INTERNAL MEDICINE ALERT

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INSIDE

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Skim Milk Gets a Move On

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD, MA

Chair, Department of Integrative Medicine, Ross University School of Medicine, Commonwealth of Dominica

Dr. Wilke reports no financial relationship to this field of study.

Synopsis: *Three 8-oz glasses of fat-free milk per day provided significant relief to patients with functional constipation.*

Source: Aydin S, et al. Fat-free milk as a therapeutic approach for constipation and the effect on serum motilin and ghrelin levels. *Nutrition* 2010;26:981-985.

THESE INVESTIGATORS FROM TURKEY HYPOTHESIZED THAT FAT-FREE MILK could improve constipation and that the hormones motilin and ghrelin are involved. Ghrelin, a "hunger" hormone produced in the stomach and pancreas, stimulates appetite. It has several other effects on the gastrointestinal (GI) tract, but for this study, its enhancement of motility was the effect of interest. Motilin is secreted in the small intestines and stimulates gastric motility and small intestinal peristalsis.

Thirty (30) constipated patients and 19 controls were recruited. All subjects underwent double-contrast barium enemas. Exclusion criteria included pre-existing GI pathology (cancer, lactose intolerance, ulcerative colitis, Crohn's disease, malabsorption syndrome, among others), and other disease or conditions associated with constipation (diabetes, thyroid disease, pregnancy, obesity, and tobacco use). The constipated subjects were classified by the Constipation Severity Instrument (CSI), a validated tool for accessing constipated patients,[1] into three groups, mild, moderate, and severe, with 10 subjects in each group. The CSI for the mild group averaged 17.8, for the moderate group 20.2, and for the severe group 26.7. The controls were divided into two groups with CSIs of 10 and 9. All groups were evenly divided between men and women with average body mass indices around 26 kg/m^2. The groups were well matched, except that the constipated patients ate fewer

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legumes, whole grains, and fresh fruits and vegetables. Milk consumption among the constipated patients was limited to 1-2 glasses of whole milk per week. None of them consumed fat-free milk.

Blood samples for electrolytes, lipids, ghrelin, and motilin were obtained at baseline and then after 3 days of fat-free milk consumption. All subjects were given a standard diet (45% carbohydrates, 35% fat, and 20% protein). The subjects in control group 1 (CG1) drank 400 mL of fat-free milk a day; those in control group 2 (CG2) drank the same amount of whole milk. The mild, moderate, and severe constipation cases received 400, 600, and 800 mL of fat-free milk, respectively, a day for 3 days.

CG1, which drank fat-free milk, saw an increase in ghrelin levels and a 3-point drop in CSI, while those subjects in CG2, who drank whole milk, saw a decrease in ghrelin and a 1-point drop in CSI. Motilin levels did not change significantly in CG1, but fell in CG2. Similar results were seen in the constipated groups, which all drank fat-free milk. In the mild group, the CSI fell 4 points, 12 points in the moderate group, and 17 points in the severe group. In fact, the post-fat-free milk CSIs in the moderate and severe groups were equal to the control groups. Ghrelin levels rose in all constipated groups. In contrast to CG1, however, motilin levels also rose.

Samples of the whole and fat-free milk were analyzed for chemical content. The only significant differences were the amount of iron (twice as much in whole milk than in fat-free milk) and the amount of ghrelin (more in fat-free milk than in whole milk). Motilin concentrations were equivalent.

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■ COMMENTARY

This study was poorly written and confusing to follow. It was not a double-blinded, randomized, placebo-controlled study. It was not clear when the CSI was repeated, 3 or 30 days after baseline. The results need to be replicated in another environment with a larger and more ethnically diverse group of subjects and a study design that minimizes bias. Even with that, the results are interesting and raise several questions. Why is the concentration of iron higher in whole milk and does that matter for this study? Primary care physicians often receive anecdotal reports of constipation with iron supplementation, and research supports this observation in pregnancy.[2] How much milk does one need to drink? For constipation, the magic number seems to be 600-800 mL (20-27 fluid oz) of fat-free milk a day. What would the effect of a similar volume of 1% or 2% milk be? These volumes of milk would cause symptoms in lactose-intolerant individuals. Would constipated, lactose-intolerant patients benefit from taking lactase before consuming fat-free milk or by drinking lactase-treated fat-free milk? What about fat-free fermented milk? How do we account for the increase in ghrelin and motilin serum values in subjects given fat-free milk? While it's safe to assume that the motilin increase represents endogenous production, since there is no significant difference between fat-free milk and whole milk in motilin concentration, the same cannot be said for ghrelin.

