Comparative Pharmacokinetics and Alkylating Activity of Fractionated Intravenous and Oral Ifosfamide in Patients with Bronchogenic Carcinoma

M. J. Lind, J. M. Margison, T. Cerny, N. Thatcher, and P. M. Wilkinson

CRC Department of Medical Oncology (M. J. L. T. C., N. T. J.) Department of Clinical Pharmacology (J. M. M., P. M. W. J.), Christie Hospital and Holt Radium Institute, Manchester, M20 9BX, United Kingdom

ABSTRACT

20 patients with advanced non-small cell lung cancer were treated with ifosfamide and mesna 1.5 g/m² daily for 5 days; 10 received the drug by mouth and 10 i.v. Both schedules resulted in a reduction in the elimination half-life with an increased total and nonrenal clearance of ifosfamide over the 5-day period. Oral administration resulted in an unacceptably high incidence of encephalopathy (5/10) which was not seen in the i.v. group. In two patients this encephalopathy manifested itself as coma which lasted for 24 to 48 h but was fully reversible and in the other three cases as somnolence occurring for more than 50% of the patients' waking hours. Nadir blood counts and response rates were similar in both arms. The encephalopathy suggests that there are metabolic differences between the i.v. and oral routes and that a metabolite rather than the parent drug is responsible for this syndrome. In addition it was shown that the total and nonrenal clearance of the drug was significantly less when the drug was administered orally.

None of the pharmacokinetic parameters either singly or in combination predicted for ifosfamide toxicity. No correlation between the creatinine clearance and ifosfamide renal clearance was demonstrated suggesting tubular reabsorption of the drug. In conclusion, ifosfamide cannot be given orally at the conventionally employed i.v. doses.

INTRODUCTION

Ifosfamide ([3-(2-chloroethyl)-2-(2-chloroethylamino)tetrahydro-2H-1,2,3 oxazaphosphorine oxide] (Mitoxana) is a structural isomer of the oxazaphosphorine cyclophosphamide, a widely used alkylating agent. It is a "prodrug" that requires biotransformation in order to become cytotoxic. This occurs mainly in the liver (1) by the action of a mixed function oxidase producing the active metabolites 4-hydroxyifosfamide (2) and isophosphoramide mustard (3). Ifosfamide is less myelosuppressive than cyclophosphamide (4) but is more urotoxic than cyclophosphamide (5). However, with the introduction of the uroprotector mesna (uromitexan) in 1982 (6), this toxicity is less pressing than cyclophosphamide (4) but is more urotoxic than cyclophosphamide (5). Ifosfamide is less myelosuppressive (4) but is more urotoxic than cyclophosphamide (5). However, with the introduction of the uroprotector mesna (uromitexan) in 1982 (6), this toxicity is less pressing than cyclophosphamide (4) but is more urotoxic than cyclophosphamide (5).

The uroprotector 2-mercaptoethane sodium (mesna) was given at a dose of 150 mg/m² i.v. in 24 h over 5 days. Cerny et al. (16) and Wagner et al. (17) have both shown in these studies Ifosfamide has been administered intravenously with mesna either as a 24-h infusion or fractionated over 3–5 days. Cerny et al. (16) and Wagner et al. (17) have both shown the bioavailability of orally administered ifosfamide to be close to 100%. However both authors found an unacceptably high level of central nervous system toxicity at conventionally employed doses. A study of patients with non-small cell lung cancer comparing fractionated doses of ifosfamide given either orally or i.v. over 5 days was planned to determine whether encephalopathy could be avoided by dividing the oral dose over several days. In addition a pharmacokinetic study was undertaken to ascertain if any pharmacokinetic parameter correlated with drug toxicity and to determine any differences in pharmacokinetic handling between the two routes of administration.

PATIENTS, MATERIALS, AND METHODS

Patients

20 patients with advanced histologically proven non-small cell lung cancer were treated with ifosfamide. Their median age was 59.5 years (range, 44–71 years) and all had pretreatment Karnofsky scores >50 and creatinine clearances of >50 ml/min.

