INTERNAL MEDICINE ALERT

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INSIDE

Financial Disclosure:
Internal Medicine Alert's editor, Stephen Brunton, MD, serves on the advisory board for Abbott, Amarin, Boehringer Ingelheim, Duchesnay, Janssen, Lilly, Novo Nordisk, Sunovion, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, and Teva. Peer reviewer Gerald Roberts, MD; executive editor Leslie Coplin; and managing editor Neill Kimball report no financial relationships relevant to this field of study.

Diminishing Returns with Long-term Steroids in COPD Exacerbations

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington

Dr. Phillips serves on the speakers bureau for PotomaCME.

Synopsis: *Five days of steroid treatment was as effective as 14 days of treatment in preventing repeat exacerbations of COPD in patients presenting to the emergency department with COPD exacerbations.*

Source: Leuppi JD, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease. The REDUCE randomized clinical trial. *JAMA* 2013;309:2223-2231.

THE SWISS INVESTIGATORS WHO CONDUCTED THIS TRIAL SET OUT TO DETERmine if there would be important clinical differences for patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) who were treated with 5 days of oral steroids compared with those who were treated with the currently recommended 14 days.

They recruited consecutive patients with COPD exacerbations from emergency departments of teaching hospitals. COPD was defined by the presence of at least two of the following: change in baseline dyspnea, cough, or sputum quantity or purulence; age older than 40 years; and a smoking history of 20 pack-years or more. People were not eligible for this study if they had asthma, normal spirometry, pneumonia, terminal illness, or were pregnant. Patients were randomized to either 5 or 14 days of systemic glucocorticoids. Randomization was designed to match patients for age, use of steroids before the study, severity of COPD, and trial site. All patients received 40 mg of intravenous methylprednisolone on day 1, followed by 40 mg of oral prednisone daily from day 2 through 5. From day 6 through 14, patients received either 40 mg of oral prednisone or matching placebo once daily. In addition, all pa-

VOLUME 35 • NUMBER 13 • JULY 15, 2013 • PAGES 97-104

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tients received a broad-spectrum antibiotic for 7 days and a nebulized, short-acting bronchodilator 4 to 6 times daily as needed while hospitalized. Inhaled glucocorticoids twice daily combined with inhaled ß2-agonist twice daily plus tiotropium 18 µg once daily were also used. Physiotherapy, supplemental oxygen, and ventilatory support were administered according to guidelines.[1] Additional steroids could be administered at the discretion of the treating physicians. Endpoints were assessed daily during hospitalization, then on days 6, 15, 30, 90, and 180.

The primary endpoint was time to next COPD exacerbation over the next 6 months. Secondary endpoints were all-cause mortality, change in FEV1, cumulative steroid dose, clinical performance, quality of life, duration of hospital stay, time to open-label steroid use therapy (generally given in cases of another exacerbation), need for mechanical ventilation during the index exacerbation, and glucocorticoid-associated adverse effects (including hyperglycemia, hypertension, and infection).

After exclusions, data from 311 patients were used in an intention-to-treat analyses. A total of 296 patients completed the 14-day treatment period according to study protocol and were included in the per-protocol analysis. In other words, they were hospitalized for 14 days and definitely received the study medications, whereas the 25 patients who were treated in the ED and discharged without hospitalization may not have. There were more women in the conventional (long-term) group than in the short-term treatment group (46.5% vs 32.7%; $P = 0.02$), but otherwise, the two treatment groups were well balanced in terms of age, severity of airway obstruction, and pretreatment with glucocorticoids. In the 25 people who did not require hospitalization, 12 were in the short-term and 13 in the long-term steroid groups.

Overall, 56 patients (35.9%) reached the primary endpoint of COPD exacerbation in the short-term treatment group compared with 57 patients (36.8%) in the conventional treatment group. Time to re-exacerbation did not differ between groups. Among patients who experienced a re-exacerbation during follow-up, the median time to the event was 43.5 days in the short-term and 29 days in the conventional treatment group. Statistical adjustment for baseline variables, including sex, provided similar results. Overall survival did not differ between the treatment groups. For those who were hospitalized, patients who received short-term treatment had a shorter hospital stay with a median of 8 days compared with 9 days in the conventional treatment group ($P = 0.04$). The FEV1 improved significantly in both groups between baseline and the sixth day, and then remained stable. In addition, improvement in breathlessness, quality of life, and patient-assessed performance did not differ between treatment groups.

