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Canadian Adverse Reaction Newsletter

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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 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

Contact Health Canada or a Regional AR Centre free of charge

Phone: 866 234-2345
Fax: 866 678-6789
Email: cadrmp@hc-sc.gc.ca

Form available at:

www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adverse_e.pdf

Fluoroquinolones and warfarin: suspected interactions

Fluoroquinolones are primarily used to treat respiratory and urinary tract infections, prostatitis, septicemia, and skin, soft-tissue, bone and joint infections.[1–6] Cases of increased anticoagulant activity have been reported in patients taking warfarin concurrently with fluoroquinolones.[7,8] The proposed mechanisms of this interaction are displacement of warfarin from protein-binding sites, reduction in gut flora that produce vitamin K and its clotting factors, and decreased warfarin metabolism.[9] Most fluoroquinolones are inhibitors of cytochrome P450-mediated metabolism and may therefore be responsible for toxicity of other co-administered drugs by decreasing their clearance, especially drugs with a narrow therapeutic index such as warfarin.[10]

As of Jan.15, 2004, Health Canada received 57 reports of suspected coagulation disorders associated with

Table 1: Reports submitted to Health Canada of suspected coagulation disorders involving fluoroquinolones and warfarin from date marketed in Canada to Jan. 15, 2004*

Variable	Ciprofloxacin	Gatifloxacin	Levofloxacin	Moxifloxacin	Norfloxacin
Date marketed in Canada	Dec 1989	Feb 2001	Nov 1997	Oct 2000	Dec 1986
Total no. of AR reports with platelet, bleeding and clotting disorders	38	15	45	15	13
No. of AR reports with coagulation disorder†	10	13	16	12	6
Median age (and range) of patients, yr	74.5 (39–90)	76 (48–90)‡	80.5 (64–90)	69.5 (30–87)§	78.5 (49–88)§
No. of AR reports in which other drug(s) also suspected	2	2	3	2	1
No. of serious¶ AR reports (and no. resulting in hospital admission)	7 (3)	13 (3)	14 (2)	11 (7)	4 (1)
No. of AR reports in which patient's INR was previously stabilized with warfarin**	3	4	3	5	0
Range of INR values	2.0–> 18.5	5.0–> 50.0	4.0–15.9	1.7–23.8	1.9–8.3

Note: AR = adverse reaction, INR = international normalized ratio.
***These data cannot be used to determine the incidence of ARs or to make quantitative drug safety comparisons between the products because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.**
†Includes coagulation time increased, prothrombin decreased, prothrombin time prolonged according to the *World Health Organization Adverse Reaction Dictionary* (WHOART).
‡Age unknown in 1 case.
§Age unknown in 2 cases.
¶A serious adverse drug reaction is defined as "a noxious and unintended response to a drug, which occurs at any dose and 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" (Food and Drugs Act).
**Data included only when reported in AR reports.

fluoroquinolones and warfarin (Table 1). Ten cases involved ciprofloxacin, 13 gatifloxacin, 16 levofloxacin, 12 moxifloxacin and 6 norfloxacin. None of the cases of coagulation disorders involved ofloxacin (marketed in Canada in December 1990). The 57 reports involved 46 patients 60 years of age and older; 6 were less than 60, and 5 did not report age. Forty-nine reports were considered serious, with 16 involving adverse reactions resulting in hospital admission. Four patients (aged 70 to 90 years) taking ciprofloxacin (1), gatifloxacin (2) and levofloxacin (1) died. Causality assessment of these cases is difficult because of confounding factors or the complexity of the cases. The international normalized ratios (INRs) reported were as high as 50 (therapeutic INR 2.0–3.0). In 15 of the reports, the INR had been stabilized with warfarin before the fluoroquinolone therapy was started.

Health Canada continues to receive reports of suspected interactions between fluoroquinolones and warfarin. This interaction is labelled in the official Canadian product monographs for these drugs. Possible risk factors for this interaction include the infectious disease and its accompanying inflammatory process, other concomitant drugs, and the age and general health status of the patient.[5] Certain fluoroquinolones may enhance the effects of warfarin or its derivatives during concomitant administration of these drugs.[2–6] The prothrombin time and INR should be monitored closely, especially in elderly patients, and the anticoagulant dose adjusted accordingly.