The two regimens employed were as follows: (a) 10 patients received i.v. ifosfamide (Boehringer Ingelheim, Mitoxana) at a dose of 1.5 g/m²/day for 5 days. The dose was rounded down to the nearest 500 mg. Ifosfamide was given as a 30-min infusion in 250 ml normal saline. The uroprotector 2-mercaptoethane sodium (mesna) was given at a dose of 1.5 g/m²/day in 2 liters of normal saline as a 24-h infusion for 5 days. (b) 10 patients received oral ifosfamide (only available as 500-mg capsules) at a dose of 1.5 g/m²/day for 5 days 30–60 min before breakfast. The dosage was rounded up or down as outlined in a. Mesna was administered in a similar manner as outlined in a with a further 500 mg of oral mesna given every 6 h for four doses after the last i.v. mesna dose on Day 5.

Serial blood samples were collected at 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 6, 9, and 24 h postifosfamide administration on each of the 5 days in addition to 24-h urine samples. Blood samples were centrifuged immediately; the serum was separated off and stored at −20°C. Urine samples were also stored at −20°C.

Analytical Methods

Plasma, Urinary Ifosfamide and Urinary 4-Keto Ifosfamide Assay. These were determined using the high-performance liquid chromatographic method of Margison et al. (18).

Metabolite Alkylating Activity. Total alkylating activity was measured using a modification of the method of Friedman and Boger (19) in which the color developed by reaction with nitro-benzyl-pyridine was extracted into ether containing 5% triethylamine. Bischloroethylamine was used as a standard and values extrapolated from the standard curve were converted to µg/ml equivalents of nor nitrogen mustard. As ifosfamide reacts weakly with nitro-benzyl-pyridine a second standard curve was constructed containing ifosfamide at concentrations in the range found in serum. The contribution of ifosfamide to the total alkylating activity of the sample could therefore be determined and a value for the alkylating activity of ifosfamide metabolites could thus be assessed.

Kinetic Analysis. For patients receiving i.v. drug the serum concentration profile was fitted to a two compartment model using the noniterative computer programme MODFIT as described by McIntosh (20). The intercept and rate constants were used to calculate the half-lives (t½), area under the curve (AUC∞) and volumes of distribution (Vd).

Total body clearance was determined by the formula, Cltot = DI/AUC∞, where D is the dose administered. By measuring the 24-h urinary excretion of ifosfamide the renal clearance of the drug can be calculated from the formula, Clr = Xr/AUC∞, where Clr is the renal clearance and Xr is the amount excreted in the urine over 24 h. From Clr the nonrenal clearance of the drug could be derived from the formula, Clnon renal = Clr − Cltot, where Clnon renal is the nonrenal clearance.

For the oral data a linear regression analysis of the terminal phase was used to determine the half-life and rate constant. The area under the curve was calculated by the trapezoidal rule and extrapolated to infinity using the Nelson Wagner correction factor, i.e., AUC∞ = AUC24 + C0/K24, where AUC24 is the area under the curve for the first 24 h,
C_{24} is the concentration of drug at 24 h, and \( K_{elim} \) is the elimination rate constant.

The volume of distribution was calculated from the formula, \( V_{\text{poe}} = X/C_0 \), where \( V_{\text{poe}} \) is the volume of distribution, \( X \) is the dose and \( C_0 \) is the concentration at time 0 when the terminal phase is extrapolated back to zero. Total body clearance, renal clearance and nonrenal clearance were calculated as described for the i.v. data.

Statistical Methods. To determine any change with time of pharmacokinetic parameters, a Friedman two-way analysis of variance was used. To compare parameters between the i.v. and oral groups a Mann-Whitney test was used. To examine any correlations between pharmacokinetic parameters and toxicity Kendall correlation tests were used.

