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INSIDE

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Chest Pain and Dyspnea? Taking Steroids? Think PE.

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: *Corticosteroid use is associated with an increased risk of symptomatic pulmonary embolism. The greatest risk is in the first 30 days of use and increases with increasing steroid dose.*

Source: Stuijver DJ, et al. Use of oral glucocorticoids and the risk of pulmonary embolism: A population-based case-control study. *Chest* 2013;143:1337-1342.

THE PURPOSE OF THIS STUDY WAS TO QUANTIFY THE RISK OF SYMPTOMatic pulmonary embolism (PE) in patients taking corticosteroids. To address this question, the authors used a large database containing demographic details and complete medication histories of more than 2 million people in The Netherlands. Because virtually all patients in The Netherlands are registered with a single pharmacy, records for prescription drug use are essentially complete. This report is the result of a population-based, case-control study of this database. For purposes of this analysis, cases were defined as adult patients with a first hospital admission for PE between 1998 and 2008. Diagnosis of PE was objectively confirmed in more than 95% of these cases. Each case had up to four age- and sex-matched controls from the same database of patients who had not been hospitalized for PE.

For each patient, the investigators identified all prescriptions for oral (systemic) glucocorticoids, including cortisone, hydrocortisone, prednisone, prednisolone, triamcinolone, methylprednisone, dexamethasone, and betamethasone. Patients were classified as never users, current users, or former users on the basis of the timing of the prescription and the PE event. For current users, duration of current

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glucocorticoid use was categorized as recent use (PE diagnosed in the first 30 days of steroid use), intermediate use (PE diagnosed between 31 and 365 days of steroid use), and long-term use (more than a year of steroid use at the time of PE). The authors also calculated cumulative steroid dose at the time of PE. Daily dose equivalents of prednisolone 10 mg were as follows: cortisone 37.5 mg, hydrocortisone 30 mg, prednisone 10 mg, triamcinolone 7.5 mg, dexamethasone 1.5 mg, and betamethasone 1.5 mg. The analysis controlled for other risk factors for PE (trauma and fractures, malignancy, pregnancy, cardiovascular disease, diabetes, and surgery) and for medications that could reduce the risk of PE (vitamin K antagonists, heparins, and antiplatelet agents [i.e., aspirin, clopidogrel bisulfate, and dipyridamole]).

The analysis included 4495 patients who had PE and 16,802 controls. Overall, the mean age was 60 years, and women comprised 57% of both groups. Current use of glucocorticoids was more frequent among those patients who had PE (13.1%) than controls (2.5%). After adjustment for confounders, the risk estimate (odds ratio [OR]) for PE among corticosteroid users was 4.4 (95% confidence interval [CI], 3.8-5.0). Former users had a much lower increased risk of PE (cases, 8.4%; control subjects, 6.7%) with an adjusted OR of 1.2 (95% CI, 1.1-1.3).

Among those currently using corticosteroids, the risk of PE was highest within the first 30 days of glucocorticoid use (adjusted OR, 5.9; 95% CI, 2.3-7.9) and gradually decreased with longer duration of use. The adjusted OR was 1.9 (95% CI, 1.3-2.9) for long-term use (> 1 year).

The association between glucocorticoids and PE varied depending on the dose of glucocorticoids used. A clear dose-response relationship was observed, with low-dose glucocorticoids carrying a two-fold increased risk of PE (adjusted OR, 1.8; 95% CI, 1.3-2.4) up to a 10-fold increased risk for the highest daily dose of glucocorticoids (adjusted OR, 9.6; 95% CI, 4.3-20.5). Almost always, the risk of PE was highest within the first 30 days of glucocorticoid use, irrespective of the dose.