These subjects almost certainly had functional constipation, which is defined by the Rome III criteria as the presence of two or more of the following symptoms occurring for at least 12 weeks in the preceding 12 months: 1) straining during at least 25% of defecations; 2) lumpy or hard stool in at least 25% of defecations; 3) a sensation of incomplete evacuation in at least 25% of defecations; 4) a sensation of anorectal obstruction or blockage in at least 25% of defecations; 5) manual maneuvers to facilitate defecation used in at least 25% of defecations; and 6) fewer than three bowel movements in a week.[3]

Constipation has many causes. As a society, we aren't physically active, and we don't keep ourselves adequately hydrated. Our consumption of fat-free (skim) milk, whole grains, and fruit and veggies is low. Some constipation is iatrogenic from narcotics and medications with anticholinergic side effects. Sometimes constipation is a red flag for a more serious disease. When a patient presents with this complaint, we need to look at lifestyle issues and medication lists and search for GI pathology. Laboratory tests include thyroid-stimulating hormone (TSH), serum calcium, glucose, electrolytes, a complete blood count, and urinalysis.[4] Advocating fat-free milk seems like a very reasonable approach, if the constipation is functional and the patient is not currently drinking it, especially since milk consumption has other benefits. For patients who complain that they don't like the taste of skim milk, sug-

gest that they "wean" themselves off milk with higher fat concentrations gradually. Going from whole milk to 2% to 1% to skim, one bottle at a time, is doable. ■

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Black and White Differences in Hemoglobin A1c Levels

ABSTRACT & COMMENTARY

By Mary Elina Ferris, MD

Clinical Associate Professor,
University of Southern California

Dr. Ferris reports no financial relationship to this field of study.

Synopsis: *American non-Hispanic black persons had higher HbA1c levels than white persons at all levels of glycemia, and this difference increased as glucose intolerance worsened.*

Source: Ziemer DC, et al. Glucose-independent, black-white differences in hemoglobin A1c levels: A cross-sectional analysis of 2 studies. *Ann Intern Med* 2010;152:770-777.

HbA1c values from two previously conducted studies, which included more than 3500 participants that had normal glycemia, prediabetes, or diabetes, were analyzed to adjust for plasma glucose levels and other characteristics. The Screening for Impaired Glucose Tolerance used 1580 volunteers, aged 18-87 years without known diabetes, and measured random glucose and HbA1c as well as a fasting and 2-hour glucose tolerance test. The other data came from the CDC's recurring NHANES III (Third National Health and Nutrition Examination Survey), from which data on 1967 participants with HbA1c levels were obtained; participants older than 40 years had fasting and glucose tolerance testing. Persons receiving treatment for diabetes were excluded from analysis.

Results showed HbA1c levels consistently higher in black vs white populations, ranging from a 0.13 percentage point increase associated with normal glucose tolerance tests, up to a 0.47 percentage point increase in those with diabetes. Diabetes was defined as fasting glucose higher than 125 mg/dL or 2-hour glucose > 199 mg/dL. These differences persisted even after adjusting for other factors such as age, sex, BMI, blood levels of vitamins A, C and E, marital status, and income.

■ COMMENTARY

As we increasingly utilize HbA1c levels as a measure of glucose control, and even for the initial diagnosis of diabetes, it behooves us to consider that baseline levels may not be identical in all persons. Other factors may decrease HbA1c, such as alcoholism and salicylate use, increase HbA1c with iron-deficiency anemia, or falsely increase HbA1c with chronic dialysis, uremia, and hyperbilirubinemia. However, none of these were thought to be present in any large amount in this study where measurements came from random samples of working people.

It does appear from this study and others[1] that black persons have higher HbA1c levels at baseline, no matter what level of glycemia they are associated with, ranging from 0.13 to 0.26 in euglycemia to 0.47 when diabetes is present. Although the reasons for this remain to be explained, the differences may need to be taken into consideration when establishing targets for optimal control; however, what this means for complications and outcomes is unclear. Since research on the benefits of tight control did not factor in these racial differences, there remain lots of unanswered questions about whether black persons should have different HbA1c targets, or would benefit from the tighter control targets that have been shown to be of benefit in population-wide studies. ■

Reference

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Pertussis Prevention

SPECIAL FEATURE

By Stan Deresinski, MD, FACP

Clinical Professor of Medicine, Stanford, Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center

