VANCOUVER HOSPITAL & Health Sciences Centre

DRUG AND THERAPEUTICS NEWSLETTER

A Publication of the Department of Pharmacy

*December, 1996* *Volume 3, Number 4*

INDEX





## UPDATED POLICY AND PROCEDURES

### 1. Expansion of the Pharmacy-Based Warfarin Dosing Service

In November 1995, pharmacy at the 12th & Oak site initiated a warfarin dosing service for DVT prophylaxis in orthopedic patients (INR 1.6-2.3). The service was offered to any orthopedic patient residing on CP W6. The service was evaluated at 12 weeks post inception and was found to effectively streamline prescribing and delivery of warfarin, as well as reduce workload at the ward level.

Due to the success of the warfarin service and requests for expansion, the program was recently increased to include orthopedic patients on CP W9 (Sept 1996). In addition, we have created a nomogram for therapeutic anticoagulation (INR 2.0-3.0). This nomogram is currently in use for vascular patients only on CP W8 (since Nov 1996) and will be assessed in 3 months.

### 2. Revised Drug Administration Policies

The following revised policies will appear in the next update of the Parenteral Drug Therapy Manual (~ Dec 1996):

**Iron Dextran cannot be administered by direct IV** (only IM, IV intermittent, or IV infusion). Test doses may be given over 5 minutes.

**Ketamine** can be administered by **subcutaneous infusion** for symptomatic relief of moderate to severe pain. This route of

administration is restricted to **critical care areas** or any nursing unit with an **Acute Pain Service** (APS) order.

**Methotrimeprazine** for **IV intermittent** must be diluted and administered at the following rates: **# 50mg in 50mL NS, D5W over 30-60 mins, > 50mg in 100-250mL NS, D5W over 1-2 hours.**

**Methylene Blue** for treatment of drug-induced methemoglobinemia may be administered by **IV intermittent** in 50mL NS over 15 minutes or **IV infusion** in 1L NS.

**Midazolam** can be administered by **SC or IM injection anywhere** in the hospital, **SC infusions** are restricted to **Palliative Care Unit**.

**Octreotide** can be administered by **IV intermittent** in 50mL NS, D5W over 15-30 minutes.

**Pamidronate maximum concentration** for IV intermittent is **60mg/250mL** given at a rate not to exceed **60mg/hour**.

**Streptokinase** may be administered **intrapleurally** by physician only for treatment of **parapneumonic pleural effusions**.

**Vancomycin intraventricular or intrathecal** should be diluted to a **2.5-5 mg/mL concentration** with preservative-free NS.

## CISAPRIDE and QT PROLONGATION

Cisapride (Prepulsid®) is an oral prokinetic drug which is metabolized by the cytochrome p450 3A4 isoenzyme (CYP 3A). Table 1 illustrates enzyme inducers and inhibitors of this system.[1,2] Drugs that inhibit CYP 3A can cause an elevation in cisapride serum levels; the significant adverse result is torsade de pointes associated with QT prolongation.[3] Cisapride has also been associated with QT prolongation in patients without interacting drugs but receiving higher than maximum doses.[4,5]

**Table 1. Drugs affecting the CYP 3A system**

| Enzyme Inducers | Enzyme Inhibitors | |
|---|---|---|
| Rifampin<br>Glucocorticoids | **Macrolide Antibiotics**<br>Clarithromycin<br>Erythromycin | **Antifungals**<br>Fluconazole<br>Itraconazole<br>Ketoconazole |
| | **Antidepressants**<br>Fluoxetine<br>Fluvoxamine<br>Nefazodone<br>Sertraline | **Other**<br>Diltiazem |

*Proposed Mechanism*

The structural similarity of cisapride to the antiarrythmic drug procainamide is one theory regarding the mechanism by which cisapride induces dysrhythmias.[6] Cisapride stimulation of serotonin-4 receptors which results in cardiac chronotropic activity has also been postulated.[6]

*Reports and Risk Factors*

There have been 5 cases of cisapride-induced dysrhythmias reported to the Canadian Adverse Drug Reaction Monitoring Program.[4] Three cases were associated with interacting drugs (clarithromycin, erythromycin, fluoxetine). Two of these patients also had a cardiac history, and 2 patients received doses greater than the recommended maximum

of 40mg/day.

There have been 57 patients, including 4 deaths, reported to the Food and Drug Administration who developed either QT prolongation (23) or torsade (34) while taking cisapride.[7] Fifty-six percent (32/57) of patients received an interacting drug. In 15 patients tested, 9 had elevated serum cisapride levels. Other risk factors included coronary disease and arrhythmia (39%), renal dysfunction (25%), electrolyte imbalance (19%), and concurrent treatment with medications which can prolong the QT interval (12%; e.g. amiodarone, phenothiazines).

A 64 year old male with diabetes was initiated on cisapride 10mg TID to improve gastroparesis.[5] The dosage was increased over 3 days to 40mg QID. On day 7 of hospitalization, the patient developed QT prolongation which did not return to normal until the cisapride dose was reduced to 5mg QID by day 13. The patient had received erythromycin IV on day 1 of hospitalization only.

Recently, a patient at VHHSC was treated for Helicobacter pylori with quadruple therapy of clarithromycin, amoxicillin, bismuth subsalicylate, and omeprazole. Cisapride was added for severe gastroesophageal reflux. After approximately 72 hours of concomitant therapy, the patient arrested and was resuscitated. The ECG showed marked prolongation of the QT interval with no evidence of myocardial infarction. Cisapride was discontinued and the patient recovered without sequelae.

