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Programme des produits thérapeutiques

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Canadian Adverse Drug Reaction Newsletter

In this issue:

New influenza drugs zanamivir (Relenza™) and oseltamivir (Tamiflu™): unexpected serious reactions

Neuraminidase inhibitors represent a new class of antiviral agents that inhibit neuraminidase, an enzyme essential for the replication of influenza A and B viruses.[1,2] Zanamivir (Relenza™) and oseltamivir phosphate (Tamiflu™), approved for sale in Canada in November 1999 and December 1999 respectively, are indicated for the treatment of uncomplicated acute illness due to influenza virus in people 12 years of age or older who have not been symptomatic for more than 2 days.[3,4] Zanamivir is supplied as a powder for inhalation via a Diskhaler™.[3] Oseltamivir is available in capsule form for oral use.[4]

From Nov. 2, 1999, to June 30, 2000, the Canadian Adverse Drug Reaction Monitoring Programme (CADRMP) received 16 domestic reports of suspected adverse reactions to zanamivir. Six reports were classified as serious and unexpected (Table 1).[5]

One death associated with the use of zanamivir was reported. The patient, a 52-year-old man with cardiomyopathy, was taking carvedilol, warfarin, digoxin, enalapril and spironolactone concomitantly. About 2 days after starting zanamivir, he was admitted to the hospital in acute renal failure. The creatinine levels were reported to be 81 Fmol/L in the month before zanamivir

administration and 600 Fmol/L on hospital admission (normal range 50–110 Fmol/L[6]) (units not specified in original report, presumably Fmol/L). The patient was treated in hospital with intravenous furosemide therapy and underwent dialysis. Blood cultures were subsequently found to be positive for *Staphylococcus aureus*. The patient died the day following hospital admission.

From Dec. 23, 1999, to June 30, 2000, the CADRMP received 9 domestic reports of suspected adverse reactions to oseltamivir, of which 8 were classified as serious. Seven of the serious reports included reactions classified as unexpected (Table 2).

One death associated with the use of oseltamivir was reported. A 58-year-old man with a history of asthma was admitted to hospital with pulmonary difficulties and hemorrhagic rash 3 days after starting oseltamivir. He was reported to have been unwell with influenza and myalgia for one week with shortness of breath, fever, laryngitis, cough and purulent nasal secretions. The patient was taking prednisone concomitantly. On admission his heart rate and serum creatinine and creatine kinase levels were elevated. His blood pressure was 100/60 mm Hg and temperature 38.8^{O}C. The patient was given intravenous imipenem and other antibiotics. Within 5 hours of hospital admission the patient experienced cardiac arrest, required intubation but died. A culture showed staphylococcal pneumonia. On autopsy the cause of death was determined to be septic shock.

The reports received at the CADRMP for these antiviral drugs lacked information to indicate whether laboratory tests such as virus cultures or serology were conducted to confirm the diagnosis of influenza in these patients.

In January 2000 the US Food and Drug Administration (FDA) issued a Public Health Advisory highlighting points to consider when prescribing influenza drugs.[7] Caution was advised when prescribing zanamivir to patients with underlying asthma or chronic obstructive pulmonary disease. The FDA received several reports of deterioration of respiratory function (e.g., bronchospasm, respiratory arrest) following inhalation of zanamivir in patients with these conditions. If zanamivir is prescribed to patients with underlying airway disease, the FDA recommends the use of careful monitoring, proper observation and appropriate supportive care, including the availability of short-acting bronchodilators. These views are also reflected in the Canadian product information for Relenza™.[3] The advisory also cautioned prescribers of the need to continue evaluation of patients receiving antiviral agents to identify those in whom primary or concomitant bacterial infection could occur. Vaccination remains the primary method of preventing and controlling influenza. The product monographs for both Relenza™ and Tamiflu™ caution that the use of these products should not affect the evaluation of individuals for annual influenza vaccination.[3,4]

A Dear Health Care Professional letter was issued in Canada by the manufacturer of Relenza™ on July 11, 2000,[8] stating that “reports of bronchospasm and decline in respiratory function among patients without evidence of underlying airways disease have also been received.” Along with the July 2000 US Relenza Drug Warning,[9] it also reminded prescribers that:

- the safety and efficacy of the drug have not been shown in patients with underlying respiratory disease; and
- the drug should be stopped if bronchospasm or a decline in lung function develops.