Dr. Deresinski does research for the National Institutes of Health, and is a consultant and an advisory board member for Merck. This article originally

appeared in the November 2010 issue of Infectious Disease Alert. *At that time it was reviewed by Timothy Jenkins, MD, Assistant Professor of Medicine, University of Colorado, Denver, Denver Health Medical Center. Dr. Jenkins reports no financial relationship to this field of study.*

The introduction of acellular pertussis vaccines represented an important advance in public health, but developing a vaccine is not synonymous with protecting a population. The latter involves convincing health care providers (HCPs) and the targeted populations of its safety and efficacy and making the vaccine readily available. The uptake of the pertussis vaccine is somewhat complicated by the fact that it is only available in combination with diphtheria and tetanus toxoids — DTaP is licensed for infants and young children and Tdap (tetanus, diphtheria, acellular pertussis) for those 10-64 years of age. The Advisory Committee on Immunization Practices (ACIP) in 2005 recommended that Tdap replace the standard TD for the latter group.

The CDC has analyzed data from the National Health Interview Survey (NHIS), and found that the self-reported tetanus vaccination coverage was 60.4% in 1999 and 61.6% in 2008 among adults ages 18-64 years.[1] Of those reporting vaccination during 2005-2008, 52% reported receiving Tdap, but total Tdap coverage in 2008 was only 5.9%. Even worse, only 15.9% of HCP and 5.0% of individuals with infant contact reported having received Tdap.

The effects of these low reported rates of uptake of Tdap are reflected in the current situation in California. As of August 24, a total of 3311 confirmed, probable, and suspected cases had been reported during 2010, corresponding to a rate of 8.5 cases/100,000 population.[2] This was a seven-fold increase from the number of reported cases during the same time period in 2009, when just 454 cases were reported, and is the largest number of cases in California since 1958. Case rates were highest in infants < 6 months of age (158 cases/100,000), and in children aged 7-9 years (26 cases/100,000), and adolescents aged 10-18 years (20 cases/100,000). Twelve percent of cases have required hospitalization. Sixty percent of hospitalized patients were infants < 3 months of age, with three-fourths of these being < 6 months of age. Eight deaths have been reported, seven of which were in infants < 2 months of age at time of disease onset; none had received any doses of pertussis-containing vaccine. The eighth fatality was a 28-week preemie who was 2 months of age and had received the first dose of DTaP 11 days prior to disease onset.

Pertussis (whooping cough) is spread by inhalation of respiratory droplets or aerosols and is highly contagious — each patient is believed to infect, on average, more than a dozen individuals, and infants are highly vulnerable. Infants are protected from many infections during their first months of life as the result of the transfer of maternal antibodies during gestation. Unfortunately, unless recently immunized, most pregnant women have waning of immunity to pertussis and are unable to provide sufficient protective antibody to their fetus. As a consequence, the California Department of Public Health (CDPH) recommends that all women of childbearing years be vaccinated with Tdap vaccine. Pregnancy is not a contraindication to vaccination,[3] although vaccination is commonly deferred until the 2nd or 3rd trimester, or immediately postpartum. In addition, all other close contacts of infants, including family members, caregivers, and HCPs, should also be vaccinated at least 2 weeks before contact. CDPH recommends that all health care personnel, particularly those who have direct contact with infants and pregnant women, be immunized with Tdap to protect their patients and themselves. This strategy provides a "cocoon" of safety for the infant.

The first dose of DTaP, the vaccine version for infants and young children, has been typically given at 2 months of age but may be given as early as 6 weeks to provide protection earlier in life. CDPH recommends that vaccination with Tdap include critical groups for whom Tdap is not licensed, including children 7-9 years of age and individuals ≥ 65 years of age. Children 7-9 years of age who had not received all of their routine childhood DTaP vaccine doses are recommended to receive Tdap. Vaccination of those ≥ 65 years of age is important because of the potential role of grandparents in transmission to infants. Pertussis in adults usually does not have the severe whooping cough characteristically seen in infants and young children and, as a consequence, frequently goes undiagnosed. Nasopharyngeal cultures are the gold standard for diagnosis, but are quite insensitive; the optimal single test is detection of *Bordetella pertussis* nucleic acid by PCR. Serological testing is generally not recommended.

Because of its lack of licensure in those > 65 years of age, questions have arisen regarding Medicare coverage. Tdap vaccine is covered by Medicare Part D, and may be obtained by Part D beneficiaries from a network pharmacy without out-of-pocket costs to the beneficiary. Tdap may also be provided in a network provider's office; however, this would require the beneficiary to pay for the vaccine costs up front and then be reimbursed by his or her Medicare Part D plan. It is recommended that beneficiaries contact their Medicare Part D plan in advance for detailed instructions on reimbursement for Tdap vaccination.

