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Report

Simulation tool for schedule-dependent etoposide exposure based on pharmacokinetic findings published in the literature

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It is the aim of this study to establish a simulation tool for etoposide (Eto) which can be used to interpret drug monitoring data in clinical practice and to design new schedules for future protocols. As schedule dependency was observed for Eto, knowledge of concentration–time profiles is important. Pharmacokinetic data from children after low-dose i.v. administration of Eto together with data reported in the literature were used to construct the simulation tool. Validation was performed by independently reproducing various published data. Dose linearity of AUC was shown over the whole dose range of 20–2000 mg/m^2 reported in the literature and fits the predictions by the simulation tool. There was no difference in clearance between children and adults. Close agreement was found between predicted and reported concentration–time profiles after various administration schedules. However, subgroups with significantly altered pharmacokinetics of Eto, such as patients with renal impairment or concurrent cisplatin chemotherapy, were excluded from the comparisons. In these patients values predicted for a 'regular' patient might be used as a base for possible dose modifications. In summary, a pharmacokinetic model of high predictive value is presented which allows simulations of Eto concentration–time profiles for low- as well as high-dose conditions and various infusion times. [© 2001 Lippincott Williams & Wilkins.]

Key words: Etoposide, simulation tool.

Introduction

Etoposide (Eto), a DNA topoisomerase II inhibitor, plays an important role in pediatric and adult oncology. Current protocols realize prolonged oral administration and a variety of i.v. schedules. The latter range from repeated low-dose short time infusions over several days (about 20–400 mg/m^2/day) or high-dose short time infusion therapy (about 400–2000 mg/m^2) with or without bone marrow transplantation to continuous i.v. infusions over a wide dose and time range (low- to high-dose infusions over a few days or up to several weeks).

The pharmacokinetics of i.v. Eto has been studied in detail (reviewed by Hainsworth and Greco[1]). In summary, Eto distribution after i.v. administration can be sufficiently described by an open two-compartment model with an initial rapid distribution phase and a terminal half-life of about 3–8 h.

The enzymatic inhibition of topoisomerase II by Eto is reversible and saturated at high concentrations. Its cytotoxicity shows marked schedule dependency in adults;[2,3] low plasma levels (about 0.5–1 mg/l) are associated with cytotoxic activity,[2,4–6] whereas higher plasma levels (above 5–10 mg/l) frequently go along with more severe myelosuppression.[7,8]

The aim of the present study is to establish a simulation tool for the i.v. administration of Eto. Scope and limitations of the model were tested by evaluating results after low-dose and high-dose schedules of Eto as published in the literature. With a view to the schedule dependency of Eto activity the pharmacokinetic profile of the drug, expressed as duration of exposure above predefined concentration ranges, was also studied wherever literature data were available.

Materials and methods

Single doses of Eto below 400 mg/m^2 were defined as a low-dose regimen, higher doses as a high-dose regimen. An infusion time of 24 h was regarded as

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the cut-off between short time and continuous i.v. infusion of Eto. The conversion of absolute dose to dose per m^2 in adults is based on a standard patient of 70 kg body weight and 1.73 m^2 body surface area.

Patients

Population pharmacokinetic parameters from a previously published study were used for further comparisons[9,10] (18 children, 0.8–17 years, 67–200 mg/m^2, Eto as 1–2 h infusion).

Pharmacokinetic analysis

Primary pharmacokinetic parameters of a two-compartment model reported in the literature (V_c, k_e, α, β, or CL, V_c, k_{12}, k_{21}) were used to calculate coefficients and exponents of the polyexponential equation (A, B, α, β).[11] Assuming linear pharmacokinetics, concentration–time curves were calculated for all infusion times and doses[12] (Excel 95).

Statistical analysis

All statistical comparisons were performed using Sigmastat 2.03.

