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In vivo distribution studies of radioactively labelled platinum complexes; *cis*-dichlorodiammine platinum(II), *cis-trans*-dichlorodihydroxy-bis-(isopropylamine) platinum(IV), *cis*-dichloro-bis-cyclopropylamine platinum(II), and *cis*-diammine 1,1-cyclobutanedicarboxylate platinum(II) in patients with malignant disease, using a gamma camera

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Summary. *The in vivo distribution in man of the four platinum derivatives cis-dichlorodiammine platinum(II) (DDP), cis-trans-dichlorodihydroxy-bis-(isopropylamine) platinum (IV) (CHIP), cis-dichloro-bis-cyclopropylamine platinum(II) (CP), and cis-diammine 1, 1-cyclobutanedicarboxylate platinum(II) (CBDCA) has been observed. The availability of these compounds labelled with the radioactive isotope of platinum, platinum-191, has made serial in vivo imaging of their distribution possible.*

Injection of 17–35 MBq (5–28 mg) of the labelled compound IV was followed by imaging, using a gamma camera, with particular reference to the kidneys, liver, and tumour site.

Hepatic and renal clearances were observed in all nine patients, but no unequivocal evidence of tumour uptake was found. The left kidney uptake was estimated at times up to 7 days after injection. Mathematical analysis of some of the uptake curves failed to show any significant difference between the clearance times observed. However, the two patients who received CBDCA did show a higher initial renal uptake, falling within the 1st day to levels comparable with those of the other compounds, and the three patients who received DDP showed consistently liver uptake.

Introduction

cis-Dichlorodiammine platinum(II) (DDP) is now established as a useful agent in the treatment of a variety of human malignancies [1, 5]. Full exploitation of the drug is limited by the major side-effect, nephrotoxicity [5]. In an attempt to improve the therapeutic index a series of other platinum-based compounds has been developed; many have demonstrated anti-tumour effects in animal models [3, 9, 11], but few have entered early clinical trial.

It is possible to observe the in vivo distribution and clearance of DDP and its analogues in man by incorporating a gamma-emitting platinum isotope during synthesis of the drugs. There are only two anecdotal reports of in vivo images after the injection of radioactive DDP [4, 8], and corresponding information about other platinum compounds is not available. The availability of the radioisotope of platinum, platinum-191, and its incorporation into DDP and its analogues, *cis-trans*-dichlorodihydroxy-bis-(isopropylamine) platinum(IV) (CHIP), *cis*-dichloro-bis-cyclopropylamine platinum(II) (CP), and *cis*-diammine 1,1-cyclobutanedicarboxylate platinum (II) (CBDCA), has allowed the measurement of blood and urinary clearances of these compounds in patients, the results of which have already been described [7, 10].

In this study, the in vivo distribution of DDP, CHIP, CP, and CBDCA has been observed, with particular reference to the kidney. The clearance and distribution data derived from studies using these labelled compounds could assist in the prediction of relative toxicity and conceivably aid the selection of particular analogues for phase-I human studies.

Materials and methods

Seven patients with bronchogenic carcinoma, one (patient 6) with malignant melanoma and one (patient 8) with ovarian carcinoma were studied, no patient having previously received chemotherapy. There were five female and four male patients with a median age of 58 years, all having routine biochemical profiles of hepatic and renal function within the normal range.

The preparation of the radioactive platinum has been described elsewhere [6]. A mixture of platinum-191 and platinum-193m was prepared by alpha particle bombardment of natural osmium sponge and used in the synthesis of the radioactively labelled platinum compounds. The prepared compounds were dissolved in isotonic saline, millipore-filtered into a sterile vial, and pyrogen-tested before administration. The amount of the compound and the amount of radioactive platinum injected in each case is given in Table 1.