The resurgence of pertussis is a reminder that we have not conquered all childhood diseases in the United States. Reasons for the continuing and worsening pertussis problem include the lack of lasting immunity after vaccination (as well as after natural infection), the lack of passively transferred protective antibody in most infants, and the role of adults as reservoirs for transmission. As HCPs, we

all have an obligation to actively promote pertussis vaccination, including for ourselves, to protect our patients and families. ■

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Pharmacology Update

Fingolimod Capsules (Gilenya™)

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 THE FIRST ORAL MEDICATION FOR the treatment of patients with relapsing forms of multiple sclerosis. Fingolimod is a sphingosine 1-phosphate receptor modulator that is believed to reduce migration of lymphocytes into the central nervous system. Fingolimod is marketed by Novartis as Gilenya™.

Indications

Fingolimod is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.[1]

Dosage

The recommended dose is 0.5 mg taken once daily. It may be taken without regard to meals.[1] Fingolimod is available as 0.5 mg capsules.

Potential Advantages

Compared to interferon beta-1a, the annualized relapse rate was significantly lower with fingolimod.[1,2]

Potential Disadvantages

Fingolimod may decrease heart rate and slow atrioventricular conduction after the first dose. Patients should be observed for signs and symptoms of bradycardia for 6 hours after the first dose.[1] The drug may also increase the risk for macular edema and infections, and may elevate liver transaminases. It may also decrease pulmonary function. Ophthalmologic evaluation should be done prior to initiation of therapy and at 3-4 months after initiation. EKG, CBC, liver transaminases, spirometry, and diffusion lung capacity for carbon monoxide should be evaluated as clinically indicated.

Comments

Fingolimod is metabolized to fingolimod-phosphate, which is active and has high affinity to sphingosine 1-phosphate receptors. This results in blocking the egress of lymphocytes from lymph nodes and ultimately reduces the number of lymphocytes in the systemic circulation to 20%-30% of baseline.[1] The result is the reduction of migration of lymphocytes into the central nervous system. The efficacy of fingolimod was shown in two studies. The first study (FREDOM) involved MS patients (n = 1272) with relapsing-remitting multiple sclerosis (RRMS) and a score of 0 to 5.5 on the Expanded Disability Status Scale (EDSS), who had one or more relapses in the previous year or two or more in the previous 2 years, and who had not received interferon beta, glatiramer acetate, or natalizumab.[1,3] Patients were randomized to fingolimod 0.5 mg or 1.25 mg daily, or placebo. The primary endpoint was the annualized relapse rate. At 24 months the annualized rate was 0.18, 0.16, and 0.4 for fingolimod 0.5 mg, 1.25 mg, and placebo, respectively. Both strengths of fingolimod were statistically significant from placebo ($P < 0.001$).

The second study (TRANSFORMS) was a comparison between fingolimod and intramuscular interferon beta-1a in subjects with RRMS (n = 1292) with inclusion criteria similar to study 1.[1,2] However, prior interferon beta and glatiramer acetate use was permitted, but not natalizumab. Patients were randomized to either of the two doses of fingolimod or interferon beta-1 (30 μg IM once weekly). The duration was 12 months with a primary endpoint of annualized relapse rate. Secondary endpoints were the number of new or enlarged lesions on MRI at 12 months. The annualized rates were significantly lower for fingolimod (0.16 and 0.20) compared to interferon beta (0.33). MRI results were also similar to that of the primary endpoints. There were no differences in disease progression. Some adverse effects were more frequent with interferon;

these included pyrexia (17.9% vs 4.2%), influenza-like illness (36.9% vs 3.5%), myalgia (10.2% vs 3.3%), and depression (7.4% vs 4.9%). Elevation of liver enzymes (6.5% vs 1.9%), bradycardia/AV block (0.6% vs 0%), and neoplasm (1.9% vs 0.2) were more frequent with fingolimod. The 1.25 mg dose of fingolimod was no more efficacious than the 0.5 mg dose, but was generally associated with a higher frequency of serious adverse events. There were two fatal infections (disseminated primary varicella zoster and herpes simplex encephalitis).

