Etoposide Pharmacokinetics in Children: The Development and Prospective Validation of a Dosing Equation

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ABSTRACT

Pharmacokinetic studies of etoposide administered at 100–200 mg/m² to 33 children are described. Twenty-seven studies were performed in children aged <10 years. Repeat studies were performed in 11 patients. Median pharmacokinetic parameters were as follows: plasma clearance, 26 ml/min/m²; volume of distribution, 4.9 liters/m²; area under the etoposide plasma concentration-time curve (AUC), 3.9 mg/ml x min per 100 mg/m². Interindividual variability in pharmacokinetic parameters was large (coefficient of variation (CV) = 30, 28, and 27%, respectively) in comparison with intraindividual variability (CV = 12, 14, and 12%, respectively). Variability in AUC was much greater in those patients treated with 150–200 mg/m² etoposide than with 100 mg/m² (CV, 35 versus 13%) and was related to variability in renal function and prior exposure to cisplatin.

Data from the first 20 studies were used to develop pharmacokinetic monitoring equations which were validated in a further 13 patients. The most accurate equation relies upon the elimination constant of 51Cr-EDTA and a single blood sample taken at the end of the etoposide infusion.

Etoposide AUC = $\frac{1.17 \times \text{peak etoposide concentration} \times \text{infusion time}}{1 - e^{-K \times \text{infusion time}}}$

where $K = 51\text{Cr-EDTA}$ elimination rate constant.

This equation showed no significant bias, and the predictive error was small with respect to AUC calculated according to a two-compartment model. Predictive error did not increase with increasing AUC, whereas a marked increase in predictive error was seen for dosing according to body surface area. Dosing according to body surface area alone led to marked over- or underexposure to etoposide in 8 patients. Pharmacokinetic monitoring using the equation described would have identified these patients and permitted dose modification. This approach provides an accurate means of monitoring etoposide AUC for administration times of 1–4 h without the need for detailed pharmacokinetic sampling. It will allow a significant reduction in the variability of exposure seen with surface area-based dosing.

INTRODUCTION

Etoposide is a semisynthetic podophyllotoxin with activity against a wide range of tumors (1, 2). It is one of the most frequently used chemotherapeutic agents in pediatric practice. In the United Kingdom, >70% of children with malignancy receive etoposide, according to many different protocols.

Etoposide cytotoxicity shows marked dependency on both concentration and duration of exposure, and it has been shown that killing of tumor cells in vitro is more closely dependent on the product of these two parameters than on either parameter alone (3, 4). Steady state concentration attained with continuous infusion etoposide in vivo has been related to patient toxicity (5), as has the area under the etoposide concentration-time curve (6), and it has been recognized for a many years that etoposide activity shows marked schedule dependency (7). In a randomized trial to evaluate the effect of schedule on the activity of etoposide in small cell lung cancer, Slevin et al. (8) treated 39 patients with either a continuous infusion of 500 mg/m² over 24 h or 5 daily infusions of 100 mg/m² over 2 h. Response rates of 10 and 89%, respectively, were seen, despite equivalent exposure as measured by AUC. Toxicity in each arm was reported as similar. Despite the known schedule dependency of etoposide, there is no consistently used dosing strategy. It is likely, therefore, that some patients receive etoposide treatment which is suboptimal, due to either inappropriate doses or schedules.

The pharmacokinetics of etoposide have been studied extensively in adults (5–20). Wide variation has been reported in peak concentration, volume of distribution, elimination half-life, total body clearance, and exposure as measured by AUC. After etoposide is administered systemically, it is generally stated that linear pharmacokinetics are seen over a wide dose range; that is, if a given dose/m² gives a particular AUC, then a multiple of that dose will give the same multiple of AUC. While this may be so for an individual patient, data from the considerable number of adult studies reported show that variability in AUC increases markedly as dose/m² increases (7, 9–12, 14, 16–18, 25). These data are summarized in Fig. 1. Dosing according to body surface area has been shown to be a poor predictor of the etoposide concentration or AUC attained, and in adults a standard dose of 260 mg has been suggested, regardless of patient size (21). Pharmacokinetic variability is, therefore, a further reason why individual patients may receive suboptimal exposure to the drug, and attempts have been made to optimize the administration of etoposide by means of therapeutic drug monitoring and adaptive control (21, 22).

