

shown (figure). The AUC_{0-8} of indinavir decreased by a mean (SD) of 57% (19)% (30.8 [8.4] to 12.3 [4.7]) after therapy with St John's wort ($p=0.0008$)*. All participants showed a reduction in C_{8s} ranging from 49 to 99%, with a fall in the mean from 0.493 $\mu\text{g/mL}$ for indinavir alone to 0.048 $\mu\text{g/mL}$ after St John's wort ($p=0.027$). The mean C_{max} of indinavir decreased from 12.3 (4.1) $\mu\text{g/mL}$ to 8.9 (3.4) $\mu\text{g/mL}$. T_{max} was not significantly altered. For C_{8s} , the mean ratio of indinavir with St John's wort to indinavir alone was 0.194 (95% CI 0.059–0.329). The point estimate for the mean ratio of AUC_{0-8} was 0.458 (95% CI 0.335–0.581).

Study drugs were well tolerated by all participants, and none withdrew. The most commonly reported adverse effects included taste changes (50%), nausea (25%), and circumoral paresthesias (25%) and were associated with indinavir. One participant developed a rash during initial dosing that did not recur during subsequent dosing. The intensity and duration of reported adverse effects were less during the second phase of indinavir.

This study shows a large reduction in indinavir concentrations by concomitant St John's wort. These results have important clinical implications for HIV-infected patients receiving these two agents since low plasma concentrations of protease inhibitors are a cause of antiretroviral resistance and treatment failure.⁵

Several case reports and two studies examining urinary markers of CYP450 activity suggest that CYP3A4 induction is the mechanism for the decrease in indinavir exposure, although effects on p-glycoprotein cannot be ruled out.¹ Because we expected CYP3A4 induction by St John's wort, we studied healthy, non-HIV-infected volunteers to avoid inadequate indinavir concentrations in HIV-infected participants. Many clinicians consider complementary medicines to be inert. These products are rarely thought a cause of adverse effects or treatment failure, and often are not included in a drug history. This study shows that drug interactions with these products do occur and might have profound clinical consequences, especially in HIV-infected patients in whom resistance can rapidly develop in the presence of suboptimum antiviral concentrations.

St John's wort should be avoided in patients receiving indinavir as their sole protease inhibitor. Since other protease inhibitors and non-nucleoside reverse transcriptase inhibitors are also metabolised by CYP3A4, it is reasonable to also avoid St John's wort with these agents in the absence of definitive data.

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Acute heart transplant rejection due to Saint John's wort

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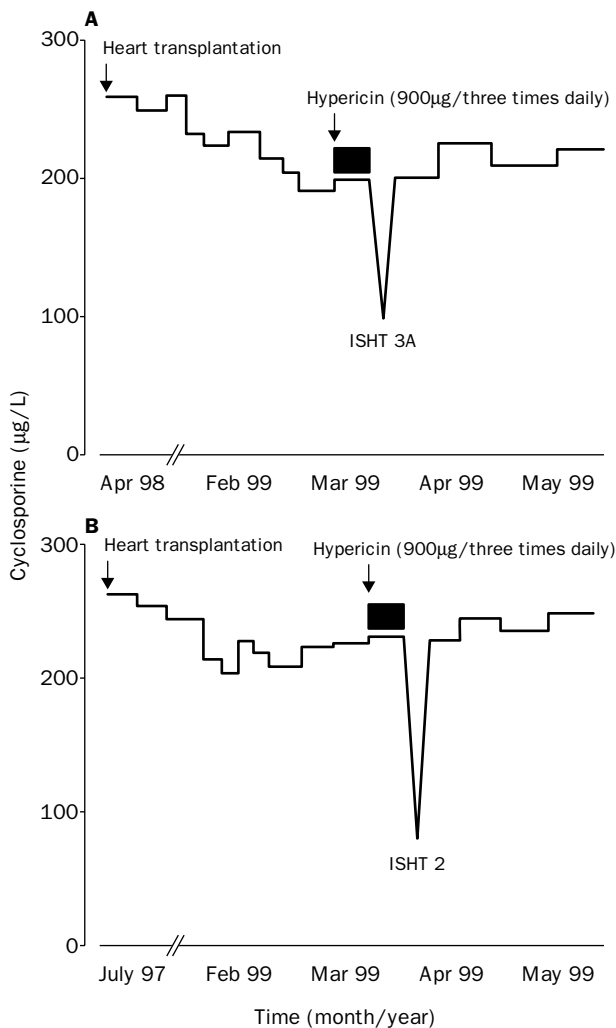
We report here acute rejection in two transplant patients due to a metabolic interaction of St John's wort and ciclosporin.

St John's wort (*Hypericum perforatum*) is a folk remedy frequently used for the treatment of skin injuries, burns, and neuralgia. Recently, it has gained a reputation as an effective treatment for depression.¹ However, the mechanism of action of the postulated antidepressant effects is unclear.

