St John's wort (*Hypericum perforatum*): drug interactions and clinical outcomes

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Aims The aim of this work is to identify the medicines which interact with the herbal remedy St John's wort (SJW), and the mechanisms responsible.

Methods A systematic review of all the available evidence, including worldwide published literature and spontaneous case reports provided by healthcare professionals and regulatory authorities within Europe has been undertaken.

Results A number of clinically significant interactions have been identified with prescribed medicines including warfarin, phenprocoumon, cyclosporin, HIV protease inhibitors, theophylline, digoxin and oral contraceptives resulting in a decrease in concentration or effect of the medicines. These interactions are probably due to the induction of cytochrome P450 isoenzymes CYP3A4, CYP2C9, CYP1A2 and the transport protein P-glycoprotein by constituent(s) in SJW. The degree of induction is unpredictable due to factors such as the variable quality and quantity of constituent(s) in SJW preparations. In addition, possible pharmacodynamic interactions with selective serotonin re-uptake inhibitors and serotonin (5-HT_{1d}) receptor-agonists such as triptans used to treat migraine were identified. These interactions are associated with an increased risk of adverse reactions.

Conclusions In Sweden and the UK the potential risks to patients were judged to be significant and therefore information about the interactions was provided to health care professionals and patients. The product information of the licensed medicines involved has been amended to reflect these newly identified interactions and SJW preparations have been voluntarily labelled with appropriate warnings.

Keywords: hypericin, *Hypericum perforatum*, induction of drug-metabolism, interactions, St John's wort

Introduction

Herbal preparations are viewed by many as natural and therefore safe. This has in part, led to the rapid increase in the number of people using such products. It has been estimated that there was a 380% increase in the use of herbal preparations between 1990 and 1997 in the USA alone [1]. However, the increased usage has also brought to light a number of problems associated with these apparently safe herbal preparations such as interactions and adverse reactions.

St John's wort

In Europe and the United States herbal preparations of St John's wort (SJW) can be bought over-the-counter to treat a variety of conditions. SJW products may also be prescribed in some European countries. As individuals view these treatments as safe they rarely inform their clinicians of their use or possible undesirable effects [2]. However, recent reports indicate that SJW interacts with a number of different medicines, which could result in potentially serious adverse reactions.

Extracts of SJW have been used for their medicinal properties since ancient times [3]. SJW (also known as Hypericum) is *Hypericum perforatum*, a member of the Hypericaceae family. Traditionally, SJW has had a number of different uses including applying it externally as a treatment for wounds and burns, or taken internally as an infusion or herbal tea to treat fevers and nervous conditions including depression [4].

Currently, subject to certain conditions, unlicensed herbal medicines may be sold or supplied as herbal remedies in the UK, exempt from licensing requirements, under Section 12 of the 1968 Medicines Act. No specific safety or quality requirements apply to unlicensed herbal remedies. In addition, no written indications about the

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Accepted 10 May 2002.

intended use of the product may be given when the product is sold under this exemption. In Sweden, the fundamental requirements placed on medicinal products in Section 4 of the 1992 Medicinal Products Act also apply to herbal remedies. Herbal remedies are licensed after assessment of quality, safety and efficacy. Bibliographic data documenting well-established use is the basis for approval of safety and efficacy.

It is hoped that the future Directive for Traditional Herbal Medicinal Products will harmonize the regulation of herbal products throughout Europe.

Active constituents

SJW has been shown to contain at least nine groups of compounds that may contribute to its pharmacological effect [5], but the pharmacology of the many constituents is not yet fully known [6] (Table 1). However, SJW is known to have significant effects on the CNS, which may account for its effect on depression.

SJW extract has been shown to inhibit the uptake of serotonin, noradrenaline and dopamine [4, 7]. Extract of SJW has been shown to have a potent affinity for the adenosine, serotonin $5HT_1$, benzodiazepine and γ-aminobutyric acid (GABA) receptors and to weakly inhibit monoamine oxidase [1, 7]. It has also been postulated that SJW's antidepressant activity may be a result of its effect on interleukin-6 [5]. The constituent hyperforin is perhaps the most likely candidate to be responsible for the antidepressant activity [8] and may be critical to the therapeutic effects of SJW [9]. This reflects the fact that only the effect on GABA receptors by hyperforin appears to be of sufficient magnitude to elicit an antidepressant effect at therapeutic doses of SJW [6]. However, the exact mechanism responsible for the therapeutic effects of SJW remains unclear.

