In September 1999, a 38-year-old female patient, who was seen regularly at 3-month intervals in the renal transplant clinic, presented earlier than usual because of an unexplained decrease in her cyclosporin A (CyA) trough levels detected during routine check-ups by her outpatient nephrologist. A week prior to her current visit, her CyA trough level had been found to be 20 ng/ml, and this was confirmed once with a 4-day interval between measurements. Sixteen years previously, she had received a kidney graft from her mother, and the postoperative course in the following years had been unremarkable, with stable and near normal kidney function (serum creatinine around 1.5 mg/dl). Her immunosuppressive regimen consisted of CyA (Sandimmune Optoral®) 80 mg b.i.d. and methylprednisolone (Urbason®) 4 mg on alternate days and had not been changed during the past several years. Her CyA trough levels had been very stable around 100 ng/ml throughout the preceding 2 years. The only concurrent medication was propranolol (Dociton®) 20 mg q.d. for hypertension. The patient’s only complaint were recurrent migraine attacks, and previous attempts of medical treatment with paracetamol and aspirin had been rather unsuccessful. She declined any changes of her dietary habits or of her medication. The CyA trough level determined in our laboratory (EMIT assay, Abbott) was 5.9 ng/ml and thus confirmed previous measurements. The serum creatinine was unchanged, and other routine laboratory tests were unremarkable.

**Question**

What should we have asked for in this patient in order to detect the reason for this unexplained decrease of the CyA trough level? (Answer on the next page)
Answer to quiz on the preceeding page

After having confirmed the low CyA trough levels, we again interviewed the patient, who was known to us as a very compliant and reliable person, and once again asked for any other medication that she might have been taking. It turned out that 3 days prior to the unexplained decrease of the CyA trough levels, she had started St John’s Wort extract as a prophylactic treatment for her recurrent migraine attacks. Neither she nor her nephrologist had considered the possibility that such a ‘natural herbal remedy’ might be of any harm with respect to a possible interaction. We then stopped the St John’s Wort without any change of the CyA dose, and the trough level subsequently returned to the therapeutically relevant previous level within 7 days. The patient then agreed to a re-exposure trial with St John’s Wort. Starting from 147 ng/ml, the trough levels immediately decreased to 39.7 ng/ml and returned to previous values after cessation of the drug with no change in the CyA dose. Renal function remained stable throughout this period, with a serum creatinine of 1.5 mg/dl.

In the following 3 months, after having been alerted by this episode, we detected three more patients who, upon specific questioning, admitted that they had been taking St John’s Wort for extended time periods. In all three cases, the CyA doses necessary to achieve therapeutic trough levels had always been unusually high, with a mean of 375 mg/day.

St John’s Wort, with hypericin and pseudohypericin thought to be the main effective substances, is widely and increasingly used for the treatment of mild-to-moderate depression, nervousness, and sleeplessness, and is part of many combination therapies for chronic pain. Its effects appear to be mediated by the inhibition of synaptic re-uptake of serotonin, noradrenaline and dopamine [1]. Several interactions with allopathic drugs have already been described. Several recent reports point to an induction of the cytochrome P450 enzyme. Bon et al. [2] reported eight patients who received St John’s Wort simultaneously with drugs that are metabolized through the CYP3A isoenzyme of the cytochrome P450 complex. In three female patients who were on oestrogens vaginal bleedings occurred, suggesting increased metabolism of these drugs; in one patient on oral anticoagulation with phenprocoumon the prothrombin time increased, suggesting increased metabolism of phenprocoumon; and in two patients on CyA, the trough levels decreased. Further interactions have been reported between St John’s Wort and two other substrates of the cytochrome P450 system, theophylline [3] and digoxin [4], whose levels decreased after of co-administration with St John’s Wort. Both hypericin and pseudohypericin belong to the family of naphtodianthrones, aromatic hydrocarbons for whom an induction of cytochrome P450 enzymes has been demonstrated [5].

The impact of over-the-counter drugs in general and of St John’s Wort in particular deserves attention by physicians who care for transplant patients who frequently are on either CyA or tacrolimus, both of which require therapeutic drug monitoring. Pharmacokinetic data on these prescription-free drugs are scarce or non-existent, and both physicians and patients tend to ignore the possibility of unwarranted effects and drug interactions of these substances. The magnitude of the problem is illustrated by the fact that St John’s Wort preparations already are second only to Gingko extracts in terms of market shares among herbal remedies, at least in Germany [6].

Patients on CyA and possibly also tacrolimus must be asked for ingestion of St John’s Wort, especially when there is an unexplained decrease of their CyA trough levels. A thorough medication history should always include the question for prescription-free drugs, on which reliable pharmacokinetic data usually are lacking.

References


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