Cancer Chemother Pharmacol (1988) 21: 57–60

Cancer Chemotherapy and Pharmacology

Pharmacokinetics of carboplatin after intraperitoneal administration

F. Elferink[1], W. J. F. van der Vijgh[1], I. Klein[1], W. W. ten Bokkel Huinink[2], R. Dubbelman[2], and J. G. McVie[2]

[1] Department of Oncology, Free University Hospital, Amsterdam, The Netherlands
[2] The Netherlands Cancer Institute, Amsterdam, The Netherlands

Summary. The pharmacokinetics of carboplatin, ultrafilterable platinum, and total platinum after intraperitoneal (i.p.) administration were studied in peritoneal fluid, plasma, red blood cells (RBCs), and urine during a phase-I trial in patients with minimal, residual ovarian cancer. Samples were collected from 7 patients who had received carboplatin (200–500 mg/m^2) in 2 l dialysis fluid. The fluid was withdrawn after a 4-h dwell. Platinum concentrations were measured by flameless atomic absorption spectrometry, and intact carboplatin was determined by HPLC with electrochemical detection. Peak concentrations of carboplatin in plasma were obtained 2 h after the end of instillation. The mean ratio of peak concentrations of carboplatin in instilled fluid and plasma was 24 ± 11. The peritoneal clearance of carboplatin was 8 ± 3 ml/min, which was 12 times less than the plasma clearance (93 ± 32 ml/min). Due to this clearance ratio, the AUCs for the peritoneal cavity were about 10 times higher than those for plasma. On average, 34% ± 14% of the dose was still present in the instillation fluid that had been withdrawn after a dwell time of 4 h. In plasma, the mean value of AUC/D_{net} (D_{net} = Dose − amount recovered from the peritoneal cavity) after i.p. administration was comparable with that of AUC/D after i.v. administration. This means that unrecovered carboplatin (66%) was completely absorbed from the peritoneal cavity. It may be expected from this bioavailability that the maximum tolerated dose (MTD) of i.p.-administered carboplatin with a 4-h dwell is around 1.5 times higher than that after i.v. administration. Overall pharmacokinetic parameters of carboplatin and platinum in plasma were comparable after i.p. and i.v. administration.

Introduction

Intraperitoneal (i.p.) administration of cisplatin to patients with minimal, residual ovarian cancer may provide significant advantages compared to other therapeutic approaches. Complete remissions were achieved in 30% of heavily pretreated patients [18], which is higher than previously observed after second-line intravenous (i.v.) chemotherapy [16]. Toxicity of i.p. cisplatin was acceptable at conventional doses (60–120 mg/m^2), and higher doses could be given by concomitant i.v. administration of sodium thiosulfate [12, 18]. We observed protection from cisplatin-induced nephrotoxicity, thought to be due to a chemical reaction between cisplatin and thiosulfate within the kidneys [8], but severe neurotoxicity was dose-limiting. As the effect of sodium thiosulfate on the antitumor activity of cisplatin is still not clear [12], an alternative drug was sought for intraperitoneal testing, namely, carboplatin (diammine (1,1-cyclobutanedicarboxylato) platinum (II), CBDCA). This drug seems to have activity against ovarian cancer comparable to that of cisplatin [21], but with less neuro- and nephrotoxicity [2].

Because carboplatin is more stable than cisplatin both in vitro [4, 8] and in vivo [1, 10], metabolic elimination is low. Principally, this means that the unaltered drug will reach the tumor by absorption from the peritoneal cavity and via the general circulation. On the other hand, it should be expected that its high hydrophilicity (water solubility is 50 m*M* [4]) will produce a low peritoneal clearance [6], resulting in a high peritoneal vs plasma concentration ratio. These properties make carboplatin a candidate for i.p. administration. A phase-I study was started and preliminary results have already been published [14]. The purpose of this study was to investigate the pharmacokinetics of carboplatin, free (unbound) platinum, and total platinum in peritoneal fluid, plasma, red blood cells (RBCs), and urine of patients participating in the phase-I study and to compare the results with those obtained after i.p. administration of cisplatin.

