Herbal drug usage with modern medicine 1: Case study of an enzyme inducer, St John’s Wort - Some perspectives

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While the usage of herbal medicines continues to be on the rise, it brings along an imminent risk of drug-drug interaction with scores of modern day medicine(s). The focus of this article is to provide an overview of a potential drug-drug interaction resulting, due to induction of cytochrome P450 enzyme(s) and/or transporters, from the use of a popular herbal product known as St. John’s Wort (SJW) with modern day medicines. Also, it provides some perspectives and considerations in rationalizing the use of SJW.

Key words: Cytochrome P450, induction, interaction, P-glycoprotein, pharmacokinetics, St. John’s Wort

INTRODUCTION

It is important to recognize the global propensity for the use of herbal medicines for combating scores of diseases.[1-6] While there is a large belief that herbal medicines are safe to use, it needs to be understood that depending on the amount and potency of the pharmacologic principle(s) contained in the herbal preparation/medicine potential exists for drug-drug interaction to occur when the herbal product is consumed with the modern day medicine. The underlying reason(s) for the purported interaction could be many-fold but primarily it is possible to explain many such interaction(s) using a pharmacokinetic and/or pharmacodynamic basis. While the drug combination use in the modern day medicine occurs under the guidance of a medical practitioner to alleviate a number of disease(s), there appears to be less of a control when herbal preparations are co-prescribed perhaps due to lack of awareness and a general belief that they are innocuous. Therefore, in simplistic terms, it should be understood that herbal preparations contain active phytochemical(s) (varying proportions) which have a tendency like any other active pharmacological substance to alter the enzymatic systems, transporters and/or the physiologic process.[7] The intent of this short report is to update on some imminent issues that may arise if the modern medicine is mixed with an unsuspecting herbal preparation. These situations may arise in our daily lives due to the following reasons: a) lack of strict adherence to regular drug prescription practices and b) unabated use of over the counter drug products and/or self prescription practices. The focus of this report is to discuss the drug-drug interaction potential and challenges posed by a popular herbal preparation known as St. John’s wort (SJW) which has been extensively used in the treatment of depression.[8]

PHARMACOLOGIC PRINCIPLE AND RATIONALE FOR THE USE OF ST. JOHN’S WORT

The major active pharmacologic principle contained in SJW is known as hyperforin,[9] however, it contains other principles which can be broadly classified under the following categories: a) phloroglucinols (hyperforin, adhyperforin), b) naphthodianthrones (hypericin, pseudohypericin) and c) flavonoids (quercetin, quercetrin, amentoflavone) are also contained in SJW.[9] SJW effectively blocks the re-uptake of neurotransmitters such as serotonin, norepinephrine, and dopamine.[10-12] The antagonistic activity of SJW has been reported to specifically target serotonergic 5-HT₁ and 5-HT₄ receptors.[13,14] This unique modulation of brain neurotransmitters has contributed for the effectiveness of SJW in clinical trials in direct comparison with placebo controlled patients and/or patients treated with conventional tricyclics such as imipramine for the treatment of mild to moderate depression states.[15,16] Additionally, data are emerging that suggests that SJW may find potential use for treating inflammatory conditions, proliferative conditions and has antibacterial activity.[17-20]
**CYTOCHROME P450 (CYP) INDUCTION**

Typically induction of CYP isozymes would not trigger safety related issues unlike enzyme inhibition but would largely translate into failure of therapy since the induction of enzymes raises the propensity for metabolism of compound(s). However, in certain cases, if metabolite(s) are active and contribute for the purported indication claims, induction of specific CYP enzymes may be either beneficial and/or inconsequential to the efficacy of the compound.

**Induction of CYP3A by SJW in Prospective Clinical Trials**

Whitten and co-workers[21] have performed a systematic review of the clinical trials that evaluated the role of SJW on the metabolism of compounds by CYP3A enzyme. As per a defined search criteria across the various clinical, scientific and research databases; and consultation with experts in the field, a total of 31 studies were selected which met the pre-assigned criteria. Interestingly, more than 66% of the trials used a straightforward before- and after- study design; less than 33% of the clinical trials employed a crossover design; and only 10% of the trials (i.e., 3 out of 31) were run as double blind with a placebo control arm. In all there were 26 studies where the content of SJW was known either by direct assaying of the SJW formulation (12 out of 26) or had a pre-stated content label for the specific SJW extract employed in the study (14 out of 26). The majority of the studies (i.e., 19 out of 26) that used high-dose hyperforin extracts (i.e., >10 mg/day) clearly demonstrated trial outcomes that were consistent with CYP3A induction. Three specific studies used low-dose hyperforin extracts (i.e., <4 mg/day) and the outcome from such studies showed no significant effect on CYP3A activity. Overall, it was concluded that high-dose hyperforin had the propensity to increase or induce CYP3A activity.[21]