RESULTS

Ifosfamide Pharmacokinetics

The pharmacokinetic parameters for the i.v. group are summarized in Table 1 and shown graphically in Fig. 1. The values are expressed as medians and ranges. The terminal elimination half-life declined from a median of 6.163 (range, 3.894–8.154) hours on Day 1 to 3.762 (range, 2.655–4.780) hours on Day 5 (\( P = 0.018 \) Friedman). The total clearance of parent drug increased from a median of 69.185 (range, 60.877–80.500) ml/min on Day 1 to 123.185 (range, 102.15–181.69) ml/min on Day 5 (\( P = 0.001 \) Friedman) and was associated with an increase in the nonrenal clearance from 46.554 (range, 34.959–53.308) ml/min on Day 1 to 85.833 (range, 69.166–109.833 ml/min on Day 5 (\( P = 0.024 \)). This was associated with an increase in the renal clearance of ifosfamide or the percentage urinary excretion of drug per 24-h period over the 5 days. In addition the area under the serum concentration time curve fell from 574.8 (range, 284.000–821.400) to 346.33 (range, 200.425–407.800) \( \mu \)g/ml (\( P = 0.001 \) Friedman).

Following oral administration of the drug, peak ifosfamide levels were reached between 1 and 2 h postadministration (see Fig. 2). The median elimination half-life declined from 5.775 (range, 4.620–6.93) h on Day 1 to 3.46 (range, 2.230–4.330) h on Day 5 (\( P = 0.031 \) Friedman). The total clearance increased from 51.334 (range, 39.000–69.600) ml/min on Day 1 to 85.833 (range, 69.166–109.833 ml/min on Day 5 (\( P = 0.024 \)). This was associated with an increase in the nonrenal clearance from 46.554 (range, 34.959–53.308) ml/min on Day 1 to 67.881 (range, 57.520–79.323) ml/min on Day 5 (\( P = 0.02 \) Friedman). However there was no significant increase in the renal clearance of ifosfamide or the percentage urinary excretion of drug from Day 1 to 5. In addition the area under the serum concentration time curve fell from 860.651 (range, 529.147–1105.535) \( \mu \)g/ml on Day 1 to 382.620 (range, 323.885–471.871) \( \mu \)g/ml on Day 5 (\( P = 0.008 \) Friedman).

Comparing the pharmacokinetic parameters between i.v. and oral administration in Tables 1 and 2 there was no significant difference on any one day between elimination half-life, area under the curve, and renal clearance, with respect to route of administration. However the total clearance and nonrenal clearance were significantly less on any one day when the drug was administered orally (\( P < 0.05 \) Mann-Whitney). In addition \( V_{\text{deto}} \) was significantly less than \( V_{\text{deto}} \) (\( P < 0.05 \) Mann-Whitney) on any one day.

Despite the wide variability in pharmacokinetic parameters there was no correlation between any such parameter and the development of hematological (measured as the nadir absolute white blood count or percentage change in white blood cell count) or CNS toxicity.

Metabolite Alkylating Levels and Excretion of 4-Ketofosfamide

These results are summarized in Tables 3 and 4 and graphically in Figs. 3 and 4.

i.v.. In those patients receiving the drug i.v. there was an increase in the area under the metabolite alkylating curve on successive days of administration but this did not reach statistical significance. However, the peak metabolite alkylating activity rose from 7.96 (range, 5.600–17.700) (\mu g equivalents of normitrogen mustard/ml) on Day 1 to 14.05 (range, 7.880–24.660) on Day 5 (\( P = 0.005 \) Friedman). In addition there was a significant increase in the 24-h urinary excretion of 4-ketoifosfamide from 0.064 (range, 0–0.32) (percentage of parent drug administered) on Day 1 to 0.32 (range, 0.15–0.72) on Day 5 (\( P = 0.001 \) Friedman).

Oral. In patients receiving the drug orally the peak metabolite alkylating levels and area under the metabolite alkylating curve increased over the 5 days. However the difference was not statistically significant. Likewise urinary levels of 4-ketoifosfamide increased over this period of time but was not statistically significantly.

