INTERNAL MEDICINE ALERT

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INSIDE

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If Your Patient Has Had an MI, Do Not Give an NSAID

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

Clinical Professor, University of California, San Diego, CA

Dr. Scherger reports no financial relationships relevant to this field of study.

Synopsis: *A large cohort study in Denmark showed that patients with a previous myocardial infarction (MI) who took any NSAID had an increased risk of death or a recurrent MI. The greater the use of an NSAID, the greater the risk.*

Source: Schjerning Olsen AM, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: A national cohort study. *Circulation* 2011;123:2226-2235.

A TEAM IN DENMARK LOOKED AT 102,138 PATIENTS WHO WERE ADMITTED with a first myocardial infarction (MI) from 1997 to 2006. A total of 83,677 (81.9%) were discharged alive from the hospital and were included in this study. The average age was 68 with a range of 55 to 81 years old and 63% were men. At least one prescription for a nonsteroidal anti-inflammatory drug (NSAID) was identified for 35,405 (42.3%) patients. The most commonly used NSAIDs were ibuprofen, diclofenac, and naproxen. The Cox-2 inhibitors celecoxib and rofecoxib also were included in the study. The risk of each drug, time of use, and quality of use were measured.

Deaths from any cause and recurrent MI were measured in all patients. During an observation period of 14 years, 35,257 (42.1%) of the patients died or had a recurrent MI. Overall, the use of NSAIDs was significantly associated with an increased risk of death or recurrent MI with a hazard (risk) ratio of 1.55 (confidence interval, 1.29-1.62). While the greatest risk is in the first 6 months after MI, the risk steadily persisted throughout the study period. Ibuprofen, naproxen, diclofenac, celecoxib, and rofecoxib were studied separately and show similar

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risk. The risk was greatest with diclofenac, especially in the first 7 days after MI, with a risk ratio of 3.26.

The authors conclude that even short-term treatment with most NSAIDs is associated with increased risk of death and recurrent MI in patients with prior MI. Neither short- nor long-term treatment with NSAIDs is advised in this population, and any NSAID use should be limited from a cardiovascular safety point of view.

■ COMMENTARY

The Scandinavian countries have an amazing ability to do large population studies. They have well-organized patient registries that cover the entire population and substantial health information that is searchable, allowing for a tracing of health indicators over time.

This well-organized study was able to track more than 80,000 patients with an MI over 14 years and look at use of NSAIDs. The bottom line is that they are risky and lead to death or recurrent MI. This risk includes the Cox-2 inhibitors.

We all have patients in cardiac rehabilitation working out on treadmills or doing other exercise. They get muscle soreness and arthritic pain. What harm could come with using a little ibuprofen or naproxen? Plenty. Hazard (risk) ratios of < 2 for unusual events make the likelihood of death or an MI small, but why take this risk? Stretching, ice, acetaminophen, and just bearing with the discomfort are healthier alternatives. We are a population of pill poppers and one of our roles is to help our patients stay off them when the need is modest and the risk is serious.

We make our risk-benefit decisions with our patients and this study is an important contribution to those deliberations. Does this study have implications for other cardiac patients beyond those with a previous MI? As the authors point out, NSAIDs have a contraindication in all patients with cardiac disease.[1,2] This study changes my practice and will make me much less likely to consider any NSAID in post-MI and other cardiac patients. Avoiding them is a rule we and our patients can live by. ■

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1. Gislason GH, et al. Increased mortality and cardiovascular morbidity associated with the use of nonsteroidal anti-inflammatory drugs in chronic heart failure. *Arch Intern Med* 2009;169:141-149.
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That Cup of Joe Affects Your Prostate Cancer Risk

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

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Dr. Gupta reports no financial relationship relevant to this field of study.

Synopsis: *Regular coffee consumption is associated with a prominent decrease in fatal or metastatic prostate cancer.*

Source: Wilson KM, et al. Coffee consumption and prostate cancer risk and progression in the health professionals follow-up study. *J Natl Cancer Inst* 2011 May 17; Epub ahead of print.

