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A Comparative Study of the Distribution in the Male Rat of Platinum-Labelled *cis*-Dichlorodiammine Platinum (II), *cis-trans*-Dichlorodihydroxy-bis-(Isopropylamine) Platinum (I), and *cis*-Dichloro-bis-Cyclopropylamine Platinum (II)

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Summary. *Three platinum derivatives, cis-dichlorodiammine platinum (II), (DDP), cis-trans-dichlorodihydroxy-bis-(isopropylamine)platinum (IV) (CHIP) and cis-dichloro-bis-cyclopropylamine platinum (II) (CP), have been prepared with a gamma-emitting platinum label. The distribution of these complexes was studied in male rats.*

The results are presented as fractions of the administered radiolabel per gram of tissue and per total organ. Accumulation in the liver was highest initially following CP and lowest after DDP, but by 14 days the levels in kidney and liver were highest with CP. The concentration in the skin was relatively high after all the compounds, but was the most conspicuous after DDP at the early times. In general, patterns of distribution between the other organs were similar with DDP and CP.

CHIP, however, exhibited a different pattern of distribution. Over the first 24 h the level of platinum in most tissues declined more rapidly than after either of the other two compounds but the residual label persisted for a longer period. In the kidney there appeared to be a secondary uptake of labelled material, presumably from other tissues. The level present at 14 days after CHIP was also significantly higher in a number of other organs than after the other two drugs. The increase in label in the spleen at the later times may be due to the removal of circulating damaged cells and consistent with the higher levels of residual platinum in the blood. There was also a higher level of residual platinum in the blood especially after IV administration of the labelled agent.

The results show that CHIP was cleared at a faster rate from blood and kidney than the other two complexes, results which closely resembled clinical findings with these three agents, to be published elsewhere.

The greater retention time of label after CHIP also suggests that longer-term toxicity may follow its repeated administration.

Introduction

cis-Dichlorodiammine platinum (II) (DDP) is widely recognised as a useful agent in the treatment of a number of human tumours [6, 16], especially those of testicular and ovarian origin. The main toxic effects associated with its clinical use are nausea, vomiting, diarrhoea, nephrotoxicity, ototoxicity, bone marrow damage, and neuropathy.

Many platinum analogues possess antitumour properties in experimental animal models [8, 20, 24], and thus relative toxicity is a predominant factor in selection for initial clinical trial. Nephrotoxicity in rats has been employed [18] for this purpose.

Comparative tracer distribution studies of platinum-labelled analogues in rats compared with their clearance and scan data in patients [23] may provide some indication of likely potential toxicity in clinical use.

This contribution describes distribution studies in the rat using three isotopically labelled analogues (Fig. 1). The

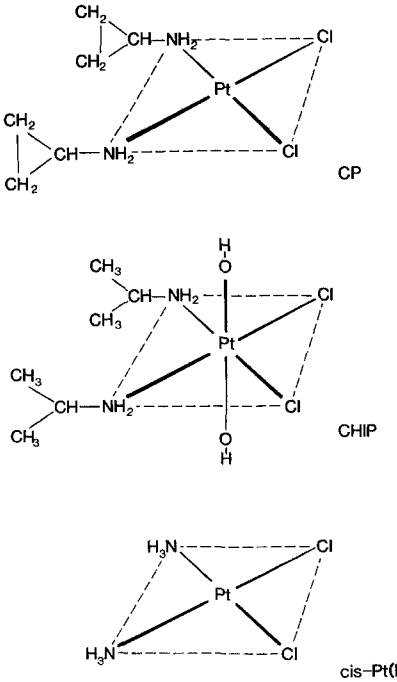

Fig. 1. Structural formulae of the three platinum complexes studied

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isotope label consisted primarily of a mixture of platinum 191 and platinum 193m, obtained by irradiating osmium sponge with alpha particles, and will be referred to as Pt* throughout the text.

Organ distribution and pharmacokinetic analysis of platinum complexes have previously been studied in mice [9, 10], rats [5, 6, 12, 25, 27], rabbits [9, 21], dogs [3, 11, 12], and man [19]. In all cases the kidney had the highest retention of platinum within the time periods. The methods of measurement used were atomic absorption spectroscopy [1, 4, 11, 13, 14, 25], 193m-Pt [4, 5, 10], 195m-Pt [7, 10, 19, 28], and X-ray fluorescence [1]. Most studies were conducted with DDP, but [Pten(Cl_2)] [22] and sulphato (*trans*)1,2-diaminocyclohexane platinum (II) (DAC sulphate) [15] have also been investigated.