Despite the fact that the pharmacology of the different constituents of SJW is not fully known, the hypericin concentration is commonly used to standardize the various SJW products. However, the amount of hypericin varies widely in different parts of the plant, under different growth conditions, and at different times of the year [5]. In addition, hypericin is probably not the only relevant constituent. It is therefore likely that different preparations vary in their content of substances contributing to the antidepressant effects of SJW [10]. Therefore there is a potential for different SJW products to have different levels of efficacy and possibly different adverse reaction profiles.

Adverse reaction profile

Herbal remedies can produce adverse reactions, some of which can be serious and even potentially fatal [2]. Individuals experiencing adverse reactions may not associate these with their use of herbal preparations. This is further complicated by the fact that the majority of herbal preparations are self-prescribed and never mentioned when consulting a doctor. Therefore adverse reactions associated with herbal preparations are likely to be under reported.

The most commonly reported adverse reactions for SJW are gastrointestinal symptoms, allergic reactions, dizziness/confusion, tiredness/sedation and dry mouth. The majority of these reactions were generally considered to be mild, moderate or transient [11, 12].

Photosensitivity reactions affecting the skin are potentially serious adverse reactions associated with SJW. Recent data suggest that photosensitivity reactions are dose related, with increased sensitivity associated with higher doses [13, 14]. However, the main body of evidence comes from anecdotal evidence in animals, particularly pale skinned cattle, which apparently gorge on *Hypericum perforatum* resulting in photosensitivity reactions presenting as severe sun burn [15].

A review of safety shows that the overall incidence of adverse reactions associated with SJW is low [11]. Meta-analysis of 1757 patients in clinical trials of SJW, showed that SJW treatment was associated with only 3 (0.8%) drop-outs due to adverse reactions, as compared with 7

Table 1 The main constituents of St John's wort.

Constituent	*Percentage of composition*	*Possible contribution to mode of action*
Phenylpropanes	Not reported	–
Flavonol glycosides (including hyperoside)	2–4%	Inhibition of MAO-A
Biflavones	Not reported	Weak affinity for the benzodiazepine receptor
Tannins and proanthocyanidins	15%	–
Xanthones	Very low concentrations	Inhibition of MAO-A
Phloroglucinols (hyperforin)	4% of the buds and flowers	Affinity for GABA receptors
Essential oils	Not reported	–
Amino acids	Not reported	–
Naphthodianthrones (including hypericin)	Not reported	–

(3%) drop-outs in patients receiving conventional antidepressants. Furthermore, adverse reactions were only reported in 19.8% of patients receiving SJW preparations, compared with 52.8% of patients receiving conventional antidepressants. Both of these differences are highly statistically significant [3]. However, it is interesting to note that the rate of adverse reactions reported varies depending on the type of study. Adverse reactions were more likely to be reported during clinical trials comparing the use of SJW with conventional antidepressants than during placebo-controlled trials, it has been suggested by the authors of the meta-analysis that this probably partly reflects patient expectation [11].

Interactions of SJW

A number of clinically significant pharmacokinetic and pharmacodynamic interactions have been identified. Herbs have the potential to influence the metabolic disposition of agents with significant clinical and toxicological relevance [16, 17]. Details of the interactions identified and possible mechanisms are summarized in Table 2.

Enzyme-inducing effect of the constituents

The constituents responsible for drug metabolizing enzyme induction have not been studied systematically. It is therefore difficult to judge which specific extracts constituent(s) are responsible for the induction. Published *in vitro* studies suggest that hypericin may induce the activity of CYP1A2 [16] and hyperforin may induce that of CYP3A4 [17–19]. However, other constituents of SJW have not been investigated regarding enzyme induction properties. As the various extract products differ in their constituent composition it is not possible to assess whether a particular preparation is more likely to cause induction than any other preparation.

As only one of the constituents is regularly standardized, it is difficult to extrapolate these *in vitro* data to the *in vivo* situation. Further studies are required and particularly investigation of the effects of prolonged exposure of SJW on the activities of the different enzymes. This may be especially important as the use of SJW in mild to moderate depression is consistent with long-term use.

Clinically significant interactions

Warfarin and phenoprocumon

The interaction between SJW and warfarin or phenoprocumon has been identified from spontaneous case reports [20]. Four cases of decreased warfarin effect during SJW treatment were published in the Swedish bulletin of the Medical Products Agency (MPA) at the end of 1998. Between 1998 and December 2000 22 spontaneous case reports of interactions with warfarin have been reported to regulatory authorities in the EU. These interactions all resulted in unstable INR values, with a decrease in the INR value being the most commonly observed effect of SJW [21, 22].