Coffee has a long history of being blamed for many ills, sometimes justly. However, emerging research indicates that it may not be so bad after all. For instance, recent studies have demonstrated that coffee may have benefits, such as protecting against Parkinson's disease, type 2 diabetes mellitus, and liver cancer.[1] In another prospective study of American men, coffee consumption was shown to prevent symptomatic gallstone disease.[2] In addition to caffeine and some of the phytochemicals, coffee also has a high content of antioxidants. This has prompted researchers to investigate the relationship of malignancies

with coffee consumption. In a study looking at two large cohorts of men and women, regular consumption of decaffeinated coffee was associated with a 52% reduction in incidence of rectal cancer compared to those who never consumed decaffeinated coffee whereas consumption of caffeinated coffee or tea with caffeine or caffeine intake was not associated with the incidence of colon or rectal cancer in either cohort.[3] Similarly, in the present study, researchers attempted to investigate the relationship between coffee intake and risk of overall prostate cancer, including that of aggressive disease.

Using data from the Health Professionals Follow-up Study, Wilson et al conducted a prospective cohort study of 47,911 men followed for more than 20 years. Beginning in 1986, the study participants were followed through biennial questionnaires to update information on lifestyle and health outcomes, and usual diet (including intake of regular and decaffeinated coffee), and were assessed every 4 years. These men, who were 40-75 years old at the start of the study, completed a questionnaire about their health and lifestyle when they enrolled. They then answered regular follow-up questionnaires to update this information. The researchers also identified diagnoses of prostate cancer initially by self-reports from the men themselves or their relatives and then confirmed these by checking medical records and pathology reports. Deaths were ascertained through reports from family members and the National Death Index and the underlying cause of death was decided based on information such as medical records, registry information, and death certificates. Total prostate cancer incidence, excluding stage T1a cancers (which are discovered incidentally during treatment for benign prostatic hypertrophy), was studied. Data for men with advanced, lethal, or non-advanced cancers were examined separately to distinguish those patients in whom the cancer was likely to progress clinically.

The study participants overall consumed an average of 1.9 cups of coffee per day. During the 20 years of follow-up (from 1986 to 2006), the researchers found that 5035 of the 47,911 men were confirmed to have developed prostate cancer. Of these, 642 patients had lethal type prostate cancers (defined as fatal or metastatic), 896 were advanced, and 3,221 were non-advanced.

Researchers found that men drinking six or more cups per day had an 18% lower risk of overall prostate cancer compared with non-coffee drinkers (relative risk [RR], 0.82; 95% confidence interval [CI], 0.68-0.98). However, when only lethal forms of the prostate cancer were considered in this group, the risk was decreased by approximately 60% vs non-coffee drinkers (RR, 0.40; 95% CI, 0.22-0.75).

Additionally, both caffeinated and decaffeinated coffee appeared to decrease the risk for lethal prostate cancer. For each one cup per day increment, the risk declined by 6% for regular coffee (RR, 0.94; 95% CI, 0.88-1.01) and by 9% for decaffeinated coffee (RR, 0.91; 95% CI, 0.83-1.00; $P = 0.05$). Men drinking at least six cups a day had an age-adjusted incidence of only 425 prostate cancers per 100,000 person-years as opposed to 529 in those not consuming coffee. Likewise, the incidence of lethal prostate cancers was 34 vs 79 per 100,000 person-years in those drinking at least six cups vs nondrinkers, respectively. However, no association was found between coffee consumption and low-grade prostate cancers.

■ COMMENTARY

Coffee contains biological compounds that improve glucose metabolism, have anti-inflammatory and antioxidant effects, and affect sex hormone levels, all of which may have played a role in prostate cancer progression. In fact, coffee is a major dietary source of antioxidants for Americans. This study provides a strong association between coffee consumption and lower risk of lethal and advanced cancers and the authors state that this appears to be related to non-caffeine components of coffee. We currently have not identified modifiable risk factors for advanced prostate cancer, which is the second-leading cause of cancer death among American men after lung cancer. However, the analyzed data from this well done large study (as well as some smaller ones in the past) are clearly insufficient for us to recommend that men start drinking gallons of coffee in an attempt to lower their prostate cancer risk.[4] We would need to see these results replicated in other large studies before we can be sure whether coffee consumption affects the risk of prostate cancer. Additionally, heavy caffeine use (four to seven cups of coffee a day) can cause other problems such as tachycardia, restlessness, anxiety, irritability and sleeplessness, gastroesophageal reflux, and risk of heart disease in susceptible people. Also, we must keep in mind that for those drinking more than plain coffee, supplements such as cream and sugar contribute fat and calories to the diet. Therefore, at this time I would stick to the old dictum, "Everything in moderation." ■

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cancer: A meta-analysis of epidemiological studies. *BJU Int* 2010;106:762-769.

