

Herbal Pharmacokinetics: A Practitioner Update With Reference to St. John's Wort (*Hypericum perforatum*) Herb-Drug Interactions .

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ABSTRACT: Pharmacokinetic data is important for understanding interactions between herbs and pharmaceuticals. Pharmacokinetic information about herbal remedies is not widely available due to several factors including lack of studies, and inadequate reporting. CYP450 and P-glycoprotein efflux pump are reviewed as determinants of oral bioavailability of drugs. Factors affecting inter-individual variability of CYP450 expression are discussed, as well as the role of these mechanisms in pharmacokinetic interactions. Assessment of individual hepatic detoxification status is a necessary prerequisite to therapeutic interventions in natural and herbal medicine. Available evidence for modulation of different CYP 450 isoforms and of P-glycoprotein by St John's Wort is reviewed. Available studies and clinical reports of specific interactions between St John's Wort and pharmaceuticals, including indinavir, digoxin and cyclosporine are reviewed. Current evidence suggests that St John's Wort may cause interactions with substrates of CYP3A4 and potentially with substrates of CYP1A2 . An action on P-glycoprotein is likely to be involved in the interactions with digoxin and cyclosporine. Guidelines for practitioners on St. John's Wort usage are suggested. Currently available mechanisms for reporting ADR's and interactions involving herbal medicines are summarized.

Why Pharmacokinetics?

Herbalists have long studied the effect of herbal medicines on the body, but have hitherto paid less attention to the effects of the body on herbal medicines. This dichotomy expresses the distinction in classical pharmacology between pharmacodynamics and pharmacokinetics. For a given dose of any herbal medicine, its physiological effect (or that of its constituents) will be governed by the effective tissue concentration of the remedy which in turn is determined by

pharmacokinetic parameters - the absorption, distribution, metabolism and excretion of its various components. Knowledge of herbal pharmacokinetics can provide valuable information to aid practitioners in prescribing herbs safely and effectively. It may also enable useful predictions to be made, for example regarding possible interactions between herbal remedies and conventional pharmaceuticals.

Drug-drug interactions constitute the bulk of the conventional pharmacokinetic literature, but currently herb-drug interactions are taking center stage, both in the popular media and in terms of increasing physician awareness of the widespread and often undisclosed use of herbal medicines by their patients, and the potential for significant pharmacokinetic interaction between herbs and prescription pharmaceuticals. Useful data about actual and potential interactions between pharmaceutical drugs comes from various sources, including clinical trials, preclinical trials investigating adverse effects, post licensing drug monitoring, controlled trials on healthy subjects required for drug licensing, *in vitro* or *in vivo* studies on animal or human cell lines or tissues, and Adverse Drug Reports (ADR's). The situation for herb-drug interactions data is very different, largely due to the different regulatory frameworks that govern pharmaceuticals and herbs. In a recent review of the literature on herbal pharmacokinetics, De Smet and Brauwerts found very few human studies in the field; the available studies covered only a handful of herbs, and most involved consumption by normal or healthy volunteers. (De Smet & Brauwerts, 1997)

Given the chemical complexities of herbal remedies, the use of multiple herbs in herbal prescriptions, and the many different parameters impacting pharmacokinetics (especially

individual factors such as age, genetic variation, dietary habits etc.) together with the lack of commercial imperatives for conducting such research, this lack of data is likely to continue for some time.

On the positive side, the recognition by herbalists of the importance of this subject is increasing; for example pharmacokinetics is emphasized in the recently published *Principles and Practice of Phytotherapy*. (Mills and Bone, 2000) It is important for herbalists to be able to evaluate for themselves the conventional literature regarding interactions and assess its significance within an informed framework of clinical practice. Equally pressing is the need for herbal practitioners to make available their own clinical experience by publication of observational studies, case reports and clinical outcome data in order to contextualize and counter inappropriate extrapolations from inadequate information which currently tend to dominate the mainstream debate. Publication of an isolated herb-drug interaction report in a mainstream medical journal is often followed by a number of "me too" letters to the editor from assorted physicians. These often lack any useful details to the point of being misleading, but according to the conventional maxim that the plural of "anecdote" is "clinical data" - such correspondence seems to confer the status of scientifically proven evidence upon the putative interaction, an ambience reinforced by subsequent repetitious citation as "evidence". This phenomenon is well known to herbal myth sleuths, and a few years ago might have been regarded simply as a predictable if tiresome phenomenon.