Studies of etoposide pharmacokinetics in children suggest similar values to those seen in adults (7, 23–27), although D’Incalci et al. (7) observed significantly higher plasma clearances (per m²), smaller volumes of distribution, and shorter terminal phase half-lives in 6 children compared to 14 adults. Given the wide range of sizes and variability in nutritional states seen in pediatric patients, there is potential for even greater inaccuracy in the dose received by children than by adults. There is accordingly a need to improve pediatric dosing strategies, with the aim of producing more predictable patient exposure.

The aims of the study reported here were to document the pharmacokinetics of etoposide in children receiving therapy according to current protocols, to identify variability in patient exposure, and to relate this to variability in renal or hepatic function. In addition, a method of etoposide administration was developed which allows the dose required for more predictable patient exposure to be determined with minimal patient inconvenience.

The study comprised two parts. Pharmacokinetic studies were performed on 33 consecutive children treated in the Children’s Cancer Unit at the Royal Victoria Infirmary, Newcastle upon Tyne. These
data, together with those from repeat studies performed in 11 patients, were used to document the pharmacokinetics of etoposide in children.

Data from the first 20 patients were used as a training set for the development of a limited sampling model for pharmacokinetic monitoring of patients receiving etoposide. The second (validation) group of 13 patients was then studied and used for the prospective validation of the pharmacokinetic monitoring equation.

MATERIALS AND METHODS

Patient Characteristics

Patient characteristics are summarized in Table 1. Thirty-three consecutive patients (12 female, 21 male) were studied, with repeat studies performed in 11.

Plasma clearance of 51Cr-EDTA varied from 30–124 ml/min/m², (median, 76 ml/min/m²). Three patients had a clearance of <47 ml/min/m² (80 ml/min/1.73 m²), EDTA clearance was measured on a second occasion in 7 of the 11 patients having repeat studies. In 4, clearance had decreased (by 17, 18, 26, and 34%), and in 3 it had increased (by 2, 44, and 77%).

Group 1: Training Set. Twenty patients (median age, 3 years, 11 months; age range, 5 months to 16 years) were studied on at least one occasion each. One patient had Down’s syndrome. Patients were receiving therapy for acute lymphoblastic leukemia (5 patients), neuroblastoma (5 patients), soft tissue sarcoma including rhabdomyosarcoma (5 patients), and pineal teratoma (1 patient). Chemotherapy administered in the same course of therapy was as follows: acute lymphoblastic leukemia: vincristine, daunorubicin, cytarabine, thioguanine, and prednisolone; soft tissue sarcomas: ifosfamide; neuroblastoma: vincristine and carboplatin or cyclophosphamide; pineal teratoma, carboplatin and vincristine.

When possible, etoposide was given before other agents, although none of these have been shown to influence etoposide kinetics in adults or children. Four patients had received cisplatin prior to the course studied, and seven had received ifosfamide. No patient was receiving anticonvulsant medication at the time of study.

Group 2: Validation Set. Thirteen patients (median age, 5 years, 1 month; age range, 13 months to 16 years, 1 month) were studied on at least one occasion, and the results of pharmacokinetic analysis of these studies were used to validate prospectively a dose-monitoring equation derived from group 1. Patients were receiving treatment for acute lymphoblastic leukemia (5 patients), neuroblastoma (1 patient), soft tissue sarcoma (4 patients patients), primitive neuro-ectodermal tumor (2 patients), and Ewing’s tumor (1 patient). The patient with a Ewing’s tumor also received vincristine, ifosfamide, actinomycin D, and doxorubicin.

Group 3: Repeat Studies. Ten patients from group 1 and one from group 2 were studied on a second occasion. In 2 patients, this was 2 days after the first study. In 8 patients, it was during one of the next 3 cycles of etoposide treatment (21–126 days), in one it was after 4 cycles (150 days), and in one the repeat study was performed after an interval of 5 cycles (182 days). The median interval between studies was 63 days.

Investigations prior to Study

Height and weight were recorded for each patient, and hemoglobin; WBC, neutrophil, lymphocyte, and platelet counts; electrolytes; urea; creatinine; albumin; total bilirubin; alanine transaminase; and alkaline phosphatase were measured. Nineteen patients in group 1 and 12 patients in group 2 had their glomerular filtration rate measured by clearance of 51Cr-EDTA as part of their current protocol (28). When possible, this was just before the cycle of chemotherapy to be studied, although for patients with leukemia assessment was made 1–2 weeks after the cycle. Patients with leukemia received etoposide as part of an intensification block 5 weeks after initial induction therapy. All were in hematological remission at this stage, and no change in renal function was anticipated between etoposide therapy and measurement of glomerular filtration rate.