The pharmacologically active S-enantiomer of warfarin is metabolized by CYP2C9 [23, 24] and the effect on the INR values suggests induction of CYP2C9 is occurring. However, this has still to be confirmed *in vitro* or *in vivo*.

Cyclosporin

An interaction with cyclosporin was initially identified from spontaneous case reports in Switzerland. Four case reports have now been published [25–27]. In addition one spontaneous case has been reported in the EU.

The published cases concerned patients who have received transplantation of heart ($n = 2$), kidney ($n = 1$) and pancreas ($n = 1$). Decreased blood concentrations of cyclosporin have been detected during SJW treatment

Table 2 Possible pharmacokinetic and pharmacodynamic interactions with SJW.

Drug	*Possible mechanism of action*
Pharmacokinetic interactions	
Warfarin and phenprocoumon	Induction of CYP2C9
Cyclosporin	Induction of CYP3A4 and the transport protein P-glycoprotein
Oral contraceptives	Induction of CYP1A2 and CYP3A4
Theophylline	Induction of CYP1A2
Digoxin	Induction of transport protein P-glycoprotein
HIV protease inhibitors	Induction of CYP3A4
HIV non-nucleoside reverse transcriptase inhibitors	Induction of CYP3A4
Anticonvulsants (carbamazepine, phenobarbitone and phenytoin)	Induction of CYP3A4
Pharmacodynamic interactions	
SSRIs	Potentiation of serotonin concentrations
Triptans	Potentiation of serotonin concentrations

and transplant graft rejection was observed in all of these cases. Some of the patients recovered spontaneously after stopping the SJW, while others required additional immunosuppressive therapy. The decrease in cyclosporin levels ranged from 25% [5] to 62% [25] within 3–4 weeks of starting SJW.

Thirty patients with kidney grafts in one institute were found to have significantly decreased levels of cyclosporin blood concentrations by a mean of 47% (range 33–62%). This led to increased cyclosporin doses by a mean of 46% (range 15–115%). After SJW was stopped, cyclosporin concentrations increased by a mean of 187% (range 84–292%) and the dose of cyclosporin had to be decreased to the levels given before SJW was taken [28].

Cyclosporin has been shown to be a substrate of P-glycoprotein and metabolized by CYP3A4 [29, 30]. Therefore the induction of both CYP3A4 and P-glycoprotein by constituent(s) of SJW may act to reduce the plasma level of cyclosporin to subtherapeutic levels [21]. This can lead to clinically significant consequences such as the rejection of a transplanted organ.

Oral contraceptives

The metabolism of oral contraceptives can vary between the products. However, all are metabolized by cytochrome P450 enzymes. The enzymes shown to be induced by SJW CYP1A2, 2C9 and 3A4 are all implicated [31–34].

Breakthrough bleeding among women taking both SJW and the oral contraceptive pill has been reported. As of December 2001, 7 cases of unplanned pregnancies possibly due to interactions with SJW have been reported through the Yellow Card Scheme in the UK and two cases have been reported in Sweden. A breakdown of these case reports is given in Table 3.

These reactions are believed to be due to a lowering of drug levels, as a result of induction of CYP3A4 [21, 22], although, no blood concentrations have been recorded in the case reports received to date. However, in one preliminary interaction study, which has been presented in abstract form only, no changes in blood oestrogen concentration were observed after administration of hypericum extract Ze 117 [35].

In general all of these interactions occurred in women who had been on the oral contraceptives without breakthrough bleeding and with effective contraception for at least 7 months prior to SJW being taken. There is no evidence to suggest that these interactions occurred with specific products such as the low dose or progestogen only oral contraceptive pills.

Theophylline

The interaction between SJW and theophylline was identified during analysis of a specific case ([16]. This case report suggests induction of the hepatic enzyme CYP1A2, which is important for theophylline clearance [16, 36].

Digoxin

This potentially serious interaction was identified in a pharmacokinetic study [8]. It is believed that the pharmacokinetics of digoxin are influenced by induction of P-glycoprotein after multiple-dose treatment with Hypericum extract. This is due to the fact that the terminal $t_{1/2}$ for digoxin elimination remained constant, but a reduction in C_{max} and AUC was observed which was believed to reflect an influence on absorption or distribution, rather than metabolism [8].

