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INSIDE

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Breaking a Vicious Circle?

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD, MA

Professor and Chair, Department of Integrative Medicine, Ross University (Bahamas) Limited, Freeport, Grand Bahama, The Bahamas

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

Synopsis: *Adding a muscle relaxer to an NSAID added no benefit in acute neck strain.*

Source: Khwaja SM, et al. Comparison of ibuprofen, cyclobenzaprine or both in patients with acute cervical strain: A randomized controlled trial. *CJEM* 2010;12:39-44.

THE THEORY BEHIND ADDING A MUSCLE RELAXANT TO A NONSTEROIDAL anti-inflammatory drug (NSAID) in acute muscle strain goes like this: When muscles (for instance, neck muscles in a whiplash injury) are strained, they reflexly go into spasm, which causes more pain. This sets up a positive feedback loop (or, in layman's terms, a vicious circle). The NSAID reduces the pain, and the muscle relaxant reduces the spasm, so the sum should be greater than the parts. Or so goes the theory. A Cochrane review of the use of cyclobenzaprine (CBP) for myofascial pain concluded that there was insufficient evidence to support its use.[1] A trial of CBP plus ibuprofen (IBU) vs CBP alone did not show a difference when treating adults with neck or back pain plus spasm.[2] A meta-analysis of CBP for back pain found it to be modestly effective, but had greater adverse effects.[3]

These researchers from Stony Brook University randomized 61 adult patients who presented to their suburban emergency department with neck pain within 24 hours of a fall or a motor vehicle collision to one of three treatment groups *(see Table, page 50)*. All medications were to be taken by mouth three times daily for 7 days or until pain was relieved. All patients received an initial dose of IBU 800 mg. They excluded pregnant women and patients who had a contraindication to the study drugs or who could not tolerate

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them. Patients and their physicians were blind to group assignment.

In addition to the usual demographic data, the patients kept a daily log of pain (measured on a 100-mm visual analog scale) and use of acetaminophen (APAP) and ice packs for rescue. They also recorded any adverse side effects, such as nausea, vomiting, or dizziness, and when they were able to resume their normal daily activities.

The three groups were similar. The patients' average age was 34 years. They were predominantly women (58%) and white (72%). Initially, the average pain score was 52.8 mm. All 3 groups got better over time, and there was a trend for Group 3 to have a greater average reduction in pain, but this did not reach statistical significance. There were nonsignificant trends for the IBU groups to use less APAP and to resume their normal daily activities sooner; 70% in Group 1, 38% in Group 2, and 65% in Group 3 returned to normal activities after one day. There was a trend (again, not statistically significant) for the groups receiving CBP to have more adverse drug effects.

■ COMMENTARY

In this small study, only pain reduction reached statistical significance. Perhaps the study was underpowered and had the investigators enrolled more subjects, their findings would have reached statistical significance. It's difficult to say since there were no power calculations. That there were more adverse side effects is not surprising, since CBP is structurally similar to the tricyclic antidepressants and has strong anticholinergic properties. It should be used with caution in people who are elderly or who might be harmed by its sedative effects. The current study did not show a benefit for adding CBP to IBU, nor did it conclusively show more adverse events. There was, however, the added expense of drug purchase. "First, do no harm" tips the balance in favor of withholding its use in this circumstance. ■

Table. Treatment groups

Group 1 = IBU 800 mg + placebo
Group 2 = CBP 5 mg + placebo
Group 3 = IBU 800 mg + CBP 5 mg
Key: IBU = ibuprofen; CBP = cyclobenzaprine

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Unaware of Best Practices for Low Back Pain Management? You're Not Alone

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

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

Synopsis: *For low back pain management, the usual care recommended by general practitioners does not follow evidence-based guidelines and does not provide best outcomes; this has not improved over time.*

Source: Williams CM, et al. Low back pain and best practice care: A survey of general practice physicians. *Arch Intern Med* 2010;170:271-277.