However recent adverse publicity regarding interactions between St. John's Wort and pharmaceutical medicines in the medical and popular media, and the deeply disturbing ruling by

the Irish government that St.John's Wort (and four other herbs) be restricted to prescription only from 2000 on, is a reminder that in the current regulatory climate, interaction issues are likely to be a matter of continuing and increasing concern for herb professionals.

Evaluating the relevant research often requires at least a basic understanding of the molecular biology and physiology of the cellular mechanisms involved. For those clinical herbalists whose priorities emphasize the care of their patients over reviewing the often obscure technical literature that dominates the field, a brief overview of two important systems involved in pharmacokinetic drug interactions - the well known Cytochrome P450 (CYP450) enzyme system and the more recently understood P-glycoprotein (P-gp) efflux pump - follows. The evidence for interactions between these systems and Hypericum extracts is covered, together with an evaluation of reports on specific interactions between Hypericum and pharmaceuticals. Finally suggested guidelines for practice are offered, together with an discussion of existing ADR and pharmacovigilance systems. The therapeutic efficacy of Hypericum and an assessment of potential direct adverse effects including phototoxicity have been recently reviewed elsewhere and are not covered here. (McIntyre, 2000)

CYP450 - Overview

The Cytochrome P-450 (CYP450) system is a family of heme based enzymes located in the smooth endoplasmic reticulum, particularly concentrated in hepatocytes and mucosal enterocytes

but also found in the kidneys, skin and lung tissues of humans. Also known as the mixed function oxidases, it is one of the most important systems for biotransformation of drugs. The CYP450 families of enzymes are responsible for Phase I of xenobiotic metabolism, catalyzing predominantly oxidation, reduction and hydrolysis reactions which render lipophilic compounds more polar, prior to the Phase II processes of thiol conjugation, glucuronidation, sulfation or acetylation which enable the metabolites to be excreted by the kidneys. The broad features of the CYP450 system are well known and have been reviewed, and therefore will not be covered in depth here. The CYP450 system is a large field of ongoing research, with annual symposia devoted exclusively to the subject. (Boobis, Edwards, Adams, et al., 1996; Flockhart, 1995; Flockhart & Oesterheld, 2000)

Of the twelve known families of CYP450 isozymes representatives of only three families are significant in humans; the most important are 1A2 found in the liver; the diverse CYP2 group including 2C19, 2C9, 2D6, and 2E1 which are all involved to some degree in drug transformation, especially 2C9. CYP3A4 is the major human enzyme involved in drug biotransformation and is found extensively in hepatocytes and in small intestinal enterocytes, two sites where it plays a key role in modulating the bioavailability of orally administered pharmaceuticals.

The interaction of a given compound with the CYP450 system will determine its fate and possible effects in the body; the majority of intermediate metabolites are less toxic than their

parent compounds but it is also possible for intermediates to be highly toxic, carcinogenic or mutagenic. For herbalists, the best known example of this process is of course the formation of hepatotoxic pyrrole metabolites from certain pyrrolizidine alkaloids present in *Symphytum* spp. and other genera. (Denham 1996)

Xenobiotics, drugs, and a variety of naturally occurring dietary or herbal constituents can interact in several ways with the CYP450 system:

- A compound may be a **substrate** of, ie metabolized by, one or several CYP isoforms. If the main isoform is saturated, it becomes a substrate for the secondary enzyme(s).
- A compound can be an **inducer** of a CYP isoform, either of the one it is a substrate for, or may induce several different enzymes at the same time. The process of induction increases the rate of metabolism of substrates of that enzyme.
- A compound may also be an **inhibitor** of CYP450 enzymes. There are several mechanisms of inhibition, and a compound may inhibit several isoforms including others than those for which it is a substrate.

These are the actions that underlie the pharmacokinetic variations in drug metabolism, and that cause interactions between two or more drugs, or between drugs and nutrients, or drugs and herbs. Induction is a slow process, dependent on the rate of synthesis of new enzyme and usually noticeable after only a few days, and maximal after two weeks. Inhibition is more rapid, and can

become maximal within the first 24 hours of exposure to the inhibitor - but likewise may reverse more rapidly.