**Linking CYP3A Induction by SJW to Hyperforin Dose**

Mueller et al.[22] carried out an interesting study using SJW that contained varied amount of the active principle, hyperforin. The clinical study involved 42 male subjects randomized into six groups (n=7 per group). Each group was assigned to a specific SJW product that offered a pre-stated hyperforin dose. The CYP3A related activity was established using midazolam as the substrate (biotransformation pathway leading to the formation of hydroxymidazolam metabolite). The baseline CYP3A activity was established prior to the oral dosing of SJW and again the CYP3A activity was measured on the 14th day of SJW dosing (daily oral doses per the assigned group). Interestingly, all SJW groups showed a decreased exposure of midazolam, the target substrate for CYP3A. However, the extent of decrease in exposure varied across the dose groups. One preparation of SJW that had the least amount of hyperforin content in the dose (approximately 0.13 mg/day) reduced midazolam AUC0-12h exposure by nearly 21%. Another preparation of SJW that delivered a much higher dose of hyperforin (approximately 12 mg/day) reduced midazolam AUC0-12h exposure by approximately 48%. The SJW preparation that had the highest content of hyperforin (approximately 41 mg/day) maximally reduced the midazolam AUC0-12h by approximately 79%. Overall, authors unequivocally established a good correlation between increasing hyperforin dose versus the reduction in midazolam’s exposure (r = 0.765; P < 0.001). Interestingly, the increasing hypercin dose in the same study produced no correlation with the reduced exposure of midazolam (r = 0.067; P = 0.673).[22]

**SJW’s Activity on Multiple CYP and Non-CYP Enzymes**

The work of Wenk et al.[23] attempted to simultaneously collate multiple activities of SJW on various CYP isozymes (CYP3A4, CYP1A2, and CYP2D6) and non-CYP enzymes (N-acetyltransferase and xanthine oxidase). This clinical study enrolled 16 subjects (8 males and 8 females) and daily intake of SJW herbal extract (total dose of 900 mg/day) was provided to the volunteers for duration of 14 days. The substrates that were used to probe the various enzymatic systems prior to SJW dosing and at the end of SJW dosing included endogenously formed cortisols (CYP3A4), dextromethorphan (CYP2D6) and caffeine (CYP1A2, N-acetyltransferase and xanthine oxidase). The data obtained from this elegant study suggested that during a 14 day daily intake of SJW potential existed for the induction of CYP3A4 in both male (50% increased activity) and female subjects (90% increased activity). While, a mild increase of CYP1A2 activity was only observed for female subjects (20% increased activity) but not in male subjects. Regardless of the gender, the activities of CYP2D6, N-acetyltransferase, and xanthine oxidase were not affected by SJW.[23]

**CYP3A4 Substrates Affected by SJW in the Clinic**

A number of CYP3A4 substrates belonging to varied therapeutic classes have been shown to demonstrate significant pharmacokinetic interaction when co-administered with SJW. Table 1 provides a list of select CYP3A4 and/or P-glycoprotein (pgp) substrates to document the exposure loss of the concerned substrate during co-administration with SJW.

**CLINICAL AND THERAPEUTIC SIGNIFICANCE**

**Oncology Area**

The area of cancer therapy continuous to be dominated by the use of multi thronged treatment modality possibly related to the poor prognosis of various tumors. Hence, understandably cancer patients always look for additional options such as herbal derived product(s) given the agony or
Table 1: Select list of substrates that showed significant pharmacokinetic interaction with the induction phenomenon of St. John’s wort

