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Disposition of ifosfamide in patients receiving ifosfamide infusion therapy for the treatment of cervical carcinoma

Robert Pearcey[1], Robert Calvert[2], and Anil Mehta[2]

[1] University Department of Radiotherapy, Cookridge Hospital, Leeds, UK
[2] Pharmacy Department, General Infirmary at Leeds, Leeds LS13EX, UK

Summary. The disposition of ifosfamide was investigated in nine patients receiving a total of 23 72-h infusions. There was no linear relationship between steady-state plasma concentrations and either vomiting or CNS toxicity. The steady-state plasma concentrations were reproducible within patients, but there was a wide variation between patients. The progress of the disease did not affect the disposition of ifosfamide.

Introduction

A phase II study using ifosfamide as a 3-day infusion concurrently with Mesna in patients presenting with advanced (FIGO stages IIIB and IV) and inoperable recurrent carcinoma of the cervix was conducted at the Regional Radiotherapy Centre, Cookridge. Previous experience in using ifosfamide in patients with pelvic malignancies at this centre suggested that the possibility of toxicity, particularly nausea and vomiting, is greater than for patients treated for non-pelvic malignancies. Others have reported encephalopathy, a more serious side effect of ifosfamide [3], particularly in patients being treated for pelvic malignancies, although this is a rare complication for patients being treated with similar regimes for thoracic malignancies [1].

It is common practice in our centre to carry out isotopic renograms on patients with pelvic malignancies prior to treatment. We have noted that these patients commonly show evidence of slight to moderate obstructive uropathy that is not detected by more simple biochemical tests of renal function (serum creatinine levels and creatinine clearance). The possibility therefore existed that the worse toxicity may be due to higher plasma levels of ifosfamide as a result of impaired renal excretion in some patients.

At present there is no information available on the steady-state plasma concentrations of ifosfamide resulting from a dose regimen of 3 g/day for 3 days. To investigate the possibility of abnormally high levels in patients with moderate obstructive uropathy, the disposition of ifosfamide was studied in a group of patients receiving regular treatment to establish the expected steady-state plasma concentration range.

Offprint requests to: R. Pearcey, Cross Cancer Institute, Edmonton, Alberta, Canada T6G1Z2

Methods

Patients received a standard first dose of 2 g/m^2 per 24 h over 3 days. This treatment was given concurrently with Mesna, using an IVAC 631 infusion pump, as three 24-h i.v. infusions. Blood samples were taken at approximately 12-h intervals from the start of the infusion and at 6 and 12 h after termination of the infusion. The plasma was separated and stored at −25° C until analysed for ifosfamide. The treatment was repeated at 4-week intervals using the same dose unless the patient had not tolerated the previous dose, in which cases the dose was reduced to 1 g/m^2 per 24 h.

Ifosfamide plasma concentrations were determined by a modification of the gas liquid chromatography procedure of Juma et al. [2] using a Perkin Elmer 8310 gas liquid chromatograph equipped with a nitrogen detector and a 3% OV17 on Gas Chrom Q stationary phase. The method was modified to estimate ifosfamide using cyclophosphamide as an internal standard. The accuracy and precision of the assay was determined and the concentration of ifosfamide in plasma samples was estimated using a standard curve in linearity, which was verified during each batch analysis using known standards of ifosfamide.

The disposition parameters of clearance (Cl), volume of distribution (V), and half-life were calculated by model independent methods based on estimation of the area under the curve of best fit to the plasma concentration-time data. The curve of best fit was obtained using the nonlinear curve-fitting programme NONLIN [4]. A full SMAC 12 analysis was carried out on each patient before each course of ifosfamide. During each course, a subjective estimate was made of the extent of vomiting and nausea experienced by the patient and of any CNS toxicity using the Meanwell et al. rating scale [3].

Results

The analytical method had a within-day coefficient of variation of 5.35% and a day-to-day variation of 7.15 at 10 mg/l. The lower limit of detection was found to be 0.1 mg/l. The ifosfamide was found to be stable at −25° C for at least 2 months and for at least 24 h at room temperature.

Plasma concentration-time profiles were obtained in nine patients receiving a total of 23 courses of treatment. Examples of the profiles obtained after 2 g/m^2 per 24 h on two occasions in one patient and 1 g/m^2 per 24 h are given

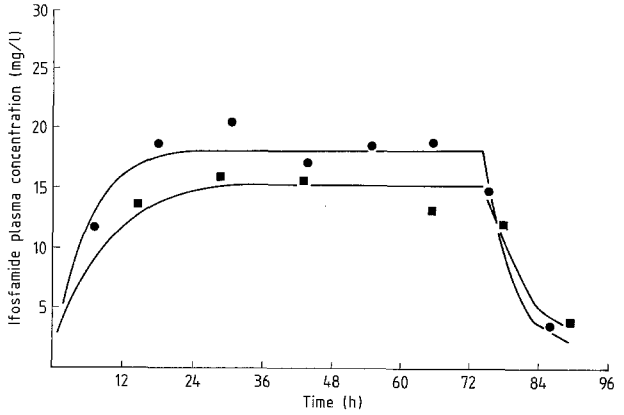

Fig. 1. Simulated plasma concentration/time profiles (------) and observed plasma concentrations for one patient receiving a 2 g/m^2 per 24 h (●) and one receiving a 1 g/m^2 per 24 h (■) infusion of ifosfamide

