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Short report

Phenobarbital administration does not affect high-dose ifosfamide pharmacokinetics in humans

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Ten patients (three males and seven females) were treated for sarcoma with high-dose ifosfamide (IFO) according to a 4 g/m² 1 h i.v. infusion schedule every day for 3 days. The courses were repeated every 4 weeks. Phenobarbital (PB) treatment was only started at the second course and was continued for the following courses at a p.o. dose of 60 mg/day on the 3 days of IFO i.v. infusion. IFO pharmacokinetic studies were performed on the first and third day of each course. The results of the pharmacokinetic analysis showed a statistical difference of the IFO parameters between the first and third day of each course with or without PB co-administration. When we compared all the first days and all the third days, the statistical analysis showed no difference for all the pharmacokinetic parameters. The meaning of these results was that IFO kinetics was not stationary with an area under the curve decreasing from the first to the third day of each course and that concomitant PB administration, in our administration schedule, did not influence IFO pharmacokinetics.

Key words: High dose, ifosfamide, pharmacokinetics, phenobarbital.

Introduction

Ifosfamide (IFO) [3-(2-chloroethyl)-2-(2-chloroethylamino)tetrahydro-2H-1,2,3 oxazaphorphorine oxide] is a structural isomer of the oxazaphosphorine cyclophosphamide (CPM). IFO like CPM is a prodrug that requires biotransformation to become active. The metabolic transformation occurs mainly in the liver[1,2] with an hydroxylation at the carbon atom in position 4 of the ring system. Spontaneous opening of the ring produces aldo-IFO, a tautomer of 4-hydroxy-IFO, and then cleavage of the ring leads to the active metabolites, IFO mustard and acrolein. IFO like CPM produces toxic side effects such as hematotoxicity, urotoxicity, nephrotoxicity and encephalopathy. This last side effect occurs more often with IFO than with CPM. Lethargy is the most common manifestation, and can progress to somnolence and coma.[3,4] Further possible manifestations are weakness, forgetfulness, confusion, hallucinations and cerebellar symptoms.[5,6] The mechanisms responsible for encephalopathy are not yet established. The plasma phamacokinetic (PK) profiles of either unmetabolized ifosfamide or its alkylating metabolites are similar with or without encephalopathy.[7] The concomitant administration of the uroprotector mesna does not seem to influence the occurence of encephalopathy.[8,9] Phenobarbital (PB) is widely used in order to prevent encephalopathy. This report describes the effects of PB pretreatment on the PK of IFO in cancer patients.

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Patients and methods

Patients and drug administration

Ten patients were included in this study. There were three males and seven females, whose mean age was 46.8 ± 15.3 years (range 18–64 years). They all received high-dose IFO for osteosarcoma (two patients) and soft tissue sarcoma (eight patients). At each course, the patients received 4 g/m² IFO as a 1 h i.v. infusion every day for 3 days. The courses were repeated every 4 weeks. PB treatment was only started at the second course and was continued for subsequent courses at a p.o. dose of 60 mg/day for the 3 days of IFO i.v. infusion. PB was taken orally by the patients only once a day at 8 a.m. The urothelial protective agent mesna was administered every day of IFO injection. The mesna schedule used was 1.5 g/m² four times a day (time 0, 4, 8 and 12 h after the start of IFO infusion). The hepatic and renal

biological status of the patients remained unchanged during the duration of this study.

Blood sampling

Serial blood samples were collected before the start of the infusion, 5 min before the end of the infusion, 15, 30 min, 1, 2, 3, 5, 7, 18 and 23 h after the end of the infusion.

IFO PK studies were performed on the first and third day of each course during three consecutive courses. Blood samples were centrifuged immediately, the plasma was separated off and stored at −30°C until analysis.

Analytical method

The plasma samples were analyzed according to the HPLC technique described by Burton and James.[10] The samples were processed using a solid phase (cyclohexyl) extraction step. The extracts were chromatographed on a C_8 reversed-phase column with a mobile phase consisting of acetonitrile 0.025 M phosphate buffer pH 4.0 (25:75) with UV detection at 200 nm. The detection limit using 250 µl of plasma was 1 µg/ml for IFO. This detection limit was sufficient for all the PK studies reported in this trial.

PK and statistical analysis

IFO PK parameters were calculated using the Micropharm program (French National Biomedical Research Institute, Créteil, France).[11] The statistical analysis was performed with Student's *t*-test for the main IFO PK parameters studied: area under the curve extrapolated to infinity (AUC), total body clearance (Clt) expressed as dose/AUC, terminal half-life ($t_{1/2}$) and the maximum concentration (C_{max}).

