Dear Sir,

The antineoplastic agent cisplatin (CP) is active against a large variety of human cancers. Under very specific circumstances, we had to administer CP to an anuric patient with a lung carcinoma who was undergoing peritoneal dialysis for end-stage renal disease (ESRD). CP was administered by peritoneal dialysis since this route has been used by Howell et al. [1] for intraperitoneal tumors. This treatment gave us the opportunity to study the systemic exposure to this chemotherapeutic agent and to evaluate the pharmacokinetics of free (FP) and total (TP) platinum.

Case Report

The patient was a 55-year-old man with ESRD who had been treated by continuous ambulatory peritoneal dialysis for 3 months. An undifferentiated lung carcinoma requiring chemotherapy with CP was discovered. The requisite dose of CP (200 mg) was diluted to isotonicity with sterile water, suspended in 2 liters of peritoneal dialysis solution and introduced through a Tenckhoff catheter into the peritoneal cavity by gravity flow over 10 min. After a single 6-hour dwell, the cavity was drained as completely as possible, and another bag of peritoneal dialysis solution without CP was instilled into the peritoneal cavity. This procedure was repeated every 6 h. Venous blood samples obtained at various times between the end of administration and day 8 were immediately centrifuged and the plasma was removed. Plasma ultra-filtrates were obtained by using micropartition system MPS-I (Amicon*) and then centrifuged at 2,000 g for 15 min. The concentrations of TP and FP were determined by means of flameless atomic absorption spectroscopy with a detection limit of 0.01 µg/ml [2].

Comments

[1] Eniargmen†

[2] Eniargmen†
Figure 1 shows the plasma FP and TP elimination curves for an anuric patient with lung carcinoma who received 120 mg CP/m² body surface area. This CP dose instilled into the peritoneal cavity produced a peak plasma TP concentration of 1.92 µg/ml. This value represents 47% of the peak plasma concentration produced by a dose of 100 mg/m² CP administered by 6-hour intravenous infusion (4.06 ± 0.41 µg/ml [3]. The peak plasma FP concentration after intraperitoneal infusion (0.495 µg/ml) was similar to that observed after giving 100 mg/m² CP with mannitol by 6-hour intravenous infusion (0.51 ± 0.043 µg/ml) [3, 4]. FP concentrations were detectable up to 8 days after the end of CP administration. The disappearance of FP, after draining of the peritoneal cavity at 6 h, followed a biexponential kinetic pattern with a prolonged elimination half-life of 199.9 h. This terminal half-life is somewhat longer than those reported in other studies [5, 6], but it seems to corroborate the observations of De Gregorio et al. [7]. Total body FP clearance was 1.58 l/h.

Total exposure of the systemic circulation to free reactive drug is proportional to the area under the curve (AUC); in doing this integration it was assumed that after drainage at 6 h there was no further drug exposure in the peritoneal cavity. This assumption is reasonable because even if one fifth of the drug-containing peritoneal fluid was not eliminated, the subsequent exposure would amount to only 1.9% of the exposure that had already taken place. Intact CP seems to be the only component that is responsible for cytotoxicity [8]. The AUC of FP was determined for up to 2 h after ending the intraperitoneal instillation because Sternson et al. [9] have showed convergence – up to 2 h – between intact CP and FP. Intraperitoneal instillation of CP led to an FP AUC of 169.5 µg · min/ml (2.83 µg · h/ml, up to 2 h after the end of instillation) and to 2.382 µg · min/ml (39.69 µg·h/ml, total AUC). Likewise, this route of administration gave a systemic circulation AUC equivalent to the one (1.73 µg·h/ml) reported for native CP after an intravenous dose of 100 mg/m² CP [4, 10]. The total FP AUC is very large in this patient, much more so than has been reported to date. This may be explained by a low albuminemia (20 g/l) and a decrease in the ability of plasma proteins to bind certain drugs, as observed in patients with chronic renal insufficiency [11, 12]. This is an important fact because CP is irreversibly bound by a covalent bond to plasma proteins and particularly to albumin [13, 14].

Peritoneal platinum (Pt) elimination was studied over the 12 h following CP administration. In the first 6 h, 1.23% of the administered dose was eliminated and 0.86% over the following 6 h. These results were compared with those of Ostrow et al. [3] who determined Pt urinary elimination in 6-hour fractions after CP 6-hour intravenous infusion (100 mg/m²) in both furosemide – and mannitol – diuresed patients. The percent of administered dose excreted from 6 to 12 h was 3.4 ± 0.8% (mannitol) and 3.4 ± 1.2% (furosemide); from 12 to 18 h it was 0.6 ± 0.2% (mannitol) and 0.8 ± 0.3% (furosemide) [3]. Platinum peritoneal elimination during the 6- to 12-hour period is about 3-fold lower than Pt urinary excretion but seems similar after this period.

Intraperitoneal administration of CP in an anuric patient results in a systemic exposure to active drug which is similar to that observed after intravenous infusion of the same CP dose in patients without renal failure. Moreover, treatment is well tolerated, with no nausea or vomiting. We
conclude that IP route can be a simple alternative for CP administration in patients on peritoneal dialysis.

References