The number of patients receiving open-label steroid treatment (presumably for an exacerbation) during the study did not differ between treatment groups, but the total amount of steroids received was substantially different. The short-term group had a mean cumulative prednisone dose of 379 mg and the conventional treatment group had a mean cumulative prednisone dose of 793 mg.

However, there did not appear to be differences in short-term side effects in this study. There were not statistically significant differences between the short-term and long-term groups in terms of blood glucose levels, hyperglycemia, and worsening or new development of hypertension.

■ COMMENTARY

This changes everything! COPD exacerbations are a very difficult, expensive, and destructive part of the disease. Exacerbations are a risk factor for loss of pulmonary function[2] and death,[3] and account for up to 70% of the cost of caring for the disease.[4] Corticosteroids are a mainstay of treatment of COPD exacerbations, but the best dose and duration of treatment is unknown. Several guidelines recommend treatment with oral prednisone for 10-14 days,[5,6] but evidence to support this is lacking. While steroids have well-documented benefits in treating exacerbations, those of us who have cared for patients who have had frequent exacerbations have witnessed the appalling side effects of serious long-term steroid toxicity, including weight gain, diabetes, osteoporosis, fractures, adrenal suppression, and ocular complications. Steroid toxicity is dose and duration dependent, so providing the lowest possible dose for the shortest possible time is clearly a benefit to patients.

Internal Medicine Alert, ISSN 0195-315X, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EXECUTIVE EDITOR: Leslie G. Coplin.
MANAGING EDITOR: Neill L. Kimball.
INTERIM EDITORIAL DIRECTOR: Lee Landenberger.

GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Internal Medicine Alert,*** P.O. Box 105109, Atlanta, GA 30348.

Back Issues: $21. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

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Questions & Comments
Please call **Neill Kimball**, Managing Editor, at (404) 262-5404.

While differences in steroid-induced side effects were not seen in this study, this was a relatively short (6 months) protocol and was not designed to assess this outcome. As Don Sin wrote in the accompanying editorial, "The clinical implications of this study are clear. Most patients with acute COPD exacerbations can be treated with a 5-day course of prednisone or equivalent (40 mg daily). Furthermore, this regimen can be applied across all...categories of disease severity."[7] ■

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Will Being Optimistic Lower Your Cholesterol Level?

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

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

Synopsis: *Optimism is associated with a significantly healthier lipid profile than is present in less optimistic persons, possibly due to healthier behaviors and lower body mass indices, which are found with increased frequency in optimistic individuals.*

Source: Boehm JK, et al. Relation between optimism and lipids in midlife. *Am J Cardiol* 2013;111:1425-1431.

Lipid levels are in part influenced by health behaviors such as eating a healthy diet, exercising, and consuming no more than a moderate amount of alcohol and, since being optimistic probably contributes to a healthier lifestyle, it has been hypothesized that being optomistic may result in a improved lipid panel.[1-4] The Midlife in the United States (MIDUS) study was started in 1995 to better understand the connections between psychosocial factors, aging, and health in men and women aged 29-74 years.[5] The authors from the Harvard School of Public Health decided to test the hypothesis that greater levels of optimism would be associated with a healthier lipid profile.

The MIDUS study obtained data from 4000 subjects who were first recruited by either random digit dialing or oversampling of select metropolitan areas.[5] The population was increased to 7108 individuals by recruiting twin pairs and siblings of the randomly selected participants. Boehm and colleagues investigated a subsample of respondents from the psychosocial and biomarker projects consisting of 990 participants who were able to engage in a telephone interview and successfully complete self-administered questionnaires. Optimism was assessed by self-reporting using the Life Orientation Test. The 990 participants were mostly Caucasian men and women who were, on average, 55.1 years old with complete data obtained on optimism, lipid levels, potential confounders, and pathway variables. Results revealed that after adjusting for covariates, greater optimism was associated with higher high-density lipoprotein (HDL) cholesterol and lower triglyceride levels. However, optimism was not associated with significant differences in the low-density lipoprotein or total cholesterol levels.

