Pharmacokinetics and Metabolism of Ifosfamide Administered as a Continuous Infusion in Children

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ABSTRACT

The pharmacokinetics and metabolism of ifosfamide was investigated in a group of 16 pediatric patients (5 girls) aged 1–17 years. Each received a dose of 3 g/m²/day for up to 3 days by continuous infusion. Plasma and urine were collected, and concentrations of ifosfamide and its principal metabolites were determined by a quantitative high-performance thin layer chromatography method. During 3 days of continuous infusion, the plasma concentrations of parent drug decreased. This was accompanied by a continuous increase in dechloroethylated products in plasma but not in urine. Estimated pharmacokinetic parameters (clearance, volume of distribution, and half-life) were dependent on body size and age but not any other patient variable. Renal clearance was a relatively minor route of elimination for parent drug and corresponded to <25% of glomerular filtration rate.

Metabolite data from plasma and urine indicated a high degree of interindividual variation in metabolism. Comparison of metabolite recoveries in urine indicated a positive correlation between activation and inactivation routes of metabolism. Prior exposure to ifosfamide was associated with a higher recovery in urine of dechloroethylated metabolites. The severity of hematological toxicity was inversely correlated with glomerular filtration rate but not to parameters of ifosfamide metabolism. There was marked variation in levels of the carboxy metabolite, which could not be detected in the plasma of 5 subjects. However, evidence for a polymorphism in metabolism to this metabolite was weaker than that seen with the isomeric oxazaphosphorine cyclophosphamide. There appeared to be a higher clearance of ifosfamide in pediatric patients compared to adults. The significance of this, and of the variation in metabolism of ifosfamide, for clinical outcome remains to be established, but the increase in the dechloroethylase route of metabolism may be associated with an increased risk of toxicity.

INTRODUCTION

The alkylating agent ifosfamide was introduced into clinical trials in 1970, but its early use was limited by severe hemorrhagic cystitis. Further research led to the development of Mesna as a safe and effective means of regional uroprotection (1). Following this discovery, phase II studies in children demonstrated activity against a wide range of tumor types (2–4). Ifosfamide is presently included in combination chemotherapy for several tumors, including Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, and other soft tissue sarcomas. Adverse effects of ifosfamide include myelosuppression, nausea and vomiting, alopecia, and urotoxicity (5, 6). Urotoxicity is minimal when Mesna is administered concurrently with ifosfamide. Encephalopathy is a serious consequence of therapy but is seen much more frequently in adults than in children (7, 8). The major chronic toxicity in pediatric patients treated with ifosfamide is nephrotoxicity, leading to rickets and growth retardation due to renal tubular acido-sis (9, 10). These side effects are unpredictable and are often severe enough to restrict treatment. Moreover, just as host toxicity varies among individuals, some tumors are chemosensitive and curable, whereas others remain resistant or recur following an initial response.

Ifosfamide itself possesses little cytotoxic effect. It is a prodrug which is metabolised in vivo to produce a variety of therapeutically active and potentially toxic metabolites (11, 12). Thus, for a given individual, variation in metabolism between host and tumor tissue may result in variability in toxicity and in differences in chemosen-sitivity of the tumor. The initial activation reaction in the metabolism of ifosfamide is thought to be mediated by a hepatic cytochrome P450 enzyme (Fig. 1) (13, 14). Hydroxylation at the carbon-4 position of the oxazaphosphorine ring produces 4-hydroxyifosfamide, which exists in equilibrium with its tautomeric form, aldo-ifosfamide. The latter form may then either be oxidized by an ALDH<sup>2</sup> enzyme (15, 16) to CX (an inactive metabolite) or spontaneously decompose to form IPM. The mustard is thought to be the primary alkylating agent (17). Acrrolein is formed as a by-product of the latter reaction and is be-lieved to be responsible for the urotoxic effects of ifosfamide. Up to 50% of a dose of ifosfamide undergoes a separate oxidative N-dealkylation reaction, resulting in the loss of one or other of the chloroethyl side chains to produce either 2-DCI or 3-DCI (18–20). An equimolar quantity of chloroacetalddehyde is formed in each of these reactions, and this toxic metabolite has been implicated in the neurotoxicity which may accompany ifosfamide therapy (21) and may also be associated with nephrotoxicity (10). Other inactive metabolites include KETO, which is thought to result from oxidation of 4-hydroxy-ifosfamide (11).