Clinical Implications

RRMS is the most common form of multiple sclerosis. Current FDA approved treatments include injectable forms of interferon beta-1a (intramuscular or subcutaneous administration), interferon beta-1b, glatiramer acetate, natalizumab, and mitoxantrone. Fingolimod is the first orally effective drug for RRMS and appears to be more effective than intramuscular interferon beta-1a. It provides an alternative for patients who have inadequate response or are intolerant of current agents. The long-term safety of fingolimod remains to be established. Fingolimod is currently in a phase III trial in patients with primary progressive MS.[4]

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CME Questions

56. Which of the following physical and biochemical changes was reported by constipated subjects who drank fat-free milk.
a. A decrease in the Constipation Severity Index
b. An increase in weight
c. A decrease in serum ghrelin
d. An increase in serum calcium
e. An increase in bone mass

57. Which of the following changes in HbA1c levels is found when comparing black non-Hispanic persons to white persons with the same plasma glucose values?
a. Decreased HbA1c levels
b. Increased HbA1c levels
c. No change in HbA1c levels
d. Increased only with age >65 years
e. Increased only with obesity

58. Which of the following is *correct*?
a. Tdap administration is contraindicated during pregnancy.
b. Tdap administration is contraindicated if the recipient is breastfeeding.
c. Tdap vaccination is indicated for infant care givers, including, e.g., elderly grandparents.
d. Tdap and TD are fully interchangeable vaccines.

Answers: 56. a, 57. b, 58. c.

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 a consultant for Abbott, AstraZeneca, Boehringer Ingelheim, Daiichi, Sankyo, Forest Pharmaceuticals, Lilly, Novo Nordisk, Takeda.

Aspirin Resistance and Established Hypertension

Source: Ozben B, et al. Aspirin resistance in hypertensive adults. *J Clin Hypertens* 2010;12:714-720.

The prophylactic use of aspirin (ASA) provides risk reduction when used for secondary prophylaxis. Nonetheless, the protective effects of ASA are imperfect, which is to some degree explained by the concept of ASA resistance, variously measured by failure of aspirin to reduce thromboxane production, platelet activation, or platelet aggregation. Because various methodologies have been used to measure antithrombotic activity of ASA (such as platelet aggregability or thromboxane), the prevalence of ASA resistance in the literature is widely variant. ASA resistance has not been the subject of much study, specifically in hypertensive patients.

Ozben et al used a device called the Ultegra Rapid Platelet Function Assay-ASA to measure the degree of platelet aggregation reduction attained in persons with established hypertension receiving 100-300 mg/d of ASA. The Ultegra device measures light transmission in whole blood to which a platelet activator has been added: If ASA is doing its job, platelets will not activate. If ASA is not doing its job, fibrinogen will agglutinate with platelets, obscuring light transmission. Patients who were taking any other agents that might influence platelet aggregation (e.g., clopidogrel) were excluded from the trial.

In the 200 study subjects, ASA resistance was found in 21%. ASA resistance was more common in uncontrolled hypertension, women, chronic kidney disease, and persons with lower platelet counts. Measurement of ASA resistance is not yet a readily applied clinical tool. Whether persons with ASA resistance merit higher doses of ASA, alternative pharmacotherapy (e.g., clopidogrel), or other intervention is unclear. ■

Dabigatran vs Warfarin for AFib

Source: Wallentin L, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation. *Lancet* 2010; 376:975-983.

Warfarin (WAR) does an impressive job of stroke reduction in patients with atrial fibrillation (AFib): Clinical trials indicate a relative risk reduction of 65%. Unfortunately, chronic WAR therapy is not without obstacles, including need for ongoing monitoring, expense, vigilance to diet and pharmacotherapy, etc. Dabigatran is an orally administered direct thrombin inhibitor that does not require routine monitoring, and is not significantly affected by vitamin K content in food. In October 2010, the FDA approved dabigatran for reduction of risk of stroke in persons with AFib.

The RE-LY trial randomized AFib patients (n = 18,113) to anticoagulation with warfarin (target INR, 2.0-3.0) or dabigatran. Dabigatran was administered as either 110 mg bid or 150 mg bid. Patients were followed for 2 years.

Initial reporting of RE-LY results found that lower-dose dabigatran (110 mg bid) was non-inferior to warfarin, and that higher-dose dabigatran (150 mg bid) was superior to warfarin. This article further examined whether trial results were impacted by the degree of success with which study sites were able to keep patients within the therapeutic range with warfarin.