■ COMMENTARY

It is not surprising that optimism and lipid levels were found to be associated because optimism had been linked to healthier behavior patterns such as eating a balanced diet, exercising, and consuming none or only moderate amounts of alcohol.[1-4] Although the effect of optimism on raising HDL levels and lowering triglyceride levels were small, they were determined to be significant and nontrivial.[6,7] The benefits of optimism were observed not only on the lipid panel, but were also associated with a beneficial smoking status, decreased alcohol consumption, and improved dietary intake and exercise patterns.[1-4] Also, other relevant factors for explaining the clinical improvement

noted in optimistic individuals may have been the positive effects of optimism on inflammation[8,9] and metabolic dysfunction.[10] Finally, optimistic individuals might be better equipped than their less optimistic subjects to meet the challenges of engaging in healthy behavior and maintaining a healthy body mass index.[11]

In summary, for very many reasons, optimistic individuals do better from an overall health perspective including the relatively minor but significant improvements that appear to be present in the lipid profile in this select group of subjects. ■

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Prolotherapy — A Neglected Treatment for Knee Osteoarthritis?

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

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

Synopsis: *The injection of a dextrose solution in and around the knee (prolotherapy) is an alternative treatment for the pain of knee osteoarthritis. A randomized, controlled trial shows that prolotherapy is effective for long-term control of knee pain and improvement in knee function.*

Source: Rabago D, et al. Dextrose prolotherapy for knee osteoarthritis: A randomized controlled trial. *Ann Fam Med* 2013; 11:229-237.

Injection therapy in a painful knee with osteoarthritis is commonly done, usually with a corticosteroid or hyaluronic acid. Corticosteroids have side effects that limit their use and hyaluronic acid solutions are expensive. An alternative therapy using concentrated dextrose solutions has been available through a limited number of practitioners for at least 75 years. This treatment was called sclerotherapy based on a belief that scar tissue was being formed,[1] but has been changed to prolotherapy with the belief that ligamentous and other tissue proliferates as a result of the irritant nature of the injection.[2] The actual mechanism of action of prolotherapy is not known.

Prior to this study, the quality of the research on prolotherapy has been weak, although the results have been positive.[3] This randomized, controlled trial at the University of Wisconsin may be the first rigorous, double-blinded study of prolotherapy. Ninety patients with osteoarthritis knee pain were randomized to a three-arm study of receiving prolotherapy, saline solutions, or a home exercise program. The injections included both extra-articular and intra-articular sites of the affected knee(s) at 1, 5, and 9 weeks with optional additional sessions at 13 and 17 weeks. Improvement scores were obtained using the Western Ontario McMaster University Osteoarthritis Index (WOMAC)[4] and the knee pain scale (KPS).[5] Pain and function analysis was done at baseline and at 5, 9, 12, 24, and 52 weeks.

All three groups showed improvement over the 52-week study period with the saline and exercise groups showing similar modest changes. The prolotherapy group showed substantially greater improvement ($P < 0.05$), with 50% of the patients having improvement at 52 weeks over a minimal change scale. The procedure was well tolerated with no reported side effects.

■ **COMMENTARY**

Recently, a patient with painful osteoarthritis of the knee asked me what I thought of prolotherapy. I had no idea what she was talking about. She told me there was a practitioner in a nearby city that offered this treatment and that a friend recommended it after having good results. My reading showed that prolotherapy was injecting concentrated dextrose solutions in and around the knee and that the mechanism of action was not known, but the dextrose caused irritation that might lead to pain relief. This method has been around for a long time but no rigorous studies have been done. I was skeptical and steered my patient away from such an alternative therapy and toward more conventional methods that usually lead to surgery.

This rigorous study by a respected university team showing good results impresses me. It seems there is an inexpensive and easy-to-administer alternative for treating the pain of osteoarthritis of the knee and possibly other joints. Training in using prolotherapy is available and it is a simple outpatient procedure taking about 15 minutes to administer. A series of treatment sessions is required. The side effects are minimal and the risks are very low. Prolotherapy is a cost-effective alternative treatment for osteoarthritis that should be further studied. Today, I would not steer my patients away from it, and may consider having our group take up this therapy. ■

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Pharmacology Update

Prothrombin Complex Concentrate (Human) Lyophilized Powder (Kcentra)

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 NEW PRODUCT HAS BEEN APPROVED FOR THE URGENT REversal of warfarin or other vitamin K antagonists anticoagulation in the setting of acute bleeding. This human plasma-derived product contains vitamin K-dependent coagulation Factors II, VII, IX, and X as well as antithrombotic Protein C and Protein S. It is heat-treated and viral filtered. Prothrombin complex concentrate (PCC) is manufactured by CSL Behring GmbH in Germany and marketed by CSL Behring LLC as Kcentra. The product has been licensed in Germany since 1996.

