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Grape Resveratrol in the Primary Prevention of Cardiovascular Disease

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

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

Synopsis: *Supplemental grape resveratrol appears to improve both inflammatory and fibrinolytic markers in patients who are on statin therapy for primary prevention of cardiovascular disease.*

Source: Tome-Carneiro J, et al. One-year consumption of a grape nutraceutical containing resveratrol improves the inflammatory and fibrinolytic status of patients in primary prevention of cardiovascular disease. *Am J Cardiol* 2012;110:356-363.

The search for treatments for the primary prevention of cardiovascular disease (CVD) has been a high-priority challenge for many years. Approximately 20 years ago, consumption of red grape wine was thought to be the explanation for the so-called French paradox, that is, for the low mortality from CVD noted in France compared to the mortality in other countries despite similar CVD risk factors.[1] The polyphenol resveratrol found in red grape wine was subsequently identified as the probable chemical responsible for the beneficial properties of red wine.[2] In animals and in-vitro models of human CVD, high resveratrol concentrations were found to be associated with cardiovascular benefits, possibly because they increase insulin sensitivity, and also were found to be associated with a decrease in ischemic heart disease, heart failure, and hypertension.[3] However, even at this late date, the benefits of resveratrol have not been clearly demonstrated in human subjects at high risk for CVD.

Dr. Tome-Carneiro and his colleagues mounted a triple-blinded, randomized, parallel, dose-response, placebo-controlled 1-year trial in human subjects to demonstrate the benefits of resveratrol in the primary

prevention of CVD in humans.[4] Seventy-five patients who were receiving standard primary CVD prevention therapies were allocated into three groups for a 6-month trial period. One group consumed a placebo, a second group was given a resveratrol-rich grape supplement containing 8 mg of resveratrol, and the third group was given a conventional grape supplement lacking resveratrol. The dosage in each group was doubled during a second 6-month period. Improved inflammatory and fibrinolytic markers were found to be present in those CVD patients who were at high risk (i.e., those with diabetes and/or hypercholesterolemia) and those who received the resversatrol-rich grape supplement in addition to statin therapy. The authors concluded that grape resveratrol could complement the gold-standard therapy, which is currently used in the primary prevention of CVD.

■ COMMENTARY

Blood cardio C-reactive protein (hs-CRP) measurements have gradually emerged as a leading biomarker of inflammation in the cardiovascular system and have been used for stratification of CVD risk.[5-7] A key finding in the Tome-Carneiro study,[4] with respect to the inflammatory status, was that the hs-CRP level decreased by 26% after 1 year of treatment with a grape nutraceutical containing 8 mg of resveratrol, which appeared to be well correlated with a decrease in the blood concentrations of the pro-inflammatory cytokine TNF-alpha and thrombogenic PAI-1. In this trial, patients were treated according to accepted guidelines for the primary prevention of CVD.[8] Therefore, since all patients received statin therapy, a synergistic effect between statins and the grape nutraceutical could not be excluded. In fact, the combination of pravastatin and resveratrol previously had been demonstrated to be more effective than statins alone in preventing myocardial infarction in hypercholesterolemic rats.[9] The authors concluded that, for the first time in human subjects, a dietary intervention with grape resveratrol was demonstrated to complement standard therapy used in the primary prevention of CVD. However, it is important to recognize that the sample size in this study was small, the follow-up period was relatively short (1 year), and this was a single-center trial; therefore, the statistical significance of the final results of the Tome-Carneiro trial[4] were, at best, somewhat uncertain.

In summary, the authors have confirmed the results of previously reported clinical studies that a grape nutraceutical containing resveratrol is beneficial in the primary prevention of CVD probably by improving the inflammatory and fibrinolytic status of subjects who consumed adequate quantities of the compound. However, it is important to recognize that a larger and longer trial is absolutely necessary before coming to firm conclusions about the effects of these grape products in the prevention of CVD. ■

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Questions & Comments
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Brief Report

When Pneumonia Occurs with Flu: Think Influenza

By Carol A. Kemper, MD, FACP

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Dr. Kemper does research for Abbott Laboratories and Merck. This article originally appeared in the August issue of Infectious Disease Alert.

