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Potentially harmful drug interaction with St. John’s wort and prescription drugs

On Apr. 7, 2000, Health Canada issued a safety advisory on potentially harmful drug interactions with St. John’s wort (*Hypericum perforatum*). St. John’s wort appears to cause drug interactions by increasing the production of certain drug-metabolizing enzymes in the liver. The resulting decrease in the blood and tissue levels of drugs metabolized by these enzymes may result in a loss of the desired therapeutic effect of these drugs. St. John’s wort has also been reported to increase levels of serotonin and other neurotransmitters found in the brain. Concomitant administration with certain prescription antidepressants that also elevate levels of these neurotransmitters has led patients to experience a pattern of adverse events known as "serotonin syndrome."

The full version of this safety advisory can be found on Health Canada’s Web site (www.hc-sc.gc.ca/english/archives/warnings/2000/2000_36e.html.)

Summarized by: Pascale Springuel, BPharm, Bureau of Licensed Product Assessment.
Olanzapine (Zyprexa®): suspected serious reactions

Olanzapine (Zyprexa®), an atypical antipsychotic, was first marketed in Canada in July 1996 for the acute and maintenance treatment of schizophrenia and related psychotic disorders. A total of 153 domestic reports of suspected adverse drug reactions (ADRs) associated with olanzapine were received by the Canadian Adverse Drug Reaction Monitoring Programme (CADRMP) between that time and Feb. 24, 2000.

Olanzapine was reported as a suspected drug in 22 deaths. Reported causes of death included suicide or overdose (8), neuroleptic malignant syndrome (2), arrhythmia (3), myocardial infarction (1), heart failure and pneumonia (1), pneumonia (1), sepsis (1), sudden death (1), mesenteric thrombosis (1), choking (1), unknown (2).

Some of the reactions classified as serious or unexpected are discussed below. The product monograph should be consulted for other ADRs.

**Suicide or overdose**

Eight reported deaths involved suicide or overdose, sometimes in combination with other drugs. Since the possibility of suicide or attempted suicide is inherent in psychosis, close supervision and appropriate clinical management of high-risk patients should accompany drug therapy.¹

**Cardiac reactions**

Five reports of deaths involving suspected cardiac reactions were received. Patient ages ranged from 20 to 89 years. Two patients had underlying heart conditions. In 1 of the 3 reports of fatal arrhythmia the contribution of olanzapine was unclear. A mixed overdose of other drugs including procyclidine and trimipramine was involved. Two other patients who had fatal cardiac reactions (myocardial infarction and arrhythmia) had received an olanzapine dose 25–30 mg/d at the time of death. This amount exceeds current dosing recommendations, which range from 5 to 20 mg/d. The safety of dosages above 20 mg/d has not been evaluated.¹ Nonfatal possible cardiac reactions included a number of reports of tachycardia or hypotension and one case of possible premature ventricular contractions. In addition, one case of QT prolongation was reported as a result of a possible overdose involving both olanzapine and quetiapine as suspect drugs, with concomitant use of valproic acid.

**Hematological reactions**

Six reports of hematological reactions were previously reviewed in this newsletter in 1998.² Since then 5 additional cases have been received. The following is a summary of all 11 cases. The reports described leukopenia, granulocytopenia, neutropenia, pancytopenia or anemia in patients taking olanzapine. The reported onset of neutropenia or granulocytopenia varied from 2 days to 6 months, with a recovery period of 1 day to 3 months. In 5 of the 11 cases the patient had a history of similar problems when taking the chemically related drug clozapine. A history of clozapine-induced leukopenia may be a risk factor for hematological reactions to olanzapine.³ However, some patients have been able to tolerate olanzapine despite a history of clozapine-related neutropenia.⁴,⁵ As well, it is not clear whether olanzapine can delay the recovery of clozapine-induced leukopenia, since the recovery time is variable.⁶
Hepatic reactions

