Cancer Chemother Pharmacol (1995) 36: 53–60

ORIGINAL ARTICLE

Alan V. Boddy · Michael Cole · Andrew D. J. Pearson
Jeffrey R. Idle

The kinetics of the auto-induction of ifosfamide metabolism during continuous infusion

Received: 4 May 1994/Accepted: 22 September 1994

Abstract It has often been reported that the oxazaphosphorines ifosfamide and cyclophosphamide induce their own metabolism. This phenomenon was studied in 21 paediatric patients over 35 courses of therapy. All patients received 9 $g\,m^{-2}$ of ifosfamide as a continuous infusion over 72 h. Plasma concentrations of parent drug and of the major metabolite in plasma, 3-dechloroethylifosfamide (3DC) were determined using a quantitative thin-layer chromatography (TLC) technique. A one-compartment model was fitted simultaneously to both ifosfamide and 3DC data. The model included a time-dependent clearance term, increasing asymptotically from an initial value to a final induced clearance and characterised by a first-order rate constant. A time lag, before induction of clearance began, was determined empirically. Metabolite kinetics were characterised by an elimination rate constant for the metabolite and a composite parameter comprising a formation clearance, proportional to the time-dependent clearance of parent drug, divided by the volume of distribution of the metabolite. Thus, the parameters to estimate were the volume of distribution of parent drug (V), initial clearance (Cli), final clearance (Cls), the rate constant for changing clearance (*K*c), the elimination rate constant for the metabolite (*K*m) and Vm/fm, the metabolite volume of distribution divided by the fractional clearance to 3DC. The model of drug and metabolite kinetics produced a good fit to the data in 22 of 31 courses. In a further 4 courses an auto-inductive model for parent drug alone could be used. In the remaining courses, auto-induction could be demonstrated, but there were insufficient data to fit the model. For some patients this was due to a long time lag (up to 54 h) relative to the infusion time. The time lag varied from 6 to 54 (median, 12) h and values for the other parameters were Cli, $3.27 \pm 2.52\,l\,h^{-1}\,m^{-2}$, Cls, $7.50 \pm 3.03\,l\,h^{-1}\,m^{-2}$, V, $22.0 \pm 11.0\,l\,m^{-2}$, *K*c, $0.086 \pm 0.074\,h^{-1}$; *K*m, $0.159 \pm 0.077\,h^{-1}$ and Vm/fm, $104 \pm 82\,l\,m^{-2}$. The values of *K*c correspond to a half-life of change in clearance ranging from 2 to 157 h, although for the majority of the patients the half-life was less than 7 h and a new steady-state level was achieved during the 72 h infusion period. This model provides insight into the time course of enzyme induction during ifosfamide administration, which may continue for up to 10 days in some protocols. Since other drugs, including common anti-neoplastic agents, are metabolised by the same P450 enzyme as is ifosfamide, auto-induction may have implications for the scheduling of combined chemotherapy.

Key words Induction · Metabolism · Kinetics · Ifosfamide

A. V. Boddy (✉) · M. Cole · A. D. J. Pearson · J. R. Idle
Cancer Research Unit and Departments of Medical Statistics, Child Health and Pharmacological Sciences, The Medical School, University of Newcastle upon Tyne, Newcastle upon Tyne NE2 4HH, UK.

Introduction

Ifosfamide is an oxazaphosphorine alkylating agent used in the treatment of a variety of malignancies. It is usually given in a series of fractionated doses or as a continuous infusion over several days, with cycles being repeated every 3–4 weeks. Both ifosfamide and its isomer cyclophosphamide require metabolic activation via a 4-hydroxy intermediate to produce what is considered to be the ultimate alkylating species [32]. This reaction is thought to be mediated by a cytochrome P450 enzyme, which may be different for the two drugs [10, 34]. Ifosfamide is subject to an inactivating route of metabolism that involves the removal of a chloroethyl group from either the endo- or exocyclic nitrogen to form either 3- or 2-dechloroethyl metabolites (3-DC or 2-DC), respectively. This reaction is thought to be

mediated by CYP3A4, the same P450 isoform as is involved in ifosfamide activation [34]. The dechloroethylation reaction produces an equimolar quantity of chloroacetaldehyde for both 2-DC and 3-DC, and this by-product of metabolism has been associated with some of the toxic effects of ifosfamide. Since dechloroethylation is only a minor route of cyclophosphamide metabolism [33] but can account for up to 50% of a dose of ifosfamide [6], chloroacetaldehyde has been implicated in the CNS and renal toxicities that are exclusive to ifosfamide [17, 31].