Ethical approval was obtained from the ethical committee at the Royal Victoria Infirmary, and consent was obtained from parents and older children before each study.

Etoposide Administration and Blood Sampling

Etoposide was administered to all patients via an indwelling central venous cannula. With double-lumen central venous catheters, samples were taken from the opposite lumen, with interruption of the infusion and removal of a 5- to 10 ml sample through the opposite lumen, with interruption of the infusion and removal of a 5- to 10 ml sample through the

Table 1 Patient characteristics and pharmacokinetic parameters for all 33 patients

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<th>Parameter</th>
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<tr>
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<tr>
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<tr>
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<tr>
<td>VD2 (liters/m²)</td>
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<td>3.22–8.4</td>
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ETOPOSIDE KINETICS IN CHILDREN

10-ml dead space before sampling. This volume was returned to the patient after sampling. With single-lumen central venous catheters, specimens were taken from a peripheral cannula inserted at the time of general anesthesia.

Etoposide was administered at a concentration of 0.25 mg/ml in 0.9% saline as an infusion over 1–4 h according to individual protocol. Doses from 88–208 mg/m² were given. Two-ml blood specimens, mixed in tubes containing lithium heparin, were obtained before infusion, twice during and at the end of infusion, and after 10, 20, and 40 min, and 1, 2, 4, 6, 8, 10, and 20 h (total, 28 ml blood). CSF specimens from 2 patients in whom the etoposide infusion had recently been completed were analyzed. Blood specimens were centrifuged immediately; plasma or CSF was stored at −20°C until analysis, which was in all cases within 1 month of collection.

Complete urine collection from the beginning of administration of etoposide to the beginning of the next dose 24 h later was possible in 10 patients, with a repeat collection in one patient.

Etoposide assay was by the method of D’Incalci et al. (7), as modified by Newell et al. (29). Briefly, etoposide was extracted from 0.5-ml aliquots of plasma into 2.5 ml of dichloromethane, with rotary mixing and clarification of layers by centrifugation at 1000 × g for 15 min at 4°C. Two ml of the organic phase were removed and evaporated to dryness under a stream of nitrogen at 37°C before resuspension in 200 μl of a high-performance liquid chromatography mobile phase. One hundred μl were analyzed for each specimen. Separation was performed using a 15- x 0.46-cm 5-μm spherisorb phenyl column (Jones Chromatography, Hengoed, Glamorgan, S Wales) and a 1- x 0.46-cm 5-μm precolumn containing the same packing or a guard column packed with 17 μm pellicular C18 (octadecylsilane) (Whatman International Ltd., Maidstone, England). Etoposide was eluted isocratically with a mobile phase of 37.5% methanol:62.5% 0.2 M acetic acid (pH 4.4) (v/v). Detection was by UV absorbance at 237 and 290 nm, and quantitation was by absorbance comparison with external standards of 5 μg/ml in plasma, extracted in the same manner as patient specimens. Intraassay coefficients of variation were calculated by comparison of external standards, and interassay coefficients of variation were calculated by comparison of four separate quality assurance samples, also with comparison of external standards, and interassay coefficients of variation were calculated by the method of Aitkin (33), where the residual variance, \( \sigma^2 \), is related to dose/m² as follows:

\[
\sigma^2 = e^{0.75 + 0.038 \times \text{dose/m}^2}
\]

The problem of increasing variance could also be overcome using logarithmic transformation of the data, and a slightly different dosing equation was obtained by this method. Only the dosing equation derived from untransformed data is described in this paper, since neither method showed greater accuracy in predicting AUC than the other. Bias is expressed in terms of ME and predictive value as the RMSE. These data are also expressed graphically throughout as residual plots.

Comparison of the predictive value of each dose-monitoring equation was made according to the method of Sheiner and Beal (34).

RESULTS

Pharmacokinetic Parameters: All Patients. Etoposide concentration–time profiles were fitted to 1- and two-compartment models for each study. In all except three cases, nonlinear least squares regression favored a two-compartment model, and this was confirmed by calculation of the Akaike Information Criterion for both models. Pharmacokinetic parameters calculated according to a two-compartment open model are given in Table 1. Nonlinear regression did not converge for a two-compartment model in 3 cases, and for these patients, a non-compartmental analysis is given. In 2 patients, the data were so closely fitted to a one-compartment model that the extra parameters in a two-compartment model became redundant. In the third patient, only 6 plasma specimens could be obtained because of technical difficulties with venous sampling, and insufficient data were available to allow a two-compartmental analysis.