The Mann–Whitney rank-sum test was applied for comparison of two independent populations; three or more groups were compared using the Kruskall–Wallis test. To weight data from different literature sources equally, only the mean value of the dependent variable of each data set was taken for statistical comparisons. The correlation was established by linear regression analysis; each data point was weighted with the respective sample size. Subgroups with significantly altered pharmacokinetics due to disease or concurrent chemotherapy were excluded from comparisons.

Results

Pharmacokinetic profile for low-dose i.v. schedules

Comparing our own results of Eto pharmacokinetics in children[10] with data reported in the literature we first focused on low-dose short time schedules. We combined those published results from children[13–15] and adults[13,16,17] where all primary pharmacokinetic parameters of the individuals or of the mean of the population were available (four parameters are necessary to describe a two-compartment model). [Individual kinetic data after i.v. infusion from Nguyen *et al.*[16] were obtained by personal communication: 14 patients received continuous i.v. infusions, 45 patients short time infusions. Since the results of Tranchand *et al.*[17] are an expansion of data published by Evene *et al.*,[18] results from Evene *et al.* were excluded from the comparisons.] The data allowed us to simulate concentration–time profiles of a 1 h i.v. infusion of

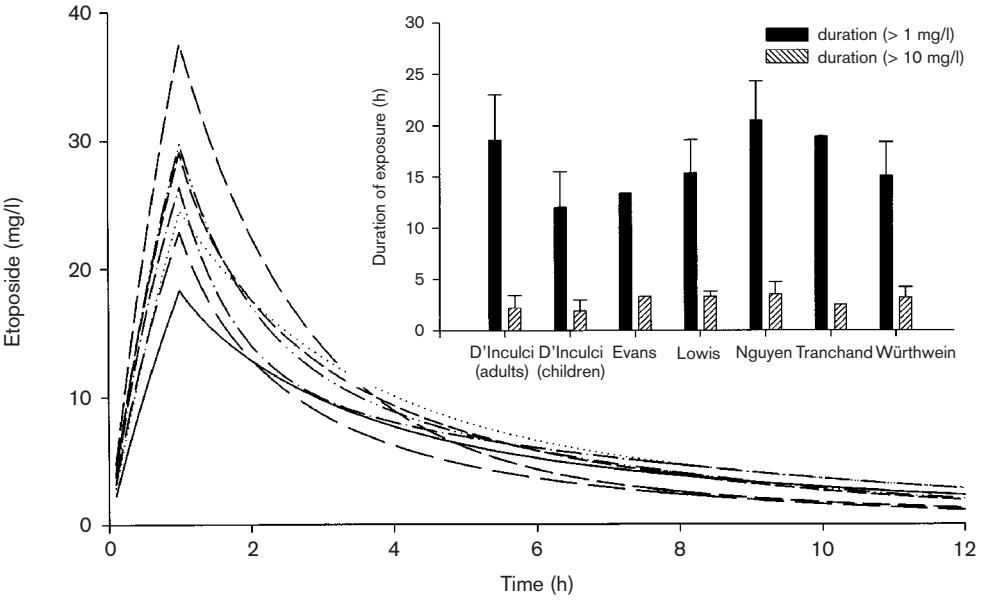

Figure 1. Concentration–time profiles after a 1 h infusion of 150 mg/m^2 Eto: simulations based on previously reported studies. Solid line, D'Incalci (adults);[13] long dash, D'Incalci (children);[13] medium dash, Evans;[14] short dash, Lowis;[15] dotted, Nguyen;[16] dash dot, Tranchand;[17] dash dot dot, Würthwein.[10] Inserts: duration of exposure >1 and >10 mg/l, respectively (mean $\pm$ SD).