Materials and Methods

Preparation and Separation of Platinum Radionuclides. A brief description of the procedure for micromole synthesis purification and purity control of the radiolabelled complexes is outlined below. A more detailed account will be published elsewhere. Alpha particle bombardment of osmium sponge produces a mixture of radionuclides shown by X-ray spectroscopy to contain predominantly Pt191 (half-life 3 days) and Pt193m (half-life 4.3 days). A third isotope, Pt(188), was present in quantities that were negligible in freshly produced material [10]. The irradiation was carried out at the Heavy Ion Linear Accelerator at the University of Manchester or the Nuffield Cyclotron of the University of Birmingham, England [17].

Following activation, the osmium was removed by oxidative distillation with aqua regia [9]. The residue was twice treated with HCl and evaporated to dryness to eliminate residual nitrate. Iridium, a product of platinum decay, was also present at this stage as H_2IrCl_6 but was removed during subsequent chemical synthesis.

Synthesis of Labelled Compounds. Inactive $Na_2PtCl_6 \cdot xH_2O$ was first added to the carrier-free H_2PtCl_6. Preparations were routinely carried out using 0.05 g (0.11 mmol) of the sodium salt but it proved possible to work with quantities as low as 0.01 g with only minor modification of the experimental procedure.

The reaction scheme used is illustrated in Fig. 2. With the exception of the final free radical oxidative addition required for CHIP alone (step 7) the synthetic routes to all three compounds were identical. In the case of the cyclopropylamine

(1) $2\ Na_2PtCl_6 + H_2NNH_2 \cdot 2\ HCl \rightarrow 2\ Na_2PtCl_4 + 6\ HCl + N_2$

(2) pH adjustment using Na_2CO_3 (pH 6–8)

(3) $Na_2PtCl_4 + 4\ NaI \rightarrow Na_2PtI_4 + 4\ NaCl$

(4) $Na_2PtI_4 + 2\ Am \rightarrow$ *cis*$[PtI_2(Am)_2] + 2\ NaI$

(5) *cis* $[PtI_2(Am)_2] \xrightarrow{2\ AgNO_3}$ *cis* $[Pt(Am)_2(OH_2)_2]\ [NO_3]_2$

(6) *cis* $[Pt(Am)_2(OH_2)_2]\ [NO_3]_2 + 2\ NaCl \rightarrow$ *cis* $[PtCl_2(Am)_2] + 2\ NaNO_3$

Additional reaction required for CHIP alone
(7) *cis* $[PtCl_2(Am)_2] + H_2O_2 \rightarrow [PtCl_2(OH)_2(Am)_2)$

Fig. 2. Scheme for the synthesis of platinum complexes

derivative, the low thermal stability of the base meant that lower reaction temperatures and consequent increased reaction times were required when preparing the platinum derivative. Using 99% of the stoichiometric amount of hydrazine dihydrochloride, based on Pt analysis of inactive $Na_2PtCl_6 \cdot xH_2O$, reduction of platinum (IV) to platinum (II) proceeded smoothly at low temperature. After reduction, the solution was made slightly alkaline by careful addition of sodium carbonate solution until effervescence just ceased. Excess sodium iodide (50%) and silver nitrate (10%) was used for steps (3) and (5), respectively (Fig. 2). The iridium contaminant was also chemically reduced in step (1) to give the inert $_d6$ Ir (III) and was removed with the supernatant liquid after step (4). It was normally possible to complete the preparation within 1 day with a 70% yield based on $Na_2PtCl_6 \cdot 6H_2O$.

Quality Control. Samples were analysed by thin layer chromatography on alumina-glass plates (20 cm × 20 cm, UV indicator, Kodak Ltd) using 9 : 1, acetone-0.12 *M* HCl for CHIP separation, 10 : 1, acetone-1 *M* HCl for CP and 7 : 3, and acetone-water for DDP. Authentic compounds were employed as markers. In all cases the radiochromatographic purity was greater than 95% and the compounds were used directly without further purification.

