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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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Lyme disease test kits and limitations

Key points

- Serologic test results are supplemental to the clinical diagnosis of Lyme disease and should not be the primary basis for making diagnostic or treatment decisions.
- Lyme disease test kits have sensitivity and specificity limitations.
- Health care professionals should be aware of these limitations and are encouraged to report suspected incidents, including false-positive and false-negative results, to Health Canada.

Lyme disease test kits are class II (IV being the highest risk class) in vitro diagnostic devices. The devices are intended for the detection of antibodies to *Borrelia burgdorferi* in human serum, plasma or cerebrospinal fluid.[1] They are used to provide serologic evidence of *B. burgdorferi* exposure.[1] Infection can result in dermatologic, neurologic, cardiac and musculoskeletal disorders.[2] Serologic testing is the only standardized type of laboratory investigation available to support the clinical diagnosis of Lyme disease in North America.[3] The public health agencies of Canada and the United States recommend a two-tiered approach for blood testing when Lyme disease is suspected.[3–7] The first tier consists of an enzyme immunoassay, such as an enzyme-linked immunosorbent assay (ELISA), or an indirect immunofluorescent assay. If the result of first-tier testing is negative, the sample is reported to be negative for antibodies to *B. burgdorferi* and is not tested further. If the result is positive or indeterminate, second-tier testing with a standardized Western blot is then performed.[3–5]

As of June 2012, Health Canada received one incident report of false-negative serologic test results for 24 patients that may have delayed treatment. Timely recognition of Lyme disease and treatment are imperative to facilitate recovery and prevent long-term sequelae.[2,7,8]

The currently available Lyme disease test kits have been found to have limitations of sensitivity and specificity, particularly when used on patients with acute infection, which is usually easily treated with antibiotics.[7,9] Even when the conventional two-tiered testing approach is used, the sensitivity and specificity of the combined test results can be less than optimal.[9–11] In a comprehensive study of 280 serum samples from well-characterized Lyme disease patients, the sensitivity of the two-tiered approach was as low as 38% for the sera of patients who had erythema migrans during the acute phase and 67% during their convalescence after antimicrobial

treatment.[10] In late Lyme disease, the sensitivity increased to 87% for the sera of patients with early neuroborreliosis and to 97% for the sera of patients with Lyme arthritis.[10]

Many factors contribute to false-negative or false-positive serologic test results for Lyme disease.[1,7,9,11–14] In general, false-negative results have been attributed to (a) a slow antibody response early in the course of the disease, (b) genetic diversity of *B. burgdorferi* and (c) treatment with antibiotics. False-positive results have been attributed to (a) cross-reacting antibodies due to other conditions or infections and (b) the persistence of antibodies after disease resolution. Variability in serologic test results for Lyme disease may also be related to interlaboratory differences and lack of interassay standardization. [9,13,14]

In contrast to the known HIV serologic testing using the two-tiered algorithm to confirm diagnosis, the Lyme disease test kits are not designed to screen patients or to establish a clinical diagnosis.[9,12] A positive test result does not necessarily indicate current infection with *B. burgdorferi*, and a negative result, especially early in the course of infection, does not exclude *B. burgdorferi* infection as the cause of illness.[9–12] Serologic test results should be used to support a clinical diagnosis of Lyme disease and should not be the primary basis for making diagnostic or treatment decisions.[1,11] Diagnosis should be based on patient history, which includes symptoms and exposure to the tick vector, and physical findings.[4,11,15]

Health care professionals should be aware of the limitations of Lyme disease test kits and are encouraged to report suspected incidents, including false-positive and false-negative results, to Health Canada (www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php).

Rana Filfil, PhD, Health Canada

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Antiandrogens and hepatotoxicity

Key points

- A recent safety review conducted by Health Canada suggested that hepatotoxicity remains an important safety concern for all antiandrogen drugs.
- The frequency of these adverse reactions and their clinical features appear to differ from one drug to another.
- Health care professionals should be aware of the risk of hepatotoxicity associated with the use of these products.

