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Canadian Adverse Reaction Newsletter

Volume 22 • Issue 2 • April 2012

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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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Minocycline: drug-induced lupus erythematosus and autoimmune hepatitis in adolescents

Key points

- Long-term use of minocycline, an antibiotic widely used off label for the treatment of acne, has been associated with drug-induced lupus erythematosus and autoimmune hepatitis.
- Since 2004, Health Canada received 7 reports of drug-induced lupus erythematosus or autoimmune hepatitis suspected of being associated with minocycline in adolescents.
- If minocycline-induced autoimmune hepatitis is unrecognized and drug exposure continues, hepatic fibrosis and chronic liver disease may develop.

Minocycline is a second-generation tetracycline that exhibits both antibacterial and anti-inflammatory properties.[1] In Canada, minocycline (first approved in 1969 under the trade name Minocin) is currently marketed by several manufacturers and is indicated for the treatment of various infections.[2]

Because the pathogenesis of acne can include bacterial proliferation (*Propionibacterium acnes*) and inflammation, oral antibiotics such as tetracyclines are frequently prescribed for the treatment of moderate to severe acne. Response to oral antibiotics is usually seen after at least 6 weeks of therapy, and treatment can last for several months.[3]

The occurrence of autoimmune disorders, such as lupus erythematosus and autoimmune hepatitis, has been associated with the use of a number of health products, including minocycline.[4–6] When these disorders are associated with drug use, the underlying mechanisms are not well established. However, long-term drug use is generally involved.[4,6] One of the most common autoimmune diseases is systemic lupus erythematosus, and about 10% of these cases can be related to drug use.[5] Drug-induced lupus erythematosus can produce symptoms that include myalgia, arthralgia and serositis, as well as abnormal laboratory results such as elevated markers of inflammation and the presence of antinuclear antibodies.[5,6] Minocycline-induced autoimmune hepatitis shares many characteristics with autoimmune hepatitis, such as the presence of antinuclear and anti–smooth-muscle antibodies, elevated immunoglobulin levels and histologic features.[4]

Minocycline is generally considered a low-risk drug in the development of drug-induced lupus erythematosus.[5,6] However, there is significant overlap of clinical presentation between drug-induced lupus erythematosus and drug-induced autoimmune hepatitis associated with the long-term use of

Table 1: Summary of 7 reports of drug-induced lupus erythematosus and autoimmune hepatitis suspected of being associated with the use of minocycline for acne in adolescents submitted to Health Canada as of Sept. 30, 2011*

Case	Age/sex	Adverse reaction (AR)†	Duration of exposure	Outcome‡
1	15/F	Drug-induced lupus erythematosus	20 mo	Recovered
2	15/F	Drug-induced lupus erythematosus	5 mo	Recovered
3	16/F	Drug-induced lupus erythematosus	9 mo	Not recovered
4	17/F	Drug-induced lupus erythematosus	3 wk	Recovered
5	16/M	Autoimmune hepatitis	8 mo	Recovered
6	15/F	Autoimmune hepatitis	2 yr	Recovered
7	18/M	Autoimmune hepatitis	Unspecified	Recovered

***These data cannot be used to determine the incidence of 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.**
†Reaction terms are listed according to the *Medical Dictionary for Regulatory Activities* (MedDRA).
‡At the time of reporting.

minocycline.[4,7,8] Also, minocycline-induced lupus erythematosus and autoimmune hepatitis are well documented.

As of Sept. 30, 2011, Health Canada received 4 reports of drug-induced lupus erythematosus and 3 reports of autoimmune hepatitis suspected of being associated with minocycline use in adolescents. All the adverse reactions (ARs) were serious, involved the use of minocycline for the treatment of acne and occurred between 2004 and 2009 (Table 1).

Three additional cases were reported in 2006, 2007 and 2011 but are not included in the table because a formal diagnosis of drug-induced lupus erythematosus (in the first two cases) or autoimmune hepatitis (in the third case) was not reported. The first case reported abnormal laboratory results commonly found in drug-induced lupus erythematosus (presence of antinuclear antibodies) and arthralgia in a 15-year-old girl who had been taking minocycline for 18 months. The second case, also involving a 15-year-old girl, reported the occurrence of an illness resembling systemic lupus erythematosus after 12 months of minocycline use. The third case involved a 14-year-old girl who had been taking minocycline for about 14 months; she presented with hepatitis, polyarthralgia and polyarthritis and was reported to be experiencing an autoimmune disorder.

