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 dechloroethylation 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 Ewings 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 associated with nephrotoxicity (10). Other inactive metabolites include KETO, which is thought to result from oxidation of 4-hydroxyifosfamide (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 superfamily, 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 tolerated 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 chemosensitivity 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 ALDH2 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). Acrolein is formed as a by-product of the latter reaction and is believed 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 chloroacetaldehyde 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-hydroxyifosfamide (11).

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3 The abbreviations used are: ALDH, aldehyde dehydrogenase; IPM, isophosphoramide mustard; CX, carboxyifosfamide; DCI, dechloroethylifosfamide; KETO, 4-ketofosfamide; CI, clearance; TLC, thin-layer chromatography; AUC, area under the plasma concentration-time curve; NBP, 4-nitrobenzylpyridine; GFR, glomerular filtration rate; Vp, volume of distribution; IFO, ifosfamide.
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) follow-up.

Blood samples (3-5 ml depending on the size of the child) were collected immediately before, at 3, 6, 12, 18, 24, 36, 48, and 60 h after the start of the infusion, at the end of the infusion, and at 1, 2, 4, 6, 12, 18, and 24 h after the end of the infusion. Blood was anticoagulated with EDTA, and plasma was separated and frozen immediately at −20°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-dechloroethylifosfamide, and 4-ketoifosfamide were determined in urine and plasma using a quantitative thin-layer chromatography-photo 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 SpE 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) which had been preeluted with methanol and dried at 150°C for 10 min. An automated, Linomat IV, TLC sample applicator was used (CAMAG, Berne, Switzerland). Chromatography was performed in glass TLC tanks, saturated with solvent. The mobile phase was dichloromethane-dimethylformamide-glacial acetic acid (90:8.1, v/v/v), which was allowed to rise to a height of at least 9.5 cm. After the plates were dried, they were run again in a second mobile phase of chloroform-methanol-glacial acetic acid (90:60:1) to a height of 2 cm. The plates were dried again and sprayed for at least 10 s with 5% NBP in acetone-0.2 M acetate buffer, pH 4.6 (8:2, v/v), dried, and then resprayed for 10 s. Plates were heated in an oven at 150°C for 10 min and left to cool.

Plates were dipped in 3% methanolic potassium hydroxide to reveal the blue spots formed from alkylated NBP. The plates were photographed within 10 s of dipping because of the unstable nature of the chromophore. To ensure uniform exposure and printing, a Kodak standard gray scale was photographed with each plate. The negative was enlarged to the exact size of the original plate. Uniform exposure was ensured by comparison of the Kodak gray scale with the original.

The photographs of the plates were scanned with a CAMAG Scanner II densitometer using the program CATS3 (CAMAG) to integrate the areas under the chromatogram peaks. The peak areas for ifosfamide and metabolites were divided by the area under the internal standard (cyclophosphamide) peak, and the peak area ratio was used for calibration. Each plate contained samples and at least 6 tracks derived from spiked urine or plasma containing known concentrations of authentic standards (2–50 μg/ml). Calibration curves were obtained for ifosfamide and each of the metabolites and used to determine the concentrations in patient urine and plasma samples.

A noncompartmental approach was used to estimate CI from concentrations of ifosfamide in plasma. A monoeexponential equation was fitted to the postinfusion data to estimate τ0 and Vp for each subject. Exposure of each patient to ifosfamide and each of its metabolites was expressed as the area under the AUC for that species. Recoveries of ifosfamide and metabolites in urine were expressed as a percentage of the administered dose. Both AUC and percentage of dose were corrected for molecular weight, and a dose-correction factor of 3/2 was used for those patients treated for only 2 days. Renal clearance of ifosfamide was determined from the product of CI, the fraction of the dose recovered unchanged in the urine, and from amount excreted in each collection interval divided by the corresponding AUC.

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

Iofosfamide 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 τ0 value determined from the exponential decline of the postinfusion plasma concentrations reflects the higher CI after 3 days of drug administration. Similarly, Vp calculated from the average CI and the reduced τ0 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 dechloroethylated 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 $\frac{Cl}{V}$ 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-

