Health Canada **Santé Canada**

Canadian Adverse Drug Reaction Newsletter

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Drugs Programme

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Thank You!

We would like to thank everyone who returned a completed questionnaire to the Adverse Drug Reaction Reporting Unit. The results of the survey will be published in a future issue of the newsletter. For those of you who have not yet completed the questionnaire, you still have time to do so. Your comments will help us publish a better newsletter.

Primary pulmonary hypertension and long-term use of appetite suppressants

Primary pulmonary hypertension (PPH) is a life-threatening condition with an estimated 4-year survival rate of 55%. About 1 to 2 cases per million adults occur in the general population each year. Recent data indicate a 23-fold increase in the risk of PPH associated with the use of appetite-suppressant drugs (mainly dexfenfluramine[1] and fenfluramine) when used for more than 3 months.<1> Thus, the estimated risk among patients taking appetite-suppressant drugs for more than 3 months is 23 to 46 cases per million patients each year. The data further suggest that the risk of PPH rises with increasing duration of treatment. However, use for less than 3 months is not associated with a significant increase in the risk of PPH.

Fenfluramine hydrochloride (Ponderal® and Pondimin®) has been available in Canada since 1972 for use as a short-term adjunct in the medical management of exogenous obesity. To date, the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) has received 4 reports of pulmonary hypertension (PH) associated with the use of fenfluramine.

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[1] Dexfenfluramine (Redux™) was granted a Notice of Compliance on July 9, 1996, but at the time of writing was not yet available from the manufacturer. Conditions of use and information regarding the risk/benefit assessment of this drug will be presented in the product monograph.

Case 1: A 49-year-old woman with a body mass index (BMI) of 45 kg/m^2 was taking fenfluramine (60 mg/d); concomitant drugs were insulin, Glucophage® and lithium. After 7 months of fenfluramine use she developed increased effort dyspnea. PH was diagnosed at 12 months (tricuspid regurgitation and mean pulmonary artery pressure of 66 mm Hg). However, the investigation is incomplete because secondary pulmonary hypertension due to sleep-related breathing disorders, thromboembolic disease or left heart failure has not been ruled out. The patient had not recovered at the time of reporting.

Case 2: A 45-year-old woman with a BMI of 23 kg/m^2 developed dyspnea on exertion about 7 months after she started taking fenfluramine (60 mg/d). PPH was diagnosed at 12 months using echocardiography. The patient had not recovered at the time of reporting.

Case 3: A 50-year-old woman with a BMI of 41 kg/m^2 received a combination of fenfluramine (60 mg/d) and phentermine (15 mg/d) for 4 months. She had no symptoms of dyspnea or exercise intolerance, but a systolic murmur was detected. An echocardiogram revealed PH.

Case 4: A recently reported case involved a 44-year-old woman with a BMI of 36 kg/m^2 who was taking fenfluramine (60 mg/d) for at least 9 months. She experienced severe abrupt onset of chest pain and dyspnea that lasted for several hours; the episodes have been recurring with variable frequency. The patient has a history of hiatus hernia and reflux, hypertension, elevated cholesterol level and pulmonary emboli. Concomitant drugs include acebutolol and, more recently, nitropatch, Aspirin®, Dyazide®, famotidine and monopril. The reporter noted that PH is unlikely but that it cannot be ruled out yet; investigations are ongoing.

The CADRMP has been made aware of 3 additional cases of PH associated with the use of appetite-suppressant drugs. However, the full details have not yet been reported.

As recommended by expert advice from the Drugs Programme, Health Canada warns physicians that:<2>

- Ponderal® and Pondimin® are indicated only for short-term use: now defined as no more than 3 months. The effect of intermittent compared with continuous use of anorexigens on the risk of PPH has not been determined.
- The indication for appetite-suppressant drugs has been further restricted to the medical management of obese patients with an initial BMI of $\geq$ 30 kg/m^2. Such drugs can also be prescribed for patients with a BMI of 27 to 29 kg/m^2 if they have other risk factors (e.g., hypertension, diabetes, hyperlipidemia).