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The X-ray photons emitted by the radioactive decay product of platinum-191, iridium-191, with energies of 63–76 keV were used for imaging. This was performed using a gamma camera with a field of view of 37 cm and digital data was stored using a Nova 3 computer (Digicamera 5LF, Nuclear Enterprises, EMI Medical Ltd, Hayes, Middlesex). For injection, each patient was seated with the gamma camera positioned posteriorly to view the kidneys and bladder, and the labelled compound was delivered as a bolus into an antecubital vein. Image acquisition was commenced on injection and continued for 30 min. The usual framing rates for the dynamic study were 60 frames at 12 frames/min followed by 30 frames at six frames/min, with the remaining frames at three frames/min.

On completion of the dynamic study a series of static images was acquired, comprising posterior views of the chest, liver, kidneys, and bladder and anterior views of the chest, liver, and abdomen. Acquisition of these images was repeated at 4, 8, 24, and 48 h and, in three cases, 6–7 days after injection.

Operating on the digitally stored dynamic study and serial static images, outlines were drawn to delineate regions of interest (ROI) for each kidney and a suprarenal region (left side) to provide a measure of vascular background activity.

Table 1

Patient	Platinum compound injected[a]	Amount of compound (mg)	Amount of radioactivity (MBq)[a]
1	DDP	15.0	30.0
2	DDP	6.7	25.3
3	DDP	6.4	30.3
4	CHIP	11.0	25.2
5	CHIP	27.3	25.0
6	CHIP	20.5	34.1
7	CP	26.9	25.1
8	CBDCA	approx. 7.0	24.3
9	CBDCA	approx. 5.0	17.2

[a] DDP, *cis*-dichlordiammine platinum(II); CHIP, *cis-trans*-dichlorodihydroxy-bis-(isopropylamine) platinum(IV); CP, *cis*-dichloro-bis-cyclopropylamine platinum(II); CBDCA, *cis*-diammine 1,1-cyclobutanedicarboxylate platinum(II); MBq, megabecquerel (i.e., 10^6 disintegrations/s)

The total number of counts obtained in each region was recorded for each image and the net counts per second calculated for each kidney, which is proportional to the amount of radioactive material (the administered radioactive compound or its metabolites) in each kidney.

Quantification of uptake was attempted in the left kidney as hepatic concentration of the compound obscured the upper border of the right kidney in some cases. By assuming a model of the kidney (constant for all patients studied), curves showing the amount of radioactive material in the left kidney up to 7 days after administration of the tracer have been constructed. The system was calibrated using a measured activity of radioactive platinum in a phantom representing kidney geometry.

Results

The multiple estimations of uptake made during the first 30 min after administration show an initial rise in the kidney concentration, followed within minutes by a fall, which is continued for up to 7 days (Table 2). For the two patients who received CBDCA a higher initial kidney uptake was observed, falling by 24 h to a level comparable with the other compounds, and for the three who received DDP consistently lower uptakes were observed compared with the other compounds. Patient 5 (CHIP) showed a slight increase in left kidney uptake 24 h after administration (Table 2). However, further values are not available to confirm this trend.

A summary of the distribution of the compounds derived from the gamma camera images is presented in Table 3. Hepatic and renal clearances were observed in all nine patients, uptake being obvious within 1 h and persisting for up to 7 days (Fig. 1). There was evidence of concentration of radioactive material within the gallbladder in two out of three patients who received CHIP, in one case visible by 1 h after injection and clearing by 48 h, and in the other case visible by 4 h and still visible at 48 h after injection (Fig. 1). There was also activity within the intestine (Fig. 1) in all seven patients.

There was evidence of uptake in the superior mediastinum in patients 2 and 3 (DDP) and patient 7 (CP), all with centrally sited bronchogenic carcinoma, the activity being above the heart image and present at a time when the heart activity (i.e., the compound remaining in the blood) was falling (Fig. 2).