Immediately prior to administration, the compounds were dissolved in isotonic saline or in sterile water as indicated. All samples were pyrogen-free.

Animals. Male Wistar rats (8–9 weeks old, approx. 220 g) fed on standard pelleted food and water ad libitum were used for the distribution studies. In some cases, rats bearing 5-day-old SC transplanted Yoshida tumours were also used.

Tissue Distribution Studies. Radiolabelled drug was administered by tail vein injection for the short-term studies to groups of five rats, so that each animal received approximately 10 μCi, corresponding to a dose of 6–8 mg/kg body weight. The doses correspond to approximately 1/10th of the LD_{50}. Groups were sacrificed by an IV injection of thiopentone (10% 0.2 ml) immediately followed by KCl solution (2 *M*, 0.3 ml) layered in the same syringe to ensure rapid killing.

The percentage of the administered label was assessed by measuring whole-body radioactivity immediately after injection and at death, correcting for decay by measuring against a sealed standard of the complex administered. Fourteen tissue samples were excised from each animal, weighed and assayed in an Autogamma counter. At the same time, samples of the injection solution were retained as controls with each series of vials.

Results

Mean organ weights of ten animals were determined (Table 1) and used as the basis for the presentation of data for all the experiments.

Tissue Distribution and Clearance of Pt-DDP*

One hour after administration of this compound by far the highest uptake per unit weight of tissue occurred in the kidney, which was largely retained during the first 3 days (Table 2). Although levels in the spleen were only 15% of those in the kidney at 1 h, the figure was 80% of the kidney value after

Table 1. Mean weights of rat organs

Organ	Mean wt. (+SD)	Organ	Mean wt. (+SD)
Adrenal	0.049 ± 0.006	Prostate	0.192 ± 0.027
Blood[a]	17.5	Skin[a]	25.0
Brain	1.674 ± 0.076	Small intestine	3.399 ± 0.239
Epididymis	0.653 ± 0.03	Spleen	1.159 ± 0.198
Heart	0.91 ± 0.071	Testes	2.696 ± 0.098
Kidney	1.789 ± 0.157	Lung	0.785 ± 0.098[a]
Liver	10.591 ± 1.040	Seminal vesicle	0.785 ± 0.098[a]
Pituitary	0.006 ± 0.002		

[a] Except where marked with an asterisk, means and standard deviations were calculated from values recorded in ten rats. An asterisk indicates that only four samples were used for the calculations

Total blood was approximated to 7% of the body weight, and the skin, to 10% of the body weight

14 days. The early changes in the small intestine may represent a phase of biliary excretion following the injection. When the levels per organ are calculated using data from Table 1 there is a relatively greater retention in the blood, kidney, liver and especially in skin when compared to other tissues. The high skin uptake has been previously noted with this compound [27]. There was no particular evidence of concentration in the testis or cardiac muscle and the similar decline in radioactivity may correlate merely with their blood content.

Tissue Distribution of Pt-CHIP*

Table 3 summarises comparable data using Pt*-CHIP. The most obvious difference from Pt*-DDP is the generally lower level of radioactivity in the tissues at early times (Table 4) after administration but with longer retention. Thus at the later stages, the levels were relatively higher than after Pt*-DDP (Table 3). Again the blood level remained constant from 24 to

