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DISTRIBUTION AND RETENTION OF THE ANTITUMOR AGENT ^{195m}Pt-*cis*-DICHLORODIAMMINE PLATINUM (II) IN MAN

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Body distribution and retention of cis-dichlorodiammine platinum, including liver uptake, were measured in two patients with cancer by whole-body counting and scanning and determinations of radioactivity in blood and excreta.

The discovery of the cytotoxic properties of certain coordination complexes of platinum by Rosenberg and his colleagues (*1*) has caused widespread interest in the evaluation of these compounds for cancer chemotherapy. One compound, *cis*-dichlorodiammine-platinum (II) (DDP), is now undergoing clinical trials but little is known about its pharmacokinetics in man.

Studies of the distribution of radioactively labeled DDP, and the related compound platinum-ethylenediamine-dichloride, in experimental animals (*2–4*) suggest that these drugs are cleared relatively slowly from the body. This report describes studies of the retention and distribution of DDP labeled with ^{195m}Pt in two cancer patients who were undergoing, or about to undergo, treatment with the drug. The results show that, as in experimental animals, the drug is cleared only relatively slowly from the blood and from the whole body. While this work was in progress, Lange, Spencer, and Harder (*5*) reported on their studies of the retention of this drug in two patients the results of which are in good agreement with those reported here.

MATERIALS AND METHODS

The ^{195m}Pt-DDP was prepared from chloroplatinic acid $H_2{}^{195m}PtCl_6$ supplied by The Radiochemical Centre, Amersham, U.K. at a specific activity of approximately 1 mCi/mg Pt. After evaporation to dryness, the chloroplatinic acid was reduced with hydrazinium chloride and converted to DDP by the method of Kaufmann (*6*). The purity of the final, recrystalized product was checked by uv spectrophotometry and by paper chromatography [Whatman No. 1, acetone: water 9:1 (v/v)] and shown to be identical with an authentic sample of DDP.

The radioactive drug was administered intravenously to two patients who had volunteered to cooperate in this investigation.

Patient 1 was a 51-year-old woman with bilateral papillary cystoadenocarcinoma of the ovaries with metastases which had been treated by surgery, radiotherapy, and chemotherapy including two courses of three daily doses of 30 mg DDP at monthly intervals. A dose of 1.1 mCi (approximately 6 mg) ^{195m}Pt-DDP was administered 7 weeks after the last course.

Patient 2 was a 58-year-old man with malignant melanoma which had previously been treated with Melphelan, ^{32}P, and x-rays. A dose of 500 μCi (approximately 7.7 mg) ^{195m}Pt-DDP was administered 6 weeks after the last course of x-ray therapy.

Blood and urine samples were obtained together with a single sample of feces from Patient 1. Whole-body retention was measured by serial counting in a whole-body counter with the patient lying first supine and then prone 2 meters below a 5-cm diam NaI(Tl) crystal. Retention was estimated from the average of the prone and supine counts at each time interval. In addition, local and whole-body scans were carried out at intervals. Local, high-resolution scans of the abdomen, chest, and brain were made using a Selo DS7 scanner fitted with TC 100/12B collimators and 12.5-cm crystals.

Whole-body scanning was performed using a moving couch system incorporating two opposed 12.5-cm diam NaI(Tl) crystals fitted with 25-hole focusing collimators (*7*). Liver uptake and retention was estimated by taking the total counts within the physical limits of the liver and expressing them as a percentage of the total-body counts.

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RESULTS

The disappearance of radioactivity from the plasma, liver, and total body of Patient 1 over the period of 7 days following injection of ^{195m}Pt-DDP is illustrated in Fig. 1. The urinary excretion of radioactivity by the two patients is listed in Table 1 which also shows the renal clearance of the drug calculated by the method of Konikowski, et al (*8*).

The liver uptake of drug at 2 hr after injection was estimated to be about 10% of dose in Patient 1 and about 13% in Patient 2. Figure 2 shows anterior scans of the abdomen of Patient 1 obtained at 8.5, 26, and 96 hr after injection. Figure 3 shows the two scans obtained from Patient 2 at 3.5 and 27.5 hr postinjection. Right and left lateral brain scans obtained from Patient 1 at 27 hr showed a normal pattern of vascular activity.

DISCUSSION

The results shown in Fig. 1 and Table 1 show that 25–30% of the injected ^{195m}Pt was excreted in the urine during the first 24 hr but that thereafter the clearance of the drug from the liver and whole body was relatively slow with half-times of 8 and 10 days, respectively. No detectable radioactivity was found in the single fecal sample obtained from Patient 1 during the first 48 hr postinjection. The very close agreement between the measured whole-body retention and that calculated from the urinary excretion (Fig. 1) suggests that the fecal excretion is low, probably less than 10% in 4 days. Insufficient measurements could be made on Patient 2 to permit estimation of the half-times of clearance of the drug from liver and whole body. The initial clearance of ^{195m}Pt from the plasma is rapid; approximately 93% of the injected activity disappears from the circulation during the first day. Thereafter the rate of loss is slower, showing half-times of 3 days in Patient 1 and about 5 days in Patient 2. This pattern of plasma clearance appears to be very similar to that observed by Lange, et al (*5*).

