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Bioavailability of ifosfamide in patients with bronchial carcinoma

T. Cerny[1], J. M. Margison[2], N. Thatcher[1], and P. M. Wilkinson[2]

[1]Departments of Medical Oncology and [2]Clinical Pharmacology, Christie Hospital and Holt Radium Institute, Manchester M20 9BX, UK

Summary. The pharmacokinetics of ifosfamide (I) were determined in ten patients with bronchogenic carcinoma. In seven patients, doses of 1 and 2 g (I) were given both as a bolus orally and later intravenously and were well tolerated. A further three patients received 5 g (I) as a single oral dose but in two this produced reversible CNS toxicity and severe vomiting. The area under the curve (AUC, $\mu g.h.l^{-1}$) for the 1-g dose was the same following oral and i. v. treatment and this was also true for the 2-g doses. There was a proportionate increase in the AUC for the 5-g oral dose, indicating 100% bioavailability at all three dose levels. We conclude that doses up to 2 g by mouth represent a well-tolerated alternative route of administration.

Introduction

The oxazaphosphorine ifosfamide (I) is a tautomer of the well-known alkylating agent cyclophosphamide (C). Ifosfamide shows considerably less bone marrow toxicity than (C) and may therefore be a more suitable agent for combination chemotherapy. There has been renewed interest in (I) in view of the fact that the dose-limiting urotoxicity can be overcome by Mesna [2]. Preliminary reports suggest that (I) is active in several (C)-resistant tumours and should therefore be regarded as a new and distinctive oxazaphosphorine derivative [4, 5, 12]. Whilst the putative lack of complete cross resistance with (C) remains unproven [for review see 1] the metabolic pathway of (I) activation is probably different.

There are recent reports describing reversible CNS toxicity with higher doses of (I), but there is no clear evidence as to whether this is due to (I) itself or to possible metabolites of Mesna. However, the fact that neurotoxicity was also noted in earlier reports [3] without administration of Mesna makes the latter possibility unlikely.

To date, (I) has been given i. v. together with Mesna, either alone or in combination with other agents, for a number of solid tumours. This treatment requires hospitalisation, and there are clearly certain advantages to oral treatment providing satisfactory bioavailability can be proven [9]. We therefore examined the kinetics of (I) from an oral formulation and compared this to the same dose given i. v.

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Offprint requests to: T. Cerny

Patients, material and methods

Ten patients with previously untreated bronchogenic carcinoma were studied; details are given in Table 1. Before inclusion, a Karnofsky Performance Score [6] of more than 50 was required and verbal information consent obtained.

The mean age of the patients was 64.5 years (range 54–73) and they consisted of four females and six males.

Drug administration. All (I) was prepared as a powder in gelatine capsules (500 mg) by Dr. M. Spring (Department of Pharmacy, Manchester University). The powder was a gift from Boehringer Ingelheim, Berkshire, UK. For intravenous use ifosfamide BP was given and prepared in the normal manner.

All patients fasted for at least 2 h before oral administration and the capsules were given as a bolus dose with 100 ml water. The i. v. dose was given 4 days before or 4 days after the oral dose. All patients also received i. v. Mesna at the same dose as (I) for 24 h and the fluid intake of 2 litres was maintained over this time period. Other drugs were given as necessary. Patients were carefully monitored for side effects during this period. Serial serum and urine samples were collected during the first 48 h after administration and stored at $-20\,^{\circ}C$ prior to assay.

Ifosfamide assay. All samples were assayed by a reverse HPLG method developed in this laboratory using UV detection at 190 nm [8]. The calibration curve was linear throughout the dose range encountered and the coefficient of variation of the assay was 5.4%.

Kinetic analysis. For the i. v. profile the serum concentration time curve was analysed by a non-iterative computer programme based on a two-compartment open model. The intercept values and rate constants were used to calculate the half-time, clearance, volume of distribution and the dispositional rate constants between compartments. The area under the curve (AUC) was calculated by extrapolating to infinity.

For the oral curve a linear regression analysis of the terminal phase was used to determine the half-time and clearance. The AUC was calculated by the trapezoidal rule but extrapolated to infinity for comparability.

