Pharmaceutical Research, Vol. 6, No. 6, 1989

Report

Pharmacokinetics of Platinum in Cancer Patients Treated with Carboplatin in Combination with High-Dose Methotrexate

Adnan El-Yazigi,[1,3] Magid Amer,[2] and Cazemiro R. Martin[1]

Received December 16, 1988; accepted January 26, 1989

The pharmacokinetics of platinum was investigated in 10 cancer patients treated with a 1-hr infusion of 300 mg/m^2 of carboplatin which was given 2–4 days after the administration of 100 mg/kg (20-mg/kg bolus and 80-mg/kg intravenous infusion) of methotrexate. Platinum was analyzed in the samples by flameless atomic absorption spectrophotometry. The concentration vs time data for total platinum in plasma followed a two-compartment model and the mean (and SE) values for β, TBC, V_c, and RC were 0.0827 (0.22) hr^{-1}, 2.355 (0.252) liters/hr · m^2, 10.74 (0.62) liters/m^2, and 2.405 (0.228) liters/hr · m^2, respectively. There was no significant change in the creatinine clearance or TBC with repeated treatment. The ultrafilterable platinum which was measured in the plasma of two patients constituted 82 and 11.3% of the total platinum at 1 and 24 hr, respectively, and the data conformed to the one-compartment model. The mean (SE) values for $t_{1/2}$, TBC, and V_d for free platinum were 1.844 (0.208) hr, 4.583 (1.059) liters/hr · m^2, and 11.88 (1.45) liters/m^2, respectively. The above data are in good agreement with those reported earlier for platinum following the administration of carboplatin as a single agent. These results suggest that high-dose methotrexate therapy, when administered 2–4 days before carboplatin, does not affect the pharmacokinetics of platinum in the plasma.

KEY WORDS: carboplatin; pharmacokinetics; platinum, total, ultrafilterable; urinary excretion; cancer patients; chemotherapy.

INTRODUCTION

Carboplatin (*cis*-diammine-1,1-cyclobutane dicarboxylate platinum) or paraplatin is a platinum coordination complex currently undergoing clinical trials as an analogue of cisplatin in the treatment of a number of malignant diseases including carcinoma of the ovary (1,2) and cancers of the testes (3), head and neck (4), and lung (5,6). While maintaining antitumor activities similar to those of cisplatin, much less nephrotoxicity, ototoxicity, and neurotoxicity are observed following conventional doses of 400–600 mg/m^2 of carboplatin. Because of an enhanced stability compared to cisplatin, carboplatin has less irreversible binding to serum and tissue protein and exhibits more rapid and complete renal excretion of platinum.

The pharmacokinetics of total and free (ultrafilterable) platinum have been investigated following intravenous (7–10) and intraperitoneal (11,12) administrations of carboplatin as a single chemotherapeutic agent. More recently carboplatin has been employed in combination with other anticancer agents in the treatment of advanced ovarian cancer (13–15) or small-cell lung malignancy (6). However, the pharmacokinetics of this drug when used in these combined chemotherapeutic modalities has not been addressed. Since these drugs including methotrexate produce pronounced toxicities to the eliminating organs, particularly the kidneys (16), the pharmacokinetics of carboplatin may conceivably be altered.

In this report, we examine the pharmacokinetics of total and free (ultrafilterable) platinum in plasma of cancer patients treated with carboplatin preceded by high-dose methotrexate. The kinetics of the urinary excretion of this metal was also investigated.

MATERIALS AND METHODS

Patients. Ten patients were entered into this study. Three had malignant lymphoma, and seven had nasopharyngeal carcinoma. The clinical characteristics of these patients are summarized in Table I. The diagnosis of the disease was based on histological and clinical findings. Creatinine clearance of each patient was measured prior to each course and a value of >48 ml/min was required to initiate the chemotherapy. All patients had complete blood count with normal creatinine, uric acid, BUN, alkaline phosphatase, total bilirubin, SGPT, and SGOT serum levels.

