

Herb-medicine interactions: St John's wort (*Hypericum perforatum*)

Useful information for pharmacists

Introduction

Because herbal products and conventional medicines have demonstrable pharmacological activity there is a potential for interactions. There have been reports of interactions between St John's wort and several prescribed medicines [see **Table 1**]¹.

This information sheet identifies the principal interacting medicines and explains the basis of the interactions. It may be used, together with other information sources, as a basis to provide advice to patients.

Most products containing St John's wort for oral use do not have a marketing authorisation. They are supplied as herbal remedies exempt from licensing under the Medicines Act, and no medical claims are permitted.

Evidence from controlled clinical trials suggests that St John's wort extracts are effective in the treatment of mild to moderate depression, and may be as effective as some standard antidepressants.² St John's wort is not considered appropriate for the treatment of major depression.

These trials suggest that St John's wort is well tolerated at recommended doses, and has a more favourable adverse effect profile than those of many conventional antidepressants.³

Key points for pharmacists

- Patients considering taking St John's wort should be asked about their prescribed medicines. If these include any medicines known to interact, advise patients not to take St John's wort, and explain the reasons for this. Interacting medicines are listed in **Table 1**

- Patients already taking St John's wort and any other interacting medicines listed in **Table 1** should be advised to stop taking St John's wort, after consulting their GP because dose adjustment of these medicines may be necessary
- Patients taking St John's wort and an **oral contraceptive** should be advised to stop taking St John's wort and to use an additional contraceptive method for at least four weeks
- Pharmacists should be aware that some patients already taking potentially interacting medicines may start St John's wort without consulting a pharmacist or GP

Table 1: Medicines known to interact with St John's wort

- anticonvulsants (*carbamazepine, phenobarbitone, phenytoin*)
- ciclosporin
- digoxin
- HIV protease inhibitors (*indinavir, nelfinavir, ritonavir, saquinavir*)
- HIV non-nucleoside reverse transcriptase inhibitors (*efavirenz, nevirapine*)
- oral contraceptives
- selective serotonin reuptake inhibitors (SSRIs) (*citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline*)
- theophylline
- triptans (*sumatriptan, naratriptan, rizatriptan, zolmitriptan*)
- warfarin

Patient management

Patients **who are considering taking St John's wort** should be asked about their prescribed medicines. Patients already taking an interacting medicine should be advised not to take St John's wort. Patients taking other medicines should be given professional advice before using St John's wort (see 'Other

medicines').

Patients already taking an interacting medicine and **who have recently started taking St John's wort** may experience reduced effects of their medicine.

Patients already taking St John's wort and interacting medicines may experience problems if they **stop taking St John's wort**. When St John's wort is stopped, the induction of CYP enzyme also stops and so drug metabolism is no longer increased. Blood concentrations of the drug may rise and can lead to adverse effects [see Pharmacokinetic basis of interactions]. These patients should be advised to see their GP before stopping St John's wort because dose adjustment of these medicines may be necessary.

The following are **not** likely to interact with St John's wort:

- ◆ medicines (other than SSRIs and triptans) that are not metabolised by the liver
- ◆ topical medicines.

Topical or homoeopathic preparations of St John's wort are not likely to interact with prescribed medicines.

Pharmacokinetic basis of interactions

Evidence suggests that St John's wort induces certain cytochrome P450 (CYP) drug-metabolising enzymes in the liver (specifically CYP1A2, CYP2C9 and CYP3A4) and P-glycoprotein (a transport protein). The constituents of St John's wort that cause induction have not been fully identified.

Certain drugs metabolised by these CYP enzymes are metabolised more rapidly after enzyme induction by St John's wort. This can lead to lower blood concentrations of the drugs and can reduce the therapeutic effect.

Pharmacodynamic basis of interactions

Constituents of St John's wort have been shown to affect the uptake of serotonin and other neurotransmitters. St John's wort extract may have effects on dopaminergic systems in the human brain.

There have been reports of increased serotonergic effects in patients taking St John's wort concurrently with selective serotonin reuptake inhibitors (SSRIs). Serotonergic syndrome has been reported in elderly patients who started St John's wort while taking *sertraline* or *nefazodone*.

Medicines with which there may be the **potential** for pharmacodynamic interactions with St John's wort include other SSRIs, such as *fluoxetine*, and other triptans, such as *sumatriptan*.