Neuraminidase inhibitors have been available for a relatively short time and typically would only be prescribed for a limited period each year. The safety profile of a new drug evolves with time, particularly as it is used in different patient populations with a variety of pre-existing conditions and taking a variety of other medications. As this year's influenza season approaches, health care professionals are requested to continue reporting any suspected reactions associated with these products to further establish their safety profiles.

Written by: Lynn Macdonald, BSP, Bureau of Licensed Product Assessment.

References

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8. *Dear Health Care Professional Letter: Important safety information for Relenza™*. Mississauga (ON): Glaxo Wellcome, 2000 Jul 11.
9. *Important revisions to safety labeling for Relenza™ (zanamivir for inhalation)*. Research Triangle Park (NC): Glaxo Wellcome, 2000 Jul 10. Available: www.fda.gov/medwatch/safety/2000/relenz.htm (accessed 2000 Aug 15).

Table 1: Unexpected adverse reactions to zanamivir (Relenza™) from 6 serious* reports submitted to the CADRMP between Nov. 2, 1999, and June 30, 2000

Case	Age/sex	Reported reactions	Outcome†	Medical history/comments
1	52/M	Acute renal failure, increased serum creatinine level, hyperkalemia, hypotension	Died	Cardiomyopathy. Positive blood culture for *Staphylococcus aureus.* Concomitant medications: carvedilol, warfarin, digoxin, enalapril and spironolactone
2	70/F	Allergic reaction, laryngitis, laryngospasm	Not yet recovered	Multiple unspecified allergies. Concomitant medications: antibiotics
3	41/M	Bronchospasm, hypoxemia, rales, hoarseness	Recovered	Bronchitis
4	71/F	Angioedema	Recovered	Asthma. Concomitant medications: fluticasone, lisinopril and salbutamol
5	NA/F	Bone marrow aplasia	Unknown	Reaction developed 4 months after zanamivir use
6	6/M	Hypoglycemia, hypotension, unconsciousness	Unknown	Concomitant medications: salbutamol inhaler, beclomethasone inhaler, guaifenesin. Decreased sleep and food intake

Note: CADRMP = Canadian Adverse Drug Reaction Monitoring Programme, NA = not available.
*Serious, as defined in the *CADRMP Guidelines for the Voluntary Reporting of Adverse Drug Reactions by Health Care Professionals.*[5]
†At the time of reporting.

Table 2: Unexpected adverse reactions to oseltamivir (Tamiflu™) from 7 serious* reports submitted to the CADRMP between Dec. 23, 1999, and June 30, 2000

Case	Age/sex	Reported reactions	Outcome†	Medical history/comments
1	58/M	Cardiac arrest, sepsis, increased creatinine and creatine kinase levels, hemorrhagic rash, pneumonia	Died	Asthma. Culture showed staphylococcal pneumonia. Concomitant medication: prednisone
2	NA/M	Hepatitis, jaundice, abnormal liver function test results, bronchopneumonia	Recovered	No information provided
3	62/F	Increased AST, ALT, alkaline phosphatase and LDH levels	Recovered	Pneumonia, meningitis, myocardial ischemia, pulmonary edema, hypokalemia, pulmonary stasis. Septic condition ongoing at time oseltamivir was started. Concomitant medications: acetaminophen, ipratropium, salbutamol, furosemide, heparin, potassium chloride, ranitidine, midazolam, Timentin®, Empracet®
4	NA/F	Acute renal failure, hyperkalemia	Unknown	No information provided
5	50/F	Acute renal failure, anemia, pneumonia	Not yet recovered	Azithromycin (other suspected drug)
6	35/F	Acute pancreatitis	Recovered	Concomitant medication: prednisone
7	29/M	Anaphylactic reaction, erythema, tremor	Unknown	No information provided

Note: AST = aspartate aminotransferase, ALT = alanine aminotransferase, LDH = lactate dehydrogenase.
*Serious, as defined in the *CADRMP Guidelines for the Voluntary Reporting of Adverse Drug Reactions by Health Care Professionals*.[5]
†At time of reporting.