Table 2. Percentage of radioactive material[a] (administered radioactive compound or its metabolites) in the left kidney at various times after injections

Pat.	Platinum compound injected	Time to peak uptake (min)	Peak uptake	Time after injection						
				30 min	1 h	4 h	8 h	24 h	48 h	6–7 days
1	DDP	5.0	1.26 ± 0.63	0.21 ± 0.11	0.06 ± 0.04	0.13 ± 0.09	0.13 ± 0.04	N/D	N/D	N/A
2	DDP	4.2	1.83 ± 0.13	0.50 ± 0.04	N/A	0.38 ± 0.02	0.46 ± 0.03	0.36 ± 0.03	0.36 ± 0.03	0.25 ± 0.02
3	DDP	9.0	2.59 ± 0.26	0.94 ± 0.10	0.86 ± 0.04	0.17 ± 0.04	0.31 ± 0.03	0.17 ± 0.04	0.22 ± 0.04	N/A
4	CHIP	2.3	1.89 ± 0.08	1.13 ± 0.05	0.97 ± 0.04	0.86 ± 0.03	0.82 ± 0.04	0.67 ± 0.03	0.69 ± 0.03	N/A
5	CHIP	5.0	2.30 ± 0.12	1.75 ± 0.09	N/A	N/A	N/A	1.68 ± 0.08	N/A	N/A
6*	CHIP	7.0	2.69 ± 0.27	1.44 ± 0.14	N/A	0.60 ± 0.06	N/A	0.41 ± 0.04	0.70 ± 0.07	0.46 ± 0.05
7	CP	3.0	1.92 ± 0.06	0.75 ± 0.02	0.62 ± 0.02	0.47 ± 0.02	0.49 ± 0.02	0.48 ± 0.02	0.29 ± 0.01	0.15 ± 0.01
8	CBDCA	3.7	6.00 ± 0.18	3.53 ± 0.11	3.00 ± 0.08	2.18 ± 0.06	N/A	0.91 ± 0.03	N/A	N/A
9	CBDCA	3.0	4.85 ± 0.17	2.13 ± 0.07	1.12 ± 0.04	0.33 ± 0.02	N/A	0.21 ± 0.01	0.13 ± 0.01	N/A

[a] N/D, not detectable; N/A, not available; * Errors estimated at ± 10% for this patient