Patients and methods

Patients. Pharmacokinetic parameters were studied during seven courses of carboplatin (dose range, 200–500 mg/m^2) administered i.p. to six patients with minimal, residual ovarian carcinoma. The median age was 60 years (range, 49–71). All patients had been pretreated with i.v. cisplatin and/or carboplatin. No chemotherapy had been given within 3 weeks of the pharmacokinetic study. Creatinine clearances (normalized to 1.73 m^2 body-surface area), white blood cell counts, and platelet counts were higher than 40 ml/min, $3{,}000 \times 10^6$/l and 100×10^9/l, respectively.

Lyophilized carboplatin was provided by Bristol Myers. The appropriate amount was dissolved in water and subsequently added to 2 l instillation fluid (CAPD, Trave-

Offprint requests to: W. J. F. van der Vijgh, Department of Oncology, Free University Hospital, De Boelelaan 1117, NL-1081 HV Amsterdam, The Netherlands

nol, Amsterdam, The Netherlands) containing chlorides of sodium, calcium, and magnesium, as well as sodium lactate and glucose. The stability of 0.5 mg/ml carboplatin in this medium was tested by HPLC (column RP-18, mobile-phase water [9], UV detection 214 nm). Degradation was less than 5% after 72 h at room temperature. The solution was administered via a Tenckhoff catheter into the peritoneal cavity within 13–21 min. The fluid was withdrawn after a 4-h dwell. Distribution of fluid throughout the peritoneal cavity was checked 1 day before treatment by a computerized tomography (CT) scan [18].

Sampling. Samples of blood and peritoneal fluid were taken before, halfway through, and at the end of i.p. instillation as well as 10, 20, and 30 min and 1, 2, 3, 4, 5, 6, 7, and 12 h thereafter. Blood samples were also drawn at 1, 2, 3, 4, and 5 days after administration. Plasma, plasma ultrafiltrate, RBCs, and ultrafiltrate of peritoneal fluid were obtained immediately by centrifugation and ultrafiltration through YMT filters of the MPS-1 micropartition system (Amicon, Oosterhout, The Netherlands; cutoff, 30,000 daltons) as previously described [19]. Urine was collected in successive intervals at 2, 4, 6, 12, 18, 24, 48, 72, 96, and 120 h after the start of i.p. instillation. All samples were frozen until analysis. The stability of carboplatin during sample processing and storage at −25° C was determined. Half-lives at room temperature and at −25° C, respectively, were 19.9 days and 28 weeks in plasma ultrafiltrate and 6.7 days and 32–212 weeks in urine [10], which permitted the analysis to be done within a few weeks.

Analysis. Platinum (Pt) concentrations were determined in plasma and peritoneal fluid (total Pt), in ultrafiltrate of plasma and peritoneal fluid (free Pt), and in RBCs and urine by fameless atomic absorption spectrometry as previously described [20]. Intact carboplatin was determined in ultrafiltrates and urine by HPLC with differential pulse polarographic detection [9]. Calibration lines were made in plasma ultrafiltrate, urine, and water.

Pharmacokinetic data analysis. Half-lives for carboplatin and Pt in the peritoneal cavity during the 4-h dwell were determined by curve stripping by hand. The areas under the plasma concentration-time curves (AUC) and first moment of plasma concentration-time curves (AUMC) were calculated with the linear trapezoidal rule and extrapolated to infinity [11]. The clearance from the peritoneal cavity CL_{pc} was determined by multiplying the peritoneal elimination rate constant (1–4 h) and the volume withdrawn after the 4-h dwell. The systemic clearance (CL) was defined as D_{net}/AUC, in which D_{net} = dose − the amount recovered from the peritoneal cavity. The volume of distribution at steady state V_{ss} was determined from $CL(AUMC/AUC - 1/k_a)$ [17], in which k_a is the rate constant of absorption calculated from plasma concentration-time points by curve stripping [11]. Renal clearance was determined from $CL_R = CUE_{(0-12\,h)}/AUC_{(0-12\,h)}$, in which CUE is the cumulative urinary excretion. Values of clearances and volumes of distribution were normalized to 1.73 m^2 standard body-surface area.

