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INTERNAL MEDICINE ALERT®

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INSIDE

NSAIDs and AMI

ABSTRACT & COMMENTARY

Synopsis: *Discontinuation of nonsteroidal anti-inflammatory drugs may increase the risk of first acute myocardial infarction in the near term. The risk is greatest for long-time users of these drugs and patients with systemic inflammatory diseases.*

Source: Fischer LM, et al. *Arch Intern Med*. 2004;164:2472-2476.

In 2002, Schlienger, Jick, and Meier, co-authors of this study, made an unexpected discovery: Long-time users of nonsteroidal anti-inflammatory drugs (NSAIDs) had a 2.7 times increased risk of first-time acute myocardial infarction (AMI) within 30 days of discontinuation of the drug.[1] That was a case-controlled study that used the United Kingdom General Practice Research Database (GPRD) and examined data from 1992 to 1997 with 3319 cases. The current study returns to the GPRD, examining data from 1995 to 2001. Inclusion criteria were age younger than 90 years and first-time diagnosis of AMI. For each case, 4 matched controls were randomly selected. Cases and controls were excluded if they were entered into the database for less than 3 years before the index date of the case's AMI. Drug exposure was classified as nonuser, current user, user discontinued 1-29 days before AMI, discontinued 30-59 days, and discontinued 60 or more days. Users were grouped according to number of NSAID prescriptions: 1-19, 20-39, and 40 or more. There were 8,688 cases and 33,923 controls. Patients were mostly male (62.9%) and elderly (50% were 70 years or older).

As expected, patients who were currently smoking and those who formerly smoked had statistically significant increased odds ratios ([ORs] of 2.07 and 1.31, respectively) for first AMI compared to those who never smoked. Other statistically significant factors (and their ORs) were: body mass ratio ≥ 30 (1.21), hypertension (1.26), hyperlipidemia (4.21), diabetes mellitus (1.84), ischemic heart disease (2.72), arrhythmias/congestive heart failure (1.46), arterial thrombosis (1.25), kidney diseases (1.23), systemic lupus erythematosus (2.80), and rheumatoid arthritis (1.47). An acute chest infection increased the risk of a first AMI, with the greatest risk among individuals who had an infection 1 to 4 days before the AMI (OR, 3.49). The risk attenuated with increasing time since the infection, but was still significantly

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increased even 10 to 14 days out (OR, 1.47).

Current NSAID users had a non-significant trend toward increased risk of first AMI. Subjects who had discontinued use within 1-29 days had an increased risk across all 3 prescription groups (OR, 1.52). The ORs increased with increasing prescription use and reached 2.60 for 40 or more prescriptions. For patients who had discontinued NSAID use within the last 30 to 59 days, the OR was 1.44. For patients who had discontinued use for 60 days or more, only those who had 40 or more prescriptions had a statistically significant increased risk (1.36).

When looking at diagnosis and drug discontinuation, patients with ischemic heart disease (IHD) who had stopped taking NSAIDs within 1 to 29 days had an OR of 2.85 compared to 1.46 for those without IHD who stopped within the same time period. Current aspirin use was protective of first AMI with an OR of 0.83. Patients who suffered from rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) who were not using NSAIDs had an OR of 1.66 compared to patients who were nonusers and didn't have RA or SLE. Patients with RA or SLE who stopped taking NSAIDs had an OR of 3.68 for the 1 to 29 days following discontinuation. Those that continued use had an OR of 1.26.

COMMENT BY ALLAN J. WILKE, MD

The GPRD is rapidly becoming my favorite clinical database. Imagine a database of more than 3 million people enrolled in primary care practices, complete with demographics, vitals, symptoms, diagnoses, hospitalizations, and detailed prescription records! Of course, it isn't perfect. Prescription of a drug is not the same thing as taking a drug, and the database would not account for OTC NSAID use. Additionally, this type of study (case-controlled) cannot prove causal relationships; perhaps the reason that the patients quit using NSAIDs had more to bear on their eventual AMI than did the NSAIDs themselves. Earlier studies[2] have not shown NSAIDs to be protective of AMI, and, of course, use of rofecoxib (Vioxx®) has been associated with an increased risk of AMI[3] and has been withdrawn from the market. (Fischer and colleagues note that during the time studied in this report COX-2 inhibitors were not in wide use, and there were not enough patients taking them to analyze their risk of AMI.)

