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ORIGINAL ARTICLE

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Cyclophosphamide metabolism in children following a 1-h and a 24-h infusion

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Abstract *Purpose*: The pharmacokinetics and metabolism of cyclophosphamide (CPA) when given as a 1-h and a 24-h infusion to children were compared. *Methods*: Thirteen children with a variety of different malignancies received an identical dose of cyclophosphamide as a 1- and 24-h infusion. In each case the concentration of CPA and its principal metabolites were measured by a thin-layer-chromatography–photographic-densitometry technique. *Results*: Cyclophosphamide clearance was greater during the 24-h infusion, following time-dependent increases in the metabolism of the drug (autoinduction) (median 5.1 vs 3.1 l/h/m^2: $P = 0.037$). Autoinduction was seen in five children (38%), producing a median end of infusion concentration of 49% (range 28–89%) of the maximum and was not accompanied by an increase in the production of the principal inactive metabolites carboxyphosphamide and dechloroethylcyclophosphamide. *Conclusions*: These results suggest potential benefits of prolonging the infusion of CPA in clinical practice.

Key words Autoinduction · Cyclophosphamide · Cytochrome P450 · Drug metabolism

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Introduction

Cyclophosphamide (CPA) continues to be widely used in the treatment of malignant disease in children. During the early development of the drug several experiments were performed on cell lines to determine the optimum administration schedule. The results of these studies demonstrated that the cytotoxicity of CPA was independent of the cell-cycle in vitro [1, 2]. The absence of cell-cycle selectivity led to the introduction of CPA into clinical practice as single-dose therapy usually administered as a short infusion (up to 1 h in duration) and repeated at three-weekly intervals [3]. In contrast to these results more recent studies have demonstrated an improved therapeutic index of CPA when multiple dosing regimens are used. In xenograft models, treatment efficacy was increased and haematological toxicity decreased when CPA was administered as a series of four short infusions at six-hourly intervals when compared to a single short infusion [4]. An increase in cytotoxicity has also been observed in cell lines when a similar ''fractionated'' administration schedule is used [5, 6]. Animal experiments have also demonstrated that continuous exposure to low levels of 4-hydroxycyclophosphamide (the activated metabolite of CPA) resulted in a greater tumour kill, whilst this technique is also less myelosuppressive, than a short exposure to high concentrations of 4-hydroxycyclophosphamide [7]. These reports suggest that intermittent single-dose therapy with CPA may not provide the optimum therapeutic response in clinical practice.

There have been several single-arm studies of the efficacy of CPA delivered as a prolonged infusion in relapsed malignancies, however, because of their study design, none of these reports provided firm evidence of a therapeutic advantage [8–10]. One of these studies described clinical responses amongst adults with relapsed or resistant non-Hodgkin's lymphoma to prolonged infusions of CPA, doxorubicin and etoposide. Several of these patients were considered to be resistant to at least one of these agents at a comparable dose when administered as a short infusion [10]. A randomised clinical study of CPA administered either as a short or as a prolonged infusion has yet to be reported.

CPA undergoes extensive metabolism in vivo to generate active alkylating species and it is possible that differing rates of delivery would alter the metabolism of the drug in such a way as to change the resulting therapeutic effects. Such a mechanism has been described for ifosfamide (a structural isomer of CPA which undergoes qualitatively similar metabolism) and irinotecan [11, 12]. Whilst prolonged infusions of CPA may produce time-dependent increases in the metabolism of the parent compound as a consequence of autoinduction, more rapid drug delivery may result in high peak concentrations and subsequent saturation of metabolism [13].

The initial activation of CPA is mediated by a hepatic cytochrome P450 reaction. Hydroxylation at the carbon-4 position of the oxazaphosphorine ring produces 4-hydroxycyclophosphamide, which exists in equilibrium with its tautomer aldophosphamide. Spontaneous β-elimination of aldophosphamide releases phosphoramide mustard and acrolein. Whilst phosphoramide mustard is thought to be the active alkylating species, acrolein is an unwanted by-product associated with haemorrhagic cystitis [14]. Alternatively, aldophosphamide may be oxidised to inactive carboxyphosphamide (CX) by aldehyde dehydrogenase [15]. The other principal metabolite, dechloroethylcyclophosphamide (DCCP), is produced by a separate oxidative *N*-dealkylation reaction which is also catalysed by cytochrome P450s. Ketocyclophosphamide (KETO), produced from the oxidation of 4-hydroxycyclophosphamide, is a minor inactive by-product of metabolism [16].