Ultimately, the efficacy of dabigatran 150 mg bid relative to WAR for stroke prevention was found not to be dependent upon the efficacy with which clinical trial centers maintained INR within the therapeutic range. On the other hand, for the endpoints of all vascular events, nonhemorrhagic events, and mortality, differences between dabigatran and WAR were greater at study sites with less efficacy at maintaining in-range INR. Dabigatran appears to be at least as effective as WAR, although some advantages of dabigatran are magnified by inconsistencies in maintaining good INR control. ■

Dementia and Aggressive Behavior

Source: Kunik ME, et al. Causes of aggressive behavior in patients with dementia. *J Clin Psych* 2010;71:1145-1152.

Metrics designed to measure aggression in dementia patients list activities such as spitting, verbal aggression, hitting, kicking, pushing, biting, and making inappropriate sexual advances either verbally or physically. Because such behaviors can be highly disruptive, it would be helpful to shed light on factors associated with aggressive behavior.

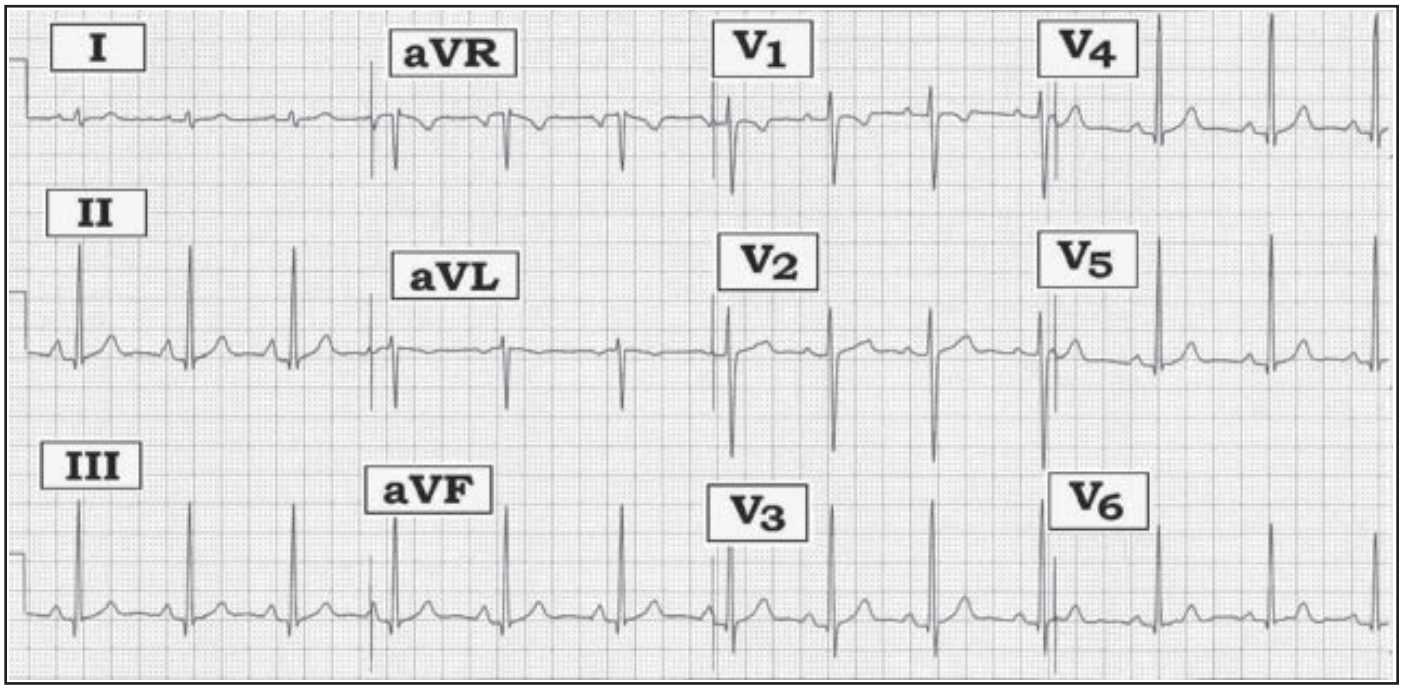
To be included in the trial, subjects had to be free of a history of aggressive behaviors for the previous 12 months. Factors that were measured included depression (Hamilton Depression Scale), pain, caregiver burden (based upon a validated scoring system that measures psychological, physical, emotional, financial, and social impact of being a caregiver), and an item titled "mutuality," which measures the positive qualities of the caregiver-to-care-receiver relationship, including frequency of contact, positive interactions, degree of attachment, and emotional support. The authors looked at data from 215 patients with dementia, of whom 41% developed aggression over a 2-year interval.

