Sclerosing lymphangitis of the penis after coadministration of tadalafil and fluconazole

do: 10.1111/j.1365-2230.2008.03068.x

Multi-drug treatment is a common practice in patients with multiple disorders. Up to 2.8% of hospital admissions are due to drug–drug interactions resulting in adverse drug reactions via metabolic inhibition.1

A 50-year-old man presented with a 3-week history of discomfort in the genital area and a lesion that had also appeared on his penis after sexual intercourse.

On physical examination, a painless, tender, flesh-coloured, subcutaneous cord-like structure was found in the coronal sulcus. There were no genitourinary symptoms or regional lymphadenopathy. Laboratory investigations, including complete blood count, urinalysis, and serological testing for syphilis and human immunodeficiency virus, showed no abnormalities.

The patient’s medical history showed that 2 years previously, he had been prescribed sildenafil citrate (100 mg to be taken 2 hours before intercourse; Viagra®; Pfizer Inc., New York, NY, USA) then switched to tadalafil 20 mg (Cialis®; Eli Lilly & Co., Indiana, IN, USA) a year later, without experiencing adverse effects. Because of onychomycosis of hands and feet, he was also being treated with fluconazole (Elazor®; Sigma-Tau SpA, Rome, Italy) 300 mg/day once weekly. He had also taken fluconazole years earlier because of tinea corporis, without any adverse events. The penile lesion had appeared approximately 24 h after the third day of fluconazole treatment, when the patient was also taking tadalafil.

A diagnosis of sclerosing lymphangitis of the penis (SLP) was made, and sexual and pharmacological abstinence were recommended. At follow-up 4 weeks later, all symptoms had resolved.

Erectile dysfunction (ED) is a medical condition affecting millions of men worldwide. Tadalafil is a widely prescribed oral agent acting on the corpora cavernosa by inhibiting a specific cyclic-guanidine monophosphate phosphodiesterase (PDE-5), which results in raised cytosolic calcium concentration and smooth-muscle contraction, consequently promoting erection. Tadalafil is metabolized predominantly by the hepatic cytochrome P450 3A4 (CYP3A4) isoenzyme.2

Fluconazole is used to treat a variety of fungal infections and inhibits fungal cytochrome P450, responsible for the conversion of lanosterol to 14α-demethyllanosterol in the ergosterol biosynthetic pathway. Azoles may inhibit CYP-mediated metabolism and may be responsible for inducing toxicity of other co-administered drugs by decreasing their clearance. In particular, fluconazole has been shown to markedly increase plasma concentrations of many CYP3A4 substrates.3

SLP is a benign pathology of the superficial dorsal penile vein, characterized by development within 24–48 h of a firm cord-like swelling of the coronal sulcus. There may be mild to moderate pain, tenderness and discomfort on erection, or there may be no symptoms. Although many causes have been proposed, the pathogenesis of penile SLP is unclear.

We recently described a case of SLP after tadalafil use, and suggested, as a possible explanation, an existing anatomical variation of the venous arcade in addition to mechanical compression by the corpora cavernosa produced by tadalafil-induced prolonged overexpansion.4 We therefore believe that pharmacokinetic interaction tadalafil-fluconazole could have produced SLP by increasing the plasma concentration of tadalafil and intensifying its pharmacological response.

Although both tadalafil and sildenafil undergo significant intestinal and hepatic CYP3A4-mediated first-pass metabolism, the major metabolite of tadalafil (methylcatechol glucuronide) is 13 000 times less potent than tadalafil itself against PDE-5.5 In contrast, sildenafil is a substrate not only of CYP3A4 but also of CYP2C9. Furthermore, one circulating metabolite of sildenafil may contribute to approximately 20% of the net pharmacological effect of the drug.6 This may explain why our patient never experienced such reactions while taking both fluconazole and sildenafil simultaneously.

Although a causal connection with SLP can only be presumed, this case underlines the importance of care in prescribing azoles with other CYP-inhibitors or substrates, and taking into consideration drug–drug interactions, especially with drugs that are not often declared by patients.

C. Guarneri and G. Polimeni*
Institute of Dermatology, Azienda OSPedaliera Universitaria G. Martino, Via Consolare Valeria, Gazzi 98125, Messina, Italy; and "Department of Clinical Experimental Medicine and Pharmacology, and IRCCS Centro Neurolesi 'Bonino-Pulejo’, University of Messina, Messina, Italy
E-mail: cguarneri@unime.it
Conflict of interest: none declared.
Accepted for publication 19 May 2008
References


2 Kim S, Narayanan S, Song JC. Tadalafil. An oral selective phosphodiesterase 5 inhibitor for treatment of erectile dys-

3 Niwa T, Shiraga T, Takagi A. Effect of antifungal drugs on cytochrome P450 (CYP) 2C9, CYP2C19, and CYP3A4
