

Research letters

Indinavir concentrations and St John's wort

Stephen C Piscitelli, Aaron H Burstein, Doreen Chaitt, Raul M Alfaro, Judith Falloon

St John's wort reduced the area under the curve of the HIV-1 protease inhibitor indinavir by a mean of 57% (SD 19) and decreased the extrapolated 8-h indinavir trough by 81% (16) in healthy volunteers. A reduction in indinavir exposure of this magnitude could lead to the development of drug resistance and treatment failure.

Herbal remedies and complementary medicines are widely used despite a lack of information about their pharmacology, pharmacokinetics, and potential drug interactions. St John's wort (*Hypericum perforatum*) is one of the most popular herbal dietary supplements. Preliminary data suggest that St John's wort induces the 3A4 isoform of the cytochrome P450 (CYP) enzyme system.¹ Because HIV-1 protease inhibitors are substrates of the CYP3A4 isozyme, induction by St John's wort might have serious clinical implications.² We evaluated the effect of St John's wort on plasma concentrations of the HIV-1 protease inhibitor indinavir.

We did an open-label study in healthy volunteers. The study was approved by the National Institute of Allergy and Infectious Diseases (NIAID) Institutional Review Board, and all participants gave written informed consent. Inclusion criteria included negative HIV-1 test, age over 18 years, laboratory values within established NIAID limits, and a normal physical examination. Volunteers were excluded if they had smoked in the past year, received St John's wort within 30 days, had a history of allergy or adverse reactions to indinavir, were pregnant or lactating, were receiving

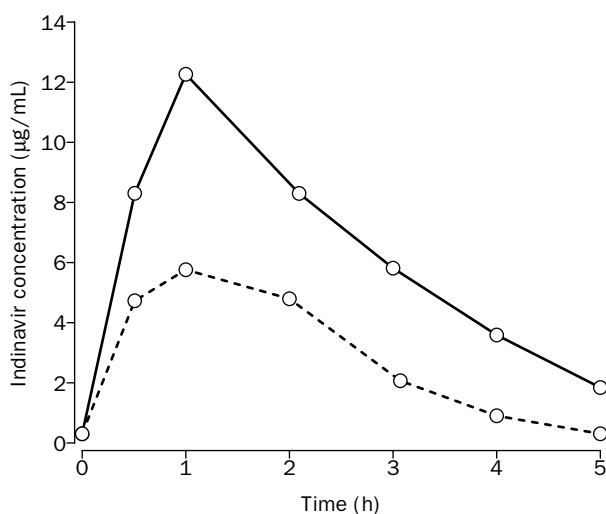
concomitant drugs metabolised via the CYP450 pathway, or had persistent diarrhoea or a history of malabsorption.

On the morning of day 1, fasting participants received indinavir 800 mg orally. They then received two more doses at 8 h intervals to achieve steady-state. On the morning of day 2, an 800 mg dose was given on an empty stomach in the clinic. Blood samples for indinavir pharmacokinetics were collected before and at 0.5, 1, 2, 3, 4, and 5 h after dosing, representing about 90% of the total area under the curve (AUC).

On day 3, participants began outpatient treatment with St John's wort (300 mg reagent grade tablets, lot 190217, Hypericum Buyers Club, Los Angeles, CA, USA). This preparation is standardised to 0.3% hypericin, which was confirmed in our laboratory by a USP/NF method.³ Each participant received 300 mg three times daily with meals, for 14 days. On day 16 (day 14 of St John's wort) participants again received indinavir 800 mg orally every 8 h on an empty stomach. On day 17, participants received 800 mg of indinavir in clinic with blood sampling before and serially for 5 h after dosing. Participants took their last dose of St John's wort with breakfast 90 min after indinavir dosing. Indinavir concentrations in plasma were measured by high performance liquid chromatography (HPLC) using modifications of a previously published method.⁴ The calibration range was from 25 to 10 000 ng/mL with a 25 ng/mL limit of quantitation. Inter-day and intra-day coefficients of variation ranged from 2% to 11%.

Indinavir pharmacokinetic indices were determined according to standard non-compartmental equations (WinNonlin V1.1, Scientific Consulting, Inc, Apex, NC, USA). Indices included maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), concentration 5 h after the dose (C_5), area under the curve from time zero to 5 h after dose (AUC_{0-5}), and oral clearance (CL/F). The concentration 8 h after dosing (C_8) and the AUC over the 8-h dosage interval (AUC_{0-8}) were extrapolated with the elimination rate constant calculated by log-linear regression of the terminal phase of the concentration-time profile. Indinavir pharmacokinetic indices in the presence and absence of St John's wort were compared with a paired Student's *t*-test. The ratio of the mean AUC in the presence of St John's wort to indinavir alone was calculated, and 95% CI around the mean point estimate were determined.

Eight participants (six male) were enrolled and completed the study. Seven were Caucasian and one was Hispanic. Their ages ranged from 29 to 50 years. Mean concentration-time profiles of indinavir alone and with St John's wort are



Mean concentration-time of indinavir alone (solid line) and with concomitant St John's wort (dotted line)

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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- 4 Li W, Coombs RW, Collier A, Raisys VA. Determination of indinavir, and HIV-1 protease inhibitor, in human plasma using ion-pair reversed-phase high performance liquid chromatography. *Ther Drug Monit* 1999; **21**: 360–66.
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Department of Pharmacy (S C Piscitelli PharmD, A H Burstein PharmD, R M Alfaro MS), **Warren G Magnuson Clinical Center and Laboratory of Immunoregulation** (D Chaitt MPH, J Falloon MD), **National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, MD 20892, USA**

Correspondence to: Dr Stephen C Piscitelli (e-mail: spisc@nih.gov)

Acute heart transplant rejection due to Saint John's wort

Frank Ruschitzka, Peter J Meier, Marko Turina, Thomas F Lüscher, Georg Noll

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

*See *Lancet* website for full results (www.thelancet.com)