Pharmacokinetic Interrelationships of Irinotecan (CPT-11) and Its Three Major Plasma Metabolites in Patients Enrolled in Phase I/II Trials

Laurent P. Rivory, Marie-Christine Haaz, Pierre Canal, François Lokiec, Jean-Pierre Armand, and Jacques Robert

Department of Medicine, University of Queensland, Princess Alexandra Hospital, Woolloongabba, Queensland 4102, Australia [L. P. R.]; Université de Bordeaux II, 146 rue Léo Saignant, Bordeaux Cedex 33076 [M-C. H.]; Centre Claudius Régaud, Toulouse 31052 [J-R.]; Centre René-Huguenin, St-Cloud 92210 [F. L.]; Institut Gustave-Roussy, Villejuif 94805 [J-P. A.]; and Institut Bergonie, 180 rue de Saint-Genès, Bordeaux 33076 [J. R.], France

ABSTRACT

Irinotecan (CPT-11) is an analogue of 20(S)-camptothecin with promising activity against several tumor types. In patients, CPT-11 is metabolized to 7-ethyl-10-hydroxycamptothecin (SN-38) and to the β-glucuronide of SN-38. Recently, we identified an additional metabolite of CPT-11, 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin (APC; L. P. Rivory et al., Cancer Res., 56: 3689-3694, 1996). The aim of this study was to investigate the interrelationships of all four compounds to identify factors that might be responsible for the large interpatient variability in CPT-11 and SN-38 kinetics. The plasma kinetics of CPT-11, SN-38, the β-glucuronide of SN-38, and APC were studied in 19 patients for a total of 33 cycles (115-600 mg/m²). Although the area under the concentration curves (AUCs) of all compounds studied increased with dose, there was considerable variability. Ratios of the AUCs of the appropriate compounds were used as estimates of the major routes of metabolism (conversion of CPT-11 to SN-38, metabolism of CPT-11 to APC, and glucuronidation of SN-38). Each ratio varied more than 10-fold across the patient population, and the apparent extent of conversion of CPT-11 to SN-38 was highest at the 115 mg/m² dose level. Interestingly, AUC_{SN-38} was greater in patients with both high AUC_{CPT-11} and AUC_{APC}. We conclude that the variability of the pharmacokinetics of CPT-11 and SN-38 is likely to be due to extensive interpatient differences in the pathways implicated in the metabolism of CPT-11.

INTRODUCTION

CPT-11 (Fig. 1) is a semisynthetic derivative of 20(S)-camptothecin (1) developed in Europe (Campto) for use in colorectal adenocarcinoma that is not responsive to standard 5-fluorouracil-based chemotherapy (2). The camptothecin family of compounds are cytotoxic agents that inhibit the nuclear enzyme topo I (3). Topo I plays an important role in overcoming some of the topological problems that arise during the replication and transcription of DNA, principally through the reduction of DNA supercoiling associated with strand separation. Relaxation of DNA by topo I proceeds through transient nicked DNA-enzyme complexes, many of which are stabilized by camptothecins, thereby preventing DNA religation and release of enzyme. These complexes result in the arrest of replication forks and the formation of permanent double-stranded breaks during the S phase of the cell cycle (3). SN-38, a metabolite of CPT-11 produced in vitro by carboxylesterases, has an activity in vitro that is 100-1000-fold superior to that of CPT-11 itself (4). In patients, SN-38 is glucuronomiated to SN-38G, which is present in significant concentrations in plasma, bile, and urine (5, 6). Recently, it has been shown that tardive diarrhea, which is an important toxicity of CPT-11 in most studies, may be associated with higher values of a biliary index calculated from the product of the AUCs of CPT-11 and SN-38 divided by that of SN-38G (7). Therefore, not only is the metabolism and disposition of CPT-11 likely to be important for the activity of the drug, but it would also seem that kinetic factors could be strong correlates of its toxicity. Recently, we reported the identity of the second polar metabolite, which we observed in the plasma of patients treated with CPT-11 (8). This metabolite, APC (Fig. 1), is the product of a ring-opening oxidation of the terminal piperidine ring of CPT-11. In this paper, we present the plasma pharma-

Received 1/29/97; revised 4/23/97; accepted 4/23/97.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

3 Supported in part by grants from the Association pour la Recherche sur le Cancer (France) and the Groupement des Entreprises Francaises dans la Lutte Contre le Cancer. L. P. R. is the recipient of a National Health and Medical Research Council (Australia)/Institut National de la Santé et de la Recherche Médicale (France) Exchange Fellowship. This investigation was completed thanks to a travel bursary awarded to L. P. R. by the Société Française du Cancer.