Table 2. Specific activity of tissues following Pt*-DDP

Tissue[a]	Time after administration				
	1 h	24 h	48 h	72 h	14 d
Adrenal	48.8 ± 12.4	24.0 ± 4.0	33.0 ± 5.0	22.4 ± 6.0	0.71
Blood	54.6 ± 14.0	29.6 ± 4.5	29.2 ± 14.0	20.2 ± 2.0	3.34
Brain	2.4 ± 0.5	1.6 ± 0.5	1.2 ± 0.5	1.1 ± 0.5	–
Epididymis	20.2 ± 2.0	10.5 ± 1.0	10.5 ± 2.0	8.0 ± 1.0	1.97
Heart	22.6 ± 2.0	11.6 ± 2.0	12.2 ± 2.6	10.2 ± 2.8	0.64
Kidney	208.0 ± 32.0	184.0 ± 13.0	186.0 ± 12.5	147.0 ± 33.0	20.62
Liver	65.4 ± 8.0	34.0 ± 5.0	38.0 ± 8.0	25.8 ± 5.0	2.34
Lung	55.8 ± 7.0	19.8 ± 11.0	26.0 ± 5.0	16.4 ± 2.0	1.22
Pituitary	38.2 ± 10.0	36.0 ± 20.0	17.5 ± 10.0	12.0 ± 2.0	–
Prostate	22.4 ± 11.0	9.0 ± 1.0	8.5 ± 1.0	6.2 ± 1.0	0.54
Skin	43.2 ± 5.0	29.2 ± 5.0	26.5 ± 1.0	20.2 ± 4.0	2.48
Small intestine	44.0 ± 6.0	9.0 ± 1.0	6.7 ± 1.0	4.6 ± 0.5	0.54
Spleen	31.4 ± 4.0	28.0 ± 5.0	36.0 ± 5.0	18.6 ± 5.0	18.00
Testes	6.8 ± 0.8	4.6 ± 1.0	4.2 ± 0.5	3.4 ± 0.5	1.09

[a] Distribution of Pt*-DDP in tissues of male Wistar rats (5 animals per time point except for 14-day values, which are mean of 2 rats) is expressed as fractions ($\times 10^4$) of the administered dose per gram of tissue

Table 3. Specific activity of tissues following Pt*CHIP

Tissue[a]	Time after administration						
	2 h	24 h	48 h	72 h	9 d IP	14 d	19 d
Adrenal	17.0 ± 8.9	6.8 ± 0.2	5.9 ± 0.3	6.1 ± 0.8	2.21	5.10	20.0
Blood	19.6 ± 2.6	7.7 ± 1.6	5.4 ± 0.9	5.2 ± 0.7	6.82	6.59	8.0
Brain	1.1 ± 0.4	0.4 ± 0.1	0.3 ± 0.1	0.3 ± 0.0	0.12	–	0.0
Epididymis	5.7 ± 1.0	3.5 ± 0.4	2.5 ± 0.1	2.4 ± 0.2	6.31	32.18	7.1
Heart	12.5 ± 1.3	7.2 ± 1.2	5.3 ± 0.8	5.0 ± 0.4	2.77	4.74	4.1
Kidney	178.6 ± 41.2	81.0 ± 7.6	57.5 ± 6.0	50.1 ± 3.2	80.12	103.31	48.4
Liver	78.5 ± 27.4	30.7 ± 12.9	16.5 ± 1.2	15.0 ± 3.2	14.97	12.78	6.5
Lung	16.2 ± 2.2	8.0 ± 1.3	5.9 ± 0.1	5.1 ± 0.4	3.82	5.13	3.3
Pituitary	15.3 ± 2.4	14.5 ± 7.6	6.3 ± 0.7	4.6 ± 0.5	–	–	–
Prostate	9.1 ± 2.6	3.4 ± 0.3	3.2 ± 0.1	2.9 ± 0.6	2.96	3.76	8.4
Skin	12.4 ± 2.0	5.7 ± 1.1	4.6 ± 0.4	4.4 ± 0.4	4.44	7.24	3.3
Small intestine	33.4 ± 7.1	3.8 ± 1.4	2.3 ± 0.3	1.7 ± 0.3	1.91	4.37	2.5
Spleen	28.9 ± 5.8	10.1 ± 1.9	9.6 ± 0.8	10.2 ± 1.0	16.02	34.32	33.8
Testes	2.8 ± 0.2	1.7 ± 0.1	1.4 ± 0.1	1.4 ± 0.3	5.29	9.55	3.2

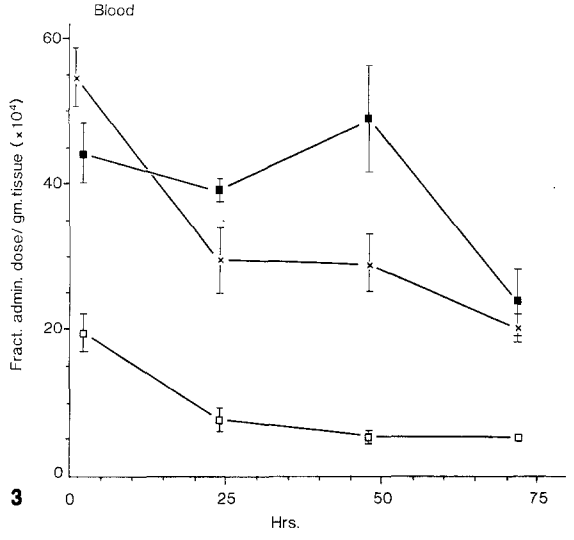
[a] Distribution of Pt*CHIP in tissues of male rats (5 animals per time point except for the 19-day values, which are mean of 2 rats) is expressed as fractions ($\times 10^4$) of the administered dose per gram of tissue

