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Canadian Adverse Reaction Newsletter

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In this issue

Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to stimulate adverse reaction reporting as well as to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk–benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

Reporting Adverse Reactions

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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.[1] 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.[2] In Canada, quetiapine has been marketed since December 1997.

Drug toxicity is a frequent cause of acute liver failure.[3] 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.[3]

As of Sept. 30, 2013, Health Canada received 3 reports of liver failure involving quetiapine use, one of which was published in the literature[4] (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 Of the two unpublished cases, one report was unassessable due to limited information and the other was considered inapplicable because it involved an acetaminophen overdose.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.[1] 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).[5,6]

Based on the temporal association between the commencement of the

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*

Case	Age/sex	Dose	Reported indication	Duration of exposure	Outcome
1[4,†]	59/F	Unspecified	Hallucinations	6 weeks	Recovered
2[5,‡]	58/F	100 mg daily	Unspecified (however patient had a history of bipolar disorder)	1 month	Died
3[6,§]	77/F	12.5 mg twice daily	Symptoms of agitation and severe insomnia	9 days	Died

*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.

†Concomitant medical conditions: Parkinson's disease; concomitant medications: carbidopa-levodopa, oxazepam and pramipexole (discontinued before administration of quetiapine).

‡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.

§No documented concomitant medical conditions; no concomitant medications.

medication and the onset of symptoms, and given the lack of plausible alternative causes, the existence of a causal relationship between quetiapine use and the occurrence of acute liver failure in the 3 published cases is probable. Two international cases reported a fatal outcome.[5,6] In the Canadian case, the patient's condition improved after discontinuing the drug.[4] The exact mechanism of this reaction is unclear.

Health care professionals are reminded that this adverse reaction may be underreported and are encouraged to report to Health Canada any cases of liver failure suspected of being associated with quetiapine.

Marie-Thérèse Bawolak, PhD, Health Canada

References

1. *Seroquel (quetiapine fumarate immediate-release tablets)* [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2013.
2. *Seroquel XR (quetiapine fumarate extended-release tablets)* [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2013.
3. Abboud G, Kaplowitz N. Drug-induced liver injury. *Drug Saf* 2007;30(4):277-94.
4. Al Mutairi F, Dwivedi G, Al Ameel T. Fulminant hepatic failure in association with quetiapine: A case report. *J Med Case Rep* 2012;6(1):418.
5. El Hajj I, Sharara AI, Rockey DC. Subfulminant liver failure associated with quetiapine. *Eur J Gastroenterol Hepatol* 2004;16(12):1415-8.
6. Naharci MI, Karadurmus N, Demir O, et al. Fatal hepatotoxicity in an elderly patient receiving low-dose quetiapine. *Am J Psychiatry* 2011;168(2):212-3.

Azithromycin and drug reaction with eosinophilia and systemic symptoms

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

and systemic symptoms (DRESS) describes a heterogeneous group of rare but severe adverse reactions to medications.[2] 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%.[3] 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).[3-5] 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.[5,6]

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.[2,7-9] One case involved an eight-year-old boy[9] and another, a two-year-old girl.[2] The latter case resulted in death.[2]

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.[1] 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.[3,10] Distinguishing DRESS from other potentially life-threatening cutaneous drug reactions such as SJS and TEN is important because treatment varies among these conditions.[10] 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.[3,10,11]

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.

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References

1. *Zithromax (azithromycin dihydrate)* [product monograph]. Kirkland (QC): Pfizer Canada Inc.; 2013.
2. Walsh S, Diaz-Cano S, Higgins E, et al. Drug reaction with eosinophilia and systemic symptoms: is cutaneous phenotype a prognostic marker for outcome? A review of clinicopathological features of 27 cases. *Br J Dermatol* 2013;168(2):391-401.
3. Criado PR, Avancini J, Santi CG, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): a complex interaction of drugs, viruses and the immune system. *Isr Med Assoc J* 2012;14(9):577-82.
4. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms: DRESS). *Semin Cutan Med Surg* 1996;15(4):250-7.
5. Kardaun SH, Sekula L, Valeyrie-Allanore L, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol* 2013;169(5):1071-80.
6. Shiohara T, Iijima M, Ikezawa Z, et al. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. *Br J Dermatol* 2007;156(5):1083-4.
7. Cascaval RI, Lancaster DJ. Hypersensitivity syndrome associated with azithromycin. *Am J Med* 2001;110(4):330-1.
8. Pursnani A, Yee H, Slater W, et al. Hypersensitivity myocarditis associated with azithromycin exposure. *Ann Intern Med* 2009;150(3):225-6.
9. Bauer KA, Brimhall AK, Chang TT. Drug reaction with eosinophilia and systemic symptoms (DRESS) associated with azithromycin in acute Epstein-Barr virus infection. *Pediatr Dermatol* 2011;28(6):741-3.
10. Husain A, Reddy BY, Schwartz RA. DRESS syndrome: Part II. Management and therapeutics. *J Am Acad Dermatol* 2013;68(5):709.e1-9e.
11. Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. *Dermatology* 2003;206(4):353-6.

