The Protective Potential of the Combination of Verapamil and Cimetidine on Cisplatin-Induced Nephrotoxicity in Man

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Nine patients (Group A) with histologically proven, nonseminomatous testicular cancer were treated with cisplatin (CDDP) according to the Einhorn regimen. Renal function studies including the measurement of the effective renal plasma flow (ERPF) and the glomerular filtration rate (GFR) were performed prior to the chemotherapy and then after treatment on days 10 and 21 of the first course. In order to prevent CDDP-induced nephrotoxicity, verapamil (a calcium entry blocker) and cimetidine were given along with CDDP. The results were compared with others from another group of nine patients (Group B) treated with CDDP, but without verapamil and cimetidine. In Group A there was much less of a decrease in ERPF as compared to Group B on day 21. In addition, the decrease in GFR on days 10 and 21 was totally prevented in the verapamil- and cimetidine-treated group.

Cancer **60:2823–2828, 1987.**

CISPLATIN (CDDD) is an antineoplastic agent frequently used in the treatment of a variety of tumors. It especially improves response rates in patients with disseminated testicular and ovarian cancer.[1,2] Many side effects are known,[3] but the dose-limiting side effect is its nephrotoxicity, expressed as an increase in the serum creatinine concentration or a decrease in creatinine clearance.[4,5]

We have already reported early changes in renal function during CDDP treatment, which included a decrease in effective renal plasma flow (ERPF) and an increase in the filtration fraction, both occurring before any changes in the glomerular filtration rate (GFR) could be observed.[6] In rats these findings could be confirmed by others using a different technique.[7] The decrease in GFR occurred later on.[8] During chemotherapy, the reduction in ERPF could be an early sign of the mechanism leading to renal dysfunction. Therefore, it is suggested that prevention of these early conditions related to ERPF may ultimately contribute to less of a fall in GFR.[9]

It is possible that the renin-angiotensin system plays an important role in the initial ERPF decrease. Direct or indirect stimulation of the angiotensin-II (AII) concentration in the kidney leads to renal vasoconstriction through a decrease in the renal blood flow.[10] Verapamil, a calcium entry blocker, is able to inhibit the local action of AII on the glomerular microcirculation, leading to vasodilatation.[11]

CDDP is filtered as well as actively secreted in the renal tubules.[12] There is evidence that this secretion takes place through the organic cation transport system.[13] With this system cimetidine is actively secreted through the kidney.[14] So cimetidine might be a competitive antagonist for the secretion of CDDP on renal tubular level.

In the study reported in this article, therefore, we administered a combination of verapamil and cimetidine to a group of CDDP-treated patients (Group A) in order to investigate a possible reduction in CDDP-induced nephrotoxicity. The results were compared with a comparable group of patients treated with CDDP alone (Group B), acting as a control group.[8,15]

Patients and Methods

Nine consecutive patients made up Group A. All had histologically proven disseminated nonseminomatous testicular cancer. None of the patients had been pretreated. Their age ranged from 21 to 40 years (mean, 28

Part of this study was presented at the 23rd Congress of the EDTA-ERA in Budapest, Hungary, June 1986.

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This study was in part supported by the Dutch Kidney Foundation (Nier Stichting Nederland; Grant C84-503).

The authors thank Willy Bruins-van der Weij for secretarial support and Aly Drent-Bremer for technical assistance.

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Accepted for publication June 5, 1987.

TABLE 1. Values of Effective Renal Plasma Flow, Glomerular Filtration Rate, and Filtration Fraction in Group B Patients

Patient no.	Age (yrs)	ERPF (ml/min)			GFR (ml/min)			FF		
		A	B	C	A	B	C	A	B	C
1	32	983	662	666	185	160	160	019	024	024
2	28	688	500	560	128	113	113	019	023	020
3	23	937	690	686	190	146	138	020	021	020
4	34	793	765	797	170	150	154	021	019	019
5	30	888	961	740	224	215	185	025	022	025
6	50	511	504	563	123	106	120	024	021	021
7	32	829	679	488	152	143	115	018	021	024
8	22	623	529	446	138	141	105	022	027	024
9	33	713	560	494	176	163	114	025	029	023
Median		793	662	563	170	146	120	021	022	023

ERPF: effective renal plasma flow; GFR: glomerular filtration rate; FF: filtration fraction; A: pretreatment; B: day 10; C: day 21.

years). None of the patients was on a salt-restricted diet, and all were normotensive with a normal renal function before therapy as expressed by a serum creatinine concentration of less than 120 μmol/l and a creatinine clearance of greater than 100 ml/min.