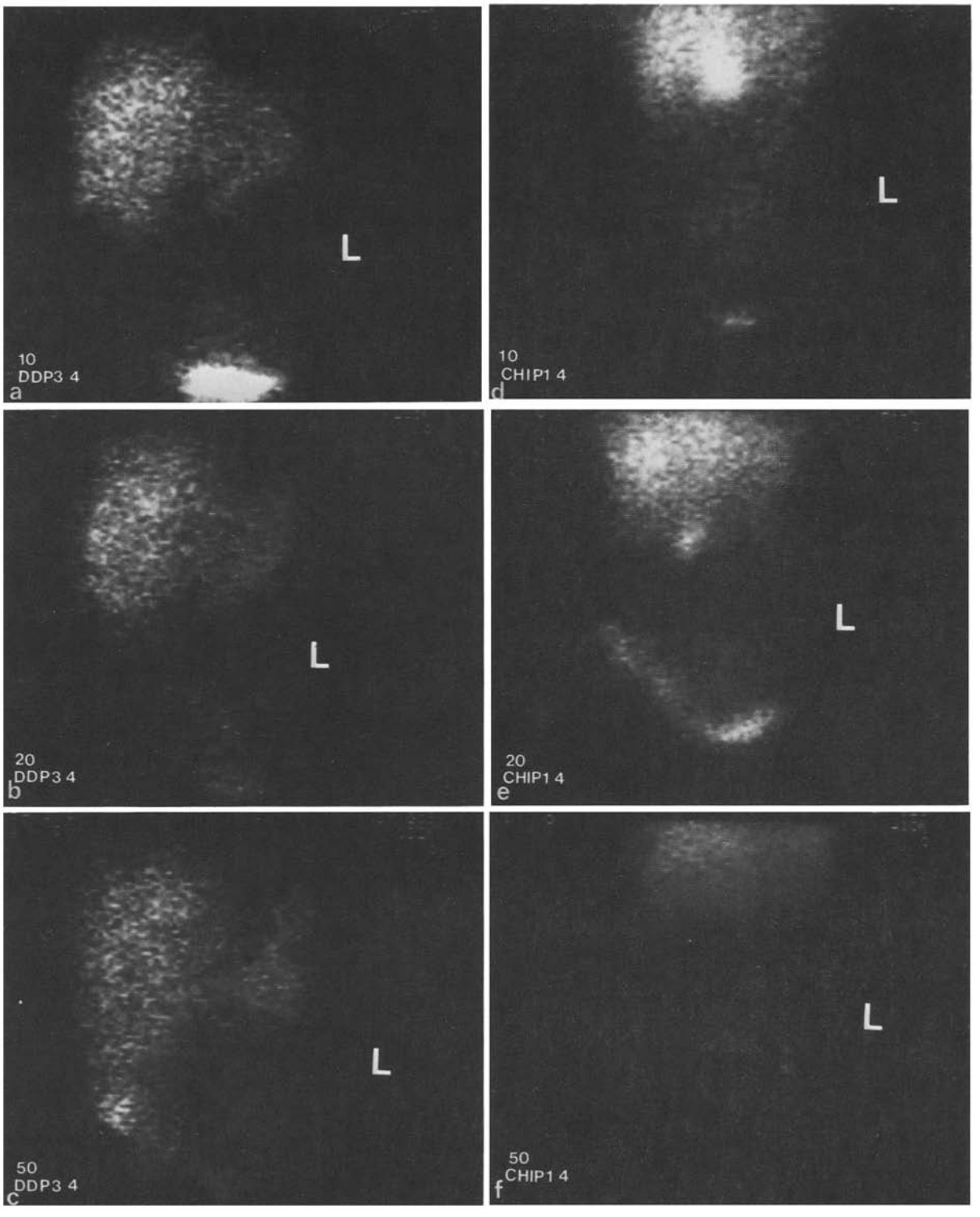

Fig. 1a–f. Anterior views showing hepatic uptake and intestinal activity in patient 3 at 1 h (**a**), 4 h (**b**), and 48 h (**c**) after administration of DDP in patient 4 at 1 h (**d**), 4 h (**e**), and 48 h (**f**) after administration of CHIP. For patient 3, the bladder can also be seen in the image recorded at 1 h and, for patient 4, the gall bladder can be seen at 1 h and 4 h

Table 3. Summary of gamma camera images

Patient	Platinum compound injected	Hepatic	Renal	Gall-bladder	Intestinal	Tumour
1	DDP	+	+	−	+	−
2	DDP	+	+	−	+	?
3	DDP	+	+	−	+	?
4	CHIP	+	+	+	+	−
5	CHIP	+	+	−	+	−
6	CHIP	+	+	+	+	−
7	CP	+	+	−	+	?
8	CBDCA	+	+	−	+	−
9	CBCDA	+	+	−	+	−