Both ifosfamide and cyclophosphamide are known to induce their own metabolism following repeated or continuous administration. Analysis of metabolite plasma levels at the beginning and end of 5 days of therapy indicate that the dechloroethylation reaction is induced and also, possibly, the 4-hydroxylation reaction [21]. In a study of ifosfamide given by continuous infusion we have shown that the apparent steady-state concentration of ifosfamide decreases by up to 70% during a continuous 3-day infusion [6]. Administration of ifosfamide as three bolus doses on consecutive days showed a similar increase in the clearance of parent drug and increase in both the area under the concentration-time curve (AUC) and urinary recovery of dechloroethylated metabolites, but revealed no increase in isophosphoramide mustard or carboxyifosfamide, the ultimate products of the 4-hydroxylation reaction [5]. The time-course of induction is very rapid and a greater understanding of the phenomenon would assist in optimising dosing schedules. Also, as CYP3A4 metabolises a variety of other anti-neoplastic agents, including etoposide [30] and the vinca alkaloids [35], which may be used in combination chemotherapy with ifosfamide, induction of this enzyme would be expected to influence the effect of these other agents.

Other drugs that induce their own metabolism include aminoglutethimide [27] and theophylline [11]. Studies with carbamazepine show that clearance increases following repeated administration [25] and that a pharmacokinetic model can be fitted to this data [29]. Clearance increases according to a model based on the kinetics of enzyme synthesis and degradation, tending asymptotically to a new induced clearance at a rate determined by a first-order rate constant for enzyme degradation, Kc [16]. This model was fitted to data on parent drug only. Although increased production of carbamazepine metabolites has been demonstrated [25], no attempt was made to fit a model of increasing metabolite formation to metabolite data in plasma. In the present study, a modified model was employed to describe simultaneously the time-dependent pharmacokinetics of ifosfamide and that of its 3-dechloroethylated metabolite.

Detailed ifosfamide pharmacokinetic and metabolite data for the majority of these patients have been published elsewhere [6, 7].

Patients and methods

Ifosfamide and its metabolites were obtained from Asta Medica AG (Frankfurt, Germany). Cyclophosphamide and 4-nitrobenzylpyridine (NBP) were purchased from Sigma (Poole, UK). All other reagents were of appropriate analytical grade.

A total of 21 patients, including 6 girls, were being treated for sarcomas with up to 17 courses of ifosfamide every 3 weeks. Their ages ranged from 1 to 16 years. Patients received ifosfamide as a continuous infusion (Gemini PC-2 volumetric infusion pump, Imed, San Diego, USA) at a dose of $3\,g\,m^{-2}$ each day for 3 days. This was accompanied by $3\,l\,m^{-2}$ of hydration each day and by mesna ($3\,g\,m^{-2}$ per day) infused during and for 12 h after ifosfamide administration. Concomitant therapy included etoposide, vincristine, actinomycin D and anti-emetics. Previous studies have not shown any acute effect of these drugs on ifosfamide metabolism. One subject (patient 7) was on long-term therapy with carbamazepine. The study was approved by the Joint Ethical Committees of the University of Newcastle upon Tyne and the Newcastle Health Authority.

Patients were studied during up to three courses. Blood samples (3–5 ml, depending on the size of the child) were collected immediately before and at 3, 6, 12, 18, 24, 36, 48 and 60 h after the start of the infusion, at the end of the infusion and at 1, 2, 4, 6, 12, 18 and 24 h after the end of the infusion. Blood was anti-coagulated with ethylenediaminetetraacetic acid (EDTA) and plasma was separated and frozen immediately at -20 C prior to analysis. Concentrations of ifosfamide and its metabolites were determined in plasma using a quantitative thin-layer chromatography (TLC)-photography-densitometry technique [4]. Briefly, 0.75 ml of plasma was added to 50 µl of internal standard (cyclophosphamide, $500\,\mu g\,ml^{-1}$ in methanol) and 0.75 ml of cold acetonitrile. After mixing, centrifugation and evaporation of the solvent from the supernatant, samples were reconstituted in methanol and applied to silica-gel TLC plates (E. Merck, Darmstadt, Germany). After chromatography and visualisation the plates were photographed. The negative was enlarged to the exact size of the original plate and the photographs of the plates were scanned. The peak areas for ifosfamide and its metabolites were divided by the area under the internal standard (cyclophosphamide) peak and the peak area ratio was used for calibration. Each plate contained samples and at least six tracks derived from spiked plasma containing known concentrations of authentic standards ($2–50\,\mu g\,ml^{-1}$). Calibration curves were obtained for ifosfamide and each of the metabolites and these were used to determine the concentrations in patients' plasma samples. Concentrations were expressed as micromolar values for drug or metabolite.