Source: Jain S, et al. Influenza-associated pneumonia among hospitalized patients with 2009 pandemic influenza A (H1N1) virus — United States, 2009. *Clin Infect Dis* 2012;54:1221-1229.

CASES OF PANDEMIC H1N1 REQUIRING HOSPITALIZATION were examined by reviewing two national case series from spring and fall 2009. During this period, a total of 451 patients with laboratory-confirmed H1N1 were hospitalized, 195 (43%) of whom were diagnosed with pneumonia based on chest radiographs. Not unexpectedly, those patients with pneumonia had higher rates of admission to the intensive care unit (52% vs 16%), and were more likely to be diagnosed with acute respiratory distress syndrome (26% vs 2%), sepsis (18% vs 3%), and mortality (17% vs 2%), than those without pneumonia. More than half of those with pneumonia had bilateral infiltrates (67%); the others had multilobar infiltrates (7%) or unilobar involvement (31%). Bacterial infection, mostly bacteremia, was confirmed in 13 patients (7%) with pneumonia and 2 (< 1%) of those without.

What was not necessarily expected was the finding that patients with influenza-associated pneumonia were less likely to receive antivirals within 48 hours of admission compared with those admitted with influenza without pneumonia (28% vs 50%, $P < 0.0001$). Eventually during the hospitalization, a similar proportion of patients with or without influenza-associated pneumonia did receive antiviral therapy (78% vs 79%); 91% of this was oseltamivir.

The key to this paradox may be that the very presence of pneumonia or infiltrates on chest radiographs was more likely to prompt a diagnosis of bacterial infection and administration of antibacterials, rather than trigger a suspected diagnosis of influenza. "Sepsis" (which was based on clinical judgment) was diagnosed in 18% of these pneumonia cases, compared with only 2% of non-pneumonia cases, suggesting either bias in the suspicion of bacterial infection — or even more possibly, a more severe systemic inflammatory response from H1N1 infection in those with pneumonia.

During influenza season, influenza (H1N1) should be included in the differential of patients admitted with severe illness and pneumonia, or "sepsis" and pneumonia, and presumptive antiviral treatment should be started as soon as possible, at least until additional information and the results of tests are available. ■

Patient Attitudes Toward Treatments for Overactive Bladder

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

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Dr. Ling reports no financial relationships relevant to this field of study. This article originally appeared in the August issue of OB/GYN Clinical Alert.

Synopsis: *Women with overactive bladder hold differing views of their treatment options in light of the severity of their symptoms as well as the risks/benefits of the modality.*

Source: Wu JM, et al. Patient preferences for different severities of and treatments for overactive bladder. *Female Pelvic Med Reconstr Surg* 2011;17:184-189.

RESEARCHERS FROM DUKE UNIVERSITY AND THE UNIVERSITY of California, San Francisco enrolled 40 patients with symptoms of overactive bladder (OAB), i.e., urgency, frequency, and/or urge incontinence, and 40 patients with no history of OAB symptoms. The women's view of symptoms and treatments were measured with a utility score.

A utility is defined as "…a quantitative measure of the value that an individual assigns to a specific health outcome." Scores range from 0 to 1.0 where 0 represents death and 1.0 is perfect health. Utilities were measured

for four levels of OAB severity as well as three urge incontinence treatments. Significant side effects and/or complications were measured as well. Three treatments/complications were assessed and were defined as the following: 1) anticholinergic agents without side effects or with constipation/dry mouth; 2) botulinum toxin injection with urinary retention; and 3) sacral neuromodulation with no complications or with subsequent irritation in the lower extremeties or vagina.

Each subject was asked to rate on a scale from 0 to 100 how she would feel about living with each set of health outcomes. The rating was converted to a score between 0 and 1.0, i.e., a rating of 93 became a utility score of .93. Each proposed clinical scenario was described in great detail. By having richer descriptions, there is less room for ambiguity in the subject's response. Subjects also were allowed to adjust their rankings in relation to their answers to all other responses that they had given. This allowed the subject to change earlier responses in light of additional situations described later in the instrument, thereby allowing her to respond to each item within the context of all the scenarios described. The highest scores (both median and mean) were for mild urge incontinence (0.92 and 0.82, respectively). As the severity of urgency increased, scores decreased. A condition of frequency/urgency without incontinence scored between mild and moderate incontinence.