Add Prunes to Your Toolkit for Constipation

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

Clinical Professor, University of California, San Diego, CA

Dr. Scherger reports no financial relationships relevant to this field of study.

Synopsis: *Dried plums (prunes) are safe and more effective than psyllium for treating mild-to-moderate constipation.*

Source: Attaluri A, et al. Randomised clinical trial: Dried plums (prunes) vs. psyllium for constipation. *Aliment Pharmacol Ther* 2011;33:822-828.

At the University of Iowa, 40 constipated subjects were randomized in an 8-week single-blind crossover trial. Thirty-seven of the 40 were women and the average age was 38. The subjects took either prunes or psyllium for 3 weeks and then crossed over after a 1-week wash-out period. Fifty grams of prunes and 11 grams of psyllium were used equaling 6 grams of fiber each. The subjects maintained a daily symptom and stool diary. The study assessments included number of spontaneous bowel movements per week, global relief of constipation, stool consistency, straining, tolerability, and taste.

The subjects taking the prunes reported more complete spontaneous bowel movements per week (primary outcome measure) and stool consistency scores improved significantly compared to psyllium ($P < 0.05$). Straining and global constipation symptoms did not differ significantly between treatments. Dried plums and psyllium were rated as equally palatable and both were safe and well tolerated.

■ COMMENTARY

Constipation is one of the most common symptoms presenting to primary care physicians. Prevention and treatment often blur into one passionate request from patients for help. Patients vary in what they have tried and what appeals to them. Having a toolkit of several effective options helps us care for more of these suffering patients.

Adequate fluid intake and daily fiber are the mainstay of prevention. My favorite is a cereal concoction I eat every day combining some regular Cheerios (oat fiber), some Fiber One cereal, yogurt, a handful of sliced walnuts and some blueberries, moistened with low fat milk. One of my partners has her own "poop pudding" focusing more on fruit than cereal. Not everyone tolerates gluten in large amounts and some get cramps from very much fruit.

My mother struggled with lifelong constipation and drank prune juice every night with limited success. When I put her on a high-fiber cereal in the morning as a medical student, my reputation in her eyes was set for life.

This is a small comparison study that puts prunes right up there with psyllium for constipation prevention and treatment, at least among younger women. When I mentioned this study to a perimenopausal patient, she quickly said that dried apricots work better for her than prunes. I know from first-hand experience that very much dried fruit of any kind will get your intestines going. Fruit juices are mostly sugar and are to be avoided. The fiber has been largely filtered out.

Too often I see physicians resorting to a bad habit learned in medical school, the "stool softener" docusate sodium (Colace). Docusate is far less effective than psyllium in managing constipation.[1]

Sometimes it is the small things to us that make a big difference with patients. I enjoy telling patients I can cure their constipation if they cooperate every day. They give me looks of joy or skepticism. Usually I am effective and I wonder how much of my reputation in the community is based on that. ■

Reference

1. McRorie JW, et al. Psyllium is superior to docusate sodium for treatment of chronic constipation. *Aliment Pharmacol Ther* 1998;12:491-497.

Pharmacology Update

Boceprevir Capsules (Victrelis™)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationship to this field of study.

The FDA has approved boceprevir, a protease inhibitor for the treatment of chronic hepatitis C (HCV) infec-

tions. Boceprevir is an inhibitor of HCV non-structural protein 3 (NS3) serine protease. It is marketed by Merck & Co. as Victrelis. Boceprevir is the first of several protease inhibitors expected to be approved for this indication in the near future.

Indications

Boceprevir is indicated for the treatment of chronic HCV genotype 1 infections in adult patients with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy.[1]

Dosage

The recommended dose is 800 mg (4 capsules) taken orally three times daily (every 7 to 9 hours) with food since food increases the absorption of boceprevir. It is taken concomitantly with peginterferon alfa-2b (1.5 mcg/kg weekly) and ribavirin (600 mg to 1400 mg per day based on weight).[1] Dosing schedules for the different subgroups are as follows:

1. Patients without cirrhosis.

Start with peginterferon/ribavirin for 4 weeks then add boceprevir for 24 weeks. Subsequent therapy is based on response. For those who have undetectable virus at week 8 and 24, treatment is completed at week 28. For those in whom virus is detectable at week 8, but undetectable at week 24, continue boceprevir through week 36 and peginterferon/ribavirin through week 48 (B0C/RGT).