Minocycline-induced lupus erythematosus and autoimmune hepatitis are serious ARs that can occur in healthy adolescents receiving treatment for acne. Their clinical course can often be reversed after the drug is stopped.[6] However, if minocycline-induced autoimmune hepatitis is unrecognized and drug exposure continues, hepatic fibrosis and chronic liver disease may develop.[8] Health care professionals are reminded of the risk of autoimmune disorders suspected of being associated with the long-term use of minocycline and are encouraged to report any suspected cases.

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Fentanyl and serotonin syndrome

Key points

- Fentanyl may be associated with serotonin syndrome, a life-threatening adverse reaction, when it is used concomitantly with a serotonergic agent.
- In the past 10 years, Health Canada received 5 reports in which fentanyl was used concomitantly with a serotonergic agent and was considered a suspected drug precipitating serotonin syndrome.
- Health care professionals and patients are encouraged to report to Health Canada any cases of serotonin syndrome suspected of being associated with the use of fentanyl.

Serotonin syndrome is a potentially life-threatening adverse reaction (AR) that may be prevented and treated.[1] It is often described as a clinical triad of changes in mental status, autonomic hyperactivity and neuromuscular abnormalities.[1] Not all of these findings, however, are consistently present in all patients with the disorder. According to the Hunter Serotonin Toxicity Criteria,[2] which are generally considered to be the

preferred diagnostic tool, clonus (spontaneous, inducible and ocular) is the most important sign in establishing a diagnosis.[1] Drugs that directly or indirectly increase the intrasynaptic serotonin concentration to threatening levels can induce serotonin syndrome. The syndrome typically occurs in the setting of multiple drugs affecting serotonin neurotransmission through different mechanisms.[3] Successful management of serotonin syndrome requires heightened clinical awareness for prevention, recognition and prompt treatment.[4]

Fentanyl is a synthetic opioid agonist used as an adjunct to anesthesia and for the postoperative management of pain following general surgical procedures and cesarean sections.[5] It is also indicated for the management of persistent, moderate to severe chronic pain that cannot be managed by other means[6] and for the management of breakthrough cancer-related pain.[7,8] Fentanyl is widely used in various clinical practices, with several routes of administration.[3] The parenteral product has been marketed in Canada since 1967.

Fentanyl is not known to precipitate serotonin syndrome when used alone. However, it may be associated with serotonin syndrome when used concomitantly with a serotonergic agent.[9] The mechanism through which fentanyl may precipitate serotonin syndrome is not fully understood.[3] Fentanyl belongs to the opioid analgesic class known as phenyl-piperidines (which also includes meperidine, tramadol, methadone and dextromethorphan), which are considered weak serotonin reuptake inhibitors.[3,10] However, data on fentanyl's serotonin transporter affinity are lacking.[10]

As of Sept. 30, 2011, Health Canada received 5 reports in which fentanyl was used concomitantly with a serotonergic agent and was considered a suspected drug precipitating serotonin syndrome (Table 1). All of the cases occurred within the past 10 years. One of these cases was fatal. Ten reports, including 1 of the 5 submitted to Health Canada,[11] have been published.[3,9,11–17] Eight were published in the past 4 years.[3,9,11,12,15–17] However, no studies on the topic were found in the literature.

There are many clinical situations when an individual could be exposed to a serotonergic agent and fentanyl concomitantly, and these may precipitate a potentially life-threatening serotonin syndrome.[3,14] Health Canada is reviewing the available evidence on the association of fentanyl and serotonin syndrome and will communicate any new safety information or action resulting from its review, if indicated. Health care professionals and patients are encouraged to report to Health Canada any cases of serotonin syndrome suspected of being associated with the use of fentanyl.

Table 1: Summary of the 5 reports in which fentanyl was used concomitantly with a serotonergic agent and was considered a suspected drug precipitating serotonin syndrome submitted to Health Canada as of Sept. 30, 2011*

Case	Age/ sex	Route of fentanyl administration	Indication	Outcome	Concomitant medications with serotonergic effects†
1[11]	49/F	Intravenous	Anesthesia: cardiac surgery	Recovered	Paroxetine, fluvoxamine, meperidine, methylene blue
2	38/F	Transdermal patch	Analgesia: chronic pain syndrome	Unknown	Sertraline
3	51/M	Transdermal patch	Analgesia: back pain	Recovered	Venlafaxine
4	27/M	Transdermal patch	Unknown	Recovered	Venlafaxine
5	74/F	Unknown	Unknown	Died	Paroxetine

***These data cannot be used to determine the incidence of 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.**
†Other concomitant agents not typically known to produce serotonergic activity have not been included.