Indications

PCC is indicated for the urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (e.g., warfarin) in adults with acute major bleeding.[1]

Dosage

The dose of PCC is individualized based on the patient's INR value and body weight, and is given as a single dose.[1] The dose is 25 units/kg of Factor IX for INR from 2-4, 35 units/kg for 4-6, and 50 units/kg if INR is > 6. Vitamin K should be given concurrently. PCC is available as single-use vials.

Potential Advantages

Compared to frozen plasma, PCC does not require blood group typing or thawing, and therefore can be administered more quickly in the setting of acute bleeding. It is also given at a significantly lower volume for a shorter time, and there is a standardized dose of clotting factors indexed to factor IX.[1,2]

Potential Disadvantages

There appears to be a higher risk of thromboembolic

events with PCC than plasma, particularly in patients with prior thromboembolic events or coronary, cerebrovascular, or peripheral vascular disease.[1] PCC contains heparin and is contraindicated in patients with known heparin-induced thrombocytopenia.[1]

Comments

The approval of PCC was based on a prospective, open-label (blinded assessor), active-controlled, non-inferiority randomized study.[1] Subjects (n = 216) who required urgent replacement of their vitamin K-dependent clotting factors to treat acute bleeding were randomized to a single dose of PCC or plasma along with intravenous vitamin K. Efficacy endpoint was hemostatic efficacy as assessed by a blinded, independent board using standard clinical assessments. This was based on vital signs, hemoglobin measurements, and CT assessments depending on the type of bleed. Treatment outcomes were categorized as "effective" or "not effective." Efficacy endpoint was assessed in the first 24 hours and the observation period lasted for 90 days. An additional endpoint was the reduction of INR to 1.3 or less at 30 minutes after the end of infusion. Success rate was 72.4% for PCC and 65.4% for plasma meeting the criteria for non-inferiority (absolute difference of -10%) but not superiority. PCC was superior to plasma in the reduction of INR (62.2% vs 9.6%). Results from a post-hoc analysis by the FDA suggested that plasma may be more effective than PCC in patients with gastrointestinal bleeding.[2] The 45-day, all-cause mortalities were nine in the PCC group and five in the plasma group (risk ratio, 1.91; 95% confidence interval, 0.66, 5.50).[3] Subjects randomized to PCC with prior history of thromboembolic events (TE) had numerically higher frequency of TE compared to those without prior history [9/69 (13%) vs 1/34 (2.9%)].[3] This did not reach statistical difference. The corresponding frequencies for plasma were 3/79 (3.8%) and 3/30 (10%).

Clinical Implications

PCC provides a new option to plasma to reverse vitamin K antagonist anticoagulation therapy in patients with acute major bleeding. It is more convenient to use than plasma. On the other hand, the risk of thromboembolism may be higher, particularly in patients with a prior TE history. To help address this risk, the FDA has required the sponsor to conduct a retrospective, case-control study as well as a randomized, controlled study to evaluate a lower dose of PCC.[2] ■

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Clarification

In the May 15, 2013, issue of *Internal Medicine Alert*, in the Clinical Briefs on page 71, in the first brief titled "Risks and Benefits of an Extended 10-year Tamoxifen Regimen for Breast Cancer," we would like to make the following clarification.

A subscriber asked why the brief stated that all-cause mortality is not decreased by a longer duration of tamoxifen. In the ATLAS trial, our subscriber is correct in noting that in the ER+ subgroup of the trial, extended tamoxifen provided significant favorable results in relation to both breast cancer and total mortality outcomes. Because the primary outcome of the ATLAS trial (all participants, total mortality) did not achieve statistical significance, evidence-based medicine guidelines would typically assert that these results remain hypothesis generating, and hence not definitive. Thanks to our subscriber for suggesting this clarification. ■

CME Questions

1. **In a recent randomized, controlled trial of either 5 days or 14 days of steroid use in patients presenting to the ED with an acute exacerbation of COPD, patients who got the short-term (5-day) treatment had:**
   a. shorter time to the next exacerbation of COPD.
   b. reduced rate and extent of improvement in FEV1.
   c. fewer side effects, such as hypertension or hyperglycemia.
   d. shorter length of hospital stay.

2. **Optimism is associated with:**
   a. a healthier lipid profile.
   b. no improvement in the body mass index.
   c. no significant decrease in alcohol consumption
   d. no improvement in exercise or cigarette smoking activities.