AUC calculated by the trapezoidal method was almost identical with that predicted from a two-compartmental analysis for all patients. A close correlation between AUC estimated according to a one-compartmental analysis and either a trapezoidal or two-compartmental AUC was seen (\( r^2 = 0.94 \)), but the one-compartmental analysis systematically underestimated the AUC (Fig. 2.) Model-dependent values obtained using a two-compartment model were used to develop pharmacokinetic monitoring equations.

Development of Dose-monitoring Equations. Dose-monitoring equations were developed using the pharmacokinetic parameters obtained. As described above, AUC was taken as the appropriate measure of exposure. Regression to a line of best fit was made with consideration of increasing variance seen at higher dosing levels. Linear regression was performed using the method of Aitkin (33), where the residual variance, \( \sigma^2 \), is related to dose/m² as follows:

\[
\sigma^2 = e^{0.75 + 0.038 \times \text{dose/m}^2}
\]

The problem of increasing variance could also be overcome using logarithmic transformation of the data, and a slightly different dosing equation was obtained by this method. Only the dosing equation derived from untransformed data is described in this paper, since neither method showed greater accuracy in predicting AUC than the other. Bias is expressed in terms of ME and predictive value as the RMSE. These data are also expressed graphically throughout as residual plots.

Comparison of the predictive value of each dose-monitoring equation was made according to the method of Sheiner and Beal (34).
Wide interpatient variability was seen for all parameters obtained. Median terminal phase half-life was 132 min (range, 81–673 min). Median volume of distribution was 4.92 liters/m² (range, 3.22–8.4 liters/m²). Median plasma clearance was 26 ml/min/m² (range, 14–54 ml/min/m²). Median AUC was 3.88 mg/ml × min per 100 mg/m² (range, 1.84–7.34 mg/ml × min (one study per patient, n = 33). Maximum values were from 3- to 8-fold larger than minimum values, with coefficients of variation of 70, 28, 30, and 27% for terminal phase half-life, volume of distribution, plasma clearance, and AUC per 100 mg/m², respectively. In contrast, for those patients where repeat studies were performed, intrapatient variation for each of these parameters was small, i.e., 17, 14, 12, and 12%, respectively.

Patients receiving 100 mg/m² showed less interpatient variability in AUC per 100 mg/m² than patients receiving >100 mg/m² (CV, 13 versus 35%). Four patients attained an AUC/100 mg/m² of >25% above the mean, and of these, three had impaired renal function (defined as glomerular filtration rate <80 ml/min/1.73 m²). Three of these four patients had received cisplatin in previous cycles of chemotherapy, and the fourth had significant renal impairment attributable to primary neuroblastoma involving one kidney. One other patient had previously received cisplatin and attained an AUC/100 mg/m² within 25% of the mean. Prior cisplatin therapy is significantly associated with increased exposure to etoposide in our patients (x² = 11.8, P < 0.001).

Seven patients in our study had previously received ifosfamide, an agent also known to be nephrotoxic in children (35), but no similar relationship with etoposide exposure was seen.

Urinary excretion of etoposide was assessed in 10 patients. The measured fraction of the administered etoposide dose excreted unchanged by these patient varied between 14 and 46% (median, 26%). Renal clearance varied from 3–22 ml/min/m² (median, 7.6 ml/min/m²). One patient was catheterized, allowing unusually accurate determination of renal elimination of etoposide (22% of dose in 24 h).

A significant correlation was seen between values for the terminal phase elimination constants of etoposide and ⁵¹Cr-EDTA (r = 0.79, P < 0.001, Fig. 3), and a low etoposide clearance was seen in those patients with impaired renal function.

Abnormalities of liver function were detected in a total of 10 patients. Plasma albumin was abnormal in 4 patients (23, 32, 33, and 34 g/liter; NR = 35–50), bilirubin was abnormal in 2 (18 and 23 μmol/liter, NR < 17), ALT was markedly elevated in 6 patients (117, 160, 160, 257, 346, 424 units/liter; NR < 45). No effect of abnormal hepatic function on etoposide clearance could be identified in this unselected group of patients. Similarly, no overall correlation was seen between plasma etoposide clearance and the fraction unbound as calculated using the formula of Stewart et al. (36) (data not shown), but it is interesting to note that the only patient with a markedly low serum albumin (patient 33, albumin 2.3 g/dl) had a clearance of etoposide which was >2 SD above the mean for the population as a whole.