Assume, though, that discontinuation of NSAIDs did cause the AMIs. Is there a plausible explanation for this? As reviewed in a recent *Internal Medicine Alert,*[4] Pai and colleagues have shown that markers for inflammation, especially C-reactive protein, are elevated in coronary artery disease.[5] Risk of AMI and stroke are both elevated after systemic respiratory infections, especially during the first 3 days of infection.[6] Patients in this study with RA or SLE, who were not taking NSAIDs, were at higher risk of AMI, and that risk increased with discontinuation. Could the NSAIDs be keeping the lid on inflammation? On the other hand, current use of aspirin, but not NSAIDs, was protective of first AMI. In light of the preceding, aspirin's effect probably is not secondary to its anti-inflammatory properties, and platelet inhibition seems less likely, because NSAIDs also inhibit platelets, albeit not irreversibly like aspirin.

So where does this leave us clinically? We should put this into some perspective. The ORs associated with NSAID use were not as large as those associated with hyperlipidemia, IHD, and acute chest infection, but they were similar to the risk of smoking. It seems prudent that

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we avoid sudden discontinuation of NSAIDs, especially in patients at risk for heart disease for other reasons, in patients who have used NSAIDs for long periods of time, and in patients with systemic inflammatory diseases, and we counsel our patients about the increased risk during the 2-month window after discontinuation. Forewarned is forearmed. ■

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Consider Colonoscopy for Young Patients with Hematochezia

ABSTRACT & COMMENTARY

Synopsis: *Rectal bleeding is quite common in patients younger than 50 years of age, but evaluation by total colonoscopy has often been reserved for older patients since serious lower GI lesions are thought to be unusual in younger individuals.*

Source: Wong RF, et al. *J Fam Pract.* 2004;53(11):879-884.

Up to one fifth of patients between 20 and 40 years of age have a history of hematochezia. This study included consecutive patients younger than age 50 who underwent colonoscopy for rectal bleeding at the Salt Lake City VA Hospital or the University of Utah Medical Center between March 1997 and November 1999 (excluding known colitis, colon cancer or polyps, severe bleeding, unexplained weight loss over 5 pounds, and strong family history of colorectal cancer). In this study, 223 patients were included, and 48 (21.5%) had normal findings. Abnormalities in the remaining 71.5% included hemorrhoids in 135 patients (60.5%) with other anorectal diseases in 14 (6.3%). Twenty six patients (11.6%) had colon neoplasia including adenomatous polyps (9.9%) or cancer. Adenocarcinoma was found in 4 patients (1.8%), all in the rectum or sigmoid colon. Biopsy-proven colitis was found in 13 patients (5.8%), diverticulosis was identified in 19 patients (8.5%). Two patients had colonic angiodysplasia.

Wong and associates assert that complete colonoscopy is appropriate in patients younger than 50 who present with rectal bleeding. Other studies have demonstrated over 20% of such individuals with significant lesions. However, others have argued that colonoscopy in younger patients is not cost effective (eg, cost-effectiveness of colonoscopy at age 25 was more than $270,000 per year of life gained). Wong et al argue that flexible sigmoidoscopy may be inadequate to define all significant pathology in young patients with rectal bleeding.

■ COMMENT BY MALCOLM ROBINSON MD, FACP, FACG

Without a much larger controlled trial of colonoscopy vs some alternative intervention in young patients with hematochezia, the correct approach will remain at issue. Most clinicians will try to use all available findings on history, physical examination, and pertinent laboratory data to select the best approach to diagnosis in younger patients who bleed rectally. As a gastroenterologist, I must admit being likely to proceed with colonoscopy in most patients who are referred with rectal bleeding regardless of age. Primary care physicians might quite reasonably be more reluctant to advise such assessments when otherwise healthy young people present with hematochezia. Wong et al of the small Utah study certainly understand that their data cannot really answer our questions about management of these younger patients. Nevertheless, they are to be commended for addressing the issue and reminding us that rectal bleeding in individuals younger than 50 years of age can indicate serious disease. ■

Diet and Colon Cancer: Meat Takes a Hit

ABSTRACT & COMMENTARY

Synopsis: *A long-term prospective study of 148,610 adults aged 50 to 74 years showed an increased risk of colon cancer with prolonged high consumption of red meat and processed meat.*

Source: Chao A, et al. *JAMA*. 2005;293:172-182.

The association of meat consumption and colon cancer is not new. Most studies have been observational or retrospective case-control populations, often starting with a study group having colon cancer. This study improves on previous studies by being prospective, large,

and covering more than a decade (1982-1993). While not the first prospective study addressing this association, it may be the largest and longest to date.

