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Short communication

Ifosfamide enantiomers: pharmacokinetics in children

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Abstract. Ifosfamide, like other oxazaphosphorine drugs, is chiral and there is some evidence, mainly from animal studies, of stereo-selective differences in metabolism, excretion and cytotoxic activity between the two enantiomers. The pharmacokinetics of racemic ifosfamide (RAC-IFO), R-ifosfamide (R-IFO) and S-ifosfamide (S-IFO) were studied in five children who received intravenous therapy with racemic ifosfamide on 3 consecutive days. The clearance of S-IFO was greater than that of R-IFO. The clearance value at the end of the infusion was faster than the respective rate measured at the beginning of or during the ifosfamide regimens in four children and, therefore, suggests autoinduction of elimination of both enantiomers.

Key words: Ifosfamide – Enantiomers – Children

Introduction

Ifosfamide, a close analogue of cyclophosphamide, has a broad spectrum of anti-neoplastic activity. It is widely used in therapeutic management against a variety of paediatric solid tumours. Although it is generally used in fractionated regimens, the actual dose, duration of infusion and days of therapy in a course vary considerably between protocols. There is evidence of a marked inter- and intra-individual variability in ifosfamide pharmacokinetics that is enhanced with autoinduction of its elimination [7, 9].

The pharmacokinetic and pharmacodynamic properties of ifosfamide are further complicated because it has an optical active chiral centre and its enantiomers are recognised by the body as two different molecules. Clinically ifosfamide is given as a racemic (RAC-IFO) mixture of R-ifosfamide (R-IFO) and S-ifosfamide (S-IFO). There are insufficient and conflicting data on the relationship between the ifosfamide enantiomers and their metabolites with respect to pharmacokinetic and pharmacodynamic properties. When the pure enantiomers were tested against a variety of transplanted tumour models in animals, S-ifosfamide demonstrated higher cytotoxic activity [6], which could not be repeated [1]. No difference in cytotoxic activity or toxicity between the ifosfamide enantiomers was reported by Masurel et al. [8] when childhood rhabdomyosarcoma was transplanted into mice.

Stereo-specific differences in the metabolism [2], clearance [10] and half-life of ifosfamide [4] have been suggested from the limited data presented. A large interspecies difference in the stereo-selectivity of oxazaphosphorine metabolism has been reported [5]. We report on the extensive pharmacokinetic evaluation of RAC-IFO, R-IFO and S-IFO in five children receiving intravenous ifosfamide therapy over a 3-day period.

Materials and methods

Patients and doses

Five children prescribed ifosfamide chemotherapy at the Yorkshire Regional Paediatric Oncology Unit were studied following the acquisition of written informed consent. This project was approved by the local ethics committee. Three different ifosfamide treatments and 5-ml blood sampling schedules were used as follows.

Schedule 1. A 1-h intravenous infusion of 2 g/m^2 was given on each of 3 consecutive days. Blood samples were taken at 0, 1, 6, 12, 18, 25, 48, 49, 54, 60 and 66 h after the start of the first infusion.

Schedule 2. A 3-h intravenous infusion of 3 g/m^2 was given on each of 3 consecutive days. Blood samples were obtained at 0, 3, 6, 12, 18, 27, 42, 51, 54, 60 and 66 h after the start of the first infusion.

Schedule 3. An intravenous infusion of 9 g/m^2 was given over 72 h. Blood samples were taken at 0, 6, 12, 24, 48, 72, 73, 75, 78 and 84 h after the start of the first infusion.

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Table 1. Patients' characteristics

Patient	Sex	Age (years)	Weight (kg)	BSA (m^2)	Diagnosis	Schedule	Other chemotherapy
A	F	3	16.1	0.65	Rh	2	Vc
B	M	14	59.6	1.60	Ew	1	Ab, Vc
C	F	7	21.9	0.87	Rh	3	Ab, Vc
D	M	15	47.5	1.48	Os	3	MTX
E	M	14	44.3	1.39	Ew	1	Vc

BSA, Body surface area; Rh, rhabdomyosarcoma; Ew, Ewing's sarcoma; Os, osteosarcoma; Vc, vincristine; Ab, actinomycin B; MTX, methotrexate

Table 2. Pharmacokinetic parameters of RAC-, R- and S-IFO

Patient	RAC-IFO			R-IFO			S-IFO		
	$Cl_{initial}$ ($l\ h^{-1}\ m^{-2}$)	Cl_{end} ($l\ h^{-1}\ m^{-2}$)	$t_{1/2}$ (h)	$Cl_{initial}$ ($l\ h^{-1}\ m^{-2}$)	Cl_{end} ($l\ h^{-1}\ m^{-2}$)	$t_{1/2}$ (h)	$Cl_{initial}$ ($l\ h^{-1}\ m^{-2}$)	Cl_{end} ($l\ h^{-1}\ m^{-2}$)	$t_{1/2}$ (h)
A	8.89	8.92	2.10	8.30	7.74	2.30	9.60	10.50	2.00
B	2.12	4.64	2.93	1.95	4.25	3.20	2.32	5.10	2.60
C	4.03[a]	6.65	4.20	3.49[a]	5.74	6.80	4.73[a]	7.92	3.70
D	3.93[a]	4.41	3.80	3.36[a]	3.73	4.20	4.72[a]	5.37	3.20
E	2.76	4.11	5.10	1.98	3.27	6.20	3.83	5.71	3.60

[a] $Cl_{average}$

Blood samples were drawn from a cannula in the central line. All subjects received uroprotection with mesna at a dose of 120% of the ifosfamide dose. The serum was separated from the blood samples and stored at –20° C prior to analysis. The serum concentrations of RAC-IFO, R-IFO and S-IFO were measured by achiral/chiral coupled high-performance liquid chromatography [3]. The limit of detection of the assay was 2.5 mg/l for each enantiomer.

