Quetiapine and acute liver failure

**Key points**

- Three published reports (one Canadian case and 2 international cases) indicated a probable causal association between quetiapine use and the occurrence of acute liver failure.
- Two international cases reported a fatal outcome. In the Canadian case, the patient’s condition improved after discontinuing the drug.
- Health care professionals are encouraged to report to Health Canada any cases of liver failure suspected of being associated with quetiapine.

Quetiapine (Seroquel) is an atypical antipsychotic drug indicated for the management of the symptoms of schizophrenia and for the acute management of manic and depressive episodes associated with bipolar disorder. The extended-release formulation is additionally indicated for the symptomatic relief of major depressive disorder when currently available approved antidepressant drugs have failed either due to a lack of efficacy and/or lack of tolerability.

In Canada, quetiapine has been marketed since December 1997. Drug toxicity is a frequent cause of acute liver failure. Acute liver failure has been defined as the development of severe acute liver injury accompanied by a prolonged prothrombin time (international normalized ratio greater than or equal to 1.5) and any degree of mental alteration occurring less than 26 weeks after the onset of illness in a patient without pre-existing cirrhosis.

As of Sept. 30, 2013, Health Canada received 3 reports of liver failure involving quetiapine use, one of which was published in the literature (Table 1). Of the two unpublished cases, one report was unassessable due to limited information and the other was considered inapplicable because it involved an acetaminophen overdose.

Quetiapine is extensively metabolized by the liver. Therefore, the quetiapine (Seroquel) Canadian product monograph (CPM) advises caution when using quetiapine in patients with pre-existing hepatic disorders, in patients treated with potentially hepatotoxic drugs, or if treatment-emergent signs or symptoms of hepatic impairment appear. The CPM also describes the occurrence of asymptomatic transaminase elevations in some patients administered quetiapine.

Liver failure is not mentioned in the CPM.

Two additional international cases of acute liver failure suspected of being associated with quetiapine use were published in the literature (Table 1). Based on the temporal association between the commencement of the
Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

**Key points**

- A potentially life-threatening condition called drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in patients using azithromycin, though the number of reports is low.
- Health Canada received one report of DRESS suspected of being associated with azithromycin.
- Early diagnosis and prompt discontinuation of the offending drug are important to achieve the best outcome in patients with DRESS.
- Distinguishing DRESS from other life-threatening cutaneous drug reactions is important because treatment varies among these conditions.

Azithromycin (Zithromax) is a widely prescribed macrolide antibiotic. It is indicated for the treatment of a variety of bacterial infections, including acute otitis media, pharyngitis and tonsillitis, acute bacterial exacerbations of chronic obstructive pulmonary disease, pneumonia, skin and skin structure infections, and genitourinary tract infections.\(^1\)

Drug reaction with eosinophilia associated with quetiapine.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex</th>
<th>Dose</th>
<th>Reported indication</th>
<th>Duration of exposure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.(^1)</td>
<td>59/F</td>
<td>Unspecified</td>
<td>Hallucinations</td>
<td>6 weeks</td>
<td>Recovered</td>
</tr>
<tr>
<td>2.(^1)</td>
<td>58/F</td>
<td>100 mg daily</td>
<td>Unspecified (however patient had a history of bipolar disorder)</td>
<td>1 month</td>
<td>Died</td>
</tr>
<tr>
<td>3.(^1)</td>
<td>77/F</td>
<td>12.5 mg twice daily</td>
<td>Symptoms of agitation and severe insomnia</td>
<td>9 days</td>
<td>Died</td>
</tr>
</tbody>
</table>

These data cannot be used to determine the incidence of adverse reactions (ARs) because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.

1. Concomitant medical conditions: Parkinson’s disease; concomitant medications: carbidopa-levodopa, oxazepam and pramipexole (discontinued before administration of quetiapine).
2. Concomitant medical conditions: diabetes mellitus, hypertension, hypothyroidism and gallstone pancreatitis for which the patient had undergone prior cholecystectomy; concomitant medications: metformin, ramipril, lithium and thyroid replacement therapy.
3. No documented concomitant medical conditions; no concomitant medications.

