*Eur J Cancer Clin Oncol*, Vol. 23, No. 11, pp. 1649–1652, 1987.
Printed in Great Britain

0277-5379/87$3.00+0.00


# Continuous Infusion of High-Dose Cisplatin in Children: Pharmacokinetics of Free and Total Platinum

MARTINE BUES-CHARBIT,* JEAN-CLAUDE GENTET,† JEAN-LOUIS BERNARD,† VALENTINE BREANT,* JEAN-PAUL CANO* and CLAUDE RAYBAUD†

*Laboratoire Hospitalo-Universitaire de Pharmacocinétique, U278, Faculté de Pharmacie, 13385 Marseille Cédex 5, France and †Service d'Oncologie Pédiatrique, Hopital d'enfants de la Timone, 13385 Marseille Cédex 5, France

**Abstract**—*A pharmacokinetic study was carried out in two infants and two (older) children with high-dose cisplatin (CP)* (40 mg/m$^2$/*day) by 5-day continuous infusion. Following interruption of the infusion, the decrease in total plasma platinum was biphasic, with a terminal half-life of* 155.5–418 h. *During administration the urinary concentrations were between* 7.66 *and* 15.2 mg/l. *Thirty to thirty five per cent of the administered dose was eliminated within* 48 h *of discontinuing infusion. Free platinum (FP) levels declined in a biphasic manner, with a mean* (± *S.E.*) *elimination half-life of* 81.25 (± 34.9) h. *FP was still detectable in the plasma* 10 *days after the end of infusion with levels above* 0.010 μg/ml. *FP availability, measured as the area under the curves (AUC) of the FP concentration—up to* 2 h *after ending the infusion—were* 768 (± 326) μg.min/ml. *Inter- or intra-individual differences in AUC values were not observed.*

## INTRODUCTION

HIGH-DOSE cisplatin (CP) has recently been evaluated in 5-day pulse and fractionated regimens in adult cancers [1] and in advanced neuroblastomas [2], with a tolerable toxicity. Based on experimental data [3], several authors have investigated standard dose CP administered as a continuous infusion [4, 5]. These infusion regimens have been associated with less toxicity than bolus delivery, probably because of the lack of peak plasma levels. In addition, response rates appeared to be comparable in both regimens, and this is in good agreement with the similarity of the free platinum (FP) areas under the curves (AUC) observed in a recent study [6]. To our knowledge, high-dose CP (40 mg/m$^2$/day) has not been reported utilizing a continuous infusion schedule. In this study, we examined pharmacokinetic parameters and body exposure to free and total platinum (TP) in children following high-dose CP administered during a 5-day infusion.

## MATERIALS AND METHODS

Four patients, aged 16 and 18 months, 6 and 12 years (the three younger ones had stage IV neuroblastomas, the oldest a metastatic rhabdomyosarcoma) received one (one patient) or two (three patients) courses of CP at a dose rate of 40 mg/m$^2$ for 5 days separated by 4 weeks. The daily dose was delivered through a central catheter during 24 h reconstituted in 50 ml 0.9% NaCl. Hydration (3 l/m$^2$) with normal saline and added KCl (1.5 g/l), $CaCl_2$ (10 ml/m$^2$/day) and $MgSO_4$ (5 ml/m$^2$/day) began with chemotherapy at day 1, and stopped 24 h after completion, at day 6. For each treatment, 23 blood samples were collected between days 1 and 28, by means of a peripheral microcatheter which was rinsed with 5 ml of normal saline and closed after use. Blood was drawn at 12, 24, 48, 72, 96, 120 h during the infusion, and at the following times thereafter: 15, 30, 60, 90, 120, 180, 240 min, 6, 12, 24, 48, 96, 144 h and 10, 14, 21, 28 days. Samples were immediately centrifuged and the plasma was removed. Plasma ultrafiltrates were obtained by using Micropartition systems MPS-1 (Amicon) and centrifuged at 2000 ***g*** for 15 min. All separations were completed within 30 min after taking the blood sample. All samples were stored at −20°C until analysis. During at least one of the courses of treatment, urine samples were collected, as voided for two patients and during

Accepted 3 July 1987.
Author to whom correspondence is to be sent: J.C. Gentet, Service d'Oncologie Pédiatrique, Hopital d'enfants de la Timone, 27 Boulevard Jean Moulin, 13385 Marseille Cédex 5, France.