Results

Peak concentrations measured in the peritoneal cavity and plasma are shown in Table 1. Peak levels in the peritoneal fluid measured at the end of instillation were equal for carboplatin, free Pt, and total Pt. These values were lower than the concentrations in the administered solutions due to the disappearance of the drug from the peritoneal cavity during instillation and to dilution by the fluid present in the peritoneal cavity at the time of administration. Concentrations of carboplatin and free Pt in the peritoneal cavity showed a rapid decline during the first 30 min (Table 2), probably due to distribution into the abdominal tissues and leakage into the general circulation, followed by a slower decrease. Peak concentrations in plasma were reached between 2 and 3 h after the start of instillation. The highest peak concentrations were obtained for total Pt; peak heights were slightly lower for carboplatin and free Pt. The small difference between the peak concentrations of the three species (Table 1) indicates that degradation of carboplatin in the peritoneal cavity and in plasma was very low during these first hours. This observation is illustrated by the semilogarithmic concentration vs time curves of a representative patient in Fig. 1.

Of the administered dose, 34%±14% (mean ± SD) was still present in the instillation fluid that was withdrawn after a 4-h dwell (Table 1). Of the administered volume, 99%±12% was recovered. The amount retained by the body (D_{net}) was calculated as the amount of Pt administered minus the amount recovered. After withdrawal of the instillation fluid, the concentrations of carboplatin and free Pt in the remaining peritoneal fluid showed a steep decline due to the decreased volume and unaltered clear-

Table 1. Doses and peak concentrations measured in the peritoneal cavity (pc) and in plasma of individual patients

Patient No.	D (mg/m²)	D (mg)	Recovered (% D)	$C_{peak,\,pc}$[a] carboplatin free Pt total Pt (μ*M*)	$C_{peak,\,plasma}$[b] carboplatin (μ*M*)	free Pt (μ*M*)	total Pt (μ*M*)
1	200	310	21	356	22.2	20.0	19.9
2	200	330	31	356	25.4	22.4	30.2
3A	200	350	52	419	8.7	9.4	10.8
3B	300	525	45	733	21.9	24.2	24.9
4	300	500	14	526	36.0	45.9	41.0
5	400	680	26	763	25.8	43.6	44.0
6	500	950	47	1084	32.6	36.3	38.4

[a] At the end of instillation
[b] At 2 h after the end of instillation

Table 2. Pharmacokinetic parameters (mean ± SD) of carboplatin and free Pt in the peritoneal cavity (pc)

Parameter		Carboplatin	Free Pt
$t_{1/2\alpha}$ (0–30 min)[a]	min	24± 6	15± 6
$t_{1/2\beta}$ (1–4 h)[a]	min	201±98	254±99
$t_{1/2}$ (5–7 h)	min	49±12	58±28
CL_{pc}[b]	ml/min	8± 3	6± 2

[a] Calculated by the curve-stripping procedure
[b] Normalized to 1.73 m^2 body-surface area

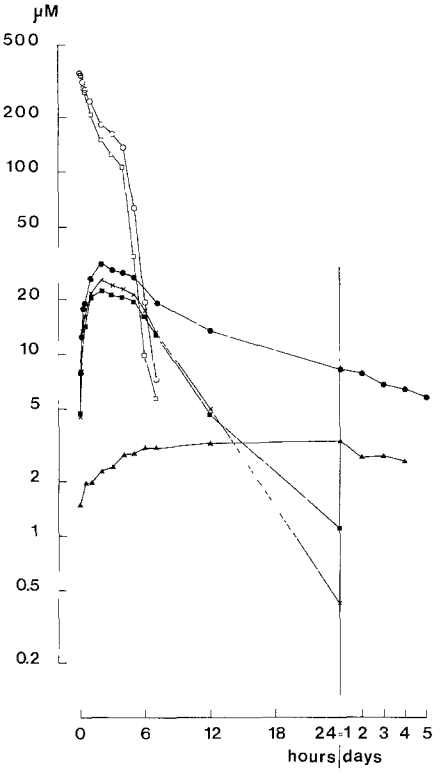

Fig. 1. Semilogarithmic concentration-time curves of carboplatin (o, x), free Pt (□, ■), and total Pt (●) in peritoneal fluid (○, □) and in plasma (x, ■, ●), and Pt in RBCs (▲) in patient no. 2 after i.p. administration of 200 mg/m^2 carboplatin for 14 min

ance. The peritoneal clearances of carboplatin and free Pt were small and not significantly different (Table 2).