Large interpatient differences in ifosfamide metabolism have been reported in adults (12), including wide variation in CX excretion. Studies of the urinary metabolites of cyclophosphamide, an isomer of ifosfamide, indicate that certain individuals may be totally deficient in the excretion of the corresponding metabolite (22, 23). It has been suggested that this may be the result of phenotypic variation in ALDH activity, which would be expected to apply equally to ifosfamide metabolism, assuming that both oxazaphosphorines are metabolized by the same ALDH enzyme. Patients with low levels of ALDH activity may deactivate ifosfamide less efficiently and may be at increased risk of toxicity, possibly accompanied by apparently greater tumor sensitivity. Conversely, tumor inactivation of ifosfamide by ALDH may result in chemoresistance.

Similarly, the activation of cyclophosphamide and of ifosfamide may be subject to great interindividual variability (23, 24). The human cytochrome P450 enzymes responsible for the initial hydroxylation reaction and inactivating dechloroethylation reactions remain uncertain. Environmental and genetic factors lead to large interindividual differences in activities of various members of the P450 superfamilies, which would, in turn, have an influence on the balance of activation and inactivation of a dose of ifosfamide in an individual.

Early studies of ifosfamide demonstrated that fractionated dosing of ifosfamide produced better therapeutic activity and was better toler-
We studied the pharmacokinetics and metabolism of ifosfamide administered as a continuous infusion over 72 h. As yet, the metabolism of ifosfamide and the rationale of fractionated dosing in lower doses administered over 3-5 days, but at present the optimum dosage schedule remains uncertain. To investigate the variation in metabolism arc unknown and are not the major focus of this investigation.

Materials and Methods

Ifosfamide and its metabolites were obtained from Asta Medica (Frankfurt, Germany). Cyclophosphamide and NBP were purchased from Sigma (Poole, United Kingdom). All other reagents were of appropriate analytical grade.

Sixteen patients (5 girls) were being treated with ifosfamide regimens for sarcomas. Ages ranged from 1-17 years (median, 4 years). Patients received successive doses of ifosfamide every 3 weeks as a continuous infusion (Gemini PC-2 volumetric infusion pump; Imed. San Diego, CA) at a dose of 3 g/m² each day for 3 days (14 patients) or 2 days (2 patients). This was accompanied by 3 liters/m² of hydration each day and Mesna (3 g/m²/day), infused during and for 12 h after ifosfamide administration. Other chemotherapy is listed in Table 1. Antiemetics (ondansetron, metoclopramide, or dexamethasone) and prophylactic antibiotics (cotrimoxazole) were also administered. For each patient, clinical status, renal function (GFR by EDTA clearance or estimated from plasma creatinine), liver function (alanine transaminase, bilirubin, and albumin), and hematological toxicity were monitored throughout the treatment period. Thirteen patients are disease free at 6-26 (median, 12 months) following diagnosis. Ten have completed therapy. Two patients relapsed at 21 months, and one child died from overwhelming infection during therapy. The study was approved by the Ethical Committees of the Medical School of the University of Newcastle upon Tyne and the Royal Victoria Infirmary, Newcastle.

Blood samples (3-5 ml depending on the size of the child) were collected immediately before, at 1, 2, 4, 6, 12, 18, and 24 h after the start of the infusion, at the end of the infusion, and at 25°C prior to analysis. Urine was collected at 6-h intervals throughout the infusion and for 24 h after. Each passage of urine was stored at 5°C until the end of the collection period. The volume of each urine collection was measured, and an aliquot was frozen at -20°C for subsequent analysis.

Concentrations of ifosfamide, isophosphoramide mustard, carboxyifosfamide, 2- and 3-dechlorocthylifosfamide, and 4-ketoifosfamide were determined in urine and plasma using a quantitative thin-layer chromatography-photography densitometry technique (27). Briefly, 1 ml of each urine sample and 50 µl of internal standard (500 µg/ml cyclophosphamide in methanol) was applied to an XAD-2 Sp-Ed solid phase extraction cartridge (500 mg/3 ml; Laboratory Impex Ltd., Teddington, United Kingdom). The cartridge was washed with 3 ml water and dried. Drug and metabolites were eluted with methanol, which was evaporated to dryness.

