Altered Irinotecan Pharmacokinetics in Pediatric High-Grade Glioma Patients Receiving Enzyme-inducing Anticonvulsant Therapy

Kristine R. Crews, Clinton F. Stewart, Dana Jones-Wallace, Stephen J. Thompson, Peter J. Houghton, Richard L. Heideman, Maryam Fouladi, Daniel C. Bowers, Murali M. Chintagumpala, and Amar Gajjar

Departments of Pharmaceutical Sciences [K. R. C., C. F. S.], Biostatistics and Epidemiology [D. J.-W.], Hematology-Oncology [S. J. T., R. L. H., M. F., A. G.], and Molecular Pharmacology [P. J. H.], St. Jude Children’s Research Hospital, Memphis, Tennessee 38105; Division of Pediatric Hematology/Oncology, University of Texas Southwestern Medical School, Dallas, Texas 75235 [D. C. B.]; and Department of Pediatrics, Baylor College of Medicine, Houston, Texas 77030 [M. M. C.]

ABSTRACT

Purpose: The purpose of this study was to determine the effect of enzyme-inducing anticonvulsants (EIAs) on the disposition of irinotecan and metabolites in pediatric patients with high-grade glioma.

Experimental Design: Pediatric patients with newly diagnosed high-grade glioma were enrolled on this study between March 1999 and February 2001. During course 1, irinotecan was administered as a 60-min i.v. infusion at a dosage of 20 mg/m²/day for 5 days of 2 consecutive weeks. On days 1 and 12 of course 1, we collected serial plasma samples to measure the concentrations of the lactone and total forms of irinotecan and its metabolites SN-38 (7-ethyl-10-hydroxycamptothecin), SN-38 glucuronide (7-ethyl-10-[3,4,5-trihydroxy-pyran-2-carboxylic acid]camptothecin), and 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecin.

Results: Thirty-one patients were enrolled. In patients receiving EIAs, the area under the concentration versus time curve (AUC) of irinotecan lactone and SN-38 lactone was significantly lower (P = 0.01 and P = 0.002, respectively), and the irinotecan lactone clearance was significantly higher (P = 0.0003), as compared with those in patients who received no EIAs. The glucuronidation ratio was higher (P = 0.0009), and the ratio of SN-38 AUC to irinotecan AUC was lower (P = 0.02) in patients who received EIAs. Two patients receiving EIAs tolerated increased irinotecan dosages of 30 and 40 mg/m²/day without toxicity. One patient receiving EIAs experienced grade 3 diarrhea when the dosage of irinotecan was increased to 60 mg/m²/day.

Conclusions: EIAs increase the clearance of irinotecan and cause a decrease in systemic exposure to the active metabolite SN-38. Patients who are receiving irinotecan and who require anticonvulsants should be placed on non-EIA therapy, when possible.

INTRODUCTION

Treatment outcome remains poor for patients with malignant or high-grade glioma; therefore, the effectiveness of newer chemotherapeutic agents is being investigated. Several new classes of drugs that are active in murine xenograft models are currently in clinical trials. One of the most promising of these drugs, irinotecan (CPT-11), is effective against pediatric and adult central nervous system tumors in preclinical xenograft studies (1). Results of studies in xenografts have also revealed that the antitumor activity of irinotecan is highly schedule dependent; protracted exposure to low doses results in increased efficacy (2). Irinotecan is a water-soluble derivative of camptothecin, a plant alkaloid isolated from Camptotheca acuminata. Irinotecan is a produg in vivo, undergoing de-esterification by carboxylesterases to yield a potent topoisomerase I inhibitor, SN-38 (7-ethyl-10-hydroxycamptothecin; Fig. 1). SN-38 is subjected to glucuronidation by UGT3 to form SN-38G (7-ethyl-10-[3,4,5-trihydroxy-pyran-2-carboxylic acid]camptothecin), which is excreted in the bile and urine. Deconjugation of SN-38G by the intestinal microflora can occur and may result in recycling of SN-38 (3). In addition, irinotecan is oxidized by CYP3A4 to yield two relatively inactive metabolites, APC and the minor metabolite NPC (4). The parent compound, SN-38, SN-38G, and APC accounted for 93% of the recovered dose in a radiochemical mass-balance study (5). Like the E-ring of other camptothecin analogues, the closed lactone ring of irinotecan can undergo pH-dependent reversible hydrolysis to an open carboxylate form. In vitro studies have shown that the closed lactone configuration of camptothecin analogues is the pharmacologically active form (6).