No etoposide was detected in the CSF of either patient from whom specimens were taken when simultaneous plasma concentrations were between 5 and 10 μg/ml.

Development of a Pharmacokinetic Monitoring Equation. Data from the first study performed on each patient in group 1 were used to develop pharmaco kinetic monitoring equations.

A correlation between AUC and administered dose/m² has been reported (11) and was seen in the current study. The degree of spread in values of our data set (Fig. 4) and also in those previously reported (Fig. 1) appears to be greater for higher dosing levels, and therefore, linear regression with adjustment for this increasing variance was made in order to define a potential dosing equation. The line of regression is shown in Fig. 4 and has the equation

\[
\text{AUC (mg/ml × min)} = (\text{Dose/m²} × 0.054) - 1.467. \quad (A)
\]

For data which can be fitted to a one-compartmental model, peak concentration \(C_{\text{max}}\) occurs at the end of infusion and may be written as:

\[
C_{\text{max}} = \frac{(D/kV) \cdot (1 - e^{-kT})}{V}
\]

where \(T = \) infusion time, \(D = \) dose, \(k = \) elimination constant, and \(V = \) volume of distribution.

\[
\text{AUC} = \frac{D}{kV}
\]

Hence,

\[
\text{AUC} = \frac{C_{\text{max}} \times T}{1 - e^{-kT}}
\]

Hence, it was possible to derive a dose-monitoring equation of a similar format to that given above. Nonlinear least squares regression led to the development of Equation B.

\[
\text{AUC} = \frac{1.48 \times C_{\text{max}} \times T}{1 - e^{-0.0418 \times T}} \quad \text{(B)}
\]
A significant correlation between values for the elimination constant of EDTA and both the one-compartment elimination constant and the $\beta$-phase elimination constant of a two-compartment model for etoposide was seen ($r = 0.77$ and $0.79$, $P < 0.001$ for both, see Fig. 3). A more complex equation, of the same general format as Equation B, was therefore derived using the EDTA elimination constant to reflect the etoposide elimination constant of a one-compartment model. Nonlinear least squares regression led to the development of Equation C.

$$\text{AUC} = \frac{1.17 \times C_{\text{max}} \times T}{1 - e^{-(0.72 \times k \times T)}} \quad (C)$$

where $K$ = EDTA elimination constant.

The correction factors of 1.48 (Equation B) and 1.17 (Equation B) are required to overcome the systematic underestimation of AUC by the one-compartment analyses used (Fig. 2).

Prospective Validation of the Dose-monitoring Formula. Prospective validation of Equations A–C was undertaken in a group of 13 patients receiving etoposide. Patient details and pharmacokinetic parameters for these patients are shown in Table 1. Patients in this group showed more variability in pharmacokinetic parameters than those in the training set. The clearance of $^{51}$Cr-EDTA for this group was similar to that for group 1 (median, 85 versus 66 ml/min/m$^2$).

The greatest inaccuracy in predicted AUC was seen using dose/m$^2$ to predict exposure, while dose-monitoring according to Equation C showed the least bias and had the least predictive error for this data set also. Nine patients attained an AUC that was close to the value predicted by Equation A, but in four patients AUC predicted by dose/m$^2$ was markedly different from the observed AUC. For example, patient 23 attained an AUC that was only 40% of the surface area-predicted value. In contrast, AUC was predicted accurately by Equation C for all patients. The least accurate case was patient 23 who attained an AUC which was 73% of that predicted by Equation C, and all other values were considerably closer. Predictive values for each of the three equations have been summarized in Table 2, together with an analysis according to the method of Sheiner and Beal (34), allowing statistical comparison of each method. From these data, it can be seen that Equation A was associated with large errors in predicted exposure. Both Equations B and C led to markedly reduced errors in predicted AUC values, and both ME and RMSE for Equation C appear to be slightly less than for Equation B. Comparison of Equations A–C failed to show any statistically significant differences at the 5% level, although a clear trend is seen favoring Equations B and C over Equation A. This lack of statistical significance was not unexpected given the small numbers of patients in the validation group. It must be remembered that with small numbers, any comparison of predictive value is difficult. We would further emphasize that a lack of statistical significance does not imply a lack of clinical relevance.

These data are expressed graphically in Fig. 5.