As for treatments for OAB, the least invasive (oral anticholinergics) with no side effects scored the highest (0.93 and 0.84). The lowest scores assigned to treatment were botulinum toxin complicated by urinary retention (0.75 and 0.64).

■ COMMENTARY

Although the concept of "utility" may be new to the reader, it is one that makes both clinical and common sense. Future studies may emphasize the importance of utility scores as newer treatments are studied. The utility score considers quality of life, a concept that many can appreciate but is difficult to measure. Understanding how a patient compares the effects of a chronic health condition vs possible complications of treatment for that condition provides insight into how significant symptoms and treatment are on a patient's lifestyle.

In this article, for example, the authors point out that low utility score of moderate urge incontinence (0.85) and severe urge incontinence (0.73) show that this condition has a "profound" effect on quality of life. For comparison, the following utilities are offered: blindness in one eye (0.93), asthma with dyspnea (0.89), moderate chest pain (0.83), and mild dementia (0.65). Findings that more severe OAB symptoms are assigned a lower utility score and that any treatment is given a higher utility than the same treatment with a complication show that this measure of utility makes clinical sense.

More importantly, in any given patient that we see in the office each day, we commonly provide choices that simulate this very process. "Mrs. Jones, is the pain bad enough that you would be willing to undergo a surgical procedure such as laparoscopy with its potential complications?" The same implied question applies to any medical or surgical therapy that is offered to a patient. Certainly the likelihood of a specific complication also will color the patient's response, since the utility is a description that presumes that the complication did occur.

Beyond the general concept of utility, the specific findings of the study should lead the clinician back to the important theme of OAB and its effect on quality of life. OAB should not be viewed as merely a nuisance, as utility of both moderate and severe urge incontinence would indicate. Since utility of anticholinergics without side effects scored higher than botulinum toxin without complications, which, in turn, scored higher than sacromodulation without side effects, it would appear that those treatments might logically be offered to patients in that order.

The reader should not be surprised to see the use of "utility" a lot more in our literature in the years to come. Remember, you heard it first here. ■

In-Home HIV Test Empowers Patients

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Chairman, Department of Medicine, Santa Clara Valley, Medical Center; Clinical Professor, Stanford University School of Medicine

Dr. Winslow is a consultant for Siemens Diagnostic. This article originally appeared in the August issue of Infectious Disease Alert.

Synopsis: *The OraQuick in-home HIV-1/2 antibody test was granted market clearance by the FDA on May 15, 2012. Data presented included a < 0.1% false-positive rate and 91.7% sensitivity to correctly detect HIV infection compared to conventional ELISA performed on blood.*

Source: OraSure Technologies, Inc. OraQuick in-home HIV test package insert. Available at http://ow.ly/ckHuF.

On May 15, the FDA Center for Biologics Evaluation and Research/Office of Blood Research and Review (CBER/OBRR) granted market clearance to the OraQuick in-home HIV-1/2 antibody test based on the recommendation of the Blood Products Advisory Committee. The in-

home assay is a rapid, CLIA-waived immunoassay using synthetic peptides as antigens formatted in a test strip format to be used on saliva. The in-home assay is similar to the OraQuick assay previously approved by FDA for rapid HIV testing of venous or fingerstick whole blood or plasma. Data submitted to the FDA included a study of 4999 individuals of unknown HIV status. Results obtained with OraQuick were compared to "gold standard" testing with a laboratory-based ELISA performed on serum or plasma.

Bottom-line results from this performance trial showed that 4902/4903 HIV-negative patients were correctly identified (i.e., one false-positive was seen). Of ELISA-positive patients, 88/96 (91.7%) were correctly identified (i.e., eight false negatives were seen). A total of 56/5055 (1.1%) failed to obtain a test result.

■ COMMENTARY

The FDA market clearance of this in-home, rapid assay to detect HIV-1/2 antibodies demonstrated fairly robust performance and seemed easy to use by most patients. The assay as performed by untrained personnel on saliva does appear to be somewhat less sensitive than the comparator laboratory-based serum or plasma HIV antibody assay. The product package insert is careful to point out the limitations of the test in laymen's terms and emphasizes that individuals should wait at least 3 months after a suspected exposure event to test themselves with OraQuick.

