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Blood Clearance of Radioactively Labelled *cis*-Diammine 1,1-cyclobutane Dicarboxylate Platinum(II) (CBDCA) in Cancer Patients

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Summary. *The blood and urinary clearances of cis-diammine 1,1-cyclobutane dicarboxylate platinum(II) (CBDCA, JM8) were determined in four patients with malignancy. A 40 μCi iv injection of $^{191}Pt/^{193}Pt$ (3 : 1)-labelled CBDCA was followed by serial blood and urine sampling to 72 h.*

The blood clearance was triphasic, mean values for the fast, intermediate, and slow phases being 10.8 min, 2.5 h, and 125 h, respectively. The fraction of activity excreted in the urine within the first 6 h had a mean value of 66.7%, contrasting with 26.4% for cisplatin. There was only a small fraction of CBDCA excreted by the slow phase (1.5%) as against an average of 20% for CHIP and 27% for cisplatin.

The early and rapid renal clearance of CBDCA may account for reduced nephrotoxicity.

Introduction

Cisplatin is now established as a useful agent in the treatment of a variety of malignant neoplasms [3]. The toxicity of cisplatin, in particular, the progressive loss of glomerular and tubular function, can severely limit the dosage that might otherwise be given [1, 5].

CBDCA (JM8) is a second-generation cisplatin congener. The agent has been selected for clinical trial on the basis of reduced nephrotoxicity in rats and increased antitumour effects in some animal models [4]. Early clinical studies have indicated that CBDCA is not significantly nephrotoxic, is less emetic than cisplatin, and has produced responses in patients with ovarian carcinoma [2].

Materials and Methods

Four patients were investigated after informed consent had been obtained. Their clinical details are given in Table 1. The peripheral blood counts and routine hepatic and renal biochemical profiles were within the normal ranges in each subject.

cis-Diamine-1,1-cyclobutane dicarboxylate platinum(II) was synthesised using radioactive platinum (a 3 : 1 mixture of ^{191}Pt and ^{193}Pt) as described previously [8]. A 40 μCi iv injection of the labelled platinum drug (equivalent to ~ 1 mg CBDCA) was followed by serial 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 for the intervals 0–1 h, 1–6 h, 6–12 h, 12–24 h, 24–48 h, and 48–72 h. The samples including standards were counted and appropriate decay corrections made; the clearance curves, half-times, and fractions cleared by each phase were calculated as before [8].

Table 1. Clinical feature and blood clearance of platinum complex

	Diagnosis				Mean ± SD
	Melanoma	Bronchus	Bronchus	Bronchus	
Patient	A	B	C	D	
Age	51	64	52	57	
Sex	F	F	M	M	
Blood clearance					
$t_{½}$ Fast (min)	9.3	9.1	13.9	10.7	10.8 ± 2.2
A%	92.8%	85.7%	94.5%	88.4%	90.4 ± 4.0%
$t_{½}$ Inter (h)	2.22	2.18	2.84	2.60	2.5 ± 0.3
B%	6.1%	12.4%	4.3%	9.7%	8.1 ± 3.6%
$t_{½}$ Slow (h)	89.2	154.5	149.2	107.0	125 ± 32
C%	1.1%	1.9%	1.2%	1.9%	1.5 ± 0.4%