The pharmacokinetic model of time-dependent clearance was based on that described by Pitlick et al. [29]. This assumes that clearance [Cl(t)] is the only time-dependent pharmacokinetic parameter, that a one-compartment model is adequate to describe the distribution of the drug and that changes in clearance depend on the relative rates of synthesis and degradation of drug-metabolising enzymes [16]. Thus, after an initial lag-time (Tind) when clearance is assumed to be constant and equal to the initial clearance Cli, Cl(t) tends towards some final value, Cls, according to the following equation:

$$Cl(t) = Cls - (Cls - Cli) \times e^{-Kc.(t - \mathrm{Tind})}, \quad (1)$$

where Kc is a rate constant for the rate of change in Cl(t) and is equivalent to the rate constant for degradation of metabolising enzyme. The plasma concentration of parent drug is then described by the following two equations for during and after the infusion:

$$C(t) = \frac{R\mathrm{inf}}{Cl(t)} \times \left(1 - e^{-\frac{Cl(t)}{V} \times t}\right) \quad (2)$$

$$C(t) = C(T) \times e^{-\frac{Cl(t-T)}{V} \times t} \quad (3)$$

where T is the duration of the infusion and $Rinf$ is the rate of drug infusion.

The kinetics of the metabolite in plasma are described by a one-compartment model with a formation clearance, Clm, proportional to the time-dependent Cl(t) and elimination described by a first-order rate constant, Km. Since the fraction of the dose converted to the metabolite (fm) was not known, a composite parameter, equal to the ratio of fm to the metabolite volume of distribution Vm, was determined. The following equations were fitted to the metabolite data during and after the infusion:

$$Cm(t) = \frac{fm\frac{Cl(t)}{V}}{Vm} \times Rinf \times \left(\frac{1}{\frac{Cl(t)}{V}Km} + \frac{e^{-\frac{Cl(t)}{V}\cdot t}}{\frac{Cl(t)}{V} \times \left(\frac{Cl(t)}{V} - Km\right)} - \frac{e - Km \times t}{Km \times \left(\frac{Cl(t)}{V} - Km\right)} \right) \quad (4)$$

$$Cm(t) = Cm(T) \times e^{-Km \times (t-T)} + \frac{fm\,Cl(t)\,C(T)}{Vm\left(\frac{Cl(t)}{V} - Km\right)} \times \left[e^{-Km(t-T)} - e^{-\frac{Cl(t)}{V}(t-T)} \right], \quad (5)$$

where $Cm(T)$ is the estimated metabolite concentration at the end of the infusion. The fractional clearance to the 3DC metabolite is assumed to be constant in both the induced and uninduced states. This may be a reasonable assumption, since a high degree of correlation has been shown between the formation of 3DC and that of the 2-dechloroethylated metabolite [6] and the same P450 enzyme has been shown to contribute to both major pathways of ifosfamide metabolism [34]. A similar model with time-independent formation of the metabolite was also fitted.

The models were fitted simultaneously to the parent drug and 3DC data using the ADAPT program with unweighted least squares and equal weighting for both sets of data. Other weighting procedures did not improve the fit to the data or the precision of the parameter estimates. The lag time for induction, Tind, was estimated empirically by repeated fitting using different values until the best fit to the data was obtained. In patients for whom there were insufficient metabolite data the auto-induction model was fitted to the parent drug data alone. A half-life for auto-induction was calculated from $0.693/Kc$ and a half-life for ifosfamide at the end of the infusion was obtained by fitting a mono-exponential equation to the post-infusion data. The half-life for elimination of the metabolite was calculated from $0.693/Km$.

