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Canadian Adverse Drug Reaction Newsletter

Therapeutic Products Programme

In this issue:

Cisapride (Prepulsid®): interactions with grapefruit and drugs

Cisapride monohydrate (Prepulsid®) is an oral gastrointestinal prokinetic agent indicated in the symptomatic management of motility disorders. It was first marketed in Canada in 1990. In previous issues of the newsletter [1,2] health professionals were alerted to interactions between cisapride and other drugs metabolized by cytochrome P_{450} 3A4 (CYP3A4) enzymes as well as drugs causing prolongation of the QT interval and torsade de pointes. Inhibition of cisapride metabolism by such drug interactions leads to raised cisapride blood levels, which may cause prolongation of the QT interval and ventricular arrhythmias.[3]

As of Sept. 16, 1999, the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) received 127 reports of suspected adverse drug reactions (ADRs) associated with the use of cisapride; 70 reports were of a serious nature. Of concern were 35 reports involving heart rate and rhythm disorders, which revealed 61 suspected ADRs (several reaction terms may be listed for one ADR report): prolongation of the QT interval (16), torsades de pointes (9), cardiac arrest (6), arrhythmia (5), tachycardia (5), ventricular tachycardia (5), ventricular fibrillation (4), bradycardia (3), bundle branch block (2), supraventricular tachycardia (2) and other (4). In all, 12 fatal reports were associated with the use of cisapride. Five were related to heart rate and rhythm disorders (2 of these involved drug interactions), and 7 had various contributory factors: confounding medical conditions (3), overdose (1), neonatal death (1),

miscarriage (1) and sudden infant death syndrome (1). Sixteen of the 127 total reports involved interactions between cisapride and other drugs, including carbamazepine, clarithromycin, diltiazem, erythromycin, fluconazole, itraconazole, metronidazole, nefazodone, omeprazole, paroxetine, tacrolimus, warfarin and zafirlukast; 9 of these reports involved heart rate and rhythm disorders.

As a result of postmarketing surveillance, important changes were introduced in September 1999 to the product monograph, prescribing information and other labelling material. A cautionary statement was added advising against concomitant use of grapefruit juice with cisapride, as it increases the bioavailability of cisapride.[4] Grapefruit juice is a CYP3A4 enzyme inhibitor and acts predominantly by impeding presystemic cisapride metabolism, mediated by CYP3A4 enzymes in the small bowel, thus raising plasma concentrations of cisapride.[5] Studies have confirmed that inhibition by grapefruit juice of CYP3A4 enzymes may affect the absorption of cisapride for up to 24 hours; grapefruit juice does not inhibit hepatic drug elimination.[5–7] Moreover, a significant amount of interindividual variation prevails.[6] The CADRMP has not received any reports of interactions between cisapride and grapefruit. This may be due to the fact that drug–food interactions frequently go undetected; therefore, health professionals must be vigilant in recognizing and reporting them.

Other revisions to the product monograph now state that the use of cisapride in patients with known congenital or familial long QT syndrome and clinically significant bradycardia is contraindicated, as is the use of concomitant medications known to prolong the QT interval.[4] These include, but are not limited to, certain anti-arrhythmics (e.g., quinidine, procainamide, disopyramide, amiodarone and sotalol), antidepressants (e.g., amitriptyline, maprotiline), antipsychotics (e.g., certain phenothiazines and pimozide), antihistamines (e.g., astemizole and terfenadine) and halofantrine.[4] Furthermore, as is already indicated in the product monograph, the use of cisapride is contraindicated in patients taking CYP3A4-inhibiting drugs, including macrolide antibiotics (e.g., erythromycin and clarithromycin), antifungals (e.g., fluconazole, itraconazole, ketoconazole), HIV protease inhibitors (e.g., ritonavir, indinavir) and antidepressants (e.g., nefazodone). The above-mentioned drugs and medical conditions are by no means an all-inclusive list affecting QT prolongation or CYP3A4 enzymes.[4]

These revisions to the product monograph further illustrate that knowledge gained through postmarketing surveillance may significantly change the perceived safety profile of a therapeutic product.