The concentration-time curves for total Pt in plasma clearly diverged from those for free Pt and carboplatin due to protein binding (Fig. 1). The final half-life of total Pt as measured over days 1–5 was 6.0±1.4 days. Half-lives of about 3 h were measured for both carboplatin and free Pt over 5–12 hours after the start of instillation (Table 3). Concentration-time curves for carboplatin and free Pt in plasma were superimposable up to 12 h after administration. The initial similarity of the pharmacokinetics of carboplatin and free Pt indicates a low rate of formation of low-molecular-weight metabolites. Despite comparable plasma concentrations of carboplatin and free Pt, the cumulative urinary excretion of carboplatin accounted for only two-thirds of the total amount of Pt excreted over the first 6 h after the start of administration (Table 3). Consequently, the renal clearance of carboplatin was lower than that of free Pt, although the systemic clearance of carboplatin was higher than that of free Pt. The volumes of distribution of carboplatin and free Pt were much lower than those of total Pt (Table 3).

Table 3. Pharmacokinetic parameters (mean ± SD) in plasma and urine

Parameter		Carboplatin	Free Pt	Total Pt
$t_{1/2}$ (5–12 h)	min	169±48	176±41	290±91[a]
k_a	$\times 10^{-3}$ min^{-1}	13± 4	17± 8	19± 8
AUC/D_{net}	min m^2 per l	21± 8	24± 6	160±65
CL[b]	ml/min	93±32	78±21	12± 4
V_{ss}[b]	l	20± 4	19± 4	125±42
CUE[c] (0–6 h)	% D_{net}	26± 7	42±12	42±12
CUE (0–5 d)	% D_{net}	–	69±11	69±11
CL_R[b]	ml/min	35±15	50±19	–

[a] Not corrected for subsequent phases
[b] Normalized to 1.73 m^2 body-surface area
[c] CUE, Cumulative urinary excretion

Table 4. Ratios (mean ± SD) of pharmacokinetic parameters in the peritoneal cavity (pc) and plasma

Parameter	Carboplatin (range)	Free Pt (range)
$C_{peak,pc}/C_{peak}$	24±11 (13.5–42.2)	24±12 (11.5–44.6)
AUC_{pc}/AUC	10±7 (3.9–22.6)	11±8 (3.3–26.3)
CL_{pc}/CL	0.10±0.06 (0.032–0.189)	0.08±0.05 (0.029–0.175)

The advantage of i.p. over i.v. administration in terms of exposing the tumor to the drug is illustrated by the high ratios of peak concentrations and AUCs for the peritoneal cavity and plasma (Table 4), explained by the low ratio of clearances from both compartments.

Maximum levels of Pt bound to RBCs (1.7–4.1 μ*M*) were reached at a median time of 8 h after instillation (range, 6–24 h). These levels represented 0.6% of the dose with a standard deviation of 0.2% (n = 6), calculated on a standard amount of 2 l blood cells. The half-life of Pt in RBCs (days 1–5) was 9±2 days (n = 4).

Discussion

Pharmacokinetic theory has provided a basis for the use of i.p. chemotherapy by predicting a long-time concentration gradient between the peritoneal cavity and plasma [5, 6]. Several drugs, including cisplatin, have been administered to patients with minimal, residual ovarian cancer [15]. Since penetration of drugs from the peritoneal cavity into the tumor is restricted to a few millimeters [13], it is important that effective plasma concentrations are reached when tumor nodules larger than a few millimeters are present [15]. Consequently, i.p. administration may be useful when peak concentrations and AUCs for the peritoneal cavity are much higher than those obtained for plasma, whereas plasma AUCs have to be comparable to those after i.v. administration. The results of this pharmacokinetic study suggest that carboplatin is suited for i.p. administration, based on these criteria.