Other inducers of digoxin clearance such as rifampicin and phenytoin have been shown to decrease digoxin plasma concentration, mediated by the multiple drug resistance gene (MDR-1) product P-glycoprotein. No spontaneous case reports of interactions between SJW and digoxin have been identified.

HIV protease inhibitors

This potentially serious interaction was identified through a specific pharmacokinetic study [37]. All participants showed a decrease in indinavir concentration 8 h after dosing. This ranged from 49 to 99%. SJW reduced

Table 3 Breakdown of unintended pregnancy case reports.

Age (years)	*Oral contraceptive (OC)*	*Duration of OC treatment*	*Duration of SJW treatment*
21	Mercilon	8 months	3 months
30	Trinovum	3 years	3 months
23	Levonelle-2, Cilest	1 year on OC	1 months
34	Marvelon	–	9 months
31	Cilest	8 months	6 months
28	Ovran 30	–	5 months
37	Noriday	2 years	4 months
31	Trinovum	7 months	4 months
28	Trinordiol	9 years	6 months

the AUC of indinavir by a mean of 57%. A decrease of this magnitude could lead to the development of treatment failure and drug resistance.

One spontaneous case has also been reported in the UK, in which the patient experienced an increase in HIV RNA viral load following the use of SJW concomitantly with indinavir and lamivudine.

Pharmacodynamic interactions between selective serotonin re-uptake inhibitors (SSRIs)

SJW and SSRIs result in symptoms characteristic of central serotonin excess [38–41]. Serotonin syndrome is characterized by at least three of the following: confusion, agitation, hyperreflexia, diaphoresis, shivering or tremor, nausea, diarrhoea, lack of co-ordination, fever, coma, flushing or rhabdomyolysis [42]. The excess serotonin is believed to be due to common pharmacological mechanisms of action on serotonin, particularly in the brain, of both SJW and conventional antidepressants [7, 43, 44].

It has been suggested in the literature that SJW should not be used with psychoactive or psychotropic drugs, as the potential for adverse effects may be increased. In the majority of clinical trials of SJW patients taking conventional antidepressant medicinal products have been excluded from the studies. Therefore the safety profile of combining these agents with SJW is not fully known and in the interests of patient safety these combinations should be avoided.

Discussion

Until relatively recently there were no recognized interactions between SJW and prescribed drugs. However, the majority of clinical trials looking at efficacy excluded patients already taking psychoactive or psychotropic drugs and therefore did not investigate this type of herb–drug interaction. Some clinical trials, however, did include patients taking medication for hypertension, circulatory disorders, bronchial asthma and menopausal symptoms with no evidence of any interactions between them and SJW [9].

The majority of interactions identified to date involve medicines that require regular monitoring of blood levels. However, the interaction identified with oral contraceptives, without blood monitoring, is likely to effect a large population of individuals. Given that the number of medicines that currently require monitoring is low, compared with the number of medicines on the market that are metabolized by either CYP1A2, 2C9 or 3A4, it is highly likely that further interactions with SJW will be identified in the future.

Table 4 provides details of the established clinically significant interactions, their implications and potential management. HIV non-nucleoside reverse transcriptase inhibitors and anticonvulsants are included on this list as it is considered that interactions with SJW also represent a potential risk to patient safety given their known pharmacology.

The dramatic rise in the use of herbal remedies including SJW means that many more patients on conventional medicines are being exposed. These types of remedies are rarely mentioned to clinicians, so there is little knowledge of who are taking these products and for what indications.

Many individuals regard herbal remedies as natural and therefore safe. However, there is a lack of general advice available to patients who wish to use these products. As the majority of these SJW interactions result in a lack of efficacy of the conventional medicine they are often not identified as interactions. Patients who notice that their conventional medicine is not working as well as it used to, may seek advice on possible alternatives to this medication, while they continue to concomitantly use SJW, not considering it as a possible culprit or mentioning the use of SJW to their physician.

Continued education of consumers and healthcare professionals about the potential for herb–drug interactions is required to ensure further interactions do not occur.

Regulatory action

Having reviewed the available evidence the regulatory authorities in Sweden and the UK have initiated a number of regulatory actions with the aim of preventing further interactions occurring. A warning relating to the herb–drug interaction has been added to the product information of the specific medicinal products, where there was sufficient evidence or the risk of a potential interaction with serious clinical implications.

