Health Canada Santé Canada

Volume 8, Number 4
October 1998

Canadian Adverse Drug Reaction Newsletter

Therapeutic Products Programme

IN THIS ISSUE

Recent news about drug risks: application to Canadians

A recent meta-analysis by Canadian investigators Lazarou and associates<1> on the incidence of serious and fatal adverse drug reactions (ADRs) among hospital patients in the US has raised public concern regarding the number of serious ADRs that occur, particularly those resulting in death. This study has generated media attention in close to 300 newspapers across North America as well as television and radio coverage.<2> Since 1965 Health Canada has had an ADR monitoring program that continually monitors the adverse effects of drugs available in Canada in order to protect the health and safety of Canadians. Unfortunately statistics of the type summarized in the meta-analysis are not collected by Health Canada and are therefore not available for direct comparison.

When a new drug reaches the market Canadians expect it to be both safe and effective. Health Canada's Therapeutic Products Programme (TPP) approves drugs for sale in Canada only after

manufacturers have submitted evidence that their products are safe, effective and of high quality. However, all drugs have associated risks that may or may not result in adverse effects. In the drug review process, reviewers must evaluate the drug's documented risks as well as its claimed therapeutic benefits to ensure that, in addition to being an effective therapeutic product, the benefits outweigh the risks. Although the review process is comprehensive, it is estimated that over 51% of approved drugs have serious side effects not detected before marketing approval.<3> This may be because the studies conducted did not last long enough for the effects to become manifest or because patients likely to experience problems are not always enrolled in the trials. In addition, in clinical trials often fewer than 3000 patients are given a new drug, making it likely that an ADR with an incidence of 1 in 10 000 will remain undetected.<4> Because of these inherent limitations of any premarketing review, the Canadian Adverse Drug Reaction Monitoring Programme (CADRMP), within the TPP's Bureau of Drug Surveillance, monitors the adverse effects of drugs distributed in Canada to ensure that they remain safe, effective and of high quality.

The CADRMP works in partnership with industry, medical and pharmaceutical associations and other regulatory agencies to collect and monitor ADR information submitted by health professionals, drug manufacturers and consumers. About 4200 spontaneous ADR reports from Canadian sources are received annually. The data collected are entered into a database and monitored on a continual basis to ensure that:

- the benefits of drugs distributed in Canada continue to outweigh the risks;
- health professionals and the public are kept informed about significant adverse effects of drugs marketed in Canada; and
- labelling and drug product information are continually updated.

Scientists and health professionals recognize that, although monitoring programs such as the CADRMP that rely on spontaneous reporting are not guaranteed to detect all new ADRs, they help to protect the public from health risks associated with marketed drugs.<5> The diligence of health professionals, industry and consumers in reporting ADRs and the quality of the information received are the cornerstones of an effective monitoring program. When significant new or unexpected ADRs are detected different actions may be taken to protect Canadians (see "Quality information in spontaneous reports" in the July issue of the newsletter [*CMAJ* 1998;159(1):80]).

The ongoing collection and evaluation of ADRs by the CADRMP is one means of providing health professionals and the Canadian public with timely information to assist them in making informed choices about therapeutic products. Knowledge about the risks associated with drugs and how they are managed in Canada allows us to place information about drug risks in the appropriate context.

Written by: Vicky Hogan, MSc, and Chris Turner, MD, Bureau of Drug Surveillance.

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New Ontario Regional ADR Centre

The CADRMP is pleased to announce the establishment of the Ontario Regional Adverse Drug Reaction (ADR) Centre. As of Sept. 1, 1998, health care professionals who reside in Ontario are encouraged to report ADRs to this new centre. Practitioners may also request information on ADRs and obtain reporting forms directly from the centre.

Ontario Regional ADR Centre
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Discontinuation reactions associated with SSRIs

Withdrawal reactions following the discontinuation of tricyclic antidepressants are well known, and general guidelines recommend reducing the dose gradually.<1> However, adverse reactions have also been identified with the discontinuation of selective serotonin reuptake inhibitors (SSRIs). The risk of SSRI discontinuation syndrome appears to be higher with SSRIs that have short half-lives (e.g., paroxetine, fluvoxamine and sertraline) and when treatment lasts 2 months or more.<2> A recent published review of articles up to October 1996 identified 47 case reports of SSRI discontinuation reactions, 30 involving paroxetine.<3> In addition, a review of the World Health Organization database of "discontinuation-related" case reports ("withdrawal syndrome," "withdrawal headache" and "withdrawal convulsions") associated with fluoxetine, sertraline and paroxetine from the US, the United Kingdom and Australia found that the reporting rate (number of reports per million defined daily doses sold per year) was highest for paroxetine.<4>

