Pharmacokinetics of ifosfamide and its enantiomers following a single 1 h intravenous infusion of the racemate in patients with small cell lung carcinoma

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Ifosfamide is a chiral pro-drug which is administered clinically in its racemic form. Serum concentrations of *rac*-ifosfamide and its enantiomers were measured in 12 patients with lung carcinoma following a mean ($\pm$ s.d.) intravenous dose of 4.2 (0.83) g infused over 1 h. The mean ($\pm$ s.d.) volumes of distribution (V_{ss}) of *rac*, (R)- and (S)-ifosfamide were 0.61 (0.17), 0.60 (0.16) and 0.61 (0.19) l kg⁻¹, respectively. The mean ($\pm$ s.d.) half-lives and clearances were 6.57 (1.69), 7.12 (1.92) and 5.98 (1.52) h and 0.065 (0.013), 0.060 (0.013) and 0.072 (0.014) l h⁻¹ kg⁻¹ for *rac*, (R)- and (S)-ifosfamide, respectively. The half-life of (S)-ifosfamide was significantly ($P < 0.001$) shorter than that of (R)-ifosfamide and it had a significantly higher clearance ($P < 0.001$). There was no significant difference in the volumes of distribution of the enantiomers. The clinical significance of the faster elimination of (S)-ifosfamide is not known.

Keywords ifosfamide (R)-ifosfamide (S)-ifosfamide pharmacokinetics

Introduction

Racemic ifosfamide, an alkylating agent, exhibits a higher therapeutic index when administered by fractionated or continuous infusion than by short term infusion [1–3]. Nevertheless, short term high dose infusions of ifosfamide have demonstrated improved responses in patients with small cell lung cancer compared with fractionated doses [4]. Ifosfamide is a pro-drug which is metabolised extensively in both ring and side-chain positions to active and inactive moieties. Variation in ifosfamide dose, schedule and route of administration has been shown to influence both the nature and extent of ifosfamide metabolism [5]. Some of this variability could reflect the fact that ifosfamide contains a chiral phosphorous atom, but is administered clinically in its racemic form.

(S)-ifosfamide had a greater efficacy, a greater toxicity and a higher therapeutic index when tested in five *in vitro* tumour models [6]. Knowledge of the stereo-specific pharmacokinetics of ifosfamide is

limited to studies in small numbers of children [7–10]. Differences in the clearance of the enantiomers may reflect their selectivity for the oxidative enzymes responsible for side-chain and ring metabolism. Stereoselectivity in the formation of the alkylating moiety, ifosfamide mustard, a product of ring oxidation should affect the cytotoxic potency of the drug. The products of side-chain metabolism, 2- and 3-dechloroethylifosfamide, are thought to be responsible for the severe CNS toxicity which is observed occasionally with ifosfamide therapy. Further complications are introduced by the fact that those metabolites of ifosfamide which contain an intact oxazaphosphorine ring, for example the dechloroethyl metabolites, are also chiral.

A method to measure serum concentrations of *rac*-, (R)- and (S)-ifosfamide using achiral/chiral h.p.l.c. has been developed and validated [11]. This method has now been used to define the pharmacokinetic

parameters of *rac*, (R)- and (S)-ifosfamide following an intravenous bolus dose of the racemate to patients with small cell lung carcinoma.

