Eur J Cancer Clin Oncol. Vol. 21, No. 4, pp. 433-437, 1985.
Printed in Great Britain.

0277-5379/85$3.00+0.00

Disorders of Serum Electrolytes and Renal Function in Patients Treated with *cis*-Platinum on an Outpatient Basis

GIUSEPPE GIACCONE,* MICHELA DONADIO, PATRIZIA FERRATI, LIBERO CIUFFREDA, MATTEO BAGATELLA, MARCO GADDI and ALESSANDRO CALCIATI
Divisione di Oncologia Medica, Ospedale S. Giovanni, Torino, Italy

Abstract—*Two hundred and eighty-one patients received* 927 *doses of* cis-*platinum, generally on an outpatient basis, at* 55 mg/m² *every* 3–4 weeks. *Mannitol and* 2.250 l *of hydration with saline and* 5% *dextrose plus* NaCl *and* KCl *were given in* 3–4 hr. *No case of acute renal failure ensued and when azotemia occurred* (3.5% *of patients*) *it was easily reversible and controlled. An abnormal level of one or more electrolytes was detected in* 194 *patients* (69%) *during chemotherapy.* K^+, Na^+, Ca^{2+} *and* Mg^{2+} *values usually decreased in serum after DDP administration, but their depletion seldom caused symptoms. Hypomagnesemia developed in* 20% *of patients, but was symptomatic in only* 1%. cis-*Platinum, at the doses utilized, is safely given to outpatients, with the hydration program employed. Serum electrolyte decrease during chemotherapy must be expected, and rapidly corrected when symptoms develop.*

INTRODUCTION

cis-DIAMMINEDICHLOROPLATINUM (II) (DDP) is a relatively new anticancer agent; its activity has been demonstrated as a single agent and in combination chemotherapy in carcinomas of testis, bladder, ovary, head and neck, uterine cervix, lung and lymphomas [1–3].

Nephrotoxicity was the limiting toxicity in phase I trials with DDP [4, 5]. Since it was demonstrated that adequate hydration programs could dramatically reduce renal side-effects, several schedules of hydration and forced diuresis were proposed [1, 6, 7]. Nevertheless, DDP, especially at high doses, is mainly administered during a period of hospitalization for safe treatment. Although the nephrotoxicity is thought to be dose-related and transient [8], many toxic effects secondary to renal tubule damage caused by DDP are still to be properly defined [9]. The present series represents a summary of our experience with a DDP regimen designed for outpatient use. The serial study of renal function and electrolyte disorders recorded in these patients during treatment with DDP-containing regimens are reported and analyzed.

MATERIALS AND METHODS

Two hundred and eighty-one patients were consecutively treated with DDP between May 1981 and October 1983. Patient characteristics are summarized in Table 1. All patients were administered chemotherapy on an out-patient basis; some patients were hospitalized for a few cycles.

Table 1. Patient characteristics

Total No. of patients	281
Tumor type:	
respiratory system	157 (55.8%)
head and neck ca.	59 (20.9%)
urogenital tract	57 (20.2%)
others	10 (3.5%)
Age: median, 56 yr; range 17–79 yr	
Sex: male 229, female 52 (ratio m/f: 4.4)	

DDP was given together with a program of hydration and forced diuresis, as follows: (1)

Accepted 6 September 1984.
*To whom requests for reprints should be addressed at: Ospedale S. Giovanni, Antica Sede, Divisione di Oncologia Medica, V. Cavour 31, 10123 Torino, Italy.

500 ml dextrose + 51.3 mEq NaCl + 26.8 mEq KCl; (2) 500 ml saline; (3) 125 ml 20% mannitol; (4) 250 ml saline + DDP; (5) the same as 3; (6) the same as 2; (7) the same as 1. The infusion usually started at 7 a.m. and lasted about 3-4 hr. DDP infusion was started as soon as the patient's diuresis reached 350 ml from the beginning of hydration. Twenty milligrams of furosemide were given occasionally to increase and speed diuresis.

Chemotherapy containing DDP was usually a combination of two or more drugs, repeated every 3-4 weeks; DDP as a single drug was given in two patients only (Table 2). DDP was given at 20 mg/m^2 daily for 5 days in 11 testicular cancer patients according to the PVB schedule [2].

