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Canadian Adverse Drug Reaction Newsletter

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Thioridazine (Mellaril) and mesoridazine (Serentil): prolongation of the QTc interval

Thioridazine and mesoridazine are phenothiazines used as tranquilizers or antipsychotic drugs. On July 31 and Sept. 22, 2000, Novartis Pharmaceuticals Canada Inc. issued a notice to health care professionals advising them that *Mellaril and Serentil has been shown to prolong the QTc interval in a dose related manner,[1,2] and that drugs with this potential, including Mellaril and Serentil, have been associated with torsade de pointes-type arrhythmias and sudden death.[1,2]*

Novartis Pharmaceuticals Canada Inc., in consultation with Health Canada, therefore recommends Mellaril and Serentil *only* for schizophrenic patients who fail to show an acceptable response to adequate treatment with other antipsychotic drugs, either because of insufficient effectiveness or the inability to achieve an effective dose because of intolerable adverse effects.[1,2] The use of thioridazine is now contraindicated in association with certain drugs such as fluvoxamine, propranolol, pindolol and any drug that inhibits the cytochrome P_{450} 2D6 isozyme (e.g., fluoxetine and paroxetine).[1] Thioridazine and mesoridazine are also contraindicated in association with drugs known to prolong the QTc interval (e.g., quinidine).[1,2]

Patients with congenital long QT syndrome or a history of cardiac arrhythmias should not receive thioridazine or mesoridazine.[1,2] Also, patients with reduced levels of the cytochrome P_{450} 2D6 isozyme[1] should not receive thioridazine.

An ECG and measurement of serum potassium levels are recommended before starting treatment with thioridazine or mesoridazine, and it may be useful to repeat these tests periodically during

treatment.[1,2] Patients with a QTc interval greater than 450 msec should not receive these drugs, and if the QTc interval is greater than 500 msec, treatment with thioridazine or mesoridazine should be discontinued.[1,2]

Similar measures have been taken in the United States.[3,4] Further information about the effect of thioridazine on the QTc interval, in the context of a study on ziprasidone (Zeldox) and other antipsychotic drugs, has been published by the Psychopharmacological Drugs Advisory Committee of the US Food and Drug Administration in the Briefing Information document of July 19, 2000 (http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3619b1.htm).

The Therapeutic Products Programme also posts public health advisories on its Web site at the addresses shown in references 1 and 2 below.

Written by: Susie Dallaire, BPharm, Program coordinator, Québec ADR Regional Centre.

References

1. *Important drug warning: Mellaril.* Dorval (QC): Novartis Pharmaceuticals Canada Inc., 2000 July 31. Available: http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/notices/mellaril_e.pdf
2. *Important drug warning: Serentil.* Dorval (QC): Novartis Pharmaceuticals Canada Inc., 2000 Sept 22. Available: http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/notices/serentil_e.pdf
3. Food and Drug Administration, US Department of Health and Human Services. Important drug warning [Mellaril]. [Retyped text of a letter from Novartis Pharmaceuticals Corporation, East Hanover, NJ, 2000 July 7.] Available: www.fda.gov/medwatch/safety/2000/mellar.htm
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Newsletter's 10th anniversary!

This edition marks the 10th anniversary of the Canadian Adverse Drug Reaction Newsletter. The first issue was produced by Dr. W. Curt Appel and Lori J. Anderson of the Bureau of Pharmaceutical Surveillance in January 1991. The newsletter's main objectives are to provide regular feedback on adverse drug reactions (ADRs) reported in Canada and to communicate important drug safety information to health professionals and individuals interested in the area of post-approval surveillance of drugs. We thank all those who have contributed to this newsletter and welcome suggestions to improve future issues of this newsletter. Your comments may be directed to the Editors, at the national address indicated on the last page.