**Hematological Toxicity.** This study was not designed to investigate the pharmacodynamics of etoposide, since a wide range of other agents were coadministered and a variable amount of prior therapy had been received by the patients. Nevertheless, hematological toxicity was followed in 21 patients; only one patient did not become neutropenic (total neutrophil count $< 10^3$ cells/ml). No overall relationship between total exposure in one course and myelosuppression was seen, although it is of interest that this one patient received the smallest total exposure to etoposide (7.5 mg/ml $\times$ min in one course, whereas all other patients received at least 11 mg/ml $\times$ min). AUC per course is calculated here from the AUC on the day of study multiplied by the number of days of treatment in that course.

One patient died as a result of drug-related toxicity during the 20 days following the course studied. This patient received the highest total exposure to etoposide of the entire patient set (24.4 mg/ml $\times$ min) in association with carboplatin and had impaired renal function as measured by EDTA clearance.

**DISCUSSION**

The pharmacokinetic parameters obtained in this study are similar to those described for children previously (Table 3). However, 27 of our patients were younger than 10 years, whereas very few such patients have been reported previously. Our data also agree with adult data, and in particular, the increasing variability in AUC with increasing dose/m$^2$ was recognized before (Fig. 1).

The majority of our patients showed elimination of etoposide which could best be described by a two-compartmental analysis, which is again in general agreement with previously reported data. One-compartment analysis gave a reasonable approximation for many patients, but AUC was systematically underestimated by this model. A two-compartmental analysis gave values which were almost identical with those from a trapezoidal method.

The mean AUC per 100 mg/m$^2$ for patients in this study was 3.96 ± 1.08 mg/ml $\times$ min (mean ± SD; coefficient of variation, 27%), and it might be concluded that dosing according to body surface area gives a range of exposure which is acceptable. While this may be the case for patients receiving 100 mg/m$^2$ (CV, 13%; range, 3.15–4.84 mg/ml $\times$ min), much greater variability in AUC per 100 mg/m$^2$ was seen at higher doses (CV, 35%; range, 1.84–7.34 mg/ml $\times$ min). The reasons for this differing variability are not clear, although variability in renal function may be a major determinant. A significant correlation between terminal phase half-life of etoposide and of EDTA was seen, although it is of interest that this one patient received the smallest total exposure to etoposide (7.5 mg/ml $\times$ min in one course, whereas all other patients received at least 11 mg/ml $\times$ min). AUC per course is calculated here from the AUC on the day of study multiplied by the number of days of treatment in that course.

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| Table 2: Predictive errors and root mean squared errors for each of the dose-monitoring equations developed |
|--------------------------------------------|-----------------------|-----------------|-----------------|
| Equation | AUC = | Mean error | (95% CI) | MSE | RMSE |
| 1 | (Dose/m$^2$ $\times$ 0.054) $\times$ 1.467 | 1.184 | $(-0.181, 2.550)$ | 5.63 | 2.372 |
| 2 | $1.48 \times \text{peak concentration} \times \text{infusion time}$ $1 - e^{-(0.67 \times \text{infusion time})}$ | 0.117 | $(-0.463, 0.697)$ | 0.776 | 0.881 |
| 3 | $1.17 \times \text{peak concentration} \times \text{infusion time}$ $1 - e^{-(0.72 \times \text{infusion time})}$ | 0.091 | $(-0.302, 0.484)$ | 0.359 | 0.599 |

Comparison of equations
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<th>Difference in ME</th>
<th>(95% CI)</th>
<th>Difference in MSE</th>
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<td>0.417</td>
<td>$(-0.203, 1.038)$</td>
</tr>
</tbody>
</table>
data in adults (37). In our study, patients receiving a dose of 100 mg/m² were mostly those with acute lymphoblastic leukemia who had not received nephrotoxic drugs, while those receiving greater doses were mostly being treated for soft tissue sarcoma or neuroblastoma, regimens which include both cisplatin and/or ifosfamide. Detailed assessment of renal function has not been made in the majority of previous studies, but accumulation of etoposide and prolonged elimination phases have been identified in adult patients with renal failure (38). This may be taken as evidence that variation in renal function is an important determinant of variability in etoposide clearance, although it is perhaps surprising that a median of only 26% of the administered dose was recovered in the urine of patients.