Drug Administration. Prior to therapy, 50 mEq of sodium bicarbonate was administered orally every 6 hr for a total of eight doses. This was followed by infusion of 576 mEq of this compound over 4 days (*viz.*, 1 day prior to and

[1] Pharmacokinetics Laboratory, Pharmacology and Toxicology Section, Department of Biological and Medical Research, King Faisal Specialist Hospital and Research Center, Riyadh 11211, Saudi Arabia.

[2] Medical Oncology Section, Department of Oncology, King Faisal Specialist Hospital and Research Center, Riyadh 11211, Saudi Arabia.

[3] To whom correspondence should be addressed.

0724-8741/89/0600-0492$06.00/0

Table I. Vital Clinical Characteristics of the Patients

Patient No.	Age (years)	Sex	Creatinine clearance (ml/min)[a]	Disease
1	40	M	56	Malignant lymphoma
2	48	M	76	Nasopharyngeal carcinoma
3	45	M	80	Malignant lymphoma
4	45	M	71	Nasopharyngeal carcinoma
5	57	M	49	Malignant lymphoma
6	49	M	60	Nasopharyngeal carcinoma
7	15	F	48	Nasopharyngeal carcinoma
8	46	M	88	Nasopharyngeal carcinoma
9	47	M	85	Nasopharyngeal carcinoma
10	42	M	130	Nasopharyngeal carcinoma

[a] Measured prior to initiation of the first course of chemotherapy.

3 days during methotrexate therapy) to render the urine pH to >8.5. The patient was then given 20 mg/kg of methotrexate (Lederle Laboratories, American Cyanamid, Pearl River, N.Y.) by intravenous bolus route followed immediately by 80 mg/kg of this drug infused over 6 hr. The rescue therapy consisted of a dose of 30 mg of folinic acid (Lederle Laboratories, American Cyanamid, Pearl River, N.Y.) given intravenously 6 hr after the completion of the infusion and repeated every 6 hr afterward for a total of 12 doses. On the third, fourth, or fifth day of chemotherapy (i.e., 48, 72, or 96 hr after the initiation of methotrexate infusion), a dose of carboplatin (David Bull Laboratories Pty. Ltd., Mulgrave, Victoria, Australia) equivalent to 300 mg/m^2 was administered by intravenous infusion over a 1-hr interval. Five patients received three courses of this combined chemotherapy, two received two courses, and three received one course. Consecutive courses were separated by a 4-week interval.

Specimens Collection. Blood (2–3 ml) was sampled via heparin lock into heparinized vacutainer tubes at 0.5, 1, 3, 6, 12, 18, and 24 hr after the initiation of carboplatin infusion. The samples were centrifuged at 2800 rpm for 10 min, and the plasma was removed and frozen at −18°C until analysis. Plasma samples from two patients were subjected shortly after collection to centrifugal ultrafiltration at 1000*g* for 20 min at 4°C by the use of Amicon CF50A ultrafiltration cones (Amicon Co., Lexington, Mass). Urine was collected from patients as 4-hr cumulative fractions. The volume of each fraction was measured and a sample was stored at −20°C until analysis.

Analysis of Platinum in Plasma or Urine. Platinum was analyzed in the samples by flameless atomic absorption spectrophotometry. The apparatus used was a model 975 equipped with a Model GTA-95 graphite tube atomizer and an auto sampler (all from Varian Techtron Pty., Ltd., Milgrave, Victoria, Australia). A background correction with a wavelength of 265.9 nm, a lamp current of 10 mA, and a spectral bandwidth of 0.2 nm were used. After a simple dilution with Triton X-100, the sample was directly injected into the graphite tube. The operating conditions of the furnace and a detailed description of the assay were reported earlier (17).

