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INSIDE

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Oral Apixaban for the Treatment of Acute Venous Thromboembolism

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: *A fixed dose of oral apixaban alone was noninferior to conventional therapy for the treatment of acute venous thromboembolism and was associated with significantly less bleeding.*

Source: Agnelli G, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369:799-808.

Venous thromboembolism occurs only one to two times per 1000 persons in the general population of the United States. However, it is the third most common cause of vascular death after myocardial infarction and stroke.[1] Conventional therapy consists of a parenteral anticoagulant such as enoxaparin for at least 5 days and warfarin, which should also be started upon diagnosis and continued for at least 3 months.[2] This classic therapeutic regimen is moderately inconvenient, especially in remote geographic regions, both because enoxaparin requires daily subcutaneous injections and because warfarin therapy requires coagulation monitoring and dose adjustment. The oral factor Xa inhibitor apixaban has a rapid onset of action and predictable pharmacokinetics that permits a fixed-dose regimen that significantly simplifies the treatment of venous thromboembolism by eliminating the need for both the initial parenteral anticoagulant therapy and subsequent laboratory monitoring of warfarin therapy.[3,4]

Although apixaban had been demonstrated to be effective for the prevention of recurrent venous thromboembolism with rates of major bleeding that are similar to those for placebo,[5] Agnelli and his colleagues decided to compare apixaban with conventional anticoagulant therapy in patients with acute symptomatic venous thromboembolism.[6] In this randomized, double-blind study, apixaban therapy (at a dose of 10 mg twice daily for 7 days, followed by 5 mg twice daily for

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6 months) was compared with conventional therapy of subcutaneous enoxaparin followed by warfarin therapy in 5395 patients with acute venous thromboembolism. The primary efficacy outcomes were the avoidance of recurrent symptomatic venous thromboembolism or death related to venous thromboembolism. The principal safety outcomes were the occurrence of major bleeding alone or clinically relevant nonmajor bleeding. The results revealed that the primary efficacy outcome occurred in 2.3% of the apixaban group compared with 2.7% in the conventional therapy group. Therefore, apixaban proved to be not inferior to conventional therapy. Major bleeding occurred in 0.6% of patients receiving apixaban and in 1.8% of patients who received conventional therapy. Major bleeding and clinically relevant nonmajor bleeding occurred in 4.3% of the patients in the apixaban group and in 9.7% of the conventional therapy group.

■ COMMENTARY

For the treatment of acute venous thromboembolism, this well-conducted, multicenter study clearly demonstrated that a fixed-dose regimen of oral apixaban alone was as effective as conventional treatment and, equally important, it was associated with a clinically relevant reduction of 69% in major bleeding episodes.[6] The reduction in major bleeding was paralleled by a decrease in clinically relevant nonmajor bleeding, which thereby provided further evidence for the safety of the apixaban regimen. These results added to the previously published evidence[3,4] that simple therapy with one of the newer oral anticoagulants proved to be an excellent alternative to conventional therapy for patients with acute venous thromboembolic conditions. The efficacy of apixaban in patients with pulmonary embolism was similar to that in patients with deep venous thrombosis. The efficacy and safety of apixaban also proved to be consistent across a broad range of subgroups, including patients who were > 75 years or who were obese. On the basis of the results obtained in this current study as well as in other studies such as the Apixaban for the Extended Treatment of Deep Vein Thrombosis and Pulmonary Embolism trial,[5] oral apixaban appears to be a simple, effective, and safe drug for the initial and long-term treatment of venous thromboembolism. ■

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The Many Emotions of the Heart

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

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

Synopsis: *In the study of myocardial infarction survivors with 10 years of follow-up, high level of anxiety was associated with an increase in all-cause mortality, with the association being strongest in the first 3 years.*

Source: Wrenn KC, et al. Anxiety, anger, and mortality risk among survivors of myocardial infarction. *Am J Med* 2013; Sep 28. [Epub ahead of print].

Heart disease is the leading cause of death for both men and women in the United States. Each year, it is estimated that approximately 600,000 people die from heart disease, accounting for 1 in every 4 deaths. Approximately 715,000 Americans have a myocardial infarction (MI) each year.[1] A significant number of patients have recurrent MI. When lost productivity costs are included, coronary heart disease costs our nation $108.9 billion each year.