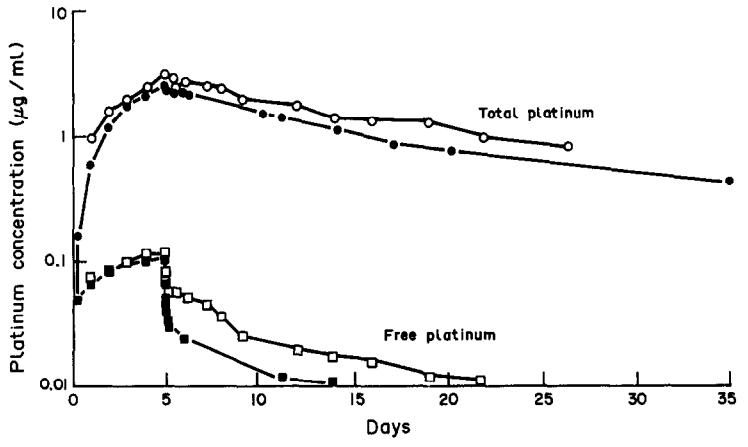


*Fig. 1. Semilogarithmic plot of TP concentrations in plasma (●—●: 1st course, ○—○: 2nd course) and FP concentrations in plasma ultrafiltrate (■—■: 1st course, □—□: 2nd course) vs. time after a 5-day continuous infusion of* 40 mg/m²/*day cisplatin.*

12 h intervals in one patient. The concentrations of TP and FP were determined by means of flameless atomic absorption spectroscopy with a detection limit of 0.010 µg/ml [7].

## RESULTS

The time course of TP and FP for a representative patient is shown in Fig. 1. After a 5-day continuous infusion of high-dose CP, the maximum plasma TP concentration at the end of infusion ranged from 1.78 to 3.575 µg/ml. TP levels drawn during the administration showed that a steady-state concentration had not been achieved at the end of infusion. After cessation, the mean terminal $T1/2$ values varied from 155.5 to 418 h. Total plasma corrected clearances ranged from 0.179 to 0.306 l/h/1.73 m².

During infusion, FP levels were about 10–20 times lower than TP levels. The decrease in FP levels, after the end of the infusion, seemed to follow a biexponential kinetic pattern, with a prolonged elimination half-life from 49.3 to 157 h. FP was still detectable in the plasma 10 days after the end of infusion, with levels above 0.010 µg/ml. AUC (0–2 h and 0–∞) were determined in order to know the total amount of FP available to the tissues during and after infusion. The mean AUC were 768 ± 328 µg.min/ml (range 529–1486, $n = 7$) at 2 h and 1324 ± 513 µg.min/ml (range 771–2339) at ∞. Inter- or intra-individual differences in AUC values were not observed, except for the youngest patient (No. 3) who showed signs of hydro-electrolytic disturbance during the first course (Table 1).

The maximum urinary concentration of platinum (Pt) attained during the 5 days of administration in urine voided varied between 7.66 and 15.2 mg/l.The maximum urinary excretion rate ranged from 0.35 to 0.48 mg/h and 30% to 35% of the administered dose was eliminated within 48 h after the end of infusion (Table 1).

## DISCUSSION

In patients receiving high-dose (40 mg/m²/day) continuous infusion CP over 5 days, plasma TP concentrations increased regularly during the infusion. At the end of the infusion TP levels were twice the levels recorded with a dose rate of 20 mg/m²/day given by 5-day continuous infusion [8]. The TP levels were between values achieved with the lower dose infusion, and those obtained after a bolus of 100 mg/m² [6]. The elimination half-lives were long and corresponded closely to those reported with the bolus and infusion regimens at a dose of 100 mg/m² [6, 8].