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2 To whom requests for reprints should be addressed, at Department of Pharmaceutical Sciences, St. Jude Children’s Research Hospital, 332 North Lauderdale, Memphis, TN 38105-2794. Phone: (901) 495-3663; Fax: (901) 525-8689; E-mail: kristine.crews@stjude.org.

3 The abbreviations used are: UGT, uridine diphosphate glucuronosyltransferase; SN-38G, SN-38 glucuronide; CYP, cytochrome P450; APC, 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]carbonyloxy-camptothecin; NPC, 7-ethyl-10-[4-(1-piperidino)-1-aminocarbonyloxy-camptothecin; EIA, enzyme-inducing anticonvulsant; HPLC, high-performance liquid chromatography; AUC, area under the concentration versus time curve.
Patients with high-grade glioma frequently require supportive therapy, which may include corticosteroids for the treatment of cerebral edema or anticonvulsants. We and others have reported that EIAAs (e.g., phenytoin, phenobarbital, and carbamazepine) increase the clearance of the camptothecin analogues topotecan and 9-aminocamptothecin (7–9). In a study of adult patients with brain tumors, the pharmacokinetics of weekly irinotecan in patients who received EIA and dexamethasone differed from those in adult patients with colon cancer who did not receive EIAs or dexamethasone (10). The authors suggested that the difference in irinotecan disposition between the two groups of patients may have been due to EIA and dexamethasone administration in the brain tumor group; however, the effect of EIAs independent of dexamethasone was not assessed. Here we report the effect of EIAs on the disposition of irinotecan administered in an up-front window to pediatric patients with high-grade glioma in a Phase II study. This report is the first to directly compare irinotecan pharmacokinetics in pediatric high-grade glioma patients who did and did not receive EIAs.

PATIENTS AND METHODS

Clinical Protocol. Patients eligible for this study were between 3 and 21 years of age, had histologically proven high-grade glioma, and had not received prior treatment, except for surgical resection and corticosteroids. Patients were required to begin irinotecan therapy within 28 days of definitive surgery. The study was approved by the institutional review board, and informed consent was obtained from patients, parents, or guardians, as appropriate, according to institutional guidelines.

Drug Administration. For i.v. administration, irinotecan (Camptosar; Pharmacia Corp., Kalamazoo, MI; concentration, 20 mg/ml) was supplied in single-dose, 5-ml vials. The drug was diluted in 250 ml of 5% dextrose injection, USP, or 0.9% sodium chloride injection, USP, before i.v. infusion. Irinotecan (20 mg/m²/day) was administered by i.v. infusion over a 60-min period once daily for 5 consecutive days. After a 2-day rest, irinotecan was administered again for 5 consecutive days (11). A second course was administered 21 days after the start of the first course. To assess the effect of intrapatient dose escalation in patients receiving concomitant EIA therapy, we designed the protocol to allow empiric intrapatient dose escalation only for patients receiving EIAs. After irinotecan therapy, patients went on to receive radiation therapy followed by six courses of temozolomide.

Supportive Care. Each patient or caregiver was instructed to begin treatment with loperamide at the first episode of poorly formed or loose stools or at the first indication of increased frequency of bowel movements after irinotecan administration. Oral administration of corticosteroids was continued as needed to counteract the effects of tumor size and edema, and doses were increased or decreased by each patient’s attending physician in response to symptoms during the course of the study.

Evaluation During Therapy. Physical examinations and serum chemistry assays were performed each week. Complete blood cell, differential, and platelet counts were obtained twice weekly during each course of irinotecan. Toxicity was graded in accordance with the National Cancer Institute Common Toxicity Criteria (Version 2.0).