Antiandrogens are a class of drugs used in androgen deprivation therapy for the treatment of advanced or metastatic prostate cancer. They are classified into two groups: nonsteroidal antiandrogens (flutamide, bicalutamide and nilutamide) and steroidal antiandrogens (cyproterone acetate).[1] Both groups work by competing with circulating androgens for receptor sites within the prostate cell, thus promoting apoptosis and inhibiting prostate cancer growth. Steroidal antiandrogens have the added ability of suppressing the production of testosterone. Depending on the drug, antiandrogens are indicated for use in monotherapy, or in combination with radiotherapy, luteinizing hormone-releasing hormone analogues or orchiectomy for complete androgen blockade.[2–5]

Antiandrogen drugs have been on the Canadian market for more than 20 years. Flutamide was approved by Health Canada in 1984 for the treatment of advanced stage B2 and stage C prostatic carcinoma and metastatic stage D2 prostate cancer.[2] Cyproterone acetate was approved in 1987 for the treatment of advanced prostatic carcinoma.[3] Bicalutamide and nilutamide were approved in 1996 and 1997 respectively for the treatment of metastatic stage D2 prostate cancer.[4,5] Although the risk of hepatotoxicity and hepatic failure is currently labelled under the Warnings and Precautions sections of the Canadian product monographs for flutamide,[2] cyproterone acetate,[3] bicalutamide[4] and nilutamide,[5] a recent safety review conducted by Health Canada suggested that hepatotoxicity remains an important safety concern.

As of Mar. 31, 2012, Health Canada received 25 case reports of hepatotoxicity in men aged 60–98 years old that were suspected of being associated with antiandrogens, 24 of which were serious (Table 1). The most common adverse reactions included jaundice, increased liver enzyme levels, nausea, hepatic necrosis, ascites and hepatitis. One report of hepatotoxicity, excluded from Table 1, involved a woman using an antiandrogen for hirsutism.

The risk of hepatotoxicity with the use of antiandrogens has also been described in the clinical literature. Although both steroidal and nonsteroidal antiandrogens have been associated with hepatotoxicity, the frequency of these adverse reactions, and their clinical features, appear to differ from one drug to another.[1,6,7] For example, the results of an observational study showed a higher occurrence of hepatotoxicity among patients taking flutamide than among those taking cyproterone acetate (15.3% v. 9.5%, $p = 0.034$).[8] Furthermore, this study found that the occurrence of serious hepatotoxicity (defined as an elevation in liver enzyme levels greater than 6 times the upper limit of normal) was 4.8% with the use of flutamide and 3.8% with cyproterone acetate. Serious hepatotoxicity is reported to be rare with bicalutamide and nilutamide.[1]

Data from published clinical studies and case reports from the Canada Vigilance database consistently suggest that the risk of hepatotoxicity has been associated with all antiandrogen products marketed in Canada. Health care professionals

Table 1: Summary of case reports of potential hepatotoxicity in men suspected of being associated with the use of antiandrogens submitted to Health Canada as of Mar. 31, 2012*

			Outcome of serious cases[§]			
Antiandrogen	Total no. of cases[†]	No. of serious cases[‡]	Recovered	Not recovered	Death	Unknown
Bicalutamide	2	2	0	1	0	1
Cyproterone acetate	9	9	2	1	6	0
Flutamide	15	14	7	1	6	0
Total[¶]	25	24	9	3	11	1

***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.**

[†]No cases involving nilutamide were reported as of Mar. 31, 2012.

[‡]In the *Food and Drugs Act* and Regulations, a serious AR is defined as "a noxious and unintended response to a drug that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death."

[§]At time of reporting.

[¶]The total no. of cases, serious cases and deaths do not equal the sum of their columns because one report involved a patient taking both cyproterone acetate and flutamide in which the outcome was death.

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.

should be aware of the risk of hepatotoxicity associated with the use of these products.

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Case Presentation

Recent Canadian cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Case presentations are considered suspicions and are presented to stimulate reporting of similar suspected adverse reactions.

