The Neurotoxicity and Pharmacokinetics of Oral Ifosfamide

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Abstract: *Purpose*: Ifosfamide can cause an unexplained encephalopathy. The incidence after intravenous infusion is 10%, but is much higher after oral administration. This study assesses the pharmacokinetics of oral ifosfamide in relation to neurotoxicity.

Patients and Methods: Eleven patients received oral ifosfamide 500 mg twice daily for 14 days, with concurrent oral mesna. The concentrations of ifosfamide, isophosphoramide mustard, 2-dechloroethylifosfamide, 3-dechloroethylifosfamide, carboxyifosfamide, ketoifosfamide, chloroethylamine and 3-oxazolidine-2-one were measured using GC-MS. Patients were evaluated clinically, and also with the EEG, psychometric testing, the national adult reading test, and the mini-mental state examination.

Results: A decrease in the electroencephalogram alpha frequency was observed, with the development of pathological slow wave activity. Psychometric performance was also impaired. Neurotoxicity was progressive during treatment, and the incidence of grade 3 neurotoxicity was 22%. The mean day 14 / day 1 Cmax ratios for 2-dechloroethylifosfamide and 3-dechloroethylifosfamide were 2.73 (± 2.11) and 2.04 (± 1.32) respectively. The metabolite with the lowest ratio was isophosphoramide mustard 1.07 (± 0.39). High chloroethylamine Cmax values were associated with lower alpha frequencies, and increased clinical neurotoxicity.

Conclusion: Oral ifosfamide 500 mg twice daily for 14 days causes unacceptable neurotoxicity. It was not possible to identify one particular metabolite responsible for the neurotoxicity, although the dechloroethyl metabolites and chloroethylamine are implicated.

Keywords: Oral ifosfamide, metabolites, pharmacology, encephalopathy, electroencephalogram, lung neoplasms, cervical neoplasms.

INTRODUCTION

Ifosfamide (IPA) is an oxazaphosphorine alkylating agent with activity against many solid tumours including sarcoma, lymphoma and carcinoma of the lung, cervix and breast. Fractionated ifosfamide therapy has become one of the most commonly used methods of administration. Routine clinical practice is to administer the drug intravenously in three or five day fractionated regimens, or as a continuous infusion [1]. An oral fractionated regimen would be advantageous, minimising hospital admissions; an oral formulation with a bioavailability of 100% has been described [2], although its use has been restricted by an increased incidence of encephalopathy. Encephalopathy of varying degrees occurs in about 10% of patients after intravenous ifosfamide [3], but following oral administration an incidence of approximately 50% has been reported [4]. Somnolence is the prime symptom, and the encephalopathy is associated with disturbances in the electroencephalogram (EEG). The aetiology of ifosfamide induced encephalopathy remains a mystery, and the chemical entity responsible has not yet been firmly identified, but is likely to be a metabolite of ifosfamide.

Ifosfamide is a pro-drug and requires activation, predominantly *via* the hepatic cytochrome mixed function oxidase P-450 system [5] (Figure **1**). Activation produces 4-hydroxyifosfamide, which exists in equilibrium with its tautermeric form aldoifosfamide. Aldoifosfamide spontaneously decomposes to form isophosphoramide mustard (IPM), the ultimate alkylating agent. IPM can be converted into chloroethylamine (CEA), which in turn generates 3-oxazolidine-2-one (OXA) in the presence of