■ COMMENTARY

Glucocorticoids have become one of the most widely prescribed medications, and are currently used by about 1% of the adult population.[1] Despite their undeniable benefits, corticosteroids are accompanied by numerous side effects, including increased cardiovascular morbidity and mortality.[2,3] Endogenous glucocorticoid excess among patients with Cushing syndrome has been associated with an increased incidence of venous thromboembolism (VTE) both during active disease and after surgery.[4] But the effect of exogenous glucocorticoids on VTE risk is less clear. For one thing, it is difficult to separate any potential effect of corticosteroids on VTE risk from the risk resulting from the indication for which they are given. However, several in vitro studies have revealed that exogenous glucocorticoids enhance both synthesis and secretion of von Willebrand factor and plasminogen activator inhibitor-1, suggesting a direct activation of coagulation and inhibition of fibrinolysis.[5-7]

This large, population-based, case-control study has demonstrated that use of oral glucocorticoids was associated with a four-fold increased risk of PE both in a time- and dose-dependent fashion. The greatest risk was within the first 30 days of glucocorticoid use and for the highest daily dose. However, even among low-dose glucocorticoid users, patients were at the highest risk of PE within the first month after treatment onset compared with long-term users.

The authors acknowledge the fact that glucocorticoids are frequently prescribed in conditions that are inflammatory (and therefore thrombogenic), such as chronic obstructive pulmonary disease, arthritides, and cancer, which makes it very difficult to parse the precise role in the increased risk of PE in those who take steroids. At the very least, however, the current study should heighten our index of suspicion for PE in patients who are taking corticosteroids, especially early in the course and at high doses. ■

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Questions & Comments
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Stroke Prevention by Screening for Atrial Fibrillation

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: *Stepwise risk factor-stratified screening in an elderly population using a handheld ECG device detected a significant number of patients with silent paroxysmal atrial fibrillation.*

Source: Engdahl J, et al. Stepwise screening of atrial fibrillation in a 75-year-old population: Implications for stroke prevention. *Circulation* 2013;127:930-937.

Atrial fibrillation (AF) is a common arrhythmia, and its prevalence is known to steeply increase with age reaching 6-8% of 75-year-old patients.[1,2] Cardioemboli occur frequently in patients with AF, especially in those patients who have not been treated with oral anticoagulants, often resulting in ischemic stroke.[3,4] Although AF is frequently symptomatic, unfortunately it also occurs asymptomatically quite frequently, especially when it occurs paroxysmally, and often, ischemic stroke can be the first clinical sign of the arrhythmia. AF is found to be present in 25-30% of patients sustaining an acute ischemic stroke.[5-7] The clinical picture of ischemic stroke associated with AF is often particularly severe and it is more frequently fatal than ischemic strokes of other etiologies.[5,8]

Engdahl and his colleagues performed a study by screening for silent AF in an at-risk population of 75- to 76-year-old patients in the municipality of Halmstad, Sweden.[10] The 848 participants received a 12-lead ECG. Those with sinus rhythm on the 12-lead ECG, no history of AF, and two or more risk factors according to the CHADS risk factor profile[9] were invited to participate in a 2-week observation period and were given a handheld ECG and asked to record their ECG for 20-30 seconds twice daily routinely or at any other time if palpitations occurred. Among the 403 persons with two or more risk factors according to the CHADS risk factor classification[9] who completed the handheld ECG event recording, 30 (7.4%) subjects were diagnosed with silent paroxysmal AF and, therefore, were candidates for starting oral anticoagulation therapy.

■ COMMENTARY

Relatively recent advances in electronic technology have resulted in the ability to attach a very small, self-contained, inexpensive ECG device to the common mobile phone permitting ECG acquisition anywhere and at any time.[11] These ECGs can be of any duration and can be instantaneously transmitted to any website. The current study has clearly demonstrated the utility of this device in detecting silent paroxysmal AF,[10] which is known to occur in a significant percentage of the elderly population. Obviously, it would be better to detect paroxysmal AF and initiate anticoagulant therapy before a cerebrovascular accident (CVA) occurs since outpatient anticoagulant therapy has proven to be so successful in diminishing acute CVA occurrences in patients with paroxysmal or fixed AF. Therefore, the results of the study prove that short-term ECG monitoring with the patient-operated device can be a useful addition to other techniques such as a single 12-lead ECG, palpation of the pulse, Holter monitoring, etc. for detecting paroxysmal AF.