To investigate potential differences in the pharmacokinetics and metabolism of CPA when administered by different administration schedules, plasma concentrations of CPA and its metabolites were measured in 13 children receiving an identical dose of CPA as either a 1- or a 24-h infusion. An infusion duration of 24 h was the maximum felt to be practicable without significantly increasing the length of in-patient stay of any subject.

Patients and Methods

Thirteen children (four female) with a median age of 4 years (range 2–17 years) were studied between February 1992 and November 1996. All patients received chemotherapy in the Paediatric Oncology Unit of the Royal Victoria Infirmary, Newcastle upon Tyne. An identical dose of CPA was given intravenously as both a 1-h and a constant-rate 24-h infusion to all subjects (Gemmini PC-2 volumetric infusion pump; Imed, San Diego Calif.). The study order was randomised so that seven children received CPA as a 1-h infusion during the initial investigation. The median time interval between these two doses of CPA was 6 weeks (range 3–10 weeks). No patient received treatment with CPA between the two arms of the study. The median dose of CPA administered was 1050 mg/m^2 (range 600–2000 mg/m^2) and did not change between administration schedules (Table 1). Concurrent chemotherapy and supportive care medication varied in accordance with clinical requirements and was carefully documented (Table 2).

Blood samples were obtained from an indwelling central venous catheter immediately before, and at 0.5, 1, 2, 4, 6, 12, 18 and 24 h after the start of the 1-h infusion. Venous blood was collected immediately before, at 3, 6, 12, and 18 h during, and at the completion of the 24-h infusion. Further samples were collected at 1, 2, 3, 4, 6 and 12 h following the completion of the 24-h infusion. Urine collections were not attempted because of the young age of many of the subjects. Serum concentrations of alanine transaminase, bilirubin and albumin were measured immediately prior to each study as indicators of hepatic function. The concentration of CPA and its principal metabolites were measured by an established high-performance thin-layer-chromatography–photographic-densitometry technique (lower limit of detection 3 μM) [16]. Unfortunately this method does not reliably detect 4-hydroxycyclophosphamide or phosphoramide mustard, which require bedside derivatisation to increase their stability.

Pharmacokinetic analyses

A one-compartment monoexponential model was fitted by use of ADAPT II [17] to the elimination of CPA following a 1-h infusion. The time-averaged clearance (Cl) of CPA during a 24-h infusion was obtained by dividing the administered dose by the area under the plasma concentration time curve (AUC). The AUCs of CPA and its principal metabolites were obtained by use of a combination of the linear and logarithmic trapezoidal rules [18]. Results were analysed by the Mann-Whitney U and the Student's paired *t*-tests where appropriate. This investigation was approved by the joint ethical committee of the medical school of the University of Newcastle upon Tyne and the Royal Victoria Infirmary, Newcastle upon Tyne.

Table 1 Patient details

Patient number	Sex	Age (years)	Diagnosis	CPA dose (mg/m^2)	Interval[b] (weeks)
1	M	2	NB	600	3
2	M	2	NB	600	4
3	F	3	NB	600	3
4[a]	F	3	RMS	2000	3
5	M	3	NB	1050	6
6[a]	F	4	NHL	1000	9
7[a]	M	4	PNET	1500	7
8[a]	F	4	NB	1050	6
9	M	5	NB	1050	6
10	M	7	NHL	1000	10
11[a]	M	7	NB	1050	6
12[a]	M	13	NHL	1000	9
13	M	17	RMS	2000	3

Diagnoses: *NB* neuroblastoma, *NHL* non-Hodgkin's lymphoma, *PNET* medulloblastoma, *RMS* rhabdomyosarcoma

[a] Children who received the first course of cyclophosphamide as a 1-h infusion

[b] Interval: elapsed time between receiving an identical dose of cyclophosphamide either as a 1-h or as a 24-h infusion

