Effects of St. John’s Wort on Irinotecan Metabolism

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St. John’s wort (SJW), a widely used herbal product, has been implicated in drug interactions resulting from the induced expression of the cytochrome P450 CYP3A4 isomorph. In this study, we determined the effect of SJW on the metabolism of irinotecan, a pro-drug of SN-38 and a known substrate for CYP3A4. Five cancer patients were treated with irinotecan (350 mg/m², intravenously) in the presence and absence of SJW (900 mg daily, orally for 18 days) in an unblinded, randomized crossover study design. The plasma levels of the active metabolite SN-38 decreased by 42% (95% confidence interval [CI] = 14% to 70%) following SJW cotreatment with 1.0 µM × h (95% CI = 0.34 µM × h to 1.7 µM × h) versus 1.7 µM × h (95% CI = 0.83 µM × h to 2.6 µM × h) (P = .033, two-sided paired Student’s t test). Consequently, the degree of myelosuppression was substantially worse in the absence of SJW. These findings indicate that patients on irinotecan treatment should refrain from taking SJW because plasma levels of SN-38 were dramatically reduced, which may have a deleterious impact on treatment outcome. [J Natl Cancer Inst 2002;94:1247–9]
irinotecan that involves the CYP3A4 isoform of cytochrome P450. The plasma concentration of SN-38 was measured in the absence (closed symbols; solid line) and presence (open symbols; dotted line) of SJW. The lines represent computer fits of the SN-38 concentration–time curves in the absence and presence of SJW, respectively.

### Table 1. Effect of St. John’s wort (SJW) on irinotecan metabolism*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Irinotecan (95% CI)</th>
<th>Irinotecan/SJW (95% CI)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan AUC (µM × h)</td>
<td>33 (5.0 to 60)</td>
<td>29 (6.6 to 52)</td>
<td>.14</td>
</tr>
<tr>
<td>Irinotecan CL (L/h)</td>
<td>36 (8.7 to 64)</td>
<td>40 (9.3 to 71)</td>
<td>.11</td>
</tr>
<tr>
<td>Irinotecan Cmax (µM)</td>
<td>6.2 (4.8 to 7.5)</td>
<td>4.9 (1.3 to 8.5)</td>
<td>.55</td>
</tr>
<tr>
<td>SN-38 AUC (µM × h)</td>
<td>1.7 (0.83 to 2.6)</td>
<td>1.0 (0.34 to 1.7)</td>
<td>.033</td>
</tr>
<tr>
<td>SN-38 Cmax (µM)</td>
<td>0.19 (0.12 to 0.28)</td>
<td>0.11 (0.044 to 0.17)</td>
<td>.016</td>
</tr>
<tr>
<td>SN-38 t1/2(h)</td>
<td>26 (0 to 72)</td>
<td>20 (6.1 to 34)</td>
<td>.52</td>
</tr>
<tr>
<td>SN-38G/SN-38</td>
<td>3.2 (2.6 to 3.8)</td>
<td>3.4 (2.6 to 4.3)</td>
<td>.33</td>
</tr>
<tr>
<td>APC/irinotecan</td>
<td>0.33 (0 to 0.97)</td>
<td>0.23 (0 to 0.55)</td>
<td>.31</td>
</tr>
</tbody>
</table>

*AUC = area under the plasma concentration versus time curve; APC = 7-ethyl-10-[4-N-((5-amino-pentanoic acid)-1-piperidino]-carboxylxycamptothecin; CI = confidence interval; CL = apparent clearance; Cmax = peak plasma concentration; t1/2 = apparent half-life of the terminal disposition phase.
†Two-sided Student’s t test for matched pairs.
‡SN-38 is the active metabolite of irinotecan, also known as CPT-11. SN-38G is a detoxified metabolite of SN-38 that involves uridine diphosphate glucuronosyltransferase. APC is a detoxified metabolite of irinotecan that involves the CYP3A4 isof orm of cytochrome P450.

### Notes

- **Fig. 1.** Effect of St. John’s wort (SJW) on the plasma concentration of the active irinotecan metabolite SN-38 over time. The plasma concentration of SN-38 was measured over time as described (13,14). Each data point represents an individual data time point of the plasma concentration of SN-38 measured in the absence (closed symbols; solid line) and presence (open symbols; dotted line) of SJW.

- SJW can be used as a treatment of high-grade glioma patients treated with irinotecan and CYP3A4-inducing anticonvulsants. Alternatively, the lack of effect on APC might be attributed to the fact that during both treatment courses, patients were receiving dexamethasone. Dexamethasone is another known inducer of CYP3A4 expression and might already stimulate APC formation during the course without SJW cotreatment (17). In the liver, SN-38 can be metabolized to a glucuronic acid conjugate (SN-38G), a process that is catalyzed by uridine diphosphate glucuronosyltransferases (UGTs). The rate of SN-38 glucuronidation (i.e., the AUC ratio of SN-38G to SN-38) was not influenced by SJW (Table 1), suggesting that increased glucuronidation through the induction of UGT was not contributing to the reduced SN-38 levels.

- Similar changes in SN-38 levels (peak plasma concentrations and AUCs) were noted among all patients, regardless of when they received SJW. The changes were, however, more pronounced for the three patients who received SJW during the second course of irinotecan than for those who received SJW during the first course. Previous work (18) has shown that the ability of SJW to induce CYP3A4 expression is dependent on the length of therapy, with no observable effects when SJW was given for 8 days or less. It has been hypothesized that this may be the result of the formation of an intermediate or slowly accumulating metabolite of the components of SJW [i.e., (pseudo)hypericin and hyperforin] with CYP3A4-inducing effects (19). Thus, one potential explanation for the schedule-dependent effects of SJW on irinotecan metabolism may be a prolonged effect of SJW on CYP3A4 expression with long-term administration regimens.

- It has also been proposed that induction of MDR1 P-glycoprotein expression may be a component of the mechanism for interactions between several other drugs and SJW (11). Preclinical studies have shown that biliary transport of SN-38 is unchanged in mice lacking mdr1-type P-glycoprotein, which suggests no major role of MDR1 P-glycoprotein in the elimination of SN-38 in patients (20). These observations, together with our current observation that the half-lives of SN-38 are unchanged in the presence and absence of SJW coadministration (Table 1), make it unlikely that MDR1 P-glycoprotein is involved in the observed interaction. This is because a prominent role of MDR1 P-glycoprotein in the interaction would be associated with increased biliary transport of SN-38, resulting in a decreased half-life of SN-38 in plasma.

- Overall, our findings suggest that irinotecan metabolism and toxicity are altered by SJW and that the two agents cannot be given safely in combination without compromising overall antitumor activity. We expect that the results presented here for irinotecan are representative of other anticancer drugs that are at least partial substrates for CYP3A4. This hypothesis is supported by recent observations that the pharmacokinetics of several commonly used agents, including taxanes [e.g., paclitaxel (21)] and camptothecines [e.g., irinotecan (22) and topotecan (23)], are altered in patients on anticonvulsants as a result of CYP3A4 induction, which leads to increased dose requirements to achieve similar pharmacologic effects. Until specific dosing guidelines are available, it is strongly recommended that patients...
receiving chemotherapeutic treatments with such agents refrain from taking SJW.

REFERENCES


NOTE

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