All patients were treated according to the Einhorn regimen.[16] According to this regimen, four courses of chemotherapy, 21 days each, are given during the remission-induction phase. Each course consists of CDDP infusion (20 mg/m^2 in 1000 ml saline 0.9%) given daily for the first 5 consecutive days over a 4-hour period. Before and after the CDDP infusions, all patients were equally hydrated with 1 l saline 0.9% given intravenously (IV) every 6 hours for the first 6 days of each course starting 12 hours before the first CDDP infusion. Vinblastine (0.15 to 0.20 mg/kg IV) was given on days 1 and 2 after CDDP dose. Bleomycin (30 mg IV) was given on day 2, and weekly for 12 weeks. There are no known observations of nephrotoxicity caused by vinblastine or bleomycin.

To protect against the CDDP-induced nephrotoxicity, verapamil and cimetidine were added to the Einhorn regimen. To prevent the first drop in the ERPF, we started with both drugs orally 1 day before the first CDDP infusion in a dose of 80 mg three times daily for verapamil and 200 mg three times daily for cimetidine. Both drugs were continued for the entire study period. During the CDDP infusions, an extra 400 mg of cimetidine was given by IV on days 1 to 5, 2 hours before every CDDP infusion to realize a maximally saturated organic cation transport system in the renal tubules.

Renal function studies consisted of the measurement of the glomerular filtration rate (GFR) and the effective renal plasma flow (ERPF) determined simultaneously in supine position with ^{125}I sodium-iothalamate and ^{131}I-hippurate, respectively.[17] With this method errors in GFR and ERPF introduced by incomplete urine collection were corrected. Filtration fraction (FF) was calculated as the quotient of GFR and ERPF. Values were not corrected for the body surface area. The day-to-day coefficients of variation of the GFR and ERPF according to this method are ≤2% and ≤5%, respectively.[17]

Renal function was studied during the first 21-day course of the remission-induction phase at different times: on day 1 before the CDDP therapy, on day 10, and, last, before the second course on day 21.

The urine samples collected for the purpose of the GFR and ERPF measurements were also used to determine the excretion of beta$_2$-microglobulin (beta$_2$-m), creatinine and the tubular enzymes alkaline phosphatase (AP), lactate dehydrogenase (LDH) and gamma-glutamyl transferase (G-GT). Beta$_2$-microglobulin concentration in the urine was determined by a radioimmunosorbent technique according to Evrin *et al.*[18] All urine samples had a pH > 5.8 at voiding. The normal urinary excretion of beta$_2$-m does not exceed 400 μg/l. Creatinine concentrations were measured on the Auto Analyser II (Technicon, U. S. A.). The urinary levels of AP, LDH, and G-GT were assayed using gel filtration techniques on Sephadex G-25 M PD-10 columns (Pharmacia, Sweden). The enzyme activities were measured on the Ra-1000 (Technicon, U. S. A.) at 37°C. To correct for variations caused by changes in the urine flow, the relative excretions of beta$_2$-m and the tubular enzymes are given. The relative urinary excretions (μg or U/mmol creatinine) are calculated as the ratio of urinary concentration of beta$_2$-m (μg/l) or tubular enzyme activity (U/l) and the corresponding urinary creatinine concentration (mmol/l).

The results of the GFR, ERPF, and FF were compared with those obtained from Group B patients, who received CDDP without verapamil or cimetidine (Table 1). No values for the renal excretion of beta$_2$-m or tubular enzymes were available for patients in this group. Differences between the groups were statistically evaluated with Wilcoxon's test for unpaired observations

TABLE 2. Values of Effective Renal Plasma Flow, Glomerular Filtration Rate, and Filtration Fraction in Group A Patients

Patient no.	Age (yrs)	ERPF (ml/min)			GFR (ml/min)			FF		
		A	B	C	A	B	C	A	B	C
1	30	741	706	684	144	150	149	019	021	021
2	21	689	676	620	137	138	136	020	020	022
3	33	674	655	655	178	168	155	026	026	024
4	29	649	576	712	155	140	168	024	024	024
5	25	514	492	518	122	118	120	024	024	023
6	24	429	536	439	92	112	101	021	021	023
7	21	641	622	583	141	161	140	022	026	024
8	40	710	684	683	164	160	181	023	023	026
9	25	761	600	714	158	145	161	021	024	022
Median		674	622	655	144	145	149	022	024	023

ERPF: effective renal plasma flow; GFR: glomerular filtration rate; FF: filtration fraction; A: pretreatment; B: day 10; C: day 21.