Table 4. Specific activity of tissues following Pt*CHIP (short times)

Tissue[a]	Time after administration				
	2–3 min	8–9 min	35 min	75 min	135 min
Adrenal	47.1 ± 1.6	43.3 ± 10.9	53.4 ± 58.5	16.1 ± 2.2	17.0 ± 8.9
Blood	79.0 ± 25.2	72.2 ± 12.3	45.5 ± 12.3	25.0 ± 5.1	19.6 ± 2.6
Brain	5.5 ± 0.8	2.9 ± 1.7	2.9 ± 1.7	1.2 ± 0.3	1.1 ± 0.4
Epididymis	51.0 ± 20.6	23.4 ± 2.1	46.1 ± 31.1	11.4 ± 7.0	5.7 ± 1.0
Heart	57.3 ± 14.0	37.1 ± 7.9	25.6 ± 4.0	17.4 ± 3.7	12.5 ± 1.3
Kidney	388.1 ± 118.2	297.7 ± 77.5	263.8 ± 50.2	273.3 ± 115.8	178.6 ± 41.2
Liver	80.4 ± 12.4	88.6 ± 9.0	86.2 ± 17.4	99.3 ± 41.3	78.5 ± 27.4
Lung	82.0 ± 11.5	55.5 ± 12.4	34.2 ± 4.0	22.8 ± 5.8	16.2 ± 22
Pituitary	60.9 ± 43.3	44.2 ± 13.2	25.3 ± 14.1	16.7 ± 7.2	15.3 ± 2.4
Prostate	31.4 ± 13.4	18.7 ± 2.5	224.9 ± 90.5[b]	10.9 ± 3.8	9.1 ± 2.6
Skin	51.8 ± 22.3	35.2 ± 6.6	53.6 ± 20.0	16.8 ± 4.8	12.4 ± 2.0
Small intestine	35.2 ± 5.8	32.6 ± 4.7	53.6 ± 18.6	90.6 ± 77.3	33.4 ± 7.1
Spleen	34.3 ± 19.1	37.8 ± 6.7	47.1 ± 17.8	42.2 ± 14.7	28.9 ± 5.8
Testes	11.0 ± 1.4	10.9 ± 1.6	9.3 ± 3.3	3.9 ± 0.8	2.8 ± 0.2
Tumor	45.1 ± 50.3	35.5 ± 6.7	28.6 ± 3.2	19.4 ± 7.4	14.3 ± 1.7

[a] Distribution of Pt*CHIP in tissues of male Wistar rats (5 animals per time point) over a short time interval is expressed as fractions ($\times 10^4$) of the administered dose per gram of tissue

[b] This high level is thought to have been due to accidental contamination of the tissue with urine



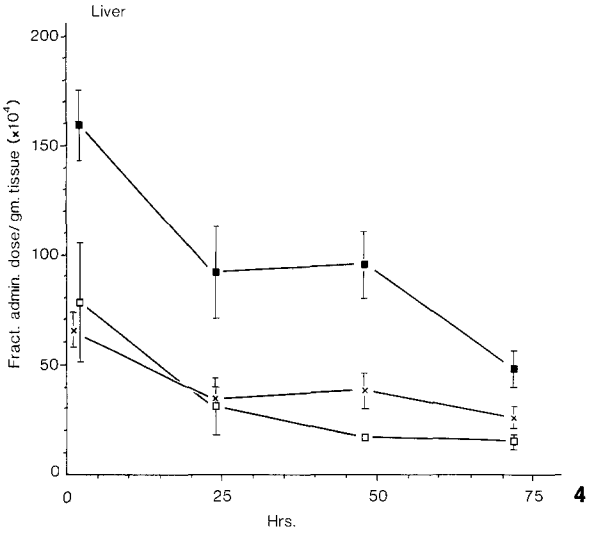


Fig. 3. Relative distribution of the three platinum complexes in the blood over 72 h. (×) DDP; (□) CHIP; (■) CP

Fig. 4. Relative distribution of the three platinum complexes in the liver over 72 h. (×) DDP; (□) CHIP; (■) CP

72 h and may represent a much more persistent, platinum-labelled binding to vascular fluid component(s) as with Pt*-DDP (Fig. 3).