Blood Collection and Plasma Isolation. The pharmacokinetics of irinotecan and its metabolites SN-38, SN-38G, and APC were evaluated after the first and last dose of the first course. Whole blood (3 ml) was obtained from a site contralateral to the irinotecan infusion site before the irinotecan infusion and 0.25, 0.5, 1, 2, 4, and 6 h after the end of the infusion. To isolate plasma, all blood samples were centrifuged immediately at the bedside at 7500 × g for 2 min in a microcentrifuge. Plasma was separated, and proteins were precipitated by the
addition of 200 µl of plasma to 800 µl of cold methanol (−30°C) and vigorous agitation on a vortex mixer. The samples were then subjected to centrifugation at 7500 × g for 2 min (11). Samples were stored at −70°C until their irinotecan and metabolite concentrations could be measured by HPLC.

**HPLC Analysis.** Concentrations of the lactone and carboxylate forms of irinotecan, SN-38, SN-38G, and APC were measured by a validated, sensitive, and specific reversed-phase HPLC assay as described below. The chromatography system included two Shimadzu LC-10AD pumps with a Shimadzu RF-10AXL fluorescence detector and a 5-µm, reversed-phase Symmetry C8 column (3.9 × 150 mm; Waters, Milford, MA). To facilitate separation of lactone and carboxylate species, we used a mobile phase gradient. Mobile phase A was 86% 0.075 M ammonium acetate, adjusted to pH 6.0 with 5 mM tetrabutylammonium phosphate, and 14% acetonitrile. Mobile phase B was 50% 0.075 M ammonium acetate, adjusted to pH 6.0 with 5 mM tetrabutylammonium phosphate, and 50% acetonitrile. The gradient program included 100% mobile phase A running for 23 min and a subsequent 5-min linear gradient to 40% mobile phase B, which ran for 2 min. The excitation wavelength was held constant at 380 nm, and the emission wavelengths were as follows: 460 nm from 0–10 min, 520 nm from 10–13.5 min, 460 nm from 13.5–17.5 min, and 530 nm from 17.5 min to the end of the run. The retention times for the individual analytes were as follows: SN-38G carboxylate, 4.9 min; APC carboxylate, 9.1 min; irinotecan carboxylate, 12.2 min; SN-38G lactone, 14.5 min; APC lactone, 16.5 min; irinotecan lactone, 18.4 min; SN-38 carboxylate, 22.3 min; and SN-38 lactone, 23.9 min. The total run time was 45 min, and the flow rate was 1.25 ml/min.

Forty-five µl of each patient sample were added to 90 µl of mobile phase A and mixed on a vortex mixer; 100 µl of this mix were injected onto the column. The intraday coefficient of variation for controls for all analytes was ≤15%, and the inter-day coefficient was ≤17%. The lower limits of quantitation for the lactone and carboxylate forms of irinotecan, SN-38, SN-38G, and APC were 2, 0.5, 1, and 1 ng/ml, respectively.

**Pharmacokinetic Analysis.** Plasma concentration-time data of the lactone and carboxylate forms of irinotecan, SN-38, SN-38G, and APC were modeled simultaneously using a Bayesian estimation algorithm with pediatric population priors as implemented in ADAPTII (12). This method was repeated for the concentration-time data of both the lactone and carboxylate forms (hereafter referred to as “total”). The AUCs from time 0 until 7 h after the start of the irinotecan infusion were calculated for each analyte by using the log-linear trapezoidal method. The systemic clearance of irinotecan was calculated using accepted methods (13). The SN-38 glucuronidation ratio was SN-38G AUC:SN-38 AUC, and the irinotecan oxidation ratio was APC AUC:irinotecan AUC. The SN-38:irinotecan ratio was SN-38 AUC:irinotecan AUC.

**Statistical Analysis.** Comparisons of irinotecan, SN-38, SN-38G, and APC median systemic exposures and metabolic ratios were made between groups by using exact Wilcoxon rank-sum tests. P < 0.05 indicated statistical significance. The incidence of toxicity associated with course 1 of irinotecan therapy was compared between groups by using Fisher’s exact test. SAS release 8.0 software (SAS Institute, Cary, NC) was used to perform the statistical analysis. Exact tests were performed using StatXact (Cytel Software Corp., Cambridge, MA).