(two-sided); changes within a group of patients were evaluated with Wilcoxon's test for paired observations (two-sided). Differences were considered significant at a P value ≤ 0.05.

Results

Table II shows the absolute values for ERPF, GFR, and FF along with their medians for patients in Group A. On day 10 there was a decrease in ERPF (median decrease, 7.7% compared to the pretreatment values, not significant), and median FF increased by 9.1% (not significant). On day 21 there was a median decrease in ERPF of 2.8%, together with an increase in the median GFR of 3.5% (both not significant compared to the pretreatment values); median FF increased by 4.6%, which is not significant.

Figures 1 and 2 show the relative change of ERPF and GFR in Group B patients *versus* Group A patients. There are no significant differences in the pretreatment values of ERPF and GFR between both groups. On day 10 the median ERPF decrease was 16.5% in Group B *versus* 7.7% in Group A (not significant). The median GFR, however, shows a decrease in Group B of 14.1% *versus* an increase in Group A of 0.7% ($P < 0.02$). On day 21 the differences in the drop in the median ERPF Group B *versus* Group A were 29.0% and 2.8%, respectively ($P < 0.02$). The median GFR decreased in Group B by 29.4% and increased in Group A by 3.5% ($P < 0.001$).

Table III shows the relative urinary excretion of $beta_2$-m, AP, LDH, and G-GT along with the absolute creatinine excretion. The $beta_2$-m excretion did not exceed the normal limit of 40 μg/mmol creatinine. The changes in urinary AP, LDH, and G-GT excretion are shown in Figure 3. The AP level did not change, but LDH and G-GT excretion increased on day 10 but returned to pretreatment values on day 21.

Discussion

In earlier studies it was found that CDDP had an acute effect on renal function expressed as a decrease in ERPF (and an increase in FF) prior to any changes in

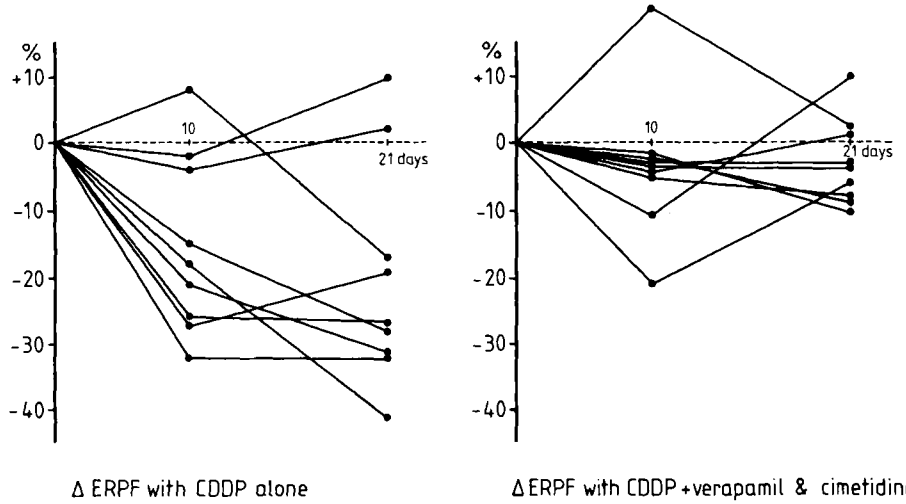

FIG. 1. Percentage change in effective renal plasma flow (ERPF) in Group B (CDDP alone) *versus* Group A (CDDP plus verapamil and cimetidine).