In summary, since patients with silent paroxysmal AF constitute the majority of the AF population, identifying and implementing the best technique for detecting silent AF is a crucial critical need to institute outpatient anticoagulant therapy prior to the occurrence of an acute cardioembolic CVA. Therefore, screening for silent AF in all elderly patients with one or more additional CHADS factors such as diabetes, hypertension, and/or congestive heart failure using a simple patient-operated ECG device attached to a cell phone should be considered for implementation by clinicians who have the capability to handle this relatively inexpensive, important patient service. Additional research studies are now in progress to determine whether this is the best screening technique for the early detection of silent AF. However, the results of these studies will not be available for at least several years and, as demonstrated by Engdahl and colleagues,[10] we have an excellent inexpensive screening technique currently available and consideration should be given to putting it to use now. ■

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Infections May Play a Role in Cognitive Decline, Dementia

ABSTRACT & COMMENTARY

By Richard R. Watkins, MD, MS, FACP

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Dr. Watkins reports no financial relationships relevant to this field of study. This article originally appeared in the May 2013 issue of Infectious Disease Alert.

Synopsis: *This study reports an association between infection burden and dementia, although the relationship may not be causal.*

Source: Katan M, et al. Infectious burden and cognitive function: The Northern Manhattan Study. *Neurology* 2013;80:1209-1215.

DO LATENT INFECTIONS CAUSE DEMENTIA? WHILE CERTAIN chronic illnesses (e.g., peptic ulcer disease, Burkitt's lymphoma, and cervical cancer) have known infectious etiologies, mainstream research has not elucidated a significant role for microbes in cognitive decline. But emerging data suggest an association between some viruses and bacteria and Alzheimer dementia (AD). Moreover, the detrimental neurocognitive effects of HIV infection are well established. Dementia represents an enormous financial burden on the health care system, comparable to heart disease and cancer.[1] Katan and colleagues present epidemiologic evidence of an association between infectious burden (IB) and dementia from a large multiethnic cohort.

The Northern Manhattan Study (NOMAS) was a multiethnic stroke-free cohort that enrolled 3298 participants ≥ 40 years of age between 1993 and 2001. Of these, 1625 subjects (65% women, mean age 69 years, 58% Hispanic) had serologic measurements taken for *Chlamydia pneumoniae*, *Helicobacter pylori*, cytomegalovirus, and herpes simplex virus type 1 and type 2. Cognitive status was assessed at baseline using the mini-mental state exam (MMSE) and then annually by a telephone interview. A subset also had the number of APOE ε4 alleles (known to increase risk for AD) identified. IB was used as the main predictor, which was determined by the relationship of individual serologic test results to the risk of stroke using estimates from Cox proportional hazard models. In a post hoc analysis, the investigators created a viral burden index (VIB) and also tested its association with cognition in the same manner as the overall IB index.

The results of the study were that the IB index was higher in black and Hispanic subjects, those with less than a high school education, no alcohol intake, and without cardiac disease. Furthermore, the IB index was associated with greater odds of having MMSE ≤ 24 compared to MMSE > 24 (unadjusted odds ratio = 1.58). The effect of the IB index on MMSE did not differ by APOE genotype. The association between IB index and MMSE was prominent among subjects who were physically inactive, women, had Medicaid or no insurance, and had less than a high school education. However, no relation was found between IB and change in cognition over time based on the annual telephone interviews, either unadjusted or adjusted for demographics and risk factors (P = 0.13). Moreover, findings were similar with both the IB and VIB in that the VIB index was associated with MMSE ≤ 24 (adjusted odds ratio = 1.22; P = 0.04) but not with change over time during follow up interviews (P = 0.24).

■ COMMENTARY

There were several limitations to the study. While prior research supports a possible role for several of the infections that were tested (i.e., CMV, HSV-1), it is possible that other common viruses, like Epstein-Barr virus, Hepatitis B and C, can also lead to cognitive decline, although this remains theoretical. Furthermore, the authors did not test for HIV and its potential impact on the cohort is unknown. Because of the cross-sectional nature of the study, definitive conclusions about the direction of the associations (i.e., which came first, the infection or the dementia) cannot be determined with certainty. It was not possible to examine

the relationship between infections and specific forms of cognitive impairment, such as AD and vascular dementia. Testing for syphilis, a known infectious etiology of dementia in late illness, was not performed. Finally, the role of threshold effect on the study (i.e., the damage is already done so there is no further decline) may have reduced the ability to detect an association between IB and cognitive decline over time.