### RESULTS

**Patient Characteristics.** Pharmacokinetic studies were completed for 31 patients with newly diagnosed high-grade glioma between March 1999 and February 2001. Ten patients were included in the EIA group: 4 were receiving EIA therapy, which continued at a stable dose for the duration of the study; a 5th patient was receiving chronic carbamazepine therapy, which was discontinued after the first day of irinotecan administration (after the day 1 pharmacokinetic study); and 5 additional patients were receiving chronic EIA therapy before enrollment, but their EIA therapy was discontinued before the start of irinotecan therapy (median time of discontinuation, 3 days before the start of irinotecan therapy; range, 2–3 days before the start of irinotecan therapy). Demographic data are recorded in Table 1. The median age of patients who received EIAs was 11.8 years (range, 3.0–17.7 years); the median age of patients who did not receive EIAs was 7.2 years (range, 3.3–21.0 years).

<table>
<thead>
<tr>
<th>Anticonvulsant</th>
<th>No. of patients who received EIAs (n = 10)</th>
<th>No. of patients who received no EIAs (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M/F</td>
<td>6/4</td>
</tr>
<tr>
<td>Tumor type</td>
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<td></td>
</tr>
<tr>
<td>AA*</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>BSG</td>
<td>0</td>
<td>11</td>
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<tr>
<td>GBM</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Otherb</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Dexamethasone dose (mg/day)</td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>1–10</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>&gt;10</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

* AA, anaplastic astrocytoma; BSG, brain stem glioma; GBM, glioblastoma multiforme.

b Anaplastic oligoastrocytoma (n = 1) and anaplastic oligodendroglioma (n = 1).

Table 1. Patient demographic data

One patient started on a dexamethasone dose of 4 mg/day on day 2 of irinotecan; day 1 pharmacokinetic studies were performed without dexamethasone coadministration.

**Effect of EIAs on Irinotecan Disposition.** We performed pharmacokinetic studies of plasma samples from all 31 patients on day 1 of irinotecan therapy. Day 12 pharmacokinetic studies were completed for 17 of the 21 patients who did not receive EIAs. Two patients refused further pharmacokinetic studies after day 1, and two patients were removed from the study before day 12, one due to clinical progression and one at the physician’s discretion. Day 12 pharmacokinetic studies were completed for all 10 patients in the EIA group.

The mean plasma concentration-time curves for irinotecan...
and its metabolites on day 1 at an irinotecan dosage of 20 mg/m²/day are presented in Fig. 2, and the pharmacokinetic parameters are summarized in Table 2. The lactone AUC calculated through 7 h for irinotecan, SN-38, SN-38G, and APC accounted for a mean of 90%, 87%, 86%, and 83% of the AUC extrapolated to infinity, respectively.

The median clearance of irinotecan lactone on day 1 was higher in patients who received EIAs than in those who did not (P = 0.0003; Fig. 3A). The median SN-38 lactone AUC on day 1 was higher in patients who received EIAs than in those who did not (P = 0.002; Fig. 3B). The median SN-38G lactone AUC on day 1 was not significantly different between the two groups (P = 0.72; Fig. 3C). The median APC lactone AUC on day 1 was higher in patients who received EIAs than in those who did not (P = 0.027; Fig. 3D).

### Table 2: Comparison of day 1 pharmacokinetics of lactone and total irinotecan, SN-38, SN-38G, and APC in patients receiving EIAs and in those who did not receive EIAs