Results

The model of time-dependent clearance provided a good fit to the drug and metabolite data in 22 out of 31 courses studied. A further 4 courses without good metabolite data could be fitted by the model for parent drug alone. Of the courses that could not be fitted by this model of enzyme induction, 3 did not show an increase in clearance until 36 to 54 h after the start of the infusion and thus lacked sufficient data to characterise the change in clearance. The model could be fitted to the data, but the parameters describing the auto-induction effect were very poorly estimated. The remaining two data sets showed a rapid onset of auto-induction, but the data were very noisy for both parent and metabolite. The model with time-independent formation of the metabolite did not fit the data as well as the model with time-dependent formation.

The results of fitting the time-dependent model to all 31 courses is shown in Table 1. Examples of the fits of the model to the data are shown in Figs 1 and 2. Figure 1 is from a patient showing rapid onset of auto-induction (Tind, 6 h), whereas Fig. 2 is from a patient with a more delayed (Tind, 24 h) increase in clearance. The combination of the time of onset (range of Tind, 6–54 h) and the rate of auto-induction (half-life of changing clearance, 2–157 h) indicates the time taken for auto-induction to be complete. For some patients this would occur within the duration of the infusion, whereas several weeks of therapy would be required for others to achieve a new steady-state situation. Thus, in patients and courses 2, 5(a), 8, 10(a), 11(c), 12 and 13(b), more than 72 h from the start of infusion would be required to reach 90% of full induction (Fig. 3). Note that for a given individual, this time to attain maximal induction can vary from 18 up to 114 h in different courses of therapy (patient 13). Thus, some patients show a degree of intra-subject variation in auto-induction, whereas others are relatively consistent. The median apparent half-life of the metabolite ($0.693/Km$) was 4.8 h (range, 2.1–25.5 h), whereas the median terminal half-life of the parent drug (obtained by fitting a mono-exponential equation to the post-infusion data) was 2.2 h (range, 1.0–6.5 h). Thus, the parent drug is eliminated more rapidly than the metabolite and 3DC can be said to exhibit elimination-rate limited kinetics [19].

For an individual patient the time of induction did not vary greatly, but there were some variations in the other model parameters. Initial clearance (Cli) increased in some subjects (patients 1, 13, 15 and 16) with increasing exposure to ifosfamide but decreased in others (patients 5, 6, 10, 11). Final clearance (Cls) matched the trend for Cli but did not always increase with increasing exposure. Kc was sometimes poorly estimated and no intra-subject comparison was possible. Values for the volume of distribution of the parent drug showed a surprisingly high degree of intra-subject variability (up to 2-fold). The rate constant for elimination of metabolite was relatively constant within an individual, although a high degree of inter-subject variability was observed. The final parameter is a composite of the metabolite volume of distribution and the fraction of the dose converted to the 3DC metabolite and varies over 10-fold amongst individuals and up to 5-fold for a single individual in different courses. The values for Cli indicate a high degree of inter-subject variability in clearance, even after correction for surface area (Table 2).

Patient 7, who was being treated with carbamazepine, had a high initial clearance relative to the

Table 1 Results of fitting the model of time-dependent clearance to ifosfamide and 3-dechloroethylated metabolite plasma data

Patient (course)	Tind (h)	Tinf (h)	Cl ($l h^{-1} m^{-2}$)	Cl ($l h^{-1} m^{-2}$)	Half-life of induction (h)	V ($l m^{-2}$)	Km (h^{-1})	Vm/fm ($l m^{-2}$)
1(a)[a]	18	73.0	1.39	4.97	9	9.2		
1(b)[a]	18	71.7	2.30	6.76	7	39.6		
2	24	76.0	1.63	9.20	66	27.0	0.091	91.3
2	6	72.3	2.02	4.54	11	11.1	0.262	26.1
4	12	71.2	1.46	4.20	10	19.6	0.133	30.8
5(a)	12	67.8	5.17	9.00	21	23.7	0.207	41.6
5(b)	12	66.3	1.75	7.70	4	44.0	0.215	87.7
6(a)	12	72.3	2.56	4.88	7	19.0	0.188	40.1
6(b)	6	72.8	2.42	6.58	4	24.0	0.085	162.6
7[a]	30	72.2	14.21	15.36	8	56.8		
8	18	72.0	4.54	16.20	158	15.1	0.213	107.6
9	6	70.3	0.94	6.36	16	15.6	0.140	79.8
10(a)	12	71.8	4.71	9.90	32	15.2	0.147	109.2
10(b)	6	65.7	2.56	7.09	7	21.3	0.120	133.1
11(a)	12	66.5	4.81	8.98	9	19.6	0.140	67.2
11(b)	12	71.2	2.79	6.76	7	37.1	0.258	46.1
11(c)	12	69.5	3.12	9.79	37	16.5	0.243	38.8
12[a]	6	71.4	3.67	7.03	23	15.4		
13(a)	12	72.0	3.00	5.54	2	17.4	0.039	350.5
13(b)	12	76.5	3.48	6.71	31	12.4	0.094	130.0
14	12	73.4	0.77	3.90	4	21.5	0.074	98.8
15(a)	6	68.9	2.34	6.51	10	16.5	0.027	309.4
15(b)	12	70.5	2.68	6.57	15	15.8	0.158	91.8
16(a)	12	72.0	1.55	3.16	5	17.0	0.223	31.5
16(b)	12	70.2	4.78	6.95	10	12.9	0.115	155.1
16(c)	12	69.1	4.35	10.27	10	29.3	0.332	50.5
6(c)[b]	12	69.7	5.68	240.00	1733	43.4	0.620	18.2
7(b)[b]	36	72.1	12.70	18.30		18.2	1.760	7.6
17[b]	6	69.1	2.42	51.69	39	12.8	0.346	38.3
18[b]	54	68.5	3.16	26.00	169	9.6	0.085	185.2
19[b]	36	69.3	4.15	65.30	533	21.5	1.300	37.6