Table 2. Chemotherapy

Combination	No. of patients
DDP-VP16	142 (50.5%)
DDP-MTX-BLM-VCR	31 (11.0%)
DDP-ADM-CTX	21 (7.4%)
Others	82 (29.1%)

Total No. of cycles: 927
Median No. of cycles per patient: 3 (range 1-11):

One cycle only	: 31	Two cycles	: 84
Three cycles	: 68	Four cycles	: 35
Five cycles	: 22	Six cycles	: 33
Seven cycles	: 2	Eight cycles	: 2
Ten cycles	: 2	Eleven cycles	: 2

The total dose for all patients was 87,048 mg, given in 927 doses; the mean number of cycles per patient was 3.3 and the mean dose of DDP given per cycle was 93.9 mg (55.2 mg/m^2 on average). The mean cumulative dose per patient was 309.7 mg (182.2 mg/m^2 on average). Eight patients received more than six courses.

cis-Platinum nephrotoxicity was carefully monitored; 24-hr diuresis was checked and BUN, serum creatinine, sodium and potassium tested before every cycle and the day after DDP administration. More determinations between cycles were obtained when abnormal values ensued. Chemotherapy was not restarted when azotemia occurred (defined as serum creatinine higher than 1.5 mg/dl). Dose reductions were not usually applied, but chemotherapy was delayed when marrow toxicity was present. Since existing literature reported cases of severe hypomagnesemia following DDP treatment [10], in November 1981 we started testing serum calcium and magnesium before and after every DDP administration.

BUN was measured by an enzymatic method, serum creatinine by a kinetic method, Na^+, K^+ and Ca^{2+} by flame photometry and Mg^{2+} by atomic absorption. The evaluated renal function tests were considered abnormal when the following values were detected: BUN $\geqslant$ 60 mg/dl, creatinine $\geqslant$ 1.7 mg/dl, sodium $\geqslant$ 150 mEq/l and $\leqslant$ 130 mEq/l, potassium $\geqslant$ 5.5 mEq/l and $\leqslant$ 3 mEq/l, calcium $\leqslant$ 8 mg/dl, magnesium $\leqslant$ 1.2 mEq/l. Borderline cases were considered as having values as follows: BUN between 50 and 60 mg/dl, creatinine between 1.4 and 1.7 mg/dl (1.2-1.7 mg/dl in women), Na^+ between 145 and 150 mEq/l and between 130 and 135 mEq/l, K^+ between 5 and 5.5 mEq/l, and between 3 and 3.5 mEq/l, Ca^{2+} between 8 and 8.5 mg/dl, Mg^{2+} between 1.2 and 1.5 mEq/l. Acute nephrotoxic effects induced by DDP and delayed or chronic renal toxicity were looked for carefully.

The chi-square test was used for comparison of percentages; Student's t test for paired samples was employed to compare electrolyte levels before and after therapy, using each patient as his or her own control [11].

RESULTS

BUN values of 60 mg/dl or higher were detected in 31 patients; 1.7 mg/dl or higher levels of serum creatinine (up to a maximum of 2.3 mg/dl) occurred in 8 patients (2.8%); in all cases but one, creatinine normalized within 3-4 weeks and did not prevent chemotherapy continuation. The patient who had abnormal creatinine for more than 4 weeks (maximum level 2.3 mg/dl) had small cell lung carcinoma with renal metastases and nephrotoxicity was likely to be partially due to disease extension.

No case of acute renal failure developed and when azotemia occurred (10 patients, 3.5%) it was easily reversible and controlled.

Alterations in serum electrolytes were frequently detected: a minimum of one abnormal level of either electrolyte was detected during therapy in 194 patients (68.7%). Abnormal and borderline values of Na^+, K^+, Ca^{2+} and Mg^{2+} detected in one or more cycles per patient are listed in Table 3.

Table 3. Electrolyte abnormal values

Electrolyte	Values	No. of patients
Na^+	$\geqslant$150 mEq/l	12
Na^+	>145 and <150 mEq/l	49
Na^+	<135 and >130 mEq/l	38
Na^+	$\leqslant$130 mEq/l	12
K^+	$\geqslant$5.5 mEq/l	19
K^+	>5.0 and <5.5 mEq/l	62
K^+	<3.5 and >3 mEq/l	9
K^+	$\leqslant$3 mEq/l	2
Ca^{2+}	$\leqslant$8.5 and >8 mg/dl	43
Ca^{2+}	$\leqslant$8 mg/dl	15
Mg^+	$\leqslant$1.5 and >1.2 mEq/l	47
Mg^{2+}	$\leqslant$1.2 mEq/l	9

Wide variations of Na^+ and K^+ levels were detected: pre- and post-cycle abnormal values are listed in Table 4; higher and lower levels of Na^+ and higher levels of K^+ are frequent, although abnormal values beyond borderline levels are uncommon.