2. Patients previously untreated or who are previous partial responders or relapsers to interferon and ribavirin.

Start with peginterferon/ribavirin for 4 weeks then add boceprevir for 32 weeks. For those who have undetectable virus at week 8 and 24 treatment is completed at week 36. For those who have detectable virus at week 8, but undetectable virus at week 24, continue boceprevir through week 36 and then peginterferon/ribavirin through week 48.

3. Patients with cirrohsis — peginterferon/ribavirin for 4 weeks and boceprevir/peginterferone/ribavirin for 44 weeks (BOC/PR48).

Treatment should be discontinued if HCV-RNA levels are greater than or equal to 100 IU/mL at treatment week (TW) 12 or detectable at TW 24.

Boceprevir is available as 200 mg capsules.

Potential Advantages

The addition of boceprevir to standard therapy (peginterferon/ribavirin) significantly increased the rates of sustained virologic response in both treatment naïve and previously treated patients with chronic HCV genotype 1 infection.[1-3]

Potential Disadvantages

The most common adverse events associated with boceprevir (compared to peginterfon/ribavirin) were anemia (45%-50% vs 20%-30%) and dysgeusia (35%-44% vs 11%-16%).[1] Treatment emergent virus in patents who have not achieved sustained viral response may be cross resistant to HCV NS3/4A protease inhibitors. Potent CYP3A4/5 inducers as well as drugs that are metabolized by the isoenzymes should be avoided. Treatment requires a high pill burden — 12 capsules per day — and a long and complex dosing schedule.

Comments

The efficacy and safety of boceprevir was evaluated in two randomized, double-blind trials, one in previously untreated patients (SPRINT-2) and the other in patients who had previously failed peginterferone/ribavirin (RESPOND-2). In SPRINT-2, patients with HCV RNA levels of 10,000 IU/mL or greater (n = 1097) were started on peginterferon alfa-2b (1.5 mcg/kg once weekly) and weight-based oral ribavirin (600 mg to 1400 mg/daily) for 4 weeks. One arm received boceprevir (800 mg three times daily) plus peginterferone/ribavirin for 24 weeks and they were followed by response-guided therapy (BOC/RGT). The second arm received boceprevir and peginterferon/ribavirn for 44 weeks (BOC/PR48). The third or control arm received placebo and peginterferon/ribavirin for 48 weeks (PR48). In response-guided therapy, those with undetectable virus at week 8-24 discontinued therapy and those detectable at week 8, but not week 24, received an additional 20 weeks of placebo plus peginterferon/ribavirin. Black patients and nonblack patients were enrolled separately into two cohorts. Each arm had a minimum follow-up of 24 weeks. The primary endpoint was sustained virologic response (SVR) defined as undetectable HCV-RNA at follow-up week 24 or week 12 if results were missing at week 24. SVR rates were 63% for BOC/RGT, 66% for BOCV/PR48, and 38% for the control arm. SVR for blacks were 42%, 53%, and 23% compared to 67%, 68%, and 40%, respectively for nonblacks ($P < 0.05$).[2] Patients with cirrhosis and those with detectable virus at week 8 responded better with BOC/PR48 compared to BOC/RGT. Boceprevir-resistant variants were found in patents who achieved < 1 log10 decrease in HCV-RNA (47% for BOC/RGT and 35% for BOC/PR48). In RESPOND-2, patients who were noresponders or had relapsed were randomized to similar regimens except the BOC/RGT regimen was 32 weeks. SVR rates were 21% for control, 59% BOC/RGT, and 66% for BOC/PR48. Those who relapsed responded better than nonresponders (69% for BOC/RGT and 75% for BOC/PR48 compared to 40% and 52%, respectively). Similar to SPRINT-2, boceprevir-resistant variants were found in patients who did not respond as well. Anemia and dysgeusia were more

common in the boceprevir group. Erythropoietin was given in approximately 40% of the cases of anemia. Common adverse events associated with triple therapy were fatigue, headache, and nausea.