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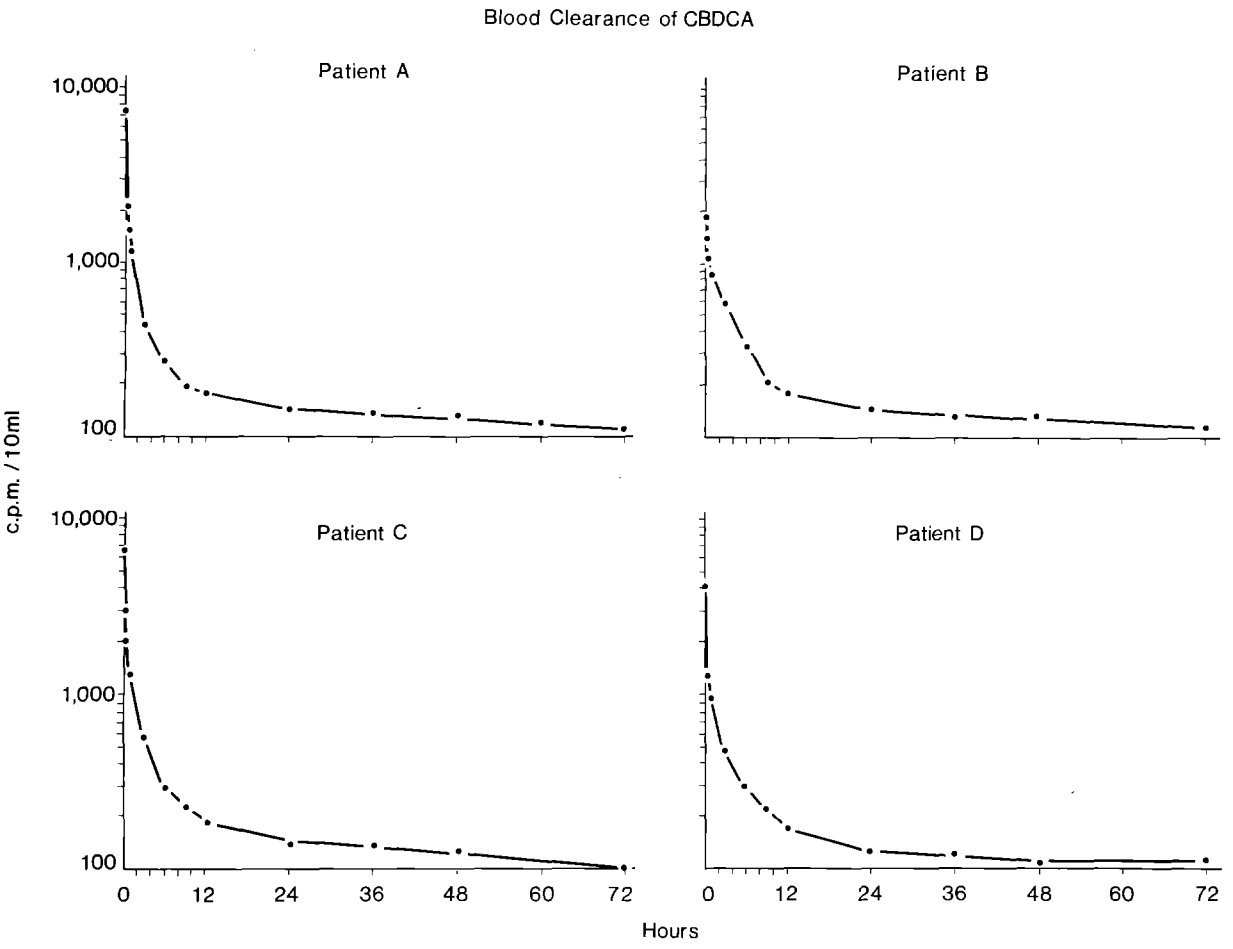

Fig. 1. Blood clearance of CBDCA

Table 2. Excretion of platinum via urine

Time interval (h)	Percentage of activity excreted			
	Patient			
	A	B	C	D
0– 1	36.1	28.2	49.5	22.8
1– 6	26.0	37.3	36.4	30.6
6–12	4.8	11.1	3.8	9.6
12–24	4.1	4.5	0.2	6.1
24–48	1.6	2.7	1.1	2.8
48–72	0.6	1.4	0.7	1.6
Total	73.2	85.2	91.7	73.5

0– 6 h: Mean ± SD 66.7 ± 13.8
0–72 h: Mean ± SD 80.9 ± 9.1

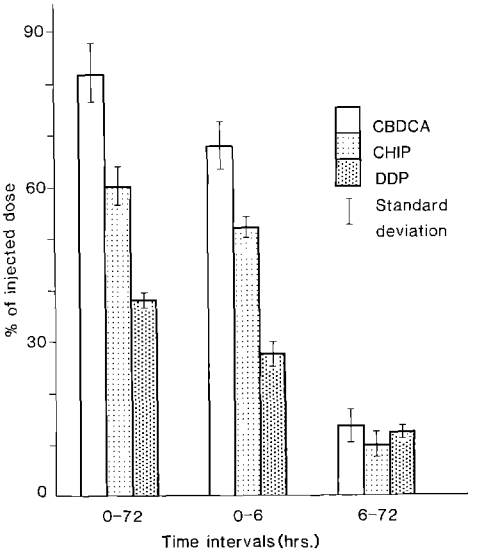

Fig. 2. Excretion of platinum complexes via the urine. *Bars* on tops of columns indicate standard deviation in each case

Results

The blood clearance curves for the four patients are shown in Fig. 1. The individual curves are very similar; each curve has been analysed by standard exponential stripping techniques and has three exponents.