Low back pain (LBP) is one of the most common reasons for a visit to the general practitioner (GP) or primary care physician in the United States. At any one time, about 15% of adults have LBP. Most episodes of LBP im-

prove after a couple of weeks and most individuals will return to work within 1 week, with 90% returning within 2 months. Initial imaging is usually not recommended. However, with increasing duration of pain and disability, the outcome gets worse. After 6 months sick leave, fewer than 50% will return to work, and after 2 years of absence, there is little chance of returning to work at all.[1] Of those improved, many patients have a recurrent course. It is vital that evidence-based practice guidelines be available and properly utilized by GPs and other primary care physicians since they are the first to be called upon in a majority of such instances.

Williams et al evaluated the usual care provided by GPs in Australia for patients presenting with LBP. Australia has a government-funded medical insurance scheme that covers most direct costs of GP visits who in turn act as gatekeepers. Therefore, the effect of insurance is eliminated. They analyzed 3533 patient visits to Australian GPs during the 3 years before and the 3 years after the publication of a clinical practice guideline for the treatment of LBP. The authors found that the introduction of a local, evidence-based clinical practice guideline had no effect on physician treatment of LBP as measured by the frequency of patient counseling, prescription of analgesics, and use of imaging. For example, GPs recommended NSAIDs or opioids in preference to the safer and equally effective acetaminophen, and when acetaminophen was recommended, the dose was typically suboptimal. Contrary to the recommendations, more patients were referred for imaging (which is not routinely recommended) than those who received advice. The authors concluded that passive release of treatment guidelines and brief workshops are insufficient to change clinical practice. They concluded that additional strategies seem necessary to educate GPs about the use of the guidelines and how to provide guideline-based care.

■ COMMENTARY

Could it be that simple — just disseminate information more widely? If so, why hasn't it been done? Similar data on the lack of adherence to LBP management guidelines exist for other nations and should be of significant concern since the problem is common and we know that adherence to such guidelines improves quality of care and contains costs. In fact, the results of this study are remarkably similar to those of a study analyzing a U.S. national health survey.[2] There was a minimum impact of the Agency for Health Research and Quality's (AHRQ) clinical practice guidelines on the management of acute LBP in primary care settings. While the use of acetaminophen increased, so did the use of NSAIDs and referrals for radiographs.

I don't think the answer is so simple. While all stakeholders can be faulted (payment structure, patients, pharmaceutical industry, professional organizations, medical education), according to researchers, the majority of the responsibility still remains with the physician.[3] It is unfortunate that often there are as many guidelines on a topic as there are professional medical societies and most of them find creative ways to state the same facts. I hope that as we progress toward comparative effectiveness research, there is a concerted effort to reduce the redundancy in the medical field in this area as well. This should start by the development of a unified guideline and recommendation system, which would then become the standard of care for some of the most common medical conditions. So, when a patient visits a primary care practice for a common medical condition (headaches, LBP, hypertension, diabetes, URI, sinusitis, asthma, etc.), the condition should dictate the management, not the type of physician (DO or MD; family or internal medicine). This would eventually not only improve the quality of care and contain costs, but also reduce the practice of defensive medicine. However, this would require both primary care physicians and subspecialists to develop consensus, and not issue their separate guidelines as if they were treating a different set of human beings. ■

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BMI or Metabolic Syndrome — Which Is More Important?

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

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

Synopsis: *Middle-aged men who are overweight or obese, with or without the metabolic syndrome, are at increased risk for cardiovascular events and total death.*

Source: Arnlov J, et al. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. *Circulation* 2010;121:230-236.

One of the main reasons behind the major impact of obesity on the development of cardiovascular disease (CVD) is that it is often accompanied by the metabolic syndrome (MetS), a cluster of comorbid illnesses including dyslipidemia, hyperglycemia, and hypertension.[1-5] MetS is a strong predictor of future CVD and death and it should be noted that the increase in risk occurs even if only one MetS component is present.[3,4] Obese individuals without MetS are sometimes referred to as the metabolically healthy obese because in two previous prospective studies the data did not appear to demonstrate an increased risk of CVD in this group;[6,7] however, it is well known that an increased CV risk is present even in normal weight individuals if they are afflicted with MetS.[4,6-8]

Arnlov and colleagues questioned reports suggesting that overweight/obesity without MetS was not associated with a higher CV risk and they therefore decided to investigate the risk of CVD and death in middle-aged men and the associations with various combinations of body mass index (BMI) and MetS. Cardiovascular risk factors were assessed in 1758 participants without diabetes. During a median follow-up period of 30 years, 788 participants died and 681 others developed CVD (i.e., a composite of CV death or hospitalization for myocardial infarction, stroke, and/or heart failure). Participants with MetS had increased risk for CV events and total deaths regardless of BMI status during the more than 30 years of follow-up and overweight and obese individuals without MetS also had an increased risk. The data in essence refuted the notion that overweight and obesity without MetS are benign conditions.