Pharmacokinetic Analysis. The concentration of total platinum in plasma vs time data were analyzed according to Eq. (1), which describes the concentration of drug (C) as function of time (t) during and after the cessation of infusion (18):

$$C = M(1 - e^{\alpha T})e^{-\alpha t} + Q(1 - e^{\beta T})e^{-\beta t} \quad (1)$$

where α and β are the rate constants for distribution (α) and postdistribution (β) phases in the two-compartment open model, respectively, $T = t$ while the infusion is continuing, and $T = 1$ hr when the infusion is ceased. M and Q are preexponential coefficients related to A and B in the equation which expresses the concentration as function of time following intravenous rapid administration in the two-compartment model as follows (18):

$$A = -\alpha TM \quad (2)$$

$$B = -\beta TQ \quad (3)$$

These equations can readily be derived by taking the ratios of A/M and B/Q and their respective equivalents in terms of α, β, k_{21}, V_c, and dose (rate of infusion × T) as specified in Ref. 18 and rearranging.

We used a nonlinear regression analysis with equal weighting (19) to generate the values of α, β, M, and Q for each data set (i.e., each course) and calculated A and B according to Eqs. (2) and (3). These estimates were then substituted in standard equations (18) using a computer subroutine to estimate the steady-state distribution volume (V_{ss}) and apparent volume of the central compartment (V_c).

With ultrafilterable (free) platinum, the plasma concentration vs time data did not conform well to Eq. (1) (i.e., large sum of square of predicted minus observed residuals); therefore, the postinfusion data were fitted to the one-compartment model and the apparent rate constant for elimination (k_d) was generated using a nonlinear regression analysis (19). For both patients, excellent fits were obtained.

We estimated the area under the curve for both total and ultrafilterable platinum ($AUC_{0-\infty}$) by adding the area under the curve up to 24 hr [$AUC_{(0-24)}$] to the area under the tail (AUC_{tail}), which was calculated by dividing the concentration of the sample collected at 24 hr by β or k_d. The total-body clearance (TBC) for both total and free platinum was estimated by dividing the dose of AUC, whereas the volume

of distribution for free platinum was calculated by dividing TBC by k_d.

The renal clearance (RC) of platinum was estimated according to the following equation:

$$RC = \frac{A_{u(0-24)}}{AUC_{(0-24)}} \quad (4)$$

where $A_{u(0-24)}$ is the cumulative amount of platinum excreted in urine in 24 hr and $AUC_{(0-24)}$ was defined above.

To examine whether platinum clearance changes with repeated treatment, the data for TBC, AUC, and creatinine clearance obtained from each course given to the five patients who received three courses of carboplatin were subjected to a two-sample unpaired t test statistical analysis in all possible permutations, and the levels of significance of the difference were computed (19).

RESULTS

The age, sex, creatinine clearance, and diseases of the patients are listed in Table I. There were nine males and one female (the youngest), with a mean (and SE) age of 43.4 (3.6) years.

The mean (SE) values of the plasma concentrations of total platinum obtained at 0.5, 1, 3, 6, 12, 18, and 24 hr from the initiation of the 1-hr infusion were 8.236 (0.725), 11.52 (0.84), 4.933 (0.415), 1.888 (0.153), 0.829 (0.14), 0.724 (0.082), and 0.523 (0.059) mg/liter, respectively. The mean (SE) values for A, α, B, β, AUC, TBC, V_{ss}, and V_c for total platinum are presented in Table II. For patients who received multiple courses, the parameters which were generated from each course were averaged prior to calculating the mean and SE. It is noteworthy that the differences in TBC [mean (SE) for course 1, course 2, and course 3 is 2.31 (0.55), 2.27 (0.51), and 1.89 (0.28) liters/hr · m^2, respectively], AUC [mean (SE) for course 1, course 2, and course 3 is 91.1 (24.6), 86 (19.2), and 90.4 (17.9) mg · hr/liter · m^2, respectively], and creatinine clearance [mean (SE) for course 1, course 2, and course 3 is 77.6 (15), 95.9 (9.4), and 76.2 (9.8) ml/min, respectively] between courses were not significant. This indicates that platinum clearance did not change significantly with repeated treatment.

