**COX-2 Inhibitors – Cardiovascular and Gastrointestinal Safety**

**Introduction**

On September 30, 2004, Merck & Co. voluntarily withdrew the selective cyclooxygenase (COX)-2 inhibitor, rofecoxib (Vioxx®), from the international pharmaceutical market. The decision by Merck followed dissemination of data from the prospective, randomized, placebo controlled APPROVE (Adenomatous Polyp Prevention on VIOXX) trial, which revealed an increased risk of confirmed cardiovascular events with administration of rofecoxib as compared to placebo. The APPROVE trial was designed to evaluate the effectiveness of rofecoxib in the prevention of recurrent colorectal polyps in patients with a known history of colorectal adenoma. Patients were randomized to receive rofecoxib 25 mg or placebo daily. The results of the study revealed that treatment with rofecoxib was associated with a significantly higher rate of thrombotic event occurrence as compared to placebo (3.5% vs. 1.9%).

**Cardiovascular safety**

Although the results of APPROVE ultimately led to the withdrawal of rofecoxib worldwide, the risk of cardiovascular events associated with COX-2 inhibitors has been a subject of considerable debate for years. Researchers theorize that COX-2 inhibitors may increase the risk of thrombotic events by reducing the production of prostaglandin I₂ (PGI₂), while exerting a negligible effect on thromboxane A₂. Prostaglandin I₂ formation is associated with vasodilatation and a reduction in platelet aggregation. In contrast, thromboxane A₂ promotes vasoconstriction and platelet aggregation. Traditional non-steroidal anti-inflammatory drugs (NSAIDs) inhibit both PGI₂ and thromboxane A₂; however, the more focused inhibition of COX-2 inhibitors, which leaves thromboxane A₂ unaffected, may tip the balance toward a prothrombotic effect.

The cardiovascular safety concerns surrounding rofecoxib became an issue after initial data from the Vioxx Gastrointestinal Outcomes Research (VIGOR) study revealed a total of 98 vascular events among enrolled patients – 65 events among 4,047 patients in the rofecoxib group and 33 events among 4,029 patients in the naproxen group. Of these 98 cases, 45 patients in the rofecoxib group and 20 patients in the naproxen group were judged to have serious thrombotic events defined as myocardial infarction, unstable angina, thrombus, resuscitated cardiac arrest, sudden death, and transient ischemic attacks. A survival analysis revealed that the relative risk of developing an adverse cardiovascular event in the rofecoxib group was 2.38 (95% CI, 1.39 to 4.00; p < 0.01). After the release of this data, a major push to explain the negative results was undertaken. Specifically, the significant antiplatelet activity of naproxen in comparison to rofecoxib was emphasized as a possible explanation for the increase in observed cardiovascular events.

Many subsequent analyses were performed, which either reinforced the cardioprotective effect...
theory of naproxen or, in contrast, found an absence of a cardioprotective effect with naproxen or any other non-aspirin NSAID. Several of these analyses were observational cohort studies, which have many inherent limitations. No prospective trial was conducted to “specifically assess the cardiovascular risk and benefit of the COX-2 inhibitors” – as was recommended by leading researchers.

A nested case-control study has estimated that 27,000 myocardial infarctions and sudden cardiac deaths may be attributed to rofecoxib use. Whether or not the other available COX-2 inhibitors, celecoxib (Celebrex®) and valdecoxib (Bextra®), may contribute to the development of cardiovascular events is an issue which will be scrutinized closely over the coming months. Until an official FDA guidance is provided, clinicians should probably limit the use of COX-2 inhibitors to patients with a low cardiovascular risk profile and a history of serious gastrointestinal events, particularly while receiving NSAIDs. In addition, healthcare providers should consider not prescribing COX-2 inhibitors to patients with existing cardiovascular disease or those with significant cardiovascular disease risk factors.

