MEDICAL PHARMACIES TABLET

Drug information and news for health care providers

May 2013

NSAIDs Risky in CVD

Recent warnings in the press regarding the risk of heart attack and stroke associated with Voltaren® (diclofenac) highlight the potential danger of NSAIDs, particularly in patients with a history of MI (myocardial infarction). In spite of this, NSAIDs are widely prescribed, and in many countries they are available over-the-counter, conveying the impression they must be safe. A Danish study published in *Circulation* (2012;126:1955-1963) showed that in patients with a prior MI, NSAID use has been associated with an increased risk of a recurrent MI and death.

In a subsequent interview with **heart*wire*** on September 11, 2012, Dr. Anne-Marie Schjerning Olsen, one of the paper's authors, stated: "NSAIDs are still dangerous to patients with a history of MI, even five years after their event. I would say there is no safe treatment window for these patients, and even short-term treatment with NSAIDs is dangerous."

Vioxx® (rofecoxib) was withdrawn from the market several years ago due to its high risk of MI, stroke, and death. In the Danish study, diclofenac had an even higher risk of cardiovascular disease (CVD), with Celebrex® (celecoxib) next in line. Naproxen appears to have the lowest relative CVD risk and thus, Dr. Schjerning Olsen commented, the results of the study might indicate that "naproxen should be preferred if NSAID treatment cannot be avoided"; however, naproxen's risk of gastrointestinal (GI) bleeding worsens the prognosis in MI patients.

What makes NSAIDs so risky?

- Taking NSAIDs may lead to new onset hypertension or worsening of pre-existing hypertension through vasoconstriction and sodium retention. In normotensive people, blood pressure may increase by about 1 mm Hg, but in hypertensive patients it can increase by about 5-6 mm Hg. Risk factors for increased blood pressure include obesity, male gender, older age, and having diabetes, heart failure, kidney or liver disease. The *Canadian Pharmacist's Letter* (Dec. 2011) reports that daily use of NSAIDs can affect blood pressure after just a week or so and that the effect is dose-dependent.

- NSAIDs can reduce the efficiency of blood pressure medications to varying degrees, with calcium channel blockers and centrally-acting adrenergic drugs (e.g., clonidine) being the least likely to be affected.

- The use of an ACEI (angiotensin converting enzyme inhibitor) or ARB (angiotensin receptor blocker) plus a diuretic and an NSAID—a combination known as the "triple whammy"—is associated with a 31% higher risk of kidney injury. The adverse renal risk increases in the elderly, in those with pre-existing renal dysfunction, people who take daily ASA dose > 325 mg, in the presence of dehydration (e.g., during acute viral illness, low fluid intake, severe diarrhea, and vomiting), heart failure, hyperkalemia, and when used concurrently with potassium-sparing diuretics. A low-dose loop diuretic such as furosemide, with slow dose titration to avoid dehydration, and close renal function monitoring is recommended to minimize the risk of renal damage. Low-dose ASA (≤ 325 mg daily) is not likely to cause renal problems.

Managing the CVD & GI Risks

No NSAID is free of risk. According to the *Canadian Pharmacist's Letter* (August 2010), patients with both high CVD and GI risk and patients at high risk of chronic renal disease should not take NSAIDs. When no other treatment is effective (e.g., acetaminophen, tramadol, opiates) and the benefit to the patient is deemed to outweigh the risk, the following information may help.

- ***Reducing GI risk:*** Adverse GI events are more likely in people who:
  - are male
  - have a history of bleeding ulcer or dyspepsia
  - are age ≥ 60
  - have CVD
  - use concomitant drugs such as ASA, antiplatelets, anticoagulants, corticosteroids
  - take high NSAID doses or use longer acting NSAIDs.