The rapid loss of radioactivity in the first 24 h from the small intestine again correlates with an episode of biliary excretion over the first few hours, which in turn appears to be related to the different lipid : water partition coefficients, viz. 0.008, 0.0012, and 0.007 for DDP, CHIP and CP, respectively [24]. However, in the case of this agent, the level in the kidney declines more rapidly than in the liver, contrasting with that after Pt*-DDP at the earlier times, but the retention is also high when later times are examined. There is a significant fall in the splenic concentration of label in the first 24 h, but thereafter the tissue retains a constant level. In this case there is a notable increase of radioactivity in 20 days. This may represent the accumulation of cell products from other parts of the body. This compound showed the highest body retention at 14 days.

Tissue Distribution of Pt-CP*

The comparative distribution of Pt*-CP in the tissues of the rat is illustrated in Table 5. There is a similar pattern of uptake to that of Pt*-DDP in terms of specific activity of the tissues, although the liver showed a greater initial uptake and retention (about 3-fold) compared with Pt*-DDP (Fig. 4).

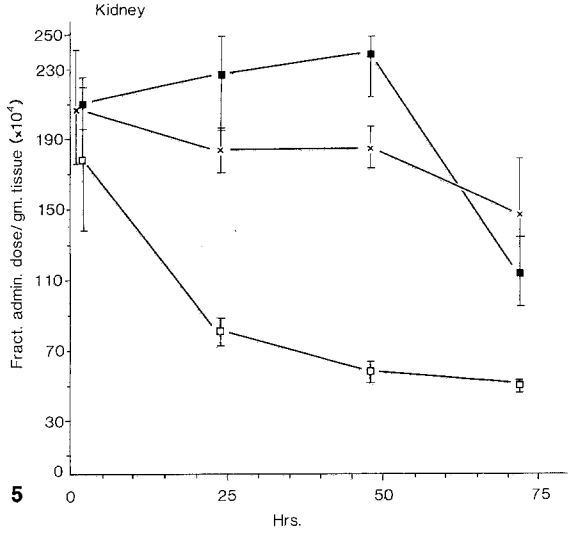
Discussion

The success of DDP as an antitumour agent in clinical practice has prompted the synthesis of many analogues. The principal objective is to reduce the toxicity whilst maintaining anti-

Table 5. Specific activity of tissues following Pt*-CP

Tissue[a]	Time after administration				
	2 h	24 h	48 h	72 h	14 d
Adrenal	18.4 ± 4.0	12.5 ± 4.2	14.4 ± 1.2	8.1 ± 1.7	6.4
Blood	44.1 ± 4.0	39.1 ± 1.5	49.0 ± 7.3	23.8 ± 4.6	3.3
Brain	2.5 ± 0.4	1.7 ± 0.2	1.8 ± 0.5	0.8 ± 0.1	0.19
Epididymis	12.7 ± 2.1	9.4 ± 2.0	11.2 ± 2.1	5.3 ± 0.5	6.4
Heart	19.5 ± 2.8	16.7 ± 2.3	18.8 ± 4.7	8.8 ± 1.1	2.4
Kidney	210.5 ± 15.0	228.3 ± 32.8	239.4 ± 24.1	114.3 ± 19.6	70.5
Liver	159.0 ± 16.0	91.7 ± 21.0	95.5 ± 15.2	47.5 ± 8.5	8.4
Lung	37.0 ± 7.3	39.9 ± 1.9	33.0 ± 5.9	16.5 ± 3.1	3.4
Pituitary	22.4 ± 2.9	15.4 ± 3.7	14.7 ± 3.0	16.5 ± 5.8	–
Prostate	43.2 ± 32.7	13.2 ± 0.4	13.4 ± 0.7	5.9 ± 1.3	3.2
Skin	26.6 ± 3.6	21.8 ± 2.8	22.4 ± 2.8	10.9 ± 2.2	2.6
Small intestine	88.4 ± 18.9	15.1 ± 3.8	10.2 ± 2.2	3.9 ± 0.6	1.1
Spleen	26.8 ± 4.1	33.1 ± 6.8	35.7 ± 5.5	26.1 ± 5.8	18.5
Testes	4.5 ± 0.8	3.4 ± 0.5	3.8 ± 0.8	1.8 ± 0.3	4.5