Table 1. Pharmacokinetic parameters of Eto after low-dose (literature for simulation[10,13–17] and other low-dose literature[20–29]), high-dose[6,23,32–40] and continuous i.v. infusion[37,41–53] together with data from the simulation tool [median (range)]

Entry	Schedule	No. of groups	CL (ml/min/m^2)		AUC (mg/l·h) (100 mg/m^2)		$t_{½\beta}$ (h)	
1	simulation tool	–[a]	23.1	(15.2–32.2)	76.5	(46.2–127.3)	3.9	(2.1–9.2)
2	low dose (simulation)	7	23.4	(19.5–39.4)	74.2	(50.2–90.2)	5.8	(3.4–9.9)
3	low dose (other literature)	14	22.4	(14.5–27.9)	75.8	(54.3–124.2)	5.6	(2.2–7.8)
4	high dose	15	21.8	(17.7–47.4)	82.9	(47.6–113.5)	in part three-compartment model	
5	continuous i.v. infusion	25	19.9	(15.0–30.1)				
6	all literature	61	21.0	(14.5–47.4)	76.7	(47.6–124.2)		

[a]27 children.

150 mg/m^2, a mean dose commonly applied in outpatient schedules (Figure 1 and Table 1, entry 2).

Whereas exponential coefficients (α, β) and coefficients (A, B) of the different studies varied within a 3- to 19-fold range (Table 2), we found a clearly smaller range for clearance (CL) and area under curve (AUC) (CL: 2.1-fold range; AUC: 2.8-fold range; Table 1, entry 2) and quite close agreement of concentration–time profiles and duration of exposure above predefined concentrations (>1 mg/l: 1.7-fold range, >10 mg/l: 1.8-fold range; Figure 1, inserts).

As Eto pharmacokinetics are described by an open two-compartment model, coefficients and exponents of the biexponential equation provide information about the elimination associated with the first and the last exponential term.[19] The fraction of elimination associated with the first (f_1) and last (f_2) exponential term can be calculated according to:

$$f_2 = \frac{B/\beta}{AUC}, \; f_1 = 1 - f_2 \qquad (1)$$

The results for fractional areas of Eto vary within a close range: we derived $f_1 = 0.18$–0.39 and $f_2 = 0.61$–0.82, which indicates that elimination of about 75% of the dose is associated with the terminal phase. However, data from Evans *et al.*[14] showed a quite different ratio: f_2 was found to be lower than f_1 (f_1=0.66 and f_2=0.34).

Constructing the pharmacokinetic model

The authors' primary research interest is focused on the treatment of pediatric tumors. Hence, we combined pharmacokinetic data from children published by Lowis *et al.*[15] and our own data[10] (total: 27 children) as a basis for the simulation tool (summary parameters, see Table 1, entry 1; coefficient and exponents of the biexponential equation, see Table 2).

Table 2. Coefficients and exponents of the biexponential equations of the simulation tool

Patient[a]	α (1/h)	β (1/h)	A[b] (mg/l)	B[b] (mg/l)
1	1.36	0.21	25.64	8.88
2	1.14	0.23	15.20	10.06
3	1.11	0.24	19.09	9.73
4	1.18	0.27	17.76	9.92
5	0.85	0.18	16.46	10.99
6	1.00	0.13	12.63	12.15
7	0.94	0.15	9.72	15.06
8	1.09	0.17	15.78	9.09
9	1.22	0.16	14.54	6.75
10	0.98	0.20	16.15	13.87
11	1.03	0.22	20.36	11.56
12	1.04	0.19	15.54	13.04
13	1.05	0.18	13.93	10.66
14	1.16	0.21	28.31	6.26
15	1.13	0.18	16.43	9.54
16	1.11	0.18	16.87	7.88
17	1.09	0.17	17.17	10.04
18	1.01	0.16	13.60	12.36
19	1.07	0.13	15.38	10.26
20	1.39	0.17	18.67	9.11
21	0.72	0.17	23.24	6.18
22	5.20	0.33	29.10	20.90
23	0.36	0.10	12.63	3.77
24	0.42	0.08	25.90	1.13
25	3.20	0.22	23.03	14.01
26	0.78	0.16	18.22	8.80
27	1.01	0.15	9.07	9.80
Median	1.07	0.18	16.46	9.92
Min	0.36	0.08	9.07	1.13
Max	5.20	0.33	29.10	20.90

[a]Patients 1–18; [10]; patients 19–27.[15]
[b]Coefficients A and B were calculated for a dose of 100 mg/m^2 Eto. The Excel worksheet can be obtained on request from the authors.