The impact of confidential in-home testing may or may not be significant in interrupting transmission of HIV on a large scale in the United States or Western Europe. However, it is hard for me to imagine a scenario (other than acute HIV infection where the test may be negative, yet the patient highly contagious) where harm could be done. I am a firm believer in empowering patients to take responsibility for their health and for transmission of sexually-transmitted infections to others. This is a step in the right direction and will be a useful development even if only a few new cases of HIV are prevented each year in North America and Western Europe. Hopefully, the OraQuick test will be priced low enough in the developing world where its impact could potentially be very large. ■

Pharmacology Update

Prednisone Delayed-Release Tablets (RAYOS®)

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 relationships relevant to this field of study.

THE FDA HAS APPROVED A NEW FORMULATION OF PREDNISONE for the treatment rheumatoid arthritis and other conditions in which an anti-inflammatory or immuosuppressive agent is indicated. This delayed-release (DR) formulation is designed to target the circadian rhythm of proinflammatory cytokines such as interleukin 6. The new product is marketed by Horizon Pharma, Inc. as RAYOS®.

Indications

Prednisone DR is indicated as an anti-inflammatory or immunosuppressive agent for diseases of various organ systems as well as endocrine or neoplastic conditions.[1]

Dosage

Prednisone DR is dosed once daily and the dose should be individualized based on disease severity and response. The timing of the dose should be based on the pharmacokinetics of the DR formulation and the disease being treated.[1] For example, rheumatoid arthritis subjects were dosed at 10 p.m. in clinical trials.[1,2] Prednisone DR should be taken whole and with food. Patients on immediate release formulation of prednisone or other glucocorticoids can be switched to prednisone DR at equivalent doses based on relative potency.[1]

Prednisone DR is available as 1 mg, 2 mg, and 5 mg tablets.

Potential Advantages

For patients with rheumatoid arthritis, prednisone DR at 10 p.m. appears to be more effective than prednisone dosed in the morning in terms of reduction of morning stiffness.[3]

Potential Disadvantages

The long-term effect of this formulation is not currently known. Prednisone DR carries the same risks of

short-acting prednisone, including hypertension, edema, elevated blood sugar, and muscle atrophy, etc.

Comments

Morning stiffness in patients with rheumatoid arthritis is believed to be due to inadequate endogenous production of adrenal cortisol to suppress the proinflammatory cytokines. Both endogenous cortisol synthesis and cytokine levels follow circadian rhythmicity.[4] The objective of prednisone DR is to augment endogenous cortisol and suppress these proinflammatory cytokines. To time the administration of prednisone according to the circadian rhythm, it would need to be given at 2 a.m. Prednisone DR is designed to provide peak levels at 2 a.m. when taken at 10 p.m.

The efficacy of prednisone DR in rheumatoid arthritis was studied in one placebo-controlled, randomized, 12-week trial (CAPRA-2).[1,2] Subjects were 18 years of age or older, had active disease based on the criteria of the American College of Rheumatology (ACR), had received non-biologic DMARD therapy for at least 6 months with inadequate response, and were not currently on corticosteroid therapy. Subjects were randomized at a 2:1 ratio to prednisone DR at 10 p.m. (n = 231) or placebo (n = 119). The primary endpoint was ACR response criteria 20, 50, and 70. A secondary endpoint was change in duration of morning stiffness between baseline and week 12. At week 12, ACR 20 was 47% vs 29% for placebo (difference [95% CI] of 17% [7.2, 27.6]). Values for ACR50 and ACR70 vs placebo were 22% vs 10%, and 7% vs 3%, respectively. Both differences in ACR20 and ACR50 were statistically significant. There was a greater median reduction from baseline in morning stiffness (55% vs 35%, $P < 0.002$).[2] This represented a change from 127 minutes to 46 minutes for prednisone and 139 minutes to 79 minutes for placebo. Stiffness occurred later in the day but was of lesser severity. When prednisone DR was compared to morning administration of immediate-release prednisone (CAPRA-1), there was a mean reduction in duration of morning stiffness of 22.7% vs 0.4%, $P = 0.045$.[3] Interleukin 6 levels were significantly reduced with DR, but no clinically relevant differences were observed with joint disease activity score (DAS28), pain intensity, C-reactive protein, erythrocyte sedimentation rate, or osteocalcin. In a 9-month open-label extension of the same study, subjects initially randomized to IR prednisone were switched to prednisone DR and achieved similar reduction in morning stiffness at 6 months and maintained for 12 months as those who stayed on the DR formulation.[5] The efficacy of prednisone DR to IR prednisone has not been compared when given at the same time. However, in a small study (n = 60) the bedtime dose of prednisolone may provide improved morning stiffness in patients clinically stable with morning dosing.[6]

Clinical Implications

Prednisone DR provides a novel approach to treating the morning stiffness of rheumatoid arthritis. It remains to be determined whether this formulation is significantly better than IR prednisone administered at bedtime. ■

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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.