A 61-year-old heart transplant patient was admitted for elective endomyocardial biopsy. Orthotopic heart transplantation had been done 11 months earlier because of end-stage ischaemic cardiomyopathy (figure, A). Subsequently, the patient had an event free course (International Society of Heart and Lung Transplantation [ISHT], grading 0 or 1A) and was maintained on a standard immunosuppressive regimen of ciclosporin (125 mg twice daily), azathioprine (100 mg daily) and low dose corticosteroids (7.5 mg daily). Ciclosporin plasma levels remained stable throughout the year. Three weeks before admission the patient started self-medication with St John's wort because of mild depression. The standardised St John's wort extract LI160 (sold under the brand name Jarsin® containing 900 μg hypericin) was taken at a dose of 300 mg three times daily (further chemical analysis of the drug was not done). On admission, the patient had nonspecific fatigue, but was otherwise feeling well. Physical examination was normal, in particular there were no signs of infection or haemodynamic compromise. Laboratory investigation showed decreased ciclosporin plasma concentrations (95 $\mu\text{g/L}$), but no further abnormalities, in particular no signs of cytomegalovirus infection. Endomyocardial biopsy revealed acute cellular transplant rejection (ISHT-grading 3A, Quilty B). Interaction of St John's wort with ciclosporin was suspected and the patient's self-medication was stopped. Ciclosporin dosage was increased to 150 mg twice daily and bolus dose of corticosteroids (1 g intravenously per day) was given for 3 days, but proved to be ineffective, as endomyocardial biopsy done 7 days later showed prolonged acute rejection (ISHT-grading 3A, Quilty B). Hence, azathioprine was substituted by mycophenolate mofetil (1 g twice daily). Anti thymocyte globulin (ATG), 1250 mg daily, intravenously was given for 10 days. These drugs resolved the rejection episode (ISHT-grading 1 A). After stopping treatment with St John's wort, plasma ciclosporin remained within the therapeutic range with no further episodes of rejection.

1 week after the first patient presented, a 63-year-old patient was referred to our clinic for elective endomyocardial biopsy. Heart transplantation was performed 20 months earlier because of end-stage ischaemic cardiomyopathy (figure, B). The patient was maintained on a triple immunosuppressive regimen of ciclosporin (125 mg twice daily), azathioprine (125 mg daily) and corticosteroids (7.5 mg daily) and had an even-free course (ISHT grading 0 or 1A) and stable ciclosporin concentrations. 3 weeks before admission, a psychiatrist started treatment with St John's wort (Jarsin® 300 tid) because of anxiety and depression. On admission, ciclosporin plasma concentrations were below the therapeutic range (87 $\mu\text{g/L}$) and endomyocardial biopsy showed acute heart transplant rejection (ISHT 2). Physical examination and laboratory values did not show any other cause of rejection. After treatment with St John's wort was stopped plasma ciclosporin returned to therapeutic values. No further

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Cyclosporin concentrations in two patients after heart transplantation

Treatment with St John's wort was associated with a drop in cyclosporin values below the therapeutic range and acute transplant rejection.

episodes of rejection occurred. The close temporal relation strongly suggests that St John's wort treatment was the cause of the drop in plasma cyclosporin.

St John's wort extracts contain at least ten different constituents or groups of components that may contribute to its pharmacological effects. These include flavonoids, xanthenes, bioflavonoids, and naphthodiantrons. In particular, the naphthodiantrons induce the CYP3A isoenzyme of the microsomal cytochrome P-450 complex which metabolises cyclosporin.² In addition, St John's wort extracts have been suggested to induce intestinal P-glycoprotein drug transporter,³ which could also contribute to a decreased oral bioavailability of cyclosporin.⁴ As the use of St John's wort is steadily increasing, these serious reported adverse reactions warn that even a folk medicine, previously regarded as safe and well tolerated, can have a potential risk, particularly when an important comedication is metabolised by the cytochrome P-450 complex.

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School-based hepatitis B vaccination programme and adolescent multiple sclerosis

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We investigated multiple sclerosis in adolescents in British Columbia before and after a hepatitis B vaccination programme was begun. There was no evidence of a link between hepatitis B vaccination and multiple sclerosis or other demyelinating disease.

In October, 1998, despite an absence of any objective scientific evidence,^{1,2} French health authorities suspended hepatitis B (HB) vaccination of adolescent schoolchildren because of public concerns that HB vaccination might be linked to new cases or exacerbations of demyelinating diseases, in particular multiple sclerosis. Since then, the overall use of HB vaccine has fallen in France, where vaccine labels now list multiple sclerosis as a contraindication.³ The World Health Organization, along with other groups such as Canada's Laboratory Centre for Disease Control (LCDC) and the US Centers for Disease Control and Prevention, decried this decision, emphasising that external experts, as part of a special consultative session in September, 1998, carefully reviewed the data and did not find evidence to support any such relation.⁴ WHO further emphasised that no definitive evidence supports a causal association between multiple sclerosis and any vaccine.⁵

The most useful data to investigate a causal association between HB vaccination and multiple sclerosis would come from a comparison of vaccinated and non-vaccinated individuals. There are scant data for adolescent populations, among whom multiple sclerosis is much less common than in adults. In British Columbia (BC), Canada, HB vaccination has been offered annually to 11–12-year-old students (grade six) since October, 1992. The number and proportion of students who completed the three-dose vaccination series has been determined by the BC Centre for Disease Control. From October, 1992, to September, 1998, when programme participation averaged 92.3%, 267 412 grade six students completed the vaccination series (A King, unpublished data), providing a follow-up of about 966 000 person-years. During the 6.75 years (January, 1986 to September, 1992) preceding the HB vaccination programme, about 41 237 children attended grade six annually, providing about 1.14 million person-years of observation.

We looked at the onset of multiple sclerosis among adolescents aged 11–17 years of age. Data were obtained from the medical records of the British Columbia's Children's Hospital (BCCH), the only paediatric hospital in the province, and the database of the provincial multiple sclerosis clinic. All paediatric neurologists in the province