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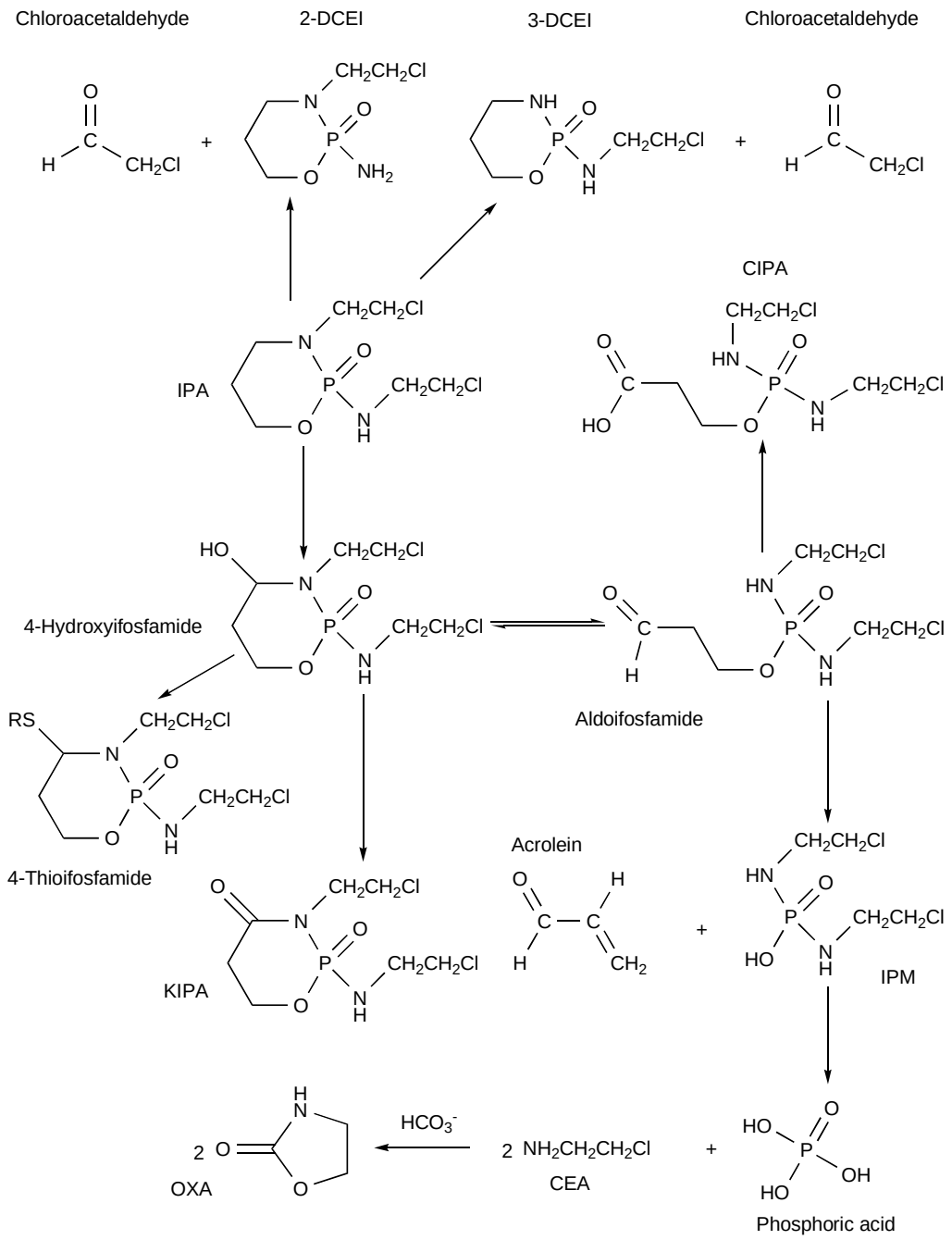

Figure 1: The metabolism of ifosfamide.

bicarbonate. Dechloroethylation leads to the formation of 2- and 3-dechloroethylifosfamide (2-DCEI and 3-DCEI) and chloroacetaldehyde.

We describe a neurological and pharmacokinetic study of oral ifosfamide, which was performed to obtain further insights into the relationship between ifosfamide metabolites and encephalopathy; in particular, we wished to explore changes in metabolite concentrations, EEG appearances, and psychometric performance.

PATIENTS AND METHODS

Patients

Seven females with advanced or recurrent carcinoma of the cervix and four males with advanced non-small cell lung cancer were entered into the study, which was performed during 1992. The protocol was approved by the ethics committees of the participating institutions, and each patient gave written informed consent. The median age was 58 years (range 33 – 70). None had received prior chemotherapy. Oral

ifosfamide, formulated as gelatin capsules, was administered at a dose of 500 mg twice daily, eight hours apart, for 14 days. A 28 day cycle was planned. Film-coated tablets containing 300 mg of mesna were given twice daily concurrently for uroprotection.

Assessments of ifosfamide induced neurotoxicity and a pharmacokinetic study were performed during the first cycle.

Assessment of Neurotoxicity

Patients were monitored for neurotoxicity and formal assessments were performed on days 0 (baseline), 2, 8 and 15, using the EEG, psychometric testing, the national adult reading test (NART) [6], and the mini-mental state examination (MMS) [7]. The EEGs were evaluated blindly and independently by a neurologist, with only the patient initials given. The day of investigation and whether the patient was receiving treatment was not indicated. Two main measures were employed. The first was a system of evaluating the basic background alpha rhythm at 27 different one second epochs. The mean alpha rhythm of each recording was then determined. The second evaluation of the recordings assessed the EEG abnormalities, particularly slow activity, episodic slow activity and paroxysmal activity. In addition, the changes in the recording due to over breathing and photic stimulation were evaluated. The results were listed, and the records given an arbitrary ranking from the most normal to the most abnormal, according to the Meanwell grading (Table **1**) [8]. The code was then broken, and the rankings compared to the actual days of the study; 0 (baseline), 2, 8 and 15.