CME Questions

1. **Grape resveratrol therapy appears to:**
   a. have no effect on the primary prevention of human CVD.
   b. complement and improve the gold standard primary prevention therapy (i.e., statin therapy, exercise, diet, etc.) of CVD.
   c. be safer and more effective than statin therapy in the primary prevention of CVD.

2. **Which one of the following is correct with regard to the OraQuick test for diagnosis of HIV infection?**
   a. A blood specimen is required for its use.
   b. It reliably detects antibodies to HIV within days after infection.
   c. The false-positive rate is less than 0.1%.
   d. False negatives are less common than false positives.

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

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

Refining the Relationship Between Thyroid Hormones and Left Ventricular Mass

Source: Iida M, et al. Thyroid hormone within the normal range is associated with left ventricular mass in patients with hypertension. *J Am Soc Hypertens* 2012;6:261-269.

Animal studies have shown that thyroid hormones (T3 and T4) induce hypertrophy of cardiac myocytes through stimulation of both structural and regulatory myocyte genes, which can be prevented by ACE inhibitors or beta-blockers. Such observations have led to the question of whether there might be a relationship between cardiac mass and thyroid hormones, even within the range currently defined as normal.

Hypothyroidism and hyperthyroidism are each considered a potential secondary cause of hypertension: the former through endothelial dysfunction that leads to vasoconstrictor hyperresponsiveness and subsequent increased peripheral resistance, and the latter through increased sympathetic tone. Iida et al investigated hypertensive subjects (n = 293) who had no known thyroid disease and whose thyroid function tests (T3, T4, and TSH) were within normal limits.

Among these euthyroid hypertensive study subjects, multiple linear regression found a positive relationship between T3 and T4 and ventricular mass (the higher the thyroid hormones, the greater the ventricular mass), and an inverse relationship between TSH and ventricular mass. When compared with normotensive controls, no such relationship could be identified. This would lead to consideration that in persons with hypertension, higher levels of thyroid hormone — even within the normal range — may be related to the development of left ventricular hypertrophy. ■

The ORIGIN Trial: Basal Insulin vs Standard Care for Early Type 2 Diabetes

Source: The ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012;367:319-328.

Type 2 diabetes reflects insulin insufficiency. Early in the disease process, plasma insulin levels may actually be higher than normal, but insufficient to maintain euglycemia. By the time of formal diagnosis, approximately half of beta cell mass has been lost, and as the disease progresses, insulin levels continue to fall.

The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial randomized subjects with prediabetes or early diabetes (n = 12,537) to insulin glargine (GLAR) or standard treatment (STND) for 6.2 years (mean). The objective of the trial was to determine whether early institution of basal insulin, as compared to STND, improves cardiovascular outcomes. Standard treatment was simply treatment of diabetes as per the treating clinician's choice; by the end of the trial, only 11% of the STND group was receiving insulin. Eighty percent of the GLAR group was on insulin at the end of the trial.

There was no difference in cardiovascular outcomes between the two treatment groups. One notable difference between treatments was the likelihood of progression from prediabetes to diabetes. The GLAR group was 28% less likely to progress than the STND group; however, there was also more hypoglycemia and weight gain in the GLAR group.

Increased incidence of cancer — a concern generated by earlier insulin trial data — was *not* seen in this large trial, and hence should be very reassuring. ■

Bronchodilators in COPD and Arrhythmias

Source: Wilchesky M, et al. Bronchodilator use and the risk of arrhythmia in COPD: Part 1: Saskatchewan Cohort Study. *Chest* 2012;142:298-304.