3. **Which of the following statements about prolotherapy for osteoarthritis of the knee is true?**
   a. It is not effective in relieving knee pain.
   b. It has been shown to be superior to corticosteroids for long-term pain relief.
   c. It has been around for about 75 years, but until now has lacked high-quality studies demonstrating its effectiveness.
   d. A single treatment is dramatically effective in relieving knee pain.

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

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

Continuing Warfarin for Pacemaker/ICD Implantation is Safer Than Bridging

Source: Birnie DH, et al. *N Engl J Med* 2013;368:2084-2093.

The decision process to determine the optimal scheduling of antithrombotic therapy in the perioperative period is complex. The most recent AT9 CHEST guidelines suggest discontinuation of warfarin 5 days prior to pacemaker/implantable cardioverter-defibrillator (PCM-ICD) implantation, complemented with heparin bridging. This method is somewhat unwieldy, expensive, and has not been confirmed by a large, randomized trial as optimizing risk reduction. During transition from warfarin to heparin, an interval of increased risk for thromboembolism occurs in some, and the use of heparin has also been shown to frequently be associated with device-pocket hematoma.

In the Bridge or Continue Coumadin for Device Surgery Randomized Controlled trial, 681 PCM-ICD patients were randomized to continued warfarin or heparin bridging. Patient selection criteria also included high baseline annual thromboembolism risk (≥ 5%). The primary outcome of the trial was incidence of significant device-pocket hematoma (DPH), which can result in prolongation of hospitalization, need to stop anticoagulation, or additional surgery.

There was a dramatic difference in risk for the DPH primary endpoint between subjects continued on warfarin uninterrupted (3.5%) and subjects randomized to heparin bridging (16%). Risk reduction through continuation of warfarin was not associated with any increased incidence of major surgical adversities compared with bridging. Continuation of warfarin, uninterrupted, was associated with more than 80% reduction in risk of DPH compared to bridging, while not compromising other measures of safety. ■

Bariatric Surgery Impact on Cholesterol Metabolism

Source: Benetti A, et al. *Diabetes Care* 2013;36:1443-1447.

Bariatric surgery techniques are often described as restrictive (e.g., gastric banding) or diversionary (e.g., biliointestinal bypass). While diversionary surgery (DIV) is associated with greater weight loss and more rapid metabolic changes than restrictive surgery (RES), the greater simplicity and reversibility of the latter are pertinent in selecting which intervention is preferred.

Although the impact of bariatric surgery on diabetes has been much publicized, the impact of bariatric surgery on cholesterol is less well recognized. To date, most of the favorable impact on cholesterol has been attributed to weight loss. Over the long term, DIV is associated with greater weight loss than RES. However, since DIV and RES are associated with similar overall weight loss during the first postoperative 6 months, one could compare cholesterol metabolism of the two types of surgery independent of weight loss.

Benetti et al compared cholesterol metabolism in DIV with RES (n = 20). They found that with DIV, reduced cholesterol absorption produced a decrease in LDL and non-HDL, associated with enhanced catabolic LDL receptor activity in the liver.

Because metabolic changes in both groups in reference to glucose, insulin, insulin resistance, and weight loss were similar, the authors suggest that these favorable cholesterol metabolic changes are induced specifically with DIV, and because weight loss over the specified interval was essentially equivalent, the changes in lipids are not fully explained by weight loss. ■

The Do-it-Yourself Diabetes Diagnosis Kit

Source: Bethel MA, et al. *Diabetes Care* 2013;36:1483-1488.

In the last decade, the threshold for diagnosis of diabetes has expanded to lower levels of fasting glucose, inclusion of reference laboratory A1c, and refinement of the definitions of prediabetes. Use of the oral glucose tolerance test (OGTT) appears to be less and less necessary, considering the relative convenience of other diagnostic tests. Could a self-administered OGTT change the balance and be a positive addition to the diagnostic portfolio?

Bethel et al report on a self-administered OGTT home use kit (SmartGRA) used by 30 diabetic and non-diabetic subjects. The kit includes instructions to guide the user through the process of timed capillary glucose measurement as well as a wireless data recorder for glucose levels, the results of which are not visible to the user (glucose measurements are wirelessly transmitted to the clinic for evaluation).

Was self OGTT accurate? In a word, yes. Comparison of OGTT reports generated by SmartGRA vs office-based testing found comparable reproducibility of results. Although the results of home OGTT tended to overestimate glucose levels compared to the reference laboratory, this emerged as a problem with device calibration, which should be able to be remediated. Overall, subjects found the device easy to use.