<table>
<thead>
<tr>
<th>Substrate(s)</th>
<th>Reference</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam[35]</td>
<td>Markowitz et al., 2003</td>
<td>AUC decreased by 2-fold; elimination half-life reduced by 50%; no drug levels post-36 h in about 50% of subjects</td>
</tr>
<tr>
<td>Amitriptyline/ noramitriptyline[36]</td>
<td>Johne et al., 2002</td>
<td>Reduced the steady state exposures of both amitriptyline (by 22%) and noramitriptyline (by 44%). Urinary excretion of compounds were also reduced</td>
</tr>
<tr>
<td>Cyclosporine[27]</td>
<td>Bauer et al., 2003</td>
<td>Cmax, AUC values decreased by about 45%; need of increased dose of cyclosporine (&gt;40%) to maintain effective levels to avoid transplant rejection</td>
</tr>
<tr>
<td>Digoxin[36]</td>
<td>Mueller et al., 2004</td>
<td>Cmax and AUC values decreased between 27 and 38%; since digoxin is not a substrate for CYP3A4, pgp induction was confirmed.</td>
</tr>
<tr>
<td>Imatinib[39,40]</td>
<td>Smith, 2004</td>
<td>Exposure of imatinib decreased by 30-32% and elimination half-life increased by 25%; the total exposure of active metabolite, N-desmethyl imatinib, did not change appreciably.</td>
</tr>
<tr>
<td>Irinotecan[24]</td>
<td>Mathijssen et al., 2002</td>
<td>The exposure of active metabolite, SN-38, was reduced by approximately 42%. Reduced exposure correlated with a lesser side effect profile (i.e., myelosuppressive effects)</td>
</tr>
<tr>
<td>Talinolol[41]</td>
<td>Schwarz et al., 2007</td>
<td>Exposure was reduced by 31% which translated into a reduction of almost 25% bioavailability. Oral clearance value was estimated to increase by 93%. Duodenal biopsy confirmed the inductive effect on intestinal MDR1 protein expression.</td>
</tr>
<tr>
<td>Verapamil/ norverapamil[33,35]</td>
<td>Tannergren et al., 2004</td>
<td>Elimination half-life values for both compounds were not altered. Exposure of both verapamil and norverapamil enantiomers decreased by 51–78%. However, oral clearance value was estimated to increase by 93%. Duodenal biopsy confirmed the inductive effect on intestinal MDR1 protein expression.</td>
</tr>
<tr>
<td>Warfarin[47]</td>
<td>Jiang et al., 2004</td>
<td>Oral clearance value was estimated to increase by 93%. Exposure of both active metabolites (SN-38 and 4-hydroxyl warfarin) was reduced by 40% and 37% respectively. Induction of intestinal CYP3A4 activity by SJW was confirmed.</td>
</tr>
</tbody>
</table>

Trauma associated with the disease such as cancers. It should also be realized that cancer patients tend to suffer from other co-morbid conditions especially related to cardiovascular ailments just like the population at large. However, more importantly, many cancer patients often times are associated with episodes of depression which needs to be treated with suitable agent(s).

As the herbal medicine use is on the rise, the use of SJW has been considered by many cancer patients to manage the mild to modern episodes of depression. However, it is important to recognize that there may be a real potential for a pharmacokinetic interaction if the cancer drug is a substrate for CYP isozymes (especially CYP3A4) and efflux transporter(s) such as p-glycoprotein. As a result of enzymatic and/or pgp transporter induction by SJW there may be a tremendous exposure loss of the anti-cancer drug such that it may be ineffective for the purported treatment. In a patient who is responding to the anti-cancer therapy this is a real set back. In order to overcome these issues two choices could be made: a) immediate discontinuation of the SJW therapy for the timely restoration of enzymes back to their normal baseline levels so that the anti-cancer drug could be continued at the same dose; b) immediate optimization of the anti-cancer drug to a higher dose and/or increased frequency of administration so that it could work in spite of the induced enzyme environment. Alternately, if SJW therapy is felt absolutely needed for the cancer patient(s), possibility of switching over to other anti-cancer drug(s) that may be less affected by the induced enzymes and/or transporters due to SJW may be considered.

Case Study of Irinotecan[24]

Irinotecan is a widely used cytotoxic chemotherapy drug belonging to the chemical class known as camptothecins and its purported mechanism of action involves the inhibition of topoisomerase I enzyme that is expressed to a large extent by many solid tumor cells. However, irinotecan is a prodrug and needs to get converted to SN-38, an active metabolite, to manifest its full anti-cancer potential. The disposition of SN-38 is complicated among other things involving secondary metabolism including glucuronic acid conjugation, enterohepatic biliary excretion and possible reabsorption from the small intestine. As a result of the increased CYP3A4 enzyme and intestinal pgp transporter expression, it was found that the exposure of SN-38 was reduced by as much as 40% when co-administered with SJW. Interestingly, in the cytotoxic therapy, the efficacy is somewhat correlated with the toxicity profile suggesting that at efficacy dose(s) the cytotoxic agents are also prone to manifest safety issues. In this study, it was found that the reduced SN-38 exposure reduced the severity of myelosuppression observed in the patients and caused a lower incidence of haematological toxicity. Unfortunately, the reduced side effect profile is a give away for compromised efficacy of the agent. Therefore, the authors recommended that cancer patients should avoid SJW therapy if they are on irinotecan based chemotherapy.