Methods

Protocol

The study was approved by the Ethics Committee of the Bradford Hospitals Trust, and all patients gave their written informed consent. Twelve patients (seven male, five female) aged 52 to 76 years (mean age 60 years) and 50 to 100 kg (mean weight 67 kg) each received either 3 or 4 g, (or 3 g m^{-2}) of racemic ifosfamide as a short term i.v. infusion over 1 h. Blood samples were drawn, through a heparinised indwelling cannula, before ifosfamide dosing and at 1, 2, 6, 12, 15, 18, 24 and 30 h thereafter. Serum was stored at -20°C prior to analysis. Standard biochemical and haematological tests were carried out according to the normal management of each patient. All patients received uroprotection with intravenous mesna (75% of the ifosfamide dose), together with metoclopramide and dexamethasone antiemetic therapy. Nine patients were given a standard 4 g dose of racemic ifosfamide according to the protocol of the 'Yorkshire collaborative small cell study'. These nine patients also received 2 mg vincristine (i.v. bolus) and 100 mg etoposide (i.v. infusion over 1 h) on day 1, followed by 200 mg oral etoposide on days 2 and 3 of therapy (EIMV regimen). One patient was not given vincristine for her second course of chemotherapy because of tingling in her hands during her first course. One patient received the EIMV regimen with a lower dose of ifosfamide (3 g) because of his poor performance status. Two patients received 3 g m^{-2} ifosfamide together with carboplatin (3 g m^{-2} i.v. infusion) and etoposide (50 mg orally twice daily for 7 days). Other concurrent drug therapies were dihydrocodeine, morphine sulphate, temazepam, diazepam and ondansetron.

Drug assay

Serum concentrations of *rac*-, (R)- and (S)-ifosfamide were measured by h.p.l.c. as described by Corlett & Chrystyn [11]. The limit of determination for each enantiomer was 1.25 mg l^{-1} . The intra-day coefficients of variation for the assay of 25 mg l^{-1} and 2.5 mg l^{-1} spiked racemic serum ifosfamide samples were 4.4% and 10.3%, respectively. The mean peak area S:R ratios for spiked racemic serum drug concentrations of 25 mg l^{-1} and 2.5 mg l^{-1} were 1.00 and 1.06, respectively, confirming that the racemic ifosfamide used was a 50:50 mixture of the enantiomers.

Data analysis

Pharmacokinetic parameters for *rac*-, (R)- and (S)-ifosfamide were calculated for each patient. The

elimination rate constant, k and half-life, $t_{1/2}$, were determined from linear regression analysis of the log serum drug concentration-time relationships. Values of AUC were estimated using the linear trapezoid rule with extrapolation (C_{last}/k). In all cases the extrapolated area was less than 25% of total AUC. Clearance was calculated from dose/AUC. The volume of distribution (V_{ss}) was calculated from $(\text{Dose} \times \text{AUMC})/\text{AUC}^2$ where AUMC is the first moment of the C - t curve [12]. Values of AUMC were extrapolated ($C_{\text{last}}t_{\text{last}}/k + C_{\text{last}}/k^2$). For each patient the extrapolated area was less than 40% of the total AUMC. Pharmacokinetic parameters for (R)- and (S)-ifosfamide were compared using Student's t -test for paired data. In addition the 95% confidence intervals of difference were calculated.

Results

Creatinine clearance and liver function tests indicated that no patients were in renal or hepatic failure. Three patients had low serum sodium concentrations, which is a classical non-malignant indication of small lung cancer. One patient had a low serum albumin and a high white blood cell count suggestive of infection. He became confused and pyrexial 24 h after being given ifosfamide. One patient had a high white blood cell count. Two patients died 10 days and 42 days, respectively, after the study. In all the other patients ifosfamide was generally well tolerated.

Figure 1 Mean ($\pm$ s.d.) serum concentrations of *rac*- (●), (R)- (■) and (S)-ifosfamide (▲) during and after a 1 h intravenous infusion (mean [$\pm$ s.d.] dose 4.2 [0.83] g) of racemic ifosfamide in 12 patients with small cell lung carcinoma.

Figure 2 Mean ($\pm$ s.d.) and individual values of (R)- and (S)-ifosfamide (a) volume of distribution (V_{ss}), (b) half-life and (c) clearance in patients with small cell lung carcinoma.