A fully automated psychometric test system, requiring the minimum of supervision, was employed to determine the ability to perform routine complex psychomotor tasks. Psychometric tests were performed in the following order: choice reaction time, salford tracker and continuous attention.

Choice Reaction Time

The reaction time evaluates motor response by requiring the subject to press a button in response to a critical stimulus. In choice reaction time, the subject is presented with a single stimulus that is one of a number of alternatives. This test assesses sensorimotor performance by adding a recognition time component (stimulus processing time) to the motor movement aspect of the simple reaction time test. The number of correct responses and the latency to respond are used as a measure of task performance.

Salford Tracker

This is a simulated car driving test in which the subject tracks an arrow using a computer mouse. The maximum distance from the target and the root mean square of this distance is recorded. The distance is measured in pixels, and when superimposition is perfect the score is zero. In addition, the subject responds to a stimulus presented in the periphery of vision while simultaneously attending to the tracking task. The maximum and average response times to ten of these peripheral stimuli per task are also used as response measures.

Continuous Attention

In this test, patients monitor a series of digits for targets of three consecutive odd or three consecutive even digits, and signal their detection by pressing a response button as quickly as possible. The outcome measures from this task are the average reaction time

Table 1: The Meanwell Grading of EEG Abnormalities [8] and the Common Toxicity Criteria Grading of Neurocortical and Neuromood Disturbances (Version 1.0)

Grade	Meanwell EEG	CTC neurocortical	CTC neuromood
0	Normal	None	No change
1	A drop in alpha frequency compared with pretreatment EEG, with or without small amounts of paroxysmal theta activity	Mild somnolence or agitation	Mild anxiety or depression
2	Predominant theta activity, with or without intermittent delta activity	Moderate somnolence or agitation	Moderate anxiety or depression
3	Predominant delta activity with or without sharp (complex) wave forms	Severe somnolence, agitation, confusion, disorientation or hallucinations	Severe anxiety or depression
4	Continuous delta activity, complex wave forms and triphasic waves	Coma, seizures, or toxic psychosis	Suicidal ideation

to respond to the targets, the number of missed responses, and the number of false responses. Two hundred numbers are presented, and each number is displayed for one second.

The NART is a universally applicable indicator of pre-morbid intelligence. Reading ability is highly correlated with the general IQ level in the normal population, and the NART was specifically designed to provide a means of estimating the pre-morbid intelligence levels of adult patients suspected of suffering from intellectual deterioration. The MMS was used to assess cognitive function. Neurotoxicity was also evaluated clinically, according to the National Cancer Institute common toxicity criteria (CTC), version 1.0 (Table **1**).

Pharmacokinetic Analysis

Blood samples were taken before the first dose of ifosfamide on days 1 and 14, and at approximately 0.5, 1, 2, 4 and 6 hours thereafter. The fasting state was maintained during the initial four hours. Plasma was separated immediately by centrifugation, and stored at -20°C until analysis. The concentrations of ifosfamide and seven of its metabolites (IPM, 2-DCEI, 3-DCEI, carboxyifosfamide (CIPA), ketoifosfamide (KIPA), CEA and OXA) were determined by GC–MS [9]. Pharmacokinetic data was obtained using the MK-MODEL programme [10]. The AUC was calculated using the trapezoidal rule to eight hours (AUC_8), the time of the second dose.

