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INSIDE

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Is LDL Cholesterol the Best CHD Lipid Marker?

SPECIAL REPORT

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

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

ILLNESSES PRODUCED BY VASCULAR DISEASES ARE FAR AND AWAY THE most common cause of death in the developed world and, amazingly enough, will become the leading cause of death even in the developing world by 2020.[1] Identifying individuals at increased risk of coronary artery heart disease (CHD) is critical in preventing CHD and, in 2002, the Adult Treatment Panel III (ATP III)[2] reaffirmed its previous position by concluding that low-density lipoprotein cholesterol (LDL-C) would remain the cornerstone of lipid management. However, the Panel also noted the increased CHD risk associated with hypertriglyceridemia in patients with the metabolic syndrome and suggested that non-HCL-C might be an appropriate treatment target for this specialized group of patients.[2] Use of apolipoprotein B (apoB) lipid measurements were not recommended because the Panel concluded that non-HDL-C and apoB measurements were highly correlated and therefore only non-HDL-C need be calculated when standard lipid studies were obtained.

Pischon and colleagues compared apoB, non-HDL-C, LDL-C and other lipid markers as predictors of CHD in a case-control study among 18,225 participants in the Health Professionals Follow-up Study.[3] When non-HDL-C and LDL-C were mutually adjusted, only non-HDL-C was predictive of CHD and, when non-HDL-C and apoB were mutually adjusted, only apoB was predictive. Triglycerides added significant information to non-HDL-C but not to apoB for CHD risk prediction. The authors concluded that although non-HDL-C and apoB were both strong predictors of CHD in this male cohort (more so than LDL-C), the findings support the concept that the plasma concentration of atherogenic lipoprotein particles measured by apoB is more useful in predicting CHD development than is the cholesterol (ie, measured by non-HDL-C) carried by these particles.

COMMENTARY

Atherosclerosis is a complex series of biological responses to

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atherogenic particles which are trapped within arterial walls and is not a response simply to cholesterol accumulation. These particles injure the endothelium and trigger an extensive and intricate series of inflammatory and healing responses. Cholesterol is simply carried as a passenger into the arterial wall within an atherogenic particle and, of course, it should be noted that the smaller LDL particles more easily enter the arterial walls than do the larger very low-density lipoprotein (VLDL) particles.

Measuring LDL-C levels only incompletely measures atherogenic lipoproteins because VLDL remnants also are likely to contribute to CHD. The apoB level is a more accurate and direct measurement of the atherogenic burden (ie, the concentration of proatherogenic particles) because each VLDL and LDL particle has one molecule of apoB.[4] ATP III guidelines recommended measuring non-HCL-C by subtracting HDL-C from the total cholesterol. Although animal experiments have suggested that a high apoB particle concentration may be more important prognostically than the cholesterol concentration,[5] the 3 measures of atherogenic lipoproteins (ie, LDL-C, non-HDL-C, and apoB) had not previously been compared directly in a large prospective study in humans. The Pischon study[3] corrected this deficiency and, in essence, demonstrated that the plasma concentration of atherogenic lipoproteins as measured by apoB may be more informative regarding the risk of development of atherosclerosis than the amount of cholesterol that the lipoproteins carry into the arterial wall. They also demonstrated that the non-HDL-C level appears to be superior to LDL-C in predicting CHD[3,6] probably because it also measures triglycerides—rich atherogenic lipoproteins such as VLDL.

