Br. J. clin. Pharmac. (1983), **16**, 61–63

PHARMACOKINETICS OF CYCLOPHOSPHAMIDE IN KENYAN AFRICANS

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1 The pharmacokinetics of cyclophosphamide was studied in 10 Kenyan Africans with Hodgkins lymphoma.

2 The mean ± s.d. elimination half-life ($t_{½}$) was 7.5 ± 1.38 h.

The mean ± s.d. volume of the central compartment (V_1) was 0.35 ± 0.12 l/kg and the apparent volume of distribution (V) was 0.64 ± 0.06 l/kg.

4 The microconstants k_{21}, k_{12} and k_{10} were 1.81 ± 0.84 h^{-1}, 1.90 ± 1.080 h^{-1} and 2.05 ± 0.86 h^{-1} respectively (mean ± s.d.).

Keywords cyclophosphamide pharmacokinetics Kenyan Africans

Introduction

Cyclophosphamide is the most widely used cancer chemotherapeutic agent and is also used as an immunosuppressive agent. It is administered both orally and parenterally over a wide dosage range depending on the therapeutic indications and acceptable adverse effects. The clinical use of cyclophosphamide has been recently reviewed (Hill, 1975; Colvin, 1978). Cyclophosphamide consists of a nitrogen mustard group (bischloroethylamine) attached to an oxazophosphorine ring. The parent compound is inactive *in vitro* and is converted to a number of active metabolites by hepatic microsomal enzymes. The kinetics of all the metabolites has not been elucidated because of technical difficulties. However, the pharmacokinetics of the parent compound has been well worked out and confirmed by several workers. The importance of using specific methods, and in particular, gas-liquid chromatography, has been highlighted by van den Bosch & De Vos (1980).

Although the pharmacokinetics of this important agent have been extensively studied, no work has been done to elucidate the kinetics of the drug in adult Africans. The purpose of this study was to investigate the pharmacokinetics of cyclophosphamide in Kenyan Africans.

Methods

Patients and samples

Ten (six male, four female) patients under the care of the Oncology clinic of Kenyatta National Hospital agreed to participate in the study. All the patients had Hodgkins lymphoma and were either stage II or III Ann Arbor classification. Their ages ranged between 27–57 years, they weighed between 56–77 kg, and they had normal renal and liver functions as shown by standard clinical tests. The patients were receiving cyclophosphamide treatment for the first time as part of their chemotherapeutic regimen. The rest of the drugs were administered after the last sample. All patients received cyclophosphamide intravenously (i.v.) as bolus (1 g) via a canullar inserted in the cubital vein. Blood was collected via a butterfly needle introduced into the cephalic vein of the opposite arm and was transferred into lithium heparin tubes at room temperature and centrifuged at 1000 *g* for 10 min within 1 h of collection. Plasma was transferred to plastic tubes and kept at −20°C. The samples were taken at 15 min, 30 min, 1, 2, 3, 4, 6, 8 and 10 h. The following morning samples were taken at 20, 22 and 24 h. Samples were stored at −20°C and were either analysed on the day of collection or within the same week of collection.

Analytical methods

The estimation of cyclophosphamide from biological fluid was accomplished by the method of Juma *et al.* (1978) which estimates the trifluoroacetyl derivative of cyclophosphamide using a gas-liquid chromatograph fitted with an alkaline flame ionisation detector.

The coefficient of variation within assay was 3.5% (at 10 μg/ml) and 4.3% (at 50 μg/ml) and between assays was 5.4% (5 μg/ml) and 5.7% (20 μg/ml).

Data analysis

The data derived from the intravenously administered cyclophosphamide was best fitted to a two compartment open pharmacokinetic model expressed by

$$C_t = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

where C_t is blood concentration at time t, A and B are coefficients with the dimensions of concentration, while α and β are exponents with dimensions of reciprocal time which correspond to first order distribution and disposition rate constants. Plasma concentration, time data was fitted to the model by a simple non-linear optimisation computer program.