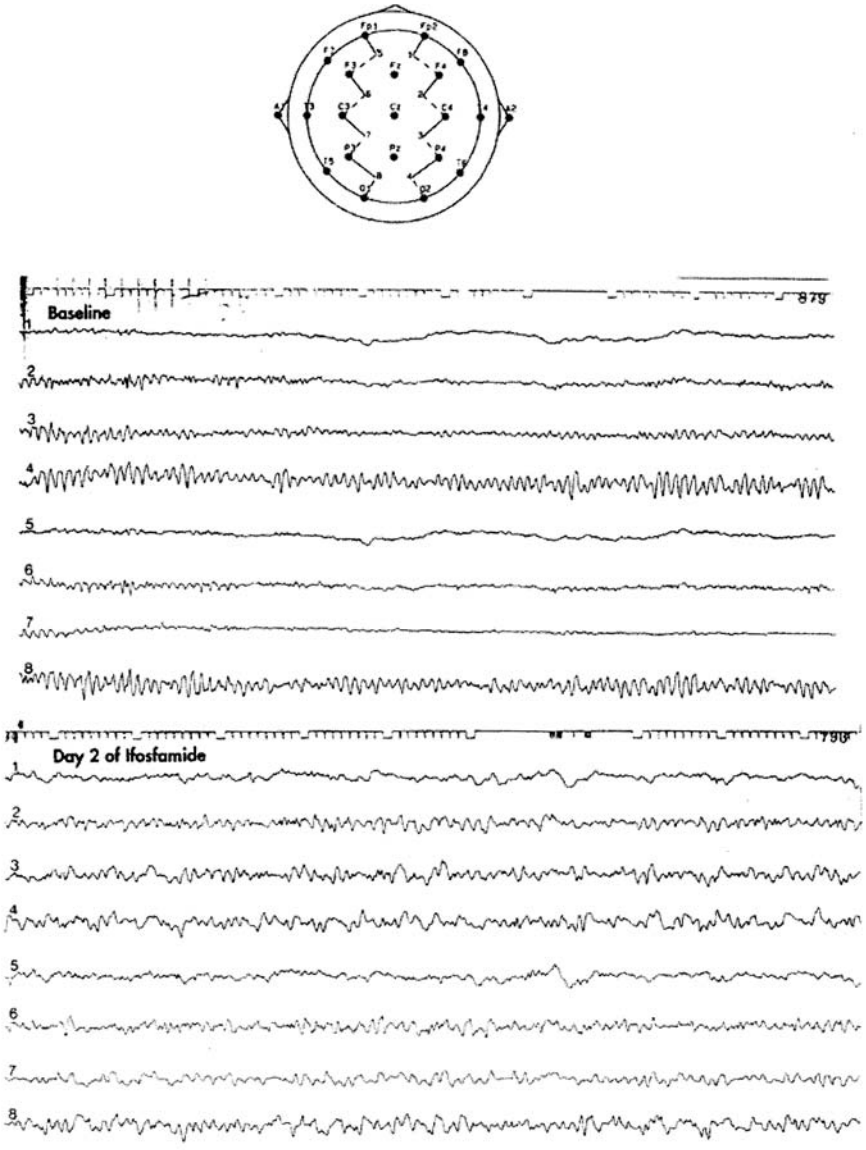

Figure 2: EEG changes on day 2 of oral ifosfamide in patient 6.

RESULTS

Neurotoxicity

Seven Patients were Assessed by the EEG

In all except one, the EEG was abnormal by day 2, with decreased alpha frequency and the development of pathological slow wave activity. The changes in the recordings were quite dramatic, showing some of the features seen in toxic encephalopathies, and even changes observed in patients with epileptigenic disturbances. The EEG of patient 6 on day 2 is shown in Figure **2**. The results in some of the patients showed a perfect ranking order. In others this was not perfect, but there was always an isolation of the records of the eighth and fifteenth days from those of the baseline and the second day. The rank correlation of day against percentage change in alpha frequency was 0.753 ($p < 0.001$).

Six Patients were Subjected to Psychometric Testing

The mean reaction time and the mean time to press the button in the choice reaction assessment was impaired in all patients except one, although this failed to reach statistical significance (data not shown). The mean response time in the continuous attention task was significantly increased on day 2 ($p = 0.018$), and the mean average distance in the salford tracker was significantly increased on day 15 ($p = 0.026$). Significant changes in the NART or MMS scores were not observed during oral ifosfamide administration, indicating that intellect and cognitive function remained unaffected. The changes in alpha frequency, Meanwell grade, and salford tracker performance are illustrated in Figure **3**.

Nine patients were assessable clinically for neurotoxicity, all of whom developed a feeling of detachment, or an inability to concentrate. In addition, four patients suffered neurocortical disturbances (patient 10 CTC grade 1, patient 7 CTC grade 2 and patients 8 and 6 CTC grade 3), whilst patient 5 developed CTC grade 1 anxiety. Neurological manifestations were evident by day 3 of treatment in all patients, and resolved on discontinuation of ifosfamide.

A comparison of the two groups of patients studied (seven females with cervical carcinoma versus four males with non-small cell lung cancer) revealed no differences in the degree of neurotoxicity experienced.

The Meanwell grading of the EEGs was not consistent with the clinical features; a Meanwell grade of 2 or 3 in patients 2, 3, 4, 5 and 10 was associated with relatively mild neurotoxicity (CTC grade 0 or 1), whilst hallucinations occurred in one patient with a Meanwell grade of 1. However, two patients in the former group developed severe neurotoxicity with subsequent cycles.