There is increasing evidence that various psychosocial stressors such as anxiety, depression, and anger may lead to a higher rate of acute cardiovascular events. such as MI and sudden cardiac death. However, when studies have been conducted, the results have not been conclusive. While some studies have demonstrated that type A personality traits such as anger, hostility, and cynicism are associated with increased long-term cardiovascular risk, others have failed to demonstrate that link.[2,3] The conflicting results may be attributed to inconsistent study methodologies applied, including different follow-up periods and study measurement instruments.

Wrenn et al conducted a prospective cohort study of 1968 participants who were recruited at the time of hospital admission for MI between 1989 and 1996 from 64 medical centers. These participants were then followed for all-cause mortality through December 31, 2007 using the National Death Index. The average age of the study participants was 60.2 years and 30.6% were women. Approximately 25.8% had a history of prior MI. Study participants were administered the anxiety and anger subscales of a widely utilized and validated research instrument called the State-Trait Personality Inventory. Over 10 years of follow-up, 525 (27%) participants died, including 326 who died of cardiovascular disease.

The researchers found that an anxiety score rating of > 90th percentile was associated with a 1.31 times higher all-cause mortality rate (95% confidence interval [CI], 0.93-1.84) compared to those with lower scores. Although this overall association was not statistically significant, there was a statistically significant association for higher all-cause mortality in the first 3 years (hazard ratio [HR], 1.78; 95% CI, 1.08-2.93), but not afterward. An anger score rating of > 90th percentile was associated with a 1.25-times higher all-cause mortality rate (95% CI, 0.87-1.80) with a stronger association in the first 3 years than in subsequent years, but neither was statistically significant. In a secondary analysis of cardiovascular mortality, there was a higher rate of cardiovascular death among those with higher anxiety scores. Compared with those scoring low on the anxiety scale, a score rating of > 90th percentile was associated with an HR of 1.17 (95% CI, 0.74-1.86) over 10 years.

The study authors concluded that in the study of MI survivors, a high level of anxiety was associated with an increase in all-cause mortality, with the strongest association in the first 3 years of follow-up.

■ COMMENTARY

Links between the heart and emotion have been postulated for centuries. However, it is only recently that data supporting this connection have become available. In the current study of MI survivors, Wrenn et al found that high levels of anxiety were significantly associated with a higher rate of all-cause mortality with the strongest association being in the first 3 years of follow-up. These data support the growing body of evidence suggesting that negative affective states, including anxiety, can lead to an increased risk for cardiovascular disease development, recurrent disease, and poor long-term prognosis. Although a wide range of evidence supporting depression as a risk factor for cardiovascular disease exists, there has not been such a clear proven link between cardiovascular disease, all-cause mortality, and anxiety. While it is not yet clear whether anxiety leads to a more rapid progression of coronary artery disease, there may be several hypothesized mechanisms by which emotional stress and anxiety might trigger an acute myocardial event. Such mechanisms may include increases in blood pressure, heart rate, vascular tone, and platelet aggregation that may ultimately cause plaque instability and rupture leading to an acute event.

It is, therefore, important that we address and manage anxiety as a symptom, especially in those patients who have existing coronary heart disease since there is evidence that psychological treatments appear effective in treating patients with these symptoms. However, uncertainty still remains regarding the subgroups of patients who would benefit most from treatment and the characteristics of successful interventions.[4] While I would address anxiety in my patients, I also hope we can conduct more research to evaluate whether such treatments would not only prevent recurrent myocardial events but also lead to a reduction in cardiovascular and all-cause mortality. ■

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BNP-Guided Heart Failure Prevention

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

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Dr. Boyle reports no financial relationships relevant to this field of study. This article originally appeared in the September 2013 issue of Clinical Cardiology Alert.

Synopsis: *The authors conclude that among patients at risk of heart failure (HF), BNP-based screening and collaborative care reduced the combined rates of left ventricular systolic dysfunction, diastolic dysfunction, and HF.*

Source: Ledwidge M, et al. Natriuretic peptide-based screening and collaborative care for heart failure. The STOP-HF randomized trial. *JAMA* 2013;310:66-74.