Predictors of increased risk for aggression were low baseline mutuality, high caregiver burden, pain, and depression. Although some of the predictors for aggression may be difficult or impossible to modify, others are clearly modifiable and might reduce likelihood for aggression. ■

P Pulmonale?

By Ken Grauer, MD, *Professor, Department of Community Health and Family 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 above was obtained from a slender and previously healthy 27-year-old woman having atypical chest discomfort. Is there evidence of chamber enlargement?

Interpretation: The ECG shows sinus rhythm with slight variation in rate (sinus arrhythmia). The PR, QRS, and QT intervals are normal. The axis is vertical at +80 degrees. The P wave is tall and peaked in each of the inferior leads (II, III, aVF). It is > 2.5 mm tall in lead II, thereby satisfying criteria for right atrial abnormality (RAA). Given the patient's age, voltage criteria for LVH are not met (QRS amplitude is often increased in adults younger than age 35). There are small q waves in multiple leads; transition occurs normally (between V_2-to-V_3) — and ST-T waves are normal. We are left with the impression of an essentially normal tracing for this 27-year-old woman, with the exception of RAA.

The reason we prefer the terms right and left atrial abnormality (RAA/LAA) instead of right and left atrial enlargement (RAE/LAE) is that altered P wave morphology does not always imply pathology. In addition to true increased atrial chamber size, other causes of altered P wave morphology include atrial conduction defects, abnormal chamber pressure, and body habitus. Tall, peaked P waves in the inferior leads are commonly seen in slender young adults with a vertical QRS axis. Assuming the patient had a normal examination, it is most likely that RAA is a benign variant pattern in her case with no clinical implications. ■

In Future Issues:

Diagnosing Systolic Murmurs

Perception of Benefit of PCI in Stable Coronary Disease

CV Effects of Omega-3 Fatty Acids

PHARMACOLOGY WATCH

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

Dabigatran Leading Race to Replace Warfarin

In this issue: FDA Advisory Committee recommends approval of dabigatran, safety of proton pump inhibitors, effectiveness of glucosamine and chondroitin, FDA Actions.

Advisory Committee recommends approval of dabigatran

In the race to find a drug to replace warfarin, Boehringer Ingelheim may have a leg up with the impending approval of dabigatran. The Cardiovascular and Renal Drugs Advisory Committee of the FDA unanimously recommended approval of the drug in September for the prevention of stroke and systemic clots in patients with atrial fibrillation. Dabigatran is a direct thrombin inhibitor that is given in a fixed dose twice a day and does not require monitoring. It is speculated that dabigatran will replace warfarin as the preferred anticoagulant in many settings, including many patients with atrial fibrillation. The approval was based on the Randomized Evaluation of Long-Term Anticoagulation Therapy trial, which was published last December. The study of more than 18,000 patients with atrial fibrillation showed that dabigatran given at a dose of 110 mg was similar in effectiveness to warfarin in prevention of strokes and systemic embolism, but had a significantly lower rate of major hemorrhage. A higher dose of 150 mg was associated with lower rates of stroke and systemic embolism compared to warfarin and similar rates of hemorrhage (*N Engl J Med* 2009;361:1139-1151). The FDA panel recommended approval of the higher dose, but was split on recommending the 110 mg dose. There was a slightly higher rate of heart attacks with dabigatran compared to warfarin, although the reviewers did not think this was serious enough to warrant holding the drug back. Dabigatran, once approved, will be marketed as Pradaxa®. Several companies are working on their own products to fill the same niche in what has been estimated to be a $10-20 billion market. Drugs in development include Bristol-Myers Squibb's apixaban and rivaroxaban, which is being jointly developed by Bayer Healthcare and Johnson & Johnson. Both drugs are direct inhibitors of Factor Xa. ■

Safety of proton pump inhibitors

Recent studies have suggested that proton pump inhibitors (PPIs) may negate some of the benefit of clopidogrel (Plavix®) in patients with cardiovascular (CV) disease. A new study refutes these findings, and at the same time raises more questions about the safety of PPIs. In a nationwide cohort study from Denmark, all patients discharged after first-time myocardial infarction (MI) were reviewed during 2000-2006. Of the more than 56,000 patients, 16% were rehospitalized for MI or stroke or experienced CV death. Nearly 25,000 patients were discharged on clopidogrel, of which nearly 30% received a concomitant PPI. Patients who were discharged on the combination of a PPI with clopidogrel or on a PPI alone had elevated but similar rates of death or rehospitalization for MI at 30 days (hazard ratio [HR], 1.29 for the combination [95% CI, 1.17-1.42]; HR, 1.29 for PPI alone [CI, 1.21-1.37]), indicating that