[a] Insufficient metabolite data to fit both the parent and the metabolite model. The model for parent drug only was fitted

[b] Courses 7(b), 18 and 19 show delayed induction with insufficient data to characterise the increase in Cl (see Figs. 4, 5). Courses 6(c) and 17 had poor-quality data. These five courses were omitted from subsequent analyses

rest of the study group. The auto-induction seen in this patient was relatively minor and the onset of auto-induction was delayed (Tind, $\geq$ 30 h). Patient 14, who was being treated with nifedipine, another CYP3A4 substrate, had the lowest initial clearance. No other patient was being treated with drugs known to interact with P450 enzymes that metabolise ifosfamide.

Discussion

Auto-induction of drug metabolism has been described for a number of different drugs, including aminoglutethimide [27], theophylline [11] *all-trans*-retinoic acid [3] and anticonvulsants . The most well-described of these is carbamazepine [20]. Following an initial observation that plasma concentrations of this drug declined during repeated dosing, a model of enzyme induction based on protein turnover could be fitted to the plasma concentrations to give the model parameters of an initial clearance, a final clearance and a rate constant for enzyme degradation. This latter rate constant determines the time for auto-induction to increase the clearance from one value to another. With a lag time of 16 h, the time to reach a new steady state was just 2 days from the start of a continuous infusion in monkeys [29]. A similar model was used to describe the time course of antipyrine auto-induction in rats [8], albeit using clearance data, not plasma concentrations. Other studies with carbamazepine in humans have indicated that clearance may be increased by up to 30% during chronic treatment [25]. This was accompanied by an increase in excretion of 6β-hydroxycortisol, a marker of CYP3A activity, and it should be noted that patient 7, who was being treated with carbamazepine, had an initial clearance almost 3-fold that of any other patient and appeared to be less responsive to the auto-inductive effects of ifosfamide. Often auto-induction is accompanied by an increase in the metabolism of concomitantly delivered drugs [11, 25] showing an increased potential for drug interaction. A