Table 1. Patient characteristics

Patient	Age (years)	Sex	KPS	Histological Type and Stage	Creatinine clearance (ml/min)	Liver function	Other abnormalities
1. S. L.	66	M	70	Squamous cell type with soft tissue metastases	98	Normal	None
2. R. E.	75	F	70	Extensive disease SCLC	69	Normal	Coronary heart disease, dysphagia
3. D. J.	56	M	80	Anaplastic Ca of lung with bone metastases	138	Normal	None
4. R. F.	56	M	60	Poorly diff. squamous cell Ca, bilateral lung, bony metastases	91	Normal	Hypercalcaemia
5. P. H.	54	M	70	Poorly differentiated, Ca of lung with chest wall involvement	108	Normal	None
6. C. H.	59	F	60	Squamous cell of lung invading oesophagus	92	Moderately impaired (alcohol)	Dysphagia
7. D. B.	63	M	50	Squamous cell Ca with extensive liver involvement	75	Severely impaired, jaundiced	None
8. H. M.	72	F	80	SCLC with extensive disease	104	Normal	Inappropriate ADH
9. H. S.	71	F	70	SCLC with extensive liver metastases	104	Moderately impaired	None
10. P. E.	73	M	70	SCLC ("relapse" after lobectomy)	77	Normal	Inappropriate ADH

SCLC, small cell lung cancer; KPS, Karnofsky Performance Score [6]

Results

The results are summarised in Table 2 and shown in Figs. 1–4. The AUC was the same for both the oral and the i. v. dose, indicating 100% bioavailability; this applied for both the 1- and 2-g doses. The mean ratio of the AUC for i. v. and AUC for oral application was 0.905 for the 1-g and 1.070 for the 2-g dose level. For those patients who received 5 g orally, the AUC showed the predicted linear increase, again suggesting 100% (I) bioavailability. However, in these cases the i. v. dose was not given because of poor tolerance and toxicity of the oral regime.

Toxicity

The doses of 1 and 2 g by mouth and i. v. were well tolerated. All patients received Mesna at the same dose as (I), and no signs or symptoms of urotoxicity or CNS toxicity were noted at any time during the study period (see Table 3).

The haematological toxicity was mild, and in no instance was a nadir white cell count of less than 3.0×10^9/litre noted. Haemoglobin and platelets showed no significant change from the pre-treatment values. Of three patients who received 5 g orally, all showed CNS toxicity and two developed somnolence and confusion in addition to their vomiting. This occured 5–6 h after administration and could not be controlled satisfactorily by anti-emetics. In view of this no further studies were undertaken with this dose and it is not possible to comment on haematological toxicity.

Discussion

This study demonstrates that oral (I) is well tolerated in doses of 1 and 2 g, with 100% bioavailability. It is interesting to note that similar findings are obtained in those patients with liver involvement from their tumour. However,

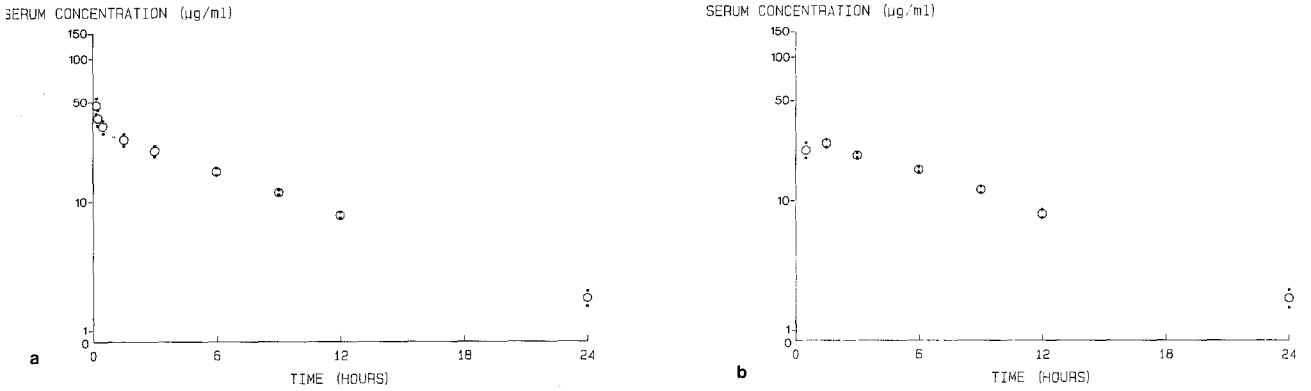


Fig. 1a, b. Concentration/time curve (mean +/− SEM) in six patients receiving 1 g ifosfamide i. v. **(a)** and orally **(b)**