Hallmark features of discontinuation syndrome associated with

SSRIs have been described as follows:<2>

- Discontinuation symptoms are not attributable to other causes. For example, they usually begin 1 to 3 days after cessation of SSRI therapy, whereas signs of depression relapse do not appear for 2 or 3 weeks.
- They emerge after abrupt discontinuation, frequent noncompliance (forgotten doses, planned "drug holidays") and, less often, dose reduction.
- In most cases symptoms are mild and self-limited (lasting on average 7 to 14 days), but they can be distressing.
- They resolve when the original drug is restarted or another drug is given that is pharmacologically similar.
- They are minimized by gradually tapering the dose or by switching to a drug with an extended half-life (e.g., fluoxetine).

A variety of symptoms have been associated with SSRI discontinuation. Most symptoms reported in the literature have been *somatic* or physical in nature and may be classified into 5 groups: *disequilibrium* (e.g., dizziness, vertigo, ataxia); *gastrointestinal symptoms* (e.g., nausea, vomiting); *influenza-like symptoms* (e.g., fatigue, lethargy, myalgia); *sensory disturbance* (e.g., paresthesia, sensations of electric shock); and *sleep disturbance* (e.g., insomnia, vivid dreams).<2> Psychological symptoms may also occur, the most commonly reported being anxiety, agitation, crying spells and irritability. Symptoms are usually not medically dangerous but may be very distressing and have a significant impact on quality of life and productivity.<5> Symptoms that appear to be unique to SSRI discontinuation are disequilibrium, sensory disturbances (notably electric-shock sensation) and possibly aggressive and impulsive behaviour.<2>

The CADRMP has received 26 reports of discontinuation symptoms for the 4 SSRIs marketed in Canada. Patient characteristics and features of the reactions are summarized in Table 1. In 1 report symptoms appeared during a dose reduction (from 20 mg daily of paroxetine to 20 mg alternating with 10 mg daily), and in 3 reports (paroxetine 2, fluoxetine 1) symptoms appeared while the dose was being tapered. Three of the 26 cases resulted in hospitalization or prolonged hospitalization.

A variety of discontinuation symptoms were reported (Table 2). Of the 85 reactions, the most common were dizziness (12), nausea (7), paresthesia (5) and headache (4).

In 3 of the 5 reports of paresthesia, the reaction was described as an electric-shock sensation. These 3 reports involved 2 men (ages 37 and 42) and 1 woman (age 33) who had been taking paroxetine for at least 3 months for depression. The daily dose ranged from 20 to 40 mg. The woman had been taking paroxetine 20 mg/d for about 2 years when she began to experience the electric-shock sensation. The dose was increased to 40 mg/d, with alleviation of symptoms. Six months later, the paroxetine was stopped. The following day she noted an electric-shock sensation

again. Treatment with fluoxetine was started the same month and given for 2 months, after which she took St. John's Wort. Symptoms improved with the initiation of fluoxetine but persisted for about 5 months. In the other 2 cases “electric-shock” symptoms began about 3 days after stopping the paroxetine; symptoms abated in both patients when the paroxetine was restarted. The 42-year-old man discontinued the paroxetine abruptly several more times, with a return of symptoms, and eventually decided to take no medication. His symptoms have persisted on no medication 4 years after the initial event.

Frost and Lal<6> reported 3 cases of electric-shock sensation following discontinuation of paroxetine (2 cases) and sertraline (1 case); the sensation persisted for 3 weeks in 1 case (paroxetine) and for 13 weeks in another (sertraline). Symptoms first appeared 1 to 2 days after the last dose, and in 1 of the patients taking paroxetine the symptoms appeared despite gradual tapering of the drug over 3 weeks.

Rosenbaum and Zajecka<5> suggested the following strategies to manage symptoms associated with the discontinuation of SSRIs:

- Reassure the patient that symptoms are usually mild and transient. In most cases they will resolve in 7 to 14 days.
- Gradually taper all SSRIs except fluoxetine. The final tapered dose should be less than the initial minimum therapeutic dose.
- If acute symptoms appear during tapering or persevere despite tapering, restart the original agent and slow the rate of taper.
- If symptoms are severe and the patient is unable to discontinue the SSRI despite tapering, consider switching to fluoxetine (long-acting).