Validation with other low-dose i.v. schedules

Data on low-dose Eto administration in children[20–22] and adults[17,23–29] from numerous other sources were combined to compare summary pharmacokinetic parameters such as CL, AUC and terminal half-life with values from our simulation tool (Table 1, entries 1 and 3) [pharmacokinetic results discussed in more than one publication were included only once: results from Pflüger *et al.*[30] are included in their subsequent publication[29]; results from Slevin *et al.*[6] and Clark *et al.*[7] are discussed in Joel *et al.*[28]]. The values for CL, AUC and terminal half-life given in the literature were comparable with data from our simulation tool.

We applied our model to calculate durations of exposure above predefined concentration ranges for schedules reported by Slevin *et al.*[6]: patients received Eto either as a single i.v. dose of 500 mg/m^2 over 24 h or as five daily infusions of 100 mg/m^2 each over 2 h every 3 weeks. Pharmacokinetic studies were performed, duration of exposure >1 and >10 mg/l was 46.3 ± 9.8 and 23.1 ± 4.4 h, respectively, with the single dose, and 94.5 ± 20.1 h and 11.4 ± 5.3 h with the divided dose. Using our model we arrived at values that were about 70–86% of the values reported by Slevin *et al.* (single dose: 37.4 ± 3.9 and 20.0 ± 3.0 h; divided dose: 67.8 ± 14.0 and 9.2 ± 2.9 h). Pinkerton *et al.*[31] investigated the pharmacokinetics of low-dose short time infusions in nine children (100–150 mg/m^2 as 1 h infusion). The duration of exposure >1 and >10 mg/l reported by Pinkerton *et al.* (14.7 and 2.5 h) could be well predicted with our own simulations (14.3 ± 3.0 and 2.6 ± 0.6 h).

Simulation tool predictive also for high-dose i.v. schedules?

So far the focus has been on the comparability of pharmacokinetic results with standard i.v. infusion of Eto. The question arises, however, whether or not our model is also able to predict results after high-dose regimens based on our simulation tool as well. In other words, can we assume dose linearity up to high-dose regimens and are we able to predict concentration–time curves for those schedules as well?

To answer these questions we summarized pharmacokinetic parameters such as CL and terminal half-life from high-dose schedules reported in adults[6,23,32–40] (Table 1, entry 4). CL of Eto after high-dose regimens was in accordance with results of our simulation tool. A comparison of terminal half-lives cannot be done as some authors[34,36–38] used a three-compartment model to fit measured concentrations.

AUC values from the publications on low-dose Eto cited above and from reports on high-dose Eto were plotted as a function of dose (Figure 2). The correlation coefficient of weighted linear regression was 0.982 (equation: $\mathrm{AUC}=0.818 \times \mathrm{dose} - 0.633$, $p < 0.001$), and demonstrated a good linear relationship between AUC and dose. Prediction ranges of AUC based on our simulation tool were calculated according to:

$$\mathrm{AUC} = \frac{\mathrm{Dose}}{\mathrm{CL}} \qquad (2)$$

for mean CL, CL $\pm$ SD and CL $\pm$ 2SD of our model (Figure 2). AUC values observed over the whole dose range of Eto as published in the literature were within the predicted range of our simulation tool.