There are many non drug inducers and inhibitors of CYP450, among the best known being grapefruit juice which inhibits CYP3A4, (Bourian, Runkel, Krisp, et al., 1999; Lown, Bailey, Fontana, et al., 1997; Ozdemir, Aktan, Boydag, et al., 1998) and vegetables such as Brussel sprouts and broccoli whose glucosilate compounds induce CYP1A2 (Fontana, Lown, Paine, et al., 1999). This enzyme metabolizes many carcinogens, including tobacco related compounds and char grilled meat, and induction of 1A2 underlies the cancer preventative reputation of the Brassicaceae. Lists of substrates, inducers and inhibitors of the different enzymes are being regularly updated by new research, and there are several internet sites where the latest information is available (for example Dr David Flockhart's useful list is at <http://www.georgetown.edu/departments/pharmacology/davetab.html> For clinicians, there is one aspect of the research which is of great importance in evaluating potential for interactions - the subject of individual variation in CYP450 expression.

CYP450 - Individual Variation

There is a wide range of variation in expression of CYP450 enzymes. This accounts for much of the inter-individual variability in responses to drugs, as well as in the occurrence and severity of adverse effects and drug interactions.

The underlying factors affecting individual variation in CYP450 expression are age; genetics including gender and race; disease, including both general infection as well as specific hepatic conditions. Beyond these factors, there is recognized a spectrum of phenotypic variation ranging from "poor metabolizers" to 'extensive metabolizers" between whom there can be 10 to 20 fold differences in the a rate of drug metabolism. (Boobis, Gooderham, Edwards, et al., 1996; Bourian, Runkel, Krisp, et al., 1999; Marinac, Balian, Foxworth, et al., 1996)

These factors inevitably complicate any simple extrapolation from in vitro findings. In addition, difficulty of interpretation is compounded by the functional status of other, co-dependent or co-regulating factors and pathways in an individual. For example, Phase I metabolites must be cleared by Phase II metabolism. Phase 2 enzymes such as glutathione-S-transferase, or N-acetyl transferase are also subject to polymorphism, and the phase II pathways are subject to rate limiting kinetics by the availability of conjugates such glutathione, its precursors (e.g. cysteine) and cofactors (e.g. selenium), and in turn the overall redox status of the individual ...and so on. This all adds to the extraordinary complexity of the whole picture. (May, 1994)

Ironically, there is here an obvious clinical point, often lost in the polemics of the mainstream debate about potential interactions; namely that the majority of natural healthcare practitioners, including medical herbalists, tend to evaluate individual hepatic detoxification status before devising therapeutic interventions involving modification of diet, consumption of nutritional

supplements or herbal medicines precisely because they understand the inherent degree of variability of this system as well as its central importance in healthy function. Restoring, supporting and optimizing hepatic detoxification functionality is a time honored and foundational component of herbal therapeutics. Conversely, most physicians tend to prescribe pharmaceuticals in terms of generic doses, and rarely making adjustment for hepatic detoxification functionality which is not a part of their routine initial assessment of a patient.

Hypericum and CYP450 modulation.

Preliminary conclusions from the few studies that have directly investigated St John's Wort extract interactions with the CYP450 system, suggest that St John's Wort may under some circumstances modulate CYP450 isoforms, particularly 3A4. Reviewing the studies does not currently enable firm conclusions to be drawn.

Experimental and isolated constituent evidence is limited. Moore has found evidence that hyperforin and St John's Wort extracts induce CYP3A4 in hepatocyte cells via the pregnane X nuclear receptor, (this controls CYP3A4 expression) (Li, Wang, Patten, et al., 1994; Moore, Goodwin, Jones, et al., 2000), while Li showed that quercetin, another St John's Wort constituent, inhibited 3A4 metabolism of acetaminophen by human hepatic microsomes.(Li,

Wang et al. 1994) Another recent in vitro study with an array of recombinant human CYP450 enzymes using substrate assay methods employed for pharmaceutical drug screening investigations of possible pharmacokinetic interactions examined crude extract of St John's Wort and isolated constituents for inhibitory activity. Crude plant extract (derived from encapsulated commercial product) showed inhibition of five isozymes: 1A2, 2C9, 2C19, 2D6, and 3A4, with 2D6 being the most sensitive with 50% inhibition at a concentration of 9.1 μ M. Several isolated constituents were found to be capable of competitively inhibiting CYP activities, with the biflavone I3,II8-biapigenin being the most potent inhibitor (toward CYP3A4 at an IC₅₀ =0.082 μ M) However this biflavone is only present in the plant in small quantities(< 0.5%), while the marker compounds hyperforin and hypericin which demonstrated 50% inhibition at concentrations below 10 μ M for CYP 2C9, CYP2D6 and CYP 3A4 are present in significantly greater (< 5.0%) amounts.(Obach, 2000). Another recent study of several plant extracts and pure compounds found that both St John's Wort extracts and pure hypericin caused in vitro inhibition of CYP3A4.(Budzinski, Foster, Vandenhoeck, et al., 2000)

