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Canadian Adverse Drug Reaction Newsletter

Therapeutic Products Programme

In this issue:

Alteplase (Activase® rt-PA) for acute ischemic stroke: special precautions for new indication

Alteplase is a serine protease that binds to fibrin in a thrombus or blood clot resulting in conversion of plasminogen to plasmin and initiation of local fibrinolysis. Alteplase has been approved in Canada since 1987 for the management of acute myocardial infarction.

On Feb. 16, 1999, the Therapeutic Products Programme (TPP) approved the drug Activase® rt-PA (alteplase) in accordance with the Notice of Compliance with Conditions policy, which was issued on May 28, 1998, for the management of acute ischemic stroke in adults to improve neurological recovery and reduce the incidence of disability. The purpose of the Notice of Compliance with Conditions Policy is to provide earlier access to promising new drugs to patients suffering from serious, life-threatening or severely debilitating diseases or conditions and to create a mechanism to ensure that the manufacturer conducts confirmatory studies to establish the link between anticipated and real benefit.

Under the conditions specifically associated with the approval of Activase® rt-PA, the Canadian sponsor Hoffmann-La Roche Limited has committed to the following:

- To develop and implement a physician education plan concerning proper use of the drug in the treatment of stroke.
- To conduct a general mailing to all Canadian Board-certified neurologists and heads of emergency medicine departments reinforcing the key conditions for drug administration in the management of stroke.
- To report the results of safety monitoring and post-marketing studies at specified times to the TPP.
- To support a study to try to identify stroke patients who would benefit most from treatment with alteplase.

The use of alteplase in acute ischemic stroke increases the risk of intracranial hemorrhage.<1> Data from the most favourable clinical study showed that the incidence of intracranial hemorrhage in patients with acute ischemic stroke was higher in the alteplase group than in the placebo group (6.4% v. 0.6% within 36 hours of administration).<1,2> There was, however, no difference in the overall rate of death at day 90 between the 2 groups, although there was a trend toward a higher death rate among patients with severe stroke in the alteplase group than among those in the placebo group.<1> Doses greater than 0.9 mg/kg may be associated with an increased risk of intracranial hemorrhage. Therefore, a dose of 0.9 mg/kg (maximum 90 mg) should not be exceeded when used in stroke treatment.<1>

The use of alteplase in the treatment of stroke is limited to the following situations:

- Physicians must be experienced in acute stroke management, and be treating patients in a hospital setting equipped with appropriate laboratory facilities to follow the neurological and hematological status of the patient.<1>
- Treatment should be started only within the first 3 hours after the onset of stroke symptoms, and only after exclusion of intracranial hemorrhage by a cranial CT scan or other diagnostic imaging method sensitive for the presence of hemorrhage.<1> *Treatment started more than 3 hours after the onset of symptoms is not recommended.* Few patients (< 10%) present to hospital emergency departments within 3 hours after onset of stroke symptoms.<3>

- Treatment is contraindicated in situations where the risk of bleeding is increased, including recent surgery, head trauma or previous stroke, active internal bleeding, anticoagulant use, low platelet count (less than 100 × 10^9/L) or uncontrolled hypertension (e.g., systolic pressure greater than 185 mm Hg or diastolic pressure greater than 110 mm Hg).<1,2>

A separate, comprehensive product monograph pertaining only to the use of alteplase in the treatment of stroke has been prepared.<1>

This Notice of Compliance with Conditions is subject to revocation if the above-mentioned conditions are not met, or result in data indicating that the risks of treatment outweigh the benefits in stroke patients.

Written by: Catherine Parker, BSc, and Harold Rode, PhD, Bureau of Biologics and Radiopharmaceuticals.

References

1. *Activase rt-PA®, alteplase: lyophilized powder for injection* [product monograph for acute ischemic stroke indication]. Mississauga (ON): Hoffmann–La Roche Limited; Feb 1999.
2. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581-7.
3. Grotta J. T-PA — the best current option for most patients. *N Engl J Med* 1997;337:1310-2.

Acute thrombocytopenia after abciximab (ReoPro™) therapy

Platelet- and thrombin-mediated thromboses contribute to the abrupt artery closure and acute ischemic complications that may follow percutaneous coronary intervention. Abciximab (ReoPro™), approved in Canada since 1996, is a potent antiplatelet agent that is increasingly being used to prevent ischemic complications of percutaneous coronary revascularization. Abciximab binds to the platelet glycoprotein IIb/IIIa receptor and inhibits platelet aggregation.

Thrombocytopenia (platelet count less than 100 x 10^9/L), including acute profound thrombocytopenia (platelet count variously defined as below 20–40 x 10^9/L), has been reported to occur with this agent.<1–4> The mechanism of profound thrombocytopenia following abciximab therapy is not clearly understood.<2,4> The risk of acute profound thrombocytopenia is estimated to be about 0.5% (95% confidence interval 0.01%-1.1%).<2>

Review of the literature documenting abciximab-induced acute thrombocytopenia provides limited information as to the timeframe over which this adverse reaction can occur, and indicates that it generally occurs within the first 24 hours of infusion.<1-3> More recently, Berkowitz and associates<4> reported 2 cases in which baseline platelet counts were normal and acute profound thrombocytopenia was documented within 2 hours of infusion of abciximab.