There are significant risks associated with obesity (e.g., hypertension, heart disease, diabetes and hyperlipidemia); thus, physicians should assess the risks and benefits for each patient.<2,3>

Patients should be advised to report immediately any

deterioration in exercise tolerance or other emergent signs and symptoms of PPH. Treatment with appetite-suppressant drugs should be stopped if new, unexplained symptoms of dyspnea, angina pectoris, syncope or lower-extremity edema develop. The cause of these symptoms and the possible presence of PPH should be investigated in these cases.

This article is under the responsibility of: Ann Sztuke-Fournier, BPharm, Bureau of Drug Surveillance

References

1. Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. *N Engl J Med* 1996;335:609-16.
2. *Increased risk of primary pulmonary hypertension with long-term use of appetite-suppressant drugs* [Dear Doctor letter no. 46]. Ottawa: Drugs Programme, Health Protection Branch, Health Canada, 21 Oct 1996.
3. Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, et al. Body weight and mortality among women. *N Engl J Med* 1995;333:677-85.

HIV protease inhibitors and increased bleeding in hemophilia?

Protease inhibitors (PIs), a new class of antiretroviral agents, are currently indicated in combination with other antiretroviral agents for the management of HIV infection. Invirase® (saquinavir), Norvir® (ritonavir) and Crixivan® (indinavir) were first approved in Canada in March, August and September 1996 respectively.

Recently there have been concerns about the occurrence of increased bleeding in hemophiliac patients treated with PIs. In July 1996 the Drugs Programme, Health Protection Branch, was informed of 16 such cases worldwide. One occurred in Canada. Eleven cases involved hematomas, 5 hemarthroses (1 patient also had hematoma), and 1 intracerebral hemorrhage. In spite of the bleeding events, most of the patients were able to continue their therapy with appropriate treatment.

In light of these reports, the Drugs Programme released an information sheet to health care providers treating patients with HIV infection and hemophilia. It was recommended that patients not discontinue their treatment but, rather, consult with their health care provider about any concerns and that these patients be monitored closely.

To date, the total number of incidents of increased bleeding in hemophiliac patients receiving PIs is 55 cases worldwide, 5 of which occurred in Canada. A summary of the Canadian cases follows:

- The average age of patients was 29 years (range 16 to 44 years).
- In 3 cases either indinavir or saquinavir was used. In the remaining 2 cases ritonavir and saquinavir were taken concomitantly. In all 5 cases PI therapy was taken with other

HIV therapies.

- The reported reactions were hemarthroses (3), hematoma (2) and intracerebral hemorrhage (1).
- All patients required an increased use of Factor VIII to control bleeding; however, one patient was unresponsive to daily Factor VIII infusion. The increase in bleeding frequency varied between patients after PI therapy was started: 1 bleed per week as compared with 1 per month before the start of therapy; 8 to 10 per month as compared with 1 per year; every 2 weeks as compared with every 6 months; and in one case bleeding occurred daily.
- Four patients continued PI therapy. The fifth made a satisfactory recovery but PI therapy was stopped.
- In 4 of the cases the reporting physicians felt that the adverse events were probably related to the PI therapy. In the fifth case the intracerebral hemorrhage was reported as being remotely related to the drug.

It is still unknown whether there is a causal relation between the use of PIs and episodes of increased bleeding in patients with hemophilia. However, because clinical experience with PIs is limited, the Drugs Programme believes it is important to investigate and report any safety concerns that arise early in the use of this new class of drugs.

This article is under the responsibility of: Amal Hélal, BSc Phm, Bureau of Drug Surveillance

Erythema multiforme and nifedipine

A recent case published in *The Canadian Journal of Hospital Pharmacy*<1> described a 46-year-old woman in whom erythema multiforme (EM) developed a few weeks after her antihypertensive therapy was changed to nifedipine XL (30 mg/d).

