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Blood Clearance of Three Radioactively Labelled Platinum Complexes: *cis*-Dichlorodiammine Platinum II, *cis, trans*-Dichlorodihydroxy-bis-(isopropylamine) Platinum IV, and *cis*-Dichloro-bis-cyclopropylamine Platinum II, in Patients with Malignant Disease

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Summary. *The blood clearances of three platinum compounds, cis-dichlorodiammine platinum II (DDP), cis, trans-dichlorodihydroxy-bis-(isopropylamine) platinum IV (CHIP), and cis-dichloro-bis-cyclopropylamine platinum II (CP), were determined in nine patients with malignant disease. The complexes were prepared using radioactive platinum (^{191}Pt and ^{193}Pt). A 10-μCi dose of each complex, containing the equivalent of 1–2 mg elemental platinum, was injected IV into groups of three patients. Serial blood and urine samples were collected over 72 h.*

No obvious difference was found between the three complexes for blood clearance, median $t_{1/2}\alpha$ being 16.8 (range 11.2–23.5) min and median $t_{1/2}\beta$ 89 (range 63.7–127) h. The urinary excretion was greatest for CHIP, 60% of injected dose as against 42.6% for CP and 38.8% for DDP.

Differences in renal excretion of DDP analogues could indicate potentially less nephrotoxic agents. The use of radioactive Pt will allow in vivo dynamic imaging of the distribution of platinum compounds in areas of interest.

Introduction

The sole platinum coordination complex in general clinical use is *cis*-diammine dichloroplatinum (II) (DDP). A large series of platinum complexes are available a number of which have antitumour activity in animals. Platinum compounds are of great interest, and represent a new class of anticancer drugs. The incorporation of DDP into chemotherapy schedules has revolutionised the treatment of testicular teratoma and has improved the therapy of many other neoplasms [3, 8].

Unfortunately DDP has a narrow therapeutic index in man. Renal damage is the major dose-limiting toxicity and represents a serious problem in the use of the drug. This consideration has stimulated interest in analogues of DDP and the search for potentially superior platinum complexes. Several analogues of DDP have been tested in animal tumour systems and appear promising candidates for future clinical study. The incorporation of radioactive platinum into the drug complex greatly facilitates tracer studies of platinum drugs in man [10].

The future clinical use of platinum drug complexes with known antitumour effects could possibly be optimised from information derived from the clearance pattern in cancer patients receiving such agents. The data could also provide a means of selecting a limited group of platinum-based compounds with acceptable toxicity for phase I human study. We chose to investigate the blood and urine clearances of three platinum compounds; DDP because it is the only compound in clinical use; CHIP (*cis, trans*-dichlorodihydroxy-bis-(isopropylamine) platinum IV) because its water-solubility is fivefold greater and its therapeutic index higher than those of DDP [7]; and the third compound, CP (*cis*-dichloro-bis-cyclopropylamine platinum II), because though less water-soluble than DDP it has a therapeutic index, in a mouse tumour model, that is substantially greater than the index for either DDP or CHIP [7]. The initial tracer clearance studies also allow radiation dosage information to be calculated and assist in determining the isotope drug concentration required for adequate gamma camera imaging for in vivo drug distribution studies.

Materials and Methods

Nine patients were studied after informed consent had been given. Each patient had extensive carcinoma, with a survival prognosis of 1 year or less. Routine biochemical profiles of hepatic and renal function were within the normal range. Clinical details are given in Table 1.

Radioactive platinum (a mixture of ^{191}Pt and ^{193}Pt) was prepared by alpha particle bombardment of osmium sponge; the details of the production procedure have been published elsewhere [9]. This platinum is used for the synthesis of labelled platinum compounds.