Pharmacokinetic Analysis

The pharmacokinetic parameters and the mean values of the ratios of day 14 Cmax / day 1 Cmax are shown in Table **2**, and the profiles from one patient are illustrated in Figure **4**. The day 14 Cmax / day 1 Cmax ratio for ifosfamide was less than 1, and the highest ratios were observed with KIPA and 2-DCEI. Overall, the ratios suggest increased formation and/or accumulation of metabolites, other than IPM, by day 14. The Cmax values on days 1 and 14 were compared, as were the AUC_8 values on days 1 and 14,

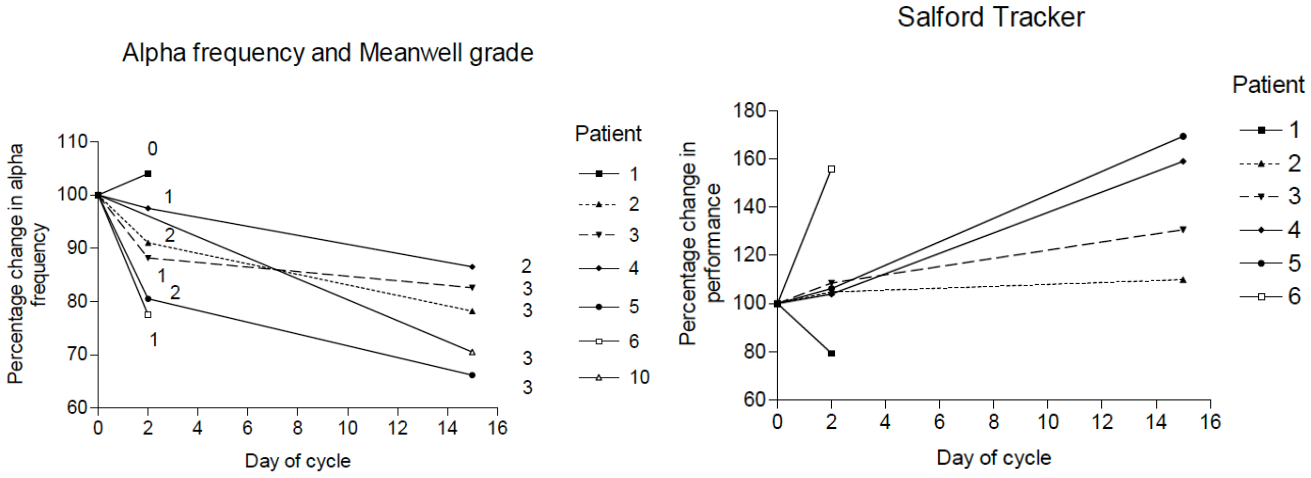

Figure 3: Changes in EEG alpha frequency and salford tracker performance during oral ifosfamide (days 2 and 15). The Meanwell EEG grade is given adjacent to the corresponding time point.

Table 2: Mean Pharmacokinetic Values During Oral Ifosfamide (SD, n)

	Cmax (μM)		Cmax ratio	Cmin (μM)	AUC_8 (μM.hr)	
	Day 1	Day 14	Day 1 / Day 14	Day 14	Day 1	Day 14
IPA						
Mean	53.1	50.7	0.94	8.0	293	256
SD	18.5	25.8	0.16	6.9	67	118
n	11	7	7	7	11	7
IPM						
Mean	1.1	1.1	1.07	0.17	8.5	8.4
SD	0.41	0.57	0.39	0.19	2.9	2.9
n	8	6	4	6	10	6
2-DCEI						
Mean	2.0	4.3	2.73	1.5	14	27
SD	0.65	1.9	2.11	1.1	5.5	12
n	10	6	6	6	9	6
3-DCEI						
Mean	4.4	7.5	2.04	3.3	30	58
SD	2.5	4.0	1.32	2.6	14	26
n	9	6	5	7	11	7
CIPA						
Mean	1.5	2.1	1.99	0.45	9.3	15
SD	0.80	1.1	1.47	0.54	3.5	8.5
n	11	7	7	7	11	7
KIPA						
Mean	0.69	1.04	3.17	0.17	5.45	7.74
SD	0.44	0.53	3.13	0.13	2.44	3.85
n	9	7	6	7	10	7
CEA						
Mean	7.6	7.3	1.21	1.3	52	53
SD	4.0	3.2	0.44	2.1	23	26
n	9	6	6	6	9	6
OXA						
Mean	0.68	0.87	1.83	0.18	9.7	10.7
SD	0.29	0.42	1.14	0.30	2.6	2.9
n	9	6	6	6	9	6

using a paired t-test. The differences between day 1 and day 14 Cmax values of 2-DCEI and CIPA, and AUC_8 values of CIPA and CEA, were statistically significant.