[a] Distribution of Pt*-CP in tissues of male Wistar rats (5 animals per time point) is expressed as fractions ($\times 10^4$) of the administered dose per gram of tissue



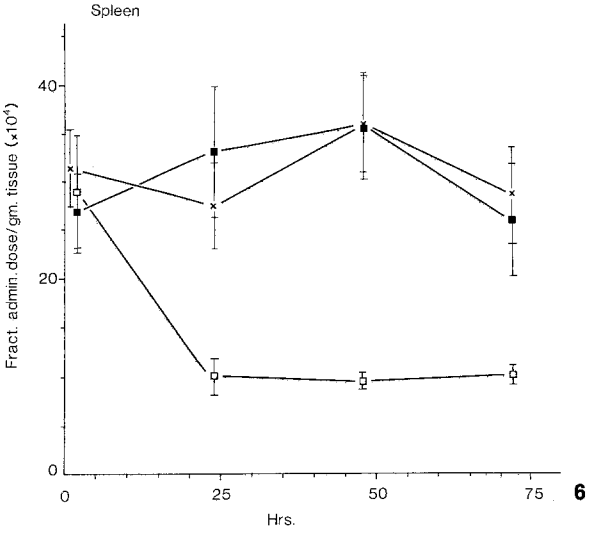


Fig. 5. Relative distribution of the three platinum complexes in the kidney over 72 h. (×) DDP; (□) CHIP; (■) CP

Fig. 6. Relative distribution of the three platinum complexes in the spleen over 72 h. (×) DDP; (□) CHIP; (■) CP

tumour effectiveness. To assist in making this decision, the principal toxicity problem associated with DDP, i.e., renal toxicity, has been investigated in rodents using a number of derivatives. From these studies [2] it was concluded that the isopropyl analogue (CHIP) a platinum (IV) complex, and the cyclopropylamine derivative (CP) were possible for initial phase I clinical trials. Other analogues showing more promise in experimental systems have since been discovered, and although CHIP has entered clinical trial [2], the cyclopropylamine analogue (CP) has not proved to be acceptable due to slightly increased blood urea and urinary protein levels over untreated controls [26]. However, the levels observed were still much lower than after DDP. It was still considered worthwhile to study the agent as a useful comparison with the other platinum analogues, as it still showed lower nephrotoxicity than DDP in animal systems [18].

The results of our studies in male rats have shown that DDP and CP are very similar in both relative distribution and rates of clearance from rat tissues, with the exception of liver in which a three-fold higher level of labelled material was found 14 days after treatment with CP than after DDP.

CHIP however, exhibited a somewhat different pattern of uptake to the other two agents. A more rapid rate of loss of labelled material occurred from most tissues (Figs. 3–6) in the first 72 h, but the residue in the tissues persisted for a longer period. More detailed studies of the levels between 9 and 19 days revealed that there was apparently a second wave of uptake in the kidney, spleen, and epididymis, maximal at the 14-day time point. In the spleen, levels of radioactive material decreased only very slowly. A comparison was also made of the mode of administration of CHIP on the subsequent distribution of label within the tissues. There were few differences in

the amount of label within the tissues under these circumstances, except for a two-fold higher level in the blood after IV than after IP administration. This may reflect an initial binding reaction of the compound. The higher retention of CHIP over the longer time interval, although only a small proportion of the initial dose, may be toxicologically important in repeated treatment schedules. However, the possibility exists that the label present in the longer-term experiments may not be platinum but a daughter radionuclide, such as iridium with similar gamma spectrum characteristics, in which case the radioactivity present will bear no relation to platinum drug distribution. Until it is possible to examine the gamma spectrum of such low levels of tissue-bound radioactive material at such late times this possibility will remain.

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