HEART FAILURE (HF) IS ASSOCIATED WITH A HIGH MORTALITY rate, debilitating symptoms, impaired quality of life, and major financial costs. As our society ages, the prevalence of HF is increasing. Current treatments for HF are imperfect and prevention of HF is the best possible option. In this study, the authors target patients at risk for developing HF and study a strategy of using serum brain-type natriuretic peptide (BNP) measurement in the primary care setting to guide referral and therapy aids in preventing left ventricular (LV) dysfunction and HF. The study recruited patients from 39 primary care practices in Ireland.

Patients were referred from primary care to the study if they were older than 40 years and had one or more risk factors for developing HF, including hypertension, hyperlipidemia, obesity (body mass index > 30), vascular disease (coronary, peripheral, or cerebral), diabetes, arrhythmia requiring treatment, or moderate/severe valvular disease. Exclusion criteria were the presence of established LV dysfunction or prior HF, or any other cause of limited life expectancy. Patients were randomized 1:1 to intervention (BNP-driven collaborative care between the primary care physician [PCP] and specialist cardiovascular center; n = 697) or control (routine PCP management; n = 677) groups. All patients had BNP testing but the results were only available to the PCP in the intervention group. The control group received advice on lifestyle modification and risk factor intervention as determined by their PCP. In the intervention group, BNP results were made available to the PCP, with protocol-driven echocardiography, referral to a cardiologist, and further lifestyle counseling and management if the BNP was > 50 ng/L. Those with BNP < 50 ng/L received usual care. Patients and treating physicians could not be blinded, but at study completion all patients underwent echocardiography and clinical evaluation by a blinded cardiologist. The primary endpoint was development of LV systolic or diastolic dysfunction with or without HF. Secondary endpoints included emergency hospitalization for arrhythmia, transient ischemic attack, stroke, myocardial infarction, peripheral or pulmonary thrombosis/embolus, or HF.

Patients were followed for 4.2 ± 1.2 years. A total of 263 patients (41.6%) in the intervention group had at least one BNP reading of 50 pg/mL or higher. The primary endpoint of LV dysfunction with or without HF occurred in 59 of 677 (8.7%) in the control group and 37 of 697 (5.3%) in the intervention group (odds ratio [OR] 0.55; $P = 0.003$). Asymptomatic LV dysfunction was found in 6.6% of control patients and 4.3% of intervention-group patients (OR 0.57; $P = 0.01$). Heart failure occurred in 2.1% of controls and 1.0% of intervention-group patients (OR 0.48; $P = 0.12$). The incidence rates of emergency hospitalization for major cardiovascular events were 40.4 per 1000 patient-years in the control group vs 22.3 per 1000 patient-years in the intervention group (incidence rate ratio, 0.60; $P = 0.002$). The intervention group underwent more cardiovascular investigations (control group, 496 per 1000 patient-years vs intervention group, 850 per 1000 patient-years; incidence rate ratio, 1.71; $P < 0.001$) and received more renin-angiotensin-aldosterone system (RAAS) inhibitors (control group, 49.6%; intervention group, 56.5%; $P = 0.01$). Blood pressure reductions were similar in the control and intervention groups. In patients with BNP < 50 ng/L, there was no change in BNP level over the 4.2-year follow-up. However, in those with BNP > 50 ng/L, the BNP level increased over the study period, but the increase was significantly attenuated in the intervention group. The authors conclude that among patients at risk of HF, BNP-based screening and collaborative care reduced the combined rates of LV systolic dysfunction, diastolic dysfunction, and HF.

■ COMMENTARY

This study is an interesting and important one. First, it confirms that BNP measurement in patients at risk of HF can predict the development of future LV dysfunction. Second, this strategy also reduces emergency admissions to the hospital from a variety of cardiovascular causes.

Unfortunately, though, there was no prespecified intervention in this study, so we are left to ponder what it was that resulted in the better outcomes in the intervention group. Was it the increased use of RAAS inhibition? Was it the extra patient counseling that improved compliance? Was it engagement of the patients with the specialist care and the extra diagnostic testing that facilitated a more tailored pharmacological management of these patients? These should all be tested in prospective studies.

Several limitations of this study should be noted. First, it was performed in a small area of Ireland and the results may not be generalizable to other populations. Second, because the participants could not be blinded, there is a possibility of some confounding, which would likely but not definitely create bias toward a negative result. Third, new onset HF was defined as requiring hospitalization for HF. This definition would have missed HF that was treated as an outpatient. Despite these limitations, BNP-guided therapy for patients at risk for HF seems to be a reasonable strategy. I hope we will see a formal cost-effectiveness analysis from this dataset, as the intervention group had higher rates of diagnostic testing but lower rates of hospitalization, and the overall effect on health care budgets remains unknown. ■

Pharmacology Update

Trametinib Tablets (Mekinist™)

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.