Clopidogrel (Plavix): hematological reactions

Clopidogrel (Plavix), a thienopyridine derivative structurally similar to ticlopidine, is a specific inhibitor of adenosine diphosphate (ADP)-induced platelet aggregation. Clopidogrel is indicated for the secondary prevention of vascular ischemic events (myocardial infarction, stroke, vascular death) in patients with a history of symptomatic atherosclerotic disease.[1]

Recent revisions to the Plavix product monograph warn of the possibility of thrombotic thrombocytopenic purpura (TTP) occurring rarely following the use of clopidogrel.[1] TTP is a serious condition requiring prompt treatment with plasmapheresis.[1] In a study examining 11 cases of TTP associated with clopidogrel,[2] TTP was shown to appear earlier with clopidogrel (as early as 3 days in 2 cases) than with ticlopidine; all except 1 of the 11 cases occurred within the first 2 weeks of initiation of treatment. The authors have suggested that the mechanism causing TTP may be different for the 2

drugs. Another author has estimated that the observed rate of TTP among clopidogrel recipients is no higher than that expected in the general population (about 3.7 cases per million population).[3]

The concern over TTP and clopidogrel prompted the Canadian Adverse Drug Reaction Monitoring Programme (CADRMP) to review the Canadian reports. Between Oct. 31, 1998, when clopidogrel was first marketed in Canada, and Aug. 31, 2000, the CADRMP received 61 domestic reports of suspected ADRs associated with clopidogrel; 51 were classified as serious.[4] The average age of patients was 70 years; 46% were women and 46% men (sex unknown in 8%).

Three of the 61 patients died. One death was associated with intracranial hemorrhage. The other 2 causes of death (myocardial infarction, cancer) were reported to be unrelated to clopidogrel.

A closer look at the suspected hematological reactions revealed 17 reports with disorders of blood components, particularly white blood cell and platelet disorders (Table 1). Although there were 11 reports of thrombocytopenia and 1 of pancytopenia, there was none of TTP in Canada.

The use of cholesterol-lowering agents, particularly the statins such as simvastatin and atorvastatin, has also been suggested to play a role in the occurence of TTP, and the possibility of adverse pharmacologic interactions with clopidogrel deserves further study.[2,5] Three reports of thrombocytopenia indicated concomitant use of cholesterol-lowering statins (Table 1, cases 13, 15 and 16).

Most of the reports of hematological reactions described elderly patients with underlying cardiovascular disease taking concomitant medications. Twelve of the 17 patients were taking multiple anticoagulant or antiplatelet medications, including ASA (Table 1). Confounding factors of age, disease and concomitant medications make interpretation of the adverse reaction data difficult. Additional studies and continual ADR reporting are required to elucidate a clearer pattern of potential risks of TTP associated with clopidogrel.

Written by: Heather Dunlop, BNSc, MLIS, Bureau of Licensed Product Assessment.

References

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Table 1: Reports of hematolgical reactions associated with clopidogrel submitted to the CADRMP between Oct. 31, 1998, and Aug. 31, 2000