Variability in hepatic function may also contribute to variability in etoposide kinetics, although the effect may be unpredictable. Impaired conjugation to inactive metabolites will cause a reduction in clearance, but coexistent hypoalbuminemia or hyperbilirubinemia will lead to a greater unbound fraction. A higher free fraction may lead to more rapid renal excretion which will oppose or even overcome the reduced clearance due to impaired conjugation. Clearance may, therefore, increase or decrease (39). It should be noted that in only one patient was plasma albumin markedly less than normal, and no patient had signs of chronic liver disease. Abnormalities in ALT may represent damage from previous recent chemotherapy, while hypoalbuminemia probably reflects poor nutritional status. It is not surprising that no correlation

Fig. 5. Prospective validation of the etoposide pharmacokinetic monitoring equation. A, relationship between etoposide AUC according to a two-compartment model using multiple sampling and that calculated using Equation A. The line of identity is shown. B, measured AUC against the difference between measured and predicted AUC from Equation A. C, relationship between measured AUC and that calculated according to Equation B using a single blood sample. The line of identity is shown. D, measured AUC against the difference between measured and predicted AUC using Equation B. E, relationship between measured AUC and that calculated according to Equation C using a single blood sample. The line of identity is shown. F, residual plot of measured AUC against the difference between measured and predicted AUC using Equation C.
between etoposide clearance and indices of liver function was seen for patients in this study.

It has been shown that coadministration of anticonvulsant medication in patients receiving the related drug, teniposide, is associated with increased systemic clearance, such that patient exposure may be reduced by a factor of one-half or more (40). No patient in our study received anticonvulsant medication during etoposide therapy, but all of the 14 patients with acute lymphoblastic leukemia had received a recent course of prednisolone, 40 mg/m², and recommenced the same dose on the day of the study. Repeat studies were performed on the third day of treatment in two of these patients, and in both, AUC attainment was less (difference ~6 and ~22%). Acute induction of metabolism is well documented for other agents, such as the oxazaphorines. Studies are in progress to investigate the variability in etoposide AUC within a 5-day course of etoposide therapy.

There were extremely high linear correlations between AUCs measured using a two-compartmental analysis and those calculated using Equations B and C for both training and validation sets. Figure 5 shows that for 9 patients in the validation set, dosing according to body surface area alone gave an AUC of etoposide close to that expected. In four patients, however, AUC was markedly less than expected, and in one patient the observed value was less than half that predicted. No patient in this group had impaired renal function as measured by clearance of 51Cr-EDTA. For each of the four patients underexposed, dose monitoring must be considered, with the goal of identifying the maximum safe patient exposure.

Limited sampling models for the prediction of pharmacokinetic parameters have been developed for a number of other chemotherapeutic agents (41, 47–51). Miller et al. (41) studied the pharmacokinetics and pharmacodynamics of etoposide given as a short infusion (1 h) in patients treated for extensive small cell lung cancer. They developed a limited sampling model for calculation of etoposide AUC based upon two blood tests taken 2 and 4 h after the end of infusion:

\[
\text{AUC (mg/ml \times h)} = 15.45 + (3.86 \times C_1) + (7.1 \times C_4),
\]

which is equivalent to

\[
\text{AUC (mg/ml \times min)} = 0.927 + (0.232 \times C_1) + (0.426 \times C_4).
\]

ME and RMSE for this equation are comparable to those seen in our study, although validation was performed in a group of 7 patients in whom 16 studies were performed. The predictive value in individual patients may, therefore, be somewhat less than indicated. Nevertheless, this equation appears to predict accurately patient exposure for patients receiving 150 mg/m² over 1 h. It has the advantage that no other investigation is required in order to predict AUC, but it is unlikely to remain accurate if there is significant variability in the duration of the etoposide infusion, and the accuracy at doses other than 150 mg/m² remains to be proven.

Adaptive control based on both pharmacokinetic and pharmacodynamic factors has been used by Ratain et al. (21) to treat patients with small cell lung cancer. Etoposide was administered as a continuous infusion over 72 h, with modification of infusion rate based in part on the plasma concentration of etoposide at 24 h. Dose escalation in a safe manner was possible in this way, and patients in the adaptive control arm received a mean dose 22% greater than in the arm without adaptive control, with no increase in toxicity.

A more comprehensive approach to adaptive control has been adopted as part of the Total XII study at St. Jude’s Children’s Hospital, where individual patient exposures to methotrexate, teniposide, and cytarabine are adjusted according to limited sampling models. The aim of this study is to avoid low or high systemic exposure for each drug, and dose modification is made to those patients in whom exposure would otherwise fall in the lower 50% or upper 10% of the initially defined range (52).