In three studies, Mross *et al.*[36–38] investigated different schedules of Eto administration (dose range: 30–45 mg/kg). To compare the pharmacokinetic profile—expressed as duration of exposure >1 and >10 mg/l, respectively—we summarized all results after 6 h infusions reported by Mross *et al.* (23 adults) and compared these data with results from our simulations. The duration of exposure >1 and >10 mg/l reported by Mross (37.0 ± 9.3 and 19.0 ± 3.8 h) was in good agreement with results from our own simulations (30 mg/kg: 30.2 ± 5.8 and 16.6 ± 3.0 h; 45 mg/kg: 32.6 ± 6.4 and 19.0 ± 3.4 h). Köhl *et al.*[35] investigated the pharmacokinetics of high-dose Eto in 10 patients (total dose 2100 mg/m^2, divided into three doses given as 30-min infusions on 3 consecutive days). Mean AUC (82.9 ± 10.5 mg/l·h/100 mg/m^2), peak level (156 ± 27 mg/l) as well as concentrations at time of BMT 30 h after the last infusion (plasma concentrations >0.5 mg/l measured in five of 27 cases: mean $\pm$ SD: 1.09 ± 0.68 mg/l; range: 0.57–2.39 mg/l) reported by Köhl *et al.* were well predicted with our simulation tool (AUC: 74.6 ± 15.6 mg/l·h/100 mg/m^2, peak level: 160.2 ± 22.9 mg/l, 30 h after infusion: in seven of 27 cases plasma concentrations >0.5 mg/l: mean $\pm$ SD: 1.17 ± 0.41 mg/l; range: 0.74–1.84 mg/l).

Continuous i.v. infusion: CL as a summary parameter for all Eto schedules

So far, the linearity of AUC increase with dose has been shown for short time infusions. Will the same dose–linear increase be seen when Eto is applied as continuous i.v. infusion or will the relationship be influenced by other factors such as accumulation or enzyme induction?

Many protocols specify continuous i.v. infusions of Eto in the treatment of children[41–44] and adults.[37,45–53]

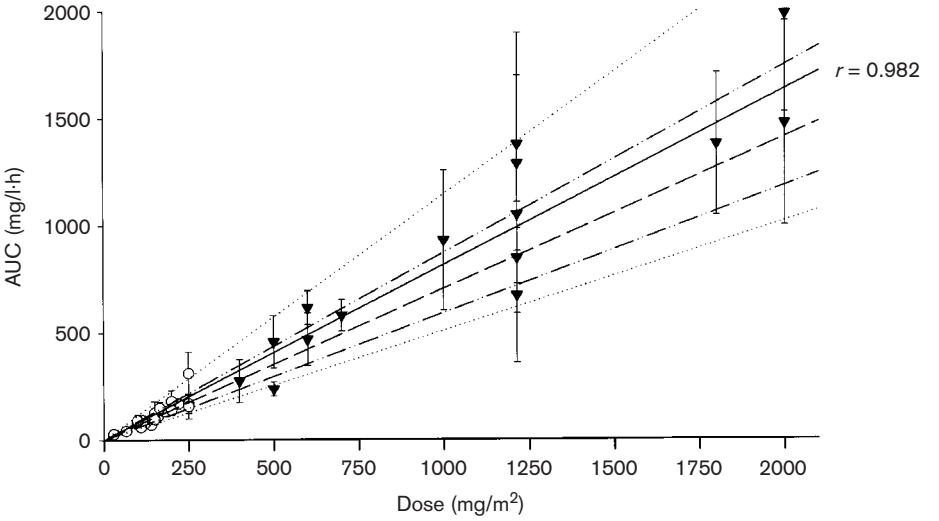

Figure 2. Relationship between AUC and dose administered after low-dose (○)[10,13–17,20–29] and high-dose (▼)[6,23,32–40] Eto. Solid line, data fitted by weighted linear regression; AUC predicted based on: dash, mean CL; dash dot dot, CL ± SD; dotted, CL ± 2SD of the simulation tool.