Pharmacokinetics and Neurotoxicity

The Cmax of ifosfamide and its metabolites was correlated with the alpha frequency in the EEG on days 2 and 15, using Pearsons correlation coefficient. On days 1 and 2, a negative and positive correlation was noted between CEA Cmax and IPM Cmax respectively. The role of dechloroethylation in the development of encephalopathy is also implicated; for the dechloroethylated metabolites, the mean day 14 / day 1 Cmax ratio was greater than 2 (Table **2**), whilst neurotoxicity was progressive in all patients during the 14 days of treatment. The patients who developed

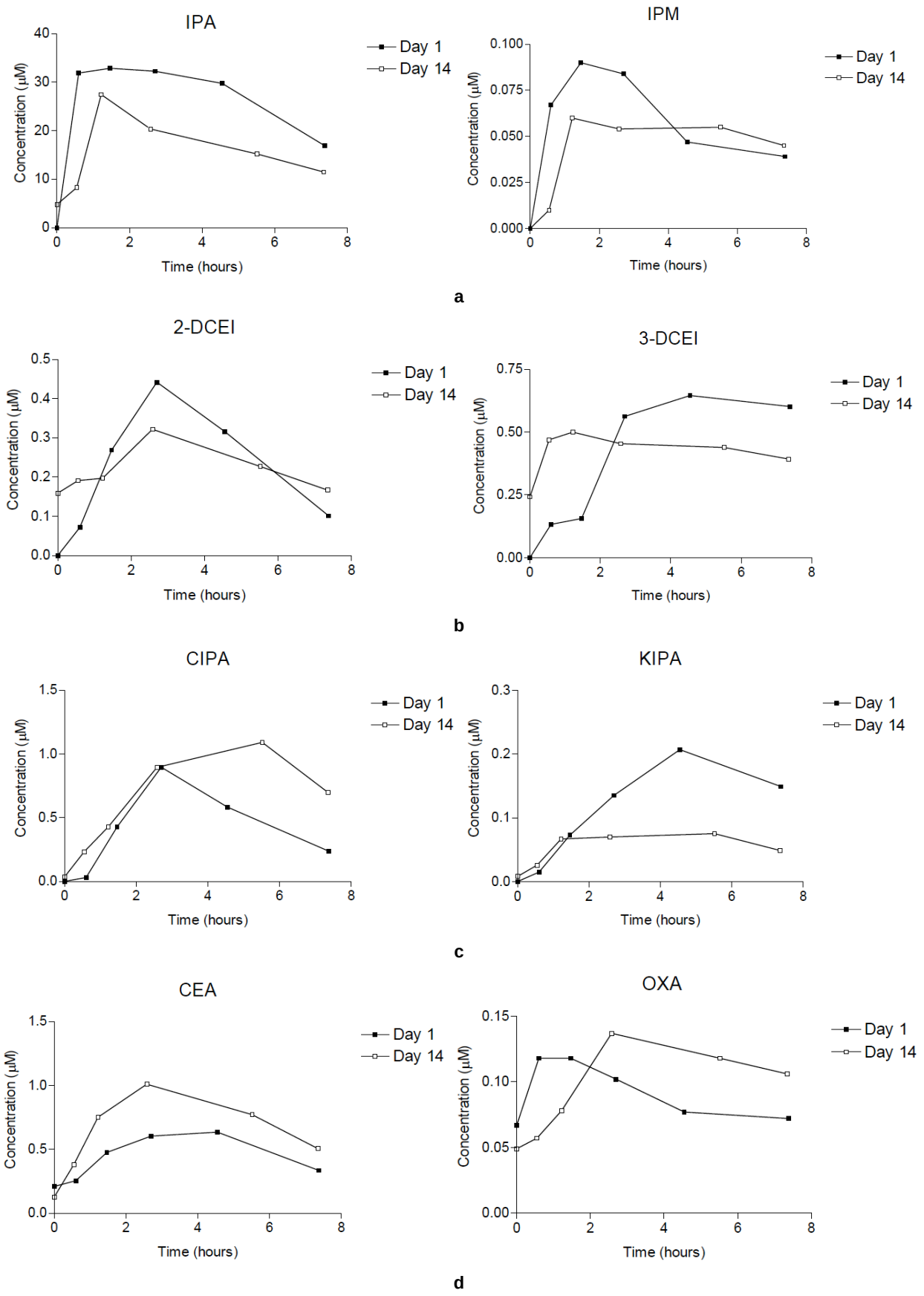

Figure 4: Plasma concentration – time curves of ifosfamide and its metabolites.

Day 1 ■–■; Day 14 □–□. **a** IPA and IPM. **b** 2-DCEI and 3-DCEI. **c** CIPA and KIPA. **d** CEA and OXA.

neurocortical or anxiety CTC grade ≥ 1 had the highest Cmax CEA concentrations on day 1 (mean 10.33 μM; SD ± 3.23; n = 5 versus 4.22 μM; SD ± 1.25; n = 4).