Overall Na^+ level on the day after DDP administration is significantly lower than before treatment (139.4 vs 141.1 mEq/l, $P < 0.001$) (Table 5). The same tendency is present in all the subgroups of cycles where abnormal Na^+ levels were recorded except the $Na^+ \geqslant 150$ mEq/l group, in which an opposite trend is encountered, although it does not reach statistical significance. Potassium overall has a similar behaviour, having lower levels in post-cycle samples than before treatment (4.75 vs 4.88 mEq/l, $P < 0.001$).

The decrease of serum electrolyte levels after DDP administration may be explained by renal tubule damage.

The unexpected tendency of highest levels of K^+ to increase in post-cycle samples could not be related to azotemia, hypercatabolic states or dehydration. Although a clear relationship between this finding and the type of hydration utilized is unlikely, it cannot be ruled out. Of interest is the fact than 17/23 patients (73.9%) of this subgroup had lung carcinoma (five had small cell type) and 20 were male, even if a statistically significant difference does not exist with the overall patient population.

Among patients who experienced low calcium values only one had symptoms, and these receded with i.v. administration of calcium gluconate:

Table 4. Electrolyte pre- and post-cycle values

Electrolyte	Values	No. of patients		No. of cycles	
		Pre-cycle	Post-cycle	Pre-cycle	Post-cycle
Na^+	$\geqslant$150 mEq/l	6	7	6	7
Na^+	>145 and <150 mEq/l	37	25	45	28
Na^+	<135 and >130 mEq/l	25	26	29	38
Na^+	$\leqslant$130 mEq/l	3	10	3	10
K^+	$\geqslant$5.5 mEq/l	7	12	7	12
K^+	>5.0 and <5.5 mEq/l	40	32	45	37
K^+	<3.5 and >3 mEq/l	1	8	1	10
K^+	$\leqslant$3 mEq/l	2	1	3	1
Ca^{2+}	$\leqslant$8.5 and >8 mg/dl	6	9	6	9
Ca^{2+}	$\leqslant$8 mg/dl	18	26	21	31
Mg^{2+}	$\leqslant$1.5 and >1.2 mEq/l	26	34	33	49
Mg^{2+}	$\leqslant$1.2 mEq/l	5	5	5	7

Table 5. Electrolyte modifications during chemotherapy

Electrolyte	Mean pre-cycle values	Mean post-cycle values	*P*
K^+ overall (mEq/l)	4.88	4.75	<0.001
$K^+ \geqslant 5.5$	5.0	5.41	<0.01
K^+ B.L.	5.04	4.83	<0.001
$K^+ < 3.5$	3.88	3.27	<0.001
Na^+ overall (mEq/l)	141.1	139.4	<0.001
$Na^+ \geqslant 150$	147.3	148.6	>0.05
Na^+ B.L.	145.0	143.8	<0.01
$Na^+ < 135$	135.9	134.0	<0.001
Ca^{2+} overall (mg/dl)	8.49	8.33	<0.02
Mg^{2+} overall (mEq/l)	1.43	1.39	>0.05

B.L. = borderline values above normal levels.

The opposite situation appears in the subgroup of cycles in which K^+ is higher or equal to 5.5 mEq/l: in this case the mean post-cycle value is significantly higher than the pre-cycle value ($P < 0.01$).

Comparison of pre- and post-cycle levels of all electrolytes is detailed in Table 5.

this was a young man, treated with PVB for testicular cancer [2], who developed trysma and muscular contractions of upper limbs during the fourth day of the first cycle.

Of the patients 20.2% (57/281) had some degree of hypomagnesemia during DDP therapy. It was a frequent finding in patients administered DDP in

five consecutive days (3/11 treated with the PVB regimen for cancer of the testis); symptoms occurred in three cases only (trysma and diffuse muscular contractions). The PVB regimen caused symptomatic hypomagnesemia in a significantly higher number of patients than the 1-day DDP schedules ($P < 0.01$). Nine out of fifty-seven patients with hypomagnesemia also developed hypocalcemia concomitantly.