Oral Versus i.v.. There was no statistical significant difference in metabolite alkylating levels between oral and i.v. administration.

Wide variability in the serum concentration of alkylating metabolites was seen; some patients produced virtually no such metabolites in the serum on certain days and others very high.

Table 1 Pharmacokinetic parameters in 10 patients with non-small cell lung cancer receiving 1.5 g/m2 of i.v. ifosfamide per day, Days 1–5

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1</th>
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<th>5</th>
<th>( P  )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_{\beta} (h) )^a</td>
<td>6.163</td>
<td>4.620</td>
<td>4.330</td>
<td>4.318</td>
<td>3.762</td>
<td>0.018</td>
</tr>
<tr>
<td>( CL_{\text{m}} (ml/min)^b )</td>
<td>(3.894–8.154)</td>
<td>(3.640–7.790)</td>
<td>(2.390–4.950)</td>
<td>(3.300–4.620)</td>
<td>(2.655–4.780)</td>
<td>(0.0001)</td>
</tr>
<tr>
<td>( CL_{\text{i}} (ml/min)^c )</td>
<td>69.185</td>
<td>82.139</td>
<td>94.003</td>
<td>112.820</td>
<td>123.185</td>
<td></td>
</tr>
<tr>
<td>( CL_{\text{f}} (ml/min)^d )</td>
<td>(64.600–112.300)</td>
<td>(85.300–143.999)</td>
<td>(81.8300–147.900)</td>
<td>(102.150–181.690)</td>
<td>(60.870–80.500)</td>
<td>(0.001)</td>
</tr>
<tr>
<td>( AUC_{\text{f}} (\mu g/ml)^f )</td>
<td>574.800</td>
<td>488.251</td>
<td>385.668</td>
<td>346.330</td>
<td>284.036</td>
<td>(0.0001)</td>
</tr>
<tr>
<td>( V_{\text{deto}} (litres)^f )</td>
<td>(284.000–821.400)</td>
<td>(334.082–724.899)</td>
<td>(238.250–555.203)</td>
<td>(227.082–468.600)</td>
<td>(200.425–407.800)</td>
<td>(0.0001)</td>
</tr>
</tbody>
</table>

\(^a\) \( T_{\beta} \) terminal elimination half-life.  
\(^b\) \( CL_{\text{m}} \) total body clearance.  
\(^c\) \( CL_{\text{r}} \) renal clearance.  
\(^d\) \( CL_{\text{f}} \) nonrenal clearance.  
\(^e\) \( AUC_{\text{f}} \) area under the curve.  
\(^f\) \( V_{\text{deto}} \) volume of distribution.
FRACTIONATED i.v. AND ORAL IFOSFAMIDE

Fig. 1. Mean ifosfamide levels in patients receiving i.v. ifosfamide (1.5 g/m²) Days 1–5.

Fig. 2. Mean ifosfamide levels in patients receiving oral ifosfamide (1.5 g/m²) Days 1–5.

levels. However there was no correlation between metabolite alkylating activity and hematological or neurological toxicity.

Clinical Data

Toxicity. The median nadir WBC (measured at 10 days after the start of chemotherapy) experienced in the i.v. group was 3.8 × 10⁹/liter and that in the oral group 5.45 × 10⁹/liter (P > 0.05 Student’s t test).

Five of the patients in the oral arm experienced CNS toxicity > WHO Grade III (20) requiring early termination of their treatment course as opposed to none of the patients in the i.v. arm (0.01 < P < 0.02, chi-squared). Two of these patients in the oral arm became comatosed for 24-48 h but recovered completely without any neurological sequelae. Mild degrees of encephalopathy, consisting mainly of somnolence (<50% of waking hours), were seen in the i.v. arm of the study. Nausea and vomiting were mild and identical in both arms.

Tumor Response. A total of eight partial responses were seen; four occurring in each arm.

