Health Canada Santé Canada

Volume 9, Number 1
January 1999

Canadian Adverse Drug Reaction Newsletter

Therapeutic Products Programme

IN THIS ISSUE

Isotretinoin: depression

Although birth defects are the most serious adverse effect of isotretinoin (Accutane™), depression has also been reported. Recently, international and domestic reports of depression, psychosis and suicidal ideation have prompted Health Canada to review the adverse reaction information for isotretinoin. Together with the manufacturer, the product monograph has been amended to strengthen warnings about depression and the possibility of suicide.

Isotretinoin was approved for use in Canada in 1983 for the treatment of severe nodular and inflammatory acne, acne conglobata and recalcitrant acne unresponsive to conventional therapies. Since 1983 the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) has received 16 reports (8 since March 1998) describing depression and other reactions of a putative psychiatric nature associated with the use of isotretinoin. In 2 cases, a second drug was also reported as suspect: trimipramine (1) and fluoxetine (1). The reported reactions included depression (5), aggressive reaction (4), emotional lability (4), irritability (3), suicidal

tendency (3), amnesia (2), abnormal thinking (1), aggravated depression (1), manic reaction (1) and suicide attempt (1). The median age of the patients (9 women, 7 men) was 20 (range 15 to 41) years. The time from the start of drug therapy to the onset of the reaction varied from 1 day to 5 months. In the reports that gave dose information, all but 1 of the patients were taking 1 to 2 mg/kg daily (the recommended maximum); the remaining patient received incremental doses up to 3 mg/kg daily. In 5 cases the drug was stopped because of the adverse reaction; however, in several cases the course of therapy was completed. In the reports that indicated an outcome, 7 patients recovered, 3 recovered with residual effects, and 1 had not yet recovered at the time of reporting.

The nature of the relation between isotretinoin and the psychiatric symptoms reported has not been established. In some cases there has been evidence of a causal association (e.g., symptoms worsened with increased dose or the reaction abated when the drug was stopped). Other factors also contributed, such as the age of the patient (those 15 to 24 years old are more prone to experience major depression than the general population<1>). It is also thought that severe acne itself may be a risk factor for depression;<2> at least one study has demonstrated that successful treatment with oral isotretinoin therapy reduced anxiety and depression.<3>

Health care professionals should be attentive to any new relevant signs and symptoms.

Written by: Claire-Marie Wray, PhD, Bureau of Drug Surveillance.

References

1. Blazer DG, Kessler RC, McGonagle KA, Swartz MS. The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. *Am J Psychiatry* 1994;15:979-86.
2. Lamberg L. Acne drug depression warnings highlight need for expert care. *JAMA* 1998;279:1057.
3. Rubinow DR, Peck GL, Squillace KM, Gantt GG. Reduced anxiety and depression in cystic acne patients after successful treatment with oral isotretinoin. *J Am Acad Dermatol* 1987;17:25-32.

Low-dose ASA and serious gastrointestinal bleeding

Experts recommend low-dose ASA (75–325 mg/d) as long-term therapy in high-risk patients for the secondary prevention of cardiovascular events.<1,2> The degree of risk of serious gastrointestinal (GI) bleeding from low doses of ASA, however, has not been fully characterized.

Since 1993 the CADRMP has received 19 reports of serious GI bleeding associated with ASA doses of 325 mg/d or less. Details of the cases are given in Table 1. GI bleeds were considered serious if they led to hospital admission or to medical treatment of a

patient already in hospital. Reports involving patients who were taking anticoagulants, other NSAIDs or corticosteroids were excluded because it is difficult to assess the contribution of low-dose ASA in such cases.

Concomitant drug therapy was reported in 12 patients, but no obvious trends were seen. Most patients recovered, and no deaths were reported.

Patients with chronic blood loss may present with signs and symptoms of anemia (e.g., weakness, easy fatiguability, pallor, chest pain or dizziness).<3> Eight patients experienced similar symptoms; all had low hemoglobin levels and 7 experienced GI symptoms as well. Patients should be informed that the symptoms of GI bleeding can include dizziness, weakness and fainting spells as well as gastric symptoms such as melena and hematemesis. The product monograph indicates that patients on long-term ASA therapy should have their hemoglobin level measured periodically in conjunction with vigilant follow-up.