In all patients serum ifosfamide concentrations were above the limits of determination at 30 h post dose, and concentrations of (S)-ifosfamide were greater than that of (R)-ifosfamide. Mean ($\pm$ s.d.) serum concentration of *rac*-, (R)- and (S)-ifosfamide are shown in Figure 1. The mean ($\pm$ s.d.) volumes of distribution, half-lives and clearances of (R)- and (S)-ifosfamide were 0.61 (0.18) and 0.63 (0.22) l kg^{-1} , 7.12 (1.92) and 5.98 (1.52) h, and 0.060 (0.013) and 0.072 (0.014) $\text{l h}^{-1} \text{kg}^{-1}$, and 95% confidence intervals for the difference between the enantiomeric values were -0.050 , 0.015 l kg^{-1} , 0.75 , 1.54 h and 0.014 , $0.009 \text{ l h}^{-1} \text{kg}^{-1}$, respectively. Individual values of V_{ss} , $t_{1/2}$ and CL of (R)- and (S)-ifosfamide are shown in Figure 2. There was no significant difference in the V_{ss} values between the enantiomers while the half-life of (S)-ifosfamide was significantly slower ($P < 0.001$) and its clearance was significantly ($P < 0.001$) greater than that of the R- form.

The mean ($\pm$ s.d.) R:S ratios of V_{ss} , $t_{1/2}$ and CL were 0.98 (0.05), 1.19 (0.03) and 0.84 (0.05), respectively.

Discussion

The mean volume of distribution of racemic ifosfamide of 0.61 l kg^{-1} was similar to that reported by others [13–15] and equates to total body water [16]. Racemic ifosfamide shows little plasma protein binding [17]. The similarities in the volumes of distribution of the enantiomers indicate a lack of stereo-specificity in their distribution.

The mean ($\pm$ s.d.) elimination half-life for racemic ifosfamide of 6.6 (1.7) h was similar to values observed by others [13, 18, 19]. The half-life of ifosfamide is reported to decrease with repeated administration giving auto-induction of metabolism [10, 13]. In this study, four patients were receiving their second course of treatment, two their third

course and one their sixth course. No correlation was found between half-life and course number.

The mean ($\pm$ s.d.) clearance of racemic ifosfamide of $0.065 (0.013) \text{ l h}^{-1} \text{kg}^{-1}$ was similar to values reported by others [13–15, 20]. The clearance of the (S)-enantiomer was significantly higher ($P < 0.001$) than that of the (R)-enantiomer. In children the clearance of both the enantiomers was higher than in the adult subjects of the present study (4.95 and $6.92 \text{ l h}^{-1} \text{m}^{-2}$ vs 2.32 and $2.78 \text{ l h}^{-1} \text{m}^{-2}$) for (R)- and (S)-ifosfamide, respectively [10, 21].

The clearance of (R)-ifosfamide varied from 0.043 – $0.080 \text{ l h}^{-1} \text{kg}^{-1}$ and that of (S)-ifosfamide from 0.053 – $0.089 \text{ l h}^{-1} \text{kg}^{-1}$. It is unlikely that this variation is explained by concomitant drug therapy since 10 to the 12 patients received the same therapeutic regimen. The intra-subject variability in R:S clearance ratio was lower with a mean ($\pm$ s.d.) of $0.84 (0.05)$ and a range of 0.77 to 0.92 . These data suggest similar metabolic pathways with different affinities within each individual for both enantiomers.

A large inter-patient variation in the metabolism of ifosfamide has been documented by other investigators. A positive correlation was observed between the appearance of active and inactive metabolites [21]. Further work has identified the role of cytochrome P450 3A4 in both the ring and side-chain oxidation of racemic ifosfamide [22]. However the enantiomers of the parent drug and the metabolites, some of which are also chiral, were not quantified. Unequal amounts of the (R)- and (S)-isomers of the side-chain metabolites, 2- and 3-dechloroethyl ifosfamide were observed in two of eight patients who preferentially cleared (S)-ifosfamide via the side-chain route and in whom severe neurotoxicity and WHO grade 2 lethargy were recorded. The side-chain isozymes responsible for enantiomeric side-chain metabolism of ifosfamide have not been characterised [23].

The clinical significance of the faster elimination of (S)-ifosfamide with respect to the efficacy and toxicity of ifosfamide is not known.

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