■ COMMENTARY

It has been suggested that the differentiation of medically healthy obese (MHO) from metabolically impaired obese (i.e., MetS) individuals is important in determining therapeutic medical decision-making[9] and, in fact, some investigators have even suggested that weight loss in MHO patients could be potentially harmful.[10] However, because the data in the Arnlov study clearly demonstrate that overweight and obese individuals are at higher cardiovascular risk regardless of their metabolic status, the potential benefits of labeling overweight or obese patients as MHO in clinical practice appears to be of limited or no value. The finding that men with MetS are at higher risk for cardiovascular events regardless of their BMI status compared with normal-weight men without MetS and/or insulin resistance is in accordance with previously published longitudinal community-based data.[4,6,7]

In summary, the present study data did not support the suggestion that cardiovascular risk is low in the healthy obese phenotype (i.e., defined as the absence of the MetS and/or insulin resistance) and, therefore, there seems to be little question that all overweight and obese individuals are at increased cardiovascular risk and that weight reduction is desirable for all of these patients whether or not they have an associated MetS. ■

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Pharmacology Update

Hydromorphone HCl Extended-Release Tablets (Exalgo™) CII

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

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor

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

A ONCE-DAILY CONTROLLED-RELEASE FORMULATION OF HYdromorphone has been approved by the FDA. The product uses an osmotically controlled oral delivery system developed by Alza Corporation. It is marketed by Neuromed Pharmaceuticals as Exalgo™.

Indications

Controlled-release hydromorphone is indicated for the management of moderate-to-severe pain in opioid-tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time.[1] Opioid tolerance is defined as those patients taking daily doses of at least 60 mg of morphine, 30 mg of oxycodone, 8 mg of hydromorphone, 25 mg of oral oxymorphone, or 25 µg of transdermal fentanyl per hour.[1]

Dosage

The dose ranges from 8 mg to 64 mg once daily. The dose should be reduced in patients with moderate-to-severe hepatic dysfunction or moderate renal dysfunction. It may be taken without regards to meals. The tablet should not be broken, crushed, chewed, or its content dissolved. This could lead to the absorption of a potentially fatal dose. If a decision should be made to discontinue the drug, the dose should be reduced by 25%-30% every 2-3 days down to a dose of 8 mg before discontinuation.[1]

The drug is available as 8 mg, 12 mg, and 16 mg tablets.

Potential Advantages

The controlled-release formulation reduces the fluctuation between peak and trough concentrations associated with the immediate-release tablet and allows it to be dosed once-daily.[1] The bioavailability of once-daily dosing of the controlled-release formulation is comparable to the immediate-release formulation taken 4 times daily.[1] The extended-release formulation may have a lower abuse potential than an immediate-release formulation.[2]

Potential Disadvantages

It takes 3-4 days for steady-state plasma concentrations to be reached.[1] The extended-release formulation should be avoided in patients with narrowing or obstruction of the gastrointestinal tract or motility abnormality. The formulation also contains sodium metabisulfite that may cause an allergic-type reaction in susceptible individuals. Results from in vivo data suggest that alcohol increases the peak concentration of hydromorphone (mean, 10%-31%), but not the extent of absorption. The use of alcohol should be avoided with hydromorphone.