For chronic obstructive pulmonary disease (COPD), except for the provision of oxygen in late-stage disease, no pharmacologic intervention has been confirmed to save lives. Nonetheless, since bronchodilators improve symptoms, quality of life, and exercise capacity, and reduce acute exacerbations of COPD, they play an important role in routine care. Concerns about the potential capacity for arrhythmogenicity of bronchodilators has arisen from clinical COPD trials such as the Lung Health Study (n = 5887), in which short-acting ipratropium bromide was associated with a three-fold greater incidence of arrhythmia than comparator groups. Other smaller trials have not confirmed these findings, hence clarification is needed.

Wilchesky et al analyzed data from the province of Saskatchewan, Canada, to identify COPD subjects (n = 6018) and compare the incidence of arrhythmia in new users of ipratropium, beta-agonists (short- and long-acting), and methyhlxanthines to non-users.

Short-acting anticholinergics were associated with a 2.4 relative risk of arrhythmia, and long-acting beta-agonists with a 4.5 relative risk. No statistically significant increased risk was seen with short-acting beta-agonists or methylxanthines. Despite these concerns, the authors remind us that the absolute risk increase was very small, and "in most cases would be outweighed by the therapeutic benefit accrued through symptomatic relief and consequent improvements to quality of life." ■

Anxiety or Atrial Fibrillation in an Older Woman?

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

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

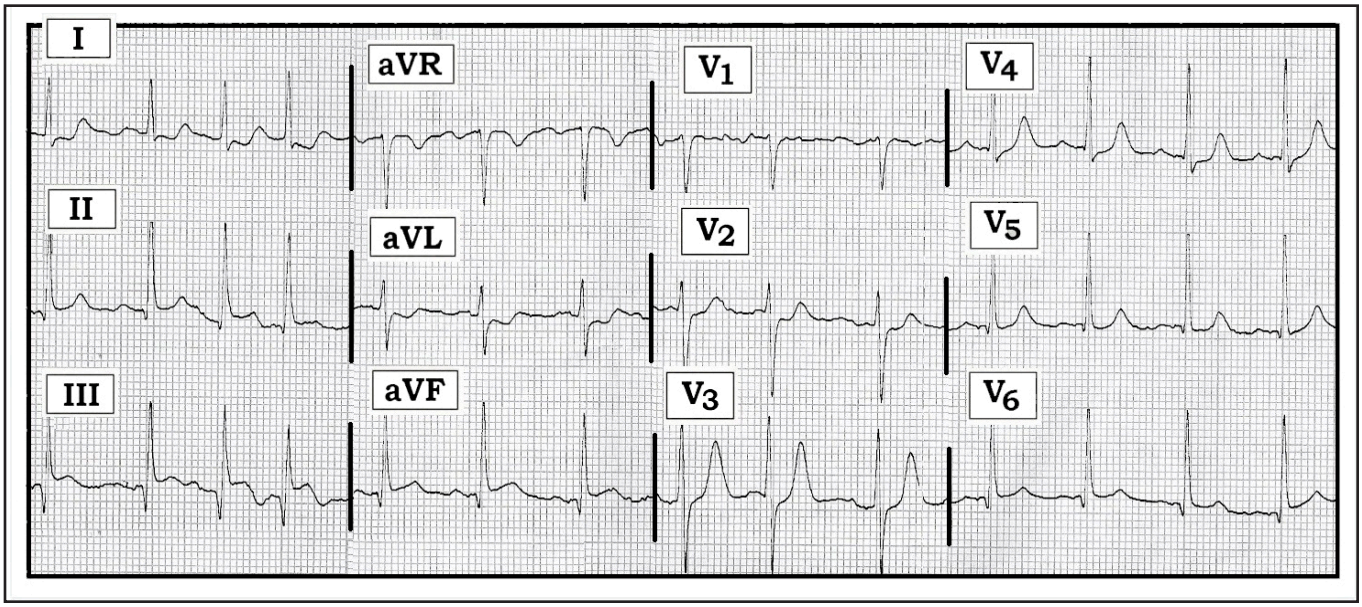

Figure — 12-lead ECG from an older woman with anxiety and "heart sensations." Is she in atrial fibrillation?

Scenario: The 12-lead ECG shown above was obtained from an older woman who was extremely anxious about her home situation. She felt some "heart sensations." Is she in atrial fibrillation?