A general warning has been added to the packaging of SJW products in Sweden and the UK. In the UK, following an agreement reached with trade associations, the labelling states 'patients should check with their doctor or pharmacist before taking a SJW product if they are taking any prescribed medication as SJW may affect the way the medicine works'. In Sweden, the MPA has requested the companies that market SJW perform product specific *in vivo* studies. Before the final results become available, the labelling has been amended to state that SJW products should not be used concomitantly with any medicinal product.

Due to the potential risks to patients, information on SJW interactions was provided to both health care professionals and public. In Sweden, several articles with updated knowledge on this issue were published in the national drug safety bulletin as well as on the internet in

Table 4 Summary of interactions and their implications.

Drug	*Effect of interaction on drug*	*Suggested management of patients already taking SJW preparations*
HIV protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir)	Reduced blood concentrations with possible loss of HIV suppression.	Measure HIV RNA viral load and stop SJW.
HIV non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine)	Reduced blood concentrations with possible loss of HIV suppression.	Measure HIV RNA viral load and stop SJW.
Warfarin	Reduced anticoagulant effect and need for increased warfarin dose.	Check INR and stop SJW. Monitor INR closely as this may rise on stopping SJW. The dose of warfarin may need adjusting.
Cyclosporin	Reduced blood concentrations with risk of transplant rejection.	Check cyclosporin blood concentrations and stop SJW. Cyclosporin concentrations may increase on stopping SJW. The dose of cyclosporin may need adjusting.
Oral contraceptives	Reduced blood concentrations with risk of unintended pregnancy and breakthrough bleeding.	Stop SJW.
Anticonvulsants (carbamazepine, phenobarbitone, phenytoin)	Reduced blood concentrations with risk of seizures.	Check anticonvulsant concentrations and stop SJW. Anticonvulsant concentrations may increase on stopping SJW. The dose of anticonvulsant may need adjusting.
Digoxin	Reduced blood concentrations and possible loss of control of heart rhythm or heart failure	Check digoxin concentrations and stop SJW. Digoxin concentrations may increase on stopping SJW. The dose of digoxin may need adjusting.
Theophylline	Reduced blood concentrations and possible loss of control of asthma or chronic airway limitation.	Check theophylline concentrations and stop SJW. Theophylline concentrations may increase on stopping SJW. The dose of theophylline may need adjusting.
Triptans (sumatriptan, naratriptan, rizatriptan, zolmitriptan)	Increased serotonergic effects with risk of increased incidence of adverse reactions.	Stop SJW.
SSRIs (citalopram, fluoxetine, fluvoxamine,paroxetine, sertraline)	Increased serotonergic effects with risk of increased incidence of adverse reactions.	Stop SJW.

1999 and 2000. A press release was issued in Sweden in November 1999. In the UK, a letter was distributed to all doctors and pharmacists in March 2000. At the same time, this information was also provided to specialist associations and the press. The initial information was then followed by a reminder article in the May 2000 edition of Current Problems in Pharmacovigilance [23].

By providing information directly to healthcare professionals and the public on SJW, awareness of the safety of herbal preparations has also been increased. This can be seen by the 167% increase in the number of Yellow Card reports received by the CSM/MCA for herbal products in the following year.

Conclusions

There is evidence that taking SJW preparations can result in pharmacokinetic or pharmacodynamic interactions that present a risk to patients taking medicines. Data at present are insufficient to indicate to what extent the use of different SJW products and dosages may produce different outcomes in terms of adverse reactions.

The pharmacokinetic interactions that have been identified so far all point toward the fact that constituent(s) of SJW induce not only a number of drug-metabolizing enzymes but also transport proteins such as P-glycoprotein.

To date there is less evidence relating to the pharmacodynamic interactions. However, due to the widespread use of these products, there is considerable potential for serious adverse reactions to occur. Therefore these interactions must also be considered as potential safety hazards.

It is therefore essential that patients are asked about the use of over-the-counter medicines, including herbal remedies when they require prescription medication or present with an adverse reaction. It is also necessary to report all suspected adverse reactions and interactions associated with herbal remedies in order for information about their safety to be established.

We would like to acknowledge the advice and help of the following colleagues: Dr Rashmi Shah, Dr Linda Anderson, Dr Patrick Waller, Dr June Raine, Professor Alasdair Breckenridge, Professor Munir Pirmohamed and Professor Martin Kendall.

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