A third kinase inhibitor, trametinib dimethyl sulfoxide, has been approved by the FDA for the treatment of metastatic BRAF V600 mutation-positive melanoma. Trametinib follows vemurafenib and dabrafenib in this category. The latter two are BRAF inhibitors while trametinib is a mitogen-activated extracellular signal regulated kinase (MEK) 1 and 2 inhibitor. BRAF activates MEK1 and MEK2 along the signaling pathway. Trametinib is marketed by GlaxoSmithKline as Mekinist.

Indications

Trametinib is indicated for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.[1] It is not indicated for use in patients with prior BRAF inhibition therapy.

Dosage

The recommended dose is 2 mg orally once daily. It should be taken at least 1 hour before or at least 2 hours after a meal. Trametinib is available as 0.5 mg, 1 mg, and 2 mg tablets.

Potential Advantages

Cutaneous squamous-cell carcinoma, a side effect of BRAF inhibitors, was not reported with trametinib in the clinical trial.[2] Trametinib improved progression-free survival (PFS) compared to chemotherapy with dacarbazine or paclitaxel.[1] Trametinib is indicated for BRAF V600E or V600K mutations while both vemurafenib and dabrafenib are indicated for the V600E mutation. Trametinib does not appear to have any clinically important drug interactions involving CYP350, P-gp, organic anion transporting polypeptides, or breast cancer resistant protein (BCRP) transporter.[1]

Potential Disadvantages

Serious adverse events in clinical trials included cardiomyopathy, retinal pigment epithelial detachment, retinal vein occlusion, interstitial lung disease pneumonitis, embryofetal toxicity, and serious skin toxicity.[1] Common adverse events include rash (57%), diarrhea (43%), lymphedema (32%), dermatitis acneiform (19%), stomatitis (15%), and hypertension (15%).[1] Trametinib may be less effective than BRAF inhibitors (e.g., vemurafenib), although there has been no direct comparison to date.[2,3]

Comments

BRAF mutation leads activation of MEK1 and MEK2 promoting tumor growth. The efficacy and safety of trametinib was studied in a randomized, open-label, active-controlled study of 322 subjects.[4] These subjects had BRAF V600E or V600K mutation-positive, unresectable, or metastatic melanoma with no more than one prior chemotherapy regimen and no prior ipilimumab, BRAF, or MEK inhibitor treatment. Subjects were randomized (2:1) to trametinib (2 mg daily; n = 214), or dacarbazine (1000 mg/m^2 every 3 weeks), or paclitaxel (175 mg/m^2 every 3 weeks; n = 108). The primary efficacy endpoint was PFS and secondary, confirmed tumor response. Subjects on chemotherapy were allowed to crossover to trametinib at the time of disease progression. PFS (disease progression or death) occurred in 55% of those treated with trametinib and 71% with chemotherapy (HR 0.47; 95% CI, 0.34, 0.65; $P < 0.0001$). Median time to PFS was 4.8 (4.3, 4.5) months compared to 1.5 (1.4, 2.7) months.

Objective response was 2% complete and 20% partial response compared to 0% and 8%, respectively. Median duration of follow-up was 4.9 months for trametinib and 3.1 months for placebo. At 6 months, survival was 81% with trametinib and 67% in the chemotherapy group, even with the crossover (HR, 0.54; 95% CI, 0.32, 0.63; $P < 0.01$).[2] Dose interruption occurred in 35% of subjects and dose reduction in 27%. Approximately 2% discontinued therapy completely. Trametinib does not appear to be effective in patients with metastatic BRAF mutation previously treated with a BRAF inhibitor.[1,3]

Clinical Implications

Approximately 45% of patients with metastatic melanoma have mutations. Current therapy includes high-dose IL2, ipilimumab as non-targeted regimens, and BRAF inhibitors (vemurafenib, dabrafenib) as targeted regimens. These are the preferred regimens recommended by the National Comprehensive Cancer Network. Trametinib is recommended for patients who are intolerant to BRAF inhibitors but not for those who have progressed.[5] There may be some benefit to combining an MEK with a BRAF inhibitor. This is being evaluated in an ongoing clinical trial where trametinib is combined with dabrafenib compared to dabrafenib alone.[6] The cost of trametinib is $8700 for 30 days. ■