Table 2 Concurrent medication (includes drugs taken in the week prior to the study). *Acy* acyclovir, *Amox* amoxycillin, *Amp* amphotericin B, *Bec* beclomethasone (nebulised), *Car* carboplatin, *Cbz* carbamazepine, *Cef* ceftazidime, *Cep* cephalexin, *Chlor* chlorpheniramine, *Cis* cisplatin, *Cyc* cyclizine, *Dex* dexamethasone, *Dih* dihydrocodeine *Doxo* doxorubicin, *Flu* fluconazole, *Frus* frusemide, *Hyr* hydrallazine, *Imip* imipenem, *Mes* mesna, *Met* metoclopramide, *MTX* methotrexate, *Nys* nystatin, *Para* paracetamol, *Pred* prednisolone, *Prop* propranolol, *Ran* ranitidine, *Salbut* salbutamol (nebulised), *Teic* teicoplanin, *Tri* trimethoprim, *Trim* trimeprazine, *Van* vancomycin, *Vcr* vincristine, *VP16* etoposide

Patient number	Cytotoxic drugs: 1-h infusion	Cytotoxic drugs: 24-h infusion	Other medication: 1-h infusion	Other medication: 24-h infusion
1	**Car,** Vcr, VP16	**Cis,** Vcr, VP16	**Imip, Teic**	None
2	**Car,** Vcr, VP16	**Cis,** Vcr, VP16	Frus, **Trim**	Frus
3	**Car,** Vcr, VP16	**Cis,** Vcr, VP16	**Amox**	None
4	None	None	Flu,Mes	Flu,Mes
5	Vcr, VP16	Vcr, VP16	**Hyr,** Mes, **Para, Prop, Salbut**	Mes
6	Doxo, MTX, Pred	Doxo, MTX, Pred	Cyc	**Bec,** Cyc
7	Vcr, VP16	Vcr, VP16	**Dex,** Mes	Mes
8	Vcr, VP16	Vcr, VP16	Cbz, Flu, Mes	Cbz, Flu, **Hdr,** Mes, **Nys, Prop**
9	Vcr, VP16	Vcr, VP16	**Chlor,** Flu, **Hyd, Imip,** Mes	Flu, Mes
10	Doxo, MTX, Pred	Doxo, MTX, Pred	**Cyc, Mes**	**Acy, Cef, Dih**
11	Vcr, VP16	Vcr, VP16	**Amiloride, Amp, Cef,** Flu, Mes, **Van**	Flu, **Imip,** Mes
12	Doxo, MTX, Pred	Doxo, MTX, Pred	**Cbz,** Mes, Met, Ran	**Acy, Cyc,** Met, **Frus,** Ran
13	None	None	Nabilone	**Imip,** Nabilone

All patients received ondansetron as an antiemetic. Drugs which differ between the 1- and 24-h infusion are in **bold type**

Results

The pharmacokinetics and metabolism of cyclophosphamide administered as a 1-h infusion

The disappearance of CPA from the plasma was monoexponential in all cases. Clearance varied fourfold with a median value of 3.1 l/h/m^2 (range 1.4–6.2 l/h/m^2). The median half-life and volume of distribution were 2.6 h (range 1.2–7.9 h) and 0.48 l/kg (range 0.12–0.78 l/kg), respectively. The most abundant metabolite was CX which was detectable in 11 children (85%). DCCP was present in nine children (69%) whilst KETO was only detected in a single child (8%). The median AUCs for CX and DCCP were 99 μM h (range ND: 274 μM h) and 32 μM h (range ND: 207 μM h) respectively. All pharmacokinetic parameters and metabolite AUCs were independent of administered dose, age, sex, albumin, liver enzymes and bilirubin.