Clinical Implications

Chronic HCV genotype 1 infections are the least responsive to pharmacotherapy. SVR with standard therapy (peginterferon/ribavirin) is around 40%.[4] Boceprevir provides an important addition to the treatment of chronic HCV genotype 1 with significant improvement in SVR rates. Peginterferon/ribavirin will likely remain the treatment option for other genotypes at this time. Telaprevir, another protease inhibitor recently approved for the same indication, will be reviewed in the next issue of *Internal Medicine Alert*.

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3. Bacon BR, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011; 364:1207-1217.
4. McHutchison JG, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009;361:580-593.

CME Questions

29. Which NSAID demonstrated the greatest short-term risk for death or a recurrent MI in patients with a prior MI?
a. Ibuprofen
b. Naproxen
c. Diclofenac
d. Celecoxib

30. In the coffee consumption and prostate cancer risk study by Wilson et al, which of the following appeared to decrease risk for lethal prostate cancer?
a. Caffeinated coffee
b. Decaffeinated coffee
c. Both
d. Neither

31. From this study, which is the most effective and best tolerated for managing mild-to-moderate constipation?
a. Psyllium
b. Dried plums (prunes)
c. Docusate sodium
d. Fiber One cereal

Answers: 29. c, 30. c, 31. b

CME Objectives

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is an advisor for Endo, Kowa, Pricara, and Takeda.

COPD in Never Smokers

Source: Lamprecht B, et al. COPD in never smokers: Results from the population-based burden of obstructive lung disease study. *Chest* 2011;139: 752-763.

Unless there is another overt cause, such as occupational exposure to toxic inhalants, we generally expect chronic obstructive pulmonary disease (COPD) to be secondary to cigarette smoking. The pulmonology literature consistently suggests that a substantial minority — at least 20% — is NOT related to cigarette smoking. This multinational survey by Lamprecht et al provides a fresh appraisal of the burden of COPD unrelated to smoking.

The Global Initiative for Obstructive Lung Disease (GOLD) guidelines were used to define COPD through spirometry. Primary cigarette smoking, exposure to secondary smoke, occupational exposure, and biomass exposure (for instance, cooking or home heating using wood, coal, dung, or crop residue) were all queried among 10,000 subjects from 14 countries.

Of the 4291 never smokers, 12.2% fulfilled GOLD criteria for COPD. Of all persons ultimately defined as meeting COPD criteria, just over one-fourth were never smokers. Women were disproportionately represented in the group of persons with moderate-severe COPD. It has been suggested that women may have greater susceptibility both to tobacco smoke as well as other potentially toxic inhalants.

COPD is now the third most common cause of death in America. Pulmonologists have suggested that COPD remains underdiagnosed. Based on these results, the authors suggest that symptomatic persons, even if never smokers, should be screened for COPD. ■

Early Prostate Cancer: Prostatectomy vs Watchful Waiting

Source: Bill-Axelson A, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2011;364:1708-1717.

The management of early prostate cancer (PCA) remains controversial. Although surgical and radiation interventions offer the opportunity for cure, many more men with early PCA die with the disease than from it. Were definitive interventions without risk, there likely would be little discussion about whether to intervene; however, because the potential consequences of intervention are significant (e.g., incontinence, erectile dysfunction), clarification of the risk:benefit ratio is critical.

A randomized multinational study of subjects from Sweden, Finland, and Iceland (n = 695) randomized men < 75 years of age with localized, moderately well to well-differentiated prostate cancer to either radical prostatectomy or watchful waiting. Men were followed for 12.8 years.

At 12.8 years, all-cause mortality was statistically significantly less in the surgery group (166/347) than the watchful waiting group (201/348). Similarly, PCA-related death was less in the surgically treated group (14.6% vs 20.7%). Benefits were clear for men < 65 years of age, but only a trend toward benefit (results not statistically significant) could be determined from the data in older men, possibly because of the smaller number of men in this age group.

Adverse effects of surgery were substantial. For instance, at 1 year, 32% of men had incontinence and 58% had impotence. Younger men with early PCA appear to enjoy mortality benefit from surgical intervention, though at a substantial adverse event cost. Competing causes of death in older men diminish the relative benefits of surgery. ■

Dietary Vitamin D and Incident Diabetes

Source: Gagnon C, et al. Serum 25-hydroxyvitamin D, calcium intake, and risk of type 2 diabetes after 5 years: Results from a national, population-based prospective study (the Australian Diabetes, Obesity and Lifestyle study). *Diabetes Care* 2011;34:1133-1138.