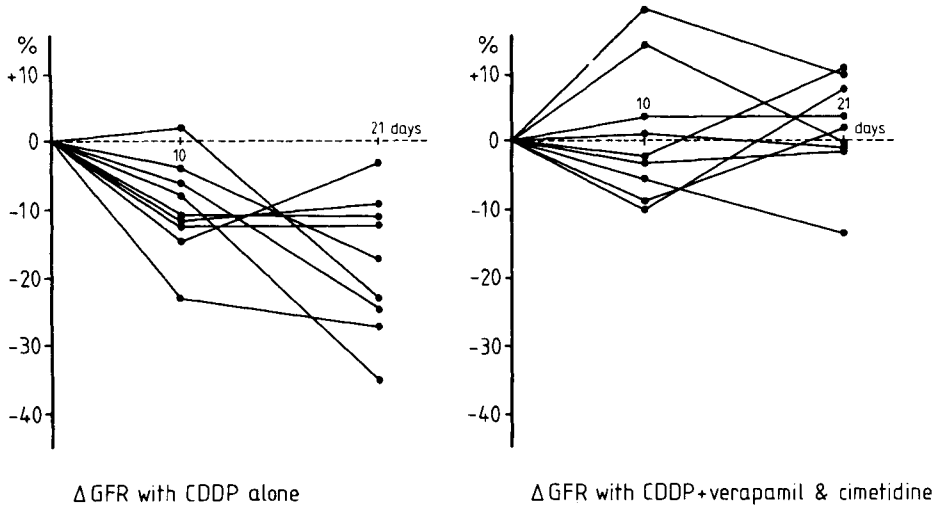

FIG. 2. Percentage change in glomerular filtration rate (GFR) in Group B (CDDP alone) *versus* Group A (CDDP plus verapamil and cimetidine).

GFR.[6] A direct or indirect stimulation of AII might be responsible for this hemodynamically induced change in renal function.[8,10]

Because calcium plays an important role in the expression of the AII activity on the glomerular microcirculation,[11] and verapamil is able both to induce vasodilatation of the renal vascular bed by inhibiting local activity of AII[19] and to potentially protect the tubular cells against ischemic cell injury,[20] the authors have previously evaluated the effect of verapamil on CDDP-induced nephrotoxicity. Verapamil was able to prevent the early decrease in ERPF, but it did not reduce the ultimate loss in GFR.[15]

As mentioned, CDDP is not only filtered but is actively secreted by proximal tubular cells.[12,21-23] In studies on renal cortical slices from rats Safirstein *et al.* observed inhibition of platinum uptake by agents such as tetraethylammonium (TEA), mepiperphenidol, and tolazoline.[24] These drugs are known to be transported in the kidney by the organic base transport system. Berg *et al.* obtained similar results from chicken and human renal cortical slices.[25] Bird *et al.* also found that quinine and cyanine 863,[26] both organic cation transport inhibitors, had a protective effect against CDDP-induced nephrotoxicity in chickens. Williams *et al.* showed in membrane vesicles from rat kidney cortex an inhibition of TEA transport by platinum without influencing the p-amino-hippurate (PAH) transport.[13] Therefore, it is reasonable to assume that platinum is secreted by the tubular cell through the organic cation transport system. It has been shown that the drug, cimetidine, is also secreted by this organic cation transport system.[14,27-29] Nelson *et al.* recently found in mice a decrease in platinum clearance in the presence of cimetidine.[30]

TABLE 3. Changes in Values of Relative $Beta_2$-microglobulin Excretion and Absolute Creatinine Excretion and Relative Urinary AP, LDH, and G-GT Excretion in Group A

Patient no.	$Beta_2$-microglobulin (μg/mmol creat.)			Creatinine (mmol/l)			AP (U/mmol creat.)			LDH (U/mmol creat.)			G-GT (U/mmol creat.)		
	Pr	Day 10	Day 21	Pr	Day 10	Day 21	Pr	Day 10	Day 21	Pr	Day 10	Day 21	Pr	Day 10	Day 21
1	8.5	7.8	13.6	7.2	5.4	6.5	1.1	1.1	1.2	0.9	1.9	1.0	0.7	4.0	0.5
2	12.9	6.2	8.3	4.1	13.0	5.3	1.9	1.7	1.8	0.4	1.3	0.9	3.1	4.8	3.7
3	6.0	11.2	8.6	5.0	2.9	4.2	3.1	3.1	2.1	2.8	1.8	0.7	5.4	5.9	3.5
4	3.4	8.5	9.6	6.9	6.1	3.0	1.2	1.6	3.3	0.6	1.6	0.7	2.0	2.7	2.4
5	5.9	5.0	9.3	16.6	18.7	10.9	1.1	1.8	1.1	0.9	3.0	1.2	3.5	5.8	3.5
6	23.7	13.8	6.0	2.6	9.5	2.9	2.8	1.4	3.1	0.7	2.0	0.6	2.1	4.1	2.5
7	8.4	20.3	4.4	3.6	5.9	3.4	2.4	3.3	2.7	0.5	6.4	1.6	3.2	5.0	3.2
8	6.3	4.9	5.3	10.3	10.1	6.1	0.8	1.1	1.3	0.9	2.9	0.3	2.6	2.8	1.9
9	17.7	0.6	16.3	2.2	9.1	2.4	3.7	0.8	2.5	1.0	1.1	0.7	3.0	1.8	3.8
Mean	10.3	8.7	9.0	6.5	8.9	5.0	2.0	1.8	2.1	1.0	2.4	0.9	2.8	4.1	2.8

