF were determined simultaneously with the patient supine, with $^{125}$I-sodium-iothalamate and $^{131}$I-hippuran, respectively, as described previously [5]. These values were not

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**Table 1.** Absolute and median values[a] in nine patients

| Patient number | GFR (ml/min) | | | ERPF (ml/min) | | | FF | | | Serum albumin (g/l) | | | Body weight (kg) | | | Serum creatinine (μmol/l) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | A | B | C | A | B | C | A | B | C | A | B | C | A | B | C |
| 1 | 111 | 88 | 79 | 420 | 451 | 412 | 0.26 | 0.20 | 0.19 | 42 | 43 | 41 | 66 | 64 | 63 | 107 | 101 | 92 |
| 2 | 135 | 85 | 104 | 607 | 495 | 477 | 0.22 | 0.17 | 0.21 | 39 | 35 | 42 | 67 | 62 | 79 | 79 | 91 | 85 |
| 3 | 157 | 141 | 141 | 732 | 638 | 607 | 0.21 | 0.22 | 0.23 | 40 | 43 | 46 | 78 | 74 | 75 | 85 | 88 | 75 |
| 4 | 158 | 118 | 122 | 895 | 521 | 531 | 0.17 | 0.22 | 0.22 | 42 | 40 | 47 | 61 | 65 | 67 | 65 | 78 | 78 |
| 5 | 146 | 147 | 162 | 690 | 728 | 752 | 0.21 | 0.20 | 0.22 | 38 | 44 | 45 | 78 | 73 | 84 | 76 | 71 | 62 |
| 6 | 153 | 118 | 108 | 764 | 596 | 447 | 0.19 | 0.19 | 0.24 | 42 | 38 | 49 | 77 | 69 | 74 | 75 | 87 | 82 |
| 7 | 135 | 128 | 97 | 767 | 592 | 514 | 0.17 | 0.21 | 0.18 | 40 | 37 | 48 | 62 | 60 | 64 | 76 | 77 | 78 |
| 8 | 126 | 101 | 97 | 586 | 440 | 411 | 0.21 | 0.22 | 0.23 | 34 | 43 | 45 | 81 | 73 | 75 | 111 | 90 | 98 |
| 9 | 161 | 160 | 135 | 705 | 806 | 645 | 0.22 | 0.19 | 0.21 | 42 | 41 | 46 | 90 | 79 | 100 | 77 | 60 | 87 |
| Median | 146 | 118 | 108 | 705 | 592 | 514 | 0.21 | 0.20 | 0.22 | 40 | 41 | 46 | 77 | 69 | 75 | 77 | 87 | 82 |

[a] A, before start of remission-induction therapy; B, 6 weeks after remission-induction therapy; C, at end of maintenance therapy