Both Ca^{2+} and Mg^{2+} levels tended to diminish the day after DDP administration, although this did not reach statistical significance for Mg^{2+}.

The number of patients who submitted to more than 6 cycles is small; however, no signs of cumulative or delayed nephrotoxicity, or worsening of renal function after suspension of chemotherapy were detected.

DISCUSSION

Since phase I trials demonstrated that the limiting toxicity of *cis*-platinum is renal toxicity, many attempts have been made to reduce this side-effect. Successful application of several hydration programs, combined or not with mannitol and/or furosemide, have permitted wider use of this active anticancer drug [1, 6, 7].

In our series the very low incidence of mild and readily reversible nephrotoxicity makes this outpatient regimen of DDP administration suitable for widespread clinical use. An incidence of nephrotoxicity as low as that reported by Vogl *et al.* [6], who used a slightly shorter hydration and routine i.v. furosemide, occurred in our study. It appears that doses around 60 mg/m^2 can be safely given to outpatients, while higher doses probably necessitate hospitalization, due to the dose-related nephrotoxic side-effect [8, 12]. New concepts, like optimal circadian timing [13] or the use of antidotes [14], might solve this problem in the future.

The impressively low incidence of nephrotoxicity that we found in our series could be explained by the hyperosmolar hydration applied: the high concentration of chloride ions present in the hydration bottles would probably achieve the same results as those obtained by adding DDP to a hyperosmolar vehicle [15, 16].

Our data show a high frequency of electrolyte disorders during chemotherapy with DDP (68.7% of patients), but its real clinical meaning is often negligible. Abnormally high and low levels of several electrolytes are found within the same patients during subsequent cycles and a clear relationship with renal function damage cannot usually be demonstrated. Most commonly all electrolytes decrease during treatment and their post-cycle values are usually less high than before DDP administration. This finding could be related to the fluid load and osmotic diuresis induced by mannitol, yielding impaired renal ability to excrete the fluid load and hemodilution. Serum and urine osmolarities have not been checked, but they would be helpful in clarifying this finding.

The tendency of K^+ at the highest levels to increase following DDP administration might be related to abnormal endocrine function, commonly occurring in small cell lung cancer patients in particular [17], and also other neoplasms.

Calcium and magnesium sometimes drop steeply during DDP chemotherapy and this may cause serious medical emergencies [18]. We observed hypomagnesemia in about 20% of patients, but it was symptomatic in only a small percentage (1%); significantly more patients who took DDP in the 5-day schedule had symptomatic hypomagnesemia. This datum has already been reported by other authors, and it could be dependent upon the higher total dose of DDP administered, although a more continuous nephrotoxic effect of this schedule cannot be ruled out [19]. Hypocalcemia was symptomatic in one patient only, and it was associated with hypomagnesemia in 15.7% of cases: it is in fact well known that hypomagnesemia can induce secondary hypocalcemia [18, 20].

No signs of delayed or worsening renal toxicity after chemotherapy discontinuation have been detected in our series, and this is confirmed by other authors [21-23].

We conclude that our results confirm the possibility of safely administering *cis*-platinum at doses around 60 mg/m^2 on an out-patient basis; the unexpectedly high incidence of electrolyte disorders during DDP treatment only unfrequently had clinical significance. While Na^+ and K^+ levels may vary widely during therapy without important clinical consequences, Ca^{2+} and Mg^{2+} levels should be checked regularly, especially when DDP is fractionated and given in subsequent days; an adequate electrolyte replacement should be given when deficiency occurs.

REFERENCES

1. Ribaud P, Gouvela J, Bonnay M, Mathé G. Clinical pharmacology and pharmacokinetics of *cis*-platinum and analogs. *Cancer Treat Rep* 1981, **65**, 97-105.
2. Einhorn L, Donohue JP. Combination chemotherapy in disseminated testicular cancer. The Indiana University experience. *Semin Oncol* 1979, **6**, 87-93.