Azithromycin and drug reaction with eosinophilia and systemic symptoms

Table 1: Summary of the 3 published reports (one Canadian case and 2 international cases) of acute liver failure suspected of being associated with quetiapine*
and systemic symptoms (DRESS) describes a heterogeneous group of rare but severe adverse reactions to medications. It is most commonly seen in anticonvulsant-treated patients with reported incidences ranging from 1 in 1000 to 1 in 10,000 exposures, and a mortality rate of about 10 to 20%. DRESS typically presents between 2 weeks and 2 months after the initiation of the drug and is associated with fever, a severe skin disease with characteristic infiltrated papules and facial edema or an exfoliative dermatitis, lymphadenopathy, hematologic abnormalities (hypereosinophilia and atypical lymphocytes) and multiorgan involvement (e.g., liver, kidney). The pathogenesis of DRESS is unknown. A definitive diagnosis of DRESS is difficult due to the high variability in clinical presentations, but different guidelines have been published describing the diagnostic criteria.

As of November 30, 2013, Health Canada received one report of DRESS suspected of being associated with azithromycin. The report describes a 60-year-old female who experienced DRESS 18 days after taking azithromycin to treat pharyngitis.

Some cases of DRESS involving azithromycin have been published in the literature. One case involved an eight-year-old boy and another, a two-year-old girl. The latter case resulted in death.

DRESS is not currently labelled in the Canadian product monograph for Zithromax, but other severe cutaneous allergic reactions (e.g., Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) are labelled. Health Canada is currently working with the manufacturer with the aim of updating the Canadian product monograph regarding this safety information.

Early diagnosis and prompt discontinuation of the offending drug are important to achieve the best outcome in patients with DRESS. Distinguishing DRESS from other potentially life-threatening cutaneous drug reactions such as SJS and TEN is important because treatment varies among these conditions. Treatment for DRESS may involve supportive measures (e.g., fluid and nutritional support) and/or systemic corticosteroid therapy depending on the severity of the condition.

Health care professionals are reminded that this adverse reaction may be underdiagnosed and underreported, and they are encouraged to report to Health Canada any cases of DRESS suspected of being associated with azithromycin.

Jiazhen Minnie Dai, PhD, Health Canada

References
Clopidogrel and acquired hemophilia

Background

Clopidogrel (Plavix) is a platelet aggregation inhibitor indicated for conditions such as myocardial infarction, stroke or established peripheral arterial disease, acute coronary syndrome and atrial fibrillation.\(^1\)* Acquired hemophilia is a rare bleeding disorder caused by autoantibodies directed against plasma coagulation factors, most notably factor VIII (i.e., acquired hemophilia A).\(^2\) While the cause is unknown in half of patients, associations with malignancy, pregnancy, autoimmune disease and drugs have been described.\(^3,4\) Clinically, it is characterized by spontaneous and often severe bleeding in patients with no history of bleeding.\(^4\) Control of acute bleeding is a priority because of the high risk of early mortality.\(^2\)

Typical laboratory findings of acquired hemophilia A include a prolonged activated partial thromboplastin time (aPTT) and a low factor VIII level.\(^5\) The thrombin and prothrombin times are normal, as are both the platelet count and function. Investigation for an antifactor VIII inhibitor should be considered if indicated by a prolonged aPTT.\(^3\) Management involves treatment of active bleeding and suppression of the inhibitory antibody.\(^2,4\)

Summary

In September 2013, the manufacturer of Plavix advised physicians in the UK of 11 cases of acquired hemophilia A and one case of acquired hemophilia B in patients treated with clopidogrel since the launch of the product.\(^6\) Patients were 65 to 81-years-old. In some cases, no previous history of abnormal hemostasis had been reported. Time to onset ranged from a few days to 4 months after starting clopidogrel treatment. No fatal cases were reported.

Acquired hemophilia suspected of being associated with the use of clopidogrel has been reported in the scientific literature.\(^3,7\)

As of Sept. 30, 2013, there were no reports of acquired hemophilia suspected of being associated with clopidogrel in Canada.

Next steps

Health care professionals should be aware of the potential association between acquired hemophilia and the use of clopidogrel.

