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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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Cisplatin and aortic thrombosis

Key points

- Six Canadian cases of aortic thrombosis have been reported in cancer patients after initiation of treatment with cisplatin, in addition to 15 published international cases.
- In many of these patients, the condition stabilized or resolved after initiation of anticoagulation therapy or surgery.
- Early detection and management of aortic thrombosis increases the chances of a favourable outcome.

Cisplatin, a platinum agent, is a DNA-modifying anticancer drug that has been marketed in Canada since 1979. It is indicated for the treatment of genitourinary cancers including cancers of the testis, bladder and ovary.[1-5]

Aortic thrombosis is a rare and potentially life-threatening disorder characterized by the formation of a clot in the aorta. It rarely occurs spontaneously in such large vessels without the presence of atherosclerotic plaques.[6,7] Aortic thrombosis may be related to concomitant hereditary or acquired hypercoagulable states, as well as to factors that promote clot formation (e.g., cancer, pregnancy, recent surgery, trauma, immobility, use of certain medications or substances, sepsis, polycythemia, autoimmune disease, inflammation of the blood vessels, smoking, etc.).[6,7]

As of April 30, 2014, 6 Canadian cases of aortic thrombosis in cancer patients after treatment initiation with cisplatin were reported to Health Canada, including 5 published cases (Table 1).[8,9] The most recent Canadian case occurred in 2011.

Of the 6 Canadian cases, 5 indicated that the patient was treated with anticoagulants and one required surgery (thrombectomy of the aorta and aortobifemoral grafts in one case). In 3 cases, the thrombus was detected after the last dose of cisplatin. The status of cisplatin treatment continuation is unknown for the remaining cases. Potential confounding factors for aortic thrombosis in these cases included a higher coagulation state associated with the underlying malignancy and other known predisposing factors such as smoking (reported in 4 cases), obesity (noted in one case), and previous history of vascular disease (transient ischemic attacks noted in one case). Fifteen additional international cases reporting the occurrence of aortic thrombosis after initiation of treatment with cisplatin were identified in the literature from 13 publications.[7,10-21]

The product monographs for cisplatin do not list aortic

Table 1: Summary of Canadian reports of aortic thrombosis after initiation of treatment with cisplatin submitted to Health Canada as of April 30, 2014*

Case	Age/ sex	Suspect health products	Indication	Cisplatin dose at each chemo-therapy cycle	Duration of exposure prior to detection	Outcome
1[8]	60/F	Cisplatin, fluorouracil, leucovorin, oxaliplatin	Recurrent recto-sigmoid adenocar-cinoma	100 mg/m^2 IV, on day 1	6 days after end of 3rd cycle	Stable thrombus at 12 months
2[8]	53/M	Cisplatin, etoposide	Small cell lung adenocarcinoma	20 mg/m^2 IV, on days 1 to 3	4 days after end of 3rd cycle	Death (10 days after initiation of anticoagulants)
3[8]	53/M	Cisplatin, vinorelbine	Lung adenocarci-noma	75 mg/m^2 IV, on day 1	14 days after end of 4th cycle	Stable thrombus at 9 months
4[8]	50/F	Cisplatin, vinorelbine	Non-small cell lung cancer	75 mg/m^2 IV, on day 1	14 days after end of 4th cycle	Resolved (complete resolution at 6 months)
5	57/M	Cisplatin	Bladder cancer	Not reported	7 days after end of 3rd cycle	Unknown
6[9]	54/F	Cisplatin, etoposide	Metastatic large-cell lung cancer	75 mg/m^2 IV, on day 1	Second cisplatin cycle was completed (no other information provided)	No recurrence more than 2 years after thrombectomy

*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.

thrombosis.[1-5] However, they indicate that cases of clinically heterogeneous vascular toxicities coincident with the use of cisplatin in combination with other antineoplastic agents have been reported rarely. These events may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (hemolytic uremic syndrome), and cerebral arteritis. The exact mechanism for the occurrence of vascular toxicities with cisplatin is unclear.

Health care professionals are reminded that aortic thrombosis has been observed in patients under treatment with cisplatin. Early detection of aortic thrombosis may help to improve prognosis.[17] Health care professionals are encouraged to report to Health Canada any cases of aortic thrombosis suspected of being associated with cisplatin.

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Hydroxychloroquine and hypoglycemia

Background

Hydroxychloroquine (Plaquenil) is indicated for the treatment of rheumatoid arthritis, discoid and systemic lupus erythematosus, and malaria (acute attacks and suppressive treatment).[1,*]

Hypoglycemia is generally defined by (a) the presence of symptoms consistent with hypoglycemia; (b) a low plasma glucose level (the lower limit of the fasting plasma glucose level is normally approximately 3.9 mmol/L); and (c) the relief of those symptoms after the plasma glucose level is raised.[2] Clinical manifestations of hypoglycemia include neuroglycopenic symptoms (e.g., confusion, fatigue, seizure, loss of consciousness, and if hypoglycemia is severe and prolonged, death) and neurogenic symptoms (e.g., sweating, hunger, palpitations, trembling, anxiety, etc.). Hypoglycemia is rare in the absence of antidiabetic therapy.

Summary

The potential for hydroxychloroquine to enhance the hypoglycemic effects of antidiabetic agents is known.[1] As of Dec. 31, 2013, Health Canada received 2 reports of hypoglycemia suspected of being associated with hydroxychloroquine. Both reports describe the reaction as occurring in the context of co-administration with insulin or metformin.

However, hypoglycemia involving hydroxychloroquine without co-administration of a hypoglycemic agent has been reported in the literature.[3-5] There is sufficient evidence to support a causal association between hydroxychloroquine use and the onset of hypoglycemia in this context, including serious cases involving a loss of consciousness and hospitalization.