Gastrointestinal safety

COX-2 inhibitors were developed in an attempt to mitigate the adverse gastrointestinal (GI) effects commonly experienced with traditional NSAIDs. Clinical efficacy trials and short-term endoscopy studies indicate that COX-2 inhibitors have a statistically reduced propensity to cause GI adverse effects in comparison to traditional NSAIDs such as naproxen, ibuprofen, or diclofenac. However, these agents may not be devoid of serious GI adverse effects. In April 1999, a Wall Street Journal article stated that 10 deaths and 11 cases of GI hemorrhage had been linked to celecoxib in the initial 3 months after the drug entered the market. In 5 of the 10 deaths, the patients suffered from GI bleeding or ulcers; whether or not a causal relationship existed between exposure to celecoxib and subsequent serious GI events was not established.

In addition, the handling of the results of a key GI study involving celecoxib has also created considerable debate. In the Celecoxib Long-term Arthritis Safety Study (CLASS), the annualized incidence of upper GI ulcer complications in patients receiving celecoxib was lower than in patients receiving conventional NSAIDs (0.76% vs. 1.45%, RR = .53; 95% CI, 0.26 to 1.11, p = .09). In addition, a reduction in the annualized incidence of upper GI ulcer complications plus symptomatic ulcers was noted in the celecoxib group compared with those receiving conventional NSAIDs (2.08% vs. 3.54%, p = .02). However, the authors of CLASS only reported 6 month data with celecoxib. Other data submitted to the FDA revealed that, at 65 weeks, celecoxib, diclofenac, and ibuprofen were associated with a similar number of ulcer complications. Although the CLASS investigators stated that they believed the 6-month data to be the most clinically and significantly valid, other clinicians have disagreed with their interpretations.

Conclusions

The removal of rofecoxib from the international pharmaceutical market has ignited a firestorm of controversy surrounding the COX-2 inhibitors. Although these agents are effective for the treatment of pain and inflammation, their overall safety profile will be scrutinized closely over the coming months to years. No definitive data exist to prove that the adverse cardiovascular events seen with rofecoxib extend to celecoxib and valdecoxib; however, the proposed mechanistic explanation for these events implies a possible class effect. With regard to GI safety, COX-2 inhibitors have been associated with a reduced incidence of GI effects as compared to conventional NSAIDs, but they are not devoid of problems. Healthcare providers should consider avoiding the use of these agents in patients with existing cardiovascular disease or those with known cardiovascular risk factors. Patients with a history of serious GI events, particularly related to NSAID use, and a low cardiovascular risk profile may still be considered candidates for therapy. However, some clinicians have proposed that patients who need treatment for pain and inflammation associated with osteoarthritis or rheumatoid arthritis may benefit from use of a conventional NSAID (such as naproxen) in combination with administration of a proton pump inhibitor (such as lansoprazole), thereby eliminating the need for COX-2 inhibitor therapy.

Oral Erythromycin and Risk of Sudden Cardiac Death

Erythromycin is a macrolide antibiotic, which has been prescribed to patients for a variety of infections for approximately 30 years. Erythromycin is generally considered to be well tolerated with a side effect profile free of serious toxicity concerns. Despite this long history of safe use, case reports have been
published documenting a prolongation of the QT interval and development of torsades de pointes in patients receiving both the intravenous and oral formulations of the drug. Most previous studies have focused on evaluating the relationship between arrhythmia development and the administration of intravenous erythromycin. A recent population-based study by Ray and colleagues shifted the focus away from the intravenous formulation to the more commonly prescribed oral formulation of erythromycin. Two main questions were evaluated by the investigators:

1) Is the risk of sudden cardiac death increased with the use of oral erythromycin?

2) Does the concurrent use of oral erythromycin with potent cytochrome P4503A inhibitors alter the risk of sudden cardiac death?

The authors used information from a cohort of Tennessee Medicaid enrollees in order to answer these questions. Within this cohort, 1,476 patients, with 1,249,943 person-years of follow-up, were identified who had experienced sudden cardiac death. The medication records of the cohort were scanned for prescriptions of erythromycin, amoxicillin, and other pertinent medications such as potent CYP4503A inhibitors. Only inhibitors that were documented to at least double the area under the time-plasma concentration curve (AUC) of a recognized substrate were considered for inclusion; not all inhibitors who met this criteria were evaluated (e.g. nefazodone, a known potent inhibitor, was not included for evaluation because it was unavailable during the study period of 1988-1993).

In this study, sudden cardiac death was defined as “a sudden pulseless condition that was fatal (within 48 hours) and that was consistent with a ventricular tachyarrhythmia occurring in the absence of a known noncardiac condition as the proximate case of death.” Only sudden cardiac deaths that occurred in a community setting were evaluated.