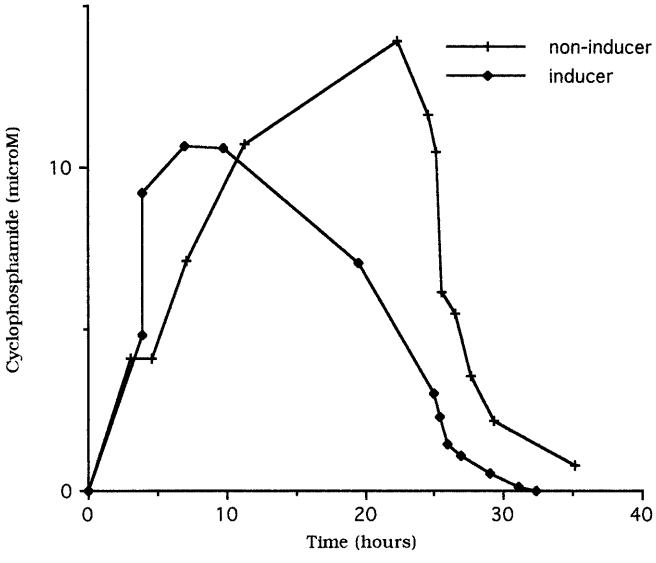

Fig. 1 Plasma concentrations of cyclophosphamide during a 24-h infusion in an inducer and a non-inducer

The pharmacokinetics and metabolism of cyclophosphamide administered as a 24-h infusion

The administration of CPA as a constant-rate infusion over 24 h produced a gradual rise in plasma concentration until an initial plateau was achieved. This plateau concentration was either sustained at a steady-state value, or declined throughout the remainder of the infusion (Fig. 1). After the infusion was complete, CPA concentrations decayed according to a first-order elimination process. Autoinduction, as defined by a reduction in the plasma concentration of CPA during the constant-rate infusion, was evident in five children (38%). These patients had a median end of infusion CPA concentration which was 49% (range 28–89%) of the maximum plasma values. The median time interval to autoinduction, defined as the time of the last plasma sample when CPA concentration was maintained at a plateau level, was 19 h (range 7.1–22.2 h). There was no difference in administered dose, age, tumour type or concurrent medication

between children who exhibited autoinduction and the remainder of the study population.

Clearance values from patients who underwent autoinduction are expressed as an apparent mean, averaged over the entire observation period. The median Cl of CPA was 5.1 l/h/m^2 (range 1.7–12.7 l/h/m^2) and was greater in children who exhibited autoinduction than in the remainder of the study population (median 6 vs 3.7 l/h/m^2, $P=0.02$) (Fig. 2). The volume of distribution of CPA following the completion of the infusion (V_B) varied thirty-four-fold with a median value of 0.63 l/kg (range 0.05–1.7 l/kg). This value is likely to be an underestimate as V_B varies inversely with the elimination constant which increases in magnitude during autoinduction. Terminal half-life varied more than threefold with a median value of 4.6 h (range 1.9–7.1 h). There was a trend towards a shorter terminal half-life in children exhibiting autoinduction (median 3.8 vs 4.2 h, $P = 0.06$). All pharmacokinetic parameters and metabolite AUCs were independent of age, sex, plasma albumin, liver enzymes and bilirubin.

The most abundant metabolite was DCCP which was detectable in nine children (69%). CX was detectable in eight children (57%) whilst KETO was detected in only a single child (7%). The median AUCs for CX and DCCP were 17 μM h (range ND: 356 μM h) and 45 μM h (range ND: 189 μM h), respectively. KETO was detected at a single time point only. There were no significant differences in the AUCs for any metabolite between the group of children exhibiting autoinduction and the remainder of the study population.

Comparison of the pharmacokinetics and metabolism of cyclophosphamide administered as a 1-h and a 24-h infusion

A typical CPA plasma concentration vs time profile following a 1-h infusion and during a 24-h infusion in a single patient is presented in Fig. 3. The Cl of CPA was

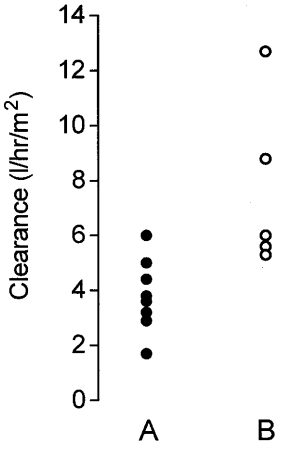

Fig. 2 Cyclophosphamide clearance in children who did (*A*) and did not (*B*) exhibit autoinduction ($P=0.02$)

