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Drugs causing prolongation of QT interval and torsades de pointes

The worldwide reporting of torsades de pointes (TdP) associated with the use of terfenadine and astemizole has prompted the Therapeutic Products Directorate to change the status of these drugs from nonprescription to prescription. TdP, a usually self-limiting ventricular tachycardia, may degenerate into ventricular fibrillation and cause sudden cardiac death. This has stimulated the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) to review the extensive number of drugs that have the potential to cause prolongation of the QT interval and TdP.

TdP may cause syncopal episodes and dizziness.[1] It is characterized by polymorphic QRS complexes that change in amplitude and cycle length, giving the appearance of oscillations around the baseline. TdP may be preceded by marked QT prolongation.[2]

TdP can result from certain medical and congenital

conditions, but it is often induced by drugs. A variety of pharmacologic agents have been reported as having the potential to cause QT prolongation[3] and TdP. Table 1 summarizes an abbreviated list of drugs available in Canada that have been associated with QT prolongation and TdP.

The incidence of TdP has not been correlated with the plasma concentrations of drugs known to precipitate this arrhythmia. However, high plasma concentrations, resulting from excessive dose or reduced metabolism of some of these drugs, may increase the risk of precipitating TdP. Such reduced metabolism may result from the concomitant use of other drugs that interfere with cytochrome P_{450} enzymes. Medications reported to interfere with the metabolism of some drugs associated with TdP include systemic ketoconazole and structurally similar drugs (fluconazole, itraconazole, metronidazole); serotonin re-uptake inhibitors (fluoxetine, fluvoxamine, sertraline) and other antidepressants (nefazodone); HIV protease inhibitors (indinavir, ritonavir, saquinavir); dihydropyridine calcium-channel blockers (felodipine, nicardipine, nifedipine);[4] and erythromycin and some other macrolide antibiotics. Grapefruit and grapefruit juice may also interact with some drugs by interfering with cytochrome P_{450} enzymes.

TdP may also result from the use of drugs causing QT prolongation in patients with medical conditions such as hepatic dysfunction or congenital long QT syndrome or in those with electrolyte disturbances (particularly hypokalemia and hypomagnesemia). Electrolyte disturbances may be induced by corticosteroids, diuretic therapy, liquid protein diet, severe diarrhea or vomiting.

It is difficult to predict which patients are at risk for TdP. However, careful assessment of the risk–benefit ratio is important before prescribing these drugs. Some factors that can increase the risk of QT prolongation include the concomitant use of drugs known to prolong the QT interval with drugs that inhibit their metabolism and the use of drugs causing QT prolongation in patients with certain medical conditions. The product monograph should be consulted to identify additional risk factors for TdP.

Because the list of drugs causing QT prolongation and TdP is continually increasing, we encourage health care professionals to report suspected adverse drug reactions to the Adverse Drug Reaction (ADR) Reporting Unit (fax 613 957-0335) or to their regional ADR reporting centre.

Table 1: Abbreviated list of drugs available in Canada reported to cause prolongation of the QT interval or torsades de pointes<1–4>

Category of drug	Drugs
Antiarrhythmic Class Ia Class III	 Disopyramide, procainamide, quinidine Amiodarone, bretylium, sotalol
Antimicrobial	Erythromycin, trimethoprim–sulfamethoxazole
Antihistamine	Astemizole, terfenadine
Antimalarial or antiprotozoal	Chloroquine, halofantrine, mefloquine, pentamidine, quinine
Gastrointestinal prokinetic	Cisapride
Psychoactive	Chloral hydrate, haloperidol, lithium, phenothiazines, pimozide, tricyclic antidepressants
Miscellaneous	Amantadine, probucol, tacrolimus, vasopressin

This article is under the direction of: Pascale Springuel, BPharm, Bureau of Drug Surveillance.

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Risk of seizures from concomitant use of ciprofloxacin and phenytoin in patients with epilepsy

Fluoroquinolones may cause central nervous system (CNS) stimulation and toxic effects.[1] Convulsions have been reported in patients taking ciprofloxacin, a synthetic fluoroquinolone, and in those taking other antibacterial agents in this class (product monograph, Bayer Inc.) A recently published case report suggests that the concomitant use of ciprofloxacin and phenytoin may affect the control of seizures in patients with epilepsy.[2] A search of the database of the CADRMP revealed 3 additional cases in which patients were taking ciprofloxacin and phenytoin concomitantly and experienced seizures. The details of these 4 cases are outlined here.