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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 Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
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3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter! ■

CME Questions

1. **Oral apixaban therapy for the treatment of acute venous thromboembolism:**
   a. proved to be inferior to conventional therapy of subcutaneous enoxaprin followed by warfarin.
   b. proved to be noninferior to conventional therapy of subcutaneous enoxaparin followed by warfarin.
   c. was associated with more episodes of major bleeding plus clinically relevant nonmajor bleeding than was conventional therapy.

2. **In the study of myocardial infarction survivors, which was found to be statistically significant?**
   a. High level of anxiety in the first 3 years of follow-up was associated with an increase in all-cause mortality.
   b. High level of anger in the first 3 years of follow-up was associated with an increase in all-cause mortality.
   c. High level of anxiety in the last 7 years of follow-up was associated with an increase in all-cause mortality.
   d. High level of anger in the last 7 years of follow-up was associated with an increase in all-cause mortality.

3. **Serum BNP measurements as a prevention strategy make sense in subjects with:**
   a. hypertension.
   b. significant valvular disease.
   c. vascular disease.
   d. All of the above

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

Dr. Kuritzky is a retained consultant for Boehringer Ingelheim, Daiichi Sankyo, Forest Pharmaceuticals, Janssen, Lilly, Novo Nordisk, Pfizer, and Sanofi.

Goldilocks Unable to Find Amount of Antioxidants That's Just Right

Source: Bjelakovic G, et al. *JAMA* 2013; 310:1178-1179.

The observation that excess oxidative stress is associated with diverse pathologic consequence has been consistently coupled with the obvious next intellectual step: antioxidants *should* be beneficial to prevent these consequences. Unfortunately, no Goldiloks has stepped forward to inform us which antioxidant is too much, which is too little, and which is just right. Or maybe the antioxidant hypothesis is just a fairy tale, after all?

This is not the first time that observational hypotheses have disappointed. In two clinical trials of antioxidant supplementation in persons at risk for lung cancer (combined n > 45,000), the first trial found an *increase* in lung cancer and mortality, and the follow-up trial was discontinued almost 2 years early because of similar outcomes.

This most recent Cochrane systematic review included 78 trials (n = 296,707) performed in both primary and secondary prevention modes. The "bottom line" is worth quoting: "Antioxidant supplements are not associated with lower all-cause mortality. Beta carotene, vitamin E, and higher doses of vitamin A may be associated with *higher* all-cause mortality." Some naysayers would suggest that we have not yet fulfilled the Goldilocks systematic approach: Maybe we used too little, maybe we used too much, or maybe we used the wrong formulation, and have not yet found the approach that's "just right." For now, the science does not support a role for antioxidants in primary or secondary prevention. ■

Antipsychotics Are Associated with Increased VTE Risk

Source: Wu CS, et al. *J Clin Psychiatry* 2013;74:918-924.

Antipsychotics have suffered a beleaguered course of late: literature showing little efficacy advantage of newer vs older agents, concerns about increased mortality associated with their use, etc. A recent report suggests that antipsychotic treatment is also associated with a clinically meaningful increase in risk for venous thromboembolism (VTE), comprised of deep vein thrombosis plus pulmonary embolism.

Wu et al performed a case-control study of enrollees in the National Health Insurance Research Database of Taiwan to compare cases of confirmed VTE (n = 2162) with age-matched controls without VTE (n = 12,966). Initial analysis looked simply at the relative risk of antipsychotic use in persons with VTE vs controls. Second-step analysis adjusted for confounders.

Overall, the adjusted odds ratio for VTE in current antipsychotic users was 1.52 (i.e., current users were 52% more likely to experience VTE than controls); the odds ratio was substantially worse (3.26: a more than 3-fold increase in risk) for new users. These concerning results were attained even after correction for confounding factors such as utilization of thrombogenic medications (e.g., oral contraceptives) and medical comorbidities associated with increased VTE risk (e.g., congestive heart failure). Analysis of different classes of antipsychotics did not find any particular distinction among them. The mechanism by which antipsychotics might increase VTE risk is uncertain, although the authors posit that antipsychotic-induced sedation could lead to less physical activity with subsequent venous stasis. In any case, these data suggest vigilance for VTE in persons prescribed antipsychotics, especially in the early months of use. ■

Physician Visits for Itching

Source: Shive M, et al. *J Am Acad Dermatol* 2013;69:550-556.

