St John’s Wort Supplements Endanger the Success of Organ Transplantation

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Hypothesis: St John’s wort is one of the most popular herbal medicines, and health care professionals often are unaware that their patients take such supplements. St John’s wort causes a decrease in cyclosporine levels, thus endangering the success of organ transplantations.

Design: Systematic review.

Methods: Five independent computerized literature searches were conducted to identify all reports of such interactions. Data were extracted and are summarized in narrative form.

Results: Eleven case reports and 2 case series were located. In most instances, causality between St John’s wort and the clinical or biochemical result is well established. The mechanism of interaction between St John’s wort and cyclosporine has been recently elucidated and involves both P-glycoprotein and cytochrome P 450 3A4 expression. Collectively these data leave little doubt that St John’s wort interacts with cyclosporine, causing a decrease of cyclosporine blood levels and leading in several cases to transplant rejection.

Conclusions: St John’s wort can endanger the success of organ transplantations. Adequate information may be the best way to avoid future incidences.

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Several recent surveys have shown that herbal medicines have become increasingly popular.¹ It is therefore not surprising that a large proportion of surgical patients are using herbal medicines, often unknown to the treating health care team. A total of 755 US surgical patients completed a questionnaire on their use of herbal medicines. The results confirm a high level of herbal use: 43% took garlic; 32%, ginkgo biloba; 30%, St John’s wort (SJW); 18%, mahuang; 12%, echinacea; and 10%, aloe.² Another survey, conducted roughly 5 years ago, showed that 20% of transplant recipients were taking herbal medicines.³

Contrary to widespread public opinion, herbal medicines are not free of adverse effects.⁴ Risks may include toxicity of herbal ingredients, contamination of herbal products (eg, with heavy metals, microorganisms, or pesticides), adulteration with conventional drugs (eg, corticosteroids), and herb-drug interactions.⁵ A recent review stressed that surgical patients are also at risk.⁶ This systematic review is dedicated to the latter aspect. Specifically, we summarize the emerging evidence suggesting that dietary supplements of SJW (Hypericum perforatum) decrease cyclosporine levels in organ transplant patients, thus endangering the success of organ transplantations.

METHODS

Computerized literature searches (1995-2001) were carried out without language restrictions in the following databases: MEDLINE (via PubMed), EMBASE, The Cochrane Library, AMED, and CISCOM. The search terms were adverse effects (events), alternative medicine, cyclosporine, herbal medicine (or therapies), Hypericum, Johanniskraut, phytomedicine, rejection, safety, side effects (events), SJW, surgery, and transplantation. The bibliographies of all articles found were hand searched for further relevant publications. All articles reporting original data on interference of SJW with transplant patients were included. Investigations into the mechanism of action of such adverse events were also considered and reviewed.

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CASE REPORTS

Since the possibility of interactions between SJW and cyclosporine became widely publicized, a flurry of interest ensued. Eleven case reports and 2 case series have been published recently, and these are summarized in the article.

A woman in her mid-20s was receiving cyclosporine therapy when she decided to take an SJW extract. Subsequently her cyclosporine level fell 75%. This first report from 1998 of an interaction between SJW and cyclosporine contains no further details and thus cannot be interpreted clearly. However, it provided an important stimulus for other investigators to study this area more rigorously.

Bon described a case of a 61-year-old woman who had received a heart transplant 10 months earlier and was taking cyclosporine. She self-medicated with SJW and her cyclosporine levels subsequently fell markedly. She also experienced a rejection episode. The author also described a 54-year-old woman who was taking prednisolone and cyclosporine for treatment of pulmonary fibrosis. After she decided to self-medicate with SJW, her cyclosporine level decreased markedly, requiring a dose increase. After discontinuation of SJW, cyclosporine levels increased again and the previous cyclosporine dose could be reinstated. Both of these case reports provide little detail, and causality is therefore not certain; nevertheless, they leave little doubt about a causal relationship between SJW and a decrease in cyclosporine levels.

A 29-year-old white woman had received a combined cadaveric kidney and pancreas transplant in 1994. After 2 early rejection episodes, she had stable renal and pancreatic function and was treated with 100 mg of cyclosporine twice daily with blood levels in the therapeutic range. In November 1998, the patient started self-medicating with SJW (1-2 tablets per day of 300 mg extract standardized to 0.3% hypericin). Subsequently, her cyclosporine level dropped to 155 ng/mL and 97 ng/mL 3 weeks later. At that point, she also had the first biochemical signs of kidney and pancreatic malfunction and acute transplant rejection. It was then discovered that the patient took SJW, and this treatment was discontinued. Her cyclosporine levels subsequently stabilized. However, the patient developed chronic transplant rejection confirmed by a transplant kidney biopsy in January 2000. As with all cases summarized in the study, causality is not in question.