The principle investigators of this research are with the American Cancer Society and the Rollins School of Public Health, Emory University, Atlanta. The 148,610 study subjects came from 21 states and had a mean age of 63 (range 50-74). They provided information on meat consumption in 1982 and 1992/1993 while enrolled in the Cancer Prevention Study II (CPS II) Nutrition Cohort. Follow-up from 1992/1993 through August 2001 identified 1667 incident colorectal cancers.

The relative risk of colon cancer was 1.50 for red meat consumption and 1.53 for processed meat consumption in the highest tertile groups compared with the lowest tertile eating more poultry and fish.

COMMENT BY JOSEPH E. SCHERGER, MD, MPH

Walter Willett, MD, DrPH, from the Harvard School of Public Health, and principal investigator of the Nurses' Health Study, provides an editorial in the same issue of *JAMA* reviewing this study and the general topic of Diet and Cancer.[1] It is worth reading to give a historical and scientific review of this important topic (available in full text at www.jama.com). The association of colon cancer with red and processed meats has been reported since the early 1980s. Attempts to identify fat alone as the culprit have been generally negative. Proposed protective agents, such as beta-carotene and fiber, have also been disappointingly negative when studied. I think we have become more lax in dietary warnings about red meat and colon cancer; and the steak houses seem to be doing very well.

This large and important study brings this issue of red and processed meats back into concern. While a relative risk of 1.5 is not earthshaking, colon cancer is something that people want to avoid, and go to great lengths (forgive the pun) in screening.

The previous issue of *JAMA* had a large study from Sweden looking at the effect of high magnesium intake on colorectal cancer in women.[2] Among a prospective cohort of 61,433 women aged 40-75 years, the highest quintile magnesium intake group had a relative risk of 0.59 compared with the lowest quintile. Magnesium is found in vegetables, fruits, whole grain foods and beans.

It only makes sense that what we eat will affect the health of our GI tract, especially the colon where the non-digested contents sit. Trans-fats, nitrites and other chemicals cause inflammation and oxidation of the fragile mucosa of our intestines. More often than cancer, these foods contribute to diverticulosis.

Returning to Willett, he states with extensive experience of the literature that among all the international correlations between dietary factors and various cancers, the relation between meat consumption and colon cancer has been the strongest.[1] This is one piece of dietary advice we can give with assurance based on solid evidence. Fewer ribs for me in the coming months. ■

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Effect of DHEA on Abdominal Fat and Insulin Action in Elderly Women and Men

ABSTRACT & COMMENTARY

Synopsis: *Administration of 50 mg of DHEA to elderly men and women for 6 months improved insulin action and decreased abdominal fat.*

Source: Villareal DT, Holloszy JO. *JAMA*. 2004;292: 2243-2248.

Abdominal fat increases with advancing age and has been linked to increased risk for diabetes and cardiovascular disease. While insufficient exercise and overeating certainly contribute to age-related acquisition of abdominal fat, hormonal and metabolic factors also have been implicated. Even thin individuals who exercise regularly display increased abdominal fat as they age. This study aimed to determine whether the age-related decline in the adrenal hormone dehydroepiandrosteroine (DHEA) was one of the hormonal factors linked to increased abdominal adiposity and insulin resistance.

Elderly men (n = 28) and women (n = 28) between the ages of 65 to 78 years were enrolled and randomly assigned to receive either placebo or 50 mg of DHEA orally each day for 6 months. The mean body mass index of the men was 28 kg/m^2 and that of the women was 27 kg/m^2. Those using other hormones and having serious illnesses were excluded. Primary outcome variables were visceral and subcutaneous abdominal fat measured by magnetic resonance imaging and glucose and insulin responses to an oral glucose tolerance test. Ancillary outcome variables included food intake and levels of IGF-1, PSA, estradiol, and testosterone.

DHEA administration raised participants' serum DHEA-sulfate (DHEAS) into the young physiological range. In women, DHEA use increased testosterone and estradiol, but only estradiol was raised in men. Both

groups showed increased IGF-1. SHBG did not change. Those who used DHEA lost about 2 pounds over the 6 months. Weight loss was similar in men and women. Recorded food intake stayed the same. Both men and women lost abdominal visceral fat, but women lost slightly more than men, 10 vs 7%. Abdominal fat declined 6% in both men and women. Insulin sensitivity improved dramatically and there was an inverse association between changes in insulin sensitivity and visceral fat. There were no adverse events and PSA did not change appreciably in men. Villareal and associates point out that the long-term safety of DHEA use remains unknown. However, based on the outcome variables followed in the study, short-term use appears to positively effect metabolism.