Case 1:[2] A 61-year-old man had been receiving long-term therapy with phenytoin (100 mg orally 3 times daily) to prevent seizures secondary to a cerebrovascular accident. He was admitted to hospital because of pneumonia. Other drugs he had been taking long term were phenobarbital, pimozide and thiamine. On admission, his serum phenytoin concentration was 12.6 (normal range 10–20) μg/mL. Eight days after admission, the patient received ciprofloxacin (750 mg orally twice daily) and clindamycin (450 mg orally 4 times daily) for a pulmonary abscess thought to be secondary to aspiration. Two days later he experienced a seizure; his serum phenytoin concentration was 2.5 μg/mL. The pimozide was stopped because of its potential to lower the seizure threshold, and the dosage of phenytoin was gradually increased to correct the low serum phenytoin level. At discharge, the phenytoin dose was 200 mg orally 3 times daily, the patient's serum phenytoin level was 12.6 μg/mL, and the ciprofloxacin was stopped.

Some time after discharge the patient had weakness, fatigue, headaches and severe ataxia, and he suffered a head injury that required consultation at the emergency department. The serum phenytoin concentration was 42.8 μg/mL, and his serum albumin level was normal. The phenytoin was temporarily withheld, and the serum phenytoin level returned to normal within 4 days. The patient had a history of significant alcohol use. However, in the last 6 years his alcohol consumption had decreased, and there was no evidence of alcohol-induced elevations of the serum transaminase levels. Also, the creatinine levels were normal during both hospital admissions.

Case 2:[3] A 65-year-old man with epilepsy, schizophrenia and organic brain syndrome had been taking phenytoin (100 mg orally 3 times daily), benztropine, clonazepam and lorazepam. Pneumonia developed, for which he was given ciprofloxacin (500 mg orally twice daily). A few days before, he was given thioridazine and chlorpromazine. On the ninth day of the ciprofloxacin treatment the patient experienced a seizure. His serum phenytoin level was 14.6 μg/mL the day before he started the ciprofloxacin and 10.8 μg/mL the day after the first seizure. A second seizure, 2 days after the first, prompted an adjustment of the phenytoin dose to 100 mg 4 times daily and the withdrawal of the ciprofloxacin. However, 2 days later the patient experienced a third seizure; the serum phenytoin level was 11.6 μg/mL. Another 5 days later, the level had increased to 14 μg/mL. The patient had no further seizures. The thioridazine and the chlorpromazine could have contributed to the occurrence of seizures by reducing the seizure thresholds.

Case 3: A 41-year-old woman with epilepsy had been taking phenytoin (200 mg orally twice daily). She was given ciprofloxacin (500 mg orally twice daily) because of psoriasis in

her ear canal. Concomitant medications were clobazam, clonazepam and omeprazole. The woman experienced a seizure 1 hour after the third dose of ciprofloxacin. She continued to experience seizures, varying from grand mal to absence types, up to 3 to 4 times daily. She stopped taking the ciprofloxacin after the fourth day of treatment. The reporter stated that the patient's phenytoin level was normal; however, the time of measurement and the level were not specified. The reporter did not indicate the patient's outcome.

Case 4: A 25-year-old hemiplegic man with a history of head trauma, aphasia and status epilepticus had been taking phenytoin (250 mg orally twice daily). He was given ciprofloxacin (500 mg orally twice daily) because of an upper respiratory tract infection. Other concomitant medications were ampicillin, phenobarbital and salbutamol inhaler. The patient, described as normally very quiet, became agitated after the administration of ciprofloxacin. He experienced seizures described as "twitching" after only 2 doses of the drug; he had no seizures after discontinuation of the treatment.

Information from case 1 suggests that the concomitant use of ciprofloxacin and phenytoin may affect the control of seizures in epileptic patients. The occurrence of seizures and the reduced serum phenytoin levels prompted an increase of the phenytoin dose that led to a high phenytoin serum level after the ciprofloxacin was stopped. However, there are very few details available on the 3 other cases described here. In case 2, the phenytoin values fluctuated within normal limits, which could have been due to factors of variability such as the time of blood sampling. In the third and fourth cases the seizures could have been caused by the antibacterial agent itself because they began soon after the ciprofloxacin treatment was started.

Although no conclusions can be drawn from these cases, the product monograph on Dilantin® indicates that fluoroquinolones may decrease phenytoin serum levels. Serum level determinations are especially helpful when possible drug interactions are suspected. In addition, as with all quinolones, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis, epilepsy and other conditions that predispose to seizures (product monograph, Bayer Inc.).