A 63-year-old patient with a liver allograft developed severe acute transplant rejection 14 months after transplantation. Two weeks previously, he had self-medicating with SJW (900 mg extract 2 times daily), which significantly lowered his cyclosporine levels. His cyclosporine dose had to be doubled at the expense of adverse effects, such as mild renal toxicity. The patient made a full recovery after the problem was recognized and use of SJW had been stopped.

A 55-year-old woman had received a kidney transplant 25 years ago and had stable organ function while taking cyclosporine medication. She self-medicating with SJW at a dose of 300 mg standardized extract a day (one third of the recommended dose). Four weeks later, a sharp drop in cyclosporine levels was noted, which was reversible on SJW withdrawal and reproducible with a rechallenge. As the problem had been identified early enough, no serious clinical consequences were incurred by the patient.

A 61-year-old man had successfully received an orthotopic heart transplant 11 months earlier and was stable while receiving cyclosporine therapy (125 mg twice daily). For about 1 year, he had stable cyclosporine blood levels. He then self-medicating with SJW (300 mg extract 3 times daily). Subsequently, his cyclosporine levels decreased markedly (95 ng/mL) and signs of tissue rejection emerged. The patient had also been taking azathioprine and corticosteroids. His self-medication regimen was stopped and his cyclosporine dose increased to 150 mg twice daily. This treatment did not prevent prolonged acute rejection as verified by biopsy results 7 days later. Subsequent drug therapy with mycophenolate mofetil and antithymocyte globulin resolved the rejection episode and no further episodes were noted at follow-up.

The same team described a 63-year-old man who had undergone heart transplantation and was receiving cyclosporine therapy and standard immunosuppressive regimen. Three weeks after his psychiatrist had prescribed SJW (300 mg 3 times daily), his cyclosporine level fell to subtherapeutic concentrations levels (87 ng/mL). He also developed signs of acute transplant rejection. After use of SJW was stopped, cyclosporine levels returned to therapeutic values and no further episodes of rejection occurred.

A 44-year-old black woman had received a living-related kidney transplant in 1996. After an early episode of acute rejection, she stabilized. She was readmitted in December 1999 when it was noted that her cyclosporine levels were consistently below the target level of 200 ng/mL. She had been self-medicating with SJW (2-3 tablets per day of 300 mg extract standardized to 0.3% hypericin) for 6 months. An herb-drug interaction was suspected, the patient discontinued use of SJW, and her cyclosporine levels promptly increased to 275 ng/mL without a dose change. She remained stable at follow-up and no graft rejection was noted.

The most recent case is of a 55-year-old woman who had received a kidney transplant in 1985 and subsequently had been stable receiving cyclosporine therapy. In 1995, she started self-medicating with SJW (300 mg extract 3 times per day). This resulted in a decrease of cyclosporine levels from 210 ng/mL to 81 ng/mL. The transplant team thus increased the dose of cyclosporine to 8.2 mg/kg body weight daily. It was only in April 2000 that an interaction was suspected and the patient’s self-medication usage was stopped. Eventually the patient was maintained using her previous cyclosporine dose. She had no permanent harm but the authors calculate that the costs of temporarily increasing the dose of cyclosporine amounted to 30000 DM (US $14000).

CASE SERIES

A case series described 30 patients whose cyclosporine levels dropped by a mean of 47% (range, 33%-62%) after self-medication of SJW. This necessitated a gradual
increase of the dose of cyclosporine of 46% on average (range, 15%-115%). This measure and the concomitant discontinuation of use of SJW led to an increase of cyclosporine levels of 187% on average (range, 84%-292%). No patient was reported to have any permanent consequences as a result.

This case series was extended to 35 patients receiving kidney transplants and 10 patients with liver transplants. All patients were treated with cyclosporine and self-medicated with SJW extracts. Subsequently, their cyclosporine level fell by 30% to 64% (49% on average). Most of these patients did not report their SJW use to the transplantation team. There were also 2 rejection episodes: 1 was experienced by a liver recipient and the other by a kidney recipient.

Collectively these data leave little doubt that use of SJW can lower cyclosporine levels, thus endangering the success of organ transplantations and causing considerable expense. Causality is well established in several cases. This raises the question as to the mechanisms of action that might be involved.

