



Health Canada

Santé Canada

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April 6, 2000

00-012891

To Associations:

Health Canada has issued a letter advising healthcare professionals of important drug interactions between St. John's Wort (*Hypericum perforatum*) and certain prescription medications. St. John's Wort appears to cause drug interactions by increasing the production of certain drug-metabolizing enzymes in the liver. The resulting decrease in the blood and tissue levels of drugs metabolized by these enzymes may result in a loss of the desired therapeutic effect of these medicines. St. John's Wort has also been reported to increase levels of serotonin and other neurotransmitters found in the brain. Concomitant administration with certain prescription antidepressants which also elevate levels of these neurotransmitters has been reported to cause a pattern of adverse events known as "serotonin syndrome".

Health Canada believes that the information contained in this letter will be helpful in averting and managing drug interactions associated with the concomitant use of conventional medications with this herbal product. A copy of this letter is provided for your information and further dissemination as appropriate.

Original signed
by

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Susan Hasnain

Dann M. Michols
Director General
Therapeutic Products
Programme

For Philip Waddington
Executive Director
Office of Natural Health
Products



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To: Health Care Professionals

**RE: RISK OF IMPORTANT DRUG INTERACTIONS BETWEEN ST.
JOHN'S WORT AND PRESCRIPTION DRUGS**

Health Canada would like to advise physicians, pharmacists, complementary medicine practitioners, and other health care professionals of the potential for clinically significant drug interactions when certain prescription medications are used in combination with St. John's Wort (*hypericum perforatum*). St John's Wort is a herbal product which is available without a prescription at supermarkets, pharmacies, and health food stores as capsules, tablets, liquids, ointments, and teas. St. John's Wort products with DIN status are labelled for use as remedies for a range of disorders including nervousness, tension, insomnia, nervous headache, and neuralgic pain. Various reports also attribute antidepressant properties to this herb.

St. John's Wort appears to decrease the blood levels of some concomitantly administered drugs, an effect which may be related to the induction of enzymes of the cytochrome P450 metabolic pathway and/or the P-glycoprotein transporter. Substances which induce drug metabolism decrease the plasma concentration of co-administered drugs that are substrates for these enzymes. Induction can be expected to reduce the therapeutic effects of medicines that are de-activated by these enzymes and to enhance the pharmacodynamic activity of prodrugs that are activated as a result of metabolism.

Another mechanism whereby St. John's Wort may cause drug interactions is by effects on neurotransmitter availability in the brain.

INDINAVIR AND OTHER ANTIRETROVIRAL AGENTS

In a study conducted by the National Institutes of Health (NIH), the concomitant administration of St. John's Wort and indinavir (Crixivan), an HIV-1 protease inhibitor used to treat HIV infection, resulted in a substantial decrease of indinavir plasma concentrations. The findings of this investigation were published in the February 12, 2000, issue of *Lancet* (1).

Although drug interaction studies with St. John's Wort are not available for antiretroviral agents other than indinavir, the possibility of significant decreases in the blood concentrations of all of the currently marketed HIV-1 protease inhibitors (PIs) should be considered. Moreover, the possibility of such reactions with other drugs that are similarly metabolized, including the non-nucleoside reverse transcriptase inhibitors (NNRTIs) cannot be excluded. The concomitant use of St. John's Wort with PIs or NNRTIs is, therefore, not recommended owing to the risk of suboptimal antiretroviral drug concentrations which may lead to therapeutic failure and promote the development of viral strains resistant to the administered drug and other members of its therapeutic class.

OTHER DRUGS

Another clinical trial has demonstrated decreased levels of the cardiac glycoside, **digoxin**, in the presence of St. John's Wort (2, 3).

Other drug interactions with St. John's Wort are suspected on the basis of published case reports. Patients with organ transplants who take the immunosuppressant, **cyclosporine**, together with St. John's Wort have been reported to experience acute graft rejection in association with decreased blood levels of cyclosporine (2, 4, 5). Use of St. John's Wort with the anticoagulant, **warfarin**, has been associated with a reduced anticoagulant effect and a need to increase warfarin levels (4, 6).

Another case report raises suspicions of interactions between St. John's Wort and the asthma therapy, **theophylline** (2, 4, 7). The occurrence of breakthrough bleeding in some patients receiving St. John's Wort together with **oral contraceptives** is suggestive of the possibility of unwanted

pregnancies in patients receiving this combination (2, 4, 6).

St. John's Wort has also been reported to inhibit the neuronal reuptake of serotonin and certain other neurotransmitters in the brain. When St. John's Wort is administered together with prescription antidepressant drugs which also elevate the availability of serotonin in the brain, patients may experience a pattern of side effects described as "serotonin syndrome", including nausea, vomiting, restlessness, dizziness, tremor and headache. Case reports have been published describing the occurrence of "serotonin syndrome" when St. John's Wort is used with certain prescription antidepressant drugs such as selective serotonin reuptake inhibitors and nefazodone (2, 8).

Other drug interactions, such as diminished plasma concentrations of the anti-epilepsy drugs, phenytoin, carbamazepine, and phenobarbital, may be anticipated on the basis of theoretical considerations.

Candidates for drug interactions with St. John's Wort are not limited to the drugs mentioned above. As research of this issue continues, it is likely that the list of confirmed and suspected interactions will expand to include many other drugs that are metabolized by enzymes in the liver.