<table>
<thead>
<tr>
<th></th>
<th>Patients who received EIAs&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Patients who received no EIAs&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Irinotecan</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactone AUC</td>
<td>237.6 (165.5–419.5)</td>
<td>324.0 (205.4–531.6)</td>
<td>0.01&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lactone clearance</td>
<td>83.1 (60.6–119.0)</td>
<td>55.5 (33.4–87.8)</td>
<td>0.0003&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total AUC</td>
<td>1317.2 (512.9–2323.5)</td>
<td>1160.5 (658.2–2077.2)</td>
<td>0.47</td>
</tr>
<tr>
<td>Total clearance</td>
<td>11.8 (6.2–37.7)</td>
<td>13.6 (4.9–24.7)</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>SN-38</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactone AUC</td>
<td>13.8 (6.1–32.9)</td>
<td>28.4 (9.0–119.1)</td>
<td>0.002&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total AUC</td>
<td>49.6 (28.7–110.4)</td>
<td>95.6 (39.1–358.1)</td>
<td>0.002&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>SN-38G</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactone AUC</td>
<td>78.2 (61.1–139.0)</td>
<td>80.8 (42.3–160.9)</td>
<td>0.72</td>
</tr>
<tr>
<td>Total AUC</td>
<td>154.9 (118.9–282.5)</td>
<td>164.3 (77.9–356.6)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>APC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactone AUC</td>
<td>81.1 (21.5–135.7)</td>
<td>57.0 (32.1–90.6)</td>
<td>0.27</td>
</tr>
<tr>
<td>Total AUC</td>
<td>130.9 (38.0–459.3)</td>
<td>142.6 (68.7–282.4)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

<sup>a</sup> Irinotecan (20 mg/m²) was administered to all patients on day 1.
<sup>b</sup> All values are the median (range); units for AUC = ng·h/ml; units for clearance = liters/h·m².
<sup>c</sup> Statistically significant difference between the group who received EIAs and those who did not receive EIAs.

Fig. 2: Mean ± SD day 1 lactone plasma concentration-time profiles for (A) irinotecan, (B) SN-38, (C) SN-38G, and (D) APC in patients who received EIAs (●) or who received no EIAs (▲). All patients received 20 mg/m² irinotecan i.v. over 60 min.
between the two groups (P = 0.002), nor did the oxidation ratio differ significantly (P = 0.27), respectively, nor did the oxidation ratio differ significantly between the two groups (P = 0.07). In contrast, the glucuronidation ratio was higher (P = 0.0009; Table 3), and the AUC ratio of SN-38 to irinotecan was lower (P = 0.02) in patients who received EIAs. It should be noted that the metabolic ratios are dependent on both formation and elimination and, as such, are not direct measures of these conversions but merely serve as estimates of the effect of EIAs on the relative disposition of the parent drug and metabolites in the plasma.

Six patients included in the EIA group had their EIAs discontinued before course 1 (n = 5) or after the first dose of irinotecan (n = 1). Fig. 4 shows the comparison between the day 12 SN-38 lactone AUCs in these six patients who had their EIAs discontinued and those in patients who had received no EIAs. In the patients who had their EIA therapy stopped a median of 13.5 days (range, 11–14 days) before day 12 pharmacokinetic studies, median systemic exposure to SN-38 lactone remained lower than that in patients who had received no EIAs (P = 0.02).

Effect of Dose Escalation on Systemic Exposure. Four patients received EIA therapy throughout course 1 of irinotecan therapy. One of these patients continued to receive irinotecan at a dosage of 20 mg/m²/day throughout course 1 because the assessment of day 1 pharmacokinetic samples was not immediately available. The other three patients received increased doses of irinotecan on day 2 in an effort to increase the systemic exposure to SN-38 lactone to the median value in patients who had received no EIAs. Increasing the dose to 40 mg/m²/day in one patient resulted in an increase in the SN-38 lactone AUC from 13.9 ng/h/ml on day 1 to 25.6 ng/h/ml on day 12. Increasing the dose to 60 mg/m²/day in a second patient resulted in an increase in SN-38 lactone AUC from 13.8 ng/h/ml on day 1 to 21.4 ng/h/ml on day 12. Both of these patients received stable doses of EIAs throughout the irinotecan course, and a less than proportionate increase in SN-38 systemic exposure was observed as the irinotecan dosage increased. In the third patient, the doses of his EIA regimen (phenytoin and carbamazepine) were increased during his irinotecan course. In this patient, the SN-38 lactone AUC decreased from 32.9 ng/h/ml on day 1 to 25.3 ng/h/ml on day 12, despite an increase in irinotecan dosage from 20 to 30 mg/m²/day.

