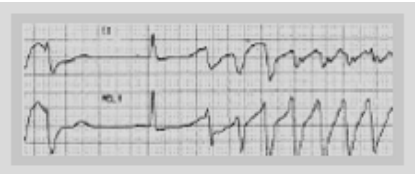
Odds & Ends

Number 93 October 2004

This *Heartbeat* will cover several current, unrelated issues and some clinical pearls gleaned from a review of recent medical literature.

Risk of SCD with erythromycin

Oral erythromycin, given alone, doubles the risk of sudden cardiac death (SCD), but when combined with the diltiazem or verapamil, the risk increases fivefold, according to results of a study in a September issue of the *New England Journal of Medicine.*[1]



Erythromycin given solo prolongs cardiac depolarization (prolonging QT interval) and has been associated with case reports of torsades de pointes. It is extensively metabolized through the cytochrome P-450 3A (CYP3A) enzyme system. Commonly used medications that inhibit the effects of CYP3A, including diltiazem and verapamil, may increase plasma concentrations of erythromycin, thereby increasing the risk of ventricular arrhythmias and SCD.

Take home point: Physicians should not combine erythromycin with verapamil or diltiazem.

Vioxx withdrawal: The jury's still out

My opinion is that there are no "perfect drugs." There are few complaints about the occasional patient death from rhabdo with statins, or CVA with ASA, e.g., although obviously these are associated with outcomes benefits. We all have to accept risk in life, and other than making Merck a stock market bargain, no real purpose was served by taking Vioxx off the market. The absolute risk of a CV event in the FDA study, Adenomatous Polyp Prevention on Vioxx (APPROVe) discussed at the 68th annual scientific meeting of the American College of Rheumatology in mid October, was really low [1.48 events per 100 patient-years on rofecoxib (Vioxx) compared to 0.75 events per 100 patient-years on placebo—explaining "doubling the risk."] There was no increase in deaths, and the increase in CV events was only after 18 months usage. Furthermore, this risk could very possibly have been erased by taking a baby aspirin in conjunction with the Vioxx. This would, however, decrease the GI benefit, and there would be no reason to prescribe the COX-2 inhibitors over the less expensive NSAIDs. The study results do not explain the mechanism of the increased cardiac risk.

From a cardiac standpoint, this type of drug should *never* be used in our HF population because of associated rises in BP, fluid retention and potential renal function alterations. In patients with high risk or known CAD, the risk-benefit profile cannot favor using a potentially pro-thrombotic COX-2 inhibitor to treat arthritis.

Take home points: Avoid the "designer" NSAIDs (COX -2 inhibitors) for now, until we have more data. Celecoxib [Celebrex] and valdecoxib [Bextra] may also have pro-thrombotic risk though also probably small—especially in high CV risk patients—although Celebrex recently has been shown to be safer than Vioxx.[2] A better alternative would be naproxen (Naprosyn/Alleve), which is a lot cheaper and may be cardio-protective. The caveat here is that all NSAIDs have risks when taken chronically, especially GI bleeding, but also liver and kidney toxicity. They should only be used continuously under physician supervision.

Declining kidney function associated with increased prevalence of MI

Data presented at the American Heart Association's 58th Annual High Blood Pressure Research Conference in mid October showed an "exponential" increased risk for MI in the US with each level of decreased kidney function. This risk appears to be

largely explained by an excess of the traditional Framingham risk factors in those with chronic kidney disease (CKD). But even after adjustment for Framingham risk factors and even non traditional risk factors such as cardio CRP, there is significant risk associated with chronic kidney disease.

Take home point: Use appropriate measures to aggressively prevent and treat diabetes, high blood pressure, tobacco cessation, and getting cholesterol/LDL-C levels down to reduce the likelihood of CVD in patients with CKD.

Shrinking waistlines and increased HDL

A small study presented at the Canadian Cardiovascular Congress 2004 at the end of October revealed a significant decrease in body weight and body mass index along with a 7.6% increase in HDL-C with a daily dose of a cup of cranberry juice (27% pure)—not too much to choke down in the morning. They also found a significant decrease in waist and hip circumference as well as waist to hip ratio. This could be a nice cosmetic effect and important preventive effect of flavonoid-rich cranberry juice, considering the increase in HDL-C with medication tends to range from 8% to 15%. A larger double-blind, placebo-controlled study is planned.