Peak concentrations in plasma were approximately 4 times lower in instilled doses than those after short-term

i.v. doses [10]. Plasma half-lives of carboplatin and free Pt, measured after withdrawal of the dialysis fluid, were somewhat longer than those after i.v. bolus administration ($t_{½\beta}$ = 2 h [10]) due to absorption of carboplatin from the remaining fluid in the peritoneal cavity. The final half-life of total Pt in plasma was in good agreement with that found after i.v. administration of carboplatin (5.8 days) [10] and cisplatin (5.3 days) [20], reflecting the turnover rates of proteins to which Pt was bound. Systemic and renal clearances of carboplatin were not significantly different from those observed after i.v. administration (101 ± 21 and 44 ± 16 ml/min, respectively) [10]. However, both clearances of free Pt were somewhat lower after i.p. than after i.v. administration (78 vs 107 and 50 vs 81 ml/min, respectively) [10], probably indicating that freely circulating platinum species may partly have a different chemical composition after i.p. administration from that after i.v. administration. The CUE of both carboplatin and free Pt were also lower after i.p. than after i.v. administration ($CUE_{0-6\,h}$ = 41% ± 14% D and 68% ± 7% D for carboplatin and free Pt, respectively) [10]. This can be considered the result of both the lower CL_R and the delayed absorption of the drug into the systemic circulation after i.p. administration. The different amounts of intact drug and elemental Pt found in the urine, whereas plasma AUCs were similar, may be explained by degradation of carboplatin in the bladder and during collection and storage of the urine samples. The apparent volume of distribution at steady state V_{ss} for carboplatin and free Pt was comparable to the values obtained after i.v. carboplatin (17 ± 2 l) [10]; binding to RBCs also compared well with that observed after i.v. administration.

The successful use of cisplatin in i.p. chemotherapy [18] led to the trial of i.p. carboplatin. The peritoneal vs plasma ratio of AUCs for carboplatin and free Pt was higher than the AUC ratio for free Pt of 4 (0–24 h) after i.p. cisplatin [3]. This is the result of the low CL_{pc} of carboplatin compared to that of cisplatin (22 ml/min [12]), probably because cisplatin is not only eliminated from the peritoneal cavity by absorption, but also by chemical degradation. In addition, carboplatin is more hydrophilic and therefore will pass from the peritoneum less quickly than cisplatin. In another study of i.p. cisplatin [12], the AUC ratio for diethyldithiocarbamate (DDTC)-reactive platinum was 15. However, since not all free Pt species are DDTC-reactive, comparison with studies measuring free Pt [3] is difficult. The low peritoneal clearance of carboplatin resulted in a high drug exposure of the tumor from the lumen of the peritoneal cavity.

The values of AUC/D_{net} for carboplatin and free Pt were comparable with those of AUC/D after i.v. administration (18 ± 5 and 17 ± 4 min m^2 per l, respectively) [10]. Therefore, it may be concluded that the amount of drug not recovered from the instillation fluid after the 4-h dwell (66%) was completely absorbed into the general circulation. Because the dose-limiting myelotoxicity of carboplatin correlates linearly with the AUC [7], it may be expected that the maximum tolerable dose of carboplatin after i.p. administration will be 1.5 times higher than that after i.v. administration.

Acknowledgements. This study was supported by a grant from the Netherlands Cancer Foundation (KWF), No. AUKC VU 83-7. We thank F. J. Varossieau for technical assistance.

