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Short communication

Comparative intraperitoneal pharmacokinetics of three platinum analogues

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Summary. The pharmakokinetic profiles of intraperitoneally infused platinum analogues were determined in 13 women exhibiting minimal residual disease following surgery and systemic chemotherapy for epithelial ovarian cancer or fallopian tube carcinoma by following the disposition of tracer doses of ^{195m}Pt radiolabel. Six patients received iproplatin, four were given cisplatin and three received carboplatin. The present data demonstrate no difference in the disposition of total platinum between these three analogues, but differences in the kinetics of free platinum may exist.

Introduction

Despite the high complete and partial clinical response rates achieved using modern platinum-based combination chemotherapy regimens in epithelial ovarian cancer, only 20%–30% of women exhibit a pathologically complete response at second-look laparotomy [5, 6]. Even following optimal initial surgery and appropriate chemotherapy, as many as 30%–50% of women are diagnosed as having residual disease at second-look surgery [9, 13]. Ultimately, these patients relapse and die of their disease. Patients with minimal residual disease following second-look laparotomy have therefore been identified as targets for new therapeutic approaches designed to eliminate any such remaining disease. A procedure currently under investigation involves the use of intraperitoneal chemotherapy.

Using modelling studies, Dedrick et al. [2] have suggested that a major pharmacokinetic advantage can be achieved by the direct instillation of certain anticancer agents into the peritoneal cavity. It has subsequently been shown that large ratios of peritoneal to plasma concentrations of cytotoxic agents can be achieved by intraperitoneal administration [4]. Some 30% of patients showing minimal residual disease following treatment with systemic therapy who are treated with intraperitoneal cisplatin eventually achieve a complete remission [11]. The ratio of peritoneal to plasma concentration achieved by intraperitoneal administration may in part be governed by the molecular weight, physical properties and systemic clearance of the drugs used [2].

Carboplatin and iproplatin are analogues of cisplatin that have physical properties and pharmacokinetic profiles that are different from those of the parent compound. The molecular weight of cisplatin is 300.08 kDA vs 371.26 kDA for carboplatin and 339.09 kDa for iproplatin. Moreover, both iproplatin and carboplatin are more water-soluble and less chemically reactive than cisplatin (aqueous solubility: carboplatin, 50 nM; iproplatin, 44 nM; cisplatin, 8.9 nM [3]). Therefore, based on physicochemical data, one would expect both carboplatin and iproplatin to be cleared more slowly than cisplatin from the peritoneal cavity. We thus decided to determine whether any pharmacokinetic advantage exists for any of these three analogues.

Patients and methods

Patients and intraperitoneal administration. In all, 13 patients (11 with epithelial ovarian cancer and 2 with carcinoma of the fallopian tube) exhibiting minimal residual disease following second-look laparotomy were treated with platinum analogues via the intraperitoneal route. All patients had previously been treated with systemic platinum-based combination chemotherapy for histologically proven epithelial ovarian cancer or fallopian tube carcinoma. Six subjects were treated with iproplatin (at doses ranging between 150 and 300 mg/m^2), four received cisplatin (50–100 mg/m^2) and three were given carboplatin (400 mg/m^2). Initial creatinine clearances, white blood cell counts and platelet counts were >50 ml/min, $3{,}500 \times 10^6$/l and 150×10^9/l, respectively, in all patients.