2 To whom requests for reprints should be addressed, at Department of Medicine, University of Queensland, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Queensland 4102, Australia. Phone: 61-7-3240-2839; Fax: 61-7-3240-5399; E-mail: Lrivory@gpo.pa.uq.edu.au.

The abbreviations used are: CPT-11, irinotecan; SN-38, 7-ethyl-10-hydroxycamptothecin; SN-38G, β-glucuronide of SN-38; APC, 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin; AUC, area under the concentration curve; AUMC, area under the moment curve; topo I, topoisomerase I; t_{1/2}, terminal half-life; REC, relative extent of conversion; REM, relative extent of metabolism; REG, relative extent of glucuronidation; V_{dSS}, volume of distribution at steady state; CL, total body clearance; MRT, mean residence time; C_{max}, maximum plasma concentration.
Fig. 1 The chemical structures and pathways implicated in the metabolism of CPT-11. There is some evidence (8) to suggest that production of APC occurs via a monohydroxylated metabolite of CPT-11 (Metabolite A) and that APC may be further metabolized (Metabolite B). Metabolites A and B, which remain to be formally identified and characterized, may participate in the production of SN-38. APC is itself not appreciably transformed to SN-38 by human liver carboxylesterase or liver microsomes (15). Although not shown above, SN-38 is also further glucuronidated.

Table 1 Characteristics of patients studied

<table>
<thead>
<tr>
<th>Dose of CPT-11 (mg/m²)</th>
<th>115</th>
<th>300</th>
<th>350</th>
<th>500</th>
<th>600</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>5</td>
<td>1</td>
<td>8</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Cycles</td>
<td>13</td>
<td>1</td>
<td>9</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>54</td>
<td>61</td>
<td>56</td>
<td>56</td>
<td>56</td>
</tr>
</tbody>
</table>

MATERIALS AND METHODS

Patients and Pharmacokinetic Studies. A total of 19 patients enrolled in Phase I and II trials in France was studied during treatment with CPT-11 for colorectal adenocarcinoma (n = 9), malignancy of the cervix (n = 3), metastatic adenocarcinoma of unknown primary origin (n = 3), and other cancers (n = 4). The patients, whose characteristics are shown in Table 1, had WHO/Eastern Oncology Cooperative Group performance scores of 0–2. They represented either newly recruited patients (Bordeaux) or those for which plasma samples had been previously collected (other centers). CPT-11 was administered i.v. over 30 or 90 min every 3 weeks at doses ranging from 115–600 mg/m², except for two patients who received CPT-11 at 115 mg/m² as part of a once a week for 3 weeks protocol. CPT-11 lactone (20 mg/ml) was provided by Rhône-Poulec Rorer SA (Antony, France) and diluted further into 250 ml of sterile 0.9% NaCl. Pharmacokinetic evaluation was performed for a total of 33 cycles. Heparinized blood samples were collected before the commencement of drug infusion, at 15 min in the case of the 30-min infusion protocol and at 30 and 60 min for the 90-min perfusion, at the end of the infusion and then at 5, 10, 15, 30, 45, and 60 min and 2, 4, 8, 12, and 24 h. In some cases, samples were also collected at 48 and 72 h. Plasma was obtained after centrifugation and stored at −20 °C until analysis.

Drug Analysis. The plasma concentrations of CPT-11, SN-38, SN-38G, and APC were quantitated by high-performance liquid chromatography after the acidification of deproteinized plasma as described previously (9). Therefore, these compounds were quantitated as total concentrations (lactone + carboxylate). Authentic standards of CPT-11, SN-38, and APC were kindly supplied by Rhône-Poulec Rorer. The concentrations of SN-38G were estimated using the calibration curve of SN-38, and the relative factor of fluorescence of 0.63 was determined under identical conditions (9).