Effect of Dexamethasone on Systemic Exposure. Seven of the patients who received EIAs also were receiving chronic dexamethasone. Of the 21 patients in our study who did not receive EIA therapy, 17 received chronic dexamethasone therapy at doses ranging from 1–16 mg/day starting before course 1 of irinotecan treatment. One patient was started on dexamethasone on day 2 of irinotecan therapy, after the day 1 pharmacokinetic study. The median day 1 SN-38 lactone AUC in the patients receiving dexamethasone but no EIAs was 28.8 ng/h/ml (range, 10.0–119.1 ng/h/ml) compared with 21.4 ng/h/ml (range, 9.0–69.7 ng/h/ml) in the four patients who did not receive dexamethasone or EIAs. Median irinotecan lactone AUC and clearance were 324.0 ng/h/ml (range, 205.4–531.6 ng/h/ml) and 55.5 liters/h/m² (range, 33.4–87.8 liters/h/m²), respectively, in patients who received dexamethasone without EIAs compared with 307.5 ng/h/ml (range, 238.9–405.8 ng/h/ml) and 61.1 liters/h/m² (range, 43.7–79.6 liters/h/m²), respectively, in patients who did not receive dexamethasone or EIAs.

Safety. Twenty-nine patients completed course 1 of irinotecan. Two patients who were not treated with EIAs received only 4 of 10 doses before irinotecan therapy was discontinued. Grade 3 or 4 toxicities reported during course 1 included grade 3 diarrhea (n = 3 patients); grade 3 nausea and vomiting (n = 2 patients); grade 3/4 neutropenia (n = 3 patients), grade 3 anemia (n = 2 patients), grade 3 hypokalemia (n = 3 patients), and grade 3 hyponatremia (n = 2 patients). The incidence of grade 3/4 toxicity in patients receiving EIA did not differ from that in patients who did not receive EIAs (P = 0.36). Of the three patients who experienced grade 3 diarrhea, one patient was receiving chronic EIA and irinotecan at a dosage of 60 mg/m²/day, whereas the other two patients had not received EIAs. The median day 1 SN-38 AUC in the three patients experiencing grade 3 diarrhea was 24.5 (range, 14.3–50.8) compared with 18.7 (range, 4.8–85.5) in those without diarrhea.
9-aminocamptothecin, topotecan, and etoposide (7, 9, 14). This finding suggests that enzyme induction may continue for as long as 14 days after EIA administration is stopped and that a longer washout period may be necessary to avoid this drug-drug interaction.

In our patient population, dexamethasone alone did not appear to affect the pharmacokinetics of irinotecan. The pharmacokinetics of irinotecan and its metabolites in patients who received dexamethasone but no EIAs did not appear different from those in the four patients who did not receive dexamethasone or EIAs, although the small sample size made statistical analyses impractical. This apparent lack of effect of dexamethasone may indicate that previously reported alterations of irinotecan pharmacokinetics in patients who have brain tumors and are receiving EIAs and dexamethasone may be attributed to EIA coadministration and not to dexamethasone (10). We noted a 1.5-fold increase in the median clearance of irinotecan lactone in patients receiving EIAs and a 2-fold decrease in the median systemic exposure to SN-38 lactone, the active metabolite. The 95% confidence interval for the median difference in the SN-38 lactone AUC between groups was 6.2–29.2, indicating that whereas there were relatively few patients in the EIA group, the difference between groups was large enough to be statistically significant.

In the five patients in whom EIA administration was stopped 2–3 days before the start of irinotecan therapy, the median day 1 systemic exposure to SN-38 lactone was below that seen for patients who had not received EIAs. The SN-38 systemic exposures remained low in this group of patients, including one patient who had carbamazepine therapy discontinued after one dose of irinotecan, through day 12 of course 1. This finding suggests that enzyme induction may continue for as long as 14 days after EIA administration is stopped and that a longer washout period may be necessary to avoid this drug-drug interaction.