The CADRMP received 2 reports of patients with an alanine aminotransferase (ALT) level more than twice the upper limit of normal, plus elevated levels of alkaline phosphatase, aspartate aminotransferase (AST) and gamma-glutamyltransferase. One of these patients developed jaundice and had the following enzyme level elevations: ALT 527 U/L (normally < 50 U/L), AST 169 U/L (normally < 40 U/L), alkaline phosphatase 211 U/L (normally < 125 U/L) and gamma-glutamyltransferase 350 U/L (normally < 49 U/L). He had taken olanzapine for approximately 5 months, starting with 5 mg/d then gradually increasing to 15 mg/d over 3 months. In 7 other patients mild increases in ALT or AST levels (less than twice the upper limit of normal) occurred in the following context: olanzapine overdose; neuroleptic malignant syndrome; an undiagnosed reaction with a slight increase in bilirubin; nausea and vomiting requiring hospital treatment; fever; pneumonia; and concomitant use of atorvastatin.

The onset of reactions occurred 12 days to 5 months after the start of olanzapine in 7 of the 9 patients (in the remaining 2 cases the onset was unknown in 1 and the other was a suicide attempt). When the drug was discontinued, the liver enzyme levels returned to normal in 5 cases; in the 4 other cases this is unknown. Precautions should be taken when using olanzapine in patients with pre-existing hepatic disorders, in patients using potentially hepatotoxic drugs or if signs or symptoms of hepatic impairment appear.¹

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome was reported in 11 cases, of which 2 resulted in death. Therefore, health care professionals should be aware of the signs and symptoms of this syndrome, which include fever, sweating, muscle rigidity, and altered mental status, irregular heart rate or blood pressure or heart rhythm (tachycardia, dysrhythmia). Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents.¹

Other reactions

Pancreatitis has been reported during olanzapine therapy in 3 patients. One patient also had diabetic ketoacidosis, and all patients were taking other drugs that could be confounding. An interaction with valproic acid was suspected in 2 patients. The serum valproic acid levels increased when olanzapine was added, but valproate toxicity was not observed.

Health care professionals are requested to continue to report any suspected reactions associated with the use of olanzapine. Full details assist in the analysis of these reactions.

Written by: Barbara Cadario, BScPhm, MSc, Program Coordinator, BC Regional ADR Centre

References
Sildenafil (Viagra™): cardiac risks

Sildenafil (Viagra™) is a cGMP-specific phosphodiesterase type 5 inhibitor used for the treatment of male erectile dysfunction. It was approved for sale in Canada in March 1999. cardiac risks associated with sildenafil use have been documented worldwide. A review of the CADRMP data between Mar. 8, 1999, and Mar. 31, 2000, revealed a total of 48 domestic reports describing 88 suspected adverse reactions to sildenafil. (Several reaction terms may be listed for one ADR report.) The most frequent ADRs were myocardial infarction (8 reports), chest pain (8) and priapism (7). Twenty-eight reports were described as serious (Table 1), reporting death (4), a life-threatening situation (4), a disability or incapacity (1), an admission to hospital or extended hospital stay (12), or another medically important condition (7).

Four deaths associated with the use of sildenafil were reported. There was limited information in the reports. The cases are described here.

Case 1: A 59-year-old man who had previously used sildenafil with no adverse reaction had a heart attack during sexual intercourse. He had a history of high blood pressure and advanced coronary artery disease, but was previously asymptomatic.

Case 2: A 70-year-old man had a cardiac arrest while exercising on a hot summer day. He was taking sildenafil, 25mg as needed for erectile dysfunction, and nifedipine XL, 60mg daily for hypertension. It is unknown if sildenafil was used shortly before death.

Case 3: A 51-year-old man who had previously suffered a heart attack died suddenly. The use of sildenafil was suspected.

Case 4: A patient died soon after the ingestion of sildenafil. The reporter noted that sildenafil may have been relevant to the death.

Myocardial Infarction

There were 8 cases of myocardial infarction, including the previously described fatal case 1. Three of the people were known to have underlying cardiovascular risk factors, as outlined in the warnings section of the product monograph. The 7 other cases are as follows:

Case 1: A 57-year-old man with coronary artery disease took sildenafil, had sexual intercourse 2 hours later and experienced chest pain 3 hours after intercourse. He was given nitroglycerin by his wife, who was unaware of his sildenafil use. He was admitted to hospital for anterior myocardial infarction and recovered without sequelae.