The half-times of each phase and the fraction of the label cleared by each phase are given in Table 1. For the calculation of the fraction of activity cleared by each phase it has been assumed that the entire dose has been uniformly mixed in the total blood volume at zero time. The blood volume has been calculated (from the known height and weight of each patient) using equations given by Nadler et al. [6].

As can be seen from Table 1, the results are very consistent in the four patients. A very large fraction of the label (mean

90.4 ± 4.0%) is cleared from the blood in a very short time, the remaining activity being cleared in two phases with mean half-times of 2.5 h and about 5 days.

The urinary excretion for CBDCA is given in Table 2 and is compared with the corresponding data for cisplatin and CHIP [8] in Fig. 2. The differences in urinary excretion between these three platinum analogues is quantitatively accounted for by the differences in clearance in the first 6 h after administration.

Discussion

The blood clearance and urinary clearance characteristics of CBDCA differ from those of cisplatin and CHIP in the following three aspects:

i) Blood clearance of CBDCA displays three exponential phases as against only two observed for cisplatin and CHIP [8].

ii) The fraction of label eliminated by the very slow phase is only 1.5%, as against an average of 20% for CHIP and 27% for cisplatin [8].

iii) The fraction of activity excreted by urine in the first 6 h after CBDCA administration has a mean of 66.7%, which contrasts sharply with the mean value of 26.4% for cisplatin, CHIP having an intermediate value between the other two platinum compounds. A very large proportion of the activity following CBDCA appears in the urine within the first 6 h. Similar clearances for CBDCA have been found in animal studies [7].

The calculations of the fast-phase clearance half-times exhibit some variation between individuals. The variation is partly due to the inherent difficulty in timing the very early blood samples accurately (at 1 min and 3 min); the proportion of the label cleared during the initial period can, however, be assessed accurately. The initial fast clearance of the label from blood and appearance in the urine are mutually consistent results, indicating a rapid renal clearance. The other two, slower, phases of the clearance suggest release from compartments in which equilibrium had been established earlier. At 1 h approx. 2% of the radioactivity in whole blood was bound to the red blood cells, and this level remained almost unchanged during the period of study (20 h). On the other hand, following an initial fast removal of approx. 50% of the radioactivity during the first hour, the half-life of the TCA-precipitable protein-bound component in the plasma was approx. 18 h and that of the 'free' component (TCA-soluble) was approximately 2 h. This is a significantly lower rate of binding in the plasma than that of cisplatin, and could thus account for the greater proportion of free material available for rapid excretion. The greater urinary excretion of CBDCA indicates less organ retention of the agent and could possibly explain the lower nephrotoxicity associated with its clinical use [2].

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References

1. Bruno S, Poster DS, Higby DJ, Burke P, Mittelman A (1980) Parameters of nephrotoxicity in relation to the administration of *cis*-DDP. Proc Am Assoc Cancer Res 21: 150
2. Calvert AH, Harland SJ, Newell DR, Siddik ZH, Jones AC, McElwain TJ, Raju S, Wiltshaw E, Smith IE, Baker JM, Peckham MJ, Harrap KR, Cobley T (1982) Early clinical studies with *cis*-diammine 1,1-cyclobutane dicarboxylate platinum II. Cancer Chemother Pharmacol 9: 140
3. Durant JR (1980) CisPlatin: A clinical overview. In: Prestayko AW, Crooke ST, Carter SK (eds) Cis-Platin: Current status and new developments. Academic Press, New York London Toronto Sydney San Francisco, pp 317–321
4. Harrap KR, Jones M, Wilkinson CR, Clink HMcD, Sparrow S, Mitchley BCV, Clake S, Veasey A (1980) Antitumour, toxic and biochemical properties of cisplatin and eight other platinum complexes. In: Prestayko AW, Crooke ST, Carter SK (eds) Cisplatin: Current status and new developments. Academic Press, New York London Toronto Sydney San Francisco, pp 193–212
5. Jones BR, Bhalla RB, Mladek J, Kaleya RN, Gralla RJ, Alcock NW, Schwartz MK, Young CW, Reidenberg MM (1980) Comparison of methods of evaluating nephrotoxicity of cisplatinum. Clin Pharmacol Ther 27: 557
6. Nadler SB, Hidalgo JU, Bloch T (1962) Prediction of blood volume in normal human adults. Surgery 51: 224–232
7. Siddik ZH, Newell R, Jones M, Boxall FE (1982) Pharmacokinetics of *cis*-diammine-1,1-cyclobutane dicarboxylate platinum (II) (CBDCA JM8) in mice and rats. Proc Am Assoc Cancer Res 23: 168

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