The patient was admitted to hospital with a 3-day history of fever, malaise, headache and a maculopapular rash. The rash progressed to a painful, non-itchy rash that covered 85% of her body, with vesicles on her lower limbs. The results of a punch biopsy led to the diagnosis of EM. Nifedipine was stopped and the patient was treated with acetaminophen, IV hydrocortisone, prednisone, hydroxyzine, IV cloxacillin and mupirocin ointment. Her skin continued to peel, and she was subsequently treated as a burn patient with daily tub baths, bacitracin dressings on the open areas of the rash and clobetasol cream on the nonblistered areas. The rash improved, although her skin continued to peel, and the patient was discharged. Overall, the sloughing of skin was relatively mild, with no major fluid or electrolyte abnormalities.

This case prompted a review of the Canadian Adverse Drug Reaction (ADR) database. Of the 290 cases retrieved of suspected adverse reactions associated with the use of nifedipine from 1982

to 1996, 109 involved skin and appendages disorders, including 2 reports of EM.

The first case of EM retrieved from the database involved another 46-year-old woman taking nifedipine (60 mg/d) for 3 months for severe hypertension. The onset of the reaction consisted of dermatitis with vasculitis, and EM was diagnosed by biopsy. Nifedipine was stopped, and the patient recovered. The second case involved a 42-year-old man with a history of chronic renal failure and alcoholic cardiomyopathy who was taking nifedipine (30 mg/d) for hypertension. When he presented for hemodialysis he had papular, pruritic lesions with excoriation of the lower extremities. Treatment with hydroxyzine and betamethasone was not successful. EM, secondary to furosemide or nifedipine, was diagnosed 1 week later. Treatment with Calamine lotion was started, and furosemide was stopped (nifedipine was continued). The pruritus resolved, and the patient was discharged.

Although the risk of EM with nifedipine appears to be low (from April 1979 to October 1994, 33 cases of EM worldwide were reported to the World Health Organization) the severity of the case reported by Barker and colleagues<1> has prompted the CADRMP to remind health care professionals that EM is a hypersensitivity reaction that can range from being mild (EM minor) to severe, and sometimes fatal (EM major, Stevens–Johnson syndrome).<2> One of the most common causes of EM is drug therapy, and almost any drug can be implicated,<2> including nifedipine.<1>

This article is under the responsibility of: Pascale Springuel, BPharm, Bureau of Drug Surveillance

References

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2. Frieden IJ. Hypersensitivity reactions. Rudolph AM, Hoffman JIE, Rudolph CD, editors. *Rudolph's pediatrics*. 20th ed. Stamford (CT): Appleton & Lange, 1996:906-8.

Congenital anomalies and fluconazole

Fluconazole (Diflucan™) has been available in Canada since 1990 as a systemic antifungal agent for the treatment of oropharyngeal and esophageal candidiasis, other serious candidal infections and cryptococcal meningitis. In 1995 Diflucan™ 150 became available as a single-dose treatment for vaginal candidiasis.

The manufacturer has recently updated the product monograph for Diflucan™ and Diflucan™ 150 to reflect new information concerning the occurrence of multiple congenital anomalies in infants whose mothers were treated with high-dose fluconazole therapy during pregnancy.

In 1992, Lee and colleagues<1> described an infant with

multiple congenital anomalies whose mother used fluconazole during pregnancy. The anomalies were felt to be consistent with a genetic disorder known as Antley–Bixler syndrome but were also noted to be similar to abnormalities observed in animal studies with fluconazole.