Results

The decline in plasma IFO level after i.v. infusion is always bi-exponential. The IFO pharmacokinetic parameters are summarized in Table 1. When comparing the values of the pharmacokinetic parameters obtained during the first course of IFO, without PB, on the first and third days of treatment, Student's paired *t*-test showed significant statistical differences for three parameters studied (Table 1). When we compared the PK parameters (first and third days) during the subsequent courses with PB, we found the same statistical differences as without PB (Table 1). When we analyzed the first day PK parameters obtained with PB versus without PB with Student's *t*-test, we found no difference (Table 2). For the third days we also found no difference (Table 2). For this reason, in order to increase the amount of data, we summed the results obtained for all the first days (with and without PB) and for all the third days (with and without PB), and the comparison of the PK parameter values, using Student's paired *t*-test, showed significant statistical differences for three of the parameters studied. The *p* values for AUC, Clt, $t_{1/2}$ and C_{max} were 0.0021, 0.0098, 0.047 and 0.35, respectively.

Discussion

The results presented indicate that fractionation of IFO dosages leads to a non-stationary PK of the drug, with decrease of the area under the curve, increase of the total body clearance and shortening of the

Table 1. IFO PK parameters

	Course 1		Course 2		Course 3	
Day	1	3	1	3	1	3
AUC (µg/ml h)	1072 ± 232	512 ± 205	1074 ± 1162	294 ± 176	908 ± 387	327 ± 167
	$p = 0.000049$		$p = 0.0085$		$p = 0.00016$	
Clt (l/h/m²)	3.74 ± 0.83	9.01 ± 4.56	7.23 ± 7.92	13.30 ± 9.05	4.32 ± 1.62	12.52 ± 5.78
	$p = 0.0056$		$p = 0.0067$		$p = 0.00021$	
$t_{1/2}$ (h)	5.50 ± 0.95	2.52 ± 0.75	5.72 ± 1.10	1.88 ± 0.37	4.01 ± 0.21	2.90 ± 0.79
	$p = 0.000024$		$p = 0.000012$		$p = 0.00098$	
C_{max} (µg/ml)	122.3 ± 42.6	126.1 ± 46.2	151.9 ± 44.0	150.2 ± 49.9	135.1 ± 42.3	83.6 ± 19.3
	$p = 0.78$		$p = 0.92$		$p = 0.20$	

Table 2. IFO combined PK parameters

	C1D1 versus C2D1 + C3D1			C1D3 versus C2D3 + C3D3		
AUC (μg/ml h)	1072 ± 232	$p = 0.79$	1033 ± 996	512 ± 205	$p = 0.13$	319 + 307
Clt (l/h/m^2)	3.74 ± 0.83	$p = 0.15$	6.49 ± 6.10	9.01 ± 4.56	$p = 0.20$	13.11 ± 7.96
$t_{1/2}$ (h)	5.50 ± 0.95	$p = 0.75$	5.13 ± 1.67	2.52 ± 0.75	$p = 0.91$	2.33 ± 0.61
C_{max} (μg/ml)	122.3 ± 42.6	$p = 0.73$	147.1 ± 41.0	126.1 ± 46.2	$p = 0.92$	131.1 ± 52.7

C1D1 = day 1 of course 1, C2D1 = day 1 of course 2, C3D1 = day 1 of course 3, C1D3 = day 3 of course 1, C2D3 day 3 of course 2, C3D3 = day 3 of course 3.

terminal half-life. Similar findings have been obtained with fractionating CPM administration.[12,13] Our data show that, if modifications of IFO PK during the multiple i.v. injections in each course occur, patients recover following the 4 weeks of rest between courses and the new first day PK profile is the same for all the courses.

In our study, PB was used to prevent encephalopathy, a distressing side effect of IFO. The IFO central nervous system toxicity is usually, but not always, fully reversible.[14] The kinetic aspects of IFO distribution, metabolism and excretion in man have already been explored in detail[15–17] but the effects of PB administration have only been studied on CPM pharmacokinetics and have shown that the rate of biotransformation of the inactive precursor to its active metabolites is increased 2- to 3-fold by PB.[18] In the present study we focused on the influence of PB and IFO co-administration on IFO PK. No difference with PB or without PB administration was noticed for the IFO PK parameters with our schedule of PB administration. Nevertheless, CPM and IFO are both activated by human cytochrome P450 enzymes and both produce auto-induction via the same oxidative chain.[19] However, the enzymes involved in hydroxylation leading to the activation of the two anticancer drugs, seem to belong to different isoforms of the cytochrome P450 family. CPM is mainly hydroxylated by the isoform 2B6, and IFO by the isoforms 3A3 and 3A4.[20] PB is also metabolized through the oxidative cytochrome P450 chain and induces activation of the enzymes responsible for its own metabolism; the isoform involved in PB metabolism is 3A, the same as the one for IFO.[21] A logical consequence would have been a PK interaction between IFO and PB, an interaction not seen in our study. A possible explanation for this phenomenon is that on the first day of the course PB is given too late to interact with IFO metabolism, and that in the days after IFO auto-induction through the cytochrome P450 chain a maximum of available enzymes are used and PB co-administration cannot further enhance IFO metabolism.