This article is under the direction of: Carol Langlois, BA, BPharm, Bureau of Drug Surveillance. The contribution by Pascale Springuel, BPharm, is greatly appreciated.

References

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2. Pollak PT, Slayter KL. Hazards of doubling phenytoin dose in the face of an unrecognized interaction with ciprofloxacin. *Ann Pharmacother* 1997;31:61-4.

Appetite suppressants — update

On Sept. 15, 1997, Health Canada issued a public health warning advising consumers of the risks of serious cardiac valve disease associated with the use of fenfluramine and dexfenfluramine.[1] The manufacturers of the drugs agreed to suspend the sale of their products in the US and in Canada as of that date. Health Canada urged all people who may have consumed these products to consult their doctor for appropriate follow-up.

The US Department of Health and Human Services issued interim recommendations for heart examination for anyone who has taken the diet drugs either alone or with any other drug or drugs.[2] The recommendations were published in the Nov. 14, 1997, issue of *Morbidity and Mortality Weekly Report*. Health Canada immediately communicated with provincial regulatory bodies of medical practice and the CMA, advising them of these recommendations. (See reference 3 for additional information from Health Canada.)

This article is under the direction of: Ann Sztuke-Fournier, BPharm, Bureau of Drug Surveillance.

References

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2. Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: US Department of Health and Human Services interim public health recommendations, November 1997. *MMWR* 1997;46:1061-6.
3. *Cardiac adverse reactions in patients following the use of fen-phen (a combination of fenfluramine and phentermine)*. Ottawa: Therapeutic Products Programme, Health Canada; 1997 July 11.

COMMUNIQUÉ

The purpose of this section is to 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 product monograph. They are intended to prompt reporting.

Vigabatrin (Sabril®) update

Because of a Health Canada safety information letter issued by Hoechst Marion Roussel on June 27, 1997, the CADRMP has received 10 reports of ophthalmological abnormalities associated with vigabatrin use in the management of epilepsy: visual field constriction (5), decreased visual acuity (4), optic disc pallor (2), tunnel vision (2), retinopathy (1), retinal detachment (1), retinal pigmentary disruption (1), optic atrophy (1) and scotoma (1). The patients (6 males, 3 females, 1 sex unknown) ranged in age from 30 months to 48 years.

Mefloquine (Lariam®)

In 1997 the CADRMP received 4 reports of neuropsychiatric reactions with the prophylactic use of the antimalarial drug mefloquine. The reported reactions were convulsions (2), anxiety (1), vertigo (1), nightmares (1), memory loss (1), and emotional and behavioural disorders (1). The patients (2 women, 2 men) were 21 to 50 years of age.

Lamotrigine (Lamictal®)

Two reports were received in 1997 describing severe cutaneous reactions associated with the use of lamotrigine in the management of epilepsy. The reactions included Stevens–Johnson syndrome, accompanied by dermatologic lesions of purpuric/morbilliform nature in one report and toxic epidermal necrolysis with lymphadenopathy in the other. One patient was a 49-year-old man and the other a 32-year-old woman.

This section is under the direction of: Amal Hélal, BSc Phm, Bureau of Drug Surveillance.

Spontaneous reporting of suspected adverse drug reactions (ADRs) is a critical ongoing source of drug-safety information. Thus, we encourage health professionals to report any suspected ADRs to one of the following addresses:

British Columbia
BC Regional ADR Centre
c/o BC Drug and Poison Information Centre
1081 Burrard St.
Vancouver BC V6Z 1Y6
fax: 604 631-5262; tel: 604 631-5625

Saskatchewan
Sask ADR Regional Centre
Dial Access Drug Information Service
College of Pharmacy and Nutrition
University of Saskatchewan
Saskatoon SK S7N 5C9
fax: 306 966-6377; tel: 306 966-6340 or 800 667-3425

Québec
Quebec Regional ADR Centre
Centre d'information pharmaceutique
Hôpital du Sacré Coeur de Montréal
5400, boul. Gouin ouest
Montréal QC H4J 1C5
fax: 514 338-3670; tel: 514 338-2961 or 338-2161 (collect calls accepted)

Nova Scotia, New Brunswick, Newfoundland and Prince Edward Island
Atlantic Regional ADR Centre
Queen Elizabeth II Health Sciences Centre
New Halifax Infirmary Building
Level 200, Drug Information Centre
1796 Summer St.
Halifax NS B3H 3A7
fax: 902 473-8612; tel: 902 473-7171

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This newsletter can be found on line, under Publications, at the following *new* address:

www.hc-sc.gc.ca/hpb-dgps/therapeut

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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 undereporting 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.