The microbe-dementia hypothesis is intriguing because it implies that dementia could be reversible with antimicrobial agents. If true, it would signify a major paradigm shift in our understanding of cognitive decline. The study by Katan and colleagues extends previous findings of the association between chronic infections and cognitive decline. It is somewhat surprising that the IB index did not correlate with cognitive decline over time. As the authors hypothesized, this could be due to the relatively advanced stage of cognitive impairment at the time the subjects were enrolled, which would have limited the ability to detect further decline. The mechanism behind the association is uncertain but might be from the inflammatory response elicited by chronic infection. This inflammation, combined with other risk factors, then leads to atherosclerosis, subclinical stroke, and dementia. The close (essentially identical) correlation between the IB and VIB in the study supports the notion that most of the effect on cognition is mediated by viral rather than bacterial infections.

Although the study showed an association between IB and cognitive performance, association does not always equal causality. As noted in an accompanying editorial, only a randomized controlled trial would be definitive.[2] Currently, there are no published clinical trials in humans on treating AD with antimicrobials. In a recent study, investigators administered minocycline to transgenic mice predisposed to AD-like amyloid pathology.[3] They found the drug down-regulated inflammatory markers that correlated with a reduction in amyloid precursor protein levels and amyloid precursor protein-related products. Minocycline has known anti-inflammatory properties and most likely did not exert a direct antimicrobial effect. Following an initial animal trial, the next step could be a randomized controlled trial in patients with AD using valacyclovir over an extended duration, perhaps 6 months or longer, to treat reactivations of herpes viridae. Study endpoints would have to be chosen carefully and would likely require detailed and comprehensive neurocognitive testing. Anti-inflammatory therapy could also be given and APOE ε4 genotype determined. Such a study could produce solid evidence-based medicine that determines the validity of the microbe-dementia hypothesis. ■

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Pharmacology Update

Fluticasone Furoate and Vilanterol Trifenatate Inhalation Powder (Breo™ Ellipta™)

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 COMBINATION OF AN INHALED CORTICOSTEROID AND a long-acting beta$_2$-adrenergic agonist has been approved for the treatment of chronic obstructive pulmonary disease (COPD). This once-daily fixed combination is comprised of the furoate form of fluticasone and a new long-acting beta$_2$-adrenergic agonist, vilanterol. The product is developed in collaboration with Theravance and is marketed by GlaxoSmithKline as Breo Ellipta. Breo is the trademark for the drugs and Ellipta for the device.

Indications

Fluticasone furoate (FF) and vilanterol (VI) is indicated for long-term maintenance treatment for airflow obstruction and for reducing exacerbations in patients with COPD.[1]

Dosage

The maintenance dose is two blister strips of powder inhaled once daily. One strip contains 100 mcg of FF and the other 25 mcg of VI.

Potential Advantages

FF is reported to have longer lung retention time compared to fluticasone propionate.[2] This allows for once-daily dosing compared to currently marketed preparations for COPD (fluticasone/salmeterol and budesonide/formoterol) that are dosed twice daily.

Potential Disadvantages

Lactose monohydrate is an inactive ingredient and contains milk protein. The product is contraindicated in patients with severe hypersensitivity to milk protein.[1]

