Nicorandil: mucocutaneous ulceration (continued)

- A very severe case report.

In 2012, a summary of an exemplary case report of adverse effects attributed to nicorandil was published in the newsletter of the Regional Pharmacovigilance Centre in Angers, France (1). Nicorandil has minor efficacy as a symptomatic treatment for angina pectoris. It is known to cause sometimes severe ulceration of the skin and mucosae (2).

An 87-year-old woman who had been taking nicorandil since 2003 developed severe aphthous stomatitis in mid-2009 (1). Nicorandil was discontinued in July 2009 and the lesions healed within a month. In August, nicorandil was reintroduced.

In December 2009, a sigmoidouterine fistula was diagnosed. In March 2011, a colostomy was performed. Then, a vesicovaginal fistula was diagnosed. The stoma area became ulcerated in August 2011. Nicorandil was withdrawn in August 2011. By late September 2011, the ulceration around the stoma had improved and the pain had stopped. By November 2011, it has almost completely healed.

In view of nicorandil’s minor efficacy in angina, these adverse effects are unacceptable: patients would be better served if nicorandil were neither prescribed, used nor licensed.

Benfluorex: lesions on a bioprosthetic heart valve too

- A troubling case.

In early 2012, a French team published a troubling case report involving a 40-year-old woman who underwent heart valve replacement surgery twice while taking benfluorex (formerly marketed under the brand name Mediator® among other names) (1,2). After 15 months of benfluorex therapy, the patient was diagnosed with mitral valve regurgitation, and a bioprosthetic valve was implanted.

Benfluorex was reintroduced, and the patient continued treatment for 33 months. Cardiovascular problems developed a second time. She was diagnosed with mitral and aortic regurgitation, and both valves were replaced with mechanical valves. The lesions on the bioprosthetic mitral valve resembled those on the native aortic valve, including thickening similar to lesions attributed to benfluorex or observed in patients with carcinoid tumours. No other possible causes of valvular heart disease were identified, such as the use of other amphetamine appetite suppressants or ergot derivatives.

Benfluorex therefore also appears to provoke serious valvular injury, even to porcine bioprosthetic valves.

In cases of valvular insufficiency, even those involving a bioprosthetic valve, benfluorex should be systematically suspected as the causative agent, along with other drugs known to damage heart valves.
SSRI antidepressants: persistent pulmonary hypertension in newborns (continued)

- Consistent data.

In January 2012, the results of a European cohort study including 1.6 million neonates born after 33 weeks of gestation were published (1). About 11,000 women had used a selective serotonin reuptake inhibitor (SSRI) antidepressant after week 20 of pregnancy. Three per 1000 exposed newborns had persistent pulmonary hypertension, versus 1.2 per 1000 unexposed newborns (statistically significant difference). Two studies conducted since 1996 had already demonstrated this increased risk (2). All of the SSRIs used carried a similar risk (1).

In 2010, the European Medicines Agency (EMA) reported that the incidence of persistent pulmonary hypertension after in utero exposure to an SSRI antidepressant was 5 cases per 1000 births (3). The incidence in the general population is 1 to 2 per 1000 births. According to the EMA, the same precautions should be taken during pregnancy with other serotoninergic antidepressants: duloxetine, mirtazapine and venlafaxine.

This is yet another reason to frequently weigh the benefits against the potential harms of antidepressant therapy throughout pregnancy.

Methylphenidate: abuse and addiction

Methylphenidate is an amphetamine marketed for the treatment of some forms of attention deficit-hyperactivity disorder and narcolepsy (1,2). Its use is only justified in rare, severe cases.

In February 2012 the French Health Products Agency released a report on the 16 June 2011 meeting of the National committee on narcotics and psychotropics concerning methylphenidate (2).

Between 2006 and 2011, 83 cases of abuse, addiction or off-label use were reported to the network of French Centres for Evaluation and Information on Pharmacodependence or to the companies. Only 21 such reports were received between 2000 and 2006.

This misuse involved the immediate- and sustained-release formulations. Most of the individuals concerned were young adults (19 to 29 years, 28%) or adolescents (20%).

The reported reasons for methylphenidate consumption included attention deficit disorder, sleep disorders, anxiety and depression, agitation, improved mental performance, cocaine replacement, stimulant effects, weight loss, and doping.

The doses ranged from 10 mg to 2520 mg per day. Methylphenidate was taken for various periods (up to 20 years in one case). The route of administration was intravenous in 10 cases, subcutaneous in 1 case, and intranasal in 6 cases.

Systemic adverse effects included neuropsychological and cardiac disorders. Withdrawal symptoms were also reported, along with local adverse effects at the site of administration.

The French committee on narcotics and psychotropics concluded that methylphenidate “is trivialised, both by prescribers and by students in schools, where the product is already circulating.”

What measures are being taken to warn them of the dangers?

Pelargonium: severe liver damage

- Harmful plants.

Root extracts of Pelargonium sidoides and *P. reniforme* are sometimes used to treat certain respiratory or ENT disorders, despite the lack of proven efficacy. In France, these products are marketed as dietary supplements (1,2).

In late 2011, the independent German pharmacovigilance centre Arznei-Telegramm reported a case of liver damage attributed to a plant belonging to the genus *Pelargonium* (3).

A 30-year-old woman took *Pelargonium* root extracts (unknown species) for 4 days. One day after the end of treatment, she developed liver damage with jaundice, dark urine, hyperbilirubinaemia and transaminase levels more than 35 times the upper limit of normal. No other potential causes of hepatitis were found.

In March 2012, the German drug regulatory agency published a review including approximately 30 reports of liver damage that were attributed to *Pelargonium* and registered in the German national database up to January 2012 (4). There were 11 cases of hepatitis and 8 cases of jaundice. One patient received a liver transplant. Some of the patients were also taking known hepatotoxic drugs (paracetamol, ibuprofen, aspirin).

In practice, “natural” is not synonymous with safe, even when it comes to plants. Patients with unexplained symptoms should also be asked whether they use herbal preparations (5).