Pharmacokinetic Analysis. The AUCs of the compounds of interest were calculated using the trapezoidal method and extrapolated to infinity using the terminal rate constant estimated from a regression of the linear semi-log concentration versus time profile at later time points. The CL of CPT-11 was estimated from the dose divided by the AUC. The AUMC was estimated for CPT-11 also using the trapezoidal rule and extrapolated to infinity. The AUMC was then used to calculate the MRT and the Vdss of CPT-11 corrected for the influence of the duration of the infusion (τ) using:

\[
MRT = \frac{\text{AUMC}}{\text{AUC}} - \frac{\tau}{2} \quad \text{and} \quad V_dss = \frac{\text{Dose} \times \text{MRT}}{\text{AUC}}.
\]
The terminal half-life of elimination ($t_{1/2}$) was estimated as 0.693 divided by the terminal rate constant. The REC of CPT-11 to SN-38, the REM of CPT-11 to APC, and the REG of SN-38 were estimated as:

$$\frac{\text{AUC}_{\text{SN-38}}}{\text{AUC}_{\text{CPT-11}}} \cdot \frac{\text{CL}_{\text{CPT-11}}}{\text{CL}_{\text{SN-38}}} \cdot \frac{\text{Vd}_{\text{SN-38}}}{\text{Vd}_{\text{CPT-11}}},$$

respectively.

It should be noted that these are not direct measures of these conversions (see "Discussion") but represent useful pharmacokinetic estimates for the analysis of the dose dependence of metabolic pathways.

**Statistical Analysis.** Pharmacokinetic parameters (CL, $Vd_{SS}$, MRT, $t_{1/2}$, REC, REM, and REG) were analyzed as a function of the CPT-11 dose level using the Kruskal-Wallis one-way analysis of ranks followed by the Dunn’s method for identifying significantly different groups. Correlations between the $t_{1/2}$ of related species were carried out with the Spearman rank-order test, as were correlations between AUCs. Multiple regression analysis of the AUCs of CPT-11 and APC as independent variables and SN-38 as the dependent variable was carried out with a partial $F$ test after testing for normality and homoscedasticity (SigmaStat; Jandel Scientific, Corte Madera, CA). Statistical significance was considered to be reached when $P < 0.05$ with a two-tailed distribution. Data are presented as mean ± SD except where indicated otherwise.

**RESULTS**

**CPT-11 Kinetics.** Total CPT-11 concentrations decreased rapidly after the end of the infusion period. There was a distinguishable shoulder in these concentration profiles, sometimes even a second maximum. This behavior, which is likely to be due to either a latent increase in CPT-11 carboxylate concentrations (10) or enterohepatic recycling (11), precluded the use of conventional multieponential kinetic analysis. The $t_{1/2}$ of elimination was 6.3 ± 1.8 h, and there was no apparent relationship with the dose level (Table 2). AUC$_{CPT-11}$, on the other hand, rose in a dose-dependent fashion (Table 2 and Fig. 2). The CL averaged 16.1 ± 4.8 liters/h/m$^2$ and was highest at the 115 mg/m$^2$ dose level (Table 2). The MRT of CPT-11 was 6.6 ± 1.8 h, and the $Vd_{SS}$ was 102 ± 34 liters/m$^2$. Neither of these parameters seemed to be influenced significantly by the CPT-11 dose level (Table 2).

**SN-38 Kinetics.** The $C_{max}$ of SN-38 occurred at varying times according to two major groups of patients, those in which peak concentrations coincided with the end of the infusion and those with whom SN-38 concentrations rose steadily, achieving a plateau phase with a maximum between 2 and 4 h postinfusion (compare Fig. 3A to 3B). The first situation was present in 14 of 33 cycles, with the peak concentration of SN-38 being manifest at or within the first 15 min postinfusion, although a second peak occurred later in many cases. This variability is reflected in the overall time of peak SN-38 concentration, which was 0.74 ± 0.86 h postinfusion. AUC$_{SN-38}$ increased with CPT-11 dose rate (Table 2; Fig. 2). The $t_{1/2}$ of elimination was 13.3 ± 7.9 h and was not dependent on the dose of CPT-11.

**APC Kinetics.** APC concentrations peaked consistently at approximately 2 h after the end of the infusion (2.0 ± 0.8 h; Fig. 3, A and B). In some patients, the concentrations of APC exceeded those of CPT-11, particularly at later times (Fig. 3B). The maximal concentrations, which ranged from 0.3 to 18.4 μM across the range of CPT-11 doses, increased with CPT-11 dose rate, as did AUC$_{APC}$ (Table 3, Fig. 2), although both were subject to important interindividual variation.