Written by: Iza Morawiecka, BSc Phm, Bureau of Drug Surveillance

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Pemoline (Cylert®): market withdrawal

The Therapeutic Products Programme (TPP), Health Canada, recently conducted a benefit–risk assessment of the use of pemoline in the treatment of attention deficit hyperactivity disorder. The assessment concluded that the risk of serious liver complications, including liver failure necessitating transplantation or resulting in death, outweighs the benefits of continued use. As a result the drug was removed from the market on Sept. 30, 1999. This conclusion was based on a number of considerations, the most important of which were: (a) despite explicit warnings in the product monograph and labelling information regarding the risk of severe liver damage, worldwide case reports of liver failure necessitating transplantation or resulting in death continued; (b) there is no evidence that liver damage caused by the drug is predictable or reversible; (c) other, safer treatment alternatives are available; and (d) a satisfactory response to the TPP's request for specific evidence to support the safety of the drug's continued use was not provided by the manufacturer.

In collaboration with Abbott Laboratories, Cylert® continues to be available through Health Canada's Special Access Program (tel 613 941-2108; fax 613 941-3194) in exceptional cases where the physician has evaluated the risks and benefits of various treatment options and does not consider other treatment alternatives to be in the patient's best interest. The Health Canada Advisory on pemoline may be seen on the TPP Web site at (www.hc-sc.gc.ca/english/archives/warnings/99_113e.htm).

Written by: Victoria Hogan, MSc, Bureau of Drug Surveillance.

Bupropion (Zyban®, sustained-release tablets): update

Adverse drug reactions (ADRs) to Zyban® (marketed in Canada since August 1998) were previously reported in the April 1999 issue of this newsletter.[1] The CADRMP continues to receive spontaneous ADR reports for Zyban® sustained-release tablets, and as of Sept. 16, 1999, received 407 reports (Table 1), of which 256 were serious. Also received were 67 reports for Wellbutrin SR®, another brand of sustained-release bupropion, which is indicated for the relief of symptoms of depression. These 2 drugs contain the same active ingredient, but because of their use in different patient populations this article will focus on Zyban® as indicated for smoking cessation. Although not all of the ADRs in Table 1 are currently listed in the product monograph, it is important to read the product monograph carefully to minimize the risk of ADRs.

Among the cases reporting cardiovascular reactions were 3 deaths, including 2 from myocardial infarction (in a 52-year-old man[1] and a woman in her 60s with a history of coronary artery disease) and 1 from cardiac arrest (in a 53-year-old man with a pulmonary embolism). In addition to the 2 cases of fatal myocardial infarction, there were 7 nonfatal cases of myocardial infarction (2 women, 5 men; age range 44–69 years). Three of these 7 patients had prior cardiovascular disease; another had unspecified risk factors.

The CADRMP received 64 reports of convulsions or grand mal convulsions. Two of the grand mal convulsions were reported as status epilepticus. In one case, a 49-year-old woman had had a single seizure 25 years earlier, and in the other a woman of unknown age had had a single seizure 20 years before this event. Neither reported the use of concomitant medications. The events were reported to have resolved without sequelae in both instances. Among the 64 reports, 29 included the following risk factors for seizure: history of head injury (1); alcohol use (5); diabetes mellitus (4); history of seizure (7); and use of concomitant medications that may lower seizure threshold: antidepressants (4), mefloquine (1) and antipsychotics (1). There were 6 reports of patients who took Zyban® in other than the recommended dose. The risk of seizures with the use of bupropion is associated with a dose-dependent effect.[2] Bupropion should be administered with extreme caution in patients at risk of seizures because of clinical conditions or concurrent medications.[2]

Seven cases of hypoglycemia were reported. In 5 cases the patients were taking insulin concomitantly. Another case involved a Zyban® overdose. Three of the 7 patients also suffered convulsions; 2 of them were taking insulin. The current product monograph indicates that the use of buproprion in diabetic patients treated with oral hypoglycemic agents or insulin is associated with an increased risk of seizure.[2]

There were 128 cases reporting predominantly allergic reactions. In an additional 35 cases allergic reactions were reported in combination with musculoskeletal disorders, including 14 cases of serum sickness (8 women and 6 men; age range 21–46, age unknown in 1 case). Four of the patients with serum sickness were admitted to hospital, and for 2 others the event was considered disabling. Four of the 14 cases of serum sickness were reported as serum-sickness-like syndrome.

There were 52 cases in which psychiatric reactions were reported predominantly. Among these were 7 cases of suicidal ideation (Table 1) in which 2 of the patients had a history of depression. One case of suicide attempt was also reported.

Sixteen reports of visual disturbances were received (8 women, 7 men, 1 sex unknown; age range 21–62 years). The following symptoms occurred: blurred vision, photosensitivity, dilated pupils, decreased vision, retinal vein occlusion, amblyopia, diplopia, difficulty reading, watery eyes, glaucoma, spots, conjunctivitis and myopia.