### Table 2: Pharmacokinetic parameters for ifosfamide administered as a continuous infusion over 3 days

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cl (liters/h/m²)</th>
<th>$V_p$ (liters/kg)</th>
<th>Half-life (h)</th>
<th>Renal clearance (liters/h/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.27</td>
<td>0.322</td>
<td>1.00</td>
<td>0.676</td>
</tr>
<tr>
<td>2</td>
<td>5.80</td>
<td>0.620</td>
<td>1.99</td>
<td>1.038</td>
</tr>
<tr>
<td>3</td>
<td>5.33</td>
<td>0.442</td>
<td>1.56</td>
<td>0.524</td>
</tr>
<tr>
<td>4</td>
<td>2.96</td>
<td>0.760</td>
<td>4.41</td>
<td>0.183</td>
</tr>
<tr>
<td>5</td>
<td>4.23</td>
<td>0.756</td>
<td>2.19</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4.90</td>
<td>0.401</td>
<td>1.29</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3.19</td>
<td>0.408</td>
<td>2.48</td>
<td>0.525</td>
</tr>
<tr>
<td>8</td>
<td>3.39</td>
<td>0.387</td>
<td>1.95</td>
<td>0.482</td>
</tr>
<tr>
<td>9</td>
<td>5.92</td>
<td>0.590</td>
<td>1.81</td>
<td>1.529</td>
</tr>
<tr>
<td>10</td>
<td>5.59</td>
<td>1.001</td>
<td>4.20</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>3.19</td>
<td>0.376</td>
<td>2.25</td>
<td>0.140</td>
</tr>
<tr>
<td>12</td>
<td>3.60</td>
<td>0.438</td>
<td>1.58</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>6.43</td>
<td>0.313</td>
<td>1.59</td>
<td>0.706</td>
</tr>
<tr>
<td>14</td>
<td>8.18</td>
<td>0.742</td>
<td>1.60</td>
<td>0.823</td>
</tr>
<tr>
<td>15</td>
<td>7.50</td>
<td>1.103</td>
<td>2.51</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>7.19</td>
<td>0.752</td>
<td>1.57</td>
<td></td>
</tr>
</tbody>
</table>

Means ± SD: 5.04 ± 1.66, 0.588 ± 0.236, 2.12 ± 0.92, 0.663 ± 0.386
TABLE 3 Areas under concentration-time curves (mM/h) of ifosfamide and metabolites in plasma following continuous administration over 3 days

<table>
<thead>
<tr>
<th>Patient</th>
<th>Ifosfamide</th>
<th>IPM</th>
<th>CX</th>
<th>3-DCI</th>
<th>2-DCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13.94</td>
<td>3.78</td>
<td>0.13</td>
<td>2.63</td>
<td>0.67</td>
</tr>
<tr>
<td>2</td>
<td>7.84</td>
<td>0.24</td>
<td>0.86</td>
<td>1.58</td>
<td>1.42</td>
</tr>
<tr>
<td>3</td>
<td>8.53</td>
<td>3.78</td>
<td>0.86</td>
<td>0.84</td>
<td>0.38</td>
</tr>
<tr>
<td>4</td>
<td>15.35</td>
<td>1.65</td>
<td>ND</td>
<td>2.17</td>
<td>1.65</td>
</tr>
<tr>
<td>5</td>
<td>7.16</td>
<td>1.16</td>
<td>0.67</td>
<td>2.94</td>
<td>0.90</td>
</tr>
<tr>
<td>6</td>
<td>9.26</td>
<td>1.66</td>
<td>0.97</td>
<td>4.08</td>
<td>1.70</td>
</tr>
<tr>
<td>7</td>
<td>14.26</td>
<td>2.27</td>
<td>ND</td>
<td>4.31</td>
<td>0.30</td>
</tr>
<tr>
<td>8</td>
<td>10.17</td>
<td>2.38</td>
<td>0.23</td>
<td>2.31</td>
<td>1.65</td>
</tr>
<tr>
<td>9</td>
<td>5.99</td>
<td>2.76</td>
<td>0.11</td>
<td>1.39</td>
<td>0.57</td>
</tr>
<tr>
<td>10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.19</td>
<td>1.37</td>
<td>ND</td>
<td>6.75</td>
<td>1.70</td>
</tr>
<tr>
<td>11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.87</td>
<td>3.08</td>
<td>0.30</td>
<td>2.93</td>
<td>0.82</td>
</tr>
<tr>
<td>12</td>
<td>9.63</td>
<td>0.54</td>
<td>0.01</td>
<td>1.94</td>
<td>0.39</td>
</tr>
<tr>
<td>13</td>
<td>6.36</td>
<td>1.76</td>
<td>0.67</td>
<td>1.62</td>
<td>0.19</td>
</tr>
<tr>
<td>14</td>
<td>5.00</td>
<td>1.79</td>
<td>0.90</td>
<td>2.84</td>
<td>0.19</td>
</tr>
<tr>
<td>15</td>
<td>5.45</td>
<td>1.98</td>
<td>0.31</td>
<td>3.25</td>
<td>0.19</td>
</tr>
<tr>
<td>16</td>
<td>4.76</td>
<td>0.79</td>
<td>ND</td>
<td>1.97</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Median 7.54, 1.78, 0.22, 2.24, 0.56
Range 4.13–15.35, 0.24–3.78, 0.00–0.97, 0.84–4.50, 0.19–1.70