Thalomid and posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (PRES), also called reversible posterior leukoencephalopathy syndrome, is a neurological syndrome that typically includes the presence of headaches, visual disturbances, seizures, altered mental function and radiologic findings that commonly involve symmetrical posterior hemispheric edema.[1] It is often associated with abrupt hypertension and can also be seen in patients who are taking immunosuppressive drugs.[2] This syndrome is generally characterized by reversibility through control of the primary instigating factors.[1]

Thalidomide (Thalomid) is an immunomodulatory agent used to treat multiple myeloma.[3] It has been suggested that its immunosuppressive effect on endothelial cells may be involved in the development of PRES.[2] Some cases of PRES suspected of being associated with thalidomide have been reported in literature.[2,4–6]

One of the published cases had been reported to Health Canada. It involved a 49-year-old woman who had been taking thalidomide 200 mg/d for maintenance therapy after autologous stem cell transplantation for multiple myeloma. She had been taking thalidomide for about 11 months before experiencing two focal motor seizures that evolved into a witnessed generalized tonic–clonic seizure. The seizure was terminated with the administration of lorazepam, and she was normotensive upon physical examination. The patient had also experienced anxiety and subjective short-term memory loss. Magnetic resonance imaging (MRI) of the brain showed findings consistent with PRES, including multiple foci of hyperintensity in the occipital and posterior parietal lobes on T_2-weighted images. The patient was prescribed phenytoin, which was later switched to valproic acid because of a possible drug allergy. Three months later, a follow-up MRI revealed complete resolution of the hyperintensity changes on T_2-weighted images. The valproic acid therapy was tapered, and the patient did not have any further seizures. Health Canada encourages the reporting of similar suspected adverse reactions to the Canada Vigilance Program.

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Quarterly summary of health professional and consumer advisories

(posted on Health Canada's Web site: May 21, 2012 – August 19, 2012)

Date*	Product	Subject
Aug 10	Hospital beds	Update on the risk of patient entrapment
July 31	Calcitonin-containing drugs	Potential cancer risk with long-term use
July 25	Weight-loss health products	Unauthorized health products removed from sale at Burnaby's U-Box store
July 23	Pulmicort Turbuhaler (budesonide)	Potential device failure
July 19	Vine Essence	Recall : unauthorized natural health product
July 16	Fu Fang Zaoren Jiaonang	Unauthorized health product removed from sale
July 11 & 13	ImmuCyst (BCG vaccine)	Update on facility issues and supply status
July 9 & 12	Volibris (ambrisentan)	Contraindication in patients with idiopathic pulmonary fibrosis
July 6	Lightning Rod	Unauthorized health product removed from sale
June 29	ZXT Gold Bee Pollen Capsules	Unauthorized health product removed from sale
June 28	Kleenex Luxury Foam Hand Sanitizer	Recall: microbial contamination
June 26	Paclitaxel for injection, 300mg/50mL	Glass vial defects for 3 lots
June 22	Counterfeit drugs	Reminder of the possible health risks
June 21	Natural Vigor Maximum	Recall: presence of undeclared dimethylhomosildenafil
June 15	Tuberculosis (BCG) vaccine	Recall: manufacturing facility problems
June 11 & 14	HepaGam B [Hepatitis B Immune Globulin (Human) Injection]	Possible risk of thrombotic events
June 1	Philips IntelliVue Patient Monitors	Alarm problem with some units
May 29 & June 1	Privigen [Immune Globulin Intravenous (Human)]	Association with risk of hemolysis and labeling updates
May 28 & 31	Xgeva (denosumab)	Risk of severe symptomatic hypocalcemia, including fatal case
May 23	X-Rock, Kaboom and One For Her	Unauthorized health products removed from sale
May 15†	Colleague Single and Triple Channel Volumetric Infusion Pumps	Important safety information
May 21 to Aug 19	Foreign products	17 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.
†Posted on Health Canada's Web site on May 22, 2012. Not included in previous quarterly summary.

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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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