Table 2 Pharmacokinetic parameters in 10 patients with non-small cell lung cancer receiving 1.5 g/m² of oral ifosfamide per day, Days 1–5

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1</th>
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<th>3</th>
<th>4</th>
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<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;w&lt;/sub&gt; (h)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.775</td>
<td>3.745</td>
<td>3.850</td>
<td>3.460</td>
<td>3.460</td>
<td>0.031</td>
</tr>
<tr>
<td>Cl&lt;sub&gt;renal&lt;/sub&gt; (ml/min)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>51.334</td>
<td>63.167</td>
<td>66.666</td>
<td>70.833</td>
<td>85.833</td>
<td>0.024</td>
</tr>
<tr>
<td>Cl&lt;sub&gt;nonrenal&lt;/sub&gt; (ml/min)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>(39.000–49.660)</td>
<td>(39.833–88.333)</td>
<td>(37.166–121.500)</td>
<td>(54.000–127.333)</td>
<td>(69.166–109.833)</td>
<td></td>
</tr>
<tr>
<td>Cl&lt;sub&gt;total&lt;/sub&gt; (ml/min)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>7.829</td>
<td>6.610</td>
<td>12.153</td>
<td>12.500</td>
<td>16.705</td>
<td>0.150</td>
</tr>
<tr>
<td>Cl&lt;sub&gt;renal&lt;/sub&gt; (ml/min)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>(0.058–16.358)</td>
<td>(3.480–16.348)</td>
<td>(3.480–27.659)</td>
<td>(0.000–34.488)</td>
<td>(0.000–21.930)</td>
<td></td>
</tr>
<tr>
<td>Cl&lt;sub&gt;nonrenal&lt;/sub&gt; (ml/min)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>46.554</td>
<td>60.860</td>
<td>57.420</td>
<td>70.138</td>
<td>67.881</td>
<td>0.020</td>
</tr>
<tr>
<td>Cl&lt;sub&gt;total&lt;/sub&gt; (ml/min)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>(34.959–53.308)</td>
<td>(51.823–76.727)</td>
<td>(29.553–93.841)</td>
<td>(44.166–93.149)</td>
<td>(57.520–79.323)</td>
<td>0.008</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;b&lt;/sub&gt; (µg/ml)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>680.651</td>
<td>525.321</td>
<td>464.482</td>
<td>441.016</td>
<td>382.620</td>
<td></td>
</tr>
<tr>
<td>V&lt;sub&gt;d&lt;/sub&gt; (liters)&lt;sup&gt;j&lt;/sup&gt;</td>
<td>(529.147–1105.535)</td>
<td>(422.230–732.915)</td>
<td>(269.830–563.522)</td>
<td>(291.270–552.000)</td>
<td>(323.885–471.875)</td>
<td>0.910</td>
</tr>
</tbody>
</table>

 Values are medians and ranges.

<sup>a</sup> Median of nine patients.
<sup>b</sup> Median of six patients.
<sup>c</sup> T<sub>w</sub>, terminal elimination half-life.
<sup>d</sup> Cl<sub>tot</sub>, total body clearance.
<sup>e</sup> Cl<sub>renal</sub>, renal clearance.
<sup>f</sup> Cl<sub>nonrenal</sub>, nonrenal clearance.
<sup>g</sup> AUC<sub>b</sub>, area under the curve.
<sup>h</sup> V<sub>d</sub>, volume of distribution.

DISCUSSION

Our initial values for the terminal half-life, clearance, and volume of distribution in the i.v. group compare well with those of other investigators (21–23). The results presented here indicate that fractionation of either an i.v. or orally administered dose of ifosfamide over 5 days results in increased nonrenal and total clearance of the parent drug. This was associated with a decrease in the elimination half-life, and an increase in the peak metabolite alkylating activity, the AUC of the metabolite alkylating activity time curve, and production of 4-ketoifosfamide.