The concentration profiles of free (ultrafilterable) and total platinum in patients for whom plasma samples were also analyzed for free platinum are demonstrated in Fig. 1. It can be seen from this figure that during infusion and 2 hr thereafter platinum was predominantly (ie., >80% in one patient and 51–64% in the other) in the free form. Indeed, the mean (SE) values of the fraction of free platinum (concentration of free platinum/concentration of total platinum) at 0.5, 1, 3, 6, 18, and 24 hr from the initiation of carboplatin infusion were 83.8 (28.6), 82 (22.2), 65.2 (20.6) 54.5 (36.3), 13.3 (0.6), and 11.3 (6.5), respectively. The mean (SE) values of the pharmacokinetic parameters obtained for free platinum in these patients are presented in Table II.

The renal excretion of platinum was also investigated in six patients, and the data acquired are presented in Fig. 2. As can be seen in this figure, the cumulative percentage of the dose excreted in the urine (f_u) in 24 hr ranged from 55 to 109 (completion). The mean (SE) value of the renal clearance of platinum in these patients was 2.405 (0.228) liters/hr · m^2 (Table II), with a range of 1.335 to 2.912 liters/hr · m^2.

DISCUSSION

In contrast to cisplatin, carboplatin is a stable compound which remains intact even in less favorable media such as biological fluids. This stability has been attributed to the bidentate cyclobutane dicarboxylate ligand and is thought to be the cause for the reduced toxicity observed following its administration (20). Undoubtedly, this has afforded the use of this drug effectively as a single agent at relatively high doses (300–600 mg/m^2). Recently, more aggressive approaches including the use of higher doses (up to 1600 mg/m^2) of carboplatin alone or in combined chemotherapy have been employed (6,13–15).

Carboplatin was used in this study in combination with high-dose methotrexate (100 mg/kg) in the treatment of malignant lymphoma or nasopharyngeal carcinoma. A major concern with this treatment is the possible effect of methotrexate and its 7-OH metabolite on the pharmacokinetics of

Table II. Mean and (SE) of Pharmacokinetic Parameters for Total and Free Platinum Obtained in Cancer Patients Treated with 300 mg/m^2 of Carboplatin

Parameter	Total platinum[a]	Free platinum[b]
A, mg/liter	12.87 (0.527)	—
B, mg/liter	1.634 (0.35)	—
α, hr^{-1}	0.608 (0.068)	—
β, hr^{-1}	0.0827 (0.022)	—
V_{ss}, liters/m^2	44.29 (10.25)	—
V_c, liters/m^2	10.74 (0.62)	11.88 (1.45)
TBC, liters/hr · m^2	2.355 (0.252)	4.583 (1.059)
k_d, hr^{-1}	—	0.381 (0.043)
AUC, mg · hr/liter · m^2	76.39 (10.53)	36.32 (8.39)
RC, liters/hr · m^2	2.405 (0.228)[c]	—
f_u, %	80.1 (8.5)[c]	—

[a] Determined according to Eq. (1) from data obtained for all patients included.
[b] Determined from fitting the data obtained for patients 4 and 7 to the one-compartment open model.
[c] Mean (and SE) of data obtained from six patients.

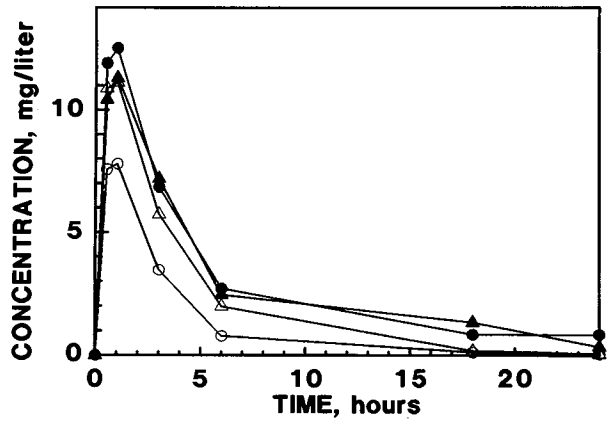

Fig. 1. Concentration vs time plots for total (filled symbols) and free (open symbols) platinum in two patients treated with 300 mg/m^2 of carboplatin by 1-hr intravenous infusion.

platinum which is totally eliminated via the kidneys since these compounds are known for their pronounced nephrotoxicity (16). To our knowledge, the pharmacokinetics of platinum in patients treated with carboplatin in combination with other anticancer drugs has not been previously addressed.