References

1. Allen LM, Creaven PJ, Nelson P. Studies on the human PK of isophosphamide (NSC-109724). *Cancer Treat Rep* 1976; **60**: 451–8.
2. Norpoth K, Müller G, Raidt H. Isolierung und charakterisierung zweier haupt-metabolite von ifosfamid aus patienten-urin. *Arzneim-Forsch (Drug Res)* 1976; **25**: 1376–7.
3. Bremmer DN, McCormick JS, Thompson JW. Clinical trial of isophosphamide (NSC-109724). Results and side effects. *Cancer Treat Rep* 1974; **58**: 889–93.
4. Nelson RL, Allen LM, Creaven PJ. Pharmacokinetics of divided dose ifosfamide. *Clin Pharmacol Ther* 1976; **19**: 365–70.
5. Fossa S, Talle K. Treatment of metastatic renal cancer with ifosfamide and mesna with and without irradiation. *Cancer Treat Rep* 1980; **64**: 1103–8.
6. Lewis LD, Meanwell CA. Ifosfamide pharmacokinetics and neurotoxicity. *Lancet* 1990; **335**: 175–6.
7. Pearcy R, Calvert R, Metha A. Disposition of ifosfamide in patients receiving ifosfamide infusion therapy for the treatment of cervical carcinoma. *Cancer Chemother Pharmacol* 1988; **22**: 353–5.
8. Cohen MH, Creaven PJ, Tejada F. Phase I clinical trial of isophosphamide (NSC-109724). *Cancer Chemother Rep* 1975; **59**: 751–5.
9. Gieron MA, Barak L, Estrada J. Severe encephalopathy associated with ifosfamide administration in two children with metastatic tumors. *J Neuro-oncol* 1988; **6**: 29–30.
10. Burton LC, James CA. Rapid method for the determination of ifosfamide and cyclophosphamide in plasma high-performance liquid chromatography with solid-phase extraction. *J Chromatogr* 1988; **431**: 450–4.
11. Urien S. MicroPham-K, a microcomputer interactive program for the analysis and simulation of PK processes. *Pharm Res* 1995; **12**: 1225–30.
12. Lind MJ, Margison JM, Cerny T, Thatcher N, Wilkinson

PM. Comparative pharmacokinetics and alkylating activity of fractionated intravenous and oral ifosfamide in patients with bronchogenic carcinoma. *Cancer Res* 1989; **49**: 753–7.
13. Graham MI, Shaw IC, Souhami RL, Sidau B, Harper PG, Maclean AE. Decreased plasma half-life of cyclophosphamide during repeated high-dose administration. *Cancer Chemother Pharmacol* 1983; **10**: 192–3.
14. Watkin SW, Husband DJ, Green JA, Warenius HM. Ifosfamide encephalopathy: a reappraisal. *Eur J Cancer Clin Oncol* 1989; **25**: 1303–10.
15. Wagner T, Heydrich D, Jork T, Voeleker G, Hohorst HJ. Comparative study on human pharmacokinetics of activated ifosfamide and cyclophosphamide by a modified fluorimetric test. *J Cancer Res Clin Oncol* 1981; **100**: 95–104.
16. Colvin M. The comparative pharmacology of cyclophosphamide and ifosfamide. *Semin Oncol* 1982; **9** (Suppl 1): 2–7.
17. Norpoth K. Studies on the metabolism of isophosphamide (NSC-109724) in man. *Cancer Treat Rep* 1976; **60**: 437–43.
18. Jao JY, Jusko WJ, Cohen JL. Phenobarbital effects on cyclophosphamide pharmacokinetics in man. *Cancer Res* 1972; **32**: 2761–4.
19. Boddy AV, Cole M, Pearson ADJ, Idle JR. The kinetics of the autoinduction of ifosfamide metabolism during continuous infusion. *Cancer Chemother Pharmacol* 1995; **36**: 53–60.
20. Chang TKH, Weber GF, Crespi CL, Waxman DJ. Differential activation of cyclophosphamide and ifosfamide by cytochrome P-450 2B and 3A in human liver microsomes. *Cancer Res* 1993; **53**: 5629–37.
21. Beaune P. Les cytochromes P-450 humains. Applications en pharmacologie. *Therapie* 1993; **48**: 521–6.

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