Clinical Briefs in Primary Care™

The essential monthly primary care update

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Febuxostat Compared with Allopurinol in Patients with Hyperuricemia and Gout

Source: Becker MA, et al. *N Engl J Med*. 2005;353:2450-2461.

THERE HAVE BEEN NO NEW AGENTS approved to treat gout for over 20 years. Because the plasma becomes supersaturated at a uric acid level of 6.0 mg/dL, it is felt that persons with a diathesis for tissue deposition of urate (gouty arthritis, tophi, or both) will optimize benefit by maintaining serum uric acid (SUA) below this level. Although allopurinol (ALP) has been used with some success for many years, it is associated with intolerance in some patients, and commonly fails to achieve the goal of serum uric acid < 6.0 mg/dL. Finally, allopurinol is uncommonly associated with a hypersensitivity syndrome; this vasculitis has been fatal in as many as 25% of victims. Febuxostat (pronounced feb-u-zo-stat) is a new xanthine oxidase inhibitor which blocks uric acid production.

A trial of patients with gout (n = 762) randomly assigned subjects to febuxostat 80 mg or 120 mg qd vs allopurinol. Allopurinol was dosed at 300 mg/d except in those requiring dosage adjustment due to renal insufficiency. The primary end point of this 1 year study was ability to achieve a SUA < 6 mg/dL, confirmed for each of the last three study months.

Febuxostat 80 mg and 120 mg were more effective than ALP for percent of individuals able to achieve and maintain SUA < 6 (53%, 62%, and 21% respectively). During the trial, frequency of gout flares was similar in all groups. ■

Prognostic Value of Serial B-Type Natriuretic Peptide Testing During Follow-up of Patients with Unstable Coronary Artery Disease

Source: Morrow DA, et al *JAMA*. 2005;294:2866-2871.

BRAIN-TYPE NATRIURETIC PEPTIDE (BNP) has been found to be useful to differentiate etiologies of dyspnea in patients presenting to emergency departments, as a diagnostic tool for heart failure, and as a metric for following adequacy of treatment in heart failure. BNP is released in relation to ventricular wall stress, and elevations of BNP are also seen after acute coronary syndromes (ACS). Elevations of BNP in ACS have been found to be strongly associated with overall mortality, and specifically with onset of new congestive heart failure. Conclusions about the utility of BNP in ACS are primarily based upon a limited number of BNP measurements temporally associated with the acute cardiac event. Whether more persistent monitoring of BNP levels might prove useful as a predictive marker for increased risk was the subject of this study.

Morrow et al monitored BNP levels in ACS patients (n = 4,266) at hospitalization, 4 months, and 12 months. The primary end point was death or new CHF. Subjects with a BNP > 80 pg/mL at each measurement cycle had a dramatically worse prognosis for the primary outcome. At 4 months, an increase BNP was associated with a 2.5 hazard ratio for death/CHF, and at 12 months a 4.7 hazard ratio. Just looking at the end point of mortality, an elevated BNP was associated with a doubled long-term risk. ■

Dietary Fiber Intake and Risk of Colorectal Cancer

Source: Park Y, et al. *JAMA*. 2005;294:2849-2857.

THERE HAVE BEEN A NUMBER OF mechanisms suggested to support the concept that increased dietary fiber might reduce risk for colon cancer (COL): dilution of fecal carcinogens, reduced fecal transit time, enhanced production of anticarcinogenic short chain fatty acids, and binding of carcinogenic bile acids. While each of these effects may occur from fiber enhancement, observational studies which evaluate the relationship between dietary fiber and COL have provided conflicting results.

Park et al performed a pooled analysis of 13 prospective cohort studies that examined dietary fiber and colon cancer. Study subjects (n = 725,628) were adults who had been followed for 6-20 years.

Although univariate analysis was optimistic in suggesting a 16% relative risk reduction for COL in the highest quintile of fiber intake versus the lowest, subsequent

multivariate analysis was unable to confirm this benefit. Despite the intellectual appeal of fiber intake as a preventative for COL, the data do not support an independent benefit. ■

Efficacy and Safety of Benazepril for Advanced Chronic Renal Insufficiency

Source: Hou FF, et al. *N Engl J Med.* 2006;354:131-140.