The results of the study revealed a 2-fold increase in the rate of sudden cardiac death among patients currently receiving erythromycin as compared to patients with no antibiotic use (incidence-rate ratio, 2.01; 95% CI 1.08-3.75; p = 0.03). In comparison, former users of erythromycin and current users of amoxicillin had no significant increase in sudden cardiac death (see table 1). In addition, current use of a CYP3A inhibitor with erythromycin resulted in an increased rate of sudden cardiac death 5 times higher than patients who received neither a CYP3A inhibitor or any antibiotic therapy (incidence-rate ratio, 5.35; 95% CI 1.72-16.64; p = 0.004). Two calcium channel blockers – verapamil and diltiazem – accounted for nearly all the use of CYP3A inhibitors in the study.

Although an increase in sudden cardiac death was observed with erythromycin monotherapy, the absolute risk of developing torsades de pointes is probably very low. This assumption can be buttressed by the fact that millions of prescriptions for erythromycin have been dispensed safely over the past 30 years. However, the authors conclude that concurrent use of erythromycin and a CYP3A inhibitor does involve a larger risk of sudden cardiac death and therefore the use of this combination of medications should be avoided.

### Common Drug Interactions between Herbal and Prescription Medications

Over the last decade a growing number of Americans have turned to “natural products” or herbal supplements to treat a broad range of illnesses. Many people believe that since these herbal products are “all natural” they will not be harmful nor interact with their prescription medications. These supplements are not regulated as drugs, but as dietary supplements; therefore, manufacturing practices, labeling, and marketing are different than for prescription drugs. The companies manufacturing and distributing herbal products are not required to register with the Food & Drug Administration (FDA). Also, since they are not regulated as prescription drugs, the manufacturing processes emphasize sanitation and not contamination or quality. As a result, many

<table>
<thead>
<tr>
<th>Antibiotic use</th>
<th>Deaths</th>
<th>Person-years</th>
<th>Incidence-rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin - current use</td>
<td>10</td>
<td>5,305</td>
<td>2.01 (1.08-3.75)</td>
</tr>
<tr>
<td>Erythromycin - former use</td>
<td>100</td>
<td>111,779</td>
<td>0.89 (0.72-1.09)</td>
</tr>
<tr>
<td>Amoxicillin - current use</td>
<td>8</td>
<td>6,846</td>
<td>1.18 (0.59-2.36)</td>
</tr>
<tr>
<td>No use</td>
<td>1358</td>
<td>1,126,013</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Table 1: Sudden death from cardiac causes related to antibiotic use.
Herbal products could contain more than just the named supplement and the potency of the product could vary from batch to batch.

Currently, the top 5 selling herbal supplements in the United States (each with 10% of the market share) include ginkgo biloba, St. John’s wort, garlic, echinacea, and ginseng. Patients use herbal supplements to treat a variety of illnesses such as memory loss, cancer, prostatic hypertrophy, headaches, weight loss, dementia, and anxiety. Many patients fail to tell their physicians about the herbal medications that they take and physicians may forget to ask.

Drug interactions between herbal products and prescription medications are variable and may involve more than one mechanism. Interactions may affect drug absorption, distribution, metabolism, excretion, and disruption at drug receptor sites. Herbal products affect drug metabolism most frequently, generally through cytochrome (CYP) 450 enzyme induction or inhibition.

Table 2 summarizes selected herbal-drug interactions involving the best selling natural products in the United States. The best way to manage these interactions is to avoid the herbal supplement. If the patient is reluctant to stop taking the supplement, then close monitoring should be performed.