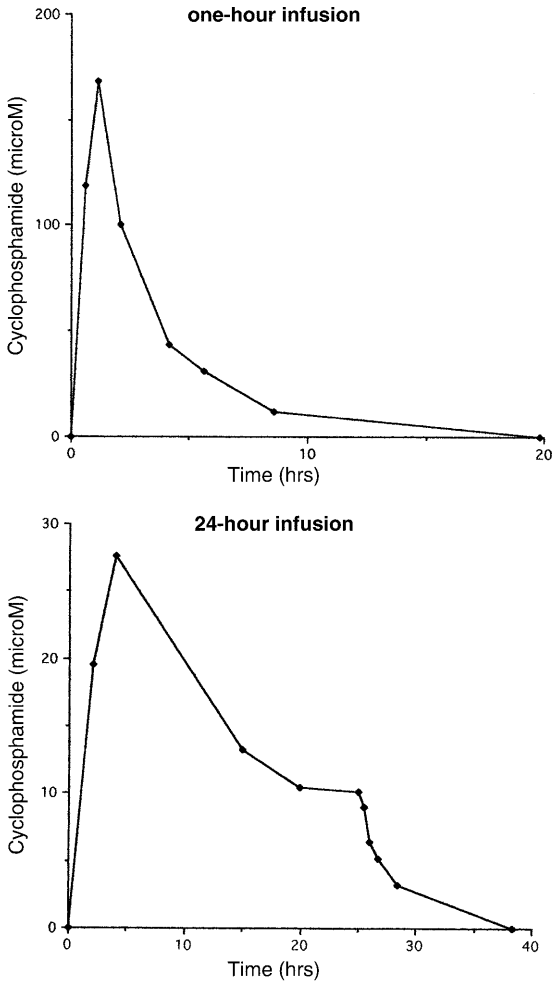

Fig. 3 Comparison of plasma concentrations achieved following a 1-h (*upper graph*) and a 24-h (*lower graph*) infusion of cyclophosphamide in a single patient

greater during the 24-h infusion than following a 1-h infusion (median 5.1 vs 3.1 l/h/m^2, $P=0.037$) (Fig. 4; Table 3). The half-life was shorter following a 1-h infusion (median 2.6 vs 4.5 h, $P=0.035$; Table 3). The proportion of children in whom CX could be detected during a 24-h infusion (57%) was less than that following a 1-h infusion (85%). The proportion of children in whom DCCP could be detected was the same following both a 1- and a 24-h infusion (69%). There were no significant differences between the administration schedules with regard to the AUC of either CX or DCCP (Table 4). No relationship was seen between the order of study and the pharmacokinetics of the parent compound or individual metabolite AUCs.

Discussion

Previous studies have shown that changes in the administration schedule of several cytotoxic drugs are

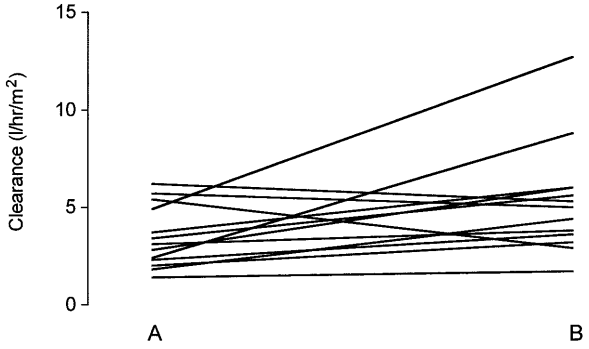

Fig. 4 Cyclophosphamide clearance in children following a 1- (*A*) and a 24-h (*B*) infusion ($P = 0.037$)

Table 3 The pharmacokinetics of cyclophosphamide when administered by a 1- and a 24-h infusion