One positive human study was conducted on 13 healthy volunteers given 300mg standardized extract St John's Wort TID for 14 days. 24 hr urinary excretion ratios of 6-beta-hydroxycortisol/cortisol were used as an index of CYP3A4 activity. A significant increase, from zero up to around 2.5x over base was found in urinary ratios in 12 subjects, suggestive of 3A4

induction. (Roby, Anderson, Kantor, et al., 2000) However, another study using dexamethorphan and alprazolam probes to determine the effect of St John's Wort extracts (330mg standardized extract TID) on 3A4 and 2D6 in seven healthy volunteers concluded that no significant differences in urinary levels were found with coadministration of St John's Wort with the probes, leading the authors to conclude "*These results suggest that St. John's wort, when taken at recommended doses for depression, is unlikely to inhibit CYP 2D6 or CYP 3A4 activity.*" (Markowitz, DeVane, Boulton, et al., 2000). A poster study using similar probe methodology to examine 3A4 and 2D6 in sixteen healthy volunteers divided into extensive and poor metabolizers was conducted by Ereshefsky and colleagues as part of a larger series of investigations into inducers and inhibitors of these isoforms. St John's Wort was administered for 8 days at 300mg TID and according to the urinary metabolite ratio measurements no significant changes were found after St John's Wort administration. The authors concluded that "*SJW does not interact with CYP2D6 or CYP3A4. SJW is a significantly weaker inhibitor of CYP3A4 than grapefruit juice.*" (Ereshefsky, Gewertz et al. 1999) The same research group also studied the effect of Hypericum extracts on CYP1A2 and the Phase 2 enzyme N-acetyltransferase (NAT2) using caffeine probe methodology in sixteen subjects. Five "slow acetylators" were excluded, and results, this time with plasma as well as urine samples, from the eleven "fast acetylators" suggested the conclusion of "*a low potential for Hypericum interactions at CYP1A2 and NAT2 metabolic pathways*". (Gewertz, Ereshefsky et al.1999).

Reviewing these studies for direct evidence of Hypericum interaction with CYP 450, the data is inconclusive. Isolated constituent studies suggest the possibility of both inhibition and induction of 3A4, with recent in vitro studies favoring an inhibition ; this is apparently in conflict with clinical data. Different experimental studies have used different methodologies for assessing CYP450 modulation. Recently, one investigator has found that fluorometric assays of CYP450 activity (such as used in the Budzinsky study above) are inherently susceptible to producing variable results depending on the assay substrate used, sometimes by an order of magnitude. (Stresser, Blanchard, Turner, et al., 2000). Of human studies on 3A4, results are also conflicting, with one study supporting induction, and one suggesting a mild inhibition. Again methodological problems are evident. In particular, several investigators have questioned the reliability of urinary 6-betahydroxycortisol/cortisol ratios as a reliable index of CYP3A4 activity, noting significant variations of circadian and menstrual rhythm in reported values.(Ohno, Yamaguchi, Ito, et al., 2000; Seidegard, Dahlstrom & Kullberg, 1998) There is negative evidence for interaction with CYP2D6 and limited evidence for *potential* interaction with 1A2. The number of subjects was small in all these studies, and further investigations are clearly needed..

Methodological factors may explain to some degree both the varying results and the conflict between experimental and clinical data. The issue becomes clearer when clinical reports of specific drug interactions with Hypericum are considered below.

P-glycoprotein (P-gp) & Multidrug resistance protein (MDRP)

overview.