In conclusion, the aims of this study were to document the pharmacokinetics of etoposide in children and to develop a method for monitoring patient exposure as measured by area under the etoposide concentration-time curve. The pharmacokinetics of etoposide have been shown to vary markedly between individuals and somewhat less within individuals. Patients receiving a dose of 100 mg/m² attained an AUC that was close to that expected, whereas those patients receiving larger doses attained an AUC that could not be predicted accurately from dose administered. It is possible that dosing according to body surface area alone may be satisfactory for patients receiving a dose of 100 mg/m², but the importance of abnormal renal function or prior nephrotoxic chemotherapy should not be underestimated. Patients with impaired renal function as measured by clearance of 51Cr-EDTA, or previous exposure to cisplatin, are likely to receive exposure which

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patient no.</th>
<th>Ages</th>
<th>Dose (mg/m²)</th>
<th>Infusion times (min)</th>
<th>( VD_{etoposide} ) (liters/m²)</th>
<th>Clearance (ml/min/m²)</th>
<th>AUC/100 mg/m²</th>
<th>( t_{1/2} ) (h)</th>
<th>Urine excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans et al. (24)</td>
<td>9</td>
<td>3 mo–18 yr</td>
<td>200–250</td>
<td>30–145</td>
<td>4.8 ± 2.8*</td>
<td>17.8 ± 11.2</td>
<td>5.7 ± 1.3</td>
<td>55 ± 15</td>
<td></td>
</tr>
<tr>
<td>Sinkule et al. (25)</td>
<td>8</td>
<td>4.2–22 yr</td>
<td>200</td>
<td>30–60</td>
<td>7.2 ± 1.7</td>
<td>20.9 ± 5.4</td>
<td>6.5 ± 1.6</td>
<td>45 ± 9</td>
<td></td>
</tr>
<tr>
<td>D'Incalci et al. (7)</td>
<td>6</td>
<td>3.7–9.5 yr</td>
<td>95–200</td>
<td>30–60</td>
<td>9.1 ± 1.0</td>
<td>40 ± 19</td>
<td>3.1 ± 1.4</td>
<td>39.3 ± 6.6</td>
<td></td>
</tr>
<tr>
<td>Hutson, et al. (27)</td>
<td>12</td>
<td>3–21 yr</td>
<td>200</td>
<td>30–60</td>
<td>6.8 ± 0.5</td>
<td>15 ± 1.6</td>
<td>4.2 ± 1.2</td>
<td>24 ± 7.5</td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>33</td>
<td>5 mo–16 yr</td>
<td>89–208</td>
<td>70–307</td>
<td>3.2 ± 8.4</td>
<td>14 – 54</td>
<td>1.8 – 7.3</td>
<td>14 – 11.2</td>
<td></td>
</tr>
</tbody>
</table>

* Mean ± SD.
is greater than expected, while those with normal or apparently supernormal renal function are at risk of marked underexposure.

The value of any limited sampling model will depend on intrapatient variability being small, which the present study has shown. Thus, it seems likely that pharmacokinetic monitoring will allow control of exposure far more accurately than administration according to body surface area. Repeat sampling would be indicated if renal function changes during the course of chemotherapy, and studies are in progress to assess the intrapatient variability in AUC, both within a course and over the duration of treatment.

An important limitation of this approach would be the presence of marked hypoalbuminemia, in which case a greater exposure to unbound etoposide can be expected. The equations described in this paper have only been validated in patients with normal hepatic function, and, although a wide range in values for glomerular filtration rate was seen in the present study, the equations have not been validated in patients with chronic renal failure. The patient population was not selected for any of these parameters, however, and hence we believe that the approach taken here will be of benefit to the majority of pediatric patients receiving etoposide.

The current study has shown that a single sample etoposide analysis provides an accurate estimate of etoposide AUC when given as an infusion over 1–4 h. It is possible that greater accuracy will be obtained if an estimate of EDTA elimination constant is obtained, although by far the greatest improvement in accuracy comes from measurement of etoposide concentration. It would seem sensible, therefore, to utilize the elimination constant of 51Cr-EDTA when this information is readily available, but when not, a single sample will still accurately estimate etoposide AUC. The models put forward in the study reported here will now form the basis for a trial involving adaptive control of etoposide exposure, in order to reduce interpatient variability in etoposide AUC.

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REFERENCES

ETOPOSIDE KINETICS IN CHILDREN


Etoposide Pharmacokinetics in Children: The Development and Prospective Validation of a Dosing Equation


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