Intravenous Rh_O [D] immune globulin [human] (WinRho SDF™): suspected hemolytic/renal adverse reactions

WinRho SDF™ (Rh_O [D] immune globulin [human]) is indicated for:

- the prevention of Rh immunization of Rh_O (D)-negative women at risk for Rh antibodies;
- the prevention of alloimmunization in Rh_O (D)-negative individuals transfused with Rh_O (D)-positive red blood cells or blood components;
- the treatment of destructive thrombocytopenia of an immune etiology in situations where platelet counts must be increased to control bleeding; and
- the treatment of nonsplenectomized Rh_O (D)-positive children and adults with chronic or acute immune thrombocytopenic purpura (ITP) or with ITP secondary to HIV infection in clinical situations requiring an increase in platelet count to prevent excessive hemorrhage.[1]

WinRho SDF™ has been associated with rare reports of acute onset of hemoglobinuria consistent with intravascular hemolysis (IVH) and accompanied by reversible acute renal impairment.[1] Since April 1996, 41 cases of suspected IVH have been reported to the US Food and Drug Administration after the administration of WinRho SDF™ to ITP patients positive for Rh_O (D) antigen (D-positive). Important prescribing information issued by the manufacturer may be obtained on the MedWatch Web site.[2] All reported cases occurred in the United States except for one case from Canada.

The Canadian case occurred in a 61-year-old man with chronic ITP, autoimmune hemolytic anemia and chronic lymphocytic leukemia. Within 2 hours of receiving a second dose of WinRho SDF™ his hemoglobin concentration dropped to 47 g/L (normal range 115–155 g/L), with a concomitant rise in the bilirubin level to 150 Fmol/L (normal range 2–18 Fmol/L) and the lactate dehydrogenase level to 698 U/L (normal range 50–150 U/L). The patient received supportive therapy but remained anemic and thrombocytopenic.

As a result of these reports a Dear Health Care Professional letter is being issued with all shipments of WinRho SDF™ through the Canadian Blood Services and Héma-Québec. Practitioners are advised that all Rh_O (D)-positive ITP patients treated with WinRho SDF™ be monitored for signs and symptoms of IVH, including decreased hemoglobin concentration and hemoglobinuria, compromising anemia and renal insufficiency.

The occurrence of IVH is currently referenced in the product monograph and package insert for WinRho SDF™ under the "Adverse Reactions/Treatment of ITP" section.[1]

Written by: Catherine Parker, BSc, Bureau of Biologics and Radiopharmaceuticals

References

1. WinRho SDF™ (Rh_O [D] immune globulin [human]): passive immunizing agent [product monograph]. Winnipeg: Cangene Corporation; 1998 Aug 24.
2. *MedWatch: Important prescribing information*. Rockville (MD): US Food and Drug Administration. Available: www.fda.gov/medwatch/safety/2000/winrho.html (accessed 2000 Aug 15).

Abboject® Unit-of-Use Syringe: reports of malfunction

The CADRMP and the Bureau of Compliance and Enforcement, Therapeutic Products Programme, received 10 serious reports of syringe failure of Atropine Sulfate Injection USP in Abboject® between December 1998 and January 2000. The Abboject® Unit-of-Use Syringe is used to dispense various drugs, including atropine and epinephrine, which are used as a last recourse in emergency situations. Although the number of reported events of syringe failure (needle entry in the side wall of the stopper, plunger would not depress, air blockage of syringe) resulting in the inability or delay in the release of the drug is small, an increase in the number of reported events was noted. Investigations have shown this problem to occur more in Canada than in the United States. Upon going to press we were informed of Abbott's intentions to modify the Canadian labelling, to provide clearer procedures for activation of syringes. Specific instructions will be provided for reinsertion if the first attempt to activate the mechanism fails.