Comments

Hydromorphone is a mu-opioid agonist that is formulated as a controlled-release formulation to provide a convenient once-daily dosing. In a double-blind, placebo-controlled, randomized withdrawal study in opioid-tolerant patients with moderate-to-severe low back pain, controlled-release hydromorphone was superior to placebo in providing analgesia.[1] In a randomized, open-label, noninferiority analysis (n = 138) once-daily hydromorphone and twice-daily oxycodone extended-release provided comparable relief of pain in patients with chronic, moderate-to-severe osteoarthritis pain.[3] The mean daily dose (SD) of hydromorphone at 6 weeks was 15.8 mg (10.5 mg) vs 24.0 mg (11.7 mg) for oxycodone. There was no statistical difference in adverse events; however, somnolence was numerically higher with hydromorphone (25.4% vs 17.9%) and dizziness higher with oxycodone (22.4% vs 14.1%). The altered rate of absorption may lower the abuse potential by delaying the penetration of hydromorphone into the central nervous system.[2]

Clinical Implications

Hydromorphone has been used as an analgesic since 1994. A controlled-release formulation provides continuous delivery of drug over 24 hours. Many patients may prefer long-acting compared to short-acting opioids.[4] A previously approved extended-release capsule (Palladone™) was voluntarily withdrawn from the market after an FDA advisory warned of overdose potential when taken with alcohol. Hydromorphone HCl extended-release tablets offers a new extended-release opioid analgesic for chronic pain patients. ■

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Clinical Report

TB in Haiti

By Carol A. Kemper, MD, FACP

Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases; Santa Clara Valley Medical Center. This report originally appeared in the April 2010 issue of Infectious Disease Alert.

Dr. Kemper conducts research for GSK Pharmaceuticals, Abbott Laboratories, and Merck.

Source: ProMED-mail post, Feb. 5, 2010; Available at: www.promedmail.org.

HAITI IS ONE OF THE POORER COUNTRIES IN THE WORLD, WITH the highest per-capita rate of tuberculosis (TB) in Latin America and the Caribbean. According to the WHO 2009 Global TB Control Report, 29,333 new cases of tuberculosis were diagnosed in Haiti in 2007 (approximate incidence, 300 cases/100,000 population). Of these, 53% were sputum smear positive, and 1.8% were multidrug resistant. An estimated 6814 people died from TB in Haiti in 2007 alone.

Since 1998, the Ministry of Health stepped up TB control efforts in the country, increasing detection efforts and initiating a directly observed therapy (DOT) program. Attempts at DOT have varied from region to region, but it was used for as many as 91% of cases in 2006, although that number declined somewhat to 70% in 2007. The situation is compounded by the high rate of HIV and TB co-infection, which occurs in as many as 30% of TB cases in some areas.

The recent earthquake not only demolished buildings and infrastructure in Haiti, but also has devastated TB control efforts. The only TB hospital/sanitorium in the country, which housed several hundred of the sickest patients, was critically damaged, and *The New York Times* reports that patients have fled and are now living in tent cities, where TB transmission seems likely. "Hundreds" still report daily to pick up their medications, but the efforts of trained personnel have been diverted, or they have died as a result of the quake. The obvious concern is the potential for increasing drug resistance and widespread infection. ■

CME Questions

14. All of the following statements about the use of ibuprofen and cyclobenzaprine for acute cervical strain are true, *except*:

a. There was a trend for groups receiving cyclobenzaprine to have more adverse side effects.
b. There was a trend for groups receiving both ibuprofen and cyclobenzaprine to have a greater reduction in pain.
c. Groups using cyclobenzaprine resumed their usual daily activities earlier than groups using ibuprofen.
d. All combinations of ibuprofen, cyclobenzaprine, or placebo resulted in pain relief over time.

15. After the introduction of a local, evidence-based clinical practice guideline in Australia, general practitioner management of low back pain changed in what way?

a. Management did not change.
b. Quality of care improved.
c. Costs were reduced.
d. Use of imaging decreased.

Answers: 14. c, 15. a.

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.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
Dr. Kuritzky is a consultant for Sucampo Pharmaceuticals, Takeda, Boehringer Ingelheim; and is a consultant and on the speaker's bureau for Novo Nordisk, Lilly, Daiichi Sankyo, Forest Pharmaceuticals, Cephalon, Novartis, and Sanofi Aventis.

Thyroid hormone analogue for dyslipidemia

Source: Ladenson PW, et al. Use of the thyroid hormone analogue eprotirome in statin-treated dyslipidemia. *N Engl J Med* 2010;362:906-916.

The role of statins in treatment of dyslipidemia is well established. There are, however, limitations of statins: Residual risk is substantial, not all persons can tolerate statins, and, even with full-dose statin treatment, some patients do not achieve lipid goals.

