

## BRIEF COMMUNICATIONS

### 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 isoform. 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/m<sup>2</sup>, 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]**

St. John's wort (SJW) has become one of the world's most popular herbal preparations, particularly among cancer patients (1) because of its alleged activity in mild to moderate forms of depression (2-4). Previous case reports and clinical investigations suggest that SJW induces the expression of the cytochrome P450 enzyme system and drug-transporting proteins (5-8). Specifically, SJW was shown to directly induce the expression of the cytochrome P450 CYP3A4 isoform in intestinal and he-

patic cells and to induce the expression of MDR1 P-glycoprotein in intestinal cells (9-11). These observations might have profound clinical implications for patients with colorectal cancer receiving the chemotherapy agent irinotecan, because the drug is, in part, eliminated *via* CYP3A4- and P-glycoprotein-mediated routes (12). Moreover, irinotecan, a topoisomerase I inhibitor, has a narrow therapeutic range, and the induction of CYP3A4 and P-glycoprotein by SJW might theoretically result in decreased systemic levels of the pharmacologically active metabolite SN-38, the consequence of which might be a loss of antitumor activity.

We evaluated the potential of SJW to affect plasma concentrations of SN-38 in a group of cancer patients treated with irinotecan in an unblinded, randomized crossover study design, with and without SJW coadministration. The clinical protocol was approved by the Erasmus MC Ethics Board, and all patients signed informed consent forms before study entry. Irinotecan was administered once every 3 weeks as a 90-minute continuous intravenous infusion at a dose of 350 mg/m<sup>2</sup>. Fourteen days before the start of the first or second irinotecan administration, patients received one SJW tablet (300 mg; Bio Nutrition Health Products, Den Bosch, The Netherlands) three times a day (i.e., one tablet with each meal). The patients continued this comedication while receiving the irinotecan therapy and stopped 4 days after irinotecan dosing. Patients were asked to abstain from alcohol, caffeine, grapefruit juice, other herbal dietary supplements, and/or substances known to influence the expression of CYP3A4 for a period of 2 weeks before the first irinotecan administration up to 3 weeks after the second irinotecan administration. Blood sampling, drug analyses, and pharmacokinetic parameter calculations were performed as described (13,14). Data are presented as mean value with 95% confidence intervals (CIs), and statistical calculations were performed on the Number Cruncher Statistical System (NCSS), version 5.X (J. L. Hintze, East Kaysville, UT).

There were five evaluable patients: two men and three women, with a median age of 58 years (range = 54-66 years) and a median World Health Organization (WHO) performance score of 1 (range = 0-1) (<http://www.who.int/>

home-page/). All five completed the study within the scheduled time without delay. Two patients had colorectal cancer, two had lung cancer, and one had sarcoma. Clinically, irinotecan-induced neutropenia, as measured by a decrease in the number of circulating neutrophils, was the most prominent side effect, and the spectrum of side effects was unchanged by SJW. The degree of myelosuppression differed substantially between the treatment course with irinotecan alone and the combination course with irinotecan and SJW. At nadir, leukocyte and neutrophil counts decreased 56% (95% CI = 32% to 80%) and 63% (95% CI = 48% to 78%), respectively, during the course with irinotecan alone but decreased only 8.6% (95% CI = 0% to 29%) and 4.3% (95% CI = 0% to 20%), respectively, during the combination course with irinotecan and SJW.