As a proof-of-concept trial, these results lend credence to the idea that OGTT — generally conceded to be sufficiently unwieldy so that other diagnostic tests are preferred — might merit reconsideration if a well-calibrated, similarly patient-friendly device comes to market. ■

Chest Pain and Pauses in Lead II

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.

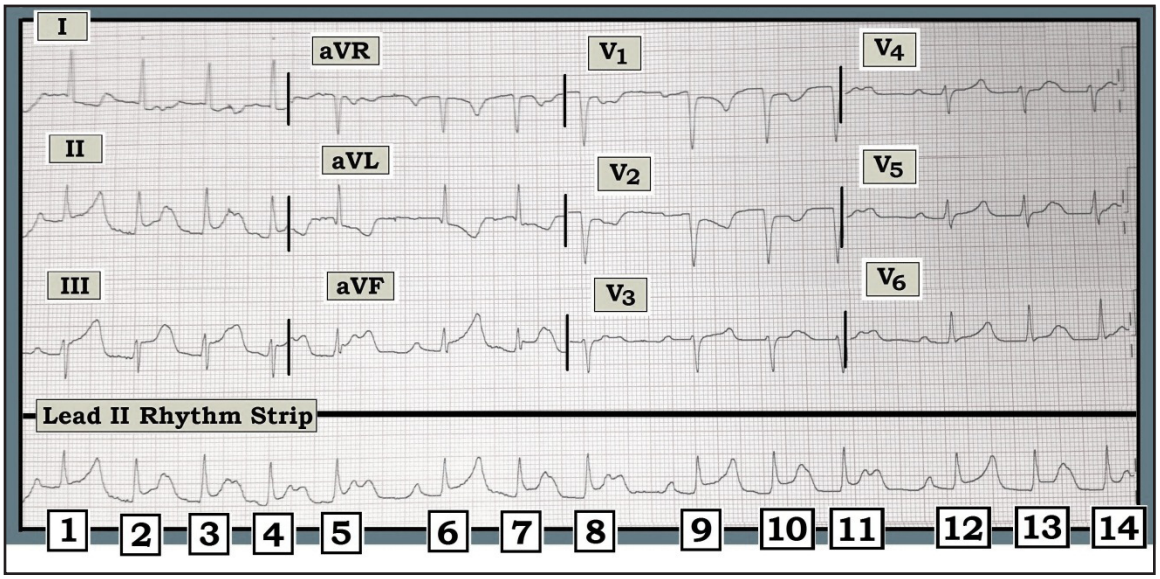

Figure — ECG from a woman with chest pain. What is the rhythm?

Scenario: The ECG shown above was obtained from a 50-year-old woman with *new-onset* chest pain. What is the rhythm? What are the clues to this rhythm diagnosis?

Interpretation: As always, it is best to begin with interpretation of the rhythm. Therefore, we focus our attention first on the lead II rhythm strip at the bottom of the tracing. Note that there are "groups" of beats (i.e., beats 1 through 5; 6-8; 9-11; and 12-14). Each of these groups is separated by a short pause. There is a pattern to what we see — each pause is approximately equal in duration — and a definite P wave with a fixed (albeit slightly prolonged) PR interval is seen at the end of each pause (i.e., before beats 6, 9, and 12). These P waves at the end of each pause are clearly conducting.

Additional P waves are present. These are seen to notch the ST segments of beats 3, 4, 5, 7, 8, 11, and 14. Close inspection suggests an extra peak to the T waves of beats 1, 6, 9, and 10. Use of calipers facilitates verifying that an underlying *regular* atrial rhythm is actually present. Setting calipers to the P-P interval between beat 6 and the *obviously hiding* P wave within the ST segment of beat 5 allows us to walk out regular P waves throughout the entire lead II rhythm strip.

Leaving the rhythm for a moment, let us interpret the rest of the 12-lead ECG obtained from this 50-year-old woman with new-onset chest pain. The QRS complex is narrow. There is marked ST segment elevation in each of the inferior leads (II, III, aVF) and reciprocal ST depression in leads aVL, V1, and V2. The overall impression suggests acute inferior (and possibly also posterior) infarction.

