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
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 arteryitis. 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.

David Duguay, PhD; Josephine Djulus, MD; Pascale Springuel, BPPharm, DESS, Health Canada

References

1. Cisplatin injection [product monograph].

Mémoire

1. Cisplatin injection [product monograph].
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). 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. 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. 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. 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.

- 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.*

David Duguay, PhD, Health Canada

**References**

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. 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.

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.

References
Quarterly summary of health professional and consumer advisories
(posted between February 25 and May 26, 2014)

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