The three compounds selected were prepared for injection by dissolving in isotonic saline followed by millipore filtration into sterile vials. All samples were pyrogen-tested. An aliquot of the material administered was also prepared and its activity recorded to calculate the absolute clearance fraction. Each labelled platinum complex was injected into a group of three patients. An IV injection of 10 μCi of the selected complex (equivalent to 1–2 mg elemental platinum) was followed by

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Table 1. Clinical details of patients

Patient	Sex	Age	Tumour	Metastases[a]	Platinum complex injected
1	M	66	Bronchus	N, P, O	DDP
2	M	69	Melanoma	N, O, ST	DDP
3	M	65	Bronchus	N, P	DDP
4	F	69	Bronchus	N, H, O	CP
5	M	69	Bronchus	N, P	CP
6	F	50	Melanoma	H, ST, N	CP
7	M	64	Bronchus	P, N, O	CHIP
8	F	51	Melanoma	N, ST	CHIP
9	F	63	Melanoma	N, ST, P	CHIP

[a] N, lymph node; P, lung; O, bone; ST, soft tissue; H, liver

serial (5 ml volume) blood sampling at 1, 3, 5, 10, 15, 30, and 60 min and 3, 6, 9, 12, 24, 36, 48, and 72 h after injection. Urine was collected concurrently for the intervals of 0–1 h, 1–6 h, 6–12 h, 12–24 h, 24–36 h, 36–48 h, and 48–72 h after injection. The total volume of each urine collection was recorded and 5-ml samples were prepared for counting in an auto-gamma counter. An aliquot of the original injection solution was diluted to 100 ml and three samples of 5 ml each were counted together with those of blood and urine for each measurement, so that correction could be made for decay.

The data were analysed to obtain clearance curves for the blood. Exponential stripping techniques were used to give the clearance half-times and the fraction cleared by each phase. The counts from urine samples allowed the calculation of the fraction of injected activity excreted during various timed urine collections.

Results

The blood clearance curves are displayed in Figs. 1–3. The disappearance of the labelled platinum from the blood was biphasic in all patients, with a fast initial phase followed by a slower later phase. Analysis of the exponential functions gave the half-lives ($t_{1/2}$ for the fast α phase and slower β phase) for each patient.

The half-lives and proportion of isotopic platinum cleared within the initial half-life α and within the slower, later half-life β are given in Table 2.

In general the isotopic platinum was eliminated from the blood in a rapid initial phase followed by a more prolonged later phase. There was little variation between patients injected with the same platinum complex (Figs. 1–3). No difference between the three complexes was obvious for the half-lives (Table 2).

The urinary excretion of the radioactively labelled platinum was greatest for CHIP (mean 60% of dose injected); intermediate (mean 42.6%) for CP; and least for DDP (mean 38.8%). There was again little variation in urinary excretion between patients given the same platinum compound (Table 3).

The differences in urinary clearances for the three platinum compounds were most obvious when the activity excreted in the first 6 h was examined. The urinary excretion of CHIP was clearly greater than that of the other two compounds (Fig. 4).