AP: alkaline phosphatase; LDH: lactate dehydrogenase; G-GT: gamma glutamyl transferase; Pr: pretreatment value.

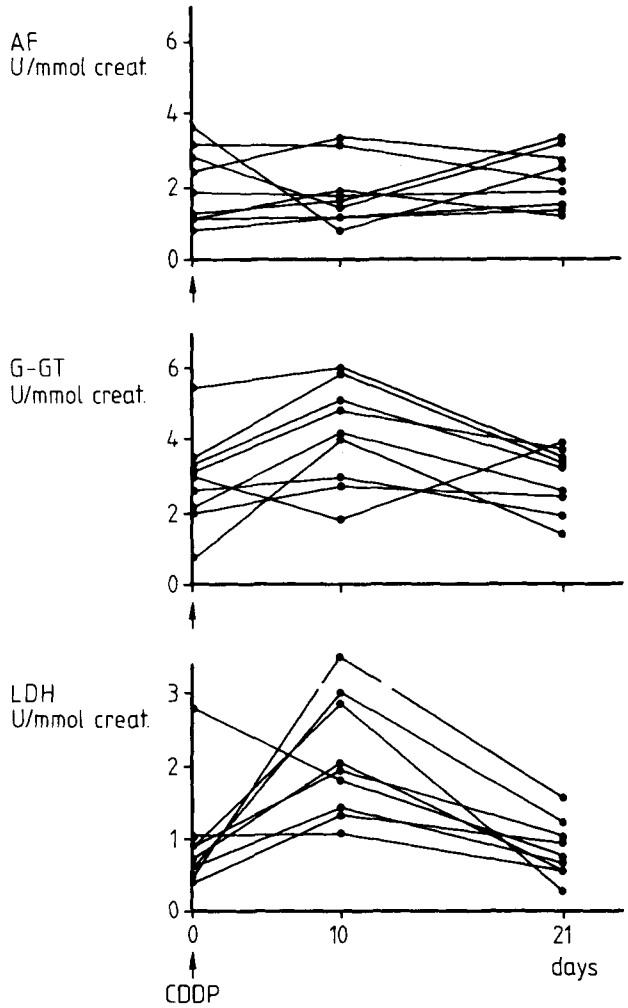

FIG. 3. Absolute change in relative tubular enzyme excretion during the 21 study days. AP: alkaline phosphatase; G-GT: gamma glutamyl transferase; LDH: lactate dehydrogenase.

The combination of verapamil and cimetidine given to CDDP-treated patients in our study produced a significantly smaller decrease in the ERPF on day 21 compared to a control group. On day 21 the decrease in GFR was found to have been almost completely prevented. By investigating the urinary excretion of $beta_2$-m, we did not observe an increase of $beta_2$-m excretion above normal levels. Also, the urinary AP (a brush-border enzyme)[31] did not change; however, on day 10 we noted a slight increase in urinary G-GT (another brush-border enzyme acting differently than AP)[31] and LDH (a dehydrogenase found through the whole nephron).[31] Both enzymes returned to their pretreatment values on day 21 before the next course of CDDP treatment. These increases in urinary G-GT and LDH may point to a minor, reversible, tubular dysfunction caused by CDDP that is not preventable.

In conclusion, we believe that the combination of verapamil and cimetidine given to patients treated with CDDP is able to prevent the GFR decrease that normally occurs during the first course of chemotherapy. A further prospective, random study is needed to confirm these data and to investigate the long-term preventive potential of verapamil and cimetidine. It is suggested that the subject of study should be the usefulness of measurements of urinary enzyme activities as potential and sensitive markers of early CDDP-induced nephrotoxicity.

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