The practical application of these findings suggests that apoB levels instead of LDL-C and non-LDL-C should be measured and treated since apoB is a direct measurement of the number of atherogenic lipoprotein particles and is more closely related to the risk of developing CHD than is the cholesterol concentration contained within these particles. ApoB has been extensively validated in epidemiological studies and clinical trials[3,7] and, therefore, when the Adult Treatment Panel next meets, it should consider approving and reimbursing widespread measurements of apoB levels. It should be noted that the measurements of apoB levels are standardized, automated, inexpensive and fasting samples are not required.[8] Whether the additional costs of switching to and subsequently measuring only apoB levels is justified by the potential improvement in risk prediction over currently available measurements (ie, LDL-C and non-HCL-C) would depend upon the results of additional studies. Finally, it should also be clearly recognized that the current guidelines are heavily identified with the cholesterol and LDL-C levels and that extensive campaigns to educate health professionals and the public over the past 25 years were necessary to achieve this admirable result. At this time, eliminating cholesterol measurements would be a major and quite difficult change but it would appear important to at least consider measuring and utilizing apoB levels in place of or along with the current lipid measurements in order to possibly improve CHD care. ■

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Questions & Comments

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Shaky Evidence for an Old Technique

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

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

Synopsis: *The use of a steroid ointment following a 20-minute soak may relieve chronic skin conditions.*

Source: Gutman AB, et al. Soak and smear: a standard technique revisited. *Arch Dermatol*. 2005;141:1556-1559.

This is a retrospective study of 28 patients with severe atopic dermatitis, xerosis, or chronic hand dermatitis. These patients attended a medical school dermatology clinic that specialized in difficult cases. After identifying 34 cases that fit their profile, the authors excluded 6 patients, 5 for lack of follow up and 1 for lack of a medical record. The 14 men and 14 women who remained ranged in age from 24 to 84 years. They all had failed numerous topical regimens and most had also taken prednisone or cyclosporine or had UV-B treatment. A combined patient-physician global assessment (complete clearance or percentage of improvement) was the outcome of interest. Each patient was instructed in an aggressive "soak-and-smear" therapy, which consisted of bathing in plain hot water for 20 minutes at night and then smearing an intermediate-potency steroid ointment (usually triamcinolone acetonide [TCA] 0.1%, however, the authors were not explicit about this) over the affected areas without drying. (A detailed patient educational instruction sheet is presented in the article.) The patients did this for up to 2 weeks at which point the responses were complete (17), 90-100% improvement (9), 80% improvement (1), and 75% improvement (1).

COMMENTARY

When study results appear too good to be true, they probably aren't. There are several methodological flaws in the design of this study which raise important questions, so its conclusions must be viewed with some skepticism. First, it was a retrospective study. The patients were not randomized to an intervention group or a control group. Would the patients have done as well with an aggressive program that substituted petrolatum for the TCA ointment? How about bear grease? The patients were referred to this tertiary center because they had failed conventional therapy. Are they representative of the patients you see? Five patients were excluded because they did not follow up. Did they not return because the treatment failed? The wide age range could be a problem because aging changes skin. Older patients produce less sebum, which is the body's natural moisturizer.[1] Were the authors treating heterogeneous conditions? The outcome measure is very subjective. For instance, what exactly would 50% improvement look like?

The gentle reader might now wonder, "If this is such a poorly done study, why should I consider this therapy for my patient?" I think you should consider it for 2 reasons. The first is that its mechanism of action is intuitively plausible: hydrate the stratum corneum and then seal in the water with petroleum jelly. If there is some element of inflammation, all the better. The TCA penetrates hydrated stratum corneum better than dehydrated stratum corneum. The second reason is that this regimen

satisfies most of the STEPS[2] mnemonic: Safety, Tolerability, Effectiveness, Price, and Simplicity. Water and petrolatum have very benign safety profiles. TCA could cause dermal thinning or systemic side effects, if used for a prolonged period of time. However, the 2-week course of therapy proposed here is unlikely to cause any major adverse effects. Tolerability could be an issue since ointment is messy, but since the advice is to use it at night and to wear old pajamas, the messiness is minimized. If you believe this study, "soak and smear" is a very effective regimen. The treatment is cheap; an 80-gram supply of TCA 0.1% ointment is available online for less than $8.00.[3] Even in our immediate gratification society, two weeks of a 20-minute bath and application of ointment seem like simplicity itself.