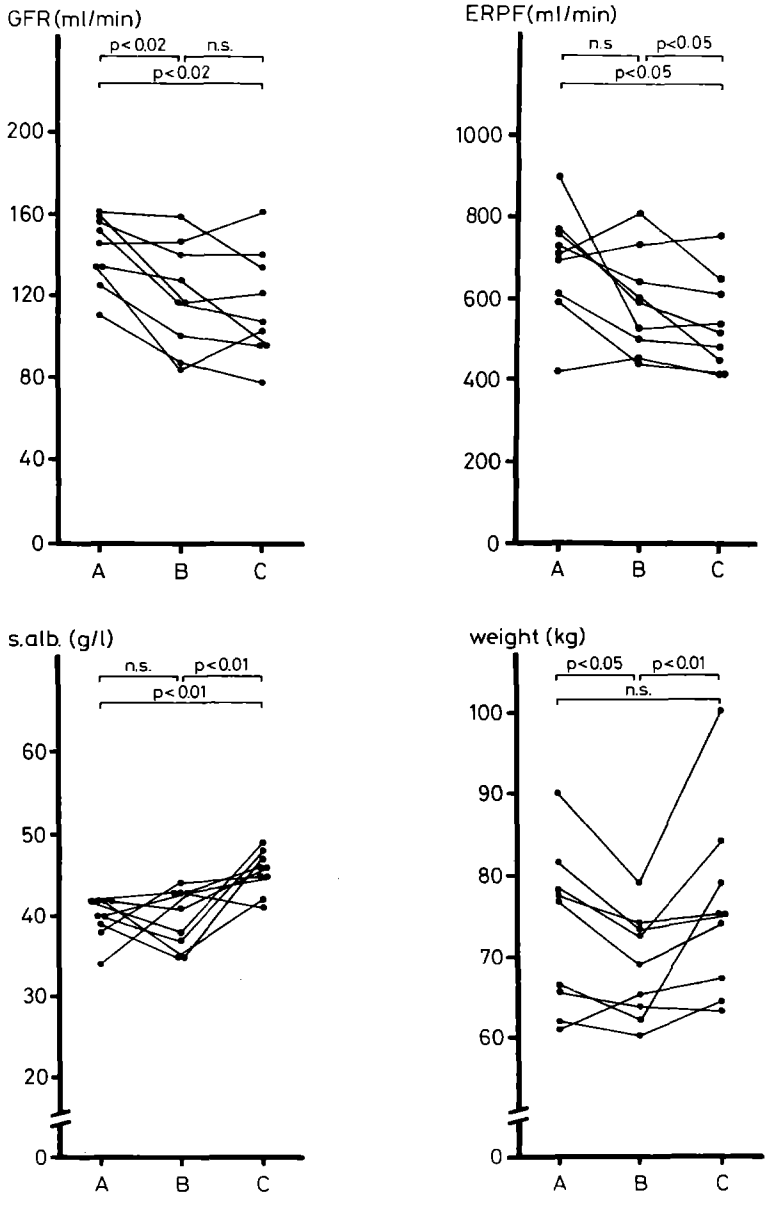


**Fig. 1.** Median change in absolute values of glomerular filtration rate (GFR), effective renal plasma flow (ERPF), serum albumin (S alb) and body weight before the start of remission-induction therapy (A), 6 weeks after remission-induction therapy (B), and at the end of maintenance therapy (C)

corrected for standard body surface area. The filtration fraction (FF) was calculated as the quotient of GFR and ERPF; it has been established that the single nephron filtration fraction is dependent on blood flow, glomerular hydraulic pressure, and renal vascular resistance in the rat [2].

*Statistical Analysis.* Changes within a group were evaluated with Wilcoxon's test for paired observations (two-sided). Spearman's rank correlation coefficients were calculated for expression of correlations.

## Results

Absolute and median values of GFR, ERPF, and FF at times A, B, and C are given in Table 1. Also noted are serum albumin level, body weight, and serum creatinine concentration with median values.

As seen in Table 1 and Fig. 1 a substantial fall of 20% in the median GFR is found ($P < 0.02$) in the first period from A to B, whereas in the second period from B to C no significant reduction in median GFR was observed. An increase in GFR was observed in patients 2, 4, and 5, however. A significant fall ($P < 0.02$) was also found during the total period from A to C.

With regard to the ERPF a fall was noted in six of the nine patients in period A to B and in seven of the nine patients in period B to C. During the second period the fall in median ERPF was statistically significant ($P < 0.05$), and the same was true for the fall over the total period from A to C ($P < 0.05$). The increase in median serum albumin concentration was only significant from B to C ($P < 0.01$) and from A to C ($P < 0.01$). A marked fall in body weight from A to B was observed in all patients except one. From B to C recovery was found in eight patients. Changes in median body weight in periods A to B and B to C were significant ($P < 0.05$ and $P < 0.01$, respectively). No statistically significant change in weight was found from A to C.

The median FF and median serum creatinine concentration did not change significantly from A to B or from B to C.