The concentration of total platinum peaked (11.52 mg/liter) at 1 hr (i.e., cessation of infusion) and declined biexponentially to 0.523 mg/liter after 24 hr from the initiation of the infusion. These data when normalized for dose per square meter and the estimates obtained in this study for α, β, TBC, and V_{ss} for total platinum (i.e., 0.608 hr^{-1}, 0.0827 hr^{-1}, 2.355 liters/hr · m^2, and 44.29 liters/m^2, respectively) are in good agreement with those reported or calculated from the reports of Van Echo *et al.* (8) (i.e., α = 0.84–1.56 hr^{-1}, β = 0.036–0.84 hr^{-1}, TBC = 0.9–2.34 liters/hr · m^2, and V_{ss} = 22.6–69.6 liters/m^2) or Harland *et al.* (10) (i.e., α = 0.37–0.88 hr^{-1}, β = 0.029–0.103 hr^{-1}). It should be noted that the age and creatinine clearance of the patients included in our study are similar to those reported for patients included in these referenced studies.

The fraction of ultrafilterable (free) platinum was 82% during infusion and declined to 11.3% after 24 hr from the initiation of the therapy. These values are similar to those previously reported for free platinum in plasma [i.e., 82% (7), >70% (8), 60–85% (9), and 69–100% during 0–4 hr from initiation of therapy (10)]. Our postinfusion concentration data exhibited a monoexponential disappearance pattern, with $t_{1/2}$, TBC, and V_d for free platinum of 1.844 hr, 4.583 liters/hr · m^2, and 11.88 liters/m^2, respectively. Similar values were reported by Curt *et al.* (9) (i.e., $t_{1/2}$ = 2–3.17 hr and TBC = 3.06–9.84 liters/hr), who also used the one-compartment model to fit the data, and even when the two-compartment model was employed (7,8,10), the values for half-life [i.e., 1.9–2.7 hr (7), 1.7–3.9 hr (8), and 1.3–2 hr (10)] and total-body clearance [i.e., 2.5–3.6 liters/hr · m^2 (7), 2.4–6 liters/hr · m^2 (8), and 7.38 liters/hr (10)] agree well with our findings.

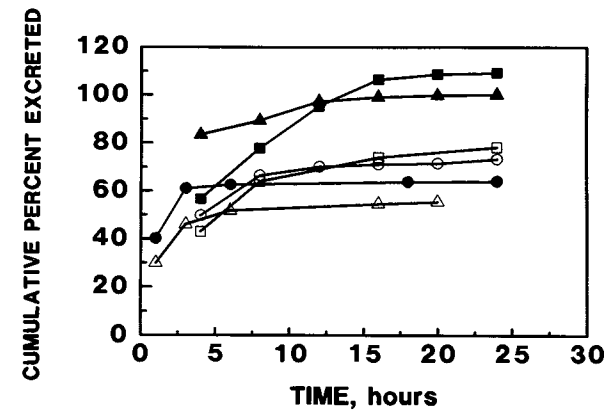

Fig. 2. Cumulative renal excretion of platinum (percentage of dose) in patients treated with 300 mg/m^2 of carboplatin by 1-hr intravenous infusion.

As demonstrated above, our results for both total and free platinum are in good agreement with those previously reported for patients treated with carboplatin as a single agent. This suggests that high-dose methotrexate as used in this study apparently does not affect the pharmacokinetics of carboplatin to a clinically important extent. This is particularly true in view of the fact that the percentage of the dose excreted in urine (0–24 hr) obtained here (i.e., 80.1%) is slightly higher than those reported earlier for this parameter [i.e., 65.7% (7), 65% (10), and 64% (11)]. Since methotrexate and its 7-OH metabolite are known for their nephrotoxicity, these urinary parameters should have been significantly reduced if the pharmacokinetics of carboplatin were indeed affected. It should be noted, however, that the only evidence that can be conclusive in this regard would have to be obtained from a control study whereby carboplatin would also be administered alone to the same patients or patients with similar vital characteristics, which, for clinical reasons, was not feasible.