COMMENT BY SARAH L. BERGA, MD

Many physiological functions change with age. Adrenal function shows a dramatic ontological pattern that includes both adrenarche during childhood and adrenopause during the senescent years. There can be no doubt that adrenarche causes phenotypic changes. These include growth of axillary and other body hair, increased sebaceous gland secretion, altered body odor, and thickening and pigmentation of the skin. The phenotypic features of adrenopause are less well chronicled, possibly because adrenopause occurs over decades (starting at age 25 years) whereas adrenarche happens over a few years (typically from ages 7-9 years). The results of this study suggest that the increased abdominal adiposity so typical of advancing age is at least partly caused by a decline in the adrenal secretion of the androgenic hormone, DHEA. The exact mechanisms by which DHEA exerts its impact is still a subject of conjecture, although Villareal et al suggest that DHEA activates the peroxisome proliferator-activated receptor alpha (PPAR), a transcription factor that regulates fatty acid transport proteins that facilitate fatty acid entry into cells and enzymes involved in the oxidation of fatty acids. In other words, DHEA modifies fundamental metabolic pathways in a way that favors fat oxidation and reduces fat deposition.

When these changes occur as part of the tightly orchestrated ontological script that gates the aging process, they are deemed physiological, but that does not necessarily mean they are always desirable. Perhaps we should think of adrenopause as hastening what could be viewed as the "metabolic syndrome of aging." And just as we have medicalized many processes associated with aging, such as osteoporosis, cognitive decline, and menopause, we are now looking to retard other aspects of the aging process by safe and feasible means. I should point out that the "we" in the above sentence does not refer to the medical or pharmaceutical industries, but to the American public. DHEA, a powerful hormone, is classified as a food supplement for FDA purposes and is sold over the counter. Given that it is a biological agent, it cannot be patented, so there is little pharmaceutical house interest in it.

The study does not describe in detail the phenotypic or cosmetic side effects found with DHEA use in this population, but previous studies by other groups have shown that chronic DHEA use can cause androgenic side effects in women, including acne, accelerated balding, or facial hair growth in women. Other studies have suggested that DHEA improves libido, muscle mass, and energy level in those older than age 70 years, but not in perimenopausal women. DHEA can be obtained from many sources, including compounding pharmacies. I would strongly caution against using dessicated bovine adrenal as the source, as this preparation carries the risk of biological contaminants, including prion disease. Of course, medications sold as food supplements are not held to good manufacturing practices, so the quality and uniformity of over-the-counter preparations cannot be guaranteed.

Compounding pharmacies also can prepare a topical preparation. If one administers DHEA, it is best to monitor serum DHEAS levels before and after to ensure that levels are low before instituting therapy and that the levels do not rise above physiological levels after chronic use. Testosterone and estradiol circulate in nanogram and picogram quantities, but DHEAS circulates in the milligram range, so the assays available to monitor levels are robust and reliable. DHEAS has a long half-life and therefore lacks a circadian pattern and can be measured at any time of day.

In summary, DHEA is yet another of the many agents being studied for use in retarding the physiological consequences of aging. Patent opportunities notwithstanding, as the American public grays, there will be increasing demand for nutraceuticals that have promise and appear safe. We can only hope that the hype will be constrained by proactive clinical investigation. ■

Pharmacology Update

Darifenacin Extended-Release Tablets (Enablex)

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

THE FDA HAS APPROVED ANOTHER MUSCARINIC RECEPtor antagonist, after trospium, for overactive bladder. Darifenacin is a potent, tertiary amine, selective, antagonist for the M3 receptor subtype. It is marketed as extended-release tablets by Novartis as Enablex®.

Indications

Darifenacin is indicated for the treatment of overactive bladder with symptoms of urge incontinence, urgency, and frequency. It may be taken without regard to meals but should not be chewed, divided, or crushed.[1]

Dosage

The recommended starting dose is 7.5 mg daily. The dose may be increased to 15 mg daily after a minimum of a 2-week trial period. The dose should not exceed 7.5 mg for patients with moderate hepatic impairment. No dosage adjustment is recommended for renal impairment or mild hepatic impairment.[1]

Darifenacin is available as 7.5 mg and 15 mg tablets.