**SN-38G Kinetics.** Plasma concentrations of SN-38G rose during the infusion, usually in parallel to those of SN-38 and reached peak concentrations at variable times (1.2 ± 0.6 h). In some of the patients in whom the SN-38 concentration peaked soon after the infusion, the maximum glucuronide concentrations corresponded to the second (later) maximum of SN-38. AUC$_{SN-38G}$ increased with the dose rate of CPT-11 (Fig. 2), although, as for APC, there was considerable variation.

### Table 2 The effect of dose on pharmacokinetic parameters of CPT-11 (mean ± SD, n = 33)

<table>
<thead>
<tr>
<th>Dose rate (mg/m$^2$)</th>
<th>AUC (μM·h)</th>
<th>$C_{max}$ (μM)</th>
<th>CL (liters/h/m$^2$)</th>
<th>$Vd_{SS}$ (liters/m$^2$)</th>
<th>$t_{1/2}$ (h)</th>
<th>MRT (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>115</td>
<td>9.3 ± 2.3</td>
<td>2.8 ± 1.0</td>
<td>19.3 ± 4.4*</td>
<td>121 ± 24</td>
<td>6.6 ± 1.4</td>
<td>6.5 ± 1.6</td>
</tr>
<tr>
<td>300-350</td>
<td>42.7 ± 12.6</td>
<td>13.3 ± 6.0</td>
<td>12.9 ± 3.9*</td>
<td>76 ± 19</td>
<td>6.1 ± 2.2</td>
<td>6.2 ± 2.2</td>
</tr>
<tr>
<td>500</td>
<td>47.7 ± 11.4</td>
<td>9.5 ± 3.4</td>
<td>16.3 ± 4.3</td>
<td>119 ± 48</td>
<td>6.8 ± 2.4</td>
<td>7.8 ± 2.0</td>
</tr>
<tr>
<td>600</td>
<td>68.3 ± 13.0</td>
<td>17.3 ± 6.7</td>
<td>13.4 ± 2.7</td>
<td>81 ± 16</td>
<td>4.7 ± 0.2</td>
<td>6.1 ± 0.2</td>
</tr>
</tbody>
</table>

* Significantly different, $P < 0.05$ (Kruskal-Wallis test followed by Dunn’s multiple comparisons).
Interrelationships of Metabolites. The average REC of CPT-11 to SN-38 ranged from 0.009 to 0.11 (0.047 ± 0.029). Although the AUC_{SN-38} was significantly correlated with AUC_{CPT-11} (r = 0.68; P < 0.001), the REC was significantly higher for the 115 mg/m² dose rate than it was for the 300–350 and 500 mg/m² dose levels (Table 3).

There was no dose dependence of the extent of metabolism of CPT-11 to APC as estimated from the REM, which ranged from 0.23 to 2.73 (0.98 ± 0.64). AUC_{APC} was correlated to AUC_{CPT-11} (r = 0.72; P < 0.001). The elimination phases of CPT-11 and APC were consistently parallel (for example, see Fig. 3). Indeed, the terminal half-lives of these compounds (7.1 ± 2.6 and 6.3 ± 1.8 h, APC and CPT-11, respectively) were strongly correlated (r = 0.87, P < 0.001).

There was no significant dose-dependence of the REG of SN-38 which ranged from 0.8 to 14.7 (6.7 ± 3.4). The elimination phases of SN-38 and SN-38G were also consistently parallel and the terminal half-lives of these compounds (13.3 ± 7.9 and 12.1 ± 6.2 h, SN-38 and SN-38G, respectively) were significantly correlated (r = 0.67, P < 0.001).

The interrelationship between SN-38 and CPT-11 and APC was probed further following the observation that patients with high AUC_{SN-38} usually had also high AUC_{APC} (Fig. 4). Multiple linear regression with AUC_{CPT-11} and AUC_{APC} as independent variables and AUC_{SN-38} as the dependent variable suggested that AUC_{APC} was a stronger determinant of AUC_{SN-38} than AUC_{CPT-11} but that both were significantly implicated. However, significant heteroscedasticity and the likely multicolinearity between the independent variables render this analysis prone to bias.