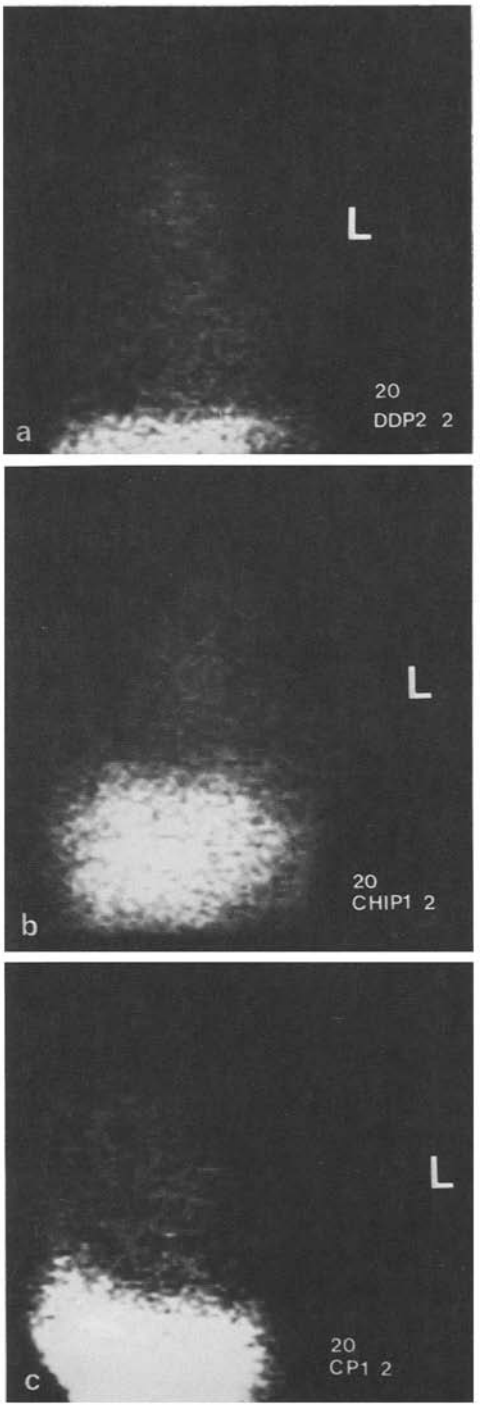

Fig. 2a–c. Hepatic uptake and activity due to the heart **a** in patient 2 at 4 h after administration of DDP, with a further area of thoracic activity; **b** in patient 4 at 4 h after administration of CHIP; and **c** in patient 7 at 4 h after administration of CP, with mediastinal activity also apparent

Discussion

The in vivo quantification of uptake of a radioactive material requires knowledge of a number of factors. These include the size and depth of the organ under study and the correction to be applied for photon attenuation. Two-dimensional imaging of three-dimensional objects gives images in which any radioactive material, either in the blood or in any other organ underlying or overlying the organ of interest, contributes to the composite image.

For the kidney, the average depth and thickness can be assumed and the edges can be defined in the two-dimensional image. Measurements of the attenuation of the photons emitted by the radionuclide can be made, using a phantom to simulate in vivo geometry. Variations in kidney geometry are a potential source of error, as for the photon energies used a change in kidney depth of 1 cm would produce a change in percentage renal uptake of 13% of the observed uptake. As this error cannot be quantified individually, it has not been included in the tabulated results. The errors given in Table 2 arise from the statistics of counting and are ± 1 SD (standard deviation) of the percentage uptake in each case.

Mathematical analysis of some of the uptake curves failed to show any significant difference between the clearance times observed. The renal curves represent two distinct biological functions: (a) renal uptake as a consequence of clearance of the label from the blood; and (b) subsequent excretion of this label to the bladder. The clearance times calculated from the later parts of these curves are probably more representative of the individual renal function than of the molecular properties of the compounds. In contrast, the rate and amplitude of the initial uptake should depend more on the properties of the compound injected. The higher initial uptake of CBDCA shows a rapid clearance via the renal route and these results are consistent with our previous finding of enhanced urinary excretion of this compound in the first 6 h after injection [7].

No patient participating had a history of cholecystectomy. Evidence of biliary excretion, which was seen in two of three CHIP patients, has been observed in the rat [2].

Of the three patients in whom uptake was observed in the mediastinium, two had superior vena cava obstruction and one a clinical diagnosis of pericardial effusion. Therefore, these findings cannot be taken as unequivocal evidence of tumour uptake.

Measurement of urinary clearance following the administration of radioactively labelled CHIP in conjunction with CHIP chemotherapy has shown a slower urinary excretion than that observed with the tracer quantity alone. (H. Sharma 1983, unpublished work). It is hoped to extend this investigation to include the administration of therapeutic quantities of some of the nonradioactive compounds simultaneously with the radioactively labelled compound to study behaviour in therapeutic conditions.

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