Putting the entire picture together suggests that the rhythm disturbance is second degree AV block, Mobitz Type I (= *AV Wenckebach*). Mobitz I is often seen during the early hours of acute inferior infarction. Additional clues to this conduction disturbance include the pattern of group beating described above and first-degree AV block for conducting beats. Although difficult to discern because of the relatively rapid atrial rate (that partially hides most P waves within preceding ST segments), the PR interval *does* progressively lengthen within each group until a beat is dropped.

For more information about this review on chest pain and pauses in lead II, please visit: http://ecg-interpretation.blogspot.com/2012/11/ecg-interpretation-review-55-mobitz-i.html. ■

In Future Issues:

Melatonin Secretion and the Incidence of Type 2 Diabetes

Dear *Internal Medicine Alert* Subscriber:

This issue of your newsletter marks the start of a new continuing medical education (CME) semester and provides us with an opportunity to remind you about the **procedures for earning CME and delivery of your credit letter.**

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- 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; and
- explain the advantages and disadvantages of new disease screening procedures.

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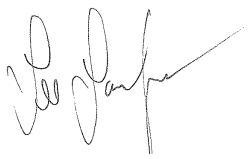

Lee Landenberger
Continuing Education Director
AHC Media

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.*

Is Naproxen the Safest NSAID for the Heart?

In this issue: NSAIDs and cardiovascular risk; new antithrombotic guidelines; warfarin during surgery; Pfizer selling Viagra online; azithromycin and cardiovascular risk; and FDA actions.

NSAIDs associated with less vascular risk

Naproxen may be the safest anti-inflammatory — at least when it comes to cardiovascular risk — according to a new study. Researchers from the United Kingdom undertook a meta-analysis of 280 trials of non-steroidal anti-inflammatory drugs (NSAIDs) vs placebo and 474 trials of one NSAID vs another. Main outcomes were major vascular events, major coronary events, stroke, mortality, heart failure, and upper gastrointestinal (GI) complications including bleeding. All NSAIDs and COX-2 inhibitors (coxibs) increased major vascular events except for naproxen (rate ratio [RR], coxibs 1.37 [95% confidence interval (CI), 1.14-1.66; $P = 0.0009$] and diclofenac 1.41 [95% CI, 1.12-1.78; $P = 0.0036$] mostly due to an increase in major coronary events). Ibuprofen also significantly increased the risk of major coronary events (RR 2.22, 95% CI, 1.10-4.48; $P = 0.0253$), but not major vascular events. Naproxen did not significantly increase the risk of major vascular events. Coxibs and diclofenac also significantly increased risk of vascular death, and there was a nonsignificant increase with ibuprofen, while there was no increase with naproxen. Heart failure risk was roughly doubled by all NSAIDs. The risk of upper GI complications was lowest with coxibs and highest with naproxen (coxibs 1.81, 95% CI, 1.17-2.81; $P = 0.0070$; diclofenac 1.89, 95% CI, 1.16-3.09; $P = 0.0106$; ibuprofen 3.97, 95% CI, 2.22-7.10; $P < 0.0001$, and naproxen 4.22, 95% CI, 2.71-6.56; $P < 0.0001$). The authors conclude that the vascular risks of diclofenac and possibly ibuprofen are comparable to coxibs, whereas high-dose naproxen is associated with less vascular risk (but higher GI risk) than other NSAIDs (*Lancet* published online May 30, 2013). The authors speculate that high-dose naproxen has fewer cardiovascular effects because it is the strongest inhibitor of COX-1, resulting in near complete suppression of platelet thromboxane biosynthesis (thus blocking platelet aggregation) throughout the 12-hour dosing interval. ■

New antithrombotic guidelines

A new guideline from the American Academy of Neurology gives primary care doctors guidance on periprocedural management of antithrombotic medications in patients with a history of stroke. Among the recommendations is that stroke patients undergoing dental procedures should routinely continue aspirin. Aspirin should also be considered for continuation in stroke patients undergoing invasive ocular anesthesia, cataract surgery, dermatologic procedures, transrectal ultrasound-guided prostate biopsy, spinal/epidural procedures, and carpal tunnel surgery. Aspirin should possibly be continued during other procedures such as virtroretinal surgery, EMG, transbronchial lung biopsy, colonoscopic polypectomy, upper endoscopy and biopsy/sphincterotomy, and abdominal ultrasound-guided biopsies. For stroke patients on warfarin, the guideline recommends continuation of the drug