Between July 29, 1997, and Mar. 18, 1999, the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) received 21 case reports of individuals experiencing adverse reactions associated with the use of abciximab. In 15 the adverse reaction was described as thrombocytopenia. One of the 15 patients died, with the cause of death attributed to intracranial bleeding; the report indicated that the baseline platelet count was normal 4 days before the start of abciximab therapy, and within 3 hours of the initial infusion of the drug, the platelet counts were reported as not countable.

The remaining 14 cases were reviewed to assess the rapidity of onset and the severity of thrombocytopenia. In 3 cases acute profound thrombocytopenia (platelet counts 6–40 × 10^9/L) was documented as occurring between 2 and 4 hours after the initiation of abciximab therapy. In 9 cases thrombocytopenia (platelet counts 5–65 × 10^9/L) was documented, but the onset after the start of abciximab therapy was less rapid (11 hours to 5 days). The baseline platelet counts, which were generally obtained within 72 hours before infusion of abciximab, were within normal limits in all 12 cases. Two reports did not provide sufficient detail regarding platelet monitoring to allow for assessment.

The dosage regimens used in the majority of the 15 cases generally appear to be in keeping with that recommended in the product monograph.<5>

In conclusion, abciximab therapy is well documented in the literature to be associated with the occurrence of acute and occasionally profound thrombocytopenia within 24 hours after the start of therapy. The product monograph currently labels thrombocytopenia as a risk of therapy and recommends that platelet counts be monitored 2-4 hours after the bolus dose of abciximab.<5> The objective of this report is to heighten physicians' awareness of the potential for acute profound thrombocytopenia to occur very rapidly after the start of abciximab therapy and to confirm the importance of monitoring the platelet count early in the course of treatment. Institution of platelet monitoring as early as 2 hours after the bolus dose may provide the greatest opportunity to diagnose, monitor and, if necessary, introduce therapy for rapidly evolving episodes of thrombocytopenia.

Written by: Mary Jean Beddall, MD, Bureau of Drug Surveillance.

References

1. Berkowitz SD, Harrington RA, Rund MM, Tcheng JE. Acute profound thrombocytopenia after c7E3Fab (abciximab) therapy. *Circulation* 1997;95(4):809-13.
2. Ferrari E, Thiry M, Touati C, Gibelin P, Baudouy M. Acute profound thrombocytopenia after c7E3 Fab therapy. *Circulation* 1997;96(10):3809-10.
3. Kereiakes DJ, Essell JH, Abbottsmith CW, Boderick TM, Runyon JP. Abciximab-associated profound thrombocytopenia: therapy with immunoglobulin and platelet transfusion. *Am J Cardiol* 1996;78(10):1161-3.
4. Berkowitz SD, Sane DC, Sigmon KN, Shavender J, Harrington RA, Tcheng JE, et al. Occurrence and clinical significance of thrombocytopenia in a population undergoing high-risk percutaneous coronary revascularization. *J Am Coll Cardiol* 1998;32(2):311-9.
5. ReoPro™ (abcimixab); solution for intravenous injection; chimeric monoclonal antiplatelet antibody [product monograph]. Leiden [Netherlands]: Centocor; 1998. [Distributed in Canada by Eli Lilly Canada Inc.]

Hepatotoxicity associated with nefazodone (Serzone®)

Nefazodone hydrochloride (Serzone®) is an antidepressant agent that has been approved for use in Canada since Apr. 27, 1994. During postmarketing surveillance, hepatic adverse reactions such as jaundice, hepatitis, hepatic necrosis and hepatic failure have been reported in patients receiving therapeutic doses of nefazodone.<1,2> On occasion, these events resulted in liver transplantation and/or death.

Clinical manifestations of hepatic injury in patients receiving nefazodone have included the following: anorexia, fatigue, asthenia, abdominal pain, nausea, vomiting, discoloured stools, dark urine, coagulopathy, weight loss, myalgia, rash, pruritus, jaundice, ascites, confusion, asterixis, encephalopathy and hepatic coma.<1,2> Laboratory evidence of hepatotoxicity has included elevated levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl-transferase and bilirubin, as well as increased prothrombin times.<1,2> The majority of these events occurred within the first 9 months of treatment.

As of Mar. 18, 1999, the CADRMP has received 9 reports of symptomatic hepatic dysfunction associated with the use of nefazodone (Table 1).

In addition to these 9 cases, 4 events of asymptomatic liver enzyme elevations have been reported in temporal association with nefazodone use.

Health Canada continues to analyse these adverse reactions and requests that health care professionals continue to report any suspect adverse drug reactions in association with the use of nefazodone.

References

1. Aranda-Michel J, Koehler A, Bejarano PA, Poulos JE, Luxon, BA, Khan CM, et al. Nefazodone-induced liver failure: report of three cases. *Ann Intern Med* 1999;130:285-8.
2. Nefazodone — looks like an SSRI, but ... hepatic dysfunction ... visual disorders. *Aust Adverse Drug React Bull* 1998;14(4):14.