Case	Age/sex	Reported reactions*	Time to onset	Outcome†	Medical history/ comments	Cosuspect‡ and concomitant drugs
1	73/M	Disseminated intravascular coagulation (DIC), hematoma	48 h	Recovered	Hypertension, hypercholesterolemia. Carotid endarterectomy complicated by stroke before clopidogrel therapy. Hematomas considered symptom of DIC	Concomitant: bisacodyl, Colace, Losec, metoprolol, Monopril
2	74/M	Pancytopenia, myeloproliferative disorder	4 d	Not yet recovered	Diabetes mellitus, congestive heart failure. Treated with clopidogrel after angioplasty with stent. Pancytopenia may have predated clopidogrel therapy	Concomitant: furosemide, glyburide, lisinopril, metformin
3	94/M	Thrombocytopenia, anemia, leucopenia, purpura	31 d	Recovered	Hypertension, coronary artery disease, osteoarthritis, myocardial infarction, benign bladder tumour	Concomitant: ASA, diltiazem, heparin, metoprolol, Monopril, nifedipine, Nitro-Dur, ranitidine
4	64/M	Agranulocytosis	19 d	Recovered	Neutropenia associated with Ticlid 1 mo before use of clopidogrel. Dialysis for unspecified reason	Concomitant: acebutolol, acetaminophen, ASA, alprazolam, cefazolin, erythropoietin, folic acid, furosemide, hydroxyzine, iron dextran, loperamide, losartan, metoclopramide, morphine, nitroglycerin, oxazepam, sertraline, Ticlid, zopiclone others§
5	73/F	Agranulocytosis	41 d	Recovered	Received clopidogrel after angioplasty	Concomitant: amlodipine, ASA enteric coated, calcium, Lipitor, vitamin D
6	NA/M	Granulocytopenia	4 mo	Not yet recovered	Positive dechallenge	NA
7	NA/M	Granulocytopenia	NA	Not yet recovered	Positive dechallenge	NA
8	71/M	Thrombocytopenia, myocardial infarction, coronary thrombosis	7 d	Died; drug may have been contributory	Smoking, hyperlipidemia, myocardial infarction, hypertension. Current condition: myocardial infarction attributed to coronary thrombosis that was attributed to stent. Thrombocytopenia likely not due to clopidogrel because drug was started after thrombocytopenic event.	Cosuspect: heparin, Reopro, rt-PA. Concomitant: ASA, metoprolol, nitroglycerin, Vasotec
9	68/F	Thrombocytopenia, acute renal failure, cardiac failure	NA	NA	Congestive heart failure, diabetes mellitus. PTCA with multiple stent placement	Cosuspect: heparin, Reopro Concomitant: ASA, folic acid, glyburide, Lanoxin, Lasix, metformin, nitroglycerin, quinapril, vitamins (B6, B12, E)
10	69/M	Thrombocytopenia, injection site reaction, erythematous rash, flushing	NA	Not yet recovered	PTCA	Cosuspect: Reopro Concomitant: ASA, metoprolol, nitroglycerin
11	NA/F	Thrombocytopenia	4 h	Recovered	Myocardial infarction. PTCA	Cosuspect: heparin, Reopro Concomitant: ASA
12	73/F	Thrombocytopenia	13 d	Recovered	Angina, hypertension, coronary arteriosclerosis	Cosuspect: heparin Concomitant: Ceftin, Entrophen, Lopresor, nitroglycerin

Table 1: . . . continued

Case	Age/sex	Reported Reactions*	Time to onset	Outcome†	Medical history/coments	Cosuspect‡ and concomitant drugs
13	60/M	Thrombocytopenia	10–12 d	Not yet recovered	Coronary artery disease, hypertension, gout, hypercholesterolemia. Received clopidogrel after stent	Concomitant: ASA enteric coated, lisinopril, Losec, nifedipine XL, nitroglycerine, Nitrong SR, Pravachol
14	NA/F	Thrombocytopenia	6 d	Recovered	Rheumatoid arthritis. Admitted for non-Q-wave myocardial infarction. Received clopidogrel after stent	Cosuspect: Reopro Concomitant: ASA, heparin, methotrexate
15	66/M	Thrombocytopenia	NA	Not yet recovered	Old myocardial infarction, CABG (x 2), hypertension, hypercholesterolemia. Acute myocardial infarction and PTCA with stent	Cosuspect: heparin, Reopro Concomitant: ASA enteric coated, digoxin, ducosate, furosemide, levothyroxin, lisinopril, metoprolol, nitroglycerin, simvastatin, spironolactone
16	69/M	Thrombocytopenia	NA	Not yet recovered	NA	Cosuspect: Epival Concomitant: atorvastatin, enalapril, metoprolol, ranitidine
17	60/M	Thrombocytopenia, myocardial infarction	1 d thrombo-cytopenia; 7 d myocardial infarction	Recovered	Stable angina. No history of myocardial infarction. PTCA. Negative rechallenge with clopidogrel	Cosuspect: heparin, Reopro