Next steps

Health care professionals should be aware of the association between hypoglycemia and hydroxychloroquine, with or without the concomitant use of antidiabetic agents. The Canadian product monograph for Plaquenil now includes the risk of hypoglycemia under the Warnings and Precautions section.[1]

- Patients treated with hydroxychloroquine should be warned about the risk of hypoglycemia and the associated clinical signs and symptoms so that they may be recognized and addressed.
- Patients presenting with symptoms suggestive of hypoglycemia should have their blood glucose level checked and the need for hydroxychloroquine treatment reviewed as necessary.
- In cases of severe hypoglycemia, hydroxychloroquine treatment should be discontinued and an alternative therapy considered.
- If patients use hydroxychloroquine concomitantly with antidiabetic agents, a decrease in dose of insulin or antidiabetic drugs may be required.

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

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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.

Suspected interaction between ginkgo biloba and efavirenz

Health Canada received a published case report of a potential drug-herb interaction between efavirenz (Sustiva) and a ginkgo biloba product. Efavirenz is a selective non-nucleoside reverse transcriptase inhibitor that is indicated for the treatment of HIV-1 infection in combination with other antiretroviral (ARV) agents. It is known to interact with various medications, foods and natural health products (NHPs).

The case involved a 41-year-old HIV-infected man on ARV therapy consisting of zidovudine, lamivudine and efavirenz, with good viral suppression (< 50 copies/mL) for 10 years.[1] Routine blood work detected a rise in the patient's HIV viral load (to 1350 copies/mL). Upon questioning, he denied any missed doses but revealed the daily use of NHPs including omega-3 fatty acid, calcium, magnesium, vitamin D, a multivitamin, flax oil, rutin, and 300 mg of an unspecified ginkgo biloba product per day for the previous 2 months. Additionally, he used horse chestnut periodically for hemorrhoids treatment.

After discontinuation of the ginkgo biloba product and horse chestnut, the patient's HIV was re-suppressed by the same ARV therapy one month later. Based on a previous published case report, a similar drug-herb interaction between ginkgo biloba and efavirenz was suspected.[2]

People living with HIV/AIDS often use a combination of prescription and non-prescription health products, including NHPs. Health care professionals are encouraged to remind patients to disclose the use of all health products, including non-prescription drugs and NHPs. Drug-NHP interactions may lead to serious adverse reactions and/or a reduction in the drugs' intended benefits.

Health Canada encourages the reporting of all suspected cases of interactions, including those that occur with the use of pharmaceuticals, NHPs, and food products to the Canada Vigilance Program.

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Quarterly summary of health professional and consumer advisories

(posted between February 25 and May 26, 2014)

Date*	Product	Subject
May 23	Heartland Natural Wild Yam Moisturizing Cream	Contains undisclosed prescription drug ingredient
May 23	PMS-Losartan-HCTZ	Recall: labelling error in one lot
May 16	Hospira Sodium Chloride 0.9% Irrigation, USP, 3000 mL flexible container	Recall: potential leakage of bags in one lot
May 16	Lite Fit USA	One lot recalled in the U.S.
May 14	Serotonin blocking drugs used to treat nausea and vomiting	Risk of serotonin syndrome
May 13	"Thyroid Gland"	No longer authorized for sale
May 13	Surgical mesh	Complications associated with transvaginal implantation

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(posted between February 25 and May 26, 2014)

Date*	Product	Subject
May 9	Biolyse Pharma Corporation	License suspended due to serious manufacturing concerns
May 9	Peace Naturals Project Inc. marijuana for medical purposes	Recall: positive bacterial testing outside of acceptable limits for one batch
May 7	Laparoscopic electric morcellators	Risk of spread of unsuspected uterine sarcoma
May 7	Temodal (temozolomide)	Risk of liver problems
Apr 22 & 25	Benlysta (belimumab)	Reports of progressive multifocal leukoencephalopathy
Apr 18	Greenleaf Medicinals marijuana for medical purposes	Recall: issues with the company's production practices which may impact one batch
Apr 17	Clinimix - 5% Travasol Amino Acid Injection with Electrolytes in 16.6% Dextrose Injection, 1 L	Recall: particulate matter found in the solution
Apr 11	Unauthorized health products	Seizure from "SVN FUEL" stores in BC
Apr 10	Neupogen (filgrastim) and Neulasta (pegfilgrastim)	Risk of capillary leak syndrome
Apr 9 & 14	Amplatzer Septal Occluder	Risk of erosion
Apr 9	Cefazolin for Injection USP 1g	Potential for longer reconstitution time and precipitation of the reconstituted solution
Apr 9	"L-Showm Weight Loss Pills"	Seizure of unauthorized health product from U-Box store in Burnaby, BC
Apr 7	Busulfex (busulfan) 6 mg/mL Injection	Potential for particulate matter in 10 mL vials
Apr 7	Zelboraf (vemurafenib)	Liver problems
Apr 5, 9 & 23	NaturaLyte Sodium Bicarbonate Liquid Concentrate	Recall: risk of bacterial contamination
Mar 28	Remeron / Remeron RD (mirtazapine)	Abnormal heart rhythms
Mar 26	Imuran (azathioprine) or Purinethol (mercaptopurine)	Hepatosplenic T-cell lymphoma
Mar 26	Emergency contraceptive pills	New warnings about reduced effectiveness in women over a certain body weight
Mar 13	Hospira infusion pumps	New intravenous pumps still unavailable due to ongoing design and quality concerns
Mar 11	Abbott FreeStyle glucose test strips	May produce false test results with certain devices
Feb 27	Herbal detox and laxative products "Formule L1" and "Detox Spring-Fall"	Recall: important risk information missing from label
February 25 to May 26	Foreign products	14 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.

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Suggestions?
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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.