- Increased bruising should not be attributed to the antiplatelet action of clopidogrel, unless the platelet count and coagulation screen are found to be normal.\(^3\)
- In cases of confirmed isolated aPTT prolongation with or without bleeding, acquired hemophilia should be considered.\(^1\)
- Patients with a confirmed diagnosis of acquired hemophilia should be managed and treated by specialists, and clopidogrel should be discontinued.\(^1\)

Acquired hemophilia has been included in the Warnings and Precautions and certain Post-Market Adverse Drug Reactions sections of some of the clopidogrel Canadian product monographs.\(^5,8-13\)

The indication for Plavix has been abbreviated for the purposes of this article. For a comprehensive description, please see the latest Canadian product monograph for Plavix by searching the Drug Product Database, available at: webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp

References

Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

Continued on next page ›
Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

<table>
<thead>
<tr>
<th>Date</th>
<th>Product</th>
<th>Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 13</td>
<td>Hospira flexible intravenous containers</td>
<td>Potential for leakage in certain lots</td>
</tr>
<tr>
<td>Jan 10</td>
<td>Sandoz liquid injectable products</td>
<td>Potential presence of particulate matter in glass vials</td>
</tr>
<tr>
<td>Jan 10</td>
<td>Jevtana (cabazitaxel)</td>
<td>Potential for medication errors leading to overdose</td>
</tr>
<tr>
<td>Jan 3</td>
<td>Sublinox (zolpidem tartrate)</td>
<td>New dosage recommendations</td>
</tr>
<tr>
<td>Jan 3</td>
<td>Alive Vitamins – Royal Jelly 1200 mg</td>
<td>Recall: contamination with chloramphenicol</td>
</tr>
<tr>
<td>Dec 27</td>
<td>Revlimid (lenalidomide)</td>
<td>Risk of liver problems</td>
</tr>
<tr>
<td>Dec 24</td>
<td>Co-Fluvoxamine (100 mg)</td>
<td>Recall: some bottles may contain ciprofloxacin pills</td>
</tr>
<tr>
<td>Dec 19</td>
<td>Phenytoin Sodium Injection USP 50 mg/mL</td>
<td>Possible presence of particulate matter in 2 mL and 5 mL vials</td>
</tr>
<tr>
<td>Dec 18</td>
<td>Methotrexate Sodium Injection 25 mg/ mL</td>
<td>Recall: possible presence of particulate matter in 2 mL and 5 mL vials</td>
</tr>
<tr>
<td>Dec 18</td>
<td>Unauthorized natural health product MaxHIMize</td>
<td>Contains bacteria and undeclared caffeine</td>
</tr>
<tr>
<td>Dec 17 &amp; 23†</td>
<td>Several natural health products</td>
<td>Recall: possible contamination with chloramphenicol</td>
</tr>
<tr>
<td>Dec 5 &amp; Jan 24</td>
<td>Unlicensed laser hair removal products</td>
<td>Risk of eye damage</td>
</tr>
<tr>
<td>Dec 5†</td>
<td>Natural health products sold by Lion King Health Enterprises Group Ltd.</td>
<td>Additional seized products found to contain hidden ingredients and unauthorized substances</td>
</tr>
<tr>
<td>Dec 3</td>
<td>Xeloda (capecitabine)</td>
<td>Risk of severe skin reactions</td>
</tr>
<tr>
<td>Nov 27 &amp; 30</td>
<td>Marcaine (bupivacaine hydrochloride injection USP) 0.25% and 0.5%, Marcaine E (bupivacaine hydrochloride and epinephrine injection USP) 0.25% and 0.5%</td>
<td>Recall: possibility of embedded particles in the glass vial</td>
</tr>
<tr>
<td>Nov 27</td>
<td>Propofol-II Injectable Emulsion 1% (10 mg/mL), 1000 mg/100 mL</td>
<td>Recall: presence of particulate matter</td>
</tr>
<tr>
<td>Nov 22 &amp; 25</td>
<td>Endometrin (100 mg progesterone effervescent vaginal tablets)</td>
<td>Recall: possible problems with effectiveness</td>
</tr>
<tr>
<td>November 22 to February 24</td>
<td>Foreign products</td>
<td>9 Foreign Product Alerts (FPAs) were posted during this period</td>
</tr>
</tbody>
</table>


*Date of issuance. This date may differ from the posting date.
†Update to a previous advisory.