

Letter to the Editor

Unwanted pregnancy on self-medication with St John's wort despite hormonal contraception

Many patients take St John's wort (SJW, *Hypericum perforatum*), a herbal remedy, to treat symptoms of depression, often without the knowledge of their physician. Widely available without prescription, it is considered by some to be a safe because it is a 'natural' alternative to more traditional antidepressants. Recent reports indicate that SJW has been implicated in numerous herb–drug interactions that may have clinical significance [1]. Women taking oral contraceptives and SJW have reported breakthrough menstrual bleeding, but this is the first published case of an unexpected pregnancy in association with SJW consumption [2].

A 36-year-old woman with depression and hypercholesterolaemia presented to a gynaecology practice with an unexpected pregnancy confirmed by ultrasound. The drug history revealed regular use of the combined oral contraceptive Valette® (ethinyl oestradiol/dienogestrol) over the last year. She had been treated with fluvastatin (20 mg day⁻¹) for 2 years, and with different antidepressants including selective serotonin reuptake inhibitors and tricyclic antidepressants after an attempted suicide in 1995. The patient began self-medicated with the over-the-counter *Hypericum* extract Helarium®425 (Bionorica) with daily doses up to 1700 mg approximately 3 months prior to conception, and until conception no other medication was taken except the hormonal contraceptive. A therapeutic abortion was carried out and revealed a healthy, 17-week-old, 144 g male foetus.

Co-administration of SJW has resulted in markedly reduced blood levels of drugs such as cyclosporin, indinavir, and digoxin. Lowered levels of cyclosporin have contributed to the rejection of transplanted organs [3]. In healthy volunteers, 10–14 days of concomitant SJW resulted in 81% reduction of indinavir trough and 30% reduction of plasma digoxin concentrations [4, 5]. This effect is likely mediated through induction of the drug metabolizing enzyme cytochrome P450 3a (CYP3a) and the efflux transporter P-glycoprotein that is encoded by the multidrug resistance gene *MDR1* [6]. Hyperforin, a major phytochemical present in SJW, is a potent activator of the human nuclear receptor pregnane X (PXR) [7]. Both *CYP3A4* and *MDR1* have PXR response elements in their 5'-upstream regulatory regions, and activation will lead to enhanced expression of the encoded proteins [8, 9]. Clinical studies with the antibiotic rifampin, like SJW a potent inducer of CYP3a and P-glycoprotein,

have demonstrated a significant decrease of the mean AUC of ethinyl estradiol and norethindrone in healthy women [9, 10]. As the steroid hormone estradiol is subject to P-glycoprotein- efflux and CYP3a metabolism, induction can lead to enhanced elimination of the hormone that would lead to ineffective contraception [11, 12].

Four other cases of ineffective contraception coincident with SJW consumption have been reported to the German authorities (German Federal Institute for Drugs and Medical Devices, Drug Commission of the German Medical Profession). Because of this pharmacokinetic interaction, alternative methods of contraception are strongly recommended when SJW is used. Accurate information regarding drug interactions and the potential failure of oral contraceptives should be provided to consumers of SJW. Thus far, product information accompanying *Hypericum* extracts does not adequately describe the potential risk for herb–drug interactions.

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