Take home point: Cranberry juice is a nice alternative morning beverage possibly with some beneficial effects.

Optimizing medical management of CAD/high-risk CAD in patients with CKD

The following is our recommended plan to decrease cardiac risk in patients with CKD:[3]

***Therapeutic Lifestyle Changes* (TLC).** The importance of exercise and appropriate diet can not be emphasized enough as a first line treatment for CVD risk reduction.

Hypertension. Goal BP should be at least < 130/80. Hypertension in CKD patients, especially those on hemodialysis (HD), is volume-dependent. Therefore, maintenance of fluid balance is paramount. Examination of neck veins, edema, and body weight can aid in managing fluid status.

ACEI: Angiotensin-converting enzyme inhibitors decreased 30-day mortality (relative risk 0.64) in dialysis patients with AMI, an effect similar to non-dialysis patients.[4] ACEIs decrease the progression of nephropathy in type 1 and 2 diabetes[5] [6] and non-diabetic renal disease.[7] In the Heart Outcomes Prevention Evaluation (HOPE) trial, risk reduction for CV death, all-cause mortality, and heart failure hospitalizations with ramipril was greater for CKD than non-CKD patients.[8] These agents should be monitored closely because they may induce hyperkalemia in patients with CKD.

ARB: Angiotensin receptor blockers have demonstrated renal protection in CKD patients but not cardio-protection. Renal protection appears to be independent of blood pressure reduction. In a randomized trial of 1,513 CKD patients with type 2 DM, nephropathy progression was reduced by losartan, but CV death incidence was similar to placebo.[9] In another trial of 1,715 CKD patients with hypertension and type 2 DM, irbesartan afforded renal protection but not cardio-protection.[10] Two new studies confirm the utility of ACEIs[11] and the non-inferiority of ARBs to ACEIs[12] in preventing the progression of renal disease in patients with T2 DM and hypertension. In the small comparison study death from CVD was much lower than expected and equal in the ACEI and ARB groups.

Questions yet to be answered are which of these angiotensin II (A II) blockers is better, and could they actually complement one another if used together? **Based on lack of proven cardio-protective effect of ARBs in CKD patients, ACEIs, in the absence of associated cough or angioedema, are the preferred form of A II blockade when possible.** Should they be proven equal (probable), then the higher cost, higher for ARBs, would also have to be considered.

Beta-blockers: Beta-blockers appear to retain their cardio-protective effects in CKD patients. In an analysis of a Medicare database of over 200,000 mild CKD patients, there was a 35% reduction in mortality with beta-blockers.[13]

Treatment of dyslipidemia. Target LDL-C in known CAD patients and those at very high risk for CAD is <100 mg/dl. Statin dose reduction is required in renal transplant patients taking cyclosporine or tacrolimus. It is not clear whether isolated high triglycerides or low levels of HDL-C should be treated with drugs in CKD patients—the vote here is a resounding yes for combination therapy with the usual precautions.

Treatment of hyperhomocysteinemia. The recommended daily allowances of folate (5 mg/day), transcobalamin (0.4 mg/day), and pyridoxine (50 mg/day) normalize the homocysteine level in mild to moderate CKD patients and renal transplant patients, but only mildly affect homocysteine levels in dialysis patients. Higher homocysteine levels are associated with increased CV events in CKD patients, but data demonstrating reduction in CV events with treatment in CKD or the general population are lacking. *The recommendation here is to normalize plasma homocysteine—no risk and possible benefit.*

Management of anemia. Anemia may increase the severity of angina and left ventricular hypertrophy, and decrease exercise tolerance, and its correction improves these abnormalities. The Normal Hematocrit Trial showed that patients with end stage renal disease and CAD or heart failure treated with erythropoietin to a target hematocrit of 42% had a higher risk ratio (1.3) for the end points of death or nonfatal AMI compared with a targeted hematocrit of 30%.[14] Alternatively, a large Medicare study of HD patients using erythropoietin demonstrated decreased risk of cardiac mortality with a hematocrit of 30% to 33%, and an even lower risk with 33% to 36%.[15] The National Kidney Foundation Dialysis Outcomes Quality Initiative recommends a target hematocrit of 33% to 36%.[16]

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