Potential Advantages

Darifenacin can be taken once daily and possesses high selectivity for the M3 receptor subtype for the bladder over the salivary gland.[2]

Potential Disadvantages

The dose of darifenacin should not exceed 7.5 mg if used concomitantly with a potent CYP3A4 inhibitor (ie, itraconazole, nelfinavir, clarithromycin). The concomitant use with drugs with a narrow therapeutic range that are metabolized by CYP2D6 (ie, tricyclic antidepressants) should be undertaken with caution.[1] Oxybutynin and tolterodine also have potential drug-drug interactions with these isoenzymes. Similar to other antimuscarinic agents, dry mouth (19-35% vs 8% for placebo) and constipation (14-21% vs 7%) are the most common side effects[1,3]

Comments

The efficacy of darifenacin was evaluated in 3 fixed-dosed, placebo-controlled, double-blind, 12-week studies and 1 dose-titration, 12-week, placebo-controlled study[1,3] In these studies, a total of 1254 patients were treated with placebo, darifenacin 7.5 mg or 15 mg. While the vast majority of differences between darifenacin and placebo for the various end points were statistically significant, the absolute differences were modest. The median reduction, compared to placebo, in incontinence episodes per week ranged from 1.4 to 4.3, reduction in micturitions per day (0.5-0.9), and volume of urine passed per void (9.1 mL-20.1 mL). Typically these studies show a large placebo response. Most common side effects were dry mouth and constipation. Darifenacin did not appear to have an effect on cognitive function in elderly volunteers treated for 2 weeks.[4] Comparative studies between darifenacin and other agents are lacking. The wholesale cost of darifenacin is about $2.70 daily and priced similarly to other available agents.

Clinical Implications

Overactive bladder is defined as detrusor overactivity. This condition is characterized by urgency with or without incontinence, usually with frequency and nocturia.[5] Overactive bladder has significant impact on one's quality of life. Treatment includes lifestyle intervention, bladder training and pelvic floor exercises, pharmacotherapy, and surgery. Pharmacotherapy primarily involves the use of an antimuscarinic agent directed at the M3 receptor subtype. This receptor subtype mediates cholinergic contraction of the detrusor muscle found in the bladder and salivary gland. Dry mouth is the most common side effect. Current choices include oxybutynin, tolterodine, trospium, and now, darifenacin. Different drug delivery systems (ie, transdermal, controlled-release) have been used to reduce anticholinergic side effects and improve dosing convenience. Darifenacin may have more selectivity for the bladder over the salivary gland. Unfortunately the magnitude of the benefit of this class of drugs in general is modest.[6,7] ■

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CME Question

6. This University of Utah study discovered what percentage of significant neoplastic lesions in patients younger than 50 years of age who presented with rectal bleeding?

a. 50% of all patients examined had polyps or cancer.
b. 1.8% of patients had neoplastic lesions documented by biopsy.
c. No patients younger than age 50 were found to have neoplastic lesions in this study.
d. Just under 12% of the patients younger than age 50 had neoplasms found.
e. Hyperplastic polyps were common in this study, but only 5% of patients had significant neoplastic lesions identified.

Answer: 6 (p)

By Louis Kuritzky, MD

Acetyl-L-Carnitine Improves Pain, Nerve Regeneration, and Vibratory Perception in Diabetes Patients

Diabetic peripheral neuropathy (DPN), with or without diabetic peripheral neuropathic pain (DPNP), is a commonplace and consequential complication of diabetes (DM). Treatment of DPNP has been enhanced by the recent FDA approval of duloxetine and pregabalin, but clinicians desire a broad range of therapies. Good control of DM has been shown to reduce progression of neuropathy, but other convincing preventative tools are lacking.

DM patients have been shown to be deficient in acetyl-L-carnitine (ALC), which may be etiologic in development of DPN. Animal data confirm preventative and therapeutic effects of ALC, including favorable impact upon generation of nitric oxide, lipid peroxidation, and prostaglandins.

To evaluate the potential clinical role of ALC, 2 identical one-year, double-blind, placebo-controlled studies were undertaken (total n = 1348). Study subjects underwent sural nerve biopsy, nerve conduction study, scoring of vibration sense, and symptom scores. Ranked symptoms included pain, numbness, paresthesias, weakness, postural dizziness, dyshidrosis, GI problems, and sexual dysfunction.

Sural nerve biopsy showed positive effects, although nerve conduction velocity and amplitude did not improve. Vibration sense was improved, and pain was reduced in subjects receiving 1000 mg t.i.d. No patient discontinued ALC due to adverse effects. ALC shows promise as a therapeutic tool for diabetic peripheral neuropathy. ■

Sima AF, et al. Diabetes Care. 2005; 28:96-101.