One possible explanation is that fractionation of the ifosfamide dosage leads to induction of those enzymes responsible for metabolism of the drug. Similar results have been obtained with fractionating cyclophosphamide administration (24). Further evidence for auto induction of cyclophosphamide metabolism comes from D’Incalci et al. (25) who compared the pharmacokinetics of the first and last courses of patients receiving cyclophosphamide continuously for 1 year and found the half-life to be shorter after continual exposure to the drug. In support of this theory Tchekmedjian et al. (26) have shown that the area under the alkylating activity time curve following a 5-day continuous infusion of cyclophosphamide was three times that expected when the same dose was given as a bolus.

More recently it has been shown that fractionating the dose of cyclophosphamide over 2 days leads to increased peak levels of the 4-hydroxy metabolite (27). Wagner (28) has also published data on the pharmacokinetic of i.v. ifosfamide dosage fractionated over a 2-day period and has shown a decrease in elimination half-life from 6.4 ± 2.4 h on Day 1 to 5.3 ± 2.8 h on Day 2. A reduction in ifosfamide half-life from 8.3 h to 6.3 h over a 3-day period has also been demonstrated (29). Our data show that a further reduction in the elimination half-life occurs with more prolonged administration of the drug.

This phenomenon of auto induction of metabolism may also explain why fractionation of ifosfamide dosage is associated with an improved therapeutic index (30, 31). Of particular interest was the high incidence and severity of CNS side-effects in patients receiving the drug by the oral route. A metabolite rather than the parent compound is likely to be responsible for this toxicity and imply with a first-pass effect is producing more active metabolites with the oral route. However, the near 100%
FRACTIONATED i.v. AND ORAL IFOSFAMIDE

Table 3 Metabolic parameters in 10 patients with non-small cell lung cancer receiving 1.5 g/m² of i.v. ifosfamide per day, Days 1-5

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tbody>
<tr>
<td>Metabolite AUC (µg/ml equivalents of nonnitrogen mustard)</td>
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<tr>
<td>132.595 (34.570-182.595)</td>
<td>135.845 (71.170-212.010)</td>
<td>130.570 (86.510-312.750)</td>
<td>120.790 (69.800-226.720)</td>
<td>166.555 (70.080-238.720)</td>
<td></td>
<td>0.095</td>
<td></td>
</tr>
<tr>
<td>Peak metabolite alkylating activity (µg/ml equivalents of nonnitrogen mustard)</td>
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<tr>
<td>7.960 (5.360-17.700)</td>
<td>10.800 (4.390-14.360)</td>
<td>8.845 (7.900-20.400)</td>
<td>9.590 (5.120-15.400)</td>
<td>14.050 (7.880-24.660)</td>
<td></td>
<td>0.005</td>
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<tr>
<td>4-Keto I (%)</td>
<td></td>
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<tr>
<td>0.064 (0.000-0.320)</td>
<td>0.222 (0.028-0.340)</td>
<td>0.217 (0.100-0.376)</td>
<td>0.233 (0.115-0.430)</td>
<td>0.320 (0.150-0.720)</td>
<td></td>
<td>0.0006</td>
<td></td>
</tr>
</tbody>
</table>

* Metabolite AUC, area under the metabolite alkylating activity time curve.
* 4-Keto I, the percentage of the administered dose excreted as 4-ketoifosfamide.

Table 4 Metabolic parameters in 10 patients with non-small cell lung cancer receiving 1.5 g/m² of oral ifosfamide per day, Days 1-5

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day</th>
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<tr>
<td>Metabolite AUC (µg/ml equivalents of nonnitrogen mustard)</td>
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<tr>
<td>63.735 (0.689-211.170)</td>
<td>90.085 (6.886-291.170)</td>
<td>124.315 (61.458-247.275)</td>
<td>182.207 (87.900-248.390)</td>
<td>90.489 (56.301-202.669)</td>
<td></td>
<td>0.275</td>
<td></td>
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<tr>
<td>Peak metabolite alkylating activity (µg/ml equivalents of nonnitrogen mustard)</td>
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<tr>
<td>4-Keto I (%)</td>
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<tr>
<td>0.158 (0.004-0.450)</td>
<td>0.165 (0.098-0.340)</td>
<td>0.240 (0.020-0.590)</td>
<td>0.280 (0.070-0.370)</td>
<td>0.250 (0.000-0.610)</td>
<td></td>
<td>0.355</td>
<td></td>
</tr>
</tbody>
</table>

