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Decreased Plasma Half-Life of Cyclophosphamide during Repeated High-Dose Administration

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Summary. *Cyclophosphamide was given as IV doses of 50 mg/kg/day on each of four successive days as treatment for ovarian and lung cancer. Blood samples were taken at regular intervals and analysed for cyclophosphamide by gas liquid chromatography.*

The plasma half-lives ($t_{1/2}$) and volumes of distribution (V_D) were calculated for each of the treatment days; $t_{1/2}$ was found to decrease with subsequent doses whereas V_D was not significantly changed.

Introduction

Cyclophosphamide (2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine,2-oxide) (CP) has been used in cancer chemotherapy at low and moderate dose levels for many years [3]. In recent years there has been interest in its use, at very high doses, for treatment of some solid tumours such as small cell bronchogenic carcinoma (SCBC) [8]. At these high doses, autologous bone marrow transplantation has been used to mitigate haematogenic toxicity. It has been shown that at lower dose levels the pharmacokinetics of CP change with subsequent doses, the $t_{1/2}$ diminishing with continual low-dose treatment [3].

There is no information on the pharmacokinetics of CP at repeated very high doses, and it is not clear whether the pharmacokinetics of the drug at these dose levels differ from those at low dose levels. Therefore it is not possible to predict whether the drug and its metabolites are likely to have been cleared from the circulation at the time of reinfusion of bone marrow. We have therefore studied the plasma half-life and volumes of distribution of CP during repeated high-dose administration.

Materials and Methods

Five patients receiving high-dose CP treatment were studied (two with ovarian cancer; three with SCBC). They were each given CP 50 mg/kg/day (Farmitalia Carlo Erba, Barnet, Herts.) for a total of 4 days. CP was administered over 30 min into a fast-running saline drip. A urine output of 3 l/day was maintained. 2-Mercaptoethanesulphonic acid (Mesna, WB Pharmaceuticals, Ltd, Bracknell, Berks, England) was given as a bolus injection at 0, 4, and 8 h with respect to each CP dose to prevent haemorrhagic cystitis. The total dose of Mesna was 75% of the CP dose. Blood samples were usually taken at 30 min, 1 h, 2 h, 3 h, 6 h, 13 h, and 24 h following CP administration on each of the 4 treatment days. Plasma was separated by centrifugation (2,000 *g*; 5 min) and analysed for CP by gas liquid chromatography [7].

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Results

The plasma CP levels are shown in Table 1 and are expressed graphically in Fig. 1 as a plot of log CP concentrations vs time. From the graphs, values of plasma $t_{1/2}$ and V_D were calculated

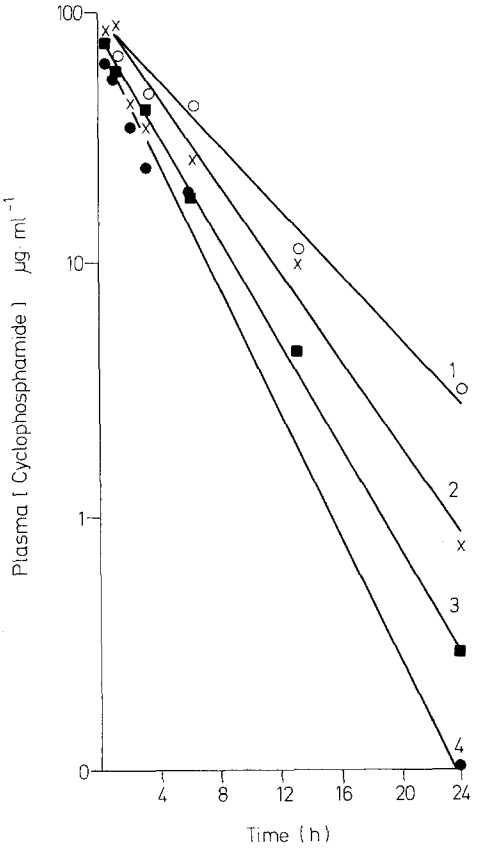

Fig. 1. Plot of log (plasma cyclophosphamide) vs time for patients receiving 50 mg/kg/day on each of 4 successive days. Each *data point* represents the mean of at least three patients (see Table 1). Linear regression coefficients: day 1 (○) = −0.99; day 2 (×) = −0.988; day 3 (■) = −0.997; and day 4 (●) = −0.998

Table 1. Plasma levels[a] of cyclophosphamide (μg/ml) in patients given 50 mg/kg/day on each of 4 successive days