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Quarterly summary of health professional and consumer advisories

(posted on Health Canada's Web site: Nov. 23, 2011 – Feb. 27, 2012)

Date*	Product	Subject
Feb 27	Gilenya (fingolimod)	Safety being reviewed by Health Canada
Feb 24	Miracle Mineral Solution and Miracle Mineral Supplement	Updated list of Web sites selling the unauthorized products
Feb 23	Unauthorized health products	Seizure of potentially dangerous products from The Love Shop retail outlets in Ontario
Feb 15	Miracle Mineral Solution and Miracle Mineral Supplement	Risk of serious health problems
Feb 13 & 15	Caprelsa (vandetanib)	Serious risk of abnormal heart rhythm
Feb 7	Non-invasive ventilation devices	Risk of being used as life-supporting ventilators
Jan 26	Doribax (doripenem for injection)	Higher mortality rate and lower clinical cure rate during a comparative clinical trial
Jan 26	Velcade (bortezomib)	Fatal if given intrathecally
Jan 25 & 30	Celexa (citalopram)	Association with abnormal heart rhythms
Jan 19	Champix (varenicline tartrate)	Updated safety information with respect to cardiovascular safety
Jan 19	Weight-loss health products	Important safety reminder
Jan 18 & 23	Rasilez (aliskiren) and Rasilez HCT (aliskiren/hydrochlorothiazide)	Potential risks of cardiovascular and renal adverse events in patients with type 2 diabetes
Jan 13	Duet TRS loading units	Urgent recall: contraindication for thoracic use
Jan 13	Excedrin Extra Strength Caplets and Excedrin Tension Headache Caplets	Recall: possible mixing of different products in the same bottle
Dec 29	Compliments Muscle and Back Pain Relief Regular Strength	Labelling error may pose serious risks to children
Dec 23	Bivona Neonatal, Pediatric and Flextend Tracheostomy Tubes	Urgent recall of certain lot numbers
Dec 22 & 23	EpiPen and EpiPen Jr. Auto-Injectors	Information on correct usage
Dec 22	Rasilez (aliskiren)	Safety being reviewed by Health Canada
Dec 19	Bisphosphonates	Small but increased risk of unusual fractures of thigh bone
Dec 5 & 8	Multaq (dronedarone)	Important revisions to product monograph
Dec 5	Yasmin and Yaz (drospirenone)	Updated information on increased risk of blood clots
Dec 2 & Jan 23	Unauthorized health products	Updated list of products removed from sale in Burnaby and Richmond stores due to possible serious health risks
Dec 2 & 7	Avastin (bevacizumab)	Cases of severe eye inflammation leading to blindness following use in the eye
Dec 1	Ursodiol (ursodeoxycholic acid, UDCA)	High dose associated with serious liver side effects
Nov 30	Stiff One Hard 169	Recall: presence of undeclared prescription medication
Nov 30 & Dec 5	Sublinox (zolpidem tartrate)	Association with complex sleep behaviours
Nov 29	Avastin (bevacizumab)	Approval suspended for use in the treatment of metastatic breast cancer
Nov 23 to Feb 27	Foreign products	8 Foreign Product Alerts (FPAs) were posted on the Health Canada Web site during this period; FPAs are available online (www.hc-sc.gc.ca/ahc-asc/media/index-eng.php) or upon request

Advisories are available at www.health.gc.ca/medeffect.
*Date of issuance. This date may differ from the posting date on Health Canada's Web site.

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Acknowledgement

We thank the following members of the Expert Advisory Committee on the Vigilance of Health Products for their review of material for this issue: Colleen J. Metge, BSc(Pharm), PhD; and Yola Moride, PhD, FISPE. We also thank Benjamin Pearson and Aleksandar Brezar, students in Health Sciences and Biopharmaceutical Sciences, respectively, for their participation in the production of the newsletter.

Suggestions?

Your comments are important to us. Let us know what you think by reaching us at mhpd_dpsc@hc-sc.gc.ca

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ISSN 1499-9447, Cat no H42-4/1-22-2E

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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.