Plasma (750 µl) was added to 750 µl cold acetonitrile and 50 µl internal standard. After vortex mixing and centrifugation, the clear supernatant was evaporated to dryness.

Dry residues from the above procedures were reconstituted in methanol (70 µl), and 30 µl were applied to silica gel TLC plates (E. Merck, Darmstadt, Germany). Cyclophosphamide and NBP were purchased from Sigma (Poole, United Kingdom). All other reagents were of appropriate analytical grade.

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Comparisons among patient groups were made using the Mann-Whitney U test. Correlations of pharmacokinetic, metabolite, and patient variables were analyzed using normal linear regression or Spearman's rank correlation where appropriate.

RESULTS

Ifosfamide and up to five of its metabolites could be detected in plasma and urine from all subjects. Typical plasma concentration and urine excretion profiles are shown in Figs. 2 and 3. The concentration of ifosfamide in plasma reached an apparent steady state after 24 h but subsequently declined throughout the administration period despite a constant rate of infusion. This indicates that the clearance is increasing during the infusion, and the CI value calculated as the ratio of the dose to the total AUC is a measure of the average CI during and after the infusion period. Thus, the $t_{1/2}$ value determined from the exponential decline of the postinfusion plasma concentrations reflects the higher CI after 3 days of drug administration. Similarly, $V_p$ calculated from the average CI and the reduced $t_{1/2}$ is likely to be an underestimate of the true volume of distribution. Plasma concentrations of parent drug decreased rapidly after the end of the infusion, but measurable concentrations of IPM, CX, and dechloroethylated metabolites persisted beyond the time when ifosfamide could be detected. In some patients, the concentration of dechloroethylated metabolites continued to increase long after ifosfamide concentrations reached a maximum and started to decline. Plasma concentrations of parent drug decreased in all patients, with a median decrease of 37% (range, 19–76%), while concentrations of dechloroethylated metabolites increased by a median of 64% (range, 7–390%). This was not accompanied by a significant increase in recovery of dechloroethylation metabolites in urine, although some patients did show an increase (Fig. 3), or by a consistent change in plasma or urine concentrations of CX or IPM (data not shown).

Pharmacokinetic parameters for ifosfamide are given in Table 2. It should be remembered that these parameter values were estimated subject to the caveats resulting from time-dependent clearance. If not
corrected for body size, clearance, $V_p$, and $f_a$, all increased with increasing age, body surface area, and weight ($P < 0.05$). Therefore, $Cl$ was corrected for body surface area, and $V_p$ was corrected for weight (28). Half-life and clearance increased in the same direction compared to body size due to a greater increase in $V_p$ and the difference between the time-averaged $Cl$ calculated and the higher clearance when the half-life was estimated. There was no significant correlation of pharmacokinetic parameters with course, dose, GFR, or other patient parameters, including concomitant medication. Renal clearance was a relatively minor pathway for elimination of ifosfamide, represented by between 11.6 and 24.0% of GFR, and did not change during the study period.

Fig. 4 is a stacked bar graph of plasma AUCs for ifosfamide and its metabolites in the 16 subjects studied. Exact values are given in Table 3. Recoveries of ifosfamide and metabolites are shown in Fig. 5 and Table 4. Because of the young age of this patient group, reliable urine collection was possible in only 10 of the 16 subjects. The major metabolites in plasma were IPM or 3-DCI. KETO was detectable in the plasma of only 3 patients and represented only a small percentage of the dose recovered in urine (median, 0.60% of dose). Carboxyifosfamide concentrations in plasma varied greatly among individuals. In 5 subjects, this metabolite was undetectable in plasma (patients 4, 7, 10, and 16) or present only at very low concentrations (patient 12). However, it was detectable in the urine in the 2 of these 5 from whom urine was available (patient 4, 1.95%; patient 7, 12.67% of dose).