Patient number	Cl 1-h	Cl 24-h	V_d 1-h	V_β 24-h	$t_{1/2}$ 1-h	$t_{1/2}$ 24-h
1	1.8	4.4	0.14	1.7	1.2	7.1
2[a]	3.4	5.6	0.55	0.63	2.6	5.4
3[a]	3.7	6	0.36	0.76	1.4	3.8
4	2	3.2	0.37	0.94	3.1	3.1
5	2.8	6	0.48	0.87	3.4	3.9
6	5.4	2.9	0.9	1.3	2.6	6.2
7	5.7	5	0.78	0.63	2.3	5.7
8[a]	4.9	12.7	0.65	0.28	2.3	3.7
9	2.3	3.6	0.47	0.92	3.2	6.6
10[a]	6.2	5.3	0.7	0.11	2.2	4
11[a]	2.4	8.8	0.56	0.17	4.8	1.9
12	3.1	3.8	0.32	0.22	7.9	4.5
13	1.4	1.7	0.12	0.08	2.3	5.9
Median	3.1	5.1	0.48	0.63	2.6	4.5
Range	1.4–6.2	1.7–12.7	0.12–0.9	0.08–1.7	1.2–7.9	1.9–7.1

Cl, clearance (l/h/m^2) (expressed as an average value over the time course of observation in patients exhibiting autoinduction); V_d, volume of distribution following a 1-h infusion (l/kg); V_β, volume of distribution following a 24-h infusion (l/kg), $t_{1/2}$, half-life (hours)
[a] Children who exhibited autoinduction during a 24-h infusion of cyclophosphamide

Table 4 Cyclophosphamide metabolite production following a 1- and during a 24-h infusion

Patient number	AUC for CX (μM h) 1-h	AUC for CX (μM h) 24-h	AUC for DCCP (μM h) 1-h	AUC for DCCP (μM h) 24-h
1	ND	ND	ND	ND
2[a]	ND	ND	ND	ND
3[a]	113	ND	32	ND
4	12	48	92	30
5	109	138	37	124
6	54	ND	55	60
7	118	87	13	137
8[a]	221	356	207	106
9	274	244	207	64
10[a]	77	ND	ND	ND
11[a]	99	17	ND	74
12	10	29	31	189
13	112	ND	74	14
Median	99	77	32	60
Range	ND–274	ND–356	ND–207	ND–189

AUC for CX area under the concentration vs time curve for carboxyphosphamide, *AUC for DCCP* area under the concentration vs time curve for dechlororoethylcyclophosphamide, *ND* not detected
[a] Subjects who exhibited autoinduction during a prolonged infusion of cyclophosphamide

accompanied by differences in their clinical effects. The cardiotoxicity of doxorubicin and the renal toxicity of cisplatin can be reduced by the administration of these agents as prolonged infusions [19, 20]. In contrast, 24-h infusions of paclitaxel are associated with greater myelosuppression and mucosal toxicity than corresponding 3-h infusions [21]. Prolonged infusions of ifosfamide are less neurotoxic but may also be accompanied by a reduced cytotoxic effect [22, 23]. This change may result from an increased production of dechloroethylated metabolites during prolonged infusions [11]. Similarly, attempts to prolong the infusion of irintotecan have been limited by unacceptable gastrointestinal toxicity following an increase in the conversion of the parent drug into the more potent metabolite SN-38 [12].

The results of our study indicate that CPA metabolism is altered by an increase in the duration of its infusion. Specifically, the Cl of CPA is significantly greater during a 24-h infusion than following a 1-h infusion because of autoinduction. This was not a universal finding: three subjects exhibited a greater Cl of the drug following a 1-h infusion. In two of these cases this may have resulted from the withdrawal of the cytochrome P450 inducers carbamazepine and dexamethasone prior to both children receiving the 24-h infusion [24, 25]. We were unable to analyse changes in CPA metabolism in terms of treatment efficacy or toxicity because of the inclusion of children with different malignancies receiving a variety of multi-agent chemotherapy regimens.

As reported previously, a high-degree of interpatient variation in metabolite production was observed during both administration schedules [16]. A similar investigation, comparing the metabolism of ifosfamide when administered as three 1-h infusions and as a continuous infusion over 72 h, described an increase in the production of inactive dechloroethylated products during the prolonged infusion. This increase occurred largely as a result of time-dependent increases in the metabolism of the parent drug (autoinduction). No significant differences were identified in the production of carboxyifosfamide [11]. Although a relative increase in the frequency of DCCP production, compared with CX, during a 24-h infusion was detected here, no significant changes in metabolite AUCs were found; this suggests that neither of the administration schedules used in this study had a clear advantage in reducing the production of inactive metabolites. This difference between CPA and ifosfamide may reflect the role of different cytochrome P450 enzymes in their metabolism and the greater importance of dechloroethylation in the metabolism of ifosfamide [26, 27].