DISCUSSION

Oral ifosfamide caused significant neurotoxic effects, with all assessable patients developing symptoms by the third day of treatment. A feeling of detachment, or an inability to concentrate, was universal, and one patient developed anxiety, two somnolence, and two suffered hallucinations. The study was therefore terminated prematurely. Other reports have also highlighted this type of toxicity; somnolence is most common, although features such as forgetfulness, nightmares, seizures, tonic clonic spasms, asterixis and extrapyramidal symptoms may occur [11-15]. With severe and progressive encephalopathy, logorrhoea, palilalia, perseveration of writing and speech, and marked disorientation appear after 20 to 50 hours, following which patients may enter a trance, and coma soon follows. Four of six patients treated by Wagner and Drings experienced neurotoxicity after 2 g m^{-2} of oral ifosfamide [2], whilst an incidence of 33% was reported after daily doses of 2 g [16]. Doses lower than 1 g daily, or a shorter duration of treatment than 14 days, appear more tolerable. Manegold *et al.* assessed four different schedules of oral ifosfamide (1 g daily for 5 days; 750 mg, 1 g or 1.25 g daily for 14 days) [4]. Meanwell grade 1 or 2 neurotoxicity occurred in 13%, 42%, 35% and 57% of patients respectively, but no grade 3 toxicity was seen. All episodes resolved on discontinuation of treatment. The time of onset of the encephalopathy was variable, but occurred in most patients on the second or third day. An increase in the daily ifosfamide dose to 1.25 g led to worsening neurotoxicity, suggesting a relationship between dose and neurotoxicity, but the total cycle dose was less important than the total daily dose.

Oral ifosfamide appears to have a prominent effect on cerebral function, at least as evaluated by the EEG, with decreased alpha frequency and the development of pathological slow wave activity. Other reports have also described a reduction in alpha frequency, or generalised or focal abnormalities, and abnormal waves [12, 13, 17, 18, 19, 20]. Danesh *et al.* detected high amplitude, frontally dominant, triphasic waves with a reduction of alpha frequency to 6 Hz [12], and an EEG pattern consistent with non-convulsive status epilepticus has been documented [21]. There is no data suggesting that pre-treatment EEGs predict the development of clinical encephalopathy. However, abnormalities in the EEG, consistent with a generalised disturbance, can precede clinical symptoms by 12 to 24 hours [11].

Psychometric performance was impaired during the course of oral ifosfamide. This was particularly so for the mean response time in the continuous attention test, and the mean average distance in the salford tracker test. Cognitive function and IQ were not affected. However, following intravenous ifosfamide, Heim *et al.* described impairment of short term memory in nephrectomised patients [17], and Park *et al.* documented impaired cognitive function persisting for ten years in one patient [22].

The pharmacokinetic study suggests that all metabolites except IPM behave similarly. There is a tendency to higher values of Cmax, implying increased generation during the treatment period. With prolonged oral ifosfamide administration, metabolism is directed more to dechloroethylation, and ifosfamide undergoing activation shows a greater tendency to form CIPA and KIPA, with lower quantities of IPM.

A metabolite of ifosfamide is probably responsible for the neurotoxicity, as the pharmacokinetics of ifosfamide itself are similar in both neurologically impaired and unaffected patients [23]. Following an intravenous dose of 1.5 g m^{-2} day^{-1} of ifosfamide for five days in adults, Kurowski and Wagner determined mean 2-DCEI Cmax concentrations of 8.6 μM and 16.7 μM on days 1 and 5 respectively, with corresponding values for 3-DCEI of 12.9 μM and 26.5 μM, almost reaching the concentrations of ifosfamide [24]. The Cmax and AUC values of 4-hydroxyifosfamide and the dechloroethylated metabolites also increased approximately two-fold. The two metabolic routes were induced to the same extent, and the relative contribution of accumulation to the total increase in metabolite AUC on day 5 was negligible. The average Cmin levels of 4-hydroxyifosfamide, chloroacetaldehyde, 3-DCEI and 2-DCEI accounted for only 2.5%, 4.0%, 5.6% and 4.3% respectively of the subsequent maximum values.

Previous studies of oral ifosfamide have not established a definitive link between any one metabolite of ifosfamide and neurotoxicity. Lind *et al.* reported a higher urinary recovery of dechloroethylifosfamide, IPM and CIPA after oral ifosfamide, compared to the intravenous route, but there was no correlation between any individual

metabolite and the development of neurotoxicity [25]. In a study of ten day continuous infusions of ifosfamide in 23 patients, one developed neurotoxicity after six days, associated with high 2-DCEI and 3-DCEI plasma levels (greater than 40 $\mu g\ ml^{-1}$ (0.2 mM) compared with less than 14 $\mu g\ ml^{-1}$ (0.07 mM) for those without encephalopathy) [26]. Although the bioavailability of oral ifosfamide is almost 100% [2], a small but significant first pass effect would be compatible with a very toxic metabolite, such as chloroacetaldehyde, being produced preferentially following oral dosing. Chloroacetaldehyde is metabolised to chloroacetic acid and then to S-carboxymethylcysteine after conjugation with cysteine. S-carboxymethylcysteine is metabolised in turn to thiodiglycolic acid [27], and both of these compounds are toxic to mouse cortical neurons [28].