Serious GI bleeding was also reported in patients using enteric-coated ASA. Although there is evidence from endoscopic studies that the risk of GI bleeding can be reduced by the use of enteric-coated ASA<4> other published articles indicate that this assumption may be mistaken.<5>

In general, the GI bleeding from ASA is dose-related, and published evidence suggests that doses of 80 mg/d may be less likely to lead to major GI bleeds than doses of 325 mg/d.<6–8> The cases reported to the CADRMP indicate that serious GI bleeds have occurred with daily doses as low as 80 mg/d. Some of the patients had known risk factors for GI bleeding, which indicates that the *usual precautions apply even to low doses of ASA*.

In summary, patients should take long-term ASA therapy only under physician supervision to ensure that the potential benefits are assessed against individual risk factors for GI bleeding.

Written by: Barbara Cadario, BSc Phm, MSc, BC Regional ADR Centre.

Table 1: Characteristics of 19 patients who experienced serious gastrointestinal (GI) bleeding while taking low-dose ASA therapy

Characteristic	ASA dose		
	80 mg/d *n = 3*	325 mg/d *n = 4*	325 mg/d, enteric-coated *n = 12*
Female:male ratio	2:1	1:3	5:7
Mean age (and range), yr	64 (32–82)	85 (77–95)	79 (67–94)
GI symptoms			
Abdominal pain	–	–	1
Hematemesis	–	3	1
Melena	1	3	6
Nausea	–	–	1
Signs and symptoms possibly due to blood loss			
Asthenia	–	1	1
Dizziness	–	1	1
Fatigue	–	–	1
Loss of consciousness	1	–	–
Low hemoglobin level (and range, g/L*)	3 (64–105)	3 (58–89)	7 (53–106)
Pallor	–	1	1
Syncope	1	1	1
Risk factors and relevant medical history			
Age > 65 yr	2	3†	11†
Diverticulitis	–	–	1
History of peptic ulcer disease	–	–	1
Previous gastric lymphoma	–	–	1
Previous GI bleed secondary to NSAID	1	–	1

*Normal hemoglobin level 115–180 g/L.
†Age was unknown in 1 case.

References

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy: I. Prevention of death, myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81-106.
2. Hennekins CH, Dyken ML, Fuster V. Aspirin as a therapeutic agent in cardiovascular disease. *Circulation* 1997;96:2751-3.
3. *Merck manual*. 16th ed. Rahway (NJ): Merck Sharp & Dohme Research Laboratories; 1992.
4. James ED, Hirsch J. Fourth ACCP Consensus Conference on Antithrombotic Therapy. *Chest* 1995;108(4 Suppl):255S.
5. Kelly JP, Kaufman DW, Jurgelon JM, Sheehan J, Koff RS, Shapiro S. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet* 1996;348:1413-6.
6. Roderick PJ, Wilkes HC, Meade TW. The gastrointestinal toxicity of aspirin:

an overview of randomised trials. *Br J Clin Pharmacol* 1993;35:219-26.
7. Slattery J, Warlow CP, Shorrock CJ, Langman MJS. Risks of gastrointestinal bleeding during secondary prevention of vascular events with aspirin – analysis of gastrointestinal bleeding during the UK-TIA trial. *Gut* 1995;37:509-11.
8. Weil J, Colin-Jones D, Langman M, Lawson D, Logan R, Murphy M, et al. Prophylactic aspirin and risk of peptic ulcer bleeding. *BMJ* 1995;310:827-30.

Guidelines for the voluntary reporting of adverse drug reactions by health care professionals

What to report

An adverse drug reaction (ADR) is a noxious and unintended response to a drug that occurs with the use or testing of the drug for the diagnosis, treatment or prevention of a disease or the modification of an organic function. This includes *any* undesirable effect suspected to be associated with drug use. ADRs that result from the use of prescription, non-prescription, biological (including blood products), complementary medicines (including herbals) and radiopharmaceutical drug products are monitored. Drug abuse, overdoses, drug interactions and unusual lack of therapeutic efficacy are also considered to be reportable as ADRs.