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.[1,8-13]

*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

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References

1. *Plavix (clopidogrel)* [product monograph]. Laval (QC): sanofi-aventis Canada Inc.; 2013.
2. Baudo F, Caimi T, de Cataldo F. Diagnosis and treatment of acquired haemophilia. *Haemophilia* 2010;16(102):102-6.
3. Haj M, Dasani H, Kundu S, et al. Acquired haemophilia A may be associated with clopidogrel. *BMJ* 2004;329(7461):323.
4. Foley PW, Pepperell D, Kazmi R, et al. Unsuspected acquired haemophilia in a patient with myocardial infarction. *J R Soc Med* 2004;97(11):542–3.
5. Giangrande P. Acquired haemophilia. Revised edition. In: Mahlangu J, ed. *Treatment of Hemophilia*. World Federation of Hemophilia. 2012;38:1-7.

6. Haemophilia risk with clopidogrel. *Reactions Weekly* 2013;1471(1):3.
7. Hwang HW, Kong JH, Yu DW, et al. A patient with acquired hemophilia A induced by clopidogrel. *Korean J Hematol* 2012;47(1):80-2.
8. *Apo-Clopidogrel (clopidogrel)* [product monograph]. Toronto (ON): Apotex Inc.; 2014.
9. *Auro-Clopidogrel (clopidogrel)* [product monograph]. Woodbridge (ON): Auro Pharma Inc.; 2013.
10. *Mylan-Clopidogrel (clopidogrel)* [product monograph]. Toronto (ON): Mylan Pharmaceuticals ULC; 2014.
11. *Mint-Clopidogrel (clopidogrel)* [product monograph]. Mississauga (ON): Mint Pharmaceuticals Inc.; 2014.
12. *Ran-Clopidogrel (clopidogrel)* [product monograph]. Mississauga (ON): Ranbaxy Pharmaceuticals Canada Inc.; 2014.
13. *Sandoz Clopidogrel (clopidogrel)* [product monograph]. Boucherville (QC): Sandoz Canada Inc.; 2014.

Quarterly summary of health professional and consumer advisories

(posted between November 22, 2013 and February 24, 2014)

Date*	Product	Subject
Feb 19	Telzir (fosamprenavir calcium)	New recommendations regarding safe use
Feb 7	Gyrus Bovie Electrosurgical Generators	Possible fire hazard
Feb 5	Lithium	Risk of hypercalcemia and hyperparathyroidism
Feb 4	Aliskiren, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers	New warnings about combining these drugs
Feb 3	Cosopt (dorzolamide hydrochloride/ timolol maleate) Preservative-Free Ophthalmic Solution	Potential risk of eye injury due to change in unit dose pipette design
Feb 3	Unauthorized health products	Products containing undeclared prescription drugs removed from Burnaby West Box store
Jan 30	Levonorgestrel-containing emergency contraceptive pills	Evaluation of the effectiveness in women over a certain weight
Jan 27	Arzerra (ofatumumab)	Recommendations to screen, monitor and manage Hepatitis B virus reactivation
Jan 24	Sandoz Glimepiride	Recall: mislabelling of boxes
Jan 17	Effient (prasugrel hydrochloride)	Increased risk of bleeding in patients treated in hospital for certain types of heart attacks
Jan 14	TRUEtrack blood glucose meters	Recall: potential error in displaying blood sugar levels

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

Advisories can be accessed at www.health.gc.ca/medeffect.
*Date of issuance. This date may differ from the posting date.
†Update to a previous advisory.

Canadian Adverse Reaction Newsletter

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Suggestions?
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