The therapeutic dose of platinum analogue was dissolved in 2 l dialysis fluid (normal saline for cisplatin and iproplatin and 5% dextrose for carboplatin). The dialysate fluid was warmed to body temperature before instillation. Immediately before intraperitoneal administration, approximately 100–200 mCi of a tracer dose of platinum 195m radio-

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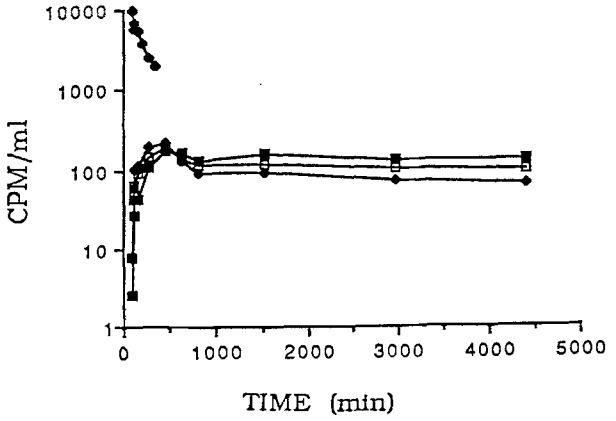

Fig. 1. Plasma, whole blood, red cell and peritoneal fluid levels of proplatin tagged with ^{195}Pt receiving 150 mg/m^2 intraperitoneally (*CPM*, Counts per minute; □, whole blood; ◆, plasma (*lower curve*); ■, red blood cells; ◆, pertioneal fluid (*upper curve*)

label was added to the infusion bag containing the therapeutic dose. The fluid was given through a temporary peritoneal dialysis catheter that had been inserted using local anaesthesia. Before delivery of the platinum analogue, 30 ml Omnapaque radiographic contrast media dissolved in 500 ml normal saline was instilled and the distribution of media was assessed using computerised tomography. The 500 ml normal saline containing Omnapaque was removed immediately after scanning. In all cases distribution was satisfactory. The dialysis fluid was left to dwell in the peritoneal cavity for 4 h; in all cases, the entire 2 l of fluid were drained after the 4-hour dwell period. Patients underwent a maximum of three courses of intraperitoneal treatment before being reassessed, when possible, by third-look laparotomy/laparoscopy. Pharmacokinetic studies were performed only during the first cycle of intraperitoneal treatment.

Preparation of radiolabelled platinum analogues. The platinum radionuclide used in these investigations was Pt 195m, which has a half-life of 4.02 days and decays predominantly by internal transition to the stable isotope ^{195}Pt. Platinum 195m was produced by neutron irradiation of enriched ^{195}Pt (95.06% purity; purchased from Oak Ridge National Laboratory, Oak Ridge, Tenn., USA) at a neutron flux of 2×10^{14} ns^{-1} cm^{-2} for up to 4 days. Typically, a 50-mg sample of ^{194}Pt was irradiated and used for synthesis of the three platinum analogues as described elsewhere [1, 10, 12].

Pharmacokinetic sampling. Samples of peritoneal fluid were taken at 5, 15 and 30 min and at 1, 2, 3 and 4 h after intraperitoneal drug administration. In addition, a sample of peritoneal fluid was taken after drainage had been completed. Heparinised serial blood samples 5 ml were drawn at 5, 15 and 30 min and at 1, 2, 3, 6, 9, 12, 24, 48 and 72 h following drug administration. Urine fractions were collected at 0–1, 1–6, 6–12, 12–24, 24–48, and 48–72 h; the total volume of each collection was recorded and a 10-ml aliquot was retained for analysis.

Measurement of samples. Concentrations of radiolabel were measured by gamma energy counting. For minimisation of errors in these measurements, a method of parallel standards was used, i.e. parallel to the dose, a standard was made, and the activity in the two samples was measured in an identical manner. During dosing of the patients, the standard was diluted by a known factor for counting in parallel with the blood, plasma and other fluids. Radioactivity was measured in whole blood, plasma, red cells, urine and intraperitoneal fluid.

Statistical analyses. The AUCs for the peritoneal and plasma concentration-time profiles were calculated using the trapezoidal rule. The amount of radioisotope absorbed from the peritoneal cavity (D_{net}) was derived from the formula $D_{net} = D_{inj} - D_{rec}$, where D_{inj} represent the dose of radiolabelled isotope injected into the peritoneal cavity and D_{rec} indicates the dose recovered from the peritoneal fluid at the end of the 4-h dwell period. The percentage of analogue absorbed (%A) into the systemic circulation was therefore $(D_{net}/D_{inj}) \times 100$. Kruskall-Wallis tests were used to compare differences in the peak ratios of total peritoneal platinum to total plasma platinum between the three analogues and the corresponding AUC ratios.