P-glycoprotein (P-gp) is an ATP-dependent pump that effluxes substrates out of cells. P-gp is an inducible membrane transport protein that was initially discovered by cancer researchers studying *multidrug-resistance* whereby cells resistant to one class of cytotoxic agents such as the vinca alkaloids showed cross-resistance to structurally unrelated compounds such as the epipodophyllotoxins. This resistance is related to an overexpression of P-gp, or a family of related proteins, known as multidrug resistance proteins (MDRP, MDRP1, MDRP2).(Yu, 1999)

While it is well established that P-gp and related transporter molecules can efflux xenobiotics out of tumor cells, the precise role of this family of transporters in normal cellular function is not yet understood, and it is possible that they may play a major part in cell differentiation, proliferation and survival. (Johnstone, Ruefli & Smyth, 2000) P-gp is found in normal human renal, intestinal and biliary epithelia, the adrenal gland, testis and pregnant uterus where it is a barrier to xenobiotic accumulation and a determinant of oral bioavailability of drugs. (Tanigawara, 2000) P-gp is also found in both the choroid plexus and cerebral endothelium where it contributes to the blood-brain barrier, and the blood-cerebrospinalfluid barrier which limit the accumulation of drugs in the brain.(Sugiyama, Kusuhara & Suzuki, 1999) P-gp is also expressed in lymphocytes and has been shown to modulate the transport of cytokines IL-4, IL-6 and IFN-gamma by activated T cells. (Drach, Gsur, Hamilton, et al., 1996) P-gp is known to be a determinant of

drug-drug interactions such as the non-competitive interaction between digoxin and verapamil which is due to inhibition of renal P-gp by decreasing tubular excretion of digoxin.

(Verschraagen, Koks, Schellens, et al., 1999) Recent research shows that P-gp can also be affected by a range of naturally occurring compounds found in foods and herbal medicines.

P-glycoprotein (P-gp) modulation by natural compounds.

P-gp expression can be modulated by numerous natural substances, some of which, like grapefruit juice, also can modulate CYP450, although this appears to be serendipitous connection rather than intrinsic coregulation (Kim, Wandel, Leake, et al., 1999). In enterocytes, P-gp may also increase pre-systemic metabolism of drugs by the removal of CYP450 generated metabolites from the intracellular compartment. (Hochman, Chiba, Nishime, et al., 2000) Reactive oxygen species (ROS) downregulate the expression of P-gp (Wartenberg, Fischer, Hescheler, et al., 2000) whilst several naturally occurring compounds, modulate P-gp. (Maitrejean, Comte, Barron, et al., 2000) Rosemary (*Rosmarinus officinalis*) extracts inhibit P-gp as evidenced by vinblastine uptake in MCF7 cells (Plouzek, Ciolino, Clarke, et al., 1999). Flavonoids may induce or inhibit P-gp, for example tangeretin inhibits P-gp (Takanaga, Ohnishi, Yamada, et al., 2000) whereas quercetin and kaempferol are inducers (Bock, Eckle, Ouzzine, et al., 2000). Inhibition takes place both by direct binding to the P-gp sites and by inhibition of the protein kinase C (PKC) which drives the P-gp efflux pump by phosphorylation. (Castro, Horton, Vanoye, et al., 1999). These natural agents could have a possible therapeutic role to play in reversing barriers to

drug availability in tumor multidrug resistance. By the same token, they have the potential to cause pharmacokinetic interactions.

Hypericum and P-glycoprotein modulation.

Currently there is no direct evidence for the influence of Hypericum extracts or isolated compounds upon P-gp activity or expression. However the preclinical study by Johne and colleagues on the digoxin -SJW interaction discussed below implicates P-gp modulation since Digoxin is a known substrate of P-gp transport. (Johne, Brockmoller, Bauer, et al., 1999) Similarly, recent reports of SJW-cyclosporine interactions imply P-gp activation, because although cyclosporine is a substrate of 3A4, it is also a known inhibitor of P-gp, and the Hypericum extracts may have reversed this inhibition hence reducing oral bioavailability. (Breidenbach, Kliem, Burg, et al., 2000)

While the emerging information about the molecular biology of transporter proteins may be arcane to some herbalists, discoveries of plant synergy in this field will not surprise most plant experts. Stermitz studied the antimicrobial activity of berberine containing plants (*B. fremontii*, *B. aquifolia* and *B. repens*) against the human pathogen *Staphylococcus aureus*. This antimicrobial activity depends on the synergistic disabling of an MDR efflux pump in the bacterium by another compound present in the plant identified as 5'-HMC (5'-methoxyhydrnocarpin). Isolated berberine alkaloids only accumulate strongly in the bacterium in the presence of 5'HMC, which on its own has no antimicrobial effect (Stermitz, Lorenz,

Tawara, et al., 2000). Finally, it should be remembered that *in vitro* or animal experiments may have little or no bearing on human clinical situations. For example, tangeretin synergizes with tamoxifen *in vitro* MCF7 cancer cell lines, but *in vivo* rodent studies show the converse, that tangeretin appears to inhibit the effect of tamoxifen. (Bracke, Depypere, Boterberg, et al., 1999)

