

Drug Interactions with St. John's Wort

John R. Horn, PharmD, FCCP, and Philip D. Hansten, PharmD

Drs. Horn and Hansten are both professors of pharmacy at the University of Washington School of Pharmacy. For an electronic version of this article, including references, visit www.hanstenandhorn.com.

Five years ago in this column, we discussed the potential for St. John's wort (SJW) to cause drug interactions. At that time, SJW had been identified as an inducer of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein

(P-gp). We discussed the interactions with alprazolam, oral contraceptives, and several antiretroviral drugs. In each case, SJW was shown to increase the metabolism of the object drug resulting in a reduction in efficacy. The information on SJW's interaction potential has continued to develop, and this column is intended to bring you up to date.

SJW has been determined to be an inducer of several CYP450 enzymes, including CYP3A4, CYP2C9, and CYP2C19. In addition, SJW appears



Table

Drugs Reported to Interact with St. John's Wort			
Object Drug	Substrate	Magnitude of Interaction on Object Drug	Comments
Alprazolam (Xanax)	CYP3A4	↓AUC 40%	Other benzodiazepines (eg, midazolam, triazolam) may be similarly affected.
Cyclosporine (Neoral)	CYP3A4, P-gp	↓AUC 30%-75%	Transplant rejection may occur; monitor CsA concentrations.
Digoxin	P-gp	↓AUC 25%-30%	Monitor plasma concentration.
Erlotinib (Tarceva)	CYP3A4	↓AUC 66%	Avoid use.
Fexofenadine (Allegra)	CYP3A4	↓AUC 40%-50%	
Glipizide (Glucotrol)	CYP2C9	↓AUC 33%	Glyburide may be similarly affected.
Ibuprofen (Advil)	CYP2C9	↓AUC 30%	Other NSAIDs may be similarly affected.
Imatinib (Gleevec)	CYP3A4	↓AUC 30%-40%	Avoid concurrent use.
Indinavir	CYP3A4	↓AUC 60%	Ritonavir, saquinavir, nelfinavir and other protease inhibitors likely to be similarly affected.
Methadone	CYP2B6, CYP2C19	↓AUC 47%	Potential to affect fentanyl, oxycodone
Nifedipine	CYP3A4, P-gp	↓AUC 45%	May also affect amlodipine, bepridil, diltiazem, felodipine, isradipine, nicardipine, nimodipine, nitrendipine, verapamil
Omeprazole (Prilosec)	CYP2C19, CYP3A4	↓AUC 40%-50%	Larger effect in CYP2C19; EMs, may also affect esomeprazole, pantoprazole, lansoprazole
Oral contraceptives	CYP3A4	Loss of efficacy	Use alternative contraception; avoid SJW.
Simvastatin (Zocor)	CYP3A4	↓AUC 50%	May also affect lovastatin and atorvastatin in a similar manner
Tacrolimus (Prograf)	CYP3A4	↓AUC 50%-60%	Transplant rejection may occur; monitor tacrolimus concentrations.
Voriconazole (Vfend)	CYP3A4, CYP2C19	↓AUC 60%	Larger effect in CYP2C19 EMs
Warfarin	CYP2C9	Loss of efficacy	↓INR

AUC = area under the curve; CSA = cyclosporine A; EM = extensive metabolizer; INR = international normalized ratio; NSAID = nonsteroidal anti-inflammatory drug; P-gp = P-glycoprotein; SJW = St. John's Wort.

to induce several transporter proteins, including P-gp and organic anion transporters. Usually 10 to 14 days of SJW administration are required to produce the maximum effect on enzyme induction and a similar time to revert back to baseline following discontinuation of SJW. SJW, in a manner similar to rifampin, binds to the pregnane X receptor, resulting in stimulation of the genes that produce several cytochrome enzymes and transporters.

The primary constituent of SJW that causes the CYP450 induction appears to be the compound hyperforin. The Table lists several common drugs whose metabolism is known to be induced by SJW. Higher doses of SJW will produce a larger reduction in the plasma concentration of the object drugs. Although data may not be available for very

many drugs that interact with SJW, one should consider that most substrates for CYP3A4, CYP2C19, CYP2C9, and P-gp will be affected to some degree by chronic SJW coadministration.


**SJW has been
determined to be an
inducer of several
CYP450 enzymes,
including CYP3A4,
CYP2C9, and CYP2C19.**


It appears that SJW can induce the activity of multiple CYP enzymes as well as drug transporters such as P-gp. One

should be alert for reduced plasma concentrations and drug response with any drug that is metabolized by CYP3A4, CYP2C9, or CYP2C19, or transported by P-gp when it is coadministered with SJW.

Patients taking any drug that has a narrow therapeutic range and may be susceptible to SJW-induced metabolic induction should be monitored for loss of drug effect during SJW coadministration. If patients are taking SJW chronically, they may be at risk to develop increased concentrations of object drugs if they discontinue SJW without appropriate monitoring of the object drug. The antidepressant efficacy of SJW is modest at best; therefore, it would be prudent to counsel patients to avoid SJW if they are taking any other drugs. ■