Comments

FF prolongs absorption from the lung into the systemic

circulation compared to fluticasone propionate.[2] Vilanterol has similar functional selectivity to salmeterol with activity for 24 hours.[1,3] The efficacy of the combination of FF/VI was mainly established in four confirmatory studies, two based on pulmonary function and two based on reduction of exacerbations. Pulmonary function studies were randomized, double-blind, placebo-controlled, 24-week studies in patients with COPD (n = 2254).[1,3,4] Each study compared two strengths of FF/VI (100/25 mcg and 50/25 mcg in one study, 100/25 mcg and 200/25 mcg in the other) to individual components, and placebo. Subjects had a mean age of 62, average smoking history of 44 pack years, postbronchodilator percent of predicted FEV_1 of 48%, and FEV_1/FVC ratio of 47%. Coprimary efficacy endpoints were weighted mean FEV_1 (0-4 h) post dose on day 168 and trough FEV_1 (23-24 h post dose on day 169). Difference in mean changes from baseline in weighted mean FEV_1 for the 100/25 mcg dose compared to placebo was 173 mL (95% CI, 123-224) in the first study and 214 mL (95% CI, 161-266) in the second study. Differences in trough FEV_1 were 115 mL and 144 mL, respectively. Improvement in measured endpoints with FF/VI was statistically significant compared to placebo in the first study and numerically improved in the second.[6] VI was statistically significant to placebo in both studies. FF/VI was statistically better than FF 100 in one study and FF/VI was not significantly better than VI 25. There were no clear benefits with the 200/25 strength compared to the 100/25 strength. The median time to onset of effect (100 mL increase in FEV_1 from baseline) was 16 minutes.[1] Two randomized, double-blind, 52-week studies evaluated the effect of FF/VI on annual rates of moderate/severe exacerbation (n = 3255).[1] Subjects had a mean age of 64, average smoking history of 46 pack years, mean postbronchodilator percent predicted FEV_1 of 45%, and mean postbronchodilator FEV_1/FVC ratio of 46%. Three strengths of FF/VI were compared to VI alone. The mean annual exacerbation rates ranged from 0.70 to 1.14. FF/VI showed statistical or numeric reduction over VI in terms of moderate-to-severe exacerbations by one-fourth to one-third of an event per year. Moderate exacerbation is worsening of symptoms that required an oral steroid and/or antibiotics. Severe exacerbation required inpatient hospitalization. In two active comparator studies, FF/VI appears to be at least as effective as fluticasone propionate/salmeterol 250/50 mcg in terms of improvement in FEV_1 from baseline at day 84.[6] The most frequently reported adverse events were nasopharyngitis, upper respiratory tract infection, headache, and oral candidiasis.[1]

Clinical Implications

FF/VI is the first once-daily fixed-combination of a corticosteroid and a long-acting beta-adrenergic agonist for the treatment of COPD. These combinations along with long-acting anticholergic agents are first-choice therapy for COPD patients with high risk of airflow limitation and exacerbation.[7] An event-driven trial, the Study to Understand Mortality and Morbidity in COPD, is planned to compare FF/VI 100/25 mcg, FF 100 mcg, VI 25 mcg, and placebo with mortality as the primary endpoint.[8] FF/VI is currently being evaluated for the treatment of asthma. The cost was not available at the time of this review, as the product is expected to be available during the third quarter of this year. ■

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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. **Use of corticosteroids is associated with an increased risk of symptomatic pulmonary embolism:**
   a. with increasing risk associated with higher duration of use.
   b. which is negligible after controlling for confounders.
   c. with highest risk associated with highest doses of steroid.
   d. only for exogenous corticosteroids.
2. **Screening for silent paroxysmal atrial fibrillation (PAF) using a handheld ECG device:**
   a. did not detect a significant number of patients with silent PAF.
   b. detected a significant number of patients with silent PAF.
   c. could not be easily performed by the subjects.
   d. was of no value.

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

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

Food Allergy in IBS: Patch Testing

Source: Stierstorfer MB, et al. Food patch testing for irritable bowel syndrome. *J Am Acad Dermatol* 2013;68: 377-384.

We have, as yet, no fully satisfactory etiologic explanation for the symptom complex recognized as irritable bowel syndrome (IBS). Yet, demonstration of various derangements — hypersensitivity to neurogenic stimuli, altered bowel flora, dysregulation of serotonin — has been seen in subgroups of persons with typical IBS. Results from IBS trials of non-systemic antibiotics (e.g., rifaximin) demonstrate improvements in IBS symptoms and support bacterial flora imbalance in some, but not all, IBS subjects.

IBS patients commonly report foods that exacerbate symptoms. Could these food sensitivities represent actual food allergy, and contribute etiologically to IBS? A variety of commonplace foods and food additives have been documented to cause allergic *cutaneous* contact dermatitis (type-4 hypersensitivity). Could similar responses lead to inflammatory changes in the gut and symptoms of IBS?