Hypericum - Drug Interactions

Cyclosporine

A recent report in the Lancet from Ruschitzka and colleagues in Switzerland discussed acute rejection of cardiac grafts in two male patients in their early sixties. In both cases, immunosuppression was maintained with a standard triple therapy of azothiaprine, cyclosporine and corticosteroids. Both were admitted three weeks after beginning standardized SJW at 300mg TID. The first patient had self-prescribed SJW while the second had been prescribed SJW by a psychiatrist for anxiety and depression. In both cases, acute signs of rejection were apparent on endomyocardial biopsy, although apart from fatigue the patients were asymptomatic with normal lab values except for the low cyclosporine levels. SJW was suspected and stopped in both cases. Aggressive immunosuppressive intervention was required to restabilize the first patient, the second stabilized after cessation of the SJW. In both cases, cessation of SJW led to increase in cyclosporine levels. (Ruschitzka, Meier, Turina, et al., 2000). A recent German report on 30 renal graft patients correlated a fall in cyclosporine levels with concomitant SJW administration, and an increase in levels after cessation of the herb. (Breidenbach, Kliem, Burg, et al., 2000)

This report was unavailable for full evaluation at the time of writing. Another case of a renal graft patient registering a drop in cyclosporine levels during co-administration of Hypericum extract has also

been recently reported. (Mai, Kruger, Budde, et al., 2000)

Cyclosporine has long been known to be a substrate of 3A4, but this does not mean that 3A4 induction by SJW is responsible for the cyclosporine interaction. Indeed much of the variation in oral cyclosporine bioavailability previously ascribed to 3A4 variability is in fact now known to be caused by P-gp affecting the rate of intestinal absorption. (Lown, Mayo, Leichtman, et al., 1997)

It is possible that SJW reversed the inhibitory effect of cyclosporine on P-gp, leading to decreased intestinal absorption at the enterocyte. In any event, the potential SJW interaction with cyclosporine is extremely serious and especially since graft rejection can proceed insidiously, coadministration of the two agents should be avoided.

Digoxin

A recent single controlled study with 25 subjects who were stabilized for 5 days on digoxin and then coadministered 900mg standardized St John's Wort daily for 14 days showed highly significant reduction digoxin plasma concentrations after 14 days coadministration (digoxin area under curve [AUC] diminished by >25%) in the St John's Wort group (n=13) while the placebo group also showed a reduction of 9% AUC. (Johne, Brockmoller, Bauer, et al., 1999) This study

points to potentially hazardous interaction between St John's Wort and digoxin, particularly given the narrow therapeutic window of the drug. The effect is probably due to P-gp modulation since digoxin is renally excreted rather than metabolized by the CYP450 system. Further investigations would be needed to eliminate other factors, especially given the reduction in AUC for the placebo group, such as interference of the herb with the digoxin assay procedure.

HIV protease Inhibitors

Indinavir (Crixivan®) is a common HIV Protease inhibitor. Piscitelli and colleagues performed a preclinical study on the effects of SJW on plasma levels of indinavir in healthy, non-HIV subjects. The study group was small (n=8) and a baseline steady state with 3 x 800mg doses of indinavir over 24 hours was established. After 8 hr fasting they received a fourth dose of 800mg which was used to plot the AUC indinavir kinetics (=90% after 5 hours). The same dosing regime was repeated after fourteen days of standardized SJW extract consumption at 300mgs TID. There was a very large reduction in the indinavir AUC, averaging 57%, after the SJW therapy. (Piscitelli, Burstein, Chaitt, et al., 2000). The mechanism of this interaction is unclear. Indinavir is metabolized by, and an inhibitor of 3A4.

There is a potential for interaction between SJW and indinavir, and by extrapolation, with other protease inhibitors (ritonavir, amprenavir, nelfinavir, saquinavir). It is also the case that HIV patients are a group likely to be taking a number of medications concurrently, including the azole

antifungals, and NNRTI's (non nucleoside reverse transcriptase inhibitors) which are well known CYP450 interactors. The same group is also likely to be taking SJW for various reasons, and extreme vigilance is recommended during SJW and drug administration in this sensitive group.