ACE INHIBITORS HAVE BEEN SHOWN to improve renal outcomes in hypertension and to reduce proteinuria. By decreasing intraglomerular pressure, ACE inhibitors can produce a decline (usually transient) in renal function; clinicians sometimes are anxious about using ACE inhibitors in persons with chronic kidney disease, for fear of producing hyperkalemia or worsening renal function. This reluctance has been particularly prominent when creatinine levels rise above 2.0-2.5 mg/dL. Indeed, in the recent past, some textbooks have explicitly stated that ACE inhibitors are to be avoided when the creatinine surpasses 2.5 mg/dL. In contrast, studies have shown that the renal benefits of ACE inhibitors increase as the degree of renal impairment rises, but there has been a paucity of data from persons with creatinine > 3.0 mg/dL.

Hou et al studied subjects with CKD (n = 422) divided into Group 1 (baseline creatinine 1.5-3.0 mg/dL) and Group 2 (baseline creatinine 3.1-5.0 mg/dL). Group 1 received treatment with benazepril 20 mg/d; Group 2 was randomized to benazepril 20 mg/d or placebo. Both groups were treated for 3.4 years. Subjects were continued on their usual antihypertensive therapies.

The risk of the composite primary end point (doubling of serum creatinine, end-stage renal disease, or death) was reduced by 43% with benazepril, compared to placebo. Proteinuria and renal function decline were favorably affected. It is critical to recognize that the authors excluded subjects whose creatinine increased by > 30% or whose potassium rose over 5.6 mmoL/L during the initial 8 week run-in; clinicians would be wise to use similar boundaries. ■

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Prognostic Value of Thyroid Hormone Levels in Acute MI: Just an Epiphenomenon?

Source: Satar S, et al. *Am Heart Hosp J*. 2005;3:227-233.

ACUTE ILLNESS MAY RESULT IN alterations in thyroid function tests commonly referred to as Sick Euthyroid Syndrome (SES). SES is characterized by lowered levels of T3 and T4, with a 'normal' TSH: the peculiarity of the syndrome is that in normal circumstances, one would anticipate a rise in TSH when T3 and T4 drop. This aberrancy suggests a transient diminution in pituitary responsivity.

Cardiac tissue is exquisitely responsive to circulating thyroid hormone. In other disease states, SES has been shown to be associated with a poor outcome. Satar et al investigated the relationship between thyroid function status and outcomes in persons with acute myocardial infarction (AMI). Subjects were comprised of 95 patients with AMI, 26 patients with acute chest pain but no MI, and 114 controls (no chest pain, no MI).

In acute MI patients, a reduced T3 or T4 was associated with poorer survival, especially if accompanied by a higher TSH. Apparently, during AMI there is a downregulation of thyroid hormone production. Lower levels of T3 and T4 associated with AMI correlate with worse outcome. ■

NSAIDs and the Risk of Actinic Keratoses and Squamous Cell Cancers of the Skin

Source: Butler GJ, et al. *J Am Acad Dermatol*. 2005;53:966-972.

CYCLO-OXYGENASE (COX) IS overexpressed in some cancer cells, including squamous cell carcinoma of the skin (SCC) and actinic keratoses (AK). Basal cell carcinoma does not exhibit COX overexpression. Because recent animal studies have found COX inhibitors to have a favorable effect in SCC, an investigation in humans is timely.

Australians have a very high incidence of SCC and AK. In a small community in Queensland, SCC patients (n = 86) were compared with controls (n = 187) in reference to regular use of NSAIDs, defined as at least 2 NSAID tablets weekly. NSAID use was divided into 'low frequency users' of NSAIDs (ie, at least 2 tablets/week) and 'high frequency users' (ie, at least 8 tablets/week)

There was a dramatic difference in NSAID use between those with SCC or AK and those without. The odds ratio for high-frequency NSAID users having SCC was 0.07, or a 93% lesser odds ratio! Similarly, the number of AK lesions for regular NSAID users was approximately half that of non-users. NSAID use may have a favorable impact upon risk for both AK and SCC. ■