There was no association between the AUCs of the metabolites and patient variables, other than that boys had higher AUC values for the CX metabolite than did girls ($P = 0.037$). There were no correlations among the AUCs of parent drug and the individual metabolites. In the urine, there was a positive correlation between the recovery of the active metabolite IPM and the dechloroethylated products of the com-
which have been made to be resistant to oxazaphosphorines have been associated with the neurotoxicity which sometimes accompanies administration. In addition to complications due to multiple drug therapy, the metabolism of these drugs are far from clear. Likewise, the role of ALDH (30). The clinical implications of interindividual variation in toxicity of oxazaphosphorines has been associated with distribution of tumor resistance (11, 29-31). While host metabolism is probably the most important determinant of tumor response, metabolism by the tumor itself may be important in some instances. Thus, it has been proposed that variation in the initial activation of ifosfamide and cyclophosphamide may underlie interindividual variation in tumor response (11). The generation of chloroacetaldehyde has been associated with the toxic metabolite chloroacetaldehyde. Although some individuals have been reported to be deficient in the excretion of the carboxy metabolite of cyclophosphamide (22, 23), a similar deficiency has not been found in studies with ifosfamide (12). In the present study, the variability in AUC of CX (0-0.97 mM/h) was greater than that for the other metabolites including IPM (0.24-3.78 mM/h). In 5 subjects, CX was undetectable or present at negligible concentrations in plasma. This suggests that these individuals are not able to form this metabolite systematically, an observation similar to that found in studies with the carboxy metabolite of cyclophosphamide in urine (22, 23). However, in 2 of these 5 patients, analysis of urine samples showed that CX accounted for an appreciable fraction of the dose administered. It is possible that CX is formed from aloidosfamide in the kidney and excreted without returning to the systemic circulation or is present in plasma at concentrations below the limit of detection of the assay. Thus, patients may be deficient in the ALDH enzyme needed to inactivate the activated oxazaphosphorines. The complex metabolism of the oxazaphosphorines has led to interest in the influence of activation and inactivation pathways on the efficacy and toxicity of these drugs and on the phenomenon of tumor resistance (11, 29-31). While host metabolism is probably the most important determinant of tumor response, metabolism by the tumor itself may be important in some instances. Thus, it has been proposed that variation in the initial activation of ifosfamide and cyclophosphamide may underlie interindividual variation in tumor response (11). The generation of chloroacetaldehyde has been associated with the toxic metabolite chloroacetaldehyde. Although some individuals have been reported to be deficient in the excretion of the carboxy metabolite of cyclophosphamide (22, 23), a similar deficiency has not been found in studies with ifosfamide (12). In the present study, the variability in AUC of CX (0-0.97 mM/h) was greater than that for the other metabolites including IPM (0.24-3.78 mM/h). In 5 subjects, CX was undetectable or present at negligible concentrations in plasma. This suggests that these individuals are not able to form this metabolite systematically, an observation similar to that found in studies with the carboxy metabolite of cyclophosphamide in urine (22, 23). However, in 2 of these 5 patients, analysis of urine samples showed that CX accounted for an appreciable fraction of the dose administered. It is possible that CX is formed from aloidosfamide in the kidney and excreted without returning to the systemic circulation or is present in plasma at concentrations below the limit of detection of the assay. Thus, patients may be deficient in the ALDH enzyme needed to inactivate the activated oxazaphosphorine intermediates systemically but still possess ALDH activity in

- **DISCUSSION**

The complex metabolism of the oxazaphosphorines has led to interest in the influence of activation and inactivation pathways on the efficacy and toxicity of these drugs and on the phenomenon of tumor resistance (11, 29-31). While host metabolism is probably the most important determinant of tumor response, metabolism by the tumor itself may be important in some instances. Thus, it has been proposed that variation in the initial activation of ifosfamide and cyclophosphamide may underlie interindividual variation in tumor response (11). The generation of chloroacetaldehyde has been associated with the toxic metabolite chloroacetaldehyde. Although some individuals have been reported to be deficient in the excretion of the carboxy metabolite of cyclophosphamide (22, 23), a similar deficiency has not been found in studies with ifosfamide (12). In the present study, the variability in AUC of CX (0-0.97 mM/h) was greater than that for the other metabolites including IPM (0.24-3.78 mM/h). In 5 subjects, CX was undetectable or present at negligible concentrations in plasma. This suggests that these individuals are not able to form this metabolite systematically, an observation similar to that found in studies with the carboxy metabolite of cyclophosphamide in urine (22, 23). However, in 2 of these 5 patients, analysis of urine samples showed that CX accounted for an appreciable fraction of the dose administered. It is possible that CX is formed from aloidosfamide in the kidney and excreted without returning to the systemic circulation or is present in plasma at concentrations below the limit of detection of the assay. Thus, patients may be deficient in the ALDH enzyme needed to inactivate the activated oxazaphosphorine intermediates systemically but still possess ALDH activity in