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during dental procedures and probably during most dermatologic procedures. Other more invasive procedures should warrant discussion. The guideline states there is insufficient evidence to support or refute periprocedural heparin-bridging therapy to reduce thromboembolic events in chronically anticoagulated patients. Bridging therapy is probably associated with increased bleeding risk as compared with warfarin cessation, but the risk difference compared with continuing warfarin is unknown (*Neurology* 2013;22:2065-2069). ■

Continuing warfarin for surgery

In related news, a new study suggests that continuing warfarin for pacemaker or defibrillator surgery is safer than heparin bridging. Nearly 700 patients with an annual risk of thromboembolic events of ≥ 5% who required pacemaker or defibrillator surgery were randomized to continued-warfarin treatment or bridging therapy with heparin. The primary outcome was clinically significant device-pocket hematoma, which occurred in 12 of 343 patients (3.5%) in the continued-warfarin group as compared with 54 of 338 (16.0%) in the heparin-bridging group. There was one episode of cardiac tamponade and one myocardial infarction in the heparin-bridging group and one stroke and one TIA in the continued warfarin group. This study was stopped early after interim analysis found that the primary outcome occurred four times as often in the heparin-bridging group. These findings suggest that a strategy of continued warfarin therapy at the time of pacemaker or defibrillator surgery markedly reduced incidence of clinically significant device pocket hematoma as compared with heparin bridging (*N Engl J Med* 2013;368:2084-2093). ■

Pfizer launches own Viagra website

Pfizer is aggressively pursuing the online market for sildenafil (Viagra) by launching its own "Viagra home delivery" website. The drug will be available online directly from Pfizer but will still require a doctor's prescription. This move is also designed to counter online marketing of counterfeit Viagra, the most commonly counterfeited drug in the world. Pfizer plans to make Viagra available online at approximately $25 a pill. Meanwhile, the company has lost patent protection for its other version of sildenafil citrate marketed for pulmonary hypertension under the trade name Revatio. This version of the drug is only available in 20 mg strength, but is otherwise identical to Viagra, which is available in 25, 50, and 100 mg strengths. It is yet to be seen whether physicians will prescribe generic 20 mg sildenafil off label for erectile dysfunction. ■

Azithromycin and cardiovascular risk

Does azithromycin increase cardiovascular (CV) risk? A recent observational study showed that azithromycin was associated with a 2-3 times higher risk of death from CV disease in patients at high risk for CV disease (*N Engl J Med* 2012;366:1881-1890). A new study looks at the risk of the drug vs placebo and a comparator antibiotic (penicillin V) in Danish adults ages 18-64. As compared with no use of antibiotics, use of azithromycin was associated with a significantly increased risk of CV death (rate ratio 2.85; 95% CI, 1.13-7.24); however, when compared to penicillin V, there was no increased risk (crude rate CV death 1.1/1000 person years azithromycin vs 1.5/1000 penicillin V). With adjustment for CV risk, current azithromycin use was not associated with increased risk of CV death compared with penicillin V in a general population of young and middle-aged adults. (*N Engl J Med* 2013;368:1704-1712). This study is reassuring, suggesting that the increased risk of death is probably due to the illness rather than the drug, especially in low-risk populations. However, the risk of the macrolides still should be considered among patients with a high baseline risk of CV disease. ■

FDA actions

The FDA has approved a new once-daily combination inhaler for the treatment of chronic obstructive pulmonary disease (COPD). The product combines the long-acting beta-agonist (LABA) vilanterol with the steroid fluticasone furoate. Vilanterol is a new LABA and fluticasone furoate is reported to have longer lung retention time compared to the proprionate allowing for once-daily dosing. The product is a dry powder that is delivered via the Ellipta device. The new inhaler was evaluated in 7700 patients with COPD and showed improved lung function and reduced exacerbations compared to placebo. Vilanterol/fluticasone furoate is marketed by GlaxoSmithKline in collaboration with Theravance as Breo Ellipta.

The FDA has approved a new cholesterol combination drug, combining ezetimibe and atorvastatin. The drug is indicated for lowering cholesterol in patients with primary or mixed hyperlipidemia and in those with homozygous hypercholesterolemia. It is approved in four strengths, each containing 10 mg of ezetimibe with 10, 20, 40, or 80 mg of atorvastatin. The combination reduces LDL cholesterol levels up to 61% in clinical trials. Like the previously marketed simvastatin/ezetimibe, there is no evidence that the combination improves cardiovascular outcomes over a statin alone. The combination will be marketed by Merck as Liptruzet. ■