Spontaneous postmarketing ADR reports constitute one of the key elements used by the TPP to detect new signals and update the product monograph and labelling information. The TPP continues to work with the manufacturer to re-evaluate and update the safety profile of Zyban®.

Written by: Heather Dunlop, BNSc, MLIS, Bureau of Drug Surveillance.

References

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Table 1: Suspected adverse reactions to bupropion (Zyban®) reported in 407 reports* submitted to the CADRMP between Aug. 18, 1998, and Sept. 16, 1999

Central and peripheral nervous system: Convulsions (48), tremor (25), dizziness (24), grand mal convulsions (16), stupor† (9), paresthesia (6), fall† (5), syncope (5), gait abnormal† (4), coordination abnormal (4), hyperkinesia† (4), hypoesthesia (3), paralysis† (3), ataxia (2), coma (2), electroencephalogram abnormal (2), oculogyric crisis† (2), aura† (1), monoplegia† (1), dysesthesia† (1), dyskinesia (1), hypertonia (1), hypokinesia (1), muscle contractions involuntary† (1), peripheral neuropathy (1), tongue paralysis† (1), vertigo (1)

Dermatological: Urticaria (111), rash (78), pruritus (68), erythematous rash† (21), angioedema (11), maculopapular rash (11), erythema multiforme (3), skin reaction localized† (2), Stevens–Johnson syndrome (2), vesicular rash† (2), dermographia† (1), exfoliative dermatitis (1), skin exfoliation (1)

Body: Peripheral edema (32), chest pain (24), allergic reaction (20), edema (20), mouth edema† (19), face edema (18), headache (14), serum sickness (14), therapeutic response decreased† (12), fatigue† (10), malaise (10), periorbital edema† (10), pain (8), sweating increased (7), condition aggravated† (6), fever (6), generalized edema† (6), anaphylactoid reaction (5), anaphylactic shock (5), asthenia (5), somnolence (4), rigors (3), speech disorder† (3), aphasia† (1), back pain (1), cyst† (1), dehydration† (1), dependent edema (1), hot flushes (1), hypersensitivity† (1), hypoxia† (1), influenza-like symptoms† (1), inflicted injury (1), leg pain† (1), pharyngeal edema† (1), skin discoloration† (1), temperature changed sensation† (1), tongue edema (1), weight increase (1)

Psychiatric: Anxiety (24), insomnia (20), agitation (12), confusion (10), emotional lability (9), nervousness (9), hallucination† (7), suicidal ideation†‡ (7), aggressive reaction† (5), amnesia (5), concentration impaired (5), depression (5), paranoid reaction (4), depersonalization (3), anorexia (2), depression aggravated† (2), sleep disorder† (2), thinking abnormal (2), appetite increased (1), crying abnormal† (1), delirium (1), delusion (1), euphoria (1), manic reaction (1), paroniria† (1), psychosis† (1), psychosis manic-depressive† (1), suicide attempt† (1)

Cardiovascular: Tachycardia (11), hypertension (9), myocardial infarction (9), palpitation (9), angina pectoris† (6), atrial fibrillation† (4), hypotension (3), cerebrovascular disorder (2), cyanosis† (2), flushing (2), pallor† (2), substernal chest pain† (2), angina pectoris aggravated† (1), bradycardia† (1), cardiac arrest† (1), complete atrioventricular block (1), extrasystoles (1), pericarditis† (1), peripheral ischemia† (1), transient ischemic attack† (1), vasospasm† (1)

Gastrointestinal: Nausea (19), vomiting (9), dysphagia (8), mouth dry (6), abdominal pain (5), dyspepsia (4), constipation (2), saliva increased (2), flatulence (1), gastrointestinal disorder† (1), glossitis (1), melena† (1), pancreatitis (1) stomatitis (1), ulcerative stomatitis (1),

Respiratory: Dyspnea (40), bronchospasm (6), throat tightness† (6), pharyngitis (4), pneumonia (4), laryngitis† (3), hyperventilation† (2), asthma† (1), chest x-ray abnormal† (1), coughing (1), pulmonary embolism (1), respiratory disorder† (1), rhinitis (1), sinusitis (1), snoring† (1)

Musculoskeletal: Arthralgia (20), myalgia (9), arthritis (7), arthropathy† (7), arthrosis† (2), joint dislocation† (1), muscle weakness† (1), rhabdomyolysis (1), rheumatoid arthritis† (1), tendon disorder† (1), tenosynovitis† (1)

Metabolic: Hypoglycemia† (7), hyperglycemia† (2), creatine phosphokinase increased† (1), diabetes mellitus† (1)