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A significant difference was seen between groups for the irinotecan AUC and irinotecan clearance for the lactone forms, but these differences were not seen with the total forms. This

**DISCUSSION**

This study is the first to directly compare the pharmacokinetics of irinotecan in pediatric high-grade glioma patients receiving EIAs with those in high-grade glioma patients who did not receive EIAs. EIA administration has been associated with increased clearance of many chemotherapeutic agents, including 9-aminocamptothecin, topotecan, and etoposide (7–9, 14). This interaction may impact disease outcome, as demonstrated by Relling et al. (15), who showed that the outcome of patients with acute lymphoblastic leukemia who receive EIAs is poorer than that of patients who do not receive EIAs. The poorer outcome was hypothesized to be the result of increased clearance of agents such as teniposide and methotrexate. The widespread use of EIAs in patients with high-grade glioma may likewise decrease the efficacy of chemotherapeutic agents, including irinotecan, in this population.

Irinotecan has shown significant preclinical activity in xenografts derived from pediatric rhabdomyosarcoma, neuroblastoma, medulloblastoma, and glioblastoma multiforme and from adult colon, gastric, breast, and lung cancer and high-grade glioma (1, 16). Activity in adult malignant glioma patients has also been reported. In a Phase II study of 60 adult patients with recurrent or progressive malignant glioma, irinotecan was given on a schedule of 125 mg/m² weekly for 4 weeks followed by 2 weeks of rest. Nine patients (15%) achieved partial responses; 33 patients (55%) had stable disease. Four patients with glioblastoma multiforme had minor responses. Toxicity was limited to infrequent grade 3 myelosuppression, diarrhea, and nausea and vomiting (10).

We noted a 1.5-fold increase in the median clearance of irinotecan lactone in patients receiving EIAs and a 2-fold decrease in the median systemic exposure to SN-38 lactone, the active metabolite. The 95% confidence interval for the median difference in the SN-38 lactone AUC between groups was 6.2–29.2, indicating that whereas there were relatively few patients in the EIA group, the difference between groups was large enough to be statistically significant.

In the five patients in whom EIA administration was stopped 2–3 days before the start of irinotecan therapy, the median day 1 systemic exposure to SN-38 lactone was below that seen for patients who had not received EIAs. The SN-38 systemic exposures remained low in this group of patients, including one patient who had carbamazepine therapy discontinued after one dose of irinotecan, through day 12 of course 1. This finding suggests that enzyme induction may continue for as long as 14 days after EIA administration is stopped and that a longer washout period may be necessary to avoid this drug-drug interaction.

In our patient population, dexamethasone alone did not appear to affect the pharmacokinetics of irinotecan. The pharmacokinetics of irinotecan and its metabolites in patients who received dexamethasone but no EIAs did not appear different from those in the four patients who did not receive dexamethasone or EIAs, although the small sample size made statistical analyses impractical. This apparent lack of effect of dexamethasone may indicate that previously reported alterations of irinotecan pharmacokinetics in patients who have brain tumors and are receiving EIAs and dexamethasone may be attributed to EIA coadministration and not to dexamethasone (10). A population pharmacokinetic analysis of data from these and additional pediatric patients is planned to further define factors such as EIA use, dexamethasone use, age, and gender that may affect the disposition of irinotecan.

**Table 3** Comparison of day 1 metabolic ratios in patients who received EIAs and in those who did not receive EIAs

<table>
<thead>
<tr>
<th>Metabolic Ratio</th>
<th>Patients who received EIAs (n = 10)</th>
<th>Patients who received no EIA (n = 21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucuronidation ratio</td>
<td>4.8 (2.8–8.2)</td>
<td>2.0 (0.3–7.6)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Oxidation ratio</td>
<td>0.3 (0.1–0.8)</td>
<td>0.2 (0.1–0.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>SN-38:irinotecan ratio</td>
<td>0.1 (0.05–0.2)</td>
<td>0.2 (0.04–0.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucuronidation ratio</td>
<td>2.2 (1.5–3.0)</td>
<td>1.2 (0.2–3.0)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Oxidation ratio</td>
<td>0.1 (0.02–0.7)</td>
<td>0.1 (0.06–0.2)</td>
<td>0.63</td>
</tr>
<tr>
<td>SN-38:irinotecan ratio</td>
<td>0.08 (0.02–0.2)</td>
<td>0.2 (0.06–0.5)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Values are expressed as median (range).
* SN-38G AUC:SN-38 AUC.
* Statistically significant difference between the group who received EIAs and those who did not receive EIAs.
* APC AUC:irinotecan AUC.
* SN-38 AUC:irinotecan AUC.