If results from the National Ambulatory Medical Care Survey conducted by the CDC are correct, pruritus as a presenting complaint in ambulatory care may merit more of our attention. In a retrospective review of data from 1999-2009, there were approximately 7 million office visits per year in which pruritus (or itching) was indicated as a presenting symptom. In comparison, there were almost 18 million visits per year for low back pain. Since itch may or may not have been specifically indicated when syndromes such as a drug allergic reaction occur, the authors suggest that these numbers likely *underestimate* the true prevalence of pruritus.

The consequences of pruritus may range from minor nuisance to intolerable. Indeed, patients taking opioid analgesia frequently mention pruritus as a treatment-limiting adverse effect. Fortunately, clinicians have a diversity of agents to treat pruritus, including multiple generations of antihistamines as well as steroids (topical and systemic). Finally, it has been recognized for more than 2 decades that doxepin — traditionally used as an antidepressant — has antihistaminic potency as much as 50 times greater than the most potent "traditional" antihistamines such as hydroxyzine. Because of this antihistaminic potency, doxepin is often used in refractory urticaria, when other antihistamines have failed, even though sedation is common at typical therapeutic doses. ■

What a Difference a History Makes

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.

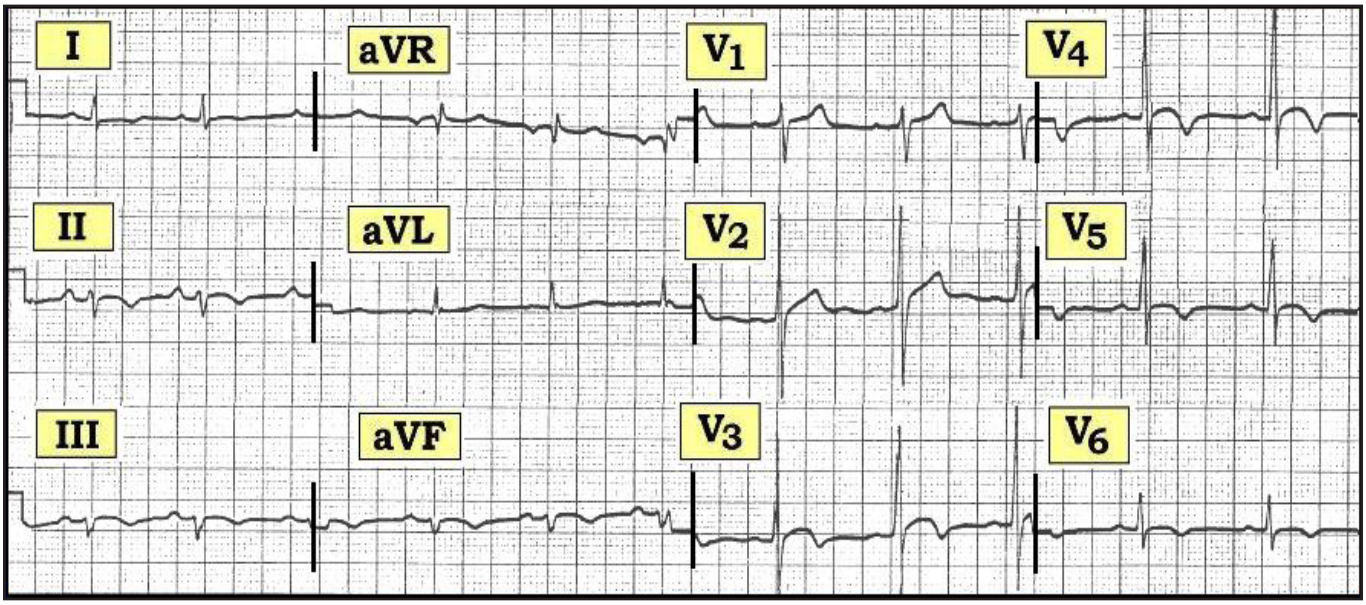

Figure — Does this ECG suggest acute ischemia and/or infarction?

