

Editorial

Insights into the Pharmacokinetics and Pharmacodynamics of Irinotecan

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Irinotecan is a relatively new anticancer agent of interest for both its clinical activity and its complex clinical pharmacology. It is a prodrug, requiring activation by carboxylesterases to SN-38, an inhibitor of topoisomerase I. Recent studies suggest that human carboxylesterase-2 is the primary carboxylesterase involved in the hydrolysis at pharmacological concentrations (1). Irinotecan is also oxidized by CYP3A4³ to the inactive metabolite 7-ethyl-10-[4-*N*-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin as well as to 7-ethyl-10-[4-(piperidino)-1-amino]carbonyloxycamptothecin, which can undergo hydrolysis to SN-38 (2–4). SN-38 undergoes glucuronidation by UGT1A1 (5) and is possibly oxidized by CYP3A4 as well (6). Mass balance studies have demonstrated that 64% of the total dose is excreted in the feces, confirming the important role of biliary excretion (7). Studies suggest that canalicular multi-specific organic anion transporter is the major transporter of irinotecan and its metabolites, although P-glycoprotein probably also participates in irinotecan excretion (8, 9).

The pharmacodynamics of irinotecan are less well understood. The major toxicities of irinotecan are diarrhea and myelosuppression, which are clearly dose dependent. In addition, schedule may also affect the relationship between dose and diarrhea, because the intermittent (every 3 weeks) dosing schedule appears to have a lower incidence of diarrhea. Prior studies at the University of Chicago have demonstrated that the biliary index, a surrogate measure of biliary excretion, correlates with the risk of diarrhea on the weekly schedule, suggesting that diarrhea is a function of the intraluminal exposure to SN-38 (10). This finding has not been confirmed using the intermittent dosing schedule. Myelosuppression has been correlated with the area under the concentration-time curve of both irinotecan and SN-38 (11).

Determinants of response are less clear. Response has been related to intracellular carboxylesterase activity in preclinical studies (12, 13). Thus, irinotecan, in contrast to the other camptothecins, may be a selective prodrug. This may explain the higher response rate to irinotecan in most solid tumors, in comparison to other camptothecins such as topotecan and 9-aminocamptothecin.

The current study by Kehrer and his colleagues from Rotterdam provides further insights into the pharmacokinetics and pharmacodynamics of irinotecan. Using a highly sensitive high-performance liquid chromatography assay and prolonged sampling (3 weeks), they demonstrate that the terminal half-life of SN-38 is ~2 days, longer than can be demonstrated with conventional sampling approaches. This finding is not surprising for any drug that is highly protein bound, and it is unclear whether the prolonged exposure to subnanomolar concentrations of SN-38 is clinically relevant. The finding of a decreased ratio of SN-38 glucuronide to SN-38 over time would not necessarily have been predicted. The pharmacokinetic findings, in concert with the elegant transport studies in Caco-2 monolayers, are evidence to support an enterohepatic circulation for SN-38.

Of particular interest is the authors' finding that individual fecal levels of β -glucuronidase did not correlate with any SN-38 kinetic parameters, suggesting that the activity of this enzyme is not of particular importance. Although the authors' sample size did not permit correlation of fecal β -glucuronidase with diarrhea, our own studies demonstrating an inverse relationship between SN-38 glucuronidation and diarrhea are in concordance with this observation (10). If fecal β -glucuronidase activity were a major determinant of diarrhea, then SN-38 glucuronidation would not be protective from diarrhea, because SN-38 would be able to be reformed from SN-38 glucuronide.

Kehrer and colleagues raise one last issue that requires comment. They include in their study a case report of a patient who developed obstructive jaundice, increased SN-38 concentrations, and fatal toxicity. The authors hypothesize that the pharmacokinetic findings are secondary to competitive inhibition by bilirubin of SN-38 glucuronidation. SN-38 glucuronidation is determined primarily by genetic factors, because there is a common polymorphism in the UGT1A1 promoter (14). Prior studies have demonstrated that there is a correlation between genotype and glucuronidation *in vitro* (15), and preliminary results of an ongoing clinical study at the University of Chicago demonstrate similar results *in vivo* (16). In addition, there is a common polymorphism in the coding region of UGT1A1 in Asian populations that has been associated with neonatal jaundice (17). Review of Fig. 3 of Kehrer's paper suggests that there is an abrupt decrease in SN-38 clearance (at ~6 h) with ongoing formation of SN-38 glucuronide. This pattern is more consistent with inhibition of biliary excretion than glucuronidation. Hyperbilirubinemia may also lead to decreased plasma protein binding and increased free SN-38, which would further increase the toxicity in this patient with markedly impaired SN-38 clearance.

Received 5/23/00; accepted 6/27/00.

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² Dr. Ratain is the principal inventor of an issued patent (held by ARCH Development Corporation, wholly owned by the University of Chicago): US Patent 5,786,344 (7/28/98) entitled, "Camptothecin Drug Combinations and Methods with Reduced Side Effects" (inventors Mark J. Ratain and Elora Gupta).

³ The abbreviations used are: CYP3A4, cytochrome P450 3A4; SN-38, 7-ethyl-10-hydroxycamptothecin.

There are many future challenges to improve the therapeutic index of this fascinating and active drug. One approach ongoing at the University of Chicago is pharmacokinetic modulation with inhibitors of biliary excretion (e.g., canalicular multispecific organic anion transporter and P-glycoprotein) and inducers of UGT1A1 (18, 19). A clinical study of irinotecan, cyclosporine A, and phenobarbital is in progress (20). Responses have been observed without significant diarrhea, despite a very low SN-38 area under the concentration-time curve. This finding is supportive of the hypothesis that intratumoral hydrolysis may be more important than plasma SN-38 concentrations. Thus, studies using gene therapy to increase intratumoral activation are of high interest and may result in a major advance in the use of camptothecins (21, 22).

Studies are also ongoing to try to use UGT1A1 genotyping to individualize dosing. Future studies will also search for relationships between toxicity (and possibly response) and polymorphisms in the other enzymes and transporters involved in the pharmacokinetics and pharmacodynamics of irinotecan.

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Clin Cancer Res 2000;6:3393-3394.

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