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Forgotten Hazards of Sedatives

ABSTRACT & COMMENTARY

By Saadia R. Akhtar, MD, MSc

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Dr. Akhtar reports no financial relationship to this field of study,

Synopsis: *This case series and prospective observational study describe propylene glycol toxicity in patients receiving IV benzodiazepines. The authors estimate the incidence of this important but unrecognized complication to be 19%.*

Source: Wilson KC, et al. *Chest*. 2005;128:1674-1681.

PROPYLENE GLYCOL IS USED AS THE CARRIER VEHICLE for a number of drugs including lorazepam and diazepam. It may cause metabolic abnormalities such as anion gap metabolic (usually lactic) acidosis and hyperosmolality. Case reports also describe it causing sepsis-like symptoms, cardiac arrhythmias, and neurological changes (agitation, seizures or coma).[1] Toxicity may be more common in patients with renal dysfunction.

A prospective, observational study was performed to determine the incidence of propylene glycol toxicity in a single medical ICU. All admissions over a 3-month period were screened. Two groups of patients were enrolled: those receiving benzodiazepines with propylene glycol vehicle (lorazepam and diazepam, 21 patients) and those receiving an alternative benzodiazepine (midazolam, 23 patients). Usual clinical data were collected by medical record review. Propylene glycol toxicity was defined as hyperosmolality or anion gap metabolic acidosis not explained by another cause and reversed by cessation of the benzodiazepine. Standard statistical methods were used to compare the 2 groups.

Patients receiving benzodiazepines with propylene glycol vehicle were more likely to have a history of heavy alcohol intake. Otherwise there were no significant differences in age, gender, co-morbid conditions, admitting diagnoses or clinical data between the 2 groups. Four (19%) of the 21 patients receiving the benzodiazepines with propylene glycol vehicle had evidence of propylene glycol toxicity. All did well after cessation of the infusions and were discharged from the ICU to the floor in stable condition.

Propylene glycol levels between 58 and 127 mg/L were measured in patients with only metabolic abnormalities. Based on their prior case reports, the authors note that levels ranging from 104 to 144 mg/dL were seen in patients with clinical deterioration felt to be secondary to propylene glycol toxicity. Toxicity almost always occurred in patients receiving greater than the usual recommended daily doses of lorazepam (0.01-0.1 mg/kg/hr) and diazepam (5-10 mg IV every 3-4 hours). However, there was at least 1 person with toxicity after as little as 68 mg of IV lorazepam by continuous infusion.

COMMENTARY

Wilson et al's report—the largest study of this topic in the published English literature—serves as an important reminder of a serious potential adverse effect of lorazepam or diazepam use in the ICU. It also suggests that at least metabolic evidence of propylene glycol toxicity may be much more common than previously realized.

The study clearly has numerous limitations. It is a small, single-center, unblinded observational study. Thus, considerable bias (in patient selection and management and data collection and interpretation) may exist, and certainly the incidence results may not be generalizable. It is unclear exactly what criteria were used to determine whether there was an alternate explanation for acidosis or hyperosmolality in patients classi-

fied as having propylene glycol toxicity. It is difficult from these data to define specific threshold levels of benzodiazepines that may lead to toxicity or to determine a threshold level of propylene glycol beyond which toxicity occurs. Further investigation is indicated to address these issues. More information is also needed to understand when and why propylene glycol toxicity may result in clinical deterioration. Long-term outcomes of toxicity (if any) ought to be investigated. Finally, the mechanism(s) of toxicity must be more clearly elucidated.

Despite its limitations, this remains an important report. Until the specifics of propylene glycol toxicity are better defined, at least awareness of and vigilance for this condition are warranted. Potential propylene glycol toxicity is yet another reason to consider limiting sedative use in the ICU. ■

Reference

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Pharmacology Update

Conivaptan Injection (Vaprisol®)

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

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

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

THE FDA HAS APPROVED THE FIRST OF A NEW CLASS OF agents, the vaptans. Conivaptan, the first arginine vasopressin receptor antagonist, is approved for the management of serious sodium/water imbalance. It will be marketed by Astellas Pharma US, Inc as Vaprisol®.