Scenario: How would you interpret the ECG shown above? Does it reflect acute coronary syndrome and/or acute ST elevation myocardial infarction? What clinical information is lacking?

Interpretation: Our descriptive analysis of this tracing begins as follows: Sinus arrhythmia; normal intervals; left axis deviation consistent with left anterior hemiblock. At this point, further interpretation requires some information about the patient (namely patient age, brief medical history, and whether the patient is symptomatic).

It is easy to overlook that this 12-lead ECG was obtained at half standardization. Note that the standardization rectangle (seen at the very beginning of the tracing) is only 5 mm (= 1 large box) tall. Actual amplitude is therefore double that seen in the Figure (i.e., the S wave in lead V2 is really 24 mm in depth — not the 12 mm that we count on this tracing).

Regarding Q-R-S-T Changes: No Q waves are seen. Transition occurs early (between V1-to-V2). That said, the most remarkable finding on this tracing relates to the ST-T waves, which show ST segment coving with slight elevation and symmetric T wave inversion in many leads.

Interpretation of the above noted findings depends on the clinical setting. This ECG was in fact obtained as part of a "pre-participation physical" performed on an otherwise healthy 20-year-old football player. Past medical history was negative, and physical exam was normal (no heart murmur). In this context, the ST-T wave changes seen in this healthy and asymptomatic 20-year old almost certainly reflect a normal repolarization variant. That said, the surprisingly tall R wave already by lead V2 suggests that there may be prominent septal forces. Given generous QRS amplitude (the tracing is recorded at half standardization), an echocardiogram was recommended prior to clearing this individual for active sports participation to rule out anatomic abnormality, such as hypertrophic cardiomyopathy.

An entirely different interpretation would be in order if the ECG was instead obtained from an older adult with chest pain. In this case, the ST segment coving, slight elevation, and symmetric T wave inversion in multiple leads might clearly reflect acute ischemia/infarction. ■

In Future Issues:

Association of Testosterone Therapy with Mortality, Myocardial Infarction, and Stroke in Men with Low Testosterone Levels

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Reglan Safe in Pregnant Women for Nausea and Vomiting

In this issue: Reglan safe in pregnancy; battle brewing over naming of biosimilar drugs; and FDA actions.

Reglan safe in pregnancy

Use of the anti-nausea medication metoclopramide (Reglan) in pregnancy is not associated with an increased risk of major congenital malformations, spontaneous abortion, or stillbirth. These were the findings of large, register-based cohort study from Denmark. The safety of metoclopramide in pregnancy has been of concern because it is increasingly used to treat pregnant women with nausea and vomiting. Metoclopramide-exposed pregnant women were matched with unexposed women in a 1:4 ratio, with more than 40,000 exposed women in the cohort, of whom more than 28,000 received the drug in the first trimester. The drug was not associated with major malformations or any of more than 20 individual malformations. There was no increase in spontaneous abortion, stillbirth, preterm birth, low birth weight, or fetal growth restriction (*JAMA* 2013; 310:1601-1611). ■

Battle over naming of biosimilar drugs

A battle is shaping up between biotech companies and the Generic Pharmaceutical Association (GPhA) over the naming of biosimilar drugs. Biosimilars, or "follow-on biologics," are products whose active ingredient is an approved version of a previously approved biopharmaceutical. Since biologics are generally manufactured in a complex process that may include molecular clones and proprietary cell lines, it is virtually impossible for the manufacturers of a biosimilar to match the process step-by-step. This results in small differences between the innovator product and the follow-on product (hence the name "biosimilar"). With billions of dollars of revenue at stake, biotech companies, such as Genentech and Amgen, have been lobbying federal and state legislators to tighten the rules regarding use of biosimilars. There has also been concern that the FDA might prohibit biosimilar manufacturers from using the same generic name as the original drug, a move that biotech companies would endorse and the GPhA would strongly oppose. A bipartisan group of senators recently entered the fray by penning a letter to the FDA urging the agency to allow biosimilars to share the name of the innovator product. Led by Republican John McCain and Democrats John Rockefeller and Tom Harkin, six senators urged the FDA to follow the intent of the Biologic Price Competition and Innovation Act, suggesting that if biosimilars were not allowed to share the same name it would undermine "the safety and accessibility of affordable biosimilars." The FDA had been in support of allowing biosimilars to share generic names, but the sudden removal of a page from the FDA website that contained a 2006 statement supporting same-name biosimilars prompted the concern of the senators. ■