The role of the thyroid in lipid metabolism has long been a matter of scientific interest. It is recommended that patients with dyslipidemia undergo thyroid function testing since hypothyroidism, although only present in a small percentage of dyslipidemic patients, is readily correctable and offers meaningful lipid improvements. Enhancement of thyroid activity has favorable lipid effects. As far back as the 1960s, investigators were curious enough about thyroid hormone and vascular disease to enroll men in the Coronary Drug Project (1965) and randomize them to d-thyroxine, which was felt at the time (mistakenly) to have essentially no effect on sympathetic nervous system sensitivity, but favorable effects on lipids.

Eprotirome (EPR) is an analogue of thyroid hormone which has preferential affinity for thyroid receptors that modulate lipid lowering, as compared to cardiac receptors. A randomized placebo-controlled, double-blind study was done among patients on an NCEP step 1 diet and a statin (simvastatin or atorvastatin). Patients (n = 329) received statin plus either EPR or placebo for 12 weeks.

At the end of the trial, very favorable lipid effects were reported with the addition of EPR to a statin: a 22%-32% reduction in LDL, a 6- to 9-fold increase in patients achieving an LDL < 100 mg/dL, as well as favorable effects on triglycerides and apoB (all dose-dependent). A small reduction in HDL was seen. There was no change in heart rate or BP. Selective activation of thyroid receptors may one day provide an additional path for successful lipid modulation. ■

Diagnostic yield of elective coronary angiography

Source: Patel MR, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med* 2010;362:886-895.

Current recommendations suggest that in stable persons under consideration for CAD evaluation, low-risk individuals be observed, high-risk patients be triaged to coronary angiography, and intermediate-risk persons be further stratified by means of non-invasive testing. Such guidance is structured to minimize unnecessary invasive investigations in low-risk individuals, and to identify — in the group of intermediate risk — those who merit follow-up with angiography.

The American College of Cardiology National Cardiovascular Data Registry provided information on patients without known CAD (n = 398,978) who received coronary angiography (electively) at hospitals in the United States during a 4-year interval commencing January, 2004.

Obstructive CAD was defined as at least 50% stenosis of the left main coronary artery (or greater degrees of stenosis of epicardial vessels). Catheterization determined that slightly more than one-third of patients had obstructive CAD. In addition to the disappointingly low percentage of individuals identified with CAD on angiography, this study also provided insights about the concordance of risk and use of non-invasive testing (i.e., stress testing). When non-invasive testing had preceded angiography, subjects' baseline risk category was at odds with the current recommendations focusing upon refinement of risk in persons at intermediate Framingham scores, in that those with high Framingham risk scores were disproportionately represented. The authors suggest that the diagnostic yield based upon current practice needs improvement. ■

Statins and risk of developing diabetes

Source: Sattar N, et al. Statins and risk of incident diabetes. *Lancet* 2010;375:735-742.

There is little dispute regarding the beneficial reduction in CV events seen with statin treatment of dyslipidemic patients. At the same time, however, conflicting evidence has suggested that statin treatment might be associated with an increased risk of new-onset diabetes.

Sattar et al performed a meta-analysis of data from large statin clinical trials (n = 13), totalling almost 100,000 patients. During a mean follow-up of 4 years, 9% more individuals developed new diabetes on a statin than patients not treated with a statin. Since CV risk reduction was still favorably influenced by statin treatment, this small increased incidence of diabetes was either not sufficient to offset other beneficial vascular effects, or, once diabetes developed, statin protection was already on board, or perhaps both factors were influential.