Levodopa and the Progression of Parkinson's Disease

Levodopa (LDPA) has proven a very valuable treatment for Parkinson's disease (PAR). Since PAR is characterized by a progressive decline in production of dopamine due to degeneration of the substantia nigra, it is pathophysiologically attractive to consider replacing insufficient dopamine by means of LDPA. Some concern has existed about whether LDPA treatment might actually accelerate decline in neurons of the substantia nigra. To address this question, the Parkinson Study Group enlisted patients with early PAR (n = 361) for randomization in a placebo controlled trial.

Subjects underwent daily treatment with carbidopa-levodopa at doses from 37.5/150 mg to 150/600 mg for 40 weeks, after which there was a 2-week withdrawal. No other anti-Parkinsonian medications were permitted during the trial. Symptoms and signs of PAR were assessed, as well as SPECT imaging to monitor the status of substantia nigra functionality.

As would be expected, PAR symptom severity was greater in patients treated with placebo than LDPA. SPECT data indicated a decrease in activity of the nigrostriatal dopamine nerve terminals, suggesting acceleration of the decline in CNS dopamine productivity (although a medication-induced alteration of the dopamine transporter could not be ruled out).

These contrasting end points leave the issue of whether LDPA treatment alters disease progress unsettled. Despite convincing evidence for favorable effects upon signs and symptoms, the underlying pathology may be unaffected, or possibly even worsened. ■

The Parkinson Study Group. N Engl J Med. 2004;351:2498-2508.

Lifestyle, Diabetes, and Cardiovascular Risk Factors 10 years after Bariatric Surgery

The long-term consequences of obesity include increased cardiovascular disease (CVD), diabetes (DM), and dyslipidemia. Although surgical interventions have provided meaningful short-term reductions in BMI and surrogate markers of cardiovascular risk, little is known about long-term impact.

This prospective study compared outcomes in subjects (n = 851) surgically treated for obesity (gastric banding, banded gastroplasty, or gastric bypass) with matched obese controls (n = 852) treated with conservative management such as lifestyle changes. Study groups did not differ meaningfully at baseline for cardiovascular risk profile. In addition to BMI, end points included mortality, incidence of diabetes, hypertriglyceridemia, and hyperuricemia.

Gastric bypass produced the greatest degree of weight loss amongst the surgical procedures; overall at 2 years, the conservative management group had experienced no statistically significant weight loss, compared to a 23.4% decrease in the surgery group.

Perisurgical mortality was 0.25%. Incident hypetriglyceridemia, DM, and hyperuricemia were lower in the surgery group. Similarly, improvement in pre-existing hypertension and DM were greater amongst patients treated surgically. Differences in mortality at 10 years were not specified, but were not sufficient to merit early study closure (either due to perceived benefit or harm). The balance of long-term effects of bariatric surgery appears favorable. ■

Sjostrom L, et al N Engl J Med. 2004;351:2683-2693.

Incomplete LBBB?