<sup>a</sup> ND, not detectable.  
<sup>b</sup> AUCs for have been multiplied by 1.5 to standardize for 3 days of administration.

peting inactivation reaction ($P < 0.05$). Recovery of IPM also corre-
related positively with albumin levels ($P = 0.007$). The recovery of
dechloroethylated metabolites increased with the course of adminis-
tration ($P < 0.05$). These relationships observed in urine were not
matched by corresponding correlations among AUCs and treatment
course. Urinary recoveries were not related to renal function as de-
determined by GFR, although renal clearance of ifosfamide was pro-
portional to GFR ($r = 0.750$, $P = 0.013$). There was no correlation
between AUC and urine recovery values individually for ifosfamide
and each of the metabolites.

There was no correlation of measures of hematological or hepatic
toxicity with AUCs of ifosfamide or of its metabolites. Hematological
toxicity, assessed by World Health Organization grading, was in-
versely related to GFR ($P < 0.01$ for thrombocytopenia, $P < 0.05$ for
neutropenia). Patients experiencing more severe thrombocytopenia
(World Health Organization grade 2 and above) had a lower GFR than
those with no or mild toxicity ($106 ± 3$ versus $151 ± 32$ ml/min/1.7
m$^2$, $P = 0.013$). Hematological toxicity was not independently
correlated with any other patient variable.

**DISCUSSION**

The complex metabolism of the oxazaphosphorines has led to in-
tense 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 asso-
ciated with the neurotoxicity which sometimes accompanies admin-
istration of ifosfamide, but not cyclophosphamide (21). Cell lines
which have been made to be resistant to oxazaphosphorines have
increased ALDH activity (29, 31). Sensitivity can be restored by
addition of inhibitors of this enzyme (32–34), and selective tissue
metabolites including IFP in the plasma of patients treated with
ifosfamide (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
aldoifosfamide in the kidney and excreted without returning to the
plasma of some patients, and, although there was no significant
change in the renal excretion of this metabolite during the infusion,
dechloroethylated metabolites also tended to increase with increase in prior ifosfamide treatment. The decline in plasma concentra-
tion of these metabolites postinfusion did not indicate elimination
rate-limited kinetics (41). Under time-independent formation kinetics,
concentrations of the metabolites should change in parallel with those
of the parent drug. It appears that the decline in ifosfamide concentra-
tions during continuous infusion may be partially explained by an
increase in metabolism to dechloroethylated products. Thus, the
autoinduction of ifosfamide metabolism following continuous or re-
peated exposure may result in an increase in metabolism to inactive
dechloroethylated metabolites, presumably accompanied by an in-
crease in the formation of 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 ($0.97$ versus $3.78$)
was similar for the other metabolites including IPM ($0.24–3.78$)
m/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 cyclophospha-
mide 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
aldoifosfamide 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 of oxazaphos-
phorine intermediates systematically but still possess ALDH activity in

**Fig. 5. Total recovery of ifosfamide and its metabolites in urine.**

KETO  
2-DCI  
3-DCI  
CX  
IPM  
IFO
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 in adults receiving 2 g/m² over 72 h or 1 g/m² over 24 h. These authors reported a clearance of 85 ± 23 ml/min and a volume of distribution of 25.6 ± 13.1 liters. Again, correcting for body size, it would appear that clearance is greater in our pediatric study group.

Apart from the study by Boos et al. (19), there have been few studies of the recovery of ifosfamide and its metabolites in urine and none of a pediatric patient group. Allen et al. (13) reported recoveries of unchanged drug of 20–50%, which is consistent with our data. Lind et al. (12) reported much lower recoveries of the individual metabolites using a quantitative TLC method similar to that used in the present study. However, modifications to the chromatographic technique have allowed us to separate and more reliably quantify both the dechloroethylated metabolites and IPM. Unlike Lind et al., we saw no evidence for an increase in the excretion of dechloroethylated metabolites during continuous administration, although an increase in plasma concentrations of these metabolites occurred in some patients. This increase in dechloroethylated metabolites in plasma may explain in part the increase in ifosfamide elimination during continuous administration.

The ultimate fate of up to 70% of the dose of ifosfamide administered i.v. remains unknown. Metabolism to some species not detected 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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