The beta cells of the pancreas possess a vitamin D receptor, so perhaps we should not be surprised that vitamin D might be associated with diabetes (DM). Preliminary evidence has suggested that dietary vitamin D (VTD) might be associated with less risk for DM, but prior to this report, no large population study has provided sufficient information to be definitive.

Gagnon et al researched subjects involved in the AusDiab studies, which included 11,247 noninstitutionalized adults free of DM at baseline who underwent a 75 g oral glucose tolerance test (GTT) at baseline. Five years later about half (6537) of these had a repeat GTT, of which 80% were still not diabetic.

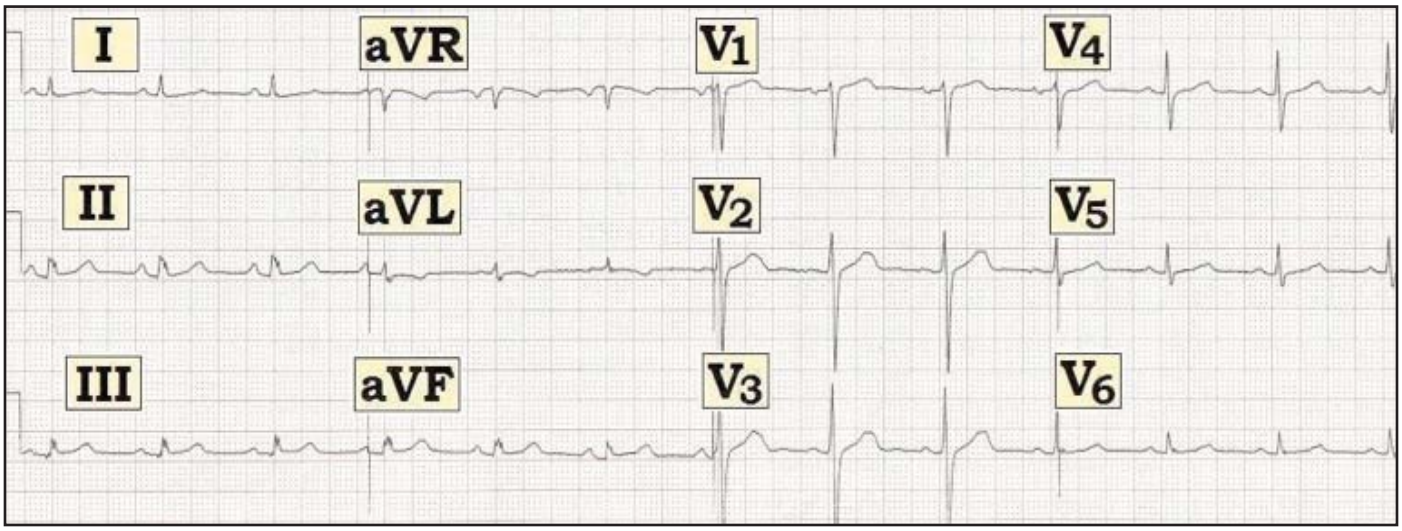
The investigators found a linear reverse relationship between reported dietary VTD and incident DM over a 5-year interval: for every 25 nmol/L increase in VTD, there was a 24% reduced risk of DM. Also studied in this same data set was calcium intake, which did not correlate with incident DM. Subjects in the top quartile of VTD intake enjoyed a 44% risk reduction for incident DM.

Because these are observational data, causation cannot be established. Prospective, randomized, placebo-controlled trials of VTD supplementation will be necessary to confirm the preventive capacity of VTD. ■

Nothing More than Nonspecific Changes?

By Ken Grauer, MD, *Professor Emeritus in Family Medicine, College of Medicine, University of Florida*

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.



Scenario: The ECG shown above was interpreted as essentially "normal," showing nothing more than minimal nonspecific ST-T wave changes. Do you agree?

Interpretation: The rhythm is sinus at a rate just under 75/minute. All intervals and the mean QRS axis are normal. There is low voltage in the limb leads (ie, QRS amplitude does not exceed 5 mm in I, II, III, aVR, aVL, or aVF). There is no chamber enlargement. Regarding Q-R-S-T changes — there may be a tiny q wave in lead III. R wave progression is normal, with transition being slightly delayed to between leads V3-to-V5.