By Ken Grauer, MD

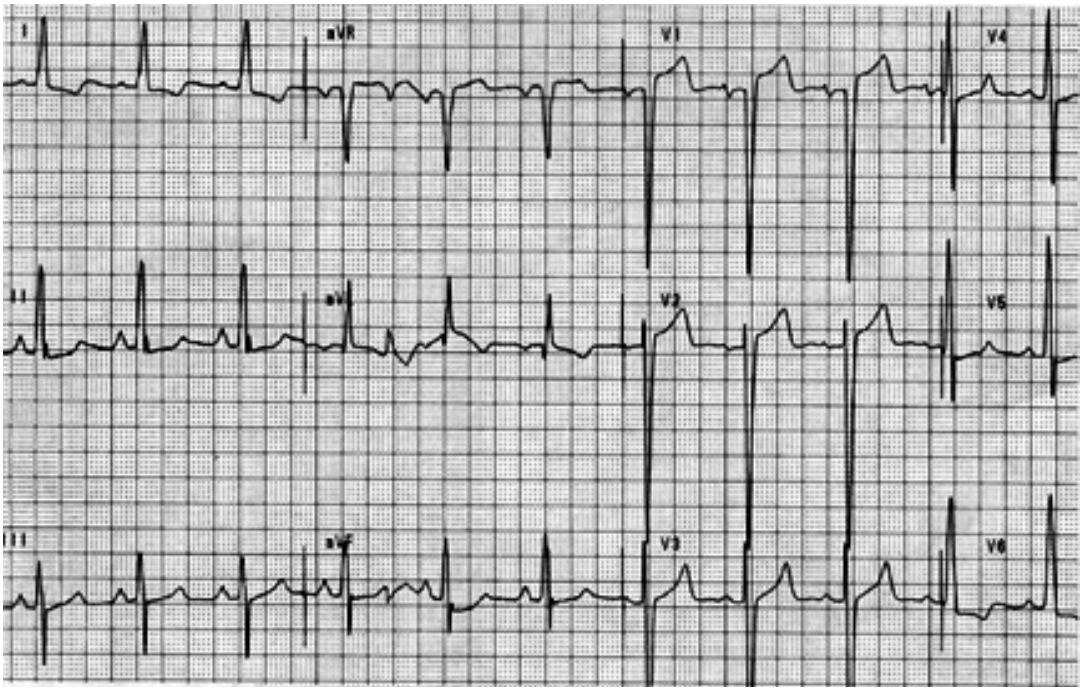

Figure. 12-lead ECG recorded from a 47-year-old man with dyspnea. Is there incomplete LBBB?

Clinical Scenario: Interpret the 12-lead ECG in the Figure, obtained from a 47-year-old man who presented with dyspnea. Is there incomplete LBBB (left bundle branch block)?

Interpretation: The rhythm is sinus at a rate of 75 beats/minute. Although PR and QT intervals are normal, the QRS complex appears to be slightly widened. Because criteria for assessment of axis, ventricular chamber enlargement and ischemia/infarction all change in the presence of a ventricular conduction defect, it is best to assess for the cause of QRS widening *before* going further. QRS morphology in the 3 key leads (I, V_1, and V_6) is consistent with a LBBB (left bundle branch block) pattern. However, the borderline amount of QRS widening (to 0.11 second) falls short of the 0.12 second duration usually required to diagnose complete LBBB. Instead, QRS widening in this tracing could represent incomplete LBBB. If this were the case, QRS voltage criteria for LVH (left ventricular hypertrophy), as well as the ST-T wave abnormalities seen in the lateral leads should not necessarily be interpreted as a strain or ischemic pattern, since they may simply reflect repolarization changes secondary to the conduction defect. Alternatively, QRS widening in this tracing might instead reflect marked ventricular enlargement, since conduction time through a hypertrophied ventricle would be expected to increase. If this were the case, then the ST-T wave changes seen here in the lateral leads would be perfectly consistent with a left ventricular strain pattern. This is in fact the situation here, as this patient demonstrated dramatic thickening on echo. Consistent with this echocardiographic picture of a dilated cardiomyopathy are the ECG findings in the Figure of right atrial enlargement (tall, peaked P wave in lead III), left atrial enlargement (deep negative component to the P wave in lead V_1), and dramatic increase in QRS amplitude (very deep S waves in leads V_1, V_2 and tall R waves in leads V_5, V_6). Diagnosis of incomplete LBBB and distinction of this entity from LVH as the cause of slight QRS widening is often extremely difficult. And at times the two conditions may coexist . . . ■

In Future Issues:

Risk of Cancer in Ulcerative Colitis

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Statins and the Incidence of Rhabdomyolysis

The most commonly prescribed statins have a low incidence of rhabdomyolysis, according to the results a new study of more than 250,000 patients. Atorvastatin, pravastatin, and simvastatin were found have very low and virtually indistinguishable rates of rhabdomyolysis of 0.44 per 10,000 person-years (95% CI, 0.20-0.84). The data were obtained from 11 managed care health plans across United States from January 1, 1998, through June 30, 2001. Cerivastatin (Baycol-Bayer), which was withdrawn from the market in 2001, was found have a much of a higher rate of rhabdomyolysis, 5.34 cases per 10,000 person-years (95% CI, 1.46-13.68). The concomitant use of a fibrate with atorvastatin, pravastatin, or simvastatin was found to have increased the rate to 5.98 (95% CI, 0.72-216.0), while use of a fibrate with cerivastatin dramatically increased the rate to 1035 cases per 10,000 person-years of treatment (95% CI, 389-2117), or nearly 1 in 10. Older patients, especially those with diabetes, were found to have higher rates of rhabdomyolysis. The authors conclude that the most commonly prescribed statins have a low incidence of rhabdomyolysis, which is increased with the addition of a fibrate (*JAMA.* 2004;292:2585-2590).