Genitourinary: Urine abnormal† (2), urine flow decreased† (2), polyuria (1), pyelonephritis† (1), urinary incontinence (1)

Hepatobiliary: Aspartate aminotransferase increased† (5), alkaline phosphatase increased† (3), jaundice (3), alanine aminotransferase increased† (3), bilirubinemia† (2), feces discoloured† (2) hepatic enzymes increased† (2), gamma glutamyl transferase increased† (1), hepatitis (1), hepatitis cholestatic† (1), lactate dehydrogenase increased† (1)

Hematological: Erythrocyte sedimentation rate increased† (4), leukocytosis (4), purpura† (4), epistaxis (2), granulocytopenia† (2), leucopenia (2), eosinophilia† (1), vaginal hemorrhage† (1)

Senses: Vision abnormal (13), taste perversion (4), conjunctivitis† (2), diplopia (1), ear ache† (1), glaucoma† (1), mydriasis (1), myopia† (1), photophobia† (1), retinal disorder† (1), tinnitus (1)

Note: CADRMP = Canadian Adverse Drug Reaction Monitoring Program, ADR = adverse drug reaction. Descriptions of ADRs are based on the "preferred term" in the World Health Organization *Adverse Reaction Dictionary*.

*Several reaction terms may be listed for one ADR report.

†Not labelled in product monograph dated Aug. 19, 1999.[2]

COMMUNIQUÉ

The CADRMP wishes to provide feedback and 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. (Reactions are expressed based on the "preferred term" in the World Health Organization *Adverse Reaction Dictionary*.)

HIV protease inhibitors: paronychia

Paronychia (inflammation of the folds of tissue around the nail of the big toes) associated with the use of indinavir (Crixivan®) was reported to the CADRMP.

Gingko biloba: bleeding disorders

Reports of prolonged prothrombin times, warfarin drug interactions, increased coagulation time, subcutaneous hematomas, intracranial hemorrhage associated with the use of gingko biloba were submitted to the CADRMP.

DRUGS OF CURRENT INTEREST

The purpose of the Drugs of Current Interest (DOCI) list is to stimulate reporting for a selected group of marketed drugs in order to identify drug safety signals. The maintenance of this list by the CADRMP facilitates regular monitoring and constitutes one element of post-approval assessment activities. The following criteria are considered for inclusion of drugs on the DOCI list:

- recently marketed drugs (< 2 years), with limited postmarketing experience and potential safety concern from premarket review;
- marketed drugs for which there are emerging safety concerns, new serious adverse drug reactions that are unlabelled in the product monograph (e.g., safety signals observed internationally);
- the first marketed drug of a new pharmacological or chemical class of medication.

abacavir (Ziagen™), alteplase (Activase® rt-PA), bupropion (Zyban®, Wellbutrin SR®), celecoxib (Celebrex™), cisapride (Prepulsid®), clopidogrel (Plavix™), delavirdine (Rescriptor™), Factor VII-recombinant, activated (NiaStase™), indinavir (Crixivan®), mefloquine (Lariam®), naratriptan (Amerge®), nefazodone (Serzone®), nevirapine (Viramune®), pramipexole (Mirapex®), ritonavir (Norvir®), rofecoxib (Vioxx™), ropinirole (Requip™), saquinavir (Invirase™), sildenafil (Viagra™), terbinafine (Lamisil®), ticlopidine (Ticlid®), trovofloxacin (Trovan™), zanamivir (Relenza®), zolmitriptan (Zomig®)

If you have observed any suspected ADRs with the drugs in Communiqué or the DOCI list, *please report them* to the :

Adverse Drug Reaction Reporting Unit
Continuing Assessment Division
Bureau of Drug Surveillance
AL 0201C2, Ottawa, ON K1A 1B9
Fax: 613 957-0335; or to a participating regional ADR centre.

The ADR form is available at:

www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf

British Columbia
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Please Note: A voluntary reporting system thrives on intuition, lateral thinking and openmindedness. Most adverse drug reactions (ADRs) can only be considered to be suspicions, for which a proven causal association has not been established. Because ADRs are underreported and because a definite causal association cannot be determined, spontaneous ADR reports cannot be used to estimate the incidence of adverse reactions. ADRs are nevertheless valuable as a source of potential new and undocumented signals. Health Canada does not assume liability for the accuracy or authenticity of the ADR information contained in the newsletter articles. Furthermore, the Therapeutic Products Programme monitors and assesses suspected ADRs as a means of continously evaluating drug safety profiles. Regulatory decisions are not made within the context of this newsletter.

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