*Onset and Management*

Onset of QT prolongation appears to occur 3-7 days after initiation of an interacting drug or administration of doses greater than 40mg/day.[4-6] There is one case report of tachycardia occurring 18 days after initiation of cisapride.[4] Dysrhythmias subside after cisapride has been discontinued, the dosage reduced, or the interacting drug is stopped. Metoclopramide or domperidone should be considered as alternates in patients requiring a prokinetic agent and a drug know to interact with cisapride.

*Conclusion*

In December 1995, a letter was issued by the manufacturer stating that concomitant administration of clarithromycin, erythromycin, fluconazole, ketoconazole, and itraconazole with cisapride is contraindicated due to an increased incidence of QT prolongation and torsades. Of note, all CYP 3A inhibitors should be considered for this potential interaction (Table 1). As the adverse events seem to be related to elevated cisapride levels, a maximum dose of 10mg QID is now recommended.[3] With renal or hepatic dysfunction, a dosage of 5mg TID should be initiated and titrated to minimum effective dose.[3] Caution is also advised in patients on medications known to prolong the QT interval, and those with a history of arrhythmia, cardiac disease or electrolyte disturbances.

*References*

1. Slaughter R et al. Ann Pharmacother 1995;619024.
2. Caley C. Ann Pharmacother 1996;30:684.
3. Janssen (Cisapride) Pharmacist Letter, December 1995.
4. Canadian Adverse Drug Reaction Newsletter 1996;6(3).
5. Murray B et al. Arch Intern Med 1995;155:765-8.
6. Pettignano R et al. Crit Care Med 1996;24:1268-71.
7. Wysowski D et al. N Engl J Med 1996;335:290-1.

Wendy Gordon, Pharm.D. Candidate

## FENFLURAMINE AND PRIMARY PULMONARY HYPERTENSION

The appetite suppressant fenfluramine (Ponderal®, Pondimin®) and its d-isomer

dexfenfluramine, have been implicated as a cause of primary pulmonary hypertension (PPH). As the use of anorexiant agents increases, it is essential to be aware of and monitor for the development of PPH.

PPH is a rare disease, occurring in one to two adults per million.[1] It is defined as an increase in mean pulmonary arterial pressure to > 25 mmHg at rest or > 30 mmHg with exercise, without an identifiable cause such as COPD.[2,3] Normal mean pulmonary arterial pressure for a young adult at rest is 13 ± 4 mmHg.[2] Breathlessness on exertion is generally the first presenting symptom, however by the time this appears, pulmonary arterial pressure is significantly elevated and the disease is well advanced. The prognosis is generally poor, with drugs such as vasodilators (calcium channel blockers, prostaglandins) providing relief in few patients and heart-lung transplantation limited by the shortage of donors.

Case reports suggesting an association between PPH and fenfluramine use began appearing in the 1980's.[4-6] Brenot et al conducted a five year retrospective study of fenfluramine use in patients referred to a French centre specializing in PPH.[6] They found that 20% of patients with PPH had taken usual doses of fenfluramine for at least 3 months (range 3-61 months) prior to onset of symptoms. A similar study conducted in the United Kingdom evaluated 55 patients with PPH from four heart-lung transplant centres.[7] Three patients were identified as having exposure to anorexiants: fenfluramine (2), diethylpropion (1). A prospective, case control study involving 95 patients with PPH and 355 controls found 31% of patients had used appetite suppressants, primarily dexfenfluramine or fenfluramine, prior to the development of symptoms.[8] Use for greater than three months was associated with an odds ratio of 23:1.

As a result of the above study[8], the Health Protection Branch has issued a warning stating that fenfluramine is indicated for short term use only of no longer than three months duration.[1] The indication for all appetite suppressant drugs has been further restricted to the management of obese patients with an initial body mass index of **$**30 kg/m$^2$ or **$**27 kg/m$^2$ in the presence of other risk factors.

PPH is a serious disease with a poor prognosis. When evaluating the appropriateness of appetite suppressants in the obese patient, one must consider the benefits of weight loss against the risk of developing this disease. All patients should be warned of the possibility of pulmonary hypertension and advised to report any breathlessness or deterioration in exercise tolerance during therapy. Unfortunately, PPH may be irreversible despite drug withdrawal.[6]

*References*

1. Health Protection Branch. Increased risk of primary pulmonary hypertension with long term use of appetite suppressant drugs. Dear Doctor 1996; October (46).
2. DiPiro JT (ed). Pharmacotherapy-A Pathophysiologic Approach. Elsevier Science Publishing 1989; 245-270.
3. Weir EK et al (eds). Pulmonary Hypertension. Futura Publishing 1984;115-68.
4. Atanassoff P et al. Pulmonary hypertension and dexfenfluramine . Lancet 1992; 339:436-7
5. Naeije R et al. High-altitude pulmonary edema with primary pulmonary hypertension. Chest 1996; 110:286-289.
6 Brenot F et al. Primary pulmonary hypertension and fenfluramine use. Br Heart J 1993;70:537-541.
7. Thomas SHL et al. Appetite suppressants and primary pulmonary hypertension in the United Kingdom. Br Heart J 1995; 74:660-663.
8. Abenhaim L et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. NEJM 1996; 335:609-616.

Nadine Lambert, Pharmacy Resident
Reviewed by Dr. D. Ostrow, Respiratory