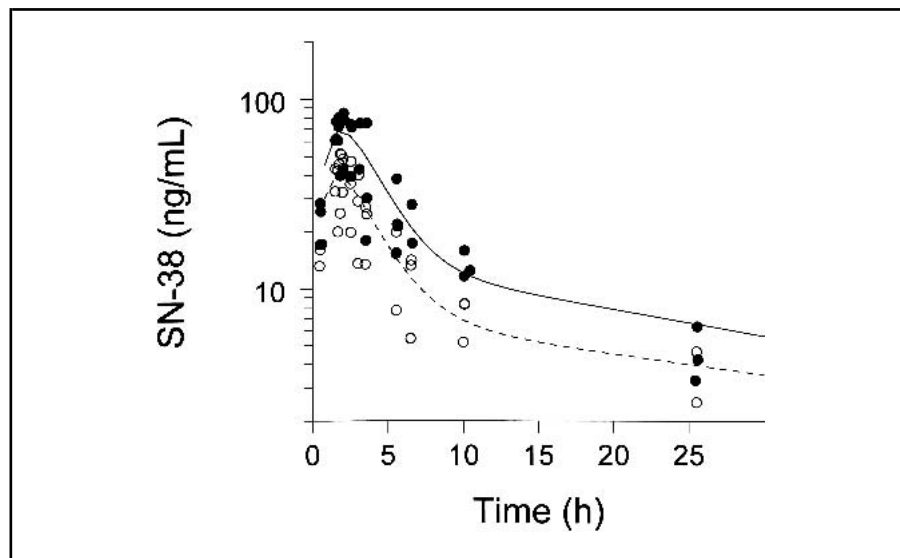
We next measured the levels of the active irinotecan metabolite SN-38 and its CYP3A4-mediated detoxified metabolite 7-ethyl-10-[4-*N*-(5-aminopentanoic acid)-1-piperidino]-carbonyl-oxy-camptothecin (APC). Compared with courses of irinotecan alone, the area under the curve (AUC) of SN-38 decreased by 42% (95% CI = 14% to 70%) in the combination course with irinotecan and SJW from 1.7 μM × h (95% CI = 0.83 μM × h to 2.6 μM × h) to 1.0 μM × h (95% CI = 0.34 μM × h to 1.7 μM × h) (*P* = .033, two-sided Student's *t* test; Fig. 1 and Table 1). Surprisingly, the AUC ratio of APC to irinotecan was also reduced by 28% (95% CI = 0% to 80%) in the combination course with irinotecan and SJW, although this reduction was not statistically significant. This result suggests that the induction of CYP3A4 expression results in the formation of presently unknown metabolites other than APC (15), as has been described previously (16) in pediatric

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**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. 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\*

Parameter	Irinotecan (95% CI)	Irinotecan/SJW (95% CI)	P†
<b>Irinotecan</b>			
AUC ( $\mu\text{M} \times \text{h}$ )	33 (5.0 to 60)	29 (6.6 to 52)	.14
CL (L/h)	36 (8.7 to 64)	40 (9.3 to 71)	.11
$C_{\text{max}}$ ( $\mu\text{M}$ )	6.2 (4.8 to 7.5)	4.9 (1.3 to 8.5)	.35
<b>SN-38‡</b>			
AUC ( $\mu\text{M} \times \text{h}$ )	1.7 (0.83 to 2.6)	1.0 (0.34 to 1.7)	.033
$C_{\text{max}}$ ( $\mu\text{M}$ )	0.19 (0.12 to 0.28)	0.11 (0.044 to 0.17)	.016
$t_{1/2(z)}$ (h)	26 (0 to 72)	20 (6.1 to 34)	.52
<b>AUC ratios</b>			
SN-38/irinotecan‡	0.054 (0.036 to 0.073)	0.036 (0.0054 to 0.067)	.054
SN-38G/SN-38	3.2 (2.6 to 3.8)	3.4 (2.6 to 4.3)	.33
APC/irinotecan	0.33 (0 to 0.97)	0.23 (0 to 0.55)	.31

\*AUC = area under the plasma concentration versus time curve; APC = 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carboxyoxycamptothecin; CI = confidence interval; CL = apparent clearance;  $C_{\text{max}}$  = peak plasma concentration;  $t_{1/2(z)}$  = 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 irinotecan that involves uridine diphosphate glucuronosyltransferase. APC is a detoxified metabolite of irinotecan that involves the CYP3A4 isoform of cytochrome P450.

high-grade glioma patients treated with irinotecan and CYP3A4-inducing anti-convulsants. 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 glucuronosyltrans-

ferases (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 camptothecins [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.

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## NOTE

Manuscript received April 24, 2002; revised June 12, 2002; accepted June 14, 2002.