The abdominal scans illustrated in Figs. 2 and 3 clearly demonstrate the high uptake of the drug in liver but it is interesting to note that, despite the fact that urine forms the major excretory pathway, the kidneys are not clearly seen in the scans taken a few hours after injection. Another interesting feature shown in Figs. 1B, 1C, and less clearly in Fig. 2B, is the band of activity stretching from below the liver diagonally upwards towards the spleen. This activity

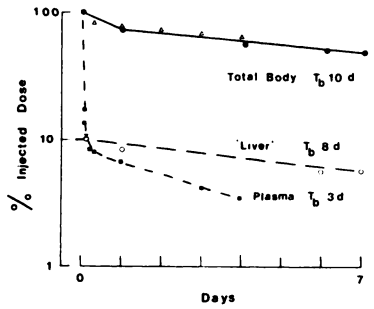

FIG. 1. Retention of ^{195m}Pt in whole-body liver and plasma of 51-year-old woman (Patient 1) over 7 days following intravenous injection of 1.1 mCi ^{195m}Pt-DDP. ●——● whole-body retention estimated by counting. △——△ whole-body retention estimated from urinary excretion. ○——○ liver retention. ■——■ plasma clearance.

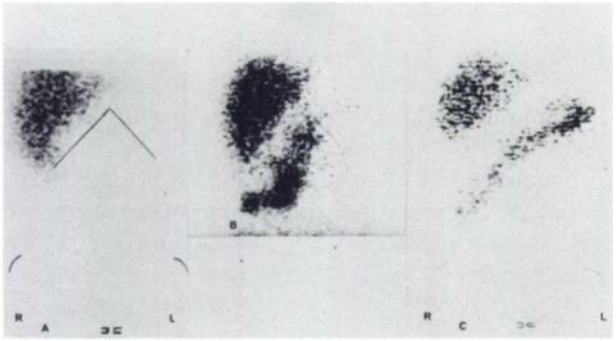

FIG. 2. Anterior abdominal scan of Patient 1 taken at (A) 8.5 hr, (B) 26 hr, and (C) 100 hr after injection of 1.1 mCi ^{195m}Pt-DDP.

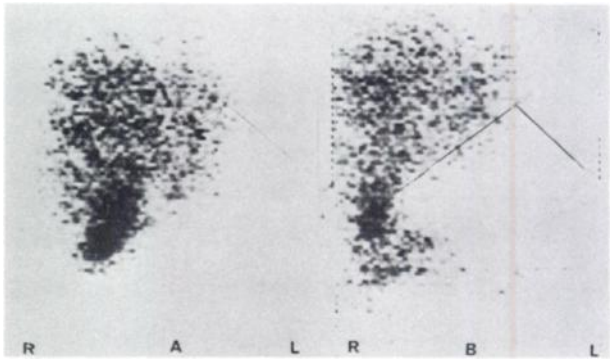

FIG. 3. Anterior abdominal scan of Patient 2 taken at (A) 3.5 hr and (B) 27.5 hr after 500 μCi ^{195m}Pt-DDP.

TABLE 1. URINARY EXCRETION OF ^{195m}Pt-DDP BY TWO HUMANS

Collection period (hr)	% dose in urine	
	Patient 1	Patient 2
0–5	—	23.1
0–8	18.4	—
5–24	—	7.9
8–24	4.8	—
24–48	5.8	4.7
48–72	3.2	—
72–86	2.9	—
Total excreted	35.1	35.7
Renal clearance (ml/min)	1.3	1.8

which was still visible on scanning Patient 1 at 7 days postinjection is thought to be uptake in the upper part of intestine. However, the failure to observe movement of this radioactivity into the lower regions of the intestine, coupled with the apparent absence of significant fecal excretion, may indicate storage of the drug in the intestinal walls or possibly some enterohepatic circulation.

The pattern of clearance of the drug from the plasma and from the liver and whole body is similar to that observed in experimental animals (*3,4*) and the half-times of retention observed in man are only slightly longer than those found in the rat.

The scans of the two patients reported here did not reveal any evidence of concentration of the drug in tumor tissue. Failure of the drug to concentrate preferentially in tumor tissue is not unexpected in the light of observations on several different types of tumor in the rat (*3,4*).

The studies reported here, together with those of Lange, et al (*5*), suggest that in man, following injection of DDP, the Pt moiety is excreted relatively slowly from the body with half-times of the order of 8–10 days. How much of the retained Pt still maintains cytotoxic properties is still to be assessed. Following injection into experimental animals, DDP rapidly interacts with proteins and other tissue components and the resulting complexes appear to be less active biologically than the free drug (*3*).

The radiation dose to the whole body was estimated as 0.837 rad/mCi administered, assuming uniform distribution of the ^{195m}Pt throughout the body and taking the effective half-life as equal to the physical half-life. Doses to the liver and kidneys, based on the animal data of Taylor, et al (*3*), were estimated to be 1.3 and 3.5 rad/mCi, respectively. Calculations and data for man were based on MIRD Pamphlet No. 5, 1969, and physical data for ^{195m}Pt was taken from Lederer, Hollander, and Perlman (*9*), as were the calculations of Lange, et al (*2*). However, the decay of ^{195m}Pt is not fully understood (*10*) and no attempt was made to calculate individually all the equilibrium dose constants. The whole-body dose agrees well with the estimate of Lange, et al (*2*) and the data presented in this paper suggest that only the liver estimate should be revised to 3.1 rad/mCi administered.

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