Table 2. Pharmacokinetic parameters of ifosfamide

Single dose of (I)	k_{el} (h^{-1})	$k_{2>1}$ (h^{-1})	$k_{1>2}$ (h^{-1})	V_1 (l)	V_d area (l)	V_d steady state (l)	V_2 (l)	$T^1/_2\alpha$ (h)	$T^1/_2\beta$ (h)	Cl_{tot} ($ml \cdot min^{-1}$)	AUC (0 to ∞) ($mg \cdot h \cdot l^{-1}$)
1 g i.v.	0.190	2.80	1.69	18.70	30.49	30.00	11.28	0.150	5.92	59.46	294.20
SD	0.048	1.41	0.75	6.30	7.40	7.40	4.20	0.073	1.15	6.40	29.82
SEM	0.020	0.57	0.30	2.57	3.00	3.00	1.70	0.030	0.47	2.60	12.17
1 g p.o.	–	–	–	–	–	–	–	–	5.33	45.33	266.30
SD	–	–	–	–	–	–	–	–	1.26	6.67	12.02
SEM	–	–	–	–	–	–	–	–	0.51	2.72	4.90
2 g i.v.	0.213	2.26	1.34	20.24	33.01	32.27	12.02	0.18	5.29	72.07	478.20
SD	0.170	1.06	6.50	6.50	5.80	5.80	9.60	0.18	0.73	7.90	34.86
SEM	0.070	0.47	2.90	2.94	2.60	2.60	4.20	0.08	0.27	3.50	13.17
2 g p.o.	–	–	–	–	–	–	–	–	5.33	50.17	511.80
SD	–	–	–	–	–	–	–	–	0.96	13.09	83.97
SEM	–	–	–	–	–	–	–	–	0.36	4.95	31.73
5 g p.o.	–	–	–	–	–	–	–	–	4.07	61.33	1229.70
SD	–	–	–	–	–	–	–	–	0.40	21.34	156.20
SEM	–	–	–	–	–	–	–	–	0.23	12.32	90.10

SD, standard deviation; SEM, standard error of mean; AUC, area under curve; k_{el}, elimination constant; $k_{2>1}$, transfer constant from peripheral to central compartment; $k_{1>2}$, transfer constant from central to peripheral compartment; V, volume of central compartment (V_1), volume of peripheral compartment (V_2) and apparent volume of distribution (V_d area); $T^1/_2$, half-life of distribution phase (α) and elimination phase (β); Cl_{tot} total body clearance

Table 3. Toxicity of ifosfamide

Patient	Nausea and vomiting					CNS toxicity	Haematotoxicity
	1 g p.o.	1 g i.v.	2 g p.o.	2 g i.v.	5 g p.o.		
1. S. L.	Grade 0	0	0	0	n.d.		
2. R. E.	Grade 0	0	2	2	n.d.		
3. D. J.	Grade 0	0	0	0	n.d.		
4. R. F.	Grade 0	0	0	0	n.d.	Grade 0	Grade 0
5. P. H.	Grade 0	0	0	0	n.d.		
6. C. H.	Grade 2[a]	2	2	2	n.d.		
7. D. B.	n.d.	n.d.	0	0	n.d.		
8. H. M.[b]	n.d.	n.d.	n.d.	n.d.	Grade 4	Grade 3 encephalopathic	–
9. H. S.[b]	n.d.	n.d.	n.d.	n.d.	Grade 4	Grade 3 encephalopathic	–
10. P. E.[b]	n.d.	n.d.	n.d.	n.d.	Grade 3	Grade 2 modorate dizziness	–

Results expressed in terms of WHO toxicity grade [10]
n.d., not done
[a] This patient showed nausea and vomiting for several weeks combined with dysphagia (coesophageal tumour involvement)
[b] These patients also received 800 mg etoposide, therefore the haematological toxicity could not be assessed