**Fig. 4** Comparison of day 12 systemic exposures to SN-38 lactone in patients who had discontinued EIA therapy and in those who had received no EIAs. Bars indicate the median values for each group.
lack of difference in total parameters is most likely due to the wide variability in total irinotecan systemic exposures caused by variability in the carboxylate form, as documented by the reported ranges for these values in Table 2.

The reason for the altered metabolism of irinotecan in patients receiving EIA is remains to be elucidated; however, several explanations are possible. The antiepileptic agents phenytoin and phenobarbital are potent inducers of CYP3A (17, 18). Oxidation of irinotecan by CYP3A4 results in the formation of APC and the minor metabolite NPC, and induction of oxidation may alter irinotecan clearance. However, the fact that we did not observe statistically significant increases in systemic exposure to APC or in the oxidation ratio may suggest that induction of CYP3A4 was not responsible for the changes observed in patients receiving EIA.

Another explanation revolves around irinotecan de-esterification by carboxylesterase to produce SN-38. Phenobarbital has been shown to up-regulate expression of carboxylesterase mRNA in human hepatocytes (19). However, we observed that the AUC ratio of SN-38 to irinotecan in patients who received EIA was significantly lower than that in patients who did not receive EIA, a finding that may suggest that the increased irinotecan clearance associated with EIA coadministration is not due solely to enhanced carboxylesterase activity.

The antiepileptic agents phenobarbital and phenytoin can also induce the activity of UGT1A1, the enzyme responsible for the conversion of SN-38 to SN-38G (20–22). Induction of this enzymatic pathway may explain the increased glucuronidation ratio in patients in the EIA treatment group. It is also possible that altered rates of glucuronidation can be attributed to polymorphisms in the UGT1A1 promoter (23, 24). We are currently evaluating the pharmacogenetic determinants of glucuronidation in the patients who received EIA and in those who did not receive EIA. However, our findings suggest that enhanced glucuronidation alone is not sufficient to explain the decrease in systemic exposure to irinotecan observed in patients who received EIA because systemic exposure to SN-38G was not increased in these patients.

Because these explanations do not fully describe the interaction between irinotecan and EIA, it is plausible that enhancement of biliary excretion of irinotecan and its metabolites may contribute to the alteration of irinotecan pharmacokinetics associated with EIA. Recent studies indicate that irinotecan and its metabolites are substrates for several members of the ATP-binding cassette family of drug transporters. Irinotecan and SN-38 are substrates of the canalicular multispecific organic anion transporter (MRP2) and the breast cancer resistance protein (25–28). In addition, there is evidence that P-glycoprotein is involved in the transport of irinotecan (29, 30). Phenobarbital induces the expression of MRP2 and P-glycoprotein in human colon carcinoma cells in vitro (31, 32). Therefore, an increase in transporter activity leading to increased excretion may explain why EIA coadministration increased the clearance of irinotecan in our patients. The increase in irinotecan clearance without a subsequent increase in systemic exposure to its metabolites may be due to an enhancement of the biliary excretion of the parent compound, its metabolites, or both, through the up-regulation of one or more drug transporters. Studies are ongoing to evaluate the effect of ATP-binding cassette transporter activity on the disposition of irinotecan.

Irinotecan therapy was well tolerated in patients who received EIA and in those who did not receive EIA; the overall incidence of grade 3 diarrhea was 10%. There was no increase in the incidence of toxicity in patients who received EIA. Two of three children treated with EIA in whom the dose of irinotecan was escalated above 20 mg/m²/day were able to tolerate this increased dose, whereas one patient experienced grade 3 diarrhea at a dose of 60 mg/m²/day.

In recent years, several new generation antiepileptic agents that have little or no enzyme-inducing potential have been introduced. The availability of these newer agents may reduce the need for EIA in patients treated for high-grade glioma. We recommend the use of non-EIA agents, when clinically indicated, in patients receiving irinotecan therapy. Additional studies of adult and pediatric patients are needed to evaluate the efficacy of irinotecan for high-grade glioma in the absence of enzyme-inducing agents.

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REFERENCES


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