The pharmacokinetic endpoint of these studies is the steady-state plasma level (c_{ss}), which is related to CL by:

$$c_{SS} = \frac{R_0}{CL} \qquad (3)$$

where R_0 is the infusion rate (mg/m^2/day).

The data on continuous i.v. infusions and the results with short time infusions of low- and high-dose regimens cited above can hence be discussed together by analyzing CL as a function of dose (Figure 3). Fitting the data by linear regression, each point weighted by its sample size, resulted in the equation: CL=0.000241 × dose+21.46 (correlation coefficient r=0.0324, p=0.804). Plasma Eto CLs are not altered by increasing the dose or the duration of drug infusion. Of the CL values published in the literature, 58 of 61 were within the predicted range of our simulation tool.

Discussion

A simulation tool was developed utilizing our own and published data from children who received standard i.v. infusion of Eto, and was validated by independently reproducing published data for low- as well as high-dose regimens, short time as well as continuous i.v. infusions. CL could be shown to be independent of the dose. Further comparisons of published CL values for low-dose, high-dose and continuous i.v. infusions indicated that there was no significant difference between these three groups (p=0.46, Figure 4a). Furthermore, reported CL values obtained after Eto administration in children and adults showed no difference (p=0.94; Figure 4b). Obviously, the plasma CL mechanism of Eto remains unaltered over a wide dose range of 20–2000 mg/m^2, no accumulation can be observed. These findings are confirmed by the linear relationship between AUC and dose of drug administered (r=0.982).

Plasma drug exposure (AUC) as a summary parameter may be of some practical use as an empirical 'exposure' quantity in pharmacodynamics. Using this kinetic parameter, however, information about the concentration–time relationship is necessarily lost by integration of concentration versus time. Information on schedule dependency, a characteristic feature of Eto, is very hard to gain from AUC or CL alone. Therefore, wherever published data were available, the pharmacokinetic profile of the drug was also studied; we were quite satisfied with the fit of predictions regarding duration of exposure above predefined concentrations, peak levels or concentrations at time of BMT after various published schedules.

Based on these validations, our model proved to be applicable for the simulation of new schedules covering a wide dose range. A concentration of 1 mg/l is regarded as the lower limit of prediction for the simulation tool.

The majority of clinical protocols using Eto involve multi-agent chemotherapy. Drug interactions and disease conditions may influence the pharmacoki-

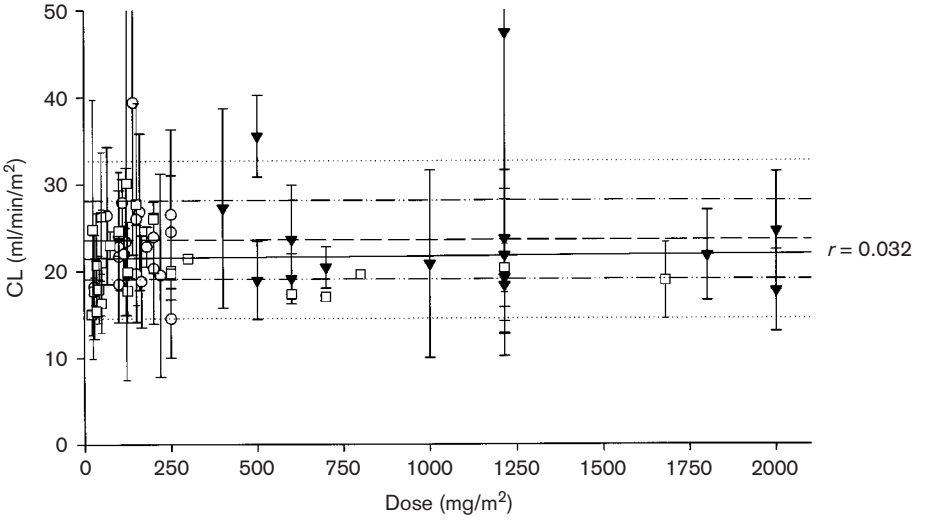

Figure 3. Relationship between CL and dose administered after low-dose (○),[10,13–17,20–29] high-dose (▼)[6,23,32–40] and continuous i.v. infusion (□)[37,41–53] Eto. Solid line, data fitted by weighted linear regression; dash, mean CL; dash dot dot, CL ± SD; dotted, CL ± 2SD of the simulation tool. For continuous i.v. infusion: *x*-axis: infusion rate R_0 (mg/m²/day).