* Median of nine patients.
* Median of six patients.
* Metabolite AUC, area under the metabolite alkylating activity time curve.
* 4-Keto I, percentage of the administered dose excreted as 4-ketoifosfamide.

Fig. 3. Mean metabolite alkylating levels in patients receiving i.v. ifosfamide (1.5 g/m²) Days 1-5.

Bioavailability demonstrated by other investigators fails to demonstrate any significant first-pass effect.

One explanation may be that rather than quantitative differences, there may be qualitative differences in the metabolism between the two routes of administration. Oral administration of cyclophosphamide results in a greater production of alkylating metabolites than i.v. administration supporting this theory.

Juma et al. (32) speculated that a different profile of metabolites was produced by oral administration. Others however have failed to show any significant difference in the levels of 4-hydroxy cyclophosphamide and phosphoramid mustard between oral and i.v. routes of administration (33). It is however important to realize that the metabolism of ifosfamide is not identical to that of cyclophosphamide. Dechloroethylation can account for up to 25% of the metabolism of ifosfamide, while this pathway is a very minor one for cyclophosphamide metabolism. In this context, dechloroethylation of ifosfamide resulting in the production of chloracetaldehyde has been suggested by Goren et al. (35) as a possible cause of the CNS toxicity and it may be that this pathway predominates in oral administration.

When the area under the metabolite alkylating activity time curve and the peak alkylating metabolite level attained on each day of ifosfamide administration in the two patient groups in Tables 3 and 4 are compared, there was at no time a significant difference between i.v. and oral routes of administration. It is however important to realize the limitations of the NBP reaction. Certain metabolites of cyclophosphamide and ifosfamide are nonreactive or only weakly positive in this test e.g., acrolein does not alkylate. It is therefore possible to envision a situation where two patients have identical alkylating activity in the serum but quite different profiles of metabolites. For this reason a simple method of assaying all the metabolites individually would be useful. Oral administration could result in a different profile of metabolites which is not reflected in the NBP test.

In our study none of the pharmacokinetic parameters measured correlated with either CNS toxicity or levels of leucopenia. Furthermore there was no correlation between the AUC for the plasma metabolite alkylating activity and the nadir white blood cell count or percentage change in white blood count. Our data is in contrast to the data of Mourisden et al. (36). This is again probably a reflection of the lack of specificity of the NBP test.
reaction and the complexity of the metabolic pathway of ifosfamide.

The values obtained for the renal clearance of ifosfamide were very much lower than the creatinine clearance and there was no correlation between the creatinine clearance and renal clearance of the drug unlike the results of Nelson (29). For a drug as water soluble as ifosfamide this data suggests some degree of tubular reabsorption.

With regard to the comparative pharmacokinetics between oral and i.v. administration, the total body clearance, nonrenal clearance, and volumes of distribution were statistically significantly less with oral administration. Our value for $V_{d0}$ agrees closely with that obtained by Allen (21) and approximates closely to the total body water. This suggests that when administered i.v. ifosfamide is distributed throughout the total body water with little tissue binding. The lower value of $V_{d0}$ is difficult to explain, but $V_{d0}$ and $V_{d(d)}$ are not strictly comparable as both parameters are model dependent. There is no clear explanation of this discrepancy but it suggests that ifosfamide is distributed differently with oral administration. We conclude that ifosfamide fractionated over 5 days leads to autoinduction of its metabolism. The clearance of the drug is lower by the oral route and may be related to the higher incidence of CNS side-effects.

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