### Table 3 Effect of dose of CPT-11 on pharmacokinetic parameters of metabolites (mean with range in parentheses, n = 33)

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Parameter</th>
<th>115</th>
<th>300–350</th>
<th>500</th>
<th>600</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>AUC (µM/h)</td>
<td>11 (4.5–23)</td>
<td>26 (7.0–83)</td>
<td>36 (11–78)</td>
<td>108 (19–167)</td>
</tr>
<tr>
<td></td>
<td>C_{max} (µM)</td>
<td>1.0 (0.30–2.0)</td>
<td>2.7 (0.80–10)</td>
<td>2.4 (0.80–4.2)</td>
<td>11 (1.9–18)</td>
</tr>
<tr>
<td></td>
<td>t_{1/2} (h)</td>
<td>7.6 (5.0–11)</td>
<td>6.7 (3.9–12)</td>
<td>8.2 (4.7–16)</td>
<td>4.9 (3.4–5.9)</td>
</tr>
<tr>
<td></td>
<td>REM</td>
<td>2.2 (0.65–3.9)</td>
<td>1.1 (0.40–3.2)</td>
<td>1.2 (0.44–2.2)</td>
<td>2.6 (0.65–3.9)</td>
</tr>
<tr>
<td>SN-38G</td>
<td>AUC (µM/h)</td>
<td>4.7 (1.9–6.3)</td>
<td>5.0 (1.9–13)</td>
<td>11 (3.8–21)</td>
<td>11 (5.3–20)</td>
</tr>
<tr>
<td></td>
<td>C_{max} (µM)</td>
<td>0.48 (0.022–0.76)</td>
<td>0.57 (0.17–2.3)</td>
<td>0.86 (0.33–1.4)</td>
<td>0.99 (0.49–1.8)</td>
</tr>
<tr>
<td></td>
<td>t_{1/2} (h)</td>
<td>13 (5.7–29)</td>
<td>12 (4.8–26)</td>
<td>13 (5.6–23)</td>
<td>5.6 (3.7–10)</td>
</tr>
<tr>
<td></td>
<td>REG</td>
<td>7.6 (3.2–11)</td>
<td>5.6 (0.80–14)</td>
<td>8.0 (3.1–14)</td>
<td>4.2 (2.8–5.3)</td>
</tr>
<tr>
<td>SN-38</td>
<td>AUC (µM/h)</td>
<td>0.66 (0.31–1.1)</td>
<td>1.2 (0.51–2.3)</td>
<td>1.4 (0.70–2.8)</td>
<td>2.4 (1.7–3.8)</td>
</tr>
<tr>
<td></td>
<td>C_{max} (µM)</td>
<td>0.08 (0.03–0.17)</td>
<td>0.12 (0.04–0.25)</td>
<td>0.15 (0.07–0.22)</td>
<td>0.30 (0.23–0.4)</td>
</tr>
<tr>
<td></td>
<td>t_{1/2} (h)</td>
<td>13 (7.2–29)</td>
<td>17 (3.8–33)</td>
<td>11 (5.3–21)</td>
<td>7.1 (5.4–11)</td>
</tr>
<tr>
<td></td>
<td>REC</td>
<td>0.07 (0.04–0.11)</td>
<td>0.03 (0.01–0.06)</td>
<td>0.03 (0.02–0.05)</td>
<td>0.04 (0.03–0.05)</td>
</tr>
</tbody>
</table>

* Significantly different from the 115 mg/m² level, P < 0.05 (Kruskal-Wallis test followed by Dunn’s multiple comparison).

DISCUSSION

This is the first pharmacokinetic study of CPT-11 to incorporate quantitation of all three major plasma metabolites of CPT-11: SN-38, SN-38G and APC. We performed this study to examine the interrelationships of the plasma kinetics of these metabolites and the dose of CPT-11 to understand better the disposition of CPT-11 in patients.