ADR reports represent, for the most part, only *suspected* associations. A temporal or possible association is sufficient for a report to be made. Reporting an ADR does not imply a causal link.

Reports should be made of all suspected ADRs that are:

- unexpected, regardless of their severity (i.e., not consistent with product information or labelling); or
- serious, whether expected or not (occurs at any dose and requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death); or
- reactions to recently marketed drugs (on the market for less than 5 years) regardless of their nature or severity.

How to report

To report a suspected adverse reaction to drug products marketed in Canada, excluding vaccines, health care professionals should complete ADR Reporting Form no. HC 4016 (Report of suspected adverse reaction due to drug products marketed in Canada [vaccines excluded]). This form may be obtained from your regional ADR centre or from the national ADR unit and is included in the *Compendium of Pharmaceuticals and Specialties* (*CPS*).

To report an adverse reaction to a vaccine, health care professionals should complete the Vaccine-Associated Adverse Event Form, also included in the *CPS*.

Fill in the applicable sections of the report as completely as possible, using a separate form for each patient. Additional pages may be attached if additional space is required.

Any follow-up information for an ADR that has already been reported can be sent on another ADR form, or it can be communicated by telephone, fax or email if convenient to the appropriate address for your region (see list on following page). This information needs to be linked to the original report;

therefore, indicate that it is follow-up information, the date of the original report and the report case number if known.

Is ADR information considered confidential?

Any information related to the reporter and the patient is kept confidential.

Where to send the report

Adverse reactions to drug products marketed in Canada are monitored by the CADRMP. Send reports of these reactions to your regional ADR centre (see list on following page).

Adverse reactions to vaccines are monitored by the Laboratory Centre for Disease Control. Send reports of these reactions to the address listed on the Vaccine-Associated Adverse Event Form.

Written by: Heather Sutcliffe, BScPharm, Bureau of Drug Surveillance

COMMUNIQUÉ

The purpose of this section is to increase awareness of ADRs recently reported to the CADRMP. 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.

Sertraline and carbamazepine: interaction
Increased carbamazepine blood levels were reported after an increase in dose of sertraline therapy. This was associated with vertigo, ataxia, vomiting and anorexia.

Azithromycin (Zithromax™): convulsions
Convulsions were reported during azithromycin therapy for acute otitis media.

Pentoxifylline (Trental®): priapism
Priapism necessitating admission to hospital was reported during pentoxifylline therapy.

If you have observed comparable cases or any other serious events, please report them to the appropriate address listed below.

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

Saskatchewan
Sask ADR Regional Centre
Dial Access Drug Information Service
College of Pharmacy and Nutrition
University of Saskatchewan
110 Science Place
Saskatoon SK S7N 5C9
tel 306 966-6340 or 800 667-3425
fax 306 966-6377
vogt@duke.usask.ca

Ontario
Ontario Regional ADR Centre
LonDIS Drug Information Centre
London Health Sciences Centre
339 Windermere Rd.
London ON N6A 5A5
tel 519 663-8801
fax 519 663-2968
adr@lhsc.on.ca

Québec
Québec Regional ADR Centre
Drug Information Centre
Hôpital du Sacré-Coeur de Montréal
5400, boul. Gouin ouest
Montréal QC H4J 1C5
tel 514 338-2961 or 888 265-7692
fax 514 338-3670
cip.hscm@sympatico.ca

New Brunswick, Nova Scotia, Prince Edward Island and Newfoundland
Atlantic Regional ADR Centre
Queen Elizabeth II Health Sciences Centre
Drug Information Centre
Rm. 2421, 1796 Summer St.
Halifax NS B3H 3A7
tel 902 473-7171
fax 902 473-8612
rxkls1@qe2-hsc.ns.ca

Other provinces and territories
National ADR Unit
Continuing Assessment Division
Bureau of Drug Surveillance
Finance Building
Tunney's Pasture
AL 0201C2
Ottawa ON K1A 1B9
tel 613 957-0337
fax 613 957-0335

Newsletter Editors: Ann Sztuke-Fournier, BPharm, and Claire-Marie Wray, PhD, Bureau of Drug Surveillance.

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 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 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.