Warfarin

A letter to The Lancet from the Swedish Medical Products Agency (MPA) reported seven cases where patients stabilized on Warfarin had experienced reduced INR (International Normalized Ratio - a standardized coagulation parameter) values during concomitant SJW consumption. No hemorrhagic complications were noted, and either the SJW was discontinued or the Warfarin dose adjusted. The cause was suggested by the authors to be an interaction between SJW and 2C9 which metabolizes S-Warfarin although there is no evidence for this. (Yue, Bergquist & Gerden, 2000). Warfarin is subject to numerous interactions, and the 2C9 isoforms have at least two known allelic variants that cause differences in metabolic rate of substrates (Aithal, Day, Kesteven, et al., 1999). In addition, Warfarin is enantiomeric, and the R-enantiomer is a substrate of 1A2. Other reports of SJW-warfarin interactions are lacking.

Oral Contraceptives

Despite popular press articles there are no reports of unwanted pregnancy caused by oral contraceptive failure due to SJW consumption. The Swedish MPA report mentioned above also detailed eight cases of irregular or breakthrough menstrual bleeding in women aged 23-31 years who had been taking long term oral contraceptives and had commenced SJW consumption.

Details are not given of the hormone type or dose, concurrent medications, nor the SJW dose.(Yue, Bergquist & Gerden, 2000) The authors suggest induction of 3A4 by SJW is responsible, since steroids are largely metabolized via 3A4. However, breakthrough bleeding is a common enough occurrence with oral contraceptive use, and the lack of detail in the reports casts reasonable doubt on the authors conclusions, especially in view of the lack of other supportive data.

Theophylline

Theophylline is metabolized by 1A2 and as already noted there is some potential for 1A2 and SJW interaction. Theophylline and SJW interaction has been cited by several authors reviewing the field, for example Fugh-Berman reviewing interactions recently in The Lancet. (Fugh-Berman, 2000)However the published report referred to is a discussion of a single case of a 42 year old woman, smoking half a pack of cigarettes daily (tobacco induces 1A2) also taking eleven other prescription medications, who had been taking SJW for two months. On cessation of SJW her plasma theophylline levels rose within seven days.(Nebel, Schneider, Baker, et al., 1999). The case obviously is hard to evaluate and certainly does not constitute prima facie "evidence" of a SJW-theophylline interaction.

Other

Whilst evidence for pharmacokinetic interactions with other drugs is currently not available,

some tentative extrapolations from known data are possible. For example, several anticonvulsants are powerful CYP inducers, and are also substrates for a variety of different CYP450 isoforms including 2C9, 2C19, and 3A4. (Tanaka, 1999a). Benzodiazepines are metabolized by 3A4 and have widespread interactions with 3A4 modulators. (Tanaka, 1999b).

Pharmacodynamic interactions

This review has been concerned with pharmacokinetic interactions. Safety, adverse reactions and pharmacodynamic interactions have been reviewed elsewhere. (De Smet & Touw, 2000; Ernst, 1999; Jobst, McIntyre, St George, et al., 2000) The pharmacodynamic study of St. John's Wort is ongoing, and the current consensus is that its actions cannot be reduced to a single constituent nor to a simple equivalent of a pharmaceutical agent such as SSRI or MAOI activity, although St John's Wort extracts do display multiple if moderate activities across a range of neurotransmitters and receptors. (Wheatley, 2000) There is currently a tendency for "over-reporting" of possible SJW interactions in the mainstream literature without careful evaluation and assessment of the quality of evidence. The suggestions of "serotonin syndrome" during concomitant administration of SSRI drugs such as fluoxetine with SJW made by Lantz are typical, all five reported cases occurring in one geriatric ward of one hospital during sertraline and SJW co-administration. The reported ADR's of nausea, restlessness, irritability and anxiety subsided on cessation of SJW. (Lantz, Buchalter & Giambanco, 1999). Enthusiastic reports of mania ascribed to SJW consumption or interactions with anti-depressants are appearing with

greater frequency: none of them allay the need for well constructed studies to establish some solid data in this complex field.

Practitioner Guidelines

In the light of recent data concerning St John's Wort interactions, regulatory authorities have responded with differing degrees of caution and issued advisories for physicians and healthcare practitioners. The FDA advisory from the CDER (center for Drug Evaluation and Research) refers principally to the indinavir study, and suggests that caution be used to prevent problems due to CYP450 induction by SJW. The British Committee for Safety on Medicines issued a more thorough advisory, which made extrapolations to suggest theoretical interactions of SJW for example with triptans (migraine medications). The extreme response of the Irish government has been noted, and has been analyzed in a recent review by McIntyre who concluded that the overall magnitude of the problem of SJW and drug interactions is small, and that the consensus of several metastudies is that SJW remains an exceptionally safe and effective botanical medicine with fewer side effects than comparable anti-depressant medications. (McIntyre, 2000). Many OTC and prescription pharmaceuticals have the potential to cause serious ADR's and interactions; traditionally risk-benefit ratio calculations, physician advice and proper product warning on labels are used to obviate the worst of these effects. Adopting the following perhaps obvious guidelines would be a sensible course for those practitioners not already doing so.