The rest of the pharmacokinetic parameters were derived using standard procedures (Gibaldi & Perrier, 1975).

Results

The pharmacokinetic data derived from the study of 10 Kenyan Africans is shown in Table 1. The mean ± s.d. elimination half-life ($t_{½}$) was 7.58 ± 1.38 h. The mean ± s.d. volume of the central compartment (V_1) and the apparent volume of distribution (V) were 0.35 ± 0.12 l/kg and 0.64 ± 0.061 l/kg respectively. These pharmacokinetic parameters are similar to those that have been reported for cyclophosphamide in Caucasians, suggesting that the Kenyan Africans handle cyclophosphamide in a similar fashion.

Discussion

The pharmacokinetic parameters obtained in this study are comparable to the pharmacokinetic parameters of cyclophosphamide that we have reported in Caucasians (Juma *et al.*, 1978, 1979, 1980), and to the pharmacokinetics of cyclophosphamide reported by other workers (Cohen *et al.*, 1970; Bagley *et al.*, 1973; Jarman *et al.*, 1979). The Kenyan Africans apparently handle cyclophosphamide in a similar fashion to the Caucasians to whom the previous studies have been limited. No previous study has been carried out to investigate the pharmacokinetics of cyclophosphamide in adult Africans.

In this study we used a gas-liquid chromatograph fitted with an alkaline flame ionisation detector as detailed by Juma *et al.* (1978). The accuracy and convenience of this method has been highlighted by van den Bosch & Vos (1980). Similar inter-individual variation obtained in this study has been reported by others (Hill, 1975; Mouridsen *et al.*, 1974; Colvin, 1978), and it probably reflects individual differences in activity of liver microsomal enzymes in the metabolism of cyclophosphamide. Large inter-individual variations in drug kinetics can arise from multiple genetic and environmental factors affecting drug absorption, distribution, biotransformation, excretion and interaction with receptor sites, or a combination of these (Vessel, 1978). Twin and family studies demonstrate that for several commonly used drugs, genetic factors are predominantly responsible for large inter-individual variations in drug disposition that occur in normal volunteers under basal conditions. Environmental factors were surprisingly small. It would therefore be expected that individual variation observed in the pharmacokinetics of cyclophosphamide by different workers and by us are due to other genetic variation other than racial.

We wish to thank Professor W. Gitau for his support and advice and Ms Margaret Kamau for secretarial help.

Table 1 Pharmacokinetic parameters determined following administration of cyclophosphamide to 10 Kenyan African patients.

Subject	β (h^{-1})	$t_{½}$ (*h*)	V_1 (*l/1 kg*)	V (*l/1 kg*)	CL_T ([*ml/kg*]/*h*)	k_{21} (h^{-1})	k_{12} (h^{-1})	k_{10} (h^{-1})
1	0.077	9.00	0.43	0.52	59.8	1.12	2.56	0.11
2	0.110	6.50	0.29	0.67	65.4	1.20	2.24	0.36
3	0.110	6.50	0.37	0.67	70.4	1.10	0.81	0.19
4	0.120	5.70	0.22	0.58	67.4	1.42	2.11	0.30
5	0.080	8.70	0.29	0.74	59.8	3.82	4.30	0.16
6	0.100	6.93	0.22	0.58	67.4	2.11	1.10	0.19
7	0.100	6.93	0.38	0.67	70.5	1.48	1.10	0.19
8	0.070	9.95	0.53	0.69	47.3	2.23	1.30	0.11
9	0.080	8.70	0.41	0.67	54.4	2.22	1.40	0.14
10	0.100	6.93	0.96	0.62	67.4	1.42	2.10	0.30
Mean	0.095	7.58	0.35	0.64	62.98	1.81	1.90	2.05
s.d.	0.017	1.38	0.12	0.06	7.60	0.84	1.03	8.63

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(Received January 31, 1983, accepted February 24, 1983)