Stierstorfer et al performed patch testing in IBS subjects (n = 51) using up to 40 different foods or food additives that have been previously recognized as implicated in food hypersensitivity. Fifty-eight percent of subjects had one or more patch test results indicating possible food sensitivity, and when the "offending" food was eliminated from the diet, about two-thirds of subjects reported symptomatic improvement. Food allergy may play a more important role in IBS than previously recognized. ■

A Relationship Between Atrial Flutter and Sleep Apnea

Source: Bazan V, et al. Obstructive sleep apnea in patients with typical atrial flutter: Prevalence and impact on arrhythmia control outcome. *Chest* 2013;143:1277-1283.

Commonly recognized consequences of obstructive sleep apnea (OSA) include increased risk for hypertension, cardiovascular events, and arrhythmias, the most common of which is atrial fibrillation (AFib). Less well understood is the relationship between atrial flutter (AF) and OSA. Even though invasive treatment through catheter ablation is highly effective for AF, over the long term, as many as one-third of AF ablation patients develop postoperative AFib, which of course has its own toxicities.

Bazan et al evaluated a preoperative population of AF patients with polysomnography, none of whom had previously been diagnosed with or suspected of OSA. Overall, 82% of subjects were diagnosed with OSA, almost half of whom were graded as severe OSA.

Over the ensuing 12 months, use of continuous positive airway pressure (CPAP) in OSA patients who had received catheter ablation for AF resulted in a dramatic reduction in new postoperative AFib: from 46% (untreated) to 6% (treated).

OSA appears to be more commonplace in AF than previously recognized. Although a much larger randomized clinical trial will be necessary for confirmation, this small study suggests that for AF patients with OSA who are undergoing catheter ablation, CPAP substantially reduces the likelihood of postoperative AFib. ■

Beyond Hypertension: Metabolic Effects of Telmisartan

Source: Takagi H, et al. Telmisartan as a metabolic sartan: The first meta-analysis of randomized controlled trials in metabolic syndrome. *J Am Soc Hypertens* 2013;7:229-235.

It has not gone unnoticed that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) can sometimes have a favorable effect on glucose metabolism in diabetics and prediabetics. Experts have opined that it is perhaps vascular dilation in the skeletal muscle compartment from renin-angiotensin-aldosterone system blockade that produces increased glucose utilization. One of the ARBs, telmisartan, in addition to its blood pressure-lowering effect, has been noted to have peroxisome proliferator-activated receptor (PPAR)-gamma activation activity, distinct from the other members of this drug class. PPAR-gamma activation could favorably impact metabolic syndrome, but individual clinical trials of telmisartan have been inconclusive in this regard.

Takagi et al performed a meta-analysis of clinical trials (n = 10) of telmisartan in patients (n = 546) with metabolic syndrome. Favorable effects were seen for fasting glucose, insulin, and A1c. Of the 10 trials analyzed, only three included data on adiponectin, but results were also favorable for this metric.

Large clinical trials of telmisartan in patients with established vascular disease (e.g., TRANSCEND, n = 5926) have shown a nonsignificant trend toward less new onset diabetes, but the number of metabolic syndrome subjects in this trial was not specified.

Whether favorable changes seen in metabolic syndrome patients treated with telmisartan are sufficient to improve "hard" outcomes (myocardial infarction, cerebral vascular accident, diabetes mellitus) would require a very large clinical trial. ■

Fatigue in a Cancer Patient: Acute STEMI?