The study confirms the safety of the most commonly used statins, but raises issues regarding the post marketing surveillance of cerivastatin. These concerns were addressed in a review in the same issue of *JAMA* regarding the potential conflict of interest once initial reports of rhabdomyolysis were reported to the company, and the delay in the availability of this information to consumers. The critique is accompanied by Bayer's rebuttal (*JAMA.* 2004;292:2622-2631, 2643-2646, 2655-2657, 2658-2659), which makes fascinating reading given the recent criticisms of the FDA and post marketing surveillance regarding coxibs.

A Crackdown on Importation of Drugs

Officials in both the United States and Canada are taking steps to crack down on the importation of prescription medications across the border. A New York District Court issued an injunction in December against Canada Care Drugs Inc., which gave the FDA authority to inspect the company to assure that they no longer import drugs to American consumers. The FDA had petitioned the court to take this action based on a sting operation run by the agency. FDA investigators purchased Neurontin and Sporanox through Canada

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Care. Instead of Neurontin, investigators received APO-gabapentin and NOVO-gabapentin, formulations of the drug that are not subject to FDA scrutiny in this country. The Sporanox shipment included 84 tablets of the correct drug, but investigators felt that the amount was excessive, determining that patients should not take Sporanox continuously without checking with their physician. The court is scheduling a trial date for Canada Care, an action that is sure to put other Canadian importation companies on alert. Meanwhile, the Canadian government is also cracking down on Internet pharmacies that export drugs to the United States without evaluation by Canadian doctors. The government is considering making it illegal for Canadian doctors to countersign prescriptions from other countries. This move in Canada is prompted by concern over shortages of drugs for Canadian citizens, especially given threats by American drug companies to withhold additional shipments of drugs to Cananda, where they have strict price controls, knowing that many of these drugs may come back to the US market were there are no price controls. These moves are strongly supported by PhRMA, the powerful pharmaceutical advocacy group.

FDA Actions

The FDA has approved a new non-benzodiazepine hypnotic for the treatment of insomnia. Sepracor, a company that specializes in marketing active isomers of currently approved drugs, has received approval to market eszopiclone, the active (S)-isomer of zoplicone, which is available outside the United States. The drug is similar to zopidem (Ambien) and zaleplon (Sonata) in that it has a lower incidence of tolerance, dependence, and withdrawal symptoms than benzodiazepines. Based on a 6-month, double-blind, placebo-controlled safety and efficacy trial, the FDA decided not to limit eszoplicone's indication to short-term use. Eszoplicone will be available in 1mg, 2mg, and 3mg tablets, and will be marketed in United States under the trade name Lunesta. Sepracor is also studying the drug for treatment of insomnia in patients with depression or pain, and in peri-menopausal women.

Novartis has received approval to market darifenacin extended release tablets for the treatment of overactive bladder with symptoms of urging incontinence, urgency, and frequency. The drug is an M3 (muscarinic) receptor blocker that increases urinary capacity and decreases urinary episodes and frequency of incontinence, along with feelings of urgency. Darifenacin, which is already available in Europe, will be marketed in the United States as Enablex.

Drugs approved under the FDAs accelerated approval program are often approved on the basis of surrogate end points, such as tumor markers that would indicate the likelihood of clinical benefit. The FDA, however, requires that cancer drugs in particular, must document clinical benefit in subsequent studies to remain marketable. A recent case-in-point is AstraZeneca's gefitnib (Iressa), which was approved for treatment of non small cell lung cancer in patients who failed other courses of cancer therapy. A recent study of gefitnib involving nearly 1700 patients failed to show a survival benefit better than placebo. The drug, which was initially approved in 2003, now faces a FDA review to determine whether the drug will be removed from the market. In a letter to physicians, AstraZeneca "urges you to consider other treatment options in recurrent non small cell lung cancer patient population." In the meantime, Genentech and Roche's erlotinib (Tarceva), which has shown survival benefit for the same patient population, remains a viable option.

The FDA has issued a Public Health Advisory regarding the use of anti-inflammatories including COX-2 inhibitors because of recent indications that the drugs may increase the risk of cardiovascular disease and stroke. The agency is requiring evaluation of all prevention studies that involve the COX-2 inhibitors celecoxib (Celebrex) and valdecoxib (Bextra) to ensure that adequate precautions are in place. Several prevention studies regarding potential benefit of these drugs on colon polyps and Alzheimer's disease are either in progress or planned in the near future. Meanwhile, the agency is recommending that physicians should prescribed Celebrex or Bextra with caution, particularly in patients at risk for cardiovascular disease, and should weigh the risk vs benefits.

The FDA is also recommending that consumers should use over-the-counter anti-inflammatories in strict accordance with the label directions, taking them for no longer than 10 days without consulting a physician. ■