Urinary Pt concentrations and urinary excretion rate were markedly less than those observed after bolus delivery, and were similar to those obtained with the same schedule at the dose of 100 mg/m² [8]. Consequently, it may be concluded that 5-day infusion schedule reduces the exposure of the kidneys to high concentrations of Pt. Thus this protocol's high degree of renal safety must probably be related to the reduction in urinary concentration of Pt, caused by the high urine volume associated with hyperhydration (corroborating Corden's results [9]—fractionated schedule during 5 days). FP concentrations were detectable up to 10 days after the end of the infusion. Once administration had ceased, the disappearance of FP followed a biexponential kinetic pattern with a prolonged elimination half-life of 81.25 ± 34.9 h. The terminal $T1/2$ is somewhat longer than in studies where a variety of schedules have been used [6, 9] and seems to corroborate the observations of De Gregorio *et al.* [10]. The FP AUC vs. time is a measure of the overall availability of ultrafilterable species which is the component responsible for cytotoxicity [11]. In order to evaluate the therapeutic efficacy of the infusion schedule, the AUC of the FP was determined for up to 2 h after ending the infusion, since Sternson *et al.* [12] showed

*Table 1. Pharmacokinetic parameters of free platinum in plasma and urine from children receiving a continuous infusion of* 40 mg/m²/day *of CP during 5 days*

| Patient-course | T1/2 (min) | T1/2β (h) | Cl (l/h/1.73m²) | Vd (l) | AUC(μg.min/ml) 0–2 h* | AUC(μg.min/ml) Total† | Maximum urine concentration(mg/l) Urine voided | Maximum urine concentration(mg/l) 12-h fraction | Maximum urine excretion rate Urine voided | Maximum urine excretion rate 12-h fraction |
|---|---|---|---|---|---|---|---|---|---|---|
| 1–1 | 9.5 | 50.9 | 11.42 | 143 | 745 | 1098.5 | — | — | — | — |
| 2–1 | — | 70.6 | 12.08 | — | 529 | 931.5 | 7.66 | 4.12 | 0.40 | 0.22 |
| 2 | 24.5 | 76.8 | 10.50 | 299 | 601 | 1031 | — | — | — | — |
| 3–1 | 32 | 65.3 | 5.67 | 101 | 1486.5 | 2339.5 | 15.2 | 5.325 | 0.36 | 0.205 |
| 2 | — | 124.0 | 9.45 | — | 761.5 | 1430 | — | — | — | — |
| 4–1 | 47.5 | 97.8 | 16.35 | 600 | 607 | 813 | — | 5.46 | — | 0.50 |
| 2 | 46 | 175.4 | 9.65 | 873 | 628.5 | 1259 | — | — | — | — |

*0–2 h: AUC determined between the start of CP infusion and 2 h after the end (at day 5).
†0–∞: AUC determined from Pt detected in ultrafiltrate until concentration < 0.010 μg/ml.

*Table 2. Comparison between FP AUC observed after very high dose by continuous infusion vs. various more rapid schedules*

| | | Present study 200 mg/m² in 5 days ($n$ = 7) | Literature data [6] Bolus ($n$ = 3) | 3 h infusion 100 mg/m² ($n$ = 2) | 24 h infusion ($n$ = 2) |
|---|---|---|---|---|---|
| AUC Mean FP exposure (μg.min/ml) | 0–∞ | 1324 ± 513 | 317 ± 33.1 | 327 ± 2.8 | 329 ± 6.4 |
| | 0–2 h | 768 ± 326 | — | — | — |

convergence—up to 2 h—between intact CP and ultrafilterable Pt. The AUC were at least twice as high as those reported by Vermorken *et al.* [6] using various infusion schedules of 100 mg/m² (see Table 2).

A role for CP metabolites in the development of the nephrotoxic lesion has been suggested [13, 14]. From experimental data [15] it can be concluded that the ultrafilterable metabolites of CP are nephrotoxic, but are less effective antitumor agents than the parent compound. Consequently, after 2 h, ultrafilterable species in the plasma were probably not free of toxicity: the determination of the total FP AUC may enable the organism's exposure to active and/or toxic Pt species to be reflected. In order to compare the efficacy and toxicity of this continuous high-dose CP protocol with the fractionated 5-day protocol [1], the FP AUC values after fractionated administration are at present being determined, since these are not given by Corden *et al.* [9].