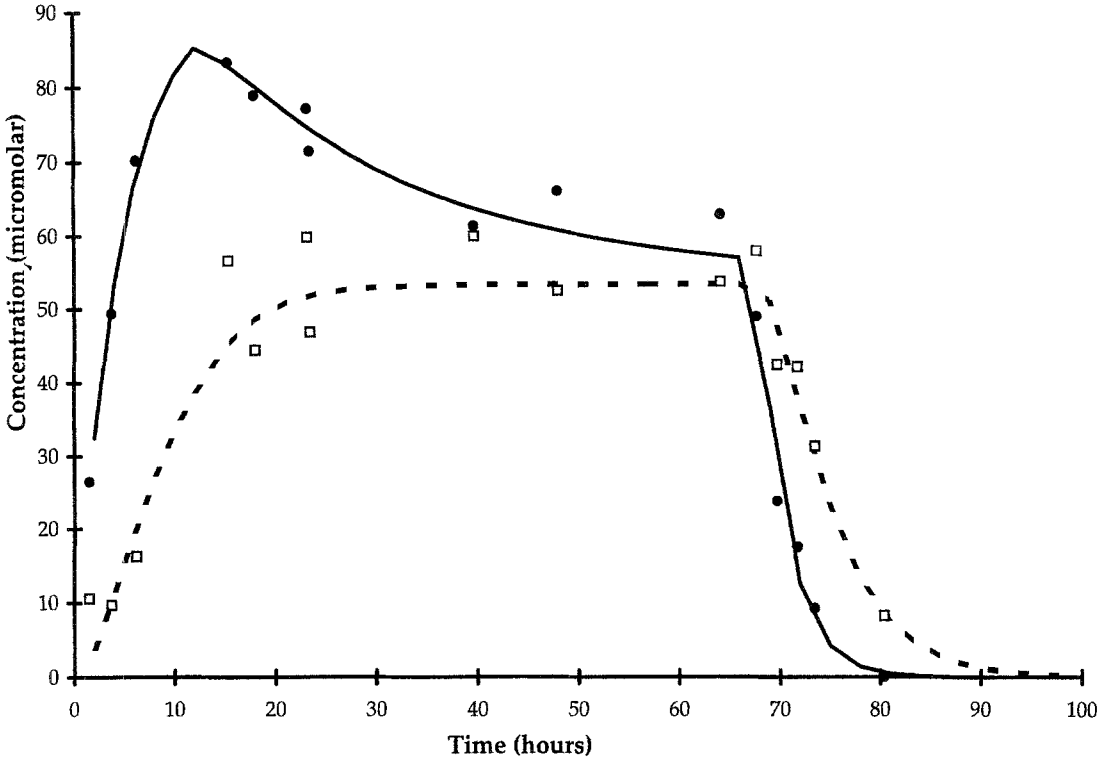

Fig. 1. Plot of ifosfamide (*solid line, filled symbols*) and 3DC metabolite (*dotted line, open symbols*) plasma concentrations against time following a 72-h infusion in patient 5, course a. *Symbols* represent data points and *lines* the fit of the model