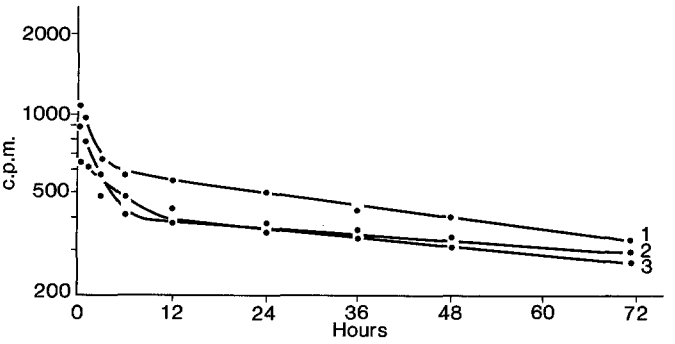

Fig. 1. DDP clearance from blood

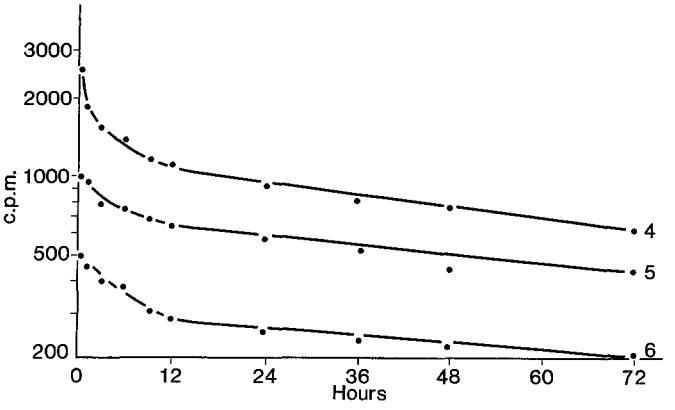

Fig. 2. CP clearance from blood

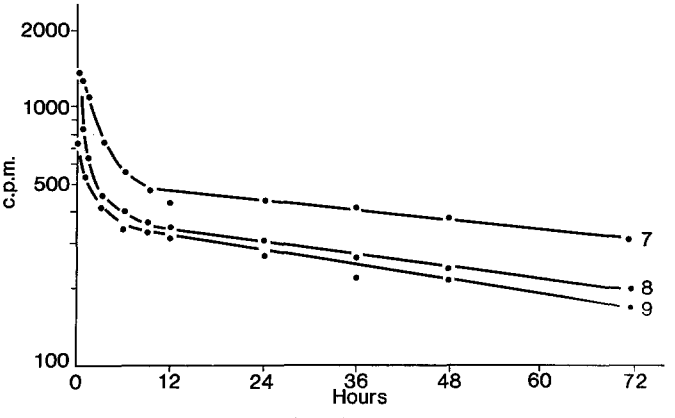

Fig. 3. CHIP clearance from blood

Discussion

The pharmacokinetics of DDP in man have been studied by several investigators [1, 2, 4–6]. The blood clearances were biphasic, with a short initial phase and a longer second phase. The present report describes a somewhat shorter $t_{1/2}\alpha$ and longer $t_{1/2}\beta$ than found by DeConti et al. [2], who also gave the drug by rapid IV injection. Clearance data of DDP administered by infusions over 1–6 h are also available (Table 4), with $t_{1/2}\alpha$ being less than 1 h and $t_{1/2}\beta$ in most reports being about 2–4 days. Differences in dosage, injection time, hydration, and diuresis regimens make direct comparisons difficult. The present results were obtained after the rapid injection of a small, subtherapeutic dose of the labelled drug;

Table 2. Clearance of platinum complexes from blood

DDP			
Patient	1	2	3
$t_{1/2}\alpha$ (min)	16.5	23.5	16.8
A (%)	71	71	76
$t_{1/2}\beta$ (h)	77.5	127	89
B (%)	29	29	24
CP			
Patient	4	5	6
$t_{1/2}\alpha$ (min)	18.6	11.2	22.3
A (%)	71	67	60
$t_{1/2}\beta$ (h)	76.5	94	118
B (%)	29	33	40
CHIP			
Patient	7	8	9
$t_{1/2}\alpha$ (min)	22.3	14.1	15.6
A (%)	80	83	77
$t_{1/2}\beta$ (h)	93.6	75.2	63.7
B (%)	20	17	23

Table 3. Excretion of Pt complexes via urine

Time interval (h)	Percentage of activity excreted			
1. DDP				
Patient	1	2	3	
0–1	18.4	26.9	18.2	
1–6	6.2	2.0	7.5	
6–12	1.5	2.1	2.4	
12–24	4.0	2.8	3.3	
24–48	4.4	3.6	4.4	
48–72	2.8	2.5	3.4	Mean ± SD
Sum	37.3	39.9	39.2	38.8 ± 1.3
2. CP				
Patient	4	5	6	
0–1	25.2	16.3	16.0	
1–6	9.0	12.4	10.6	
6–12	4.9	4.4	4.0	
12–24	1.7	4.3	5.0	
24–48	1.7	4.0	0.5	
48–72	2.4	2.7	2.8	
Sum	44.9	44.1	38.9	42.6 ± 3.3
3. CHIP				
Patient	7	8	9	
0–1	23.8	25.7	23.4	
1–6	25.2	26.9	26.8	
6–12	–	3.8	1.2	
12–24	5.1	2.6	3.8	
24–48	3.7	2.7	1.6	
48–72	1.9	1.9	–	
Sum	59.5	63.6	56.8	60.0 ± 3.4