Indications

Conivaptan is indicated for the treatment of euvolemic hyponatremia (eg, syndrome of inappropriate secretion of antidiuretic hormone, or in the setting of hypothyroidism, adrenal insufficiency, pulmonary disorder, etc) in hospitalized patients.[1]

Dosage

The recommended initial loading dose is 20 mg administered intravenously over 30 minutes followed by 20 mg infused over 24 hours. Conivaptan may be given for an additional 1 to 3 days at 20 mg daily. If the desired increase in serum sodium is not achieved, the drug may be given at a daily dose of 40 mg.

Potential Advantages

Conivaptan provides a new approach for the treatment of hyponatremia. As an arginine vasopressin receptor antagonist it promotes free-water excretion while maintaining levels of sodium and other electrolytes (aquaresis).

Potential Disadvantages

Conivaptan should not be administered with potent CYP450 3A4 inhibitors. Side effects include dehydration, hyperglycemia, hypoglycemia, hypokalemia, hypomagnesemia, and infusion site reactions. Other adverse events include thirst, headache, vomiting, peripheral edema, pollakiuria, diarrhea, polyuria, and phlebitis. It is currently not approved for use in congestive heart failure.[1]

Comments

Conivaptan is a non-peptide, dual V_{1A} and V_2, arginine vasopressin receptor antagonist. Antagonism of the V_{1A} receptor reverses vasoconstrictive effects, increases cardiac output, reduces peripheral resistance, and reduces mean arterial blood pressure. At the V_2 receptor, free water excretion is promoted without loss of sodium and other electrolytes.[2] In animal models, conivaptan showed similar aquaretic effects to 100 mg/kg of furosemide without urinary excretion of electrolytes.[3] In a randomized, double-blind, placebo-controlled study in hospitalized patients with mild-to-moderate euvolemic hyponatremia (n = 56), conivaptan treatment resulted in significant improvement in serum sodium with the first day of treatment.[1] A dose of 40 mg following a 20 mg infusion produced an increase in sodium levels of at least 4 mEq/L in 52% of patients and 6 mEq/L or normalization in 39% after 2 days.[3] Sixty seven percent (67%) had an increase of 6 mEq/L or normalization after 4 day. The mean change after 2 days was 5.7 mEq/L. In patients with advanced heart failure, conivaptan produces favorable changes in hemodynamics and urine output without affecting blood pressure or heart rate.[5]

Clinical Implications

Current management of euvolemic hyponatremia includes hypertonic saline with a loop diuretic, fluid restriction, or demeclocycline. These therapeutic

options are not ideal and all have limitations. An arginine vasopressin antagonist and aquaretic, such as conivaptan, provides a new therapeutic option. ■

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CME Questions

5. **Apolipoprotein B (apoB):**
   a. is the same as non-HDL cholesterol.
   b. is expensive and difficult to measure.
   c. is a more accurate measurement of atherogenic lipoprotein particles then are LDL cholesterol and/or non-HDL cholesterol.

6. **Choose the correct answer. The "soak and smear" technique involves:**
   a. a 20-minute shower.
   b. application of a steroid cream.
   c. bear grease.
   d. none of the above.

Answers: 5 (c); 6 (d)

CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances; and
- to describe cost-effective treatment regimens.