The interesting findings relate to the inferior leads. There is subtle but real ST segment elevation in leads II, III and aVF. ST segment deviations are judged with respect to the preceding PR segment baseline — and the takeoff of the J-point in each of the inferior leads is above this baseline. Support that this finding is real comes from the subtle ST segment coving and shallow, symmetric T- wave inversion in lead aVL.

Given the small amplitude and admittedly subtle nature of the above findings — we are not at all certain that they represent acute inferior infarction. However, this possibility should be considered. Clinical correlation and comparison with prior tracings is needed to clarify the situation. If this patient had presented with new-onset chest pain and no prior tracings — serial troponins and repeat ECG would be needed to rule out an acute event. Even without a history of new-onset chest pain, this tracing should not be interpreted as "normal." Clinical correlation is essential before determining disposition of the patient. ■

In Future Issues:

Obesity, Race, and Risk for Death or Functional Decline Among Medicare Beneficiaries

Effect of Concomitant Use of Clopidogrel and Proton Pump Inhibitors After Percutaneous Coronary Intervention

Telaprevir for the Treatment of Chronic Hepatitis C

PHARMACOLOGY WATCH

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Women's Health Issue — Adverse Medication Effects

In this issue: Calcium supplements and MI; birth control pills and VTE; ACE inhibitors and breast cancer risk; spending on pharmaceuticals; and FDA actions.

Calcium supplements and MI risk

Do calcium supplements increase the risk of myocardial infarction (MI)? Researchers from New Zealand recently reanalyzed data from the Women's Health Initiative (WHI) in an attempt to answer this question. In 2008 the same group published a randomized, placebo-controlled trial of calcium supplements in nearly 1500 healthy postmenopausal women that showed upward trends in cardiovascular event rates with calcium use (*BMJ* 2008;336:262-266). The same group subsequently carried out a meta-analysis of cardiovascular events in randomized, placebo-controlled trials of women taking calcium supplementation without vitamin D. In that study, calcium supplementation significantly increased the risk of MI by about 30% (*BMJ* 2010;341:c3691). Although these studies garnered some interest, they were also viewed with skepticism, and most physicians, especially in this country, did not change their practice of recommending calcium supplementation for postmenopausal women. The New Zealand group then turned to the WHI data, a rather strange place to look considering that one of the main outcomes of WHI was the finding of no adverse effect of calcium and vitamin D on cardiovascular risk. However, the researchers found one major caveat: WHI did not consider whether women were taking calcium on their own prior to entry into the study. The New Zealand group got access to the original NIH data and were able to tease out women who were not using personal calcium supplements at randomization. They found nearly 17,000 women who fit that category. Women in this subgroup who were randomized to calcium and vitamin D had small but significant increased risk for cardiovascular events with hazard ratios that ranged from 1.13-1.22 ($P = 0.05$ for clinical MI or stroke, $P = 0.04$ for clinical MI or revascularization). When the WHI data were added to the previously done meta-analysis of three placebo-controlled trials, calcium and vitamin D were found to increase the risk of MI (relative risk [RR] 1.21 [95% confidence interval [CI] 1.01-1.44]; $P = 0.04$), stroke (1.20 [CI 1.00-1.43], $P = 0.05$), and the composite of MI or stroke (1.16 [CI 1.02-1.32], $P = 0.02$). Trial level data was available for more than 28,000 women who were randomly assigned to calcium plus vitamin D or placebo. Calcium or calcium plus vitamin D increased the risk of MI (RR 1.24 [CI 1.07-1.45], $P = 0.004$) and a composite of MI or stroke (1.15 [CI 1.03-1.27], $P = 0.009$). The authors conclude that calcium supplements with or without vitamin D modestly increase the risk of cardiovascular events, especially MI. They suggest that a reassessment of the role of calcium supplementation in osteoporosis management is warranted (*BMJ* 2011;342:d2040 doi:1136/*BMJ*.d2040, published April 19, 2011). This study has been hotly debated and was even criticized in an editorial in the same issue of *BMJ*. Nonetheless there is a bit of irony in using WHI data, which are largely responsible for millions of women stopping hormone replacement therapy, to show a relationship between calcium and

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cardiovascular disease disease. There is no suggestion in any of these data that dietary calcium leads to adverse events. It is postulated that the rapid increases in calcium that occur with calcium supplementation may somehow play a role in increased cardiovascular risk.