Iza Morawiecka, BScPhm; Ilhemme Djelouah, BScPhm, DIS, AFSA, Medical Biology (University of Paris V); Debra Willcox, BSP, Health Canada

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Suspected warfarin–cranberry juice interaction

In September 2003 the United Kingdom's Committee on Safety of Medicines and the Medicines and Healthcare products Regulatory Agency highlighted the possible interaction between warfarin and cranberry juice and advised patients taking warfarin to limit or avoid drinking cranberry juice.[1] They had received 8 reports since 1999 of a possible interaction that led to changes in the international normalized ratio (INR) or bleeding: in 1 case the patient died, in 4 cases there was an increase in INR or bleeding, in 2 cases the INR was unstable, and in 1 case the INR decreased.[2] In the fatal case, the patient's previously stable INR increased to > 50 (therapeutic INR 2.0–3.0) following 6 weeks of cranberry juice consumption.[2] The patient died of a gastrointestinal and pericardial hemorrhage. In another case a patient with a prosthetic mitral valve was taking warfarin. A persistently elevated INR was noted 2 weeks after he began to drink cranberry juice (almost 2 L/d). Subsequent surgery led to postoperative bleeding complications.[3]

In theory, the interaction between warfarin and cranberry juice is biologically plausible: warfarin is predominantly metabolized by cytochrome P450 (CYP2C9), and cranberry juice contains flavonoids, which inhibit CYP enzymes.[1,2] In the United States, the National Center for Complementary and Alternative Medicine at the National Institutes of Health, will investigate cranberry–drug interactions as part of a larger cranberry research initiative.[4] Suspected interactions have been documented between anticoagulants and herbal products such as devil's claw, ginkgo biloba, Panax ginseng, green tea, papain (papaya extract), St. John's wort,[5,6] dong quai, dan shen[6,7] and certain brands of *quilinggao*.[7] Vitamins (e.g., A, E, C and K),[8,9] fish oil supplements[10] and food products (e.g., soy milk)[11] may also interact with anticoagulants. Given warfarin's narrow therapeutic margin, patients should be aware of which drugs, natural health products and food products may be associated with interactions.

Health Canada will continue to monitor these interactions and will inform the public when more information becomes available to help increase consumer and health professional awareness about the possibility of interactions between warfarin and natural health products, drugs or food.

Jenna Griffiths, MSc, PhD; Mano Murty, MD, CCFP, FCFP; Karen Pilon, RN, Health Canada

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Case presentations

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.

Tutoplast Dura graft: possible association with Creutzfeldt–Jakob disease

Tutoplast Dura mater is commercially processed dura mater obtained from human donors.[1] Regulated as a medical device, Tutoplast Dura mater was available in Canada between January 1982 and April 2002 for use in various surgical treatments, including neurosurgery.[1] In June 2003, a 59-year-old Canadian woman presented with slight memory loss, decreased level of consciousness, myoclonus, focal seizures, decreased ability to speak and nystagmus. The patient had received a Tutoplast Dura mater graft in 1992 during a surgery for excision of a benign brain tumour. Investigations showed hydrocephalus and surgery sequelae on MRI, and electroencephalography changes not typical for Creutzfeldt–Jakob disease (CJD). The patient underwent a ventriculoperitoneal shunt. She died in July 2003. Autopsy confirmed classic CJD.

Worldwide there has been only 1 documented case of CJD associated with the use of Tutoplast Dura.[2] Health care providers should be aware of the possibility of iatrogenic CJD in recipients of dura mater grafts in whom neurological signs and symptoms develop. The incubation period can be up to 20 years or more. Appropriate infection prevention and control precautions should be taken for recipients of dura mater grafts when they present a risk of transmitting the CJD agent.[3]

Health care professionals are advised to report to Health Canada's CJD Surveillance System any suspected or confirmed cases of CJD in recipients of dura mater grafts, as well as other cases of CJD, by calling 888 489-2999 (toll free).

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Toxic shock syndrome and tampons: the risk remains

In Canada, menstrual tampons are regulated as medical devices.[1] The Health Products and Food Branch Inspectorate of Health Canada recently received 2 reports of toxic shock syndrome (TSS) associated with the use of menstrual tampons. In one case, a 16-year-old woman was admitted to hospital and treated with antibiotics after a possible prolonged use of a tampon. The other case involved a 26-year-old woman who spent several days in an intensive care unit before recovering.