By Louis Kuritzky, MD

Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

Efficacy and Safety of Benazepril for Advanced Chronic Renal Insufficiency

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

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

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

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

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

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

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

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

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

Nonsteroidal Anti-inflammatory Drugs and the Risk of Actinic Keratoses and Squamous Cell Cancers of the Skin

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

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

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

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

A 73-Year-Old Man with Dyspnea

By Ken Grauer, MD

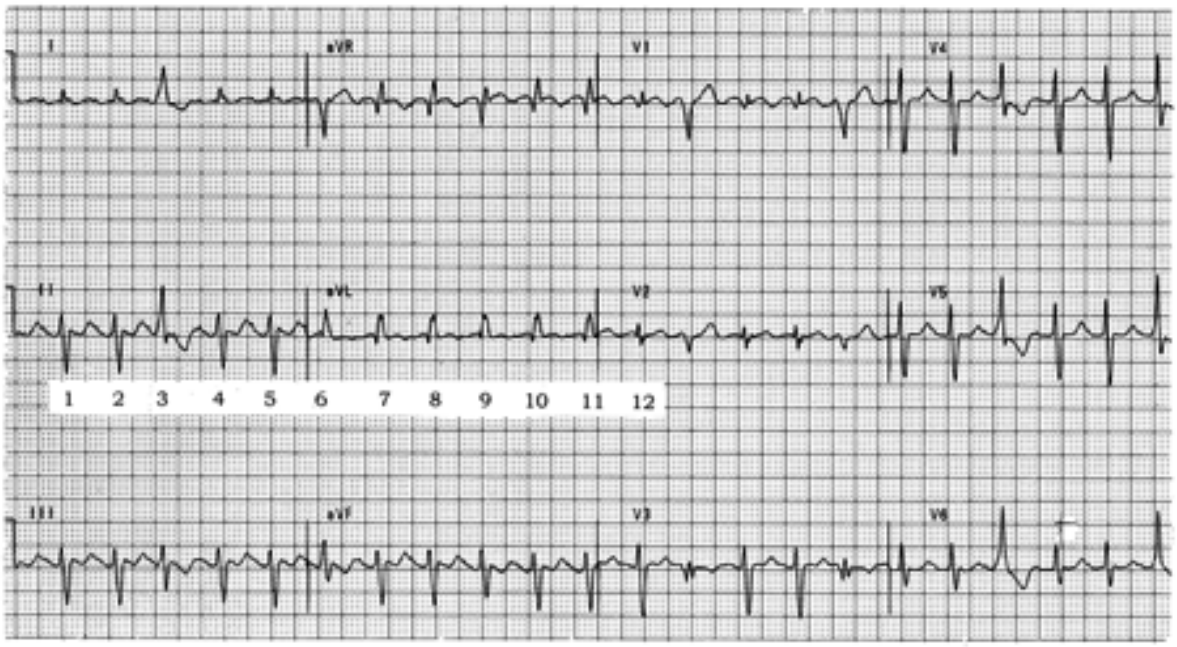

Figure. 12-lead ECG obtained from a 73-year-old man with dyspnea.

Clinical Scenario: The 12-lead ECG in the Figure was obtained from a 73-year-old man with dyspnea. What ECG findings do you see that may account for his symptoms?

Interpretation/Answer: The underlying regular rhythm is interrupted every third or fourth beat. The frequency of this interruption is easy to overlook unless one pays careful attention to QRS morphology in *each* of the 12 leads. For example, beats #3, 6, and 9 do not look much different from the normal beats in leads III, aVL, and aVF. However, it is obvious that something different is occurring for beat #3 from inspection of leads I and II, and equally obvious from lead aVR that beats #6 and 9 are different. We suspect that the reason QRS morphology is not that different for many of these interrupting beats, is that these widened and only slightly early occurring complexes are *fusion* beats, produced by near simultaneous occurrence of PVCs (premature ventricular contractions) with the underlying rhythm.