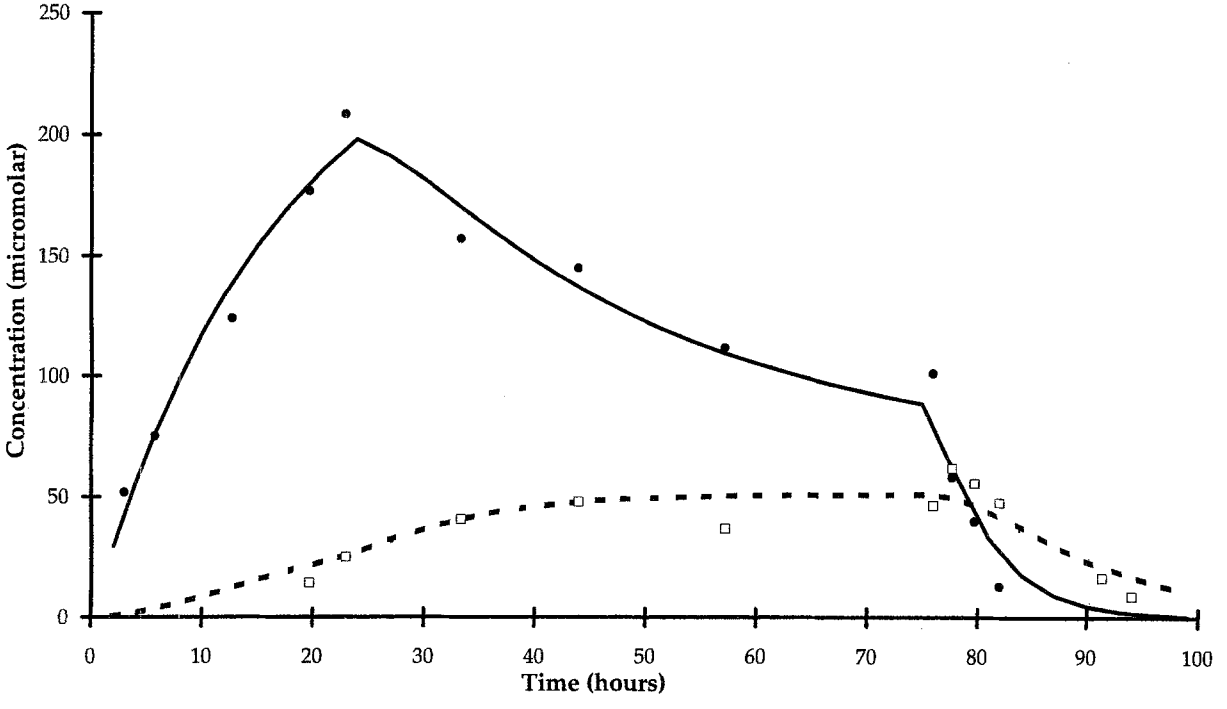

Fig. 2. Plot of ifosfamide (*solid line, filled symbols*) and 3DC metabolite (*dotted line, open symbols*) plasma concentration against time following a 72-h infusion in patient 2. *Symbols* represent data points, and *lines* the fit of the model

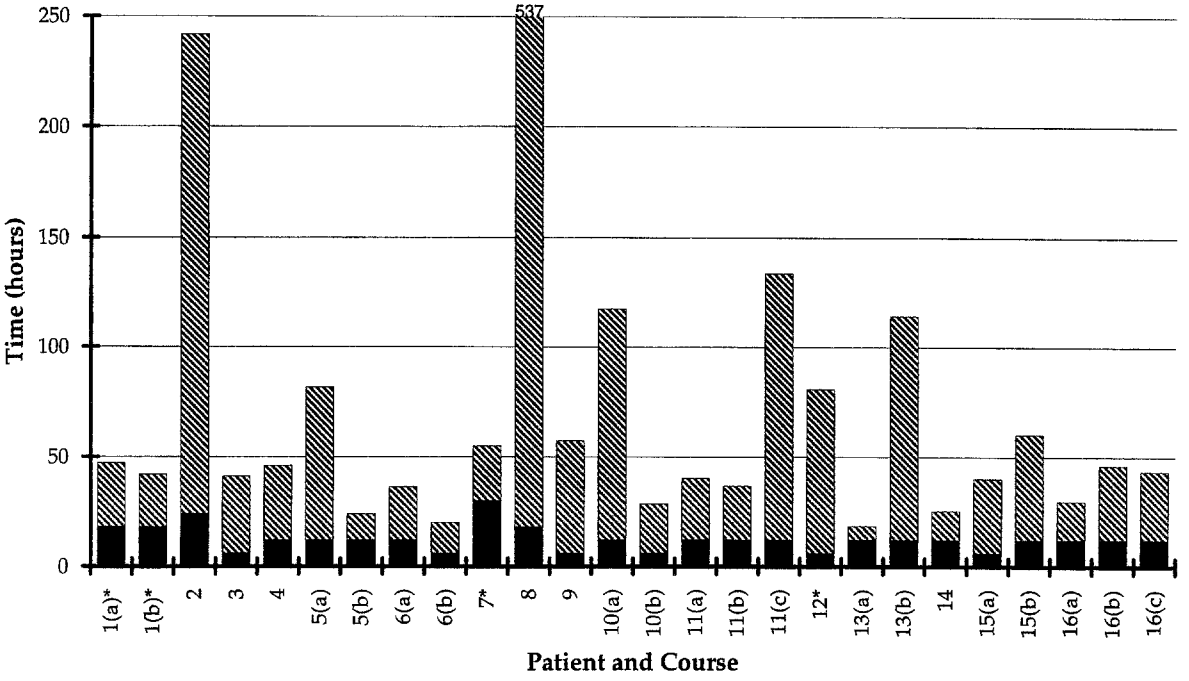

Fig. 3. Time to reach 90% of fully induced clearance as based on the auto-induction model for each patient and course studied. The *lower bar* is the time lag before the onset of induction. The *upper bar* is the time to reach 90% of full auto-induction.

Table 2 Summary of parameters for the model of auto-induction of ifosfamide

	Tind (h)	Cli ($l h^{-1} m^{-2}$)	Cls ($l h^{-1} m^{-2}$)	Half-life of induction (h)	V ($l m^{-2}$)	*Km* (h^{-1})	Vm/fm ($l m^{-2}$)
Min	6	0.77	3.16	1.9	9.2	0.027	26
Max	30[a]	14.21	16.20	158	56.8	0.332	351
Median	12	2.62	6.76	9.9	18.2	0.144	90

[a] Longer lag time (36 and 54 h) were seen in some patients, but the model could not be fitted to these data sets as there were insufficient data beyond the lag time

possible interaction with nifedipine is indicated by the low clearance values obtained for patient 14.