Case 2: A 64-year-old man who had angioplasty 9 years previously was taking 325 mg of ASA daily. He had chest pain 2 hours after taking sildenafil but did not have sexual intercourse. He was admitted to hospital because of myocardial infarction.
Case 3: A 58-year-old man taking no concomitant medications and described as generally healthy experienced a myocardial infarction 2 days after taking sildenafil and recovered with unspecified sequelae.

Case 4: A 64-year-old man had a myocardial infarction while being titrated from 50 to 100 mg of sildenafil. The outcome of the patient was not reported.

Case 5: A 64-year-old man had severe epigastric discomfort 1 hour after taking sildenafil. He was diagnosed with acute inferior-wall myocardial infarction, which required thrombolytic therapy.

Case 6: A man of unknown age took sildenafil and had a myocardial infarction during sexual intercourse. He was not taking nitroglycerin, and his outcome is unknown.

Case 7: A man of unknown age took sildenafil and had a heart attack. The report contained limited information, and the patient's outcome is unknown.

Increased details in reports would possibly strengthen an association during causality assessments.

Other adverse reactions

ADRs associated with the use of sildenafil and another suspect drug occurred in 4 reports. The concomitant drugs were warfarin, interferon beta-1b, celecoxib and testosterone enanathate. An increase in the International Normalized Ratio (INR) occurred in a man when sildenafil and warfarin were taken concomitantly. A 49-year-old man taking interferon beta-1b for chronic progressive multiple sclerosis took 50 mg of sildenafil and 2 hours later had a spasmodic episode. He was awake but unable to move because of stiffness. Two cases of gynecomastia were reported following the concomitant use of sildenafil with celecoxib in one man and with testosterone enanathate injection in another man.

Any treatment for erectile dysfunction should include warnings for people with cardiovascular disease, as there is a potential cardiac risk involved with sexual activity. Sildenafil is contraindicated in patients taking any type of nitrate therapy.

Caution should be used in patients:
• who have had a myocardial infarction, stroke or life-threatening arrhythmia within the last 6 months;
• with resting hypotension (blood pressure < 90/50 mm Hg) or hypertension (blood pressure > 170/110 mm Hg);
• with cardiac failure or coronary artery disease causing unstable angina.1,2

Written by: Heather Morrison, BSc, MLIS, Bureau of Licensed Product Assessment

References
Table 1: Suspected adverse reactions to sildenafil (Viagra™) from 28 serious* reports† submitted to the CADRMP between Mar. 8, 1999, and Mar. 31, 2000.

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>ADVERSE REACTIONS</th>
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<tbody>
<tr>
<td>Body</td>
<td>Chest pain (6), death (3), sudden death (1), medication error (1), therapeutic response increased (1)</td>
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<tr>
<td>Cardiovascular</td>
<td>Myocardial infarction (8), cerebrovascular disorder (2), hypotension (1), hypertension (1), ECG abnormal (1), heart disorder (1), angina pectoris (1), flushing (1), transient ischemic attack (1), cerebral hemorrhage (1), atrial fibrillation (1), tachycardia (1), cardiac arrest (1)</td>
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<td>Central and peripheral nervous system</td>
<td>Hypertonia (1), fecal incontinence (1), dyskinesia (1), oculogyric crisis (1), paralysis (1)</td>
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<tr>
<td>Hematological</td>
<td>Embolism - blood clot (1)</td>
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<tr>
<td>Metabolic and nutritional</td>
<td>Hyperglycemia (1), BUN increased (1), increased lipase (1), increased creatine phosphokinase (1)</td>
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<tr>
<td>Musculoskeletal</td>
<td>Skeletal pain (1)</td>
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<td>Neoplasm</td>
<td>Sarcoma (1)</td>
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<tr>
<td>Psychiatric</td>
<td>Suicide attempt (1), aggressive reaction (1), amnesia (1)</td>
</tr>
<tr>
<td>Reproductive disorders</td>
<td>Priapism (2)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Chest x-ray abnormal (1)</td>
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</tbody>
</table>

Note: CADRMP = Canadian Adverse Drug Reaction Monitoring Program.
* Serious, as defined in the Food and Drugs Act and Regulations.
† Several reaction terms may be listed for one ADR report.