The question remains as to what the underlying rhythm is. The answer almost always can be found in the relative pause that follows the slightly early occurring, abnormal-looking beats. Thus, in leads I and II, a subtle but real notch is seen immediately after the abnormal-looking QRS complex (beat #3). Careful inspection of the baseline in lead I reveals small amplitude but repetitive notching at a regular interval of approximately one large box (corresponding to a rate of 300/minute). Stepping back to look at the ECG from a short distance should now allow appreciation of the underlying "sawtooth" pattern of the baseline in leads II, III, and aVF. Thus, the rhythm is atrial flutter with 2:1 AV conduction, with frequent interruption by PVCs that produce fusion beats. The marked left axis (net negativity of the QRS complex in lead II) suggests LAHB (left anterior hemiblock). Additional findings of relatively low QRS voltage, R wave greater than S in lead V1, and S waves in all precordial leads are consistent with the pulmonary disease (and possible right ventricular hypertrophy) that this patient had, which together with his tachyarrhythmia were responsible for his symptoms of acute dyspnea. ■

In Future Issues: Let the Sun Shine In!

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.

Letrozole for Postmenopausal Women with Breast Cancer

Letrozole (Femara) is a potent aromatase inhibitor that is used to treat women with metastatic breast cancer and, in a neoadjuvant role, for women who have failed tamoxifen. Aromatase inhibitors exert their effect by blocking the conversion of androgens to estrogens and reducing estrogen levels in tissue and plasma. Recently, letrozole was compared with tamoxifen for adjuvant therapy in postmenopausal women with steroid-hormone-receptor-positive breast cancer.

A total of 8010 women were randomized to 5 years of letrozole (4003) or tamoxifen (4007). After a median follow-up of 25.8 months, there were 351 events (local or distant recurrence) in the letrozole group and 428 events in the tamoxifen group, with 5-year disease-free survival estimates of 84% and 81.4%, respectively. Adverse effects of the drugs were different with tamoxifen, resulting in a higher rate of thromboembolism, endometrial cancer, and vaginal bleeding, while letrozole was associated with a higher incidence of skeletal and cardiac events and hypercholesterolemia.

The authors suggest that in women with endocrine-responsive breast cancer, adjuvant treatment with letrozole, as compared with tamoxifen, reduced the risk of recurrent disease (Thurlimann B, et al. A Comparison of Letrozole and Tamoxifen in Postmenopausal Women with Early Breast Cancer. *N Engl J Med*. 2005;353:2747-2757). In an accompanying editorial Sandra Swain, MD, from the National Cancer Institute, states that "all the evidence points to aromatase inhibitors as critically important for improving the outcome among postmenopausal women with breast cancer who have positive or negative lymph nodes and who are at a substantial risk for recurrent disease." (Swain SM, et al. Aromatase Inhibitors—A Triumph of Translational Oncology. *N Engl J Med*. 2005;353:2807-2809). Based on this study, the FDA has recently approved letrozole for adjuvant treatment (immediately after surgery) in postmenopausal women with hormone sense of breast cancer.

Do Antidepressants Increase Risk of Suicide?

An article in the January issue of the *American Journal of Psychiatry* asks "Is the FDA Warning About Antidepressants Wrong?" Researchers from Group Health Cooperative in the Pacific Northwest used population-based data to evaluate the risk of suicide death and serious suicide attempt in relation to the initiation of antidepressant treatment.

Computerized health plan records for over 65,000 patients with over 82,000 episodes of antidepressant treatment between 1992 and 2003 were reviewed. In the 6 months after initiation of antidepressant treatment, the risk of suicide was found be no higher than at any other time during treatment. The risk of suicide attempt was highest in the month before starting treatment, and declined progressively after starting medication. When newer drugs were compared to older drugs, an increase in suicidality was

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only seen with the older drugs.

The authors conclude that the risk of suicide during acute-phase antidepressant treatment is approximately 1 in 3000 treatment episodes, and the risk of serious suicide attempt is approximately one in 1000. Available data do not indicate significant increase in risk of suicide or serious suicide attempt after starting treatment with newer antidepressant drugs (Simon GE, et al. Suicide Risk During Antidepressant Treatment. *Am J Psychiatry*. 2006;163:41-47, available free at ajp.psychiatryonline.org). The study calls into question the March 2004 FDA public health advisory regarding worsening depression and suicidality in pediatric and adult patients being treated with 10 newer antidepressants (bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, escitalopram, and venlafaxine).