Interpretation: At first glance, the patient appears to be in atrial fibrillation. The rhythm is irregular, and normal upright P waves are not seen preceding each QRS complex in lead II. That said — artifact is present, and there is some baseline wander in lead II. The rhythm is fairly regular in other leads and careful inspection before the QRS complex in lead aVF and in lead V4 *does* suggest the presence of an upright P wave with fixed PR interval. Thus, although impossible to know for sure, we strongly suspect an underlying sinus mechanism with frequent premature atrial contractions (PACs) as the rhythm. The occurrence of frequent PACs is clearly one cause of heart sensations.

Continuing with our systematic interpretation — intervals and axis are normal, and there is no chamber enlargement. However, assessment of Q-R-S-T changes is of definite concern. Specifically, Q waves are present in the inferior and lateral precordial leads. The Q waves in leads III and aVF are relatively deep and wide. The Q wave in lead V6 is wider than anticipated for a normal septal q wave. Transition occurs at a normal point (between leads V2-to-V3), however, there is a fairly abrupt increase in R wave amplitude in lead V3.

The most concerning finding is ST segment elevation in each of the inferior leads. Although the amount of ST elevation varies from beat-to-beat in simultaneously recorded leads II and III (due to baseline wander), the finding of coved ST elevation above the PR segment baseline is unmistakable. There is also a hint of ST elevation in lead V6. Support that these findings are truly acute is forthcoming from the presence of reciprocal ST segment depression in multiple leads (leads I, aVL, V2, V3, V4). An additional subtle reciprocal change is disproportionate peaking of the T wave in leads V3 and V4. Taken together, these findings suggest acute *infero-lateral-postero* STEMI (ST segment elevation myocardial infarction) as a more important contributing cause to this older woman's "heart sensations." ■

In Future Issues:

Comparison of Novel Risk Markers for Improvement in Cardiovascular Risk Assessment in Intermediate-Risk Individuals

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.*

Does Finasteride Cause Permanent Sexual Side Effects?

In this issue: Side effects of finasteride; new ruling on pharmaceutical companies paying generic manufacturers; and FDA actions.

Sexual side effects of finasteride

Finasteride — the popular drug used to treat male pattern baldness and symptomatic benign prostatic hypertrophy — may cause long-term sexual dysfunction, according to a new study. Several recent studies have shown that the drug, which is marketed as 1 mg (Propecia) and 5 mg (Proscar), can cause sexual side effects that persist after stopping the drug in as many as 20% of men. In April, the FDA required new labeling for both strengths regarding libido, ejaculation, orgasm disorders, and even infertility that may persist after treatment ends. The new study looked at 54 men, with an average age of 31, who reported ≥ 3 months of sexual side effects after taking the 1 mg strength for male pattern baldness. All men were previously healthy without previous history of sexual dysfunction, medical conditions, psychiatric conditions, or prescription medication use. After 9-16 months of follow-up, 96% of subjects reported persistent sexual side effects (based on the Arizona Sexual Experience Scale). The duration of finasteride use did not correlate with changes in sexual dysfunction scores. The authors urge prescribers of finasteride to warn men of potential adverse effects (*J Sex Med* published online July 12, 2012). ■

Pharmaceutical company ruling

Is it legal for pharmaceutical companies to pay generic manufacturers to keep their products off the market? Until now it has been. Brand-name manufacturers have written enormous checks to keep their low-cost generic competitors off the market. That may change, however, after a federal appeals court in Philadelphia ruled that the practice is anticompetitive, a decision that is counter to three previous federal circuit courts rulings. *The New York Times* cites the example of Bayer Pharmaceuticals which paid generic drug maker Barr Laboratories and other generic houses $400 million to withhold their generic version of ciprofloxacin, their $1 billion a year blockbuster antibiotic. The case could eventually end up at the Supreme Court. At stake is billions of dollars in lost profits for pharmaceutical manufacturers, but an equal amount of savings for Medicare/Medicaid, health plans, and consumers. ■

FDA actions

The FDA has approved the second new weight-loss medication within a month. The new product combines phentermine along with topiramate in an extended-release product. Phentermine has been marketed since 1959 and was part of the infamous "fen-phen" combination that was popular in the 1990s (fenfluramine was eventually banned due to cardiac valvulopathy in 1997). Topiramate is currently marketed as an anticonvulsant and for migraine prophylaxis as Topamax. The combination was rejected by the