The evaluation of the effectiveness of these measures will be enhanced if health care professionals report to the CADRMP any syringe malfunction encountered during the use of Atropine Sulfate Injection USP, Epinephrine Injection USP or other parenteral drugs administered with the Abboject® Unit-of-Use Syringe.

Written by: Francine Jacques, BSc, Bureau of Compliance and Enforcement

COMMUNIQUÉ

The CADRMP wishes to provide feedback and increase awareness of recently reported ADRs. The following cases have been selected on the basis of their seriousness, or the fact that the reactions do not appear in the official Canadian product monograph. (Reactions are expressed based on the "preferred term" in the World Health Organization *Adverse Reaction Dictionary*.)

Glucosamine sulfate: hyperglycemia
Unexpected increases in blood glucose levels occurred in diabetic patients using glucosamine sulfate or glucosamine with chondroitin orally.

Ketotifen (Zaditen®): sleep apnea
Sleep apnea was reported in a 7-month-old boy receiving ketotifen for asthma prophylaxis. Sleep apnea abated when ketotifen was discontinued (positive dechallenge).

Diclofenac (Voltaren Ophtha®) and ketorolac tromethamine (Acular®): corneal ulceration
Corneal ulceration was reported with the use of diclofenac ophthalmic drops for 7 weeks. Another case involved the concomitant use of ketorolac and diclofenac ophthalmic drops following a cataract extraction.

DRUGS OF CURRENT INTEREST

The purpose of the Drugs of Current Interest (DOCI) list is to stimulate reporting for a selected group of marketed drugs in order to identify drug safety signals. The maintenance of this list by the CADRMP facilitates regular monitoring and constitutes one element of post-approval assessment activities.

abacavir (Ziagen™)
alteplase (Activase® rt-PA)
bupropion (Zyban®, Wellbutrin SR®)
celecoxib (Celebrex™)
clopidogrel (Plavix™)
delavirdine (Rescriptor™)
Factor VII-recombinant, activated (NiaStase™)
Hypericum perforatum (St. John's wort)
indinavir (Crixivan®)
mefloquine (Lariam®)
naratriptan (Amerge®)
nevirapine (Viramune®)
oseltamivir (Tamiflu™)
ritonavir (Norvir®)
rituximab (Rituxan®)
rofecoxib (Vioxx™)
rosiglitazone (Avandia™)
saquinavir (Invirase™)
sildenafil (Viagra™)
terbinafine (Lamisil®)
trastuzumab (Herceptin®)
trovofloxacin (Trovan™)
zanamivir (Relenza™)
zolmitriptan (Zomig®)

If you have observed any suspected ADRs with the drugs in the Communiqué or the DOCI list, *please report them* to the :

Canadian Adverse Reaction Monitoring Program (CADRMP)
Bureau of Licensed Product Assessment
AL: 0201C2, Ottawa, ON K1A 1B9
Tel: (613) 957-0337 Fax: 613 957-0335
cadrmp@hc-sc.gc.ca
or to a participating regional ADR centre.

The ADR form is available from the *Compendium of Pharmaceuticals and Specialties* and the National and Regional ADR Centres, and at:

http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf
http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/guides/adr/adr_guideline_e.pdf

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Other provinces and territories
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Canada

Please Note: A voluntary reporting system thrives on intuition, lateral thinking and open mindedness. Most adverse drug reactions (ADRs) can only be considered to be suspicions, for which a proven causal association has not been established. Because ADRs are under reported and because a definite causal association cannot be determined, spontaneous ADR reports cannot be used to estimate the incidence of adverse reactions. ADRs are nevertheless valuable as a source of potential new and undocumented signals. Health Canada does not assume liability for the accuracy or authenticity of the ADR information contained in the newsletter articles. Furthermore, the Therapeutic Products Programme monitors and assesses suspected ADRs as a means of continuously evaluating drug safety profiles. Regulatory decisions are not made within the context of this newsletter.

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