Table 1. Disposition parameters for ifosfamide in patients receiving an i.v. infusion of ifosfamide over 72 h

Patient	Number of courses	Clearance ifosfamide (ml/min ± SD)	Volume of distribution (l ± SD)
1	3	111, 123, 82	15, 44, 40
2	4	116±20	40±14
3	2	67, 64	37, 21
4	2	74, 93	13, 13
5	2	65, 72	17, 23
6	1	80	24
7	3	57, 88, 99	13, 16, 47
8	3	66, 79, 90	16, 16, 20
9	2	68, 61	24, 19
10	1	58	11
Mean		85±23	25.6±13.1

in Fig. 1. The disposition parameters of Cl, V, and half-life are given in Table 1. The mean steady-state plasma concentrations after each dose together with estimates of renal function and serum albumin concentrations are given in Table 2. The subjective estimate of vomiting (scale, 1–3) and toxic effects on the CNS are given in Table 2.

Discussion

A wide range of steady-state plasma concentrations was found in this group of patients. After a 2 g/m^2 per 24 h dose steady-state plasma concentration varied from 15.2 to 36 mg/l and after a 1 g/m^2 per 24 h dose varied from 10 to 18 mg/l, as shown in Fig. 2. The higher plasma levels were associated with frequent vomiting; however, no correlation between vomiting and plasma concentration was found in this group. Only one patient experienced any CNS toxicity (patient 8), which occurred during the second course of treatment at the lower dose 1 g/m^2 per 24 h and at a lower steady-state plasma concentration than the first course of treatment. Many patients had much higher plasma concentrations of ifosfamide but did not exhibit

Table 2. Creatinine clearance, plasma albumin concentrations, and estimates of toxicity observed in patients receiving an i.v. infusion of ifosfamide over 72 h

Patient	Course number	Dose (g)	Plateau plasma concentration (mg/l)	CLcr (ml/min)	Albumin (g/l)	Toxicity	
						Vomiting	CNS
1	1	9.9	19.1	87	43	1	0
	2	9.9	18.2	113	45	2	0
	3	9.0	24.6	84	38	1	0
2	1	10.8	21	120	42	2	0
	2	9.6	20	63	40	1	0
	3	9.0	21	70	42	2	0
	4	9.0	15	67	39	2	0
3	1	4.5	15.2	29	31	0	0
	2	4.5	16.6	46	21	0	0
4	1	9.0	28.7	60	34	1	0
	2	9.0	21.3	54	36	1	0
5	1	9.0	34	70	N.A.	3	0
	2	4.5	14.4	118	N.A.	1	0
6	1	4.3	12.6	63	34		
7	1	9.0	35.8	70	36	2	0
	2	4.3	12.7	37	40	1	0
	3	4.3	11.4	63	38	1	0
8	1	4.5	18	104	31	1	0
	2	4.5	15	132	45	0	0
	3	4.5	11.6	131	48	0	0
9	1	9.0	32	54	35	3	0
	2	4.5	18	36	39	3	2
10	1	9.9	39	145	37	2	0

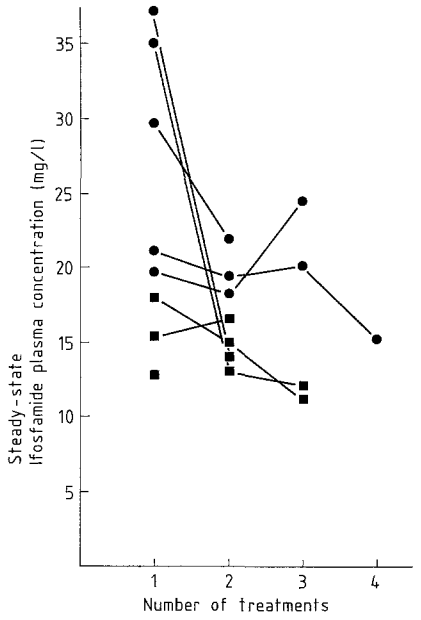

Fig. 2. Steady-state plasma concentrations of ifosfamide in patients receiving repeated courses of IV infusions of ifosfamide at a dose of 1 g/m^2 per 24 h (■) or 2 g/m^2 per 24 h (●)

any CNS toxicity. It is therefore unlikely that obstructive uropathy would be a factor in CNS toxicity. Further support for this given by the lack of correlation between ifosfamide clearance and creatinine clearance in these patients. This could be expected, since the drug is eliminated principally by metabolism. The obstructive uropathy could inhibit the elimination of metabolites of ifosfamide that may be a factor in CNS toxicity; these were not investigated in this study.

The steady-state plasma concentrations obtained in patients on repeat dosing were reproducible within patients, suggesting that the progress of the disease had little effect on the disposition of ifosfamide. There was a trend to lower steady-state concentrations on repeat dosing; the final steady-state concentration was lower in five of the eight patients who received more than one course after adjustment for dose (Fig. 2). The variation between patients in steady-state concentration was more a reflection of differences in volume of distribution (25.6 l ± 13 l) than in clearance (85.2 ml/mm ± 23 ml/min). At present there is no known relationship between steady-state plasma concentration and efficacy; the wide range of metabolite levels must be a major source of variation in efforts to find any correlation, which should be controlled in such studies by individual dose adjustment. The present investigation found no support for the effect of obstructive uropathy as a major cause of CNS toxicity. It demonstrated that ifosfamide infusion gives reproducible steady-state plasma concentrations in the same patient but that there is a wide variation between patients.

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