Management of HIV Infections

Similar to cancer area, this is a dreaded disease which in addition to trauma and suffering, carries some sort of social stigma. While the cure has been elusive, the effective management of HIV patients with scores of approved medicines is possible with well defined treatment protocols that ensure that the viral spread is limited and well controlled. As was the case with cancer patients, the introduction of SJW to such patients has been rationalized...
to combat the depressive episodes encountered by these patients. There was a report that claimed that SJW by itself may possess anti-viral activity and therefore, may benefit select anti-infective therapy(ies) with other approved medicines. The loss of exposure due to CYP3A4 induction has been previously demonstrated in the combination use of rifampicin with efaviranz. Since tuberculosis manifests as an opportunistic infection in the immuno-compromised patients, the use of rifampicin has been commonly practiced in patients being treated with efaviranz for the management of HIV infection. However, rifampicin is an inducer of CYP3A4 and was reported to drastically reduce the exposure of efaviranz. The reduction of the exposure of efaviranz would seriously compromise the efficacy in treating HIV infection. Therefore, the literature evidence from other CYP3A4 inducer(s) such as rifampicin is very convincing on the occurrence of serious interactions with anti-HIV agents. Therefore, the use of SJW concomitant with the various anti-HIV agents that possibly undergo metabolism via CYP3A4 and/or manifest transporter dependent disposition, needs to be seriously questioned.

Case Study of Indinavir
A few years ago Piscitelli et al. published a report that showed appreciable loss of exposure of indinavir, an important anti-HIV drug, when co-administered with SJW. In this clinical investigation, a multiple dose treatment with SJW resulted in an exposure loss of approximately 57% for indinavir. However, more importantly, the trough levels were reduced by as much as 81%, which is a matter of great concern in anti-infective and anti-HIV therapies. The authors opined that such a drastic drop in the exposure values and trough levels of indinavir may translate into increased drug resistance and HIV treatment failure in such patients receiving SJW.

Case Study of Saquinavir
Saquinavir, an interesting and extensively used anti-HIV agent, manifested wide variability in its oral bioavailability (<9% reported in humans). The work of Mouly et al. probed the roles of CYP3A4 and pgp transporter in tandem to possibly explain the observed low oral bioavailability of saquinavir. Using specific markers and varied experimental conditions, it was concluded that the observed low bioavailability in HIV infected patients was due to varied first pass extraction of saquinavir, where there was a dual interplay between CYP3A4 mediated metabolism and pgp mediated transport which restricted the systemic entry of intact saquinavir. Hence, the co-administration of SJW with a substrate such as saquinavir could result in an unprecedented pharmacokinetic interaction and may possibly wipe out the oral bioavailability of saquinavir. Although combination use of saquinavir with SJW has not been reported, it appeared prudent in not administering saquinavir along with SJW.

DISCUSSION
Induction phenomenon has been observed with other agents namely rifampicin, dexamethasone, etc. In spite of the issues posed by rifampicin, it is widely used drug for its therapeutic value and the use of rifampicin is guided by pre-specified protocol(s) especially in HIV infected patients who are being treated for opportunistic infections. Therefore, one could draw inferences from the literature evidences of rifampicin’s use and make intelligent conjunctures applicable for SJW.

In order to understand the complexities, few examples are cited where data could be compared from various studies to judge the propensity for induction of CYP3A4/ pgp of rifampicin versus SJW. Rifampicin reduced the oral clearance of verapamil, a substrate for CYP3A4, by almost 32 to 57 fold; whereas, SJW reduced the oral clearance of verapamil by 6 to 8 fold. Similarly, when comparisons were made for pgp substrates, namely fexofenadine and digoxin, there was a marked difference observed between rifampicin and SJW pretreatments. While rifampicin, reduced the oral clearance of both fexofenadine and digoxin by approximately 50%, SJW caused a mild reduction of approximately 20-23% in the oral clearance of fexofenadine and digoxin.

While it is a good practice not to use SJW with agents that are known suspects to elicit a pharmacokinetic/pharmacodynamic interaction, it may be difficult to follow this in real clinical situations. Nevertheless, if an unsuspected interaction occurs during the therapy with SJW, it is important to ascertain the significance of the purported clinical interaction observed with SJW and remedial steps be taken to minimize the interaction (reducing dose of SJW and/or increasing the dose of the other agent) and/or stop SJW treatment and switch to another therapy.

It should be noted that in some situations, the concomitant SJW therapy might be inconsequential for the metabolic disposition of the interacting agent. If a compound is known to cause auto-induction phenomenon (via a CYP3A4 induction), the co-administration of SJW is not expected to cause much more exposure loss of the agent since the induced CYP3A4 enzyme perhaps has already reached a plateau.

Overall, it appears prudent to justify the use of SJW in a poly-pharmacy situation with modern medicines. If new treatment option(s) is/are being explored in cancer patients, HIV patients, and patients undergoing transplantation, the use of SJW need to be seriously evaluated to ensure that...
suspected pharmacokinetic interaction is unlikely to happen and/or could be controlled with a proper manipulation of the dosing regimens without the risk of treatment failure(s). If the risk of treatment failure is imminent, it is best to avoid the use of SJW.

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