**Acknowledgements**—Supported in parts by INSERM grant 486022 and by Ligue Nationale pour la lutte contre le Cancer.

## REFERENCES

1. Ozols RF, Deisseroth AB, Javadpour N *et al.* Treatment of poor prognosis nonseminomatous testicular cancer with a 'high-dose' platinum combination chemotherapy regimen. *Cancer* 1983, **51**, 1803–1807.
2. Philip T, Hartmann O, Zucker JM *et al.* Etoposide and very high dose cisplatin: salvage therapy for patients with advanced neuroblastoma XVIIth S.I.O.P. Meeting, Venice, 1985, abstracts 246–247.
3. Drewinko B, Brown BW, Gottlieb JA. The effect of *cis*-diamminedichloroplatinum (II) on cultured human lymphoma cells and its therapeutic implications. *Cancer Res* 1973, **33**, 3091–3095.
4. Lokich JJ. Phase I study of *cis*-diamminedichloroplatinum (II) administered as a constant 5-day infusion. *Cancer Treat Rep* 1980, **64**, 905–908.
5. Salem P, Khalyl M, Jabboury K, Hashimi L. *Cis*-diamminedichloro-platinum (II) by 5-day continuous infusion. A new dose schedule with minimal toxicity. *Cancer* 1984, **53**, 837–840.

6. Vermorken JB, van der Vijgh WJF, Klein I *et al.* Pharmacokinetics of free and total platinum species after rapid and prolonged infusions of cisplatin. *Clin Pharmacol Ther* 1986, **39**, 136–144.
7. Cano JP, Catalin J, Bues-Charbit M. Platinum determination in plasma and urine by flameless atomic absorption spectrophotometry. *J Appl Toxicol* 1982, **2**, 33–38.
8. Bues-Charbit M, Cano JP, Bruno R *et al.* Pharmacokinetic study of *cis*-dichlorodiammine platinum II (CDDP) administered as a constant 5-day infusion. 8th Annual Meeting of European Society for Medical Oncology. Nice, December 1982. *Cancer Chemother Pharmacol* 1982, **9**, (Supp) 8.
9. Corden BJ, Fine RL, Ozols RF, Collins J. Clinical pharmacology of high-dose cisplatin. *Cancer Chemother Pharmacol* 1985, **14**, 38–41.
10. DeGregorio MW, Wilbur JR, Crowley TJ, Cadman EC, Deisseroth A. Concerning the paper clinical pharmacology of high dose cisplatin by Corden *et al. Cancer Chemother Pharmacol* 1985, **15**, 183–184.
11. Holdener EE, Park CH, Belt RJ, Stephens RL, Hoogstraten B. Effect of mannitol and plasma on the cytotoxicity of cisplatin. *Eur J Cancer Clin Oncol* 1983, **19**, 515–518.
12. Sternson LA, Repta AJ, Shih H, Himmelstein KJ, Patton TF. Disposition of cisplatin versus total platinum in animals and man. In: Hacker MP, Douple EB, Krakoff IH, eds. *Platinum Coordination Complexes in Cancer Chemotherapy*. Martinus Nijhoff, Boston, 1984, 126–137.
13. Earhart RH, Martin PA, Tutsch KD, Erturk E, Wheeler RH, Bull F. Improvement in the therapeutic index of cisplatin (NSC 119875) by pharmacologically induced chloruresis in the rat. *Cancer Res* 1983, **43**, 1187–1194.
14. Daley-Yates PT, McBrien DCH. The inhibition of renal ATPase by cisplatin and some biotransformation products. *Chem Biol Interactions* 1982, **40**, 325–334.
15. Daley-Yates PT, McBrien DCH. Cisplatin metabolites in plasma, a study of their pharmacokinetics and importance in the nephrotoxic and antitumor activity of cisplatin. *Biochem Pharmacol* 1984, **33**, 3063–3070.