References

1. Calvert AH, Harland SJ, Newell DR, Siddik ZH, Harrap KR (1985) Phase I studies with carboplatin at the Royal Marsden Hospital. Cancer Treat Rev 12 [Suppl A]: 51
2. Canetta R, Rozencweig M, Carter SK (1985) Carboplatin: the clinical spectrum to date. Cancer Treat Rev 12 [Suppl A]: 125
3. Casper ES, Kelsen DP, Alcock NW, Lewis JL Jr (1983) Ip cisplatin in patients with malignant ascites: pharmacokinetic evaluation and comparison with the i.v. route. Cancer Treat Rep 67: 235
4. Cleare MJ, Hydes PC, Malerbi BW, Watkins DM (1978) Anti-tumour platinum complexes: relationships between chemical properties and activity. Biochimie 60: 835
5. Dedrick RL (1985) Theoretical and experimental bases of intraperitoneal chemotherapy. Semin Oncol 12 [Suppl 4]: 1
6. Dedrick RL, Meyers CE, Bungay PM, DeVita VT Jr (1978) Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. Cancer Treat Rep 62: 1
7. Egorin MJ, Van Echo DA, Tipping SJ, Olman EA, Whitacre MY, Thompson BW, Aisner J (1984) Pharmacokinetics and dosage reduction of cis-diammine (1,1-cyclobutanedicarboxylato)-platinum in patients with impaired renal function. Cancer Res 44: 5432
8. Elferink F, Van der Vijgh WJF, Klein I, Pinedo HM (1986a) Interaction of cisplatin and carboplatin with sodium thiosulfate: reaction rates and protein binding. Clin Chem 32: 641
9. Elferink F, Van der Vijgh WJF, Pinedo HM (1986b) On-line differential pulse polarographic detection of carboplatin in biological samples after chromatographic separation. Anal Chem 58: 2293
10. Elferink F, Van der Vijgh WJF, Klein I, Vermorken JB, Gall HE, Pinedo HM (1988) Pharmacokinetics of carboplatin after intravenous administration. Cancer Treat Rep (in press)
11. Gibaldi M, Perrier D (1982) Pharmacokinetics, 2nd edn. Marcel Dekker Inc, New York
12. Howell SB, Pfeifle CE, Wung WE, Olshen RA (1983) Intraperitoneal cisdiamminedichloroplatinum with systemic thiosulfate protection. Cancer Res 43: 1426
13. Levin VA (1986) Clinical anticancer pharmacology: some pharmacokinetic considerations. Cancer Treat Rev 13: 61
14. McVie JG, Ten Bokkel Huinink WW, Dubbelman R, Franklin H, Van der Vijgh WJF, Klein I (1985) Phase I study and pharmacokinetics of intraperitoneal carboplatin. Cancer Treat Rev 12 [Suppl A]: 35
15. Myers C (1984) The use of intraperitoneal chemotherapy in the treatment of ovarian cancer. Semin Oncol 11: 275
16. Neijt JP, Van der Burg MEL, Vriesendorp R, Van Lindert ACM, Van Lent M, Ten Bokkel Huinink WW, Van Oosterom AT, Kooyman CD, Hamerlynck JVTH, Van Houwelingen JC, Pinedo HM (1984) Randomized trial comparing two combination chemotherapy regimens (HEXA-CAF vs CHAP-5) in advanced ovarian carcinoma. Lancet 2: 594
17. Perrier D, Mayersohn M (1982) Noncompartmental determination of the steady-state volume of distribution for any mode of administration. J Pharm Sci 71: 372
18. Ten Bokkel Huinink WW, Dubbelman R, Aartsen E, Franklin H, McVie JG (1985) Experimental and clinical results with intraperitoneal cisplatin. Semin Oncol 12 [Suppl 4]: 43
19. Van der Vijgh WJF, Klein I (1986) Protein binding of five platinum compounds. Comparison of two ultrafiltration systems. Cancer Chemother Pharmacol 18: 129
20. Vermorken JB, Van der Vijgh WJF, Klein I, Gall HE, Van Groeningen CJ, Hart GAM, Pinedo HM (1986) Pharmacokinetics of free and total platinum species after rapid and prolonged infusions of cisplatin. Clin Pharmacol Ther 39: 136
21. Wiltshaw E (1985) Ovarian trials at the Royal Marsden. Cancer Treat Rev 12 [Suppl A]: 67

Received February 19, 1987/Accepted September 10, 1987