It has also been proposed that CEA may be an important metabolite in the aetiology of ifosfamide induced neurotoxicity [29]. CEA is oxidised within mitochondria *via* monoamine oxidase, generating chloroacetaldehyde, and can also conjugate with cysteine, producing thialysine, which is then metabolised to thialysine ketamine. Both chloroacetaldehyde and thialysine ketamine can inhibit the electron binding flavoproteins in the mitochondrial respiratory chain, and thialysine ketamine can additionally act directly on the central nervous system. Glutaric acid and sarcosine have been identified in abnormal amounts in the urine during ifosfamide induced encephalopathy, a finding which has led to the use of methylene blue as a prophylactic agent [30]. A relationship between glutaric aciduria and CEA, but not other ifosfamide metabolites, has been identified in rats [29].

Aeschlimann *et al.* reported a daily urinary excretion of between 128 mg (1.61 mM) and 480 mg (6.03 mM) of CEA during high dose (16 $g\ m^{-2}$) intravenous ifosfamide administration [31]. In a subsequent study performed by the same group, oral ifosfamide was administered daily for three days with methylene blue to prevent encephalopathy [32]. One of the first two cycles was given intravenously for comparison. Appreciable amounts of CEA were again found in urine, but there was no difference in the urinary recovery of ifosfamide, 2-DCEI, 3-DCEI or CEA with respect to the two routes of administration. The recovery of CEA in the urine over the three days of administration, as a percentage of the ifosfamide dose, was 12.7 ± 6.7 % and 6.5 ± 3.3 % after intravenous and oral dosing respectively. Urinary excretion of ifosfamide decreased during therapy, but that of 2-DCEI and 3-DCEI increased. There was no significant shift in the metabolic pattern according to the route of administration. Two patients showed marked N-dechloroethylation after oral administration on day 1, but were free of neurotoxicity. No link was identified with encephalopathy, but urine analysis has limitations. The interpatient variation in the urinary excretion of CEA was large, possibly the result of the variable pH and bicarbonate content of urine. In the present study, a high plasma CEA Cmax was associated with more severe clinical neurotoxicity, and a more marked reduction in EEG alpha frequency. It has been postulated that the plasma concentration of chloroacetaldehyde is mainly determined by the hepatic metabolism of ifosfamide, and may therefore not reflect the intracellular concentration, nor the in situ formation of chloroacetaldehyde in brain mitochondria, one source of which is CEA [33].

We have found that oral ifosfamide causes changes in the EEG and diminishes psychometric performance. Higher ifosfamide AUC_8 values on day 1 were associated with less impairment of the EEG, implying that higher rates of ifosfamide metabolism result in greater neurotoxicity. An elevated Cmax of 2-DCEI was associated with less impairment, whereas the converse was true for the Cmax of 3-DCEI.

The incidence of grade 3 neurotoxicity (2/9, 22%) precludes the use of the administration schedule described. The reversibility of ifosfamide induced encephalopathy, the EEG findings of a generalised cortical disturbance, and an increased incidence with higher doses, suggest a metabolic encephalopathy. The results of this curtailed study imply that increased metabolism of ifosfamide, and/or an accumulation of its metabolites, is associated with a greater impairment of EEG appearances. It was not possible to identify one particular responsible metabolite. The dechloroethyl metabolites, CIPA, and CEA may be important, and require further study. The data is consistent with previous reports implicating dechloroethylation in the aetiology of neurotoxicity. Neurotoxicity was progressive throughout the 14 day period, as metabolites accumulated. The phenomenon remains to be adequately explained, and although chloroacetaldehyde may have a role, other as yet unidentified metabolites, or mechanisms, could also be important. The erythrocyte compartment is increasingly recognised as a significant contributor to pharmacokinetic processes [34], and it is possible that erythrocyte ifosfamide metabolite levels may reflect the development of encephalopathy more closely.

Ifosfamide remains an important cytotoxic in clinical use today. The advent of the newer targeted therapies has led to the evaluation of these agents, particularly the orally administered tyrosine kinase inhibitors, with cytotoxic agents, and the combination of ifosfamide and sunitinib has been studied [35]. A more detailed understanding of ifosfamide pharmacokinetics will aid these developments.

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