- **Audit all medications, prescription drugs, OTC drugs, and dietary supplements, including dosage, at initial intake. Review all actual product, packaging and labeling. Check recent PDR for manufacturer's ADR data. Update audit each visit. Assess hepatic detoxification status during intake/history.**
- **Be aware of patients using "red flag" type medications especially those with narrow therapeutic window: anticoagulants, immunosuppressives, anticonvulsants, antiarrhythmics etc.**
- **Be aware of patients in "red flag" groups, where polypharmacy and high interactor drug use is common: e.g. psychiatric, HIV-AIDS, long-term cardiac patients.**
- **Any patient taking Hypericum as part of a multiherb prescription or formula should be advised they are doing so in case they wish to inform their physician or pharmacist.**
- **Where stable levels of Warfarin or digoxin with concomitant long term Hypericum use have been confirmed by regular monitoring, patients should be advised that altering herb use (e.g. stopping) may alter drug levels. Ensure patients are actually obtaining serum drug level (or INR etc) tests results.**
- **Patients already stable on Warfarin or digoxin proposing to start Hypericum must have plasma levels monitored carefully before doing so, and dose of drugs adjusted to maintain therapeutic levels in consultation with prescribing physician.**
- **Organ graft recipients should be warned against self-prescription of Hypericum. No patient requiring cyclosporine should be given Hypericum without exceptional and powerful justification and notification of transplant physician team. Plasma cyclosporine levels must be monitored regularly and correlated with any herbal prescriptions for potential interactions e.g. Milk Thistle.**
- **HIV patients using protease inhibitors should avoid taking Hypericum if possible. Polypharmacy is common, and HIV medication protocols can contain several potential interactors. Drug substitutions can be made under some circumstances to reduce potential interactions. Obtain expert advice if this not your clinical specialty.**
- **Individuals using anti-depressant drugs, especially SSRI's should not be prescribed Hypericum unless the practitioner is able to provide strong justification. Self-prescription of anti-depressants and Hypericum should be avoided. Particular vigilance required with elders.**

- **Be aware of signs and symptoms of SSRI and benzodiazepine withdrawal if Hypericum is to be used in this context. Recommended withdrawal and phased reduction period for SSRI's is four weeks.**
- **Women using oral contraceptives in conjunction with known 3A4 interactors such as anticonvulsants, should avoid concurrent Hypericum use.**
- **Report ADR's and possible interactions. Use available local reporting mechanisms such as the NIMH yellow card system and PhytoNet system. It essential to maintain a responsible and professional attitude to interactions issues to counter inappropriate and ill informed initiatives to limit the availability of herbal medicines.**

Pharmacovigilance - endnote

In Europe, there are several schemes for reporting herbal ADR's and drug interactions. Members of the National Institute of Medical Herbalists (NIMH) use a Yellow card scheme for reporting adverse events associated with herbal medicines in the UK, whilst ESCOP (the European Scientific Co-Operative on Phytotherapy) has established PhytoNET at <http://www.ex.ac.uk.phytonet/> which is an on-line reporting mechanism to parallel and augment orthodox reporting schemes.

The EHPA (the European Herbal Practitioners Association) actively lobbies both media and government on regulatory issues such as the recent restriction of St. John's Wort in Ireland and has established a Pharmacovigilance Committee. The situation in the USA is less satisfactory.

The FDA has an on-line web site open for public ADR's reports involving herbal products which unfortunately are remarkable only for their lack of informative detail and minimal credibility.

The FDA was even criticized by the US General Accounting Office (GAO) for using unreliable and unsubstantiated ADR's to support its regulatory measures for the sale and supply of *Ephedra*

sinica . There has been at least one initiative to establish a HERBWATCH hotline reporting system in the US, which to date has not attracted sufficient funding or interest. More recently an independent herbal pharmacovigilance web site supported by a loose consortium of US practitioner and industry organizations has been established at

<http://www.InteractionReport.org>

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