Pharmacokinetic calculations

The elimination rate (k) and, hence, half-life ($t_{1/2}$) was calculated from end-of-infusion serum-concentration data on days 1–3 for schedules 1 and 2 and on day 3 for schedule 3 using linear regression analysis. The area under the curve (AUC) was obtained from the sum of the area between the time of administration and the final blood measurement (trapezoid rule) plus the residual area from the final sampling time to infinity. The residual area was calculated by dividing the final serum concentration by the elimination rate constant. For calculation of the AUC on day 3 for schedules 1 and 2, the proportion of the area due to previous ifosfamide doses, that is, the residual area from day 2, was subtracted. For schedules 1 and 2 the clearance values on days 1 and 3 ($Cl_{initial}$ and Cl_{end}, respectively) were obtained by dividing the daily dose by the AUC. For subjects receiving schedule 3, the average clearance ($Cl_{average}$) and the clearance at the end of the infusion (Cl_{end}) were obtained by dividing the total dose by the total AUC and by dividing the infusion rate by the serum concentration at the end of the infusion, respectively.

Statistical analysis of the R:S clearance ratio between $Cl_{initial}$/$Cl_{average}$ and Cl_{end} was performed using a paired t-test. Other variables were not statistically compared due to the small number of patients enrolled in the study.

Results

Two patients (B and E) received schedule 1, one (A) received schedule 2 and two (C and D) received schedule 3. Their demographic details are shown in Table 1. All children had normal renal and liver function according to their biochemistry and clinical and radiological examinations.

Table 2 shows that S-IFO was cleared ($CL_{average}$, $CL_{initial}$ or CL_{end}) faster than R-IFO and that the half-life of S-IFO was shorter than that of R-IFO in all children studied. The clearance of R-IFO at the end of the therapy was greater than either the initial clearance (schedules 1 and 2) or the average clearance throughout the sampling period (schedule 3) in four patients (B–E). The clearance of S-IFO in all patients was faster at the end of the therapy.

The mean (SD) R:S clearance ratio at the beginning ($Cl_{initial}$ and $Cl_{average}$) and end of the infusion (Cl_{end}) was 0.73 (0.14) and 0.71 (0.09), respectively. Statistical analysis revealed no significant difference in the clearance ratio of the enantiomers. The elimination half-life determined for RAC-IFO on day 1 for patients A, B and E was 2.70, 6.20, and 6.20 h, respectively. The half-life determined on day 1 was longer than the corresponding half-life obtained on day 3 in these patients (Table 2).

Discussion

The faster clearance of S-IFO has previously been demonstrated in five children (age, 3–23 years) following the intravenous administration of RAC-IFO at 1.6 g/m^2 daily for 5 days [10]. Serial samples obtained following the end of the first infusion were used to calculate a mean clearance of R-IFO on day 1 of 1.65 $l\ h^{-1}\ m^{-2}$ as compared with a respective mean value of 1.94 $l\ h^{-1}\ m^{-2}$ for S-IFO. The clearance of ifosfamide on day 5 of therapy in this study was not reported. In our study the clearance of R- and S-IFO on day 1 in the three patients who received fractionated regimens was faster, ranging from 1.95 to 8.30 $l\ h^{-1}\ m^{-2}$ and from 2.32 to 9.60 $l\ h^{-1}\ m^{-2}$, respectively. The clearance of the enantiomers at the end of the infusion in

these patients ranged from 3.27 to 7.74 l h^{-1} m^{-2} and from 5.10 to 10.50 l h^{-1} m^{-2} for R- and S-IFO, respectively. Similarly, in the two patients who received continuous-infusion therapy, the clearance of R- and S-IFO at the end of the infusion (5.37 and 7.92 l h^{-1} m^{-2}, respectively) was greater than the average clearance (4.72 and 4.73 l h^{-1} m^{-2}, respectively) during the infusion. That the clearance values were higher at the end of the 3-day ifosfamide regimens indicates autoinduction of ifosfamide metabolism for both enantiomers. Autoinduction of RAC-IFO metabolism with successive fractionated doses has been documented [7]. The similarity of the R:S clearance ratios obtained during and at the end of the dosing periods suggests that the extent of induction of the metabolism of the two enantiomers is equivalent.

An understanding of the clinical significance of the faster clearance of the S-enantiomer from the body requires a comprehensive knowledge of the dispostion of both enantiomers. This demands further extensive studies in a larger population of children.

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