Sample time (h)	Treatment (day)			
	1	2	3	4
0.5	89.3±6.6	83.5±19.6	79.4±10.9	65.3±15.4
1.0	68.5±5.1	85.6±20.3	59.4± 6.8	57.6±18.3
2.0	45.0*	45.3± 8.8	43.5± 6.1	36.1±11.9
3.0	48.7±5.6	35.0± 8.6	42.8±17.0	24.9± 3.2
5.0	43.8±9.1	26.1±12.9	18.7± 5.2	20.1± 5.3
13.0	11.4*	10.0**	4.6**	ND
24.0	3.2±2.1	0.8± 0.6	0.3± 0.1	0.1**

[a] Results are expressed as mean ± SD ($n \geqq 3$ is $\leqq 5$): * mean of two values; ** single value; ND = not determined

Table 2. Plasma $t_{1/2}$ and V_D of cyclophosphamide in patients receiving 50 mg/kg/day on each of 4 successive days

Treatment (day)	Plasma $t_{1/2}$ (h)	V_D (l)
1	5.1	40.5
2	3.7	38.0
3	2.9	39.5
4	2.6	43.5

for each day of treatment. The $t_{1/2}$ and CP on day 1 was 5.1 h, but it shortened progressively, with values on each of the 3 successive days of 3.7 h, 2.9 h, and 2.6 h. The V_D did not change during this period (Table 2).

Discussion

The finding that at high dose levels of CP its plasma $t_{1/2}$ values decrease with subsequent doses is in accord with the findings for lower-dose regimens [3]. The $t_{1/2}$ of CP has been shown to decrease during the course of continued low-dose treatment. After a single dose of 100 mg CP the $t_{1/2}$ was 7.33 h, and following a minimum of 6 months' treatment (100 mg/day) the $t_{1/2}$ fell to 4.87 h [3]. The V_D, however, was shown not to change throughout the high-dose treatment; on the other hand prolonged low-dose treatment with CP has been shown to markedly decrease the V_D; in a recent study [3] D'Incalci et al. demonstrated that the V_D of CP prior to prolonged low-dose treatment with the drug was 63.7 l, and that following at least 6 months' treatment the V_D was reduced to 32.2 l.

It has been suggested that the changes in $t_{1/2}$ are due to induction of CP metabolism. However, Marinello et al. [5] have shown that levels of cytochrome P-450 in the rat were reduced following CP treatment, a finding which does not support the metabolic activation hypothesis.

Renal tubular reabsorption of CP [2] may be impaired by subsequent doses of the drug; this may, at least in part, account for the decreased plasma $t_{1/2}$ of CP following multiple doses.

Since CP and its metabolites bind to plasma proteins [1, 4], the availability of binding sites might possibly be reduced following each dose of CP. As a result of a sequential decrease in the availability of protein binding sites, the concentration of free CP in plasma might be increased, leading in turn to a faster rate of elimination. This could result in a faster rate of elimination of CP from the blood.

If autologous bone marrow transplantation is used as an adjunct to very-high-dose CP treatment, the marrow reinfusion must occur when there is little or no CP remaining in the plasma. The decreased $t_{1/2}$ of CP with repeated high doses is reassuring from this point of view; however, the mechanism remains to be explained.

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References

1. Bagley CM Jr, Bostick FW, DeVita VT Jr (1973) Clinical pharmacology of cyclophosphamide. Cancer Res 33: 226
2. Cohen JL, Jao JY, Jusko WJ (1971) Pharmacokinetics of cyclophosphamide in man. Br J Pharmacol 43: 677
3. D'Incalci M, Bolis G, Facchinetti T, Mangioni C, Morasca L, Morazzoni P, Salmona M (1979) Decreased half-life of cyclophosphamide in patients under continual treatment. Eur J Cancer 15: 7
4. Jardine I, Fenselau C, Appler M, Kan M-N, Brundrett RB, Colvin M (1978) Quantitation by gas chromatography-chemical ionisation mass spectometry of cyclophosphamide, phosphoramide mustard and nornitrogen mustard in the plasma and urine of patients receiving cyclophosphamide therapy. Cancer Res 38: 408
5. Marinello AJ, Gurtoo HL, Struck RF, Paul B (1978) Denaturation of cytochrome P-450 by cyclophosphamide metabolites. Biochem Biophys Res Commun 83: 1347
6. Mullins GM, Colvin M (1975) Intensive cyclophosphamide (NSC-26271) therapy in solid tumours. Cancer Chemother Rep 59: 411
7. Pantarotto C, Bossi A, Belvedere G, Martini A, Donelli MG, Frigerio A (1974) Quantitative GLC determination of cyclophosphamide and isophosphamide in biological specimens. J Pharm Sci 63: 1554
8. Souhami RL, Harper PG, Linch D, Trask C, Goldstone AH, Tobias J, Spiro SG, Geddes DM, Richards JM (1982) High-dose cyclophosphamide with autologous marrow transplantation as initial treatment of small cell carcinoma of the bronchus. Cancer Chemother Pharmacol 8: 31

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