St John’s wort affects the clearance of many other drugs, including antidepressants (predominately selective serotonin reuptake inhibitors), digoxin, indinavir, and phenprocoumon. No single unifying mechanism explains all of these interactions. The basis of the herb-drug interactions seems to be multifactorial. One explanation is that SJW interacts with P-glycoprotein, an adenosine triphosphate-dependent drug efflux transporter known to decrease the availability of many other drugs by pumping them out of the cell membrane, thus decreasing intracellular concentrations. In a recent study, the administration of SJW extract to rats during 14 days resulted in a 3.8-fold increase of intestinal P-glycoprotein expression and in a 2.5-fold increase in hepatic CYP3A4 expression. Similarly, the administration of SJW extract to healthy volunteers during 15 days caused a significant (25%) decrease of digoxin levels after 10 days of SJW administration. These results render the induction of the P-glycoprotein drug transporter by SJW, which is a likely mechanism to explain the findings that we have summarized.

Another possibility is that SJW enhances the cytochrome P450 system, which is responsible for the metabolism of a multitude of drugs. Treatment of human hepatocytes with SJW extracts or with hyperforin (1 of SJW’s active constituents) resulted in induction of CYP3A4 expression. In vitro experiments show that SJW also induces CYP3A4, which is responsible for the metabolism of about one fourth of all drugs (including cyclosporine, estrogen, indinavir, phenprocoumon, and warfarin). However, results of isoenzyme studies are mixed. While 3 enzyme marker studies indicated a potent inducing effect of SJW (300 mg 3 times daily for 14 days) on CYP3A4, 2 other investigations found no effect of SJW (both 300 mg 3 times daily, 1 for 3 days and the other for 8 days) on CYP2D6 or 3A4. The trials with negative results might have been too short in duration for detecting the enzyme induction effect. Alternatively, differences in quality of the extracts used might explain this discrepancy.

Little evidence supports any effect on CYP1A2. One study examining the effect of SJW on CYP1A2 (using a caffeine/dextromethorphan probe) found that SJW (300 mg 3 times daily for 8 days) had no effect on dextromethorphan/caffeine ratios, indicating that it has a low potential for drug interactions at CYP1A2. The only clinical study of the effect of SJW on CYP1A2 demonstrated a low potential for interaction, but the study was only 8 days long. The only case report of a drug metabolized primarily by CYP1A2 interacting with SJW is an incident where SJW was suspected to lower theophylline levels, the case is, however, insufficient in several respects for establishing causality with any degree of certainty.

There are, of course, many other drugs that interact with cyclosporine. Thus the question arises as to the relative importance of the SJW interaction. Based on a recent analysis of 100 cases, the magnitude of the SJW interaction is similar to that of other drugs and should therefore not be dismissed as unimportant. The frequency of SJW interactions cannot be estimated at present. Underreporting might be a prominent factor determining the number of cases published. It is noteworthy that most cases originate in Germany where sales figures for SJW are highest. More systematic investigations are required to generate reliable incidence figures.

How can interactions between SJW and cyclosporine (or other drugs) be avoided in future? After the possibility of such interactions had been widely publicized, many national regulatory agencies issued warnings to health care professionals. These summarized case reports suggest that such warnings were not sufficient to prevent all incidents. In most countries, SJW is freely available from outlets such as pharmacies, health food shops, and the Internet. The public continues to believe that herbal medicines are safe, and the media contributes to perpetuating this myth. The truth is, however, that numerous herb-drug interactions must be considered. In many of the instances detailed in this study, a lack of communication between patients and health care professionals was an important part of the problem. It seems to follow that health care professionals need to inform their patients accurately about the potential dangers of such self-medication. Adequate history taking must include questions about use of herbal medicines, and adequate patient information must include the essentials about safety issues related to the herbal medicines used by each patient.

In conclusion, SJW has repeatedly led to lowering of cyclosporine levels in transplant patients and thus endangered the success of organ transplantations and increased hospital costs. One way of avoiding future incidents is for adequate information to be shared between all parties involved.

REFERENCES


Although the causal relationship between SJW and the lowering of cyclosporine levels has been well documented and the potential loss of allograft owing to rejection is real, several points of discussion arise:

1. The identity of the chemical makeup of SJW should be presented and its structure compared with some similar compounds that have either interaction with P-glycoprotein or the cytochrome P450 system. This will enhance the possible direct effect of SJW on cyclosporine A levels.

2. The authors need to be sure that no other confounding medication can also affect cyclosporine A metabolism since, though it is not clearly stated, these transplant recipients are supposed to be receiving only standard immunosuppressive medication at that time since transplantation has taken place months or years prior to taking SJW.

3. Although one cannot avoid SJW active ingredients in all common foodstuffs, it is important to not actively supplement oneself daily with SJW since it might be the cumulative dosage of SJW that causes alteration in cyclosporine A metabolism.

The transplant community (health care personnel as well as transplant patients) needs to be aware of this important report.

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