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

the risk of a PPI with clopidogrel was no higher than a PPI alone. The authors conclude that there seems to be no significant interaction between PPIs and clopidogrel; however, PPIs may be associated with an increased risk for adverse CV outcomes after discharge. The authors postulate that the increased CV risk from PPIs is likely caused by unmeasured confounders (*Ann Intern Med* 2010;153:378-386). As pointed out in an accompanying editorial, this study may be very confusing for clinicians who have recently received warnings regarding the combination of clopidogrel with a PPI. It further highlights the potential risks of PPIs in patients with questionable or inappropriate indications for the drugs and the need for further studies into their risks and benefits (*Ann Intern Med* 2010;153:413-415). ■

Glucosamine and chondroitin

Millions of patients take glucosamine and chondroitin on a daily basis, hoping it is a safe alternative treatment for osteoarthritis. A new study suggests that the combination is ineffective but harmless. In a meta-analysis of 10 trials and more than 3800 patients, glucosamine, chondroitin, or the combination was compared to placebo with regard to pain scores and X-ray appearance of the hip and knee joint. None of the endpoints crossed the boundary of the minimal clinical important difference (95% credible intervals). The authors conclude that compared with placebo, glucosamine, chondroitin, and the combination do not reduce joint pain or have an impact on narrowing of joint space of the hip or knee. They further state that insurers should not cover the cost of these preparations, but since there is little harm, patients may wish to continue buying and taking it (*BMJ* 2010;341:c4675). ■

FDA Actions

The FDA has announced that it will significantly restrict the use of rosiglitazone (Avandia®) to patients with type 2 diabetes who cannot control the disease on other medications. The FDA had the option of removing the drug from the market, a move that was recently taken by the European Medicines Agency; however, the agency decided to limit access at least for now. Rosiglitazone has been associated with an elevated risk of cardiovascular events.

The FDA has approved fingolimod (Gilenya®), the first oral drug to reduce relapses and delay disability progression in patients with relapsing-remitting multiple sclerosis. The drug is the first of a new class called sphingosine 1 phosphate receptor modulators. Patients need to be closely monitored for symptomatic bradycardia. Fingolimod will be marketed by Novartis Pharmaceuticals.

The Endocrinologic and Metabolic Drugs Advisory Committee of the FDA has voted against recommending approval of lorcaserin hydrochloride for the treatment of obesity (see September *Pharmacology Watch*). Although the drug was shown to be effective, resulting in at least a 5% body weight loss for half of patients taking the drug over 1 year, there were concerns over valvular heart disease. Arena Pharmaceuticals argued that valvulopathy was not a significant issue and that they met the FDA's predefined goals for safety. The FDA is not required to follow subcommittee recommendations, however it usually does.

The same subcommittee also recently reviewed the weight-loss drug sibutramine (Meridia-Abbott Laboratories) and delivered a **split vote on whether sibutramine should stay on the market.** Sibutramine has been the subject of controversy since last November when initial data from the Sibutramine Cardiovascular Outcomes trial revealed a higher rate of cardiovascular disease associated with the drug. The full study was published in September and showed that cardiovascular events were observed significantly more frequently in the sibutramine group than in the placebo group (11.4% vs 10.0%; $P = 0.02$). The rate of cardiovascular death or death from any cause, however, was no different in the two groups (*N Engl J Med* 2010;363:905-917). The FDA subcommittee voted 8-8, with 8 members voting to remove the drug from the market and the other 8 voting to allow the drug to remain on the market with tougher warnings and a restricted distribution pattern. The FDA vote is expected later this fall.

The **FDA has approved pegloticase for the treatment of refractory gout in patients who have not responded to or can't tolerate conventional therapy.** The drug is administered intravenously every 2 weeks. It appears to work by metabolizing uric acid to allantoin, which is then cleared through the kidneys. The approval was based on two 6-month trials in more than 200 patients that showed the drug reduces uric acid levels and reduces uric acid deposits in joints and soft tissue. About one in four patients will experience severe allergic reactions to the infusion, so patients should be given an antihistamine and a corticosteroid prior to administration. The drug was not studied in patients with congestive heart failure and should not be used in this population. Savient Pharmaceuticals will market pegloticase as Krystexxa™. ■