In 1996, Pursley and colleagues<2> described two infants with multiple congenital anomalies whose mothers took fluconazole during pregnancy. One was a sibling of the infant described by Lee and colleagues.<1>

In all three cases the women were receiving high doses of fluconazole (400 to 800 mg/d) for the treatment of coccidioidal meningitis (an unapproved indication in Canada) for at least the first 4 months of their pregnancies. The similarities of the anomalies in all three cases to those observed in mouse and rat embryos exposed to fluconazole suggest that the drug may cause teratogenic effects in humans, including craniofacial, skeletal and cardiac anomalies.<2>

There is some evidence to indicate that the teratogenic effects may be dose dependent. This evidence includes the dose dependence observed in animal studies described in the product monograph and the report by Tiboni<3> and the observation that the mother who had two infants with multiple congenital anomalies after exposure to high-dose fluconazole therapy during pregnancy had a normal child during a period when she was noncompliant with her fluconazole therapy (as indicated by subtherapeutic levels of the drug in her serum).<2> In addition, a retrospective review of adverse events following the introduction of fluconazole for vaginal candidiasis in the United Kingdom did not reveal any unusual pattern of fetal abnormalities among the women who received a single dose of 150 mg during pregnancy.<4> However, this observation was based on a relatively small number of patients exposed to fluconazole during pregnancy. Thus, even the use of low-dose fluconazole therapy during pregnancy is not recommended unless the benefits outweigh the risk to the fetus.

To date, the CADRMP has not received any reports of suspected congenital anomalies associated with the use of fluconazole.

In summary, fluconazole is not recommended in pregnant women unless the potential benefit outweighs the risk to the mother and fetus. In addition, women of child-bearing age who are taking fluconazole should be counselled regarding the use of adequate contraception because of the potential for birth defects.

This article is under the responsibility of: Claire-Marie Wray, PhD, Bureau of Drug Surveillance

References

1. Lee BE, Feinberg M, Abraham JJ, Murthy ARK. Congenital malformations in an infant born to a woman treated with fluconazole. *Pediatr Infect Dis J* 1992;11:1062-4.

2. Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis* 1996;22:336-40.
3. Tiboni GM. Second branchial arch anomalies induced by fluconazole, a bis-triazole antifungal agent, in cultured mouse embryos. *Res Commun Chem Pathol Pharmacol* 1993;79:381-4.
4. Inman W, Pearce G, Wilton L. Safety of fluconazole in the treatment of vaginal candidiasis. A prescription-event monitoring study, with special reference to the outcome of pregnancy. *Eur J Clin Pharmacol* 1994;46:115-8.

Spontaneous reporting of suspected adverse drug reactions (ADRs) is a critical ongoing source of drug-safety information. Thus, we encourage health professionals to report any suspected ADRs to one of the following addresses:

British Columbia
BC Regional ADR Centre
c/o BC Drug and Poison Information Centre
1081 Burrard St.
Vancouver BC V6Z 1Y6
fax: 604 631-5262; tel: 604 631-5625

Saskatchewan
Sask ADR Regional Centre
Dial Access Drug Information Service
College of Pharmacy and Nutrition
University of Saskatchewan
Saskatoon SK S7N 5C9
fax: 306 966-6377; tel: 306 966-6340 or 800 667-3425

Quebec
Quebec Regional ADR Centre
Centre d'information pharmaceutique
Hôpital du Sacré Coeur de Montréal
5400, boul. Gouin ouest
Montréal QC H4J 1C5
fax: 514 338-3670; tel: 514 338-2961 or 338-2161 (collect calls accepted)

Nova Scotia, New Brunswick, Newfoundland and Prince Edward Island
Atlantic Regional ADR Centre
Queen Elizabeth II Health Sciences Centre
New Halifax Infirmary Building
Level 200, Drug Information Centre
1796 Summer St.
Halifax NS B3H 3A7
fax: 902 496-8612; tel: 902 496-7171

Other provinces and the territories
Adverse Drug Reaction Reporting Unit
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Please Note: A voluntary reporting system thrives on intuition, lateral thinking and openmindedness. For these reasons, most adverse drug reactions (ADRs) can be considered only to be *suspicions*, for which a proven causal association has not been established. Because there is gross underreporting of ADRs and because a definite causal association cannot be determined, this information cannot be used to estimate the incidence of adverse reactions.

ADRs are nevertheless invaluable as a source of potential new and undocumented *signals*.