Can Viagra Improve Heart Function?

Concern still lingers regarding the safety of erectile dysfunction drugs in patients with heart failure. A new study from Australia suggests that sildenafil (Viagra) actually improves heart function in patients with systolic dysfunction. In a randomized, placebo-controlled, double-blind, 2-way crossover study, 20 patients with controlled left ventricular failure and ejection fractions < 35% received sildenafil 50 mg or matching placebo. Cardiac output was determined by Doppler echocardiography, aortic pressure waveform, and aortic and femoral arterial stiffness was also evaluated. With a peak effect at 60 minutes after administration, sildenafil resulted in an increase in cardiac index of 0.37 L/min, decrease in total systemic resistance, decreased aortic and lower limb pulse-wave velocity, and decreased wave reflection (all significant at $P < .0001$). The authors conclude that sildenafil improved cardiac performance by decreasing LV load, resulting in increased cardiac output and increase in exercise capacity in heart failure patients (Hirata K, et al. Effect of Sildenafil on Cardiac Performance in Patients with Heart Failure. *Am J Cardiol*. 2005;96:1436-1440).

Can Tamoxifen Increase Your Height?

Tamoxifen may increase height potential in short pubertal periods, according to new study in the journal *Pediatrics*. The study was a retrospective chart review of 7 boys with a mean age of 15 who took tamoxifen 10-20 mg twice a day for a mean of 26 months. Six of the boys were also receiving growth hormone. Tamoxifen significantly decreased the rate of skeletal maturation and improved predicted adult height without negative effects on sexual maturation. Skeletal maturation was determined by review of bone radiographs by independent endocrinologists. The authors state that "additional evaluation of this therapy is now required to determine if the increase in predicted adult height results in a clinically significant increase in final adult height." (Kreher NC, et al. The Use of Tamoxifen to Improve Height Potential in Short Pubertal Boys. *Pediatrics*. 2005;116:1513-1515).

A Dramatic Increase of Clostridium difficile

Clostridium difficile is increasing in frequency and severity in both hospital and community settings. Widespread use of acid suppressing proton pump inhibitors (PPIs) and H2 receptor agonists (H2RAs) may be a contributing factor, according to new study. Two population-based, case-control studies from England reviewed all 1672 cases of *C. difficile* reported between 1994 and 2004, while a second study looked at cases defined as community acquired. All cases were matched 10 controls. The incidence of *C. difficile* increased dramatically between 1994 and 2004. The adjusted rate ratio of *C. difficile* associated disease with current use of PPIs was 2.9 (95% CI, 2.4-3.4) and, with H2RAs, the rate ratio was 2.0 (95% CI, 1.6-2.7). The authors conclude that the use of acid-suppressive therapy is associated with an increase risk of community-acquired *C. difficile*. Parenthetically, they also found an increased risk associated with use of nonsteroidal anti-inflammatory drugs (*JAMA*. 2005;294:2943-3048).

FDA Actions

The FDA has approved Bristol-Myers Squibb's abatacept (Orencia) for the treatment of rheumatoid arthritis. The drug, which is produced by recombinant DNA technology, is a T cell costimulation modulator. It is approved for patients with moderately-to-severely active rheumatoid arthritis who had an inadequate response to one or more DMARDs, including TNF antagonists. It may be used as monotherapy or with other non-TNF inhibitor DMARD. Abatacept is administered as a 30-minute IV infusion at 0, 2, and 4 weeks, then every 4 weeks thereafter.

The FDA and GlaxoSmithKline have issued a "Dear Doctor" letter regarding rare reports of macular edema in patients receiving rosiglitazone (Avandia). The majority of the cases involved concurrent peripheral edema and, in the majority of cases, macular edema improved with discontinuation of the drug. Macular edema presents as blurred or distorted vision, decrease color sensitivity, and decreased dark adaptation. ■