Note: CADRMP = Canadian Adverse Drug Reaction Monitoring Programme, NA = not available,
PTCA = percutaneous transluminal coronary angioplasty, CABG = coronary artery bypass grafting.
* Based on the "preferred term" of the World Health Organization Adverse Reaction Dictionary (WHOART).
† At the time of reporting.
‡ Drugs suspected by the reporter in addition to clopidogrel.
§ Other drugs were calcium carbonate, ducosate, lactulose, and vitamins B6, B12, B complex and D.

Gentamicin ear drops and ototoxicity: update

Aminoglycoside ear drops have a potential for ototoxicity (both cochlear and vestibular) when administered in the presence of a tympanic membrane perforation.[1,2] This ototoxicity appears to develop in only a small number of patients despite widespread product use; however, the actual incidence is unknown.[1,2] Some investigators have suggested that vestibulotoxicity may be unrecognized and underreported.[2] In 1997 we summarized 7 cases of ototoxicity associated with the use of Garasone Ophthalmic/Otic Solution (gentamicin sulfate with betamethasone sodium phosphate), an aminoglycoside otic preparation.[3] Individual reports of vestibulotoxicity in patients given Garasone ear drops in the presence of tympanic membrane defects have also been published.[1,2,4,5] Because topical aminoglycoside ototoxicity may be more common than once thought, in June 2000 the Ontario Medical Association's Section of Otolaryngology sent an alert to Ontario physicians.[6]

Between 1981 and Oct. 6, 2000, the CADRMP received 18 domestic suspected reports of ototoxicity (including published cases) associated with the use of Garasone ear drops in the presence of tympanic membrane perforation or tympanoplasty tubes. Sixteen were of vestibular disorders and 2 of hearing loss. Tympanic membrane defects were either unilateral or bilateral. In most cases the conditions being treated were middle ear disorders with otorrhea. Duration of treatment ranged from 5 days to "long term." In 6 cases patients used the product for no longer than 5 to 7 days. At the time of reporting, 15 patients had not recovered from their symptoms.

In addition to these 18 cases, 2 reports were associated with the use of gentamicin ear drops (brand not specified): one of persistent dizziness and imbalance and another of temporary hearing loss in a patient being treated for Ménière's disease. In the latter case, gentamicin ear drops were used as an adjunct to high-dose gentamicin infusion (26 mg 3 times daily) in the middle ear.

Labelling changes were made by the sponsor to both Garasone Ophthalmic/Otic Solution and Garamycin Ophthalmic/Otic Solution (gentamicin sulfate) in March 1996 and April 1996 respectively.[7] The changes are as follows:

- limit the indications and clinical uses of these products to topical treatment of lesions in the external ear canal (acute otitis externa, eczematoid-dermatitis, seborrheic dermatitis and contact dermatitis) secondarily infected with susceptible organisms;
- expand the contraindications to patients with absent or perforated tympanic membranes; and
- recommend patient monitoring.

Written by: Margaret Stockwell, MD, FRCPC, Bureau of Licensed Product Assessment.

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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)
celecoxib (Celebrex)
clopidogrel (Plavix)
delavirdine (Rescriptor)
Factor VII-recombinant, activated (NiaStase)
Hypericum perforatum (St. John's wort)
indinavir (Crixivan)
naratriptan (Amerge)
nevirapine (Viramune)
oseltamivir (Tamiflu)
pioglitazone (ACTOS)
ritonavir (Norvir)
rituximab (Rituxan)
rofecoxib (Vioxx)
rosiglitazone (Avandia)
saquinavir (Invirase)
trastuzumab (Herceptin)
zaleplon (Starnoc)
zanamivir (Relenza)
zolmitriptan (Zomig)

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

Canadian Adverse Reaction Monitoring Program (CADRMP)
Adverse Reaction Review and Information Unit
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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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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