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

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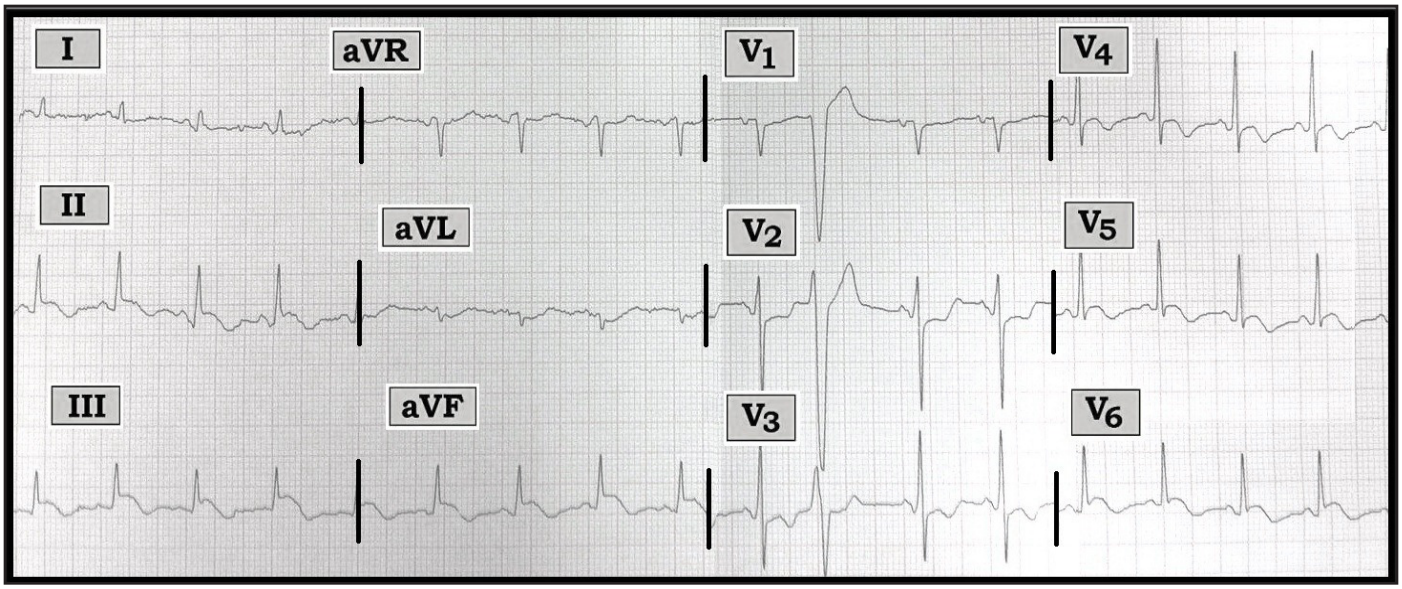

Figure — ECG from a 60-year-old man with lung cancer.

Scenario: The ECG shown above was obtained from a 60-year-old man undergoing chemotherapy and radiation therapy for lung cancer. He presented to the emergency department with weakness and palpitations, but no chest pain. Should the cath lab be activated for acute ST elevation myocardial infarction (STEMI)? Is anything else likely to be going on given this clinical history?

Interpretation: The rhythm in the figure is sinus tachycardia with one premature ventricular contraction. The PR and QRS intervals are normal; the QT is borderline prolonged. The axis is normal. There is no chamber enlargement. Regarding Q-R-S-T changes, there are no definite q waves and transition is normal (occurring between leads V2-to-V3). The most remarkable finding relates to ST-T wave changes.

There is coved ST elevation in inferior leads (II, III, aVF) and in lateral precordial (V4, V5, V6). In each of these leads, there appears to be T wave inversion following descent of the ST segment. In addition, there is scooped (reciprocal) ST depression in leads aVL and V2, V3.

The clear concern from the ECG above relates to the possibility of acute STEMI. As a result, emergent cardiac catheterization was performed. Surprisingly, the catheterization was unremarkable. There was absolutely no sign of acute coronary occlusion. Subsequent follow-up revealed a serum calcium level that was markedly elevated at 17 mg/dL.

There are several teaching points from this tracing. First, acute myocardial infarction is not the only cause of ST elevation. In addition to the more common other causes of ST elevation (early repolarization, acute pericarditis), ventricular aneurysm, cardiomyopathy, and hypercalcemia should be considered as potential "STEMI-mimics." Second, comparison with prior tracings may be of invaluable assistance. Third, marked hypercalcemia (as was present in this case) may produce not only early ST segment peaking and coving, but also ST elevation. Fourth, even knowing that the serum calcium in this case was markedly elevated, the presence of seemingly reciprocal ST depression in leads aVL and V2 makes it impossible to rule out acute STEMI. Only by comparison with prior tracings did it become apparent that ST depression was longstanding and not acute. ■

In Future Issues:

Screening for Hypertension Annually Compared with Current Practice

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. ■