GENERAL RECOMMENDATIONS

Given the widespread availability of herbal products in foods and over-the-counter medications, it is important that healthcare professionals actively question their patients about the use of St. John's Wort preparations before issuing drug prescriptions or while monitoring the effectiveness of a prescription treatment. In many cases, it may be advisable for the patient to discontinue products containing this herbal ingredient prior to initiating treatment with a conventional medication (e.g. HIV-1 protease inhibitors, non-nucleoside reverse transcriptase inhibitors, cyclosporine, warfarin, digoxin, theophylline, oral contraceptives). In the case of patients who have been stabilized on a higher than usual dose of a prescription drug in the presence of St. John's Wort, attention should be directed to the possibility of undesirable increases in the blood levels of the interacting drug when St. John's Wort is discontinued. For drugs with a narrow therapeutic range (e.g. warfarin, digoxin, and cyclosporine), monitoring and dosing adjustment may be necessary in this situation to avoid an increased risk of toxicity.

Patients receiving serotonergic antidepressants or migraine therapies (e.g. the triptan class) should avoid St. John's Wort products due to the possibility of an increased risk of serotonin syndrome during concomitant administration.

The capacity of St. John's Wort products to cause drug interactions may vary between preparations and batches, owing to differences in the content of the active ingredients. In the absence of controlled testing of the available preparations, it is not possible to comment on the comparative potency of individual products in this regard.

No information is available to determine the long-term consequences of increased liver enzyme production in individuals receiving St. John's Wort. The possibility that the drug may affect the enzymatic breakdown of exogenous chemicals entering the body through dietary or environmental exposure should be considered.

Cases of adverse events or therapeutic failure associated with the concomitant use of prescription drugs and St. John's Wort products should be reported to the Adverse Reaction and Medication Error Assessment Division of the Bureau of Licensed Product Assessment by phone at (613) 957-0337 or by fax at (613) 957-0335.

Dann M. Michols
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Programme

Philip Waddington
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TABLE OF IDENTIFIED OR SUSPECTED INTERACTIONS
BETWEEN PRESCRIPTION DRUGS AND ST. JOHN'S WORT (SJW)

Interacting Drug(s)	Characteristics of Interaction	Recommendations
<p>HIV-1 protease inhibitors (e.g. indinavir, ritonavir, saquinavir)</p>	<p>Reduced plasma levels of indinavir when administered with SJW. May be generalizable to other HIV-1 protease inhibitors. Potential loss of HIV suppression and development of drug resistance.</p>	<p>Combined use not recommended. In patients already receiving these drugs with SJW, SJW should be discontinued and the viral RNA load measured.</p>
<p>HIV non-nucleoside reverse transcriptase inhibitors (e.g. delaviridine, nevirapine)</p>	<p>Interactions with SJW suspected on theoretical grounds as these drugs are metabolized in a similar way to the protease inhibitors.</p>	<p>Combined use not recommended. In patients already receiving these drugs with SJW, SJW should be discontinued and the viral RNA load measured.</p>
<p>Digoxin</p>	<p>Reduced plasma levels of digoxin when administered with SJW. May decrease inotropic effect in heart failure or rate control in atrial fibrillation or flutter.</p>	<p>Combined use not recommended. In patients already receiving this drug with SJW, digoxin plasma levels should be monitored and dosage adjustments considered when SJW is discontinued.</p>
<p>Cyclosporine</p>	<p>Case reports of decreased cyclosporine plasma levels and acute organ transplant rejection when administered with SJW.</p>	<p>Combined use not recommended. In patients already receiving this immunosuppressant with SJW, cyclosporine plasma levels should be monitored and dosage adjustments considered when SJW is discontinued.</p>
<p>Warfarin</p>	<p>Case reports of decreased anticoagulant effect and increased warfarin requirement when administered with SJW.</p>	<p>Combined use not recommended. In patients already receiving this anticoagulant with SJW, warfarin plasma levels should be monitored and dosage adjustments considered when SJW is discontinued.</p>

Interacting Drug(s)	Characteristics of Interaction	Recommendations
Theophylline	Case report of decreased plasma levels and increased dose requirement	Combined use not recommended. In patients already receiving theophylline with SJW, theophylline plasma levels should be monitored and dosage adjustments considered when SJW is discontinued.
Oral Contraceptives	Case reports of breakthrough bleeding. Theoretical risk of unwanted pregnancy.	Combined use not recommended.
Antidepressants (e.g. selective serotonin reuptake inhibitors, nefazodone, trazodone)	Case reports of "serotonin syndrome" pattern of adverse events when used in combination with SJW.	Combined use not recommended. In patients already receiving conventional antidepressants with SJW, consideration should be given to discontinuing SJW.
Anti-epilepsy Drugs (e.g. phenytoin, carbamazepine, phenobarbital)	Interactions suspected on theoretical grounds. Decreased plasma levels of these drugs would be expected to increase risk of seizures.	Combined use not recommended. In patients already receiving these drugs with SJW, plasma levels of the anti-epilepsy drugs should be monitored and dosage adjustments considered with SJW is discontinued.

Note: The above information has not been independently validated by Health Canada, but represents information available in the public domain literature.