Discontinuation symptoms may appear when SSRI therapy is stopped or the dose is reduced. Patients should be counselled to avoid abrupt discontinuation of SSRI therapy and to avoid taking “drug holidays.” Tapering the dose before discontinuation is recommended, but patients should be advised that symptoms may still appear.

Written by: Lynn Macdonald, BSP, Bureau of Drug Surveillance.

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Table 1: Characteristics of patients and features of reactions to discontinuation of SSRIs reported to the CADRMP as of June 30, 1998

Characteristic	Paroxetine	Sertraline	Fluoxetine	Fluvoxamine
No. of patients*	17	4	3	2
Mean patient age (and range), yr	35 (23–43)	40 (35–49)	36 (36)	30.5 (22–37)
Female:male ratio	15:2	3:0†	3:0	1:1
Duration of SSRI therapy, mo	3 to > 48	2 to 24–36	5 to 12	6 to 13
Mean duration (and range) from discontinuation to onset of symptoms, d	3 (1–14) *n = 14*	4 (1–14) *n = 4*	23 (21–26) *n = 2*	1 *n = 1*
No. of patients in whom drug was restarted / symptoms abated	10/6 (4 unknown)	4/3 (1 partial relief)	0	1/1

Note: SSRI = selective serotonin reuptake inhibitor, CADRMP = Canadian Adverse Drug Reaction Monitoring Programme.
*These data cannot be used to determine the incidence of ADRs because neither the prescribing rates nor the amount of time the drug was on the market have been taken into consideration.
†Sex unknown in 1 case.

Table 2: Symptoms reported with discontinuation of SSRIs

	SSRI; no. (and %) of reactions				
Symptom	Paroxetine	Sertraline	Fluoxetine	Fluvoxamine	Total
Disequilibrium*	14 (29)	2 (11)	2 (22)	–	18 (21)
Gastrointestinal disturbance†	6 (12)	4 (22)	–	2 (22)	12 (14)
Influenza-like symptom‡	2 (4)	2 (11)	1 (11)	2 (22)	7 (8)
Sensory disturbance§	5 (10)	–	–	–	5 (6)
Sleep disorder¶	1 (2)	1 (6)	–	–	2 (2)
Psychiatric disturbance**	10 (20)	7 (39)	2 (22)	2 (22)	21 (25)
Other	11 (23)	2 (11)	4 (45)	3 (33)	20 (24)
Total	49 (100)	18 (100)	9 (100)	9 (100)	85 (100)

*Ataxia, dizziness, abnormal gait, vertigo.
†Abdominal pain, diarrhea, dyspepsia, nausea, vomiting.
‡Asthenia, chills, fatigue, fever, lethargy, myalgia, malaise.
§Paresthesia.
¶Insomnia.
**Aggressive reaction, agitation, anxiety, impaired concentration, confusion, aggravated depression, depersonalization, hallucination, manic reaction, paranoid reaction, somnolence, suicidal tendency.

COMMUNIQUÉ

The purpose of this section is to increase awareness of recently reported ADRs. The following cases have been selected on the basis of their seriousness, or the fact that the reactions do not appear in the product monograph. They are intended to prompt reporting.

Amantadine and warfarin: increased INR

Increased INR (international normalized ratio) values were reported after the start of amantadine therapy in patients receiving warfarin.

Pantoprazole (Pantoloc™): “heart attack”

Episodes of chest pain and “heart attack” were reported during pantoprazole therapy.

If you have observed comparable cases or any other serious events, *please report* them to the Adverse Drug Reaction Reporting Unit, Continuing Assessment Division, Bureau of Drug Surveillance, AL 4103B1, Ottawa ON K1A 1B9, fax 613 957-0335; or to a participating regional centre.

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We thank the Chair of the Expert Advisory Committee on Pharmacovigilance, and the staff of the Adverse Drug Reaction Regional Centres and the Therapeutic Products Programme for their valuable comments.

Canada The Canadian Adverse Drug Reaction Monitoring Newsletter is prepared and funded by the Therapeutic Products Programme, Health Canada and published in the CMAJ regularly. It can be found on line, under Publications, at **www.hc-sc.gc.ca/hpb-dgps/therapeut**

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 undereporting 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.