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FDA in 2010 due to safety concerns, but Vivus Pharmaceuticals submitted additional data to the agency and recently won approval in July. In the process, the company changed the brand name from Qnexa to Qsymia. Similar to the recently approved lorcaserin (Belviq), phentermine/topiramate is approved as an addition to a reduced-calorie diet and exercise for weight management in adults with a BMI of 30 or greater, or with a BMI of 27 or greater with at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia. In two placebo-controlled trials, 3700 obese and overweight patients lost an average of 6.7-8.9% of their body weight, depending on the recommended or higher dose therapy (slightly better results than those seen with lorcaserin). Patients who have not lost at least 3% of their body weight by week 12 should discontinue the drug. Because of continued safety concerns, the drug was approved with a Risk Evaluation and Mitigation Strategy (REMS), which consists of a medication guide, prescriber training, and pharmacy certification. The drug cannot be used during pregnancy or in patients with recent stroke or heart disease, and patients should have their heart rates monitored during therapy. Vivus will market Qsymia immediately, but will be required to conduct 10 postmarketing studies to assess safety.

The FDA has approved aclidinium bromide, a dry powder inhaler for long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). Aclidinium is a long-acting antimuscarinic agent that works primarily on the M3 receptor causing sustained bronchodilation. The approval was based on three studies of nearly 1300 patients with COPD. The drug may cause anticholinergic side effects, including worsening narrowing-angle glaucoma and urinary retention. It should not be used as a rescue inhaler and is not recommended for those 18 years of age or younger. It is dosed twice a day. Aclidinium inhaler is the second anticholinergic inhaler to be approved after tiotropium (Spiriva), which was approved in 2004. Aclidinium will be distributed by Forest Laboratories and will be marketed as Tudorza Pressair.

The FDA has approved mirabegron to treat adults with overactive bladder. The drug is a novel, once-daily beta-3 adrenergic agonist that works by enhancing storage function and relaxing the urinary bladder, a unique effect and distinct from currently marketed antimuscarinics that inhibit bladder contraction. The once-a-day medication will be available in 25 mg pills. The dose can be increased to 50 mg after 2 months if needed. The approval was based on three placebo-controlled trials that showed statistically significant improvement in incontinence episodes and number of urinations per 24 hours. The most common adverse effects were hypertension, nasopharyngitis, urinary tract infection, and headache. Mirabegron will be marketed by Astellas Pharma as Myrbetriq.

The FDA has approved a new colon cleansing agent for colonoscopy prep. The new prep is sodium picosulfate, magnesium oxide, and citric acid in powder form that is dissolved in water and taken in two doses the night before and the morning of the procedure. It may also be taken the afternoon and the evening before the procedure (Day-Before regimen). The safety and efficacy of the new agent was studied in two studies of about 1200 patients undergoing colonoscopy in which standard PEG plus electrolytes was used as a comparator, and the new prep was found to be at least as effective as the standard prep. Ferring Pharmaceuticals will market the new two-dose prep as Prepopik.

The FDA has approved icosapent ethyl, a new fish oil preparation for the treatment of hypertriglyceridemia. It is approved as an adjunct to diet to treat patients with triglyceride levels greater than 500 mg/dL. The drug contains ultra purified ethyl EPA, an omega-3 fatty acid. The new product follows GlaxoSmithKline's Lovaza, another fish oil that is currently marketed for the same indication and generates more than $1 billion in annual sales. The new product is manufactured by Amarin Corporation and will be marketed as Vascepa. Fish oils are effective at lowering triglycerides but evidence is lacking that they are effective for secondary prevention of cardiovascular disease (*Arch Intern Med* 2012;172:686-694).

An FDA advisory committee has recommended an new indication for Genentech's ranibizumab (Lucentis) for the treatment of diabetic macular edema, an indication for which there is currently no approved therapy. The drug is approved to treat neovascular age-related macular degeneration and macular edema following retinal vein occlusion. Diabetic macular edema is commonly treated with laser therapy, a procedure that has the potential side effect of some vision loss. The FDA generally follows its advisory committee's recommendations and should make a final recommendation later this year. ■