Toxic shock syndrome is a rare and potentially fatal condition that is associated with use of tampons. Young women (under the age of 30) are at greater risk because they have not yet developed the antibodies to the toxin that causes TSS.[1] In the early 1980s a large number of cases of TSS resulted in substantial media attention, thereby alerting consumers to the potential hazard and the signs and symptoms to watch for.[1,2] From 1980 to 1986 the number of TSS cases reported yearly in the United States declined to about 1 per 100 000 women aged 15–44 years.[2] A review of recent passive surveillance data confirms the declining trend previously noted by active surveillance in 1986.[2] Over the last number of years, only a few cases have been reported, about half of which were associated with tampon use.[1]

Women may delay seeking timely medical attention if they do not associate early symptoms of TSS with tampon use.

- Women should be informed of the potential hazard of TSS and reminded of the warnings clearly indicated on all tampon boxes.
- Physicians must remain vigilant to the possibility of TSS in young menstruating women using tampons who present with flu-like symptoms (e.g., fever, vomiting, diarrhea), hypotension or rash.
- Suspected cases should be reported to the Health Products and Food Branch Inspectorate through a toll-free hot line (800 267-9675).

References

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New MHPD address

The Marketed Health Products Directorate (MHPD) has moved. Telephone and fax numbers remain the same. The new mailing address and address locator for MHPD (including the Canadian Adverse Drug Reaction Monitoring Program) are as follows:

Marketed Health Products Directorate
Address Locator 0701B
Ottawa ON K1A 0K9
Tel: (613) 954-6522
Fax: (613) 952-7738

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Address Locator 0701C
Ottawa ON K1A 0K9
Tel: (613) 957-0337
Fax: (613) 957-0335

The Market Authorization Holders should continue to use this fax number to fax Adverse Reaction reports.

Health professionals and consumers should continue to use the following toll free telephone and fax numbers to report adverse reactions:
Tel: (866) 234-2345
Fax: (866) 678-6789

Summary of health professional and consumer advisories posted from Feb. 10, 2004, to May 17, 2004
(advisories are available at www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_advisories_e.html)

Date	Product	Subject and type
May 17 & 13	Orthoclone OKT 3	Serious adverse reactions in pediatric patients treated with Orthoclone OKT 3 (muromonab-CD3) — Janssen-Ortho Inc — notice to hospital and consumer information
May 7	Absorbable Hemostatic agents	Association of Absorbable Hemostatic Agents with paralysis or other neural deficits — notice to hospitals
May 3 & Apr 28	Zelnorm	Important safety update: diarrhea and ischemic colitis in patients using Zelnorm (tegaserod hydrogen maleate) — Novartis Pharma Canada Inc. — consumer information and health professional communication
Apr 21	Acetabular Reamer	Inadequate cleaning/sterilization of EZ Clean Monobloc Acetabular Reamer — notice to hospitals
Apr 19 & 14	Accolate	Important safety information regarding reports of serious hepatic events in patients receiving Accolate (zafirlukast) — AstraZeneca Canada Inc. — consumer information and health professional communication
Apr 16	Infusion pumps	Health risks associated with use of infusion pumps — notice to hospitals
Mar 18 & 10	Zyprexa	Important drug safety information: Zyprexa (olanzapine) and cerebrovascular adverse events in placebo-controlled elderly dementia trials — Eli Lilly Canada Inc. — consumer information and health professional communication
Mar 8	Viread	Viread (tenofovir disoproxil fumarate) conditional marketing authorization — Gilead Sciences Inc. — notice of compliance with conditions (NOC/c)
Feb 20	Viramune	Important new safety information clarifying risk factors for severe, life-threatening and fatal hepatotoxicity with Viramune (nevirapine) — Boehringer Ingelheim (Canada) Ltd. — health professional communication
Jan 22	Tazocin	Association of Tazocin (piperacillin/tazobactam) with false positive results of the Bio-Rad *Aspergillus* Assay — Wyeth Pharmaceuticals Canada — health professional communication

To receive the Newsletter and health product Advisories free by email, join Health Canada's ***Health_Prod_Info*** mailing list. ***Go to*** **www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/subscribe_e.html**.

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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.