Table 1: Details of 9 reports of symptomatic hepatic dysfunction associated with nefazodone

Case	Age/ sex	Dose at time of event and duration of treatment	Concomitant medications	Signs, symptoms and biopsy findings	Laboratory test results*	Intervention	Outcome†
1	42/F	150 mg/d x 5 wk	Zopiclone, norethindrone, ethinylestradiol, sertraline x 9 d (1 wk after nefazodone discontinued)	Maculopruritic rash, abdominal pain, nausea, vomiting, conjunctival icterus; biopsy showed drug-induced hepatitis with secondary intrahepatic cholestasis	AP 256 U/L, total bilirubin 247 µmol/L	Nefazodone and sertraline discontinued, patient admitted to hospital	Positive dechallenge
2	53/F	100 mg bid x 3 mo	Clonazepam, flurazepam, trimethotrimeprazine	Nausea, vomiting, epigastric pain, hepatic cytolysis	AST 500 U/L, ALT 450 U/L, AP 343 U/L	Nefazodone discontinued	Positive dechallenge
3	47/F	150 mg every morning, 300 mg every night x 7–8 mo	Synthroid, Tylenol #3 as needed	After 5–6 mo: nausea, weight loss (11–14 kg), increased fatigue, hair loss After 7–8 mo: anorexia, nausea, vomiting, further weight loss (2–4kg), jaundice, scleral icterus	AST 500–700 U/L, ALT 600–900 U/L, GGT 80 U/L, bilirubin 200–300 µmol/L, AP 150-200 U/L, negative for hepatitis virus A, B and C	Patient admitted to hospital, nefazodone discontinued, prednisone initiated	Jaundice resolved, liver enzyme levels (except AP) returned to normal
4	30/F	150 mg bid x 4 wk	None	Jaundice	ALT 2258 U/L, negative for hepatitis virus A, B and C	Nefazodone discontinued 1 wk after onset of jaundice	Positive dechallenge ALT returned to normal
5	68/F	50 mg bid x 6–7 mo	Conjugated estrogens, medroxyprogesterone	Anorexia, weight loss (10.4 kg), fatigue, hepatitis, slight icterus	AST 375 U/L, ALT 420 U/L, bilirubin 34 µmol/L	Nefazodone discontinued 3 wk after onset of symptoms, concomitant medications continued	Positive dechallenge
6	50/F	NA 5–6 mo	NA	Jaundice, hepatitis confirmed by liver biopsy, liver necrosis	Abnormal liver function test results	Patient admitted to hospital, nefazodone discontinued	Positive dechallenge
7	26/F	150 mg bid at 4 mo; 150 mg/d at 8 mo x 8 mo	Oral contraceptive	Jaundice, nausea, fatigue, dark urine	NA	Nefazodone reduced after first onset of symptoms (at 4 mo); discontinued after second onset (at 8 mo)	Positive dechallenge
8	NA	NA	NA	Jaundice	NA	Nefazodone discontinued	Positive dechallenge
9	35/F	150 mg bid x 4 wk	NA	Nausea	AST 620 U/L, ALT 1044 U/L, negative for hepatitis virus A, B and C	Nefazodone discontinued	Positive dechallenge

Note: NA = information not available, AP = alkaline phosphatase, AST = aspartate aminotransferase, ALT = alanine aminotransferase, GGT = gamma-glutamyl-transferase.
*Normal ranges vary among laboratories; however, typical reference values are as follows: ALT< 50 U/L, AST < 40 U/L, total bilirubin < 25 µmol/L, GGT < 49 U/L and AP < 125 U/L.
†Dechallenge = outcome after drug discontinued.

COMMUNIQUÉ

The purpose of this section is to increase awareness of ADRs recently reported to the CADRMP. The following cases have been selected on the basis of their seriousness, or the fact that the reactions do not appear in the product monograph. They are intended to prompt reporting. (The terminology used for expressing reactions is based on the World Health Organization's Adverse Reaction Dictionary using the "preferred term.")

Amlodipine (Norvasc™): hearing loss
Sudden hearing loss with residual effects was reported during amlodipine therapy.

If you have observed comparable cases or any other serious events, *please report them* to the Adverse Drug Reaction Reporting Unit, Continuing Assessment Division, Bureau of Drug Surveillance, AL 0201C2, Ottawa ON K1A 1B9; fax 613 957-0335; or to a participating regional ADR centre.
The ADR form is available at:
www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf

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Please Note: A voluntary reporting system thrives on intuition, lateral thinking and openmindedness. For these reasons, most adverse drug reactions (ADRs) can be considered only to be suspicions, for which a proven causal association has not been established. Because there is gross underreporting of ADRs and because a definite causal association cannot be determined, this information cannot be used to estimate the incidence of adverse reactions. ADRs are nevertheless invaluable as a source of potential new and undocumented signals. For this reason, Health Canada does not assume liability for the accuracy or authenticity of the ADR information contained in the newsletter articles.

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