- **Table 3**

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<th>2-DCI</th>
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Median: 7.54, Range: 4.13-15.35. AUCs for have been multiplied by 1.5 to standardize for 3 days of administration.

- **Fig. 5.** Total recovery of ifosfamide and its metabolites in urine.
Although the ultimate alkylating species is thought to be IPM, release of phosphoramid mustard from 4-hydroxycyclophosphamide to the kidney. A positive correlation of IPM recovery with albumin levels is interesting, given a report that this plasma protein can catalyze the release of phosphoramid mustard from 4-hydroxycyclophosphamide (42). Although the ultimate alkylating species is thought to be IPM, it has been suggested that this is not active unless formed intracellularly and that circulating concentrations of 4-hydroxyifosfamide/aldoifosfamide are the most likely predictors of pharmacological effect (24). Thus, measurement of IPM in plasma may not be the most useful predictor of pharmacological response.

This study was not designed to investigate systematically the relationship between therapeutic outcome and ifosfamide pharmacokinetics and metabolism, which will be confounded by the effects of other chemotherapeutic agents. The correlation of platelet nadir and GFR may reflect the ability to eliminate toxic metabolites from the body or the toxic effect of etoposide, which depends on renal function. Renal function has previously been shown to be an important risk factor for the development of both central nervous system (43) and renal (9, 44) toxicity with ifosfamide.

Comparison of pharmacokinetic parameters derived from the present study and those previously reported is complicated by differences in patient populations and administration protocols. Very few studies have been performed on children. Ninane et al. (45) examined the pharmacokinetics of ifosfamide following the administration 3 g/m² on 2 consecutive days in a group of patients similar to ours. However, the analytical method used in that paper is very questionable, i.e., alkylating activity was converted directly to ifosfamide concentrations in plasma and urine. Boos et al. (19) examined the excretion of the enantiomers of ifosfamide and its dechloroethylated metabolites in urine in a group of slightly older children. Their results are consistent with ours, 3-DCI representing the major dechloroethylated metabolite and the total recovery of unchanged drug, 2- and 3-DCI being approximately 40%. Comparison with other reports of the pharmacokinetics of ifosfamide in other patient groups is difficult because of the autoinduction seen after 3 days of continuous administration. Lind et al. (39) found that the half-life of ifosfamide in adults ranged from 2.4-5.0 h after 3 consecutive days of 1.5 g/m²/day administered as a short infusion. These authors saw an increase in Cl by the current techniques remains a possibility, but studies using radiolabeled material and 31P-nuclear magnetic resonance have failed to account for a significantly greater fraction of the administered dose (11, 20). Other alternatives are conjugation of parent drug or reactive metabolites to Mesna or endogenous species, such as glutathione, possibly followed by biliary excretion and removal in the feces. In a study with radiolabeled cyclophosphamide, only 6.5% of the dose was recovered as total radioactivity in bile (46).

In conclusion, we have examined the pharmacokinetics and metabolism of ifosfamide in a pediatric population. Although the dose and mode of administration was constant, there was marked interindividual variability in the pharmacokinetics of the parent drug, dependent on age and previous exposure to ifosfamide, even with a 3-week break between courses. Metabolism also showed a wide degree of interindividual variation, with some patients apparently unable to form the inactive carboxy metabolite systemically. Clearance of ifosfamide increased during continuous administration, with an apparent increase in dechloroethylated metabolites. The clinical significance of this is not yet known. The long-term influence of ifosfamide metabolism on tumor response and toxicity in these patients continues to be monitored.

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REFERENCES


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