Other medicines

There are many other substances whose metabolism involves the CYP enzymes concerned, or P-glycoprotein, or both. [See the MCA website: www.open.gov.uk/mca]. These have the **potential** to interact with St John's wort. However, the interactions are predicted on a theoretical basis and there is no evidence of clinical importance. Pharmacists should be vigilant to the possibility of interactions between St John's wort and these substances and, where appropriate, should consider asking about use of other medicines.

CSM advice to health professionals

This advice on the management of patients taking St John's wort and certain prescribed medicines can be summarised as follows.

- *Warfarin, ciclosporin, digoxin, theophylline, and anticonvulsants.* Risk of reduced therapeutic effect, eg risk of reduced anticoagulant effect, transplant rejection, loss of control of heart rhythm, loss of asthma control, seizures. Check plasma drug concentrations. Dose adjustment may be necessary. Stop St John's wort. With warfarin, the patient's INR (international normalised ratio) should be checked.
- *HIV protease inhibitors and HIV non-nucleoside reverse transcriptase inhibitors.* Risk of reduced blood concentrations, with possible loss of HIV suppression. Measure HIV RNA viral load and stop St John's wort.
- *Oral contraceptives:* Risk of reduced blood concentrations, breakthrough bleeding and unintended pregnancy. Stop St John's wort.
- *Triptans and SSRIs:* Risk of increased serotonergic effects with the possibility of an increased risk of adverse reactions. Stop St John's wort.

Monoamine oxidase inhibitors

There are earlier reports that St John's wort had monoamine oxidase inhibitory (MAOI) activity and concerns that (in large doses) it may potentiate MAOI therapy. However, it is now generally accepted that monoamine oxidase inhibition plays little or no part in the antidepressant activity of St John's wort.⁴ Therefore, it is not necessary to avoid medicines containing sympathomimetic agents (which interact with MAOIs), such as cough and cold remedies, or tyramine-containing foodstuffs, such as cheese, wine, meat and yeast extracts, while taking St John's wort.

Reports of interactions

Reports of suspected interactions between St John's wort and conventional medicines received by the Committee on Safety of Medicines (CSM) between October 1996 and June 2002 are summarised in **Table 2**.

The CSM encourages community and hospital pharmacists to submit yellow card reports for all adverse reactions associated with herbal products.

| Table 2. Reports of suspected interactions between St John's wort and conventional medicines received by the UK Committee on Safety of Medicines for the period October 1996 to June 2002 | | |
|--|----------------|---|
| Compound or medicine | Reports | Comment |
| Warfarin | 4 | Increased INR (2 reports); decreased INR (2 reports) |
| SSRIs | 4 | Paroxetine (3 reports); Sertraline (1 report) |
| Theophylline | 1 | Reduced serum theophylline concentration |
| Indinavir, lamivudine, stavudine | 1 | HIV viral load increased |
| Tacrolimus | 1 | Medicine ineffective |
| Oral contraceptives | 14 | Intermenstrual bleeding (6 reports); unintended pregnancy (8 reports) |
| Others | 15 | Including: HRT (2 reports), atorvastatin (1 report), moclobemide (1 report), verapamil (1 report), enalapril (1 report), lithium (1 report), thyroxine (1 report) |
| † Source: Medicines Control Agency Adverse Drug Reactions Online Information Tracking (ADROIT) INR = international normalised ratio; SSRIs = selective serotonin reuptake inhibitors | | |

References

1. Breckenridge A. Important interactions between St John's wort (*Hypericum perforatum*) and prescribed medicines. [Dear Doctor/Pharmacist letter]. <http://www.open.gov.uk/mca>
2. Linde K., Mulrow C. D. St John's wort for depression (Cochrane review). In: The Cochrane Library, Issue 1, 2002. Oxford: Update Software
3. Barnes J., Anderson L. A., Phillipson J. D. St John's wort (*Hypericum perforatum*): a review of its chemistry, pharmacology and clinical properties. *J Pharm Pharmacol* 2001, **53**, 583-600
4. Barnes J., Anderson L. A., Phillipson J. D. Herbal medicines. A guide for healthcare professionals. London: Pharmaceutical Press, 2002

Further reading

Committee on Safety of Medicines. Reminder: St John's wort (*Hypericum perforatum*) interactions. *Current Problems in Pharmacovigilance* 2000; 26: 6-7

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This Information Sheet can be found on the Society's website at: www.rpsgb.org.uk

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