Birth control pills and VTE risk

A progestin commonly used in birth control pills may increase the risk of venous thromboembolism (VTE). A recent report suggests that women taking oral contraceptives containing drospirenone may be at increased risk of VTE compared to women taking contraceptives containing other progestins. Two studies were recently published in *BMJ*. The first was a case-controlled study of U.S. women that showed that women taking drospirenone-containing contraceptives were twice as likely to develop nonfatal VTE compared to women taking levonorgestrel (*BMJ* 2011;342:d2151). The other study, a case-controlled study of British women, showed a three-fold higher rate of VTE with drospirenone-containing contraceptives compared to levonorgestrel (*BMJ* 2011;342:d2139). Oral contraceptives containing drospirenone include Yaz, Yasmin, and Angeliq.

ACE inhibitors and breast cancer risk

Researchers at UCLA and Kaiser Permanente in northern California recently published data suggesting that angiotensin converting enzyme inhibitors (ACEi) may increase the risk of breast cancer recurrence in breast cancer survivors. Using a database of nearly 1800 women with a history of breast cancer, there were 292 recurrences, 174 breast cancer deaths, and 323 total deaths. Twenty-three percent of the women in the study were exposed to either a beta-blocker or an ACEi. ACEi exposure was associated with breast cancer recurrence 1.5 times baseline (HR 1.56, 95% CI 1.02-2.39, $P = 0.04$) but not increased cause-specific or overall mortality. Beta-blocker exposure was associated with lower hazard of recurrence and cause-specific mortality. There was no dose-response with either medication. When a beta-blocker was combined with an ACEi, there was a lower hazard ratio for recurrence than with ACEi alone. The authors suggest that ACEis may be associated with an increased risk of breast cancer recurrence; although beta-blockers may be somewhat protective, more research is needed (*Breast Cancer Res Treat*, published online, DOI: 1007/s10549-011-1503-3). Beta-blockers have been shown to be protective against breast cancer recurrence in other studies, but the ACEi findings were unexpected.

Spending on U.S. pharmaceuticals

Spending on pharmaceuticals in the United States grew at its smallest level in years in 2010, according to a report by the IMS Institute for Healthcare Informatics. Pharmaceutical spending increased 2.3% in 2010 compared to 5.1% in 2009. Generics dominated the pharmaceutical market in 2010 making up 78% of total market share compared to 63% in 2006. Of the top 25 drugs by volume, only three were brand-name products: atorvastatin (Lipitor), clopidogrel (Plavix), and montelukast (Singulair). By spending dollars, however, Lipitor was the top grossing product at $7.2 billion in 2010, down from $7.6 billion in 2009. Esomeprazole (Nexium) was second at $6.3 billion, while Plavix ranked third at $6.1 billion. The domination of generics is of major concern to the pharmaceutical industry since there are few new drugs in the development pipeline and several high-profile drugs are due to lose protection soon. Foremost among these is Pfizer's Lipitor. Pfizer has been battling to maintain its patent protection, but generic manufacturer Watson Pharmaceuticals is expected to introduce the first generic atorvastatin in November of this year. Likewise, Merck's Singulair will likely lose its patent protection next year. The economy also has played a role in the decrease in pharmaceutical spending as the total volume of medicines consumed decreased 0.5% in 2010 along with a decrease in the number of doctor office visits of 4.2%. This extends a decline that began in mid 2009 — likely due to higher unemployment and rising health care costs.

FDA actions

The FDA has approved rituximab (Rituxan) for the expanded indication to treat Wegener's granulomatosis and microscopic polyangiitis, two rare vasculitides. The effectiveness of rituximab was demonstrated in a single control trial in which 197 patients with either condition were randomized to rituximab plus glucocorticoids or oral cyclophosphamide plus glucocorticoids. After 6 months, 64% of the patients treated with rituximab had a complete remission compared to 53% of patients treated with cyclophosphamide. Rituximab is manufactured by Genentech.

The FDA has approved gabapentin enacarbil for the treatment of moderate-to-severe restless leg syndrome. The approval was based on two 12-week clinical trials in adults showing the effectiveness of the drug vs placebo. Gabapentin enacarbil is formulated as a once a day extended-release tablet. It is marketed by GlaxoSmithKline and Xenoport as Horizant. ■