Auto-induction of cyclophosphamide and ifosfamide metabolism has been reported previously [12, 15, 18]. In the case of ifosfamide this has been associated with an increase in either the formation of dechloroethylated metabolites [6, 23] or both dechloroethylation and 4-hydroxylation [21]. Other studies have shown how cyclophosphamide can differentially modify the expression of individual P450 enzymes in rat liver [22, 26] and how pre-treatment can induce the metabolism of other drugs [13, 28]. Recent studies have identified the P450 isoenzymes involved both in the 4-hydroxylation of cyclophosphamide and ifosfamide [9] and in the dechloroethylation of ifosfamide [34]. The CYP3A4 isoenzyme predominates for both metabolic pathways of ifosfamide, wheras CYP2B forms are possibly more important for cyclophosphamide. After auto- or hetero-induction, however, CYP3A may become the major contributor to the metabolism of both drugs, this being consistent with the observation that prednisone, a steroid substrate of CYP3A, first inhibits and then induces the metabolism of cyclophosphamide [14].

In the present study a model of auto-induction was fitted to plasma concentrations of ifosfamide and its principal metabolite 3DC. This model is based on the concept that enzyme induction is dependent on the turnover of protein and that metabolic activity is dependent on the amount of enzyme present [16]. This is appropriate for ifosfamide whose clearance is low relative to hepatic blood flow. The exponential term in the model of increasing clearance, *Kc*, is equivalent to the rate constant for enzyme degradation. Alternative models of enzyme induction have been described [24], including complex models based on plasma concentration of the inducer [1, 2]. The more simple model employed herein appeared to fit both parent drug and metabolite data well. To our knowledge, this is the first time such a model has been fitted simultaneously to both parent and metabolite data.

The half-life for induction or protein turnover in the present study varied from a very rapid 2 h up to over

6 days. Similarly, there were variations in the time of onset of induction from 6 h up to 54 h. The variation in the apparent rate of enzyme degradation also applies to the decline in enzyme activity after exposure to ifosfamide. Thus, those patients showing a rapid increase in enzyme activity would be expected to return rapidly to non-induced levels. This is consistent with the observed lack of a consistent increase in ifosfamide clearance following repeated, intermittent treatment [7]. The lack of a good fit with the model based on a constant formation clearance of the metabolite indicates that this route of metabolism is involved in auto-induction.

The time course of induction as illustrated by this model may allow for better optimisation of ifosfamide administration. More evenly spaced administration of shorter infusions may result in less auto-induction and less exposure to potentially toxic metabolites such as the chloroacetaldehyde produced as a by-product of dechloroethylation. This is consistent with the observation that less dechloroethylation is seen following bolus administration on 3 consecutive days as compared with continuous 72-h infusion (Boddy, manuscript in preparation]. However, such a fractionation of dose may result in reduced activation of ifosfamide, since the same P450 enzyme is involved in these two routes of metabolism [34]. Also, the therapeutic implications of the auto-induction phenomenon cannot yet be predicted given that the mechanisms of ifosfamide's therapeutic and toxic effects are not well understood.

The possibility of interactions due to induction of ifosfamide metabolism have not been investigated in detail, although ifosfamide has been reported to affect the metabolism of dapsone [28]. Since metabolism of different drugs can now be associated with individual P450 isoenzymes, the possibility of interactions can be explored in vitro. Thus, one metabolic pathway of etoposide metabolism has been shown to be mediated by CYP3A enzymes [30], as has the metabolism of vinca alkaloids [35]. Since both of these drugs are used in combination chemotherapy with ifosfamide, there is potential for an increase in their metabolism depending on the relative times of administration. Administration of etoposide or vincristine after or during the later stages of ifosfamide infusion could result in reduced plasma concentrations of parent drug and increased levels of metabolites as compared with those resulting from administration prior to ifosfamide infusion.

In this study we attempted to describe the time course of the auto-induction phenomenon observed with ifosfamide. The model fits the data well in the majority of courses studied and indicates some variation both in the time to the onset of enzyme induction and in the rate of increase in clearance. In the majority of cases maximal induction is complete within the duration of the infusion and would be predicted to return to baseline before the next course of treatment. Increased understanding of the nature of this phenomenon would be useful in optimising the administration of ifosfamide and the scheduling of other drugs used in combination chemotherapy.

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