FDA Actions

The FDA is recommending that hydrocodone-containing pain medications (Vicodin, Norco,

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Lortab, and others) be upgraded from schedule III to schedule II. The move would put significant restrictions on the drugs, including requiring a physician signature for each prescription, no refills, and no phone or fax prescriptions. Hydrocodone would join other powerful opioids including oxycodone, morphine, fentanyl, and methadone in the more restricted schedule II category. The FDA is reacting to the epidemic of prescription drug abuse and addiction that has decimated some communities in this country and has led to the overdose by tens of thousands, including teenagers and young adults. Prescription drug overdoses now outnumber illegal drug overdoses 3:1. The Drug Enforcement Agency has been pushing for stronger controls on hydrocodone for years, but physician and pharmacy organizations have successfully argued that the change unfairly impacts legitimate patients and would increase physician and pharmacy workloads. Hydrocodone/acetaminophen combination drugs were the most frequently prescribed medications in the United States last year. The change is likely to take effect by mid-2014.

Meanwhile, the FDA has approved an extended-release hydrocodone product for the management of severe pain requiring daily, around-the-clock treatment. The drug is an extended-release formulation of hydrocodone that is dosed twice a day. It is available in six strengths — 10, 15, 20, 30, 40, and 50 mg capsules. Because of concerns of addiction and abuse, and the greater risk of overdose and death associated with extended-release and long-acting formulations, hydrocodone extended-release should be reserved for patients in whom alternative treatment options are ineffective, not tolerated, or one otherwise provides inadequate pain management. The approval of hydrocodone extended-release was controversial given that the drug is not packaged as a tamper-proof capsule, theoretically allowing it to be crushed, chewed, or even injected. Experience with abuse of extended-release oxycodone (OxyContin) prompted the FDA to require Purdue Pharmaceuticals to reformulate the drug into a tamper-proof capsule in 2010. Some in the FDA felt this new formulation of hydrocodone should be similarly packaged, but the drug was approved without such restrictions. Hydrocodone extended-release will be schedule II, and marketed by Zogenix Inc. as Zohydro.

Pharmacology Watch is going digital!

Beginning with the January issue, *Pharmacology Watch* can be found exclusively online. It will no longer be inserted in your newsletter. You will find the same high-quality, evidence-based updates in clinical pharmacology that you know and trust. You will be able to access the online edition anywhere. We hope this transition will better meet your needs as a subscriber. Stay tuned for more information about this digital transition. We will keep you posted on all the details!

The FDA has approved two new drugs to treat pulmonary arterial hypertension (PAH). Macitentan is a dual endothelin-receptor antagonist, while riociguat is a first in class soluble guanylate cyclase stimulator. Macitentan is a once-daily pill that is approved to treat PAH. Its safety and efficacy was established in a 2-year, randomized, placebo-controlled trial of 742 patients. Patients in the active treatment group had delayed progression of the disease and improved symptoms. Macitentan is manufactured by Actelion Pharmaceuticals and will be marketed as Opsumit. Riociguat is also an oral agent given three times a day. It is approved for PAH and also for chronic thromboembolic pulmonary hypertension (CTEPH), the first drug to be approved for this latter indication. Safety and efficacy for PAH was shown in a trial of 443 patients in which treated patients had improved 6-minute walk times after 12 weeks. It was shown to be effective for CTEPH in a study of 261 patients in which treated patients had improved walk times at 16 weeks. Riociguat is marketed as Adempas by Bayer HealthCare.

An FDA advisory group has recommended approval of simeprevir and sofosbuvir, two long-awaited agents to treat hepatitis C virus (HCV). Both are oral drugs and have higher cure rates compared with currently available agents. Simeprevir is a protease inhibitor, similar to currently available agents such as telaprevir and boceprevir, while sofosbuvir is a new type of hepatitis c antiviral called a nucleotide analogue (or "nuke"). Sofosbuvir has been highly anticipated as clinical trials suggest that it results in sustained virological responses as high as 90%, and may eventually be part of an all-oral regimen for HCV along with ribavirin. The FDA is expected to approve both drugs by mid-December. Simeprevir will be marketed by Johnson & Johnson while sofosbuvir will be marketed by Gilead Sciences. ■