ACKNOWLEDGMENTS

The authors wish to thank the administration of the King Faisal Specialist Hospital & Research Centre for its support of the pharmacokinetics program in this institution.

REFERENCES

1. B. D. Evans, K. S. Raju, A. H. Calvert, S. J. Harland, and E. Wiltshaw. *Cancer Treat. Rep.* 67:997–1000 (1983).
2. R. F. Ozols, B. C. Behrens, Y. Ostchega, and R. C. Young. *Cancer Treat. Rev.* 12 (Suppl. A):59–66 (1985).
3. M. J. Peckham, A. Horwich, M. Brada, A. Drury, and W. F. Hendry. *Cancer Treat. Rev.* 12 (Suppl. A):101–110 (1985).
4. R. Canetta, M. Rozencqeig, and S. K. Carter. *Cancer Treat. Rev.* 12 (Suppl. A):125–136 (1985).
5. M. E. Gore, A. H. Calvert, and I. E. Smith. *Eur. J. Cancer Clin. Oncol.* 23:1391–1397 (1987).
6. I. E. Smith and B. D. Evans. *Cancer Treat. Rev.* 12 (Suppl. A):73–75 (1985).
7. J. M. Koeller, D. L. Trump, K. D. Tutsch, R. H. Earhart, T. E. Davis, and D. C. Tormey. *Cancer* 57:222–225 (1986).
8. D. A. Van Echo, M. J. Egorin, M. Y. Whitacre, E. A. Olman, and J. Aisner. *Cancer Treat. Rep.* 68:1103–1114 (1984).
9. G. A. Curt, J. J. Grygiel, B. J. Corden, R. F. Ozols, R. B. Weiss, D. T. Tell, C. E. Meyers, and J. M. Collins. *Cancer Res.* 43:4470–4473 (1983).
10. S. J. Harland, D. R. Newell, Z. H. Siddik, R. Chadwick, A. H. Calvert, and K. R. Harrap. *Cancer Res.* 44:1693–1697 (1984).

11. D. W. DeGregorio, B. L. Lum, W. M. Holleran, B. J. Wilbur, and B. I. Sikic. *Cancer Chemother. Pharmacol.* 18:235–238 (1986).
12. J. G. McVie, W. ten Bokkel Huinink, R. Dubbelman, H. Franklin, W. van der Vijgh, and I. Klein. *Cancer Treat. Rev.* 12 (Suppl. A):35–41 (1985).
13. W. ten Bokkel Huinink, M. E. L. van der Burg, J. B. Vermorken, and A. van Oosterom. *Proc. Eur. Conf. Clin. Oncol.* 3:177 (1985) (abstr.).
14. J. Wagstaff and D. Crowther. *Proc. Eur. Conf. Clin. Oncol.* 3:119 (1985) (abstr.).
15. R. Rosso, P. F. Conte, M. Bruzzone, S. Chiara, G. Giaccone, E. Materman, and C. R. Franks. *Proc. Eur. Conf. Clin. Oncol.* 3:115 (1985) (abstr.).
16. B. A. Chabner, C. E. Myers, and V. T. Oliverio. *Semin. Oncol.* 4:165–191 (1977).
17. A. El-Yazigi and I. Al-Saleh. *Ther. Drug Monit.* 8:318–320 (1986).
18. M. Gibaldi and D. Perrier. *Pharmacokinetics,* Marcel Dekker, New York, 1975.
19. D. J. Dixon (ed.), *BMDP Statistical Software,* University of California Press, Berkeley, 1983.
20. L. Lenaz. *Paraplatin (Carboplatin) Compendium of Recent Data,* Bristol-Meyers International Group, New York, 1986.