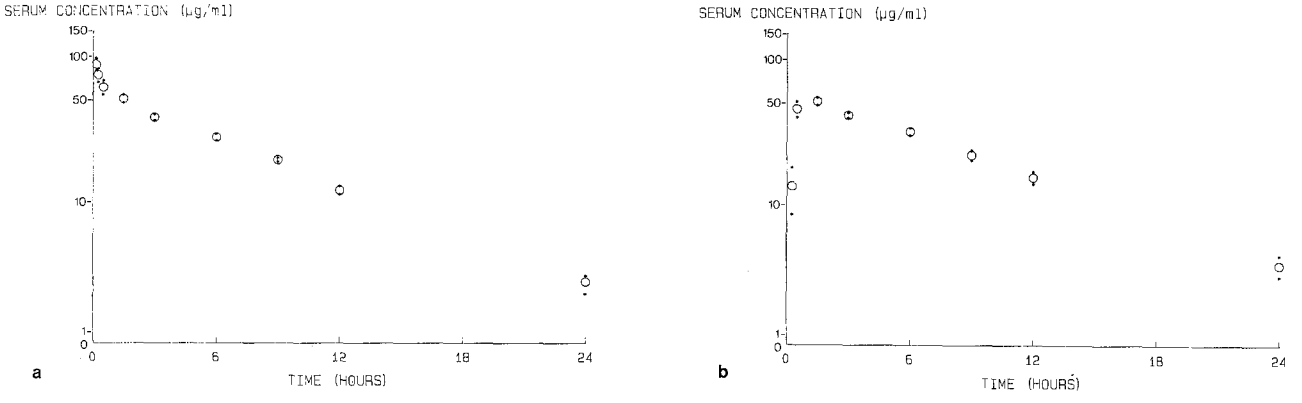


Fig. 2a, b. Concentration/time curve (mean +/− SEM) in seven patients receiving 2 g ifosfamide i. v. **(a)** and orally **(b)**

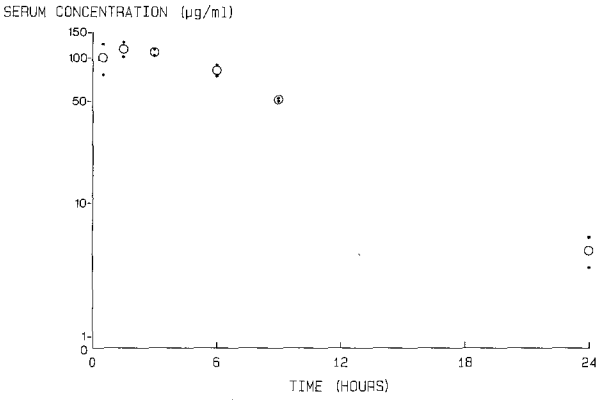
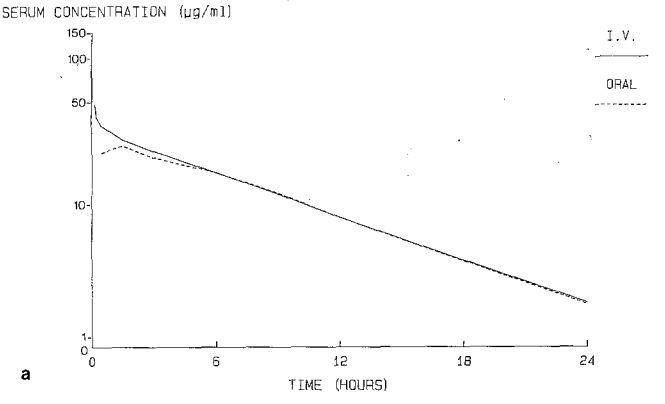


Fig. 3. Concentration/time curve (mean +/− SEM) in three patients receiving 5 g ifosfamide orally



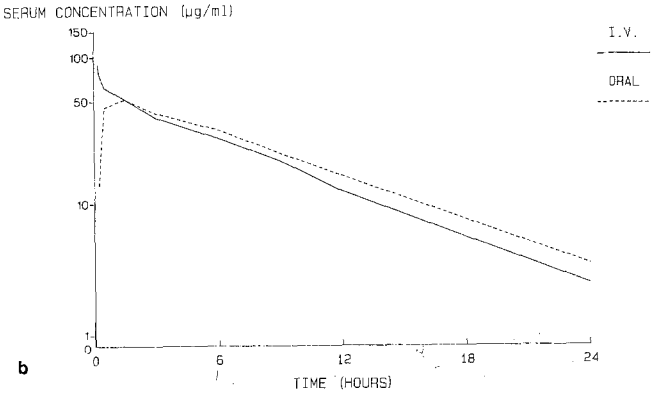


Fig. 4a, b. Comparison of concentration/time curves (means) of 1 g **(a)** and 2 g **(b)** ifosfamide given i. v. and orally

since it is only possible to estimate the parent compound with the analytical method employed here, no comment can be made concerning possible variation in metabolism between those patients with normal liver function and those with liver metastases. Further investigations of the metabolites will be required to elucidate this point.

The decay of i. v. (I) was a first-order process and there was no evidence of saturable metabolism, even with doses up to 5 g. We have previously reported that with (C) there is no evidence of saturation of metabolism even with doses of up to 8 g [13]. The terminal half-life of (I) showed a consistent decrease with an increase in body clearance, suggesting a dose-dependent inducible metabolism.

In conclusion, oral (I) in doses of up to 2 g now requires evaluation in clinical studies, as several reports suggest that fractionated doses may have a better therapeutic index [7, 11].

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