Patients should be routinely asked about their use of herbs and dietary supplements as part of the medical history. Patients who suffer from complications of their disease states or are sub-therapeutically treated with prescription medications are more likely to turn to herbals as an effective therapeutic option. Clinicians are encouraged to ask patients about their use of herbal supplements and be open to questions regarding these products. Through adequate communication and well documented medication

<table>
<thead>
<tr>
<th>Herbal supplement</th>
<th>Use</th>
<th>Prescription medication</th>
<th>Drug interaction</th>
<th>Clinical Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. John’s Wort</td>
<td>Mild to moderate depression</td>
<td>Oral contraceptive</td>
<td>Contraceptive failure</td>
<td>Discontinue St. John’s Wort; use non-estrogen containing product</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Warfarin</td>
<td>Decreased anticoagulant effect</td>
<td>Monitor INR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SSRI (i.e. sertraline, paroxetine)</td>
<td>Inhibits SSRI metabolism; may result in mild serotonin syndrome</td>
<td>Monitor for signs/symptoms of serotonin syndrome (i.e. confusion, agitation, tremor, dizziness)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anti-retrovirals (i.e. indinavir, nevirapine)</td>
<td>Anti-retroviral failure</td>
<td>Discontinue St. John’s Wort</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyclosporine</td>
<td>Decreased cyclosporine levels</td>
<td>Monitor cyclosporine levels</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Improvement of memory and blood circulation</td>
<td>Warfarin, heparin, aspirin</td>
<td>Increases anticoagulation effects</td>
<td>Monitor INR/PTT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcium channel antagonists (i.e. dil-tiazem)</td>
<td>Increased hypotensive effects</td>
<td>Monitor blood pressure</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Stress reliever; energy enhancer; decrease cholesterol</td>
<td>Warfarin</td>
<td>Possible interaction - case reports of spontaneous bleeding or increased clotting</td>
<td>Monitor INR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Digoxin</td>
<td>Elevated digoxin levels</td>
<td>Monitor digoxin levels</td>
</tr>
<tr>
<td>Garlic</td>
<td>Decrease cholesterol; prevent blood clots</td>
<td>Warfarin</td>
<td>Increases anticoagulation effects</td>
<td>Monitor INR</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Boost immune system function; prevent bacterial and viral infections</td>
<td>P450 CYP3A4 substrates (e.g. phenytoin, theophylline, cyclosporine)</td>
<td>Theoretically, a CYP3A4 inducer; important for drugs with narrow therapeutic indexes</td>
<td>Monitor drug levels</td>
</tr>
</tbody>
</table>

*SSRIs - selected serotonin reuptake inhibitors; Bolded items are well documented in medical literature, whereas non-bolded items are probable interactions or have been reported to a lesser extent.
histories, drug interactions between herbals and prescription medications can be prevented and avoided.

HIGH-ALERT MEDICATIONS – Patient Safety

In compliance with JCAHO Medication Management Standard MM.7.10, the Medical Center identified high-alert medications utilized in the organization and implemented a variety of safety strategies to improve safety related to the use of these medications.

High-Alert Medications refers to drugs that have a high-risk of causing injury, either as a result of a narrow therapeutic range or high incidence of reported serious errors in the past.

Particular safety strategies implemented for each medication were determined by their particular propensity for error as has been reported in the literature. The details of the strategies employed for a particular medication are located in the Medical Center intranet home page under: UI Medical Center / Clinical Care Guidelines / Medication Use / Drug Information & Education / G-MU 3.1 High Alert Medications – or use the following link: http://www.hospital.uic.edu/docs/mcmpp/Clinical%20Care%20Guidelines/High%20Alert%20Meds%207.04.htm

You should be able to identify high-alert medications that are used in your practice or work area and their applicable safety strategies that relate to your responsibilities. The document details safety strategies related to access/storage, ordering, preparing, dispensing, administering and monitoring designated High-Alert Medications. A particular safety strategy may not be evident to you personally, as it may be related to ordering on Gemini, how it’s stored or labeled by the pharmacy or administration precautions. Refer to this document if you have questions or are questioned on how high-alert medications are safeguarded.

The following medications have been deemed High-Alert Medications for the University of Illinois Medical Center:

Adrenergic agonists: epinephrine, isoproterenol and norepinephrine
Dobutamine and dopamine
IV esmolol and propranolol
Midazolam

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IV calcium salts
Chemotherapeutic agents
Chloral Hydrate
Digoxin
Heparin
Hypertonic Saline
Insulin
IV potassium chloride
IV magnesium
Narcotics and opiates, including Patient-Controlled Analgesia (PCA)
Neuromuscular blocking agents (e.g. vecuronium, pancuronium)
IV phosphate salts (sodium and potassium)
Warfarin