The CL of CPT-11 was highest at the lowest dose rate (115 mg/m²). Apart from the results obtained by Negoro et al. (12), this observation is at odds with most of the literature concerning CPT-11 pharmacokinetics, although some other studies have reported higher clearances at the lower end of CPT-11 dose ranges (11). The higher CL at 115 mg/m² CPT-11 was associated with a greater relative extent of the conversion of CPT-11 to SN-38 (REC). Although a causative link could be proposed between these two observations, this is unlikely given that only a small fraction of the dose appears converted to SN-38 (6), indicating that conversion to SN-38 is a minor route of elimination for CPT-11. Also, the apparent K_{m} of this biotransformation reaction is approximately 60 µM for human liver carboxylesterase (13), which is significantly greater than the range of concentrations encountered in the study. Finally, it must be stressed that even in a simplistic pharmacokinetic model such as the one shown in Fig. 5, REC can be shown to represent the ratio of the rate constant of the formation of SN-38 to that of its elimination and, therefore, not be dependent solely on the formation of SN-38. That is, REC will also be dependent on the effect of dose on the elimination and metabolism of CPT-11 via other pathways (such as formation of APC), not to mention the saturation of SN-38 glucuronidation or enterohepatic recycling.

In any case, the relatively small number of patients studied suggests that care should be taken when interpreting these results.

We reported previously the parallel nature of the elimination kinetics of SN-38 and SN-38G (5). The present study confirms these results although the coefficient of determination (r²) of the correlation of the terminal half-lives of these two compounds was modest. This may be in part due to the difficulty in identifying correctly the terminal phase of elimination because the plasma concentrations of SN-38 rose and fell at the late time points in some instances, usually in parallel with those of SN-38G (Fig. 3). The REG was variable between patients and this would be expected to influence the disposition of SN-38.

The concentration time profiles of SN-38 were, in some cases, very different from one patient to the next with some exhibiting delayed peak concentrations with plateau-like behavior whilst in some patients, the peak SN-38 concentration oc-
curred closely following the end of the infusion. This heterogeneity in kinetic behavior, which we also observed previously in a smaller study, may affect the therapeutic outcome of treatment because it has been demonstrated that protracted exposure to CPT-11 and other camptothecins is accompanied by enhanced anticancer activity in mice bearing human xenografts (14). The reason for this heterogeneity is as yet unknown.

Although \( \text{AUC}_{\text{APC}} \) was correlated to CPT-11 dose there was considerable variability in the extent of formation of APC and, in some patients, APC concentrations were superior to those of CPT-11 several hours following the end of the infusion. Because APC differs from CPT-11 only in the distal piperidine ring, APC is a also a potential prodrug of SN-38. However, APC is not significantly converted to SN-38 by either human liver microsomes or purified human liver carboxylesterase in comparison to CPT-11 (8). CPT-11 itself is a relatively poor substrate in these systems (8, 13) and it is, therefore, unlikely that direct transformation of APC to SN-38 occurs significantly in vivo. Nevertheless, we observed that patients with high \( \text{AUC}_{\text{SN-38}} \) usually had both high \( \text{AUC}_{\text{CPT-11}} \) and high \( \text{AUC}_{\text{APC}} \) when the data were analyzed graphically (see Fig. 4). Although this is at first surprising, it is possible that either a precursor or a metabolite of APC is extensively hydrolysed to SN-38 in vivo (Fig. 1). Indeed, other metabolites of CPT-11 which are probable intermediates of the oxidative route of metabolism of CPT-11 have been observed in plasma, albeit at much lower concentrations than APC (8). APC may, therefore, be an indicator of the importance of this overall route of metabolism rather than a direct precursor of SN-38.

In conclusion, our current study demonstrates that the kinetics of the two newly described metabolites of CPT-11,
namely APC and the glucuronide of SN-38 are both subject to considerable interpatient variability. The interrelationships between the kinetics of these metabolites and CPT-11 and SN-38 are complex. Also, it is apparent from our results (8) and those of others (6) that the pathways of the metabolism of CPT-11 are still not completely defined.

ACKNOWLEDGMENTS

We are indebted to Dr. F. Bonichon for assistance with the statistical aspects of the study and to C. Garcia for many of the high-performance liquid chromatography analyses.

REFERENCES


Downloaded from clincancerres.aacrjournals.org on May 29, 2017. © 1997 American Association for Cancer Research.
Pharmacokinetic interrelationships of irinotecan (CPT-11) and its three major plasma metabolites in patients enrolled in phase I/II trials.

L P Rivory, M C Haaz, P Canal, et al.


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/3/8/1261

E-mail alerts  
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.