the faster initial clearance for DDP could indicate a dose insufficient to saturate the clearance mechanism.

No previous reports are available describing the clearance of CHIP or CP in man. The blood clearances of the two compounds were similar to that of DDP. The urinary clearance for CHIP was about 20% higher than for DDP or CP, and occurred within 6 h of injection of the agent. This could be a reflection of the greater water-solubility of CHIP than of the other two compounds (Table 5). As the blood clearances of these compounds were similar, the greater urinary excretion of

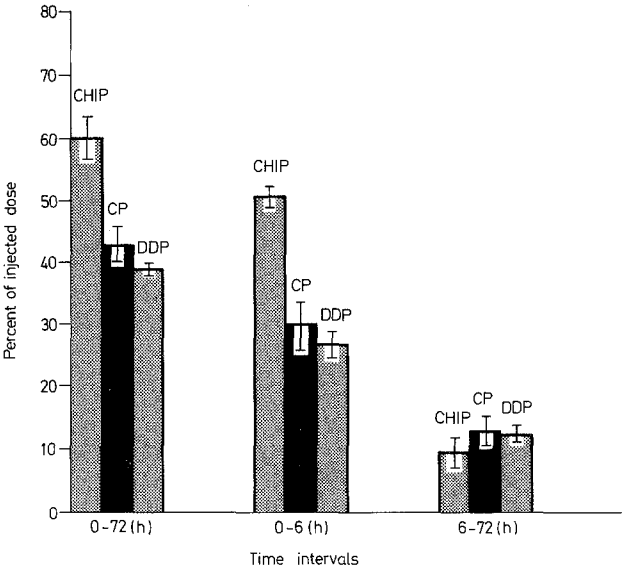

Fig. 4. Excretion of Pt complexes in urine

Table 4. Published clearance values of DDP

Administration	$t_{1/2}\alpha$	$t_{1/2}\beta$	Reference
Rapid IV 0.07–3.15 mg/kg	25–49 min	58.5–73 h	2
IV over 1 h, 70 mg/m^2	23 min	67 h	5
IV over 1 h, 50 mg/m^2	8.7–22.5 min	46.6–106 h	6
IV over 2 h, 100 mg/m^2	37.8–103.8 min	14.4–57.7 h	4
IV over 6 h, 90 mg/m^2	0.42 h	44.4 h	1

Table 5. Water solubility and therapeutic index of DDP, CHIP, and CP

	Solubility	Therapeutic index
DDP	8.9 m*M*	8.1
CHIP	44 m*M*	12.9
CP	1.6 m*M*	24.6

Therapeutic index derived from murine ADJ/PCJ tumours Data from Harrap et al. [7]

CHIP suggests less organ retention of this particular platinum compound.

The use of gamma-emitting isotopes enables distribution studies of drug in areas of interest – kidneys, tumour etc. to be performed. The techniques are non-invasive and potentially of great use in the study of platinum pharmacokinetics in humans [10]. The dynamic study of distribution and clearance in various target areas is an obvious extension of the work, and would assist interpretation of the clearance data of the present study. It would be possible to determine whether the kidney was retaining more platinum when injected in the form of DDP or CP than when CHIP was the agent used. Direct measurement of organ retention is possible by means of appropriate imaging techniques and analyses, and is currently being undertaken. The data would contribute to the selection and clinical use of platinum compounds and conceivably assist in devising techniques to modify the major problem of nephrotoxicity.

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