The relative change in ERPF from A to C was inversely related ($r = -0.69$, $P < 0.05$) with the absolute change in FF from A to C, as shown in Fig. 2a. A negative relationship was also found between the initial FF and the change in FF from A to C ($r = -0.81$, $P < 0.01$), as is illustrated in Fig. 2b.

## Discussion

During remission-induction therapy with a platinum-containing regimen a fall in GFR was noticed in six of nine patients. Deterioration of the renal function occurred despite hyperhydration. The same amount of CDDP given during the maintenance phase did not result in a significant further reduction of GFR. Although the body recovers during this period from the insult of both tumor and its eradication as far as weight and albumin are concerned, no recovery of GFR is present. It is important to notice that no change in serum creatinine concentration was found during this observation period. During the initial period production and elimination of creatinine, especially, are probably out of balance in such a way that the creatinine level is not a suitable parameter to monitor the renal side-effects of platinum administration.

The lack of a further reduction of GFR during the maintenance phase indicates the absence of cumula-

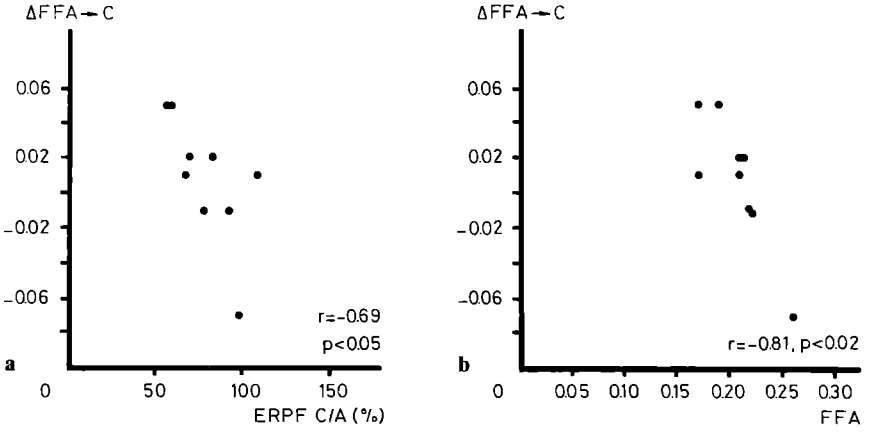


**Fig. 2a and b.** (**a**) Correlation between absolute change in FF and relative change in ERPF from A (before the start of therapy) to C (after maintenance therapy). (**b**) Correlation between absolute change in FF from A (before start of therapy) to C (after maintenance therapy) and initial FF at A

tive drug toxicity. The lack of recovery of renal function, however, does not necessarily indicate irreversible damage, as platinum will have been present during all observation periods. Further studies after discontinuation of the drug will be necessary to elucidate this.

As far as the ERPF is concerned, this study suggests that the deterioration in this parameter is delayed compared with the reduction in GFR. This could inidcate that the change in ERPF is secondary to the changes that lead to GFR reduction. However, a better way to study this phenomenon would be early and frequent measurement of GFR and ERPF during the induction phase.

With regard to the mechanism of the platinum-induced injury, the relationship between the degree of relative reduction in ERPF and the absolute change in FF (Fig. 2a) suggests a change in intrarenal vascular resistance. This is also depicted in Fig. 2b, which gives the relationship of the initial FF and change in FF over the total period from A to C. For other heavy metals evidence has been found that hemodynamic changes occur early after exposure. Balint et al. [1] and Hollenberg et al. [10] have reported changes in intrarenal blood flow after mercuric chloride exposure in man; similar phenomena in dogs and rats after uranyl nitrate administration have been described by Flamenbaum et al. [7] and Ryan et al. [13].

Indeed, if indications of initial change in renal blood flow during platinum therapy could be established, manipulation of the hemodynamic situation could possibly diminish the nephrotoxic effect.

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