3. Sierocki JS, Hilaris BS, Hopfan S *et al. cis*-Dichlorodiammineplatinum(II) and VP-16-213: an active induction regimen for small cell carcinoma of the lung. *Cancer Treat Rep* 1979, **63,** 1593-1597.
4. Higby DJ, Wallace HJ, Albert DJ, Holland JF. Diamminedichloroplatinum: a phase I study showing responses in testicular and other tumors. *Cancer* 1974, **33,** 1219-1222.
5. Rossof AH, Talley RW, Stephens RL *et al.* Phase II evaluation of *cis*-diamminedichloroplatinum(II) in advanced malignancies of the genitourinary and gynecologic organs. *Cancer Treat Rep* 1979, **63,** 1567-1571.
6. Vogl SE, Zaravinos T, Kaplan BH, Wollner D. Safe and effective two-hour outpatient regimen of hydration and diuresis for the administration of *cis*-diamminedichloroplatinum (II). *Eur J Cancer* 1981, **17,** 345-350.
7. Hayes DM, Cvitkovic E, Golbey RB. High-dose *cis*-platinumdiamminedichloride. Amelioration of renal toxicity by mannitol diuresis. *Cancer* 1977, **39,** 1372.
8. Gusberg SB, Frick HC II. *Corscaden's Gynecologic Cancer.* Baltimore, MD, Williams & Wilkins, 1978.
9. Bitran JD, Desser RK, Billings AA, Kozloff MF, Shapiro CM. Acute nephrotoxicity following *cis*-dichlorodiammineplatinum. *Cancer* 1982, **49,** 1784-1788.
10. Schilsky RL, Anderson T. Hypomagnesemia and renal magnesium wasting in patients receiving cisplatin. *Ann Intern Med* 1979, **90,** 929-931.
11. Colton T. *Statistics in Medicine.* Boston, MD, Little Brown, 1974.
12. Campbell AB, Kalman SM, Jacobs C. Plasma platinum levels: relationship to cisplatin dose and nephrotoxicity. *Cancer Treat Rep* 1983, **67,** 169-172.
13. Levi FA, Hrushesky WJM, Halberg F, Langevin TR, Haus E, Kennedy BJ, Lethal nephrotoxicity and hematologic toxicity of *cis*-diamminedichloroplatinum ameliorated by optimal circadian timing and hydration. *Eur J Cancer Clin Oncol* 1982, **18,** 471-477.
14. Uozumi J, Sagiyama K, Aoki K, Iwamoto Y, Baba T. Effectiveness of "two-route chemotherapy" using cisplatin and its antidote, sodium thiosulfate, on lifespan of rats bearing metastatic liver tumors. *Cancer Treat Rep* 1983, **67,** 1067-1074.
15. Litterst CL. Alterations in the toxicity of *cis*-dichlorodiammineplatinum-II and in tissue localization of platinum as a function of NaCl concentration in the vehicle of administration. *Toxicol Appl Pharmacol* 1981, **61,** 99-108.
16. Corden BJ, Hill JB, Collins J, Ozols RF. High dose cisplatin (HDP) in hypertonic saline: absence of nephrotoxicity and pharmacokinetics of 40 mg/m^2 × 5 schedule of administration. *Proc ASCO* 1983, **2,** C-132.
17. Bondy PK, Gilby ED. Endocrine function in small cell undifferentiated carcinoma of the lung. *Cancer* 1982, **50,** 2147-2153.
18. Gonzalez C, Villasanta U. Life-threatening hypocalcemia and hypomagnesemia associated with cisplatin chemotherapy. *Obstet Gynecol* 1982, **59,** 732-734.
19. Schilsky RL, Barlock A, Ozols RF. Persistent hypomagnesemia following cisplatin chemotherapy for testicular cancer. *Cancer Treat Rep* 1982, **66,** 1767-1769.
20. Agus ZS, Goldfarb S, Wasserstein A. The patient with disorders of the serum calcium and phosphate. In: Schrier RW, ed. *Manual of Nephrology—Diagnosis and Therapy.* Boston, MD, Little Brown, 1981, 70-76.
21. Dentino M, Luft FC, Yum MN, Williams SD, Einhorn LH. Long term effect of *cis*-diamminedichloroplatinum (CDDP) on renal function and structure in man. *Cancer* 1978, **41,** 1274-1281.
22. Meijer S, Mulder NH, Sleijfer DT *et al.* Influence of combination chemotherapy with *cis*-diamminedichloroplatinum on renal function: long term effects. *Oncology* 1983, **40,** 170-173.
23. Chiuten D, Vogl S, Kaplan B, Camacho F. Is there cumulative or delayed toxicity from *cis*-platinum? *Cancer* 1983, **52,** 211-214.