Results

Following intraperitoneal administration of the platinum analogue, the concentration of Pt 195m in the peritoneal cavity reached a peak immediately after the end of the infusion. Peak plasma concentrations of analogue were attained some 3–6 h after drug administration. An example of the disposition of total platinum in red blood cells, plasma, whole blood and peritoneal fluid is shown in Fig. 1.

The median peak peritoneal to plasma concentration ratios between cisplatin, carboplatin and iproplatin were 17.5 (range, 15.8–19.4), 38.1 (range, 32–73.7) and 24.1

Table 1. Pharmacokinetic parameters in 13 patients receiving intraperitoneal platinum analogues

	Analogue			P value[a]
	Cisplatin ($n = 4$)	Carboplatin ($n = 3$)	Iproplatin ($n = 6$)	
AUC_{ip}/ $AUC_{p\ 0-6}$[b]	10.6 (2.1–134.3)	14.4 (2.2–19.3)	12.6 (2.5–31.6)	$P > 0.5$
$Cpeak_{ip}$/ $Cpeak_{pl}$[c]	17.5 (15.8– 19.4)	38.1 (32 –73.7)	24.1 (2.9–55.7)	$0.2 > P > 0.1$
% absorbed[d]	84.4 (79.1– 85.3)	62.8 (56 –91.7)	66.8 (43.9–77.6)	$0.1 > P > 0.05$
% excreted over 0–24 h	5.3 (2 –18.1)	49.4 29.9–56.4)	37.5 (30.8–62.4)	$0.02 < P < 0.05$

Data represent median values; ranges are indicated in parentheses. n, Number of patients

[a] Kruskall-Wallis test

[b] $AUC_{ip}/AUC_{pl\ 0-6}$ = peritoneal to plasma AUC ratio (0–6 h)

[c] Ratio of peak peritoneal concentration ($Cpeak_{pe}$) to peak plasma concentration ($Cpeak_{pl}$)

[d] Percentage absorbed from the peritoneal cavity

(2.9–55.7), respectively (Table 1). There was no statistically significant difference in peak concentration ratios, AUC ratios or the percentage absorbed from the peritoneal fluid between any of the three analogues. However, the 24-h excretion of cisplatin was significantly lower than that of the other two analogues. Following the removal of the intraperitoneal fluid, there was a prolonged decline in the concentration of isotope in the plasma, which continued for several days.

Discussion

It must be stressed that these results refer only to the disposition of total platinum and not to that of free ultrafiltrable platinum, which may be the more important species in terms of the active pharmacological moiety. The reason for this is that platinum analogues react with proteins and other biological macromolecules to form relatively stable complexes and, in the case of cisplatin, this happens very readily [8]. Since the half-life of Pt 195m is approximately 4 days, measurement of this isotope provides information only about both bound and free platinum together. Hence, this assay lacks the specificity of flameless atomic absorption spectroscopy or high-performance liquid chromatography.

Nevertheless, there were no apparent differences in the pharmacokinetics of total platinum disposition between the three analogues tested. More importantly, nearly 70%–80% of each of the three analogues was absorbed from the peritoneal cavity, suggesting that there may have been no difference in total platination among the three analogues. Moreover, these data do not reveal any cellular pharmacokinetic advantage that may exist for one particular analogue over the others. Animal studies have demonstrated that cisplatin may penetrate tumour nodules more readily than carboplatin [7].

In conclusion, the data presented in this report demonstrate that there are no significant differences in any of the total platinum pharmacokinetic parameters measured between intraperitoneally delivered cisplatin, carboplatin or iproplatin and that most of each of the three analogues is absorbed from the peritoneal cavity.

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