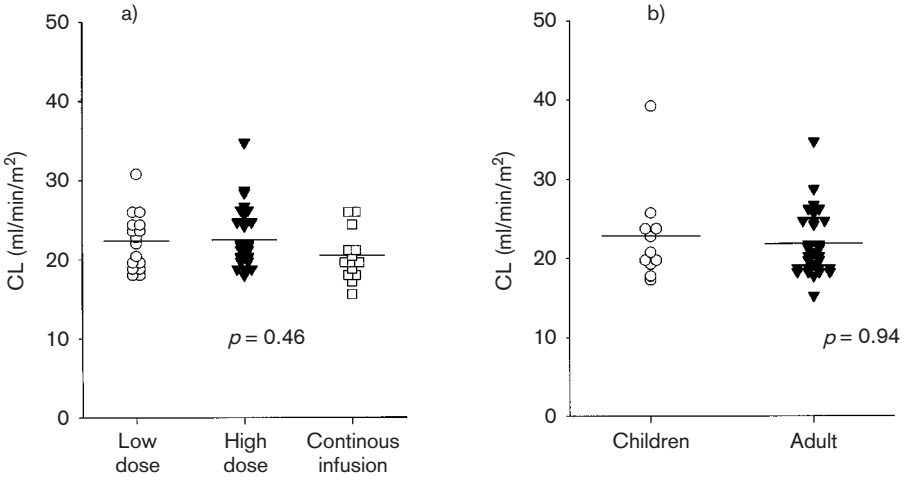

Figure 4. (a) CL after low-dose (○),[10,13–17,20–29] high-dose (▼)[6,23,32–40] and continuous i.v. infusion (□)[37,41–53] Eto (Kruskall–Wallis test, p=0.46). (b) CL in children (○)[10,13–15,20–22,41–44] and adults (▼)[6,13,16,17,23–29,32–40,45–53] (Mann–Whitney rank-sum test, p=0.94).

netics of Eto. Therefore, results from patient groups with significantly altered pharmacokinetics of the drug due to disease or concurrent chemotherapy were excluded from our comparisons. As up to 40% of Eto is eliminated by the kidney, renal impairment leads to significantly decreased plasma CL.[24,28–30,54] Concurrent administration of cisplatin results in impaired renal function due to the nephrotoxicity of the drug.[22,24,29,30,43] Cyclosporine is hepatically metabolized and competitively inhibits cytochrome P450 enzymes.[20,55] Rodman *et al.*[56] found reduced Eto CL associated with high-dose carboplatin. Hepatic enzyme induction (CYP3A4) associated with anticonvulsant therapy (co-administration of phenytoin or phenobarbital)[36,56,57] or prednisone[58] lead to a substantial increase in Eto CL.

Conclusions

The simulation tool can be used for therapeutic drug monitoring in clinical practice. In this respect, monitoring patients with organ dysfunction or concurrent chemotherapy with drugs altering Eto phar-

macokinetics might be of particular interest. Dose modifications may be based on the results predicted for a 'regular' patient as defined by our model. Furthermore, the simulation tool serves to define concentration–time profiles of high predictive value for new Eto schedules, covering a wide dose range. Based on these profiles, Eto-containing regimens can be designed from solid pharmacokinetic hypotheses of target levels and exposure times, to allow subsequent development of pharmacokinetic/pharmacodynamic modeling.

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