Relative risk varies with the study, but generally ibuprofen and celecoxib have the lowest GI risk. Diclofenac, meloxicam, ketoprofen, indomethacin, and naproxen have a moderate risk. Highest GI risk occurs with piroxicam and ketorolac. Of note is the fact that the COX-2 inhibitor celecoxib, when used > 6 months, is not safer than traditional NSAIDs. Gastroprotective agents (e.g., proton pump inhibitors, misoprostol) and, to a lesser extent, H2 blockers may reduce GI risk.

• ***Reducing CVD risk:*** CVD risk increases in patients with a history of a CVD event, diabetes, hypertension, obesity, hyperlipidemia, high NSAID dose, use of longer acting NSAIDs, and COX-2 selective agents. Naproxen has the lowest CVD risk, followed by meloxicam, etodolac, etc. The highest CVD risk is with diclofenac 100 mg daily and celecoxib ≥ 400 mg daily. In **all cases** NSAIDs should be taken at the lowest effective dose for the shortest duration. Patients on low-dose ASA and occasional ibuprofen or naproxen should take immediate-release ASA and NSAID only (not enteric-coated or extended-release) to minimize drug interactions. ASA is best taken one hour before or eight hours after the NSAID. **MPT**

Cambia® (diclofenac potassium) 50 mg powder for oral solution

Tribute Pharmaceuticals

Cambia is indicated for the acute treatment of migraine attacks with or without aura in adults 18 years and older. Diclofenac potassium powder dissolves very quickly in water; therefore, Cambia solution starts working within 15 to 30 minutes of ingestion, compared with about 60 minutes for diclofenac potassium tablets (Voltaren Rapide®).

As with other NSAIDs (nonsteroidal anti-inflammatory drugs), Cambia should not be taken by patients at high risk of gastrointestinal bleeding, patients at high risk of cardiovascular disease, or patients with a history of cardiovascular disease. Cambia is contraindicated during the third trimester of pregnancy and in patients with severe renal or hepatic impairment.

Dose & Administration: The contents of 1 sachet of Cambia should be emptied into a cup of 30 to 60 mL (1 to 2 ounces) of water and mixed well until completely dissolved. The water-powder mixture should be drunk immediately, preferably on an empty stomach; food delays absorption. No liquids other than water should be used to dissolve the powder.

The safety and efficacy of a second dose has not been studied.

Cambia is not recommended in patients with renal or hepatic impairment. The elderly, frail, and debilitated patients are at an increased risk of serious gastrointestinal adverse events and are more likely to have decreased renal function.

Availability & Storage: Cambia is available in individual dose sachets containing 50 mg of diclofenac potassium. The product is supplied in a box containing 9 doses and should be stored between 15°-30°C. **DN**

Divigel® (estradiol) 0.1% gel

Ferring

Divigel is a topical gel indicated for the treatment of moderate to severe vasomotor symptoms of menopause.

Women with an intact uterus should take a concomitant progestin to prevent endometrial hyperplasia and reduce the risk of endometrial cancer.

***Adverse Effects* (≥ 5%):** breast tenderness, irregular vaginal bleeding or spotting, vaginal yeast infections, nasopharyngitis, and upper respiratory tract infections.

Dose & Administration:
Initial dose: The contents of a single 0.25 g dose packet of gel is applied with a dry (or gloved) hand to a clean and dry area of skin (about 5 by 7 inches) on the upper thigh, once daily. The application sites should be rotated, alternating between the left and right upper thighs. It is not necessary to massage or rub in Divigel.

Following application, the hands should be washed with soap and water immediately, and the application area should be dry before covering with clothing.

Divigel should never be applied in or around the vagina, the face, breast, or irritated skin. The application site should not be washed, and contact of the area with another person should be avoided within one hour of applying the gel. Divigel is an alcohol-based product; therefore, close proximity to fire, flame, or smoking should be avoided until the gel is completely dry.

Dose adjustments are made according to individual requirements. It is recommended that the need for treatment be reviewed periodically (e.g., every 3 to 6 months).

Availability: 0.25 g, 0.5 g, and 1 g single dose foil packets. **DN**

(Refer to the product monographs for complete information.)