Time-dependent increases in CPA metabolism following repeated daily doses of CPA have been reported

previously and were identified in 38% of the children during a 24-h infusion in this study [28–30]. Surprisingly, such increases in the rate of metabolism were not accompanied by an increased production of inactive metabolites; this suggests a potential advantage of this approach in clinical practice. Whilst two recent studies described an increased production of 4-hydroxycyclophosphamide during repeated CPA dosing at 24-h intervals, they provide conflicting information as to whether autoinduction was also associated with an increased formation of inactive metabolites [28, 30].

Pharmacological studies of prolonged infusions of CPA have not provided a consistent picture of the incidence and extent of autoinduction. Time-dependent increases in metabolism were not reported in a group of adults receiving CPA as a 120-h infusion [31]. In contrast, another study described a rapid peak in the plasma concentration of CPA prior to a decrease in every patient [32]. Another group of investigators described autoinduction in 87% of adults receiving a 96-h infusion of CPA [13]. The reasons for these differences are unclear. The duration of infusion was similar in all three reports (4–5 days). Drug-induced enzyme induction is known to be dose-dependent, thus the absence of autoinduction in one adult study may reflect the smaller administered dose (2 vs 6 g/m^2) [33]. There was no association between administered dose and the development of autoinduction in our investigation, although all of the children received a considerably smaller dose than that administered during the adult studies described above. Cytochrome P450 induction is known to be genetically regulated, thus variation in the incidence of autoinduction may result from differences in genotype [34]. Interestingly, a recent adult study also described a high degree of interpatient variation in the extent and pattern of autoinduction of CPA metabolism during three doses given at 24-h intervals [29].

It is possible that the variation in the incidence of autoinduction reported here may reflect differences in the time to detection rather than an absolute effect. Our study defined the time interval between the start of the infusion and the appearance of autoinduction as being between 7 and 22 h. This figure is considerably shorter than the 29-h mean time interval reported in adults [13]. These figures suggest that prolonging the infusion of CPA beyond 24 h may permit autoinduction to become evident in all patients. It should be remembered that absolute time intervals represent abstract values as time-dependent increases in Cl may develop immediately following the initiation of drug infusion, but only become evident when autoinduction produces a decay in plasma concentrations.

The effect of other drugs on autoinduction is unknown. Concurrent treatment with the cytochrome P450 inhibitor fluconazole did not prevent autoinduction [35]. Previous studies have suggested that CPA autoinduction is less marked in patients who have received prior treatment with phenytoin [13, 36]. The authors of these reports suggested that this was secondary to maximal prior cytochrome P450 induction by the anticonvulsant. In contrast, a previous study characterising the autoinduction of ifosfamide described a significant increase in Cl in a child receiving carbamazepine [37]. Similarly, the single patient receiving carbamazepine in this investigation exhibited a marked time-dependent increase in CPA Cl. Whether these conflicting results are due to differences in the pharmacological effects of the two anticonvulsants is unclear.

The results presented here suggest that autoinduction of CPA metabolism exhibits considerable interpatient variation, both in its incidence and in the magnitude of its effect. Its occurrence is seemingly unpredictable and may be subject to genetic regulation. The development of autoinduction led to an increase in Cl during a 24-h when compared to a 1-h infusion. In the absence of a corresponding increase in the production of inactive metabolites, time-dependent increases in the metabolism of CPA may be of potential clinical benefit. Wider use of prolonged infusions of CPA would also prevent the development of high peak concentrations, thus reducing concerns over possible saturation of metabolising enzymes at high doses [13, 38].

Whilst the relationship between CPA metabolism and efficacy is incompletely understood, one study demonstrated an inverse correlation between the AUC of the parent drug and disease-free survival in adults undergoing high-dose therapy for the treatment of metastatic breast cancer, indicating a potential therapeutic benefit of more extensive metabolism in vivo [32]. It is possible that further increases in Cl may be achieved by a lengthening of the infusion duration beyond 24 h. These results suggest a potential therapeutic advantage of prolonged infusions of CPA, which should be tested further in clinical trials.

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