**New Bureau Name**

Organizational changes resulting from the 1999 Functional Review and the Therapeutic Products Programme’s Post-Approval Assessment Activities Strategy have led to the creation of the new **Bureau of Licensed Product Assessment**. Formerly the Bureau of Drug Surveillance, the new bureau will focus on delivering the post-licensing assessment component of the proposed Product Licensing Framework.

Additional information on the Post-Approval Assessment Activities Strategy may be found at: www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/strategy.html.
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.)

Citalopram (Celexa®) and clarithromycin (Biaxin®): interaction

Serotonin syndrome (including symptoms of cogwheel rigidity, myoclonus, hyperreflexia, akathisia [motor restlessness], tremor and agitation) and QT prolongation occurred after clarithromycin was administered concurrently for 4 days with citalopram.

Itraconazole (Sporanox®): serum sickness-like disorder

Serum sickness-like reactions were reported during itraconazole therapy for fungal infections.

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.

- abacavir (Ziagen™)
- alteplase (Activase® rt-PA)
- bupropion (Zyban®, Wellbutrin SR®)
- celecoxib (Celebrex®)
- cisapride (Prepulsid®)
- clopidogrel (Plavix®)
- delavirdine (Rescriptor™)
- Factor VII-recombinant, activated (NiaStase™)
- Hypericum perforatum (St. John’s wort)
- indinavir (Crixivan®)
- mefloquine (Lariam®)
- naratriptan (Amerge®)
- nefazodone (Serzone®)
- nevirapine (Viramune®)
- oseltamivir (Tamiflu™)
- pramipexole (Mirapex®)
- ritonavir (Norvir®)
- rofecoxib (Vioxx®)
- ropinirole (Requip™)
- saquinavir (Invirase™)
- sildenafil (Viagra™)
- terbinafine (Lamisil®)
- ticlopidine (Ticlid®)
- trastuzumab (Herceptin®)
- trovafloxacin (Trovan™)
- zanamivir (Relenza®)
- zolmitriptan (Zomig®)
If you have observed any suspected ADRs with the drugs in the Communiqué or the DOCI list, please report them to the:

Adverse Reaction Review and Information Unit
Bureau of Licensed Product Assessment
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

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<th>Ontario</th>
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<tr>
<td>BC Regional ADR Centre</td>
<td>Ontario Regional ADR Centre</td>
<td>Atlantic Regional ADR Centre</td>
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<tr>
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<td>London Health Sciences Centre</td>
<td>Queen Elizabeth II Health Sciences Centre</td>
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<tr>
<td>1081 Burrard St.</td>
<td>339 Windermere Rd.</td>
<td>Drug Information Centre</td>
</tr>
<tr>
<td>Vancouver BC V6Z 1Y6</td>
<td>London ON N6A 5A5</td>
<td>Rm. 2421, 1796 Summer St.</td>
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<tr>
<td>tel 604 806-8625</td>
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<td>Halifax NS B3H 3A7</td>
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<tr>
<td>fax 604 806-8262</td>
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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

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, ext. 2961 or 888 265-7692
Fax 514 338-3670
cip.hscm@sympatico.ca

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Adverse Reaction Review and Information Unit
Bureau of Licensed Product Assessment
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AL 0201C2, Ottawa ON K1A 1B9
Tel 613 957-0337
Fax 613 957-0335
cadrmp@hc-sc.gc.ca

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www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/publicat.html

Canada

Please Note: A voluntary reporting system thrives on intuition, lateral thinking and open mindedness. 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 under reported 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 continuously evaluating drug safety profiles. Regulatory decisions are not made within the context of this newsletter.
Newsletter Editors: Ann Sztuke-Fournier, BPharm, and Marielle McMorran, BSc (Pharm), Bureau of Licensed Product Assessment.

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