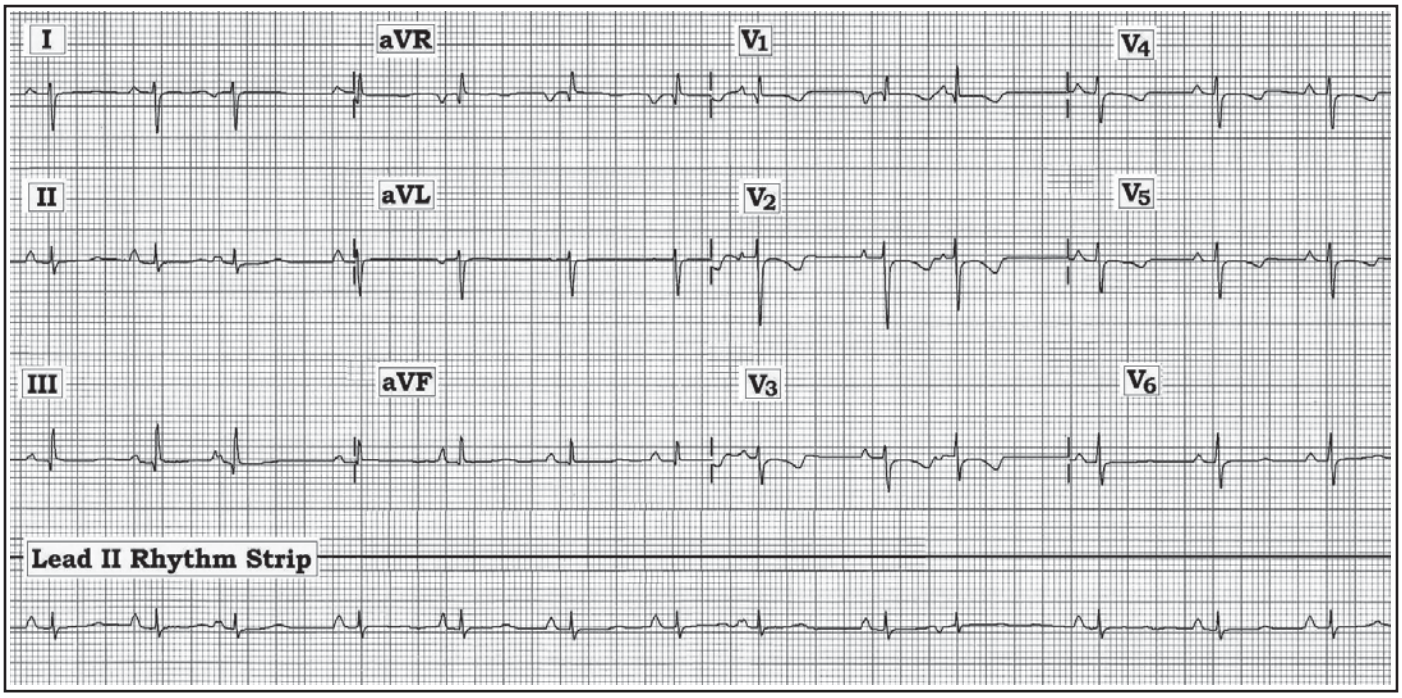
You may recall that in hypertension treatment trials, a similar problem has been identified. Chlorthalidone (ALLHAT) had a significantly greater risk for incidence of new diabetes than comparators, yet this adverse effect did not seem to adversely affect CV event rates.

The mechanism by which statins increase risk for diabetes is obscure. This data analysis calculated that 255 subjects would have to be treated with a statin for 4 years to incur 1 additional new case of diabetes. Fortunately, if the small increase is real, it is strongly counterbalanced by well-documented reductions in CV events. ■

Some Pulmonary Diagnoses

By Ken Grauer, MD, *Professor, Department of Community Health and Family Medicine, University of Florida*

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



Scenario

The ECG shown above was obtained from a 54-year-old woman with shortness of breath. What pulmonary findings on ECG might explain her symptoms?

Interpretation

The lead II rhythm strip seen at the bottom of this 12-lead tracing reveals an underlying sinus rhythm with irregularity. Close inspection shows frequent variation in P wave morphology. We interpret this rhythm as sinus with frequent premature atrial contractions. Given the clinical suspicion for pulmonary disease, we view this arrhythmia as part of a spectrum with multifocal atrial tachycardia (MAT) at its extreme. The heart rate here is not fast enough to qualify as tachycardia — but the cause, treatment, and clinical implications of the rhythm for this patient are the same as if the rhythm were MAT. Other findings consistent with pulmonary disease on this tracing include: 1) right axis deviation (RAD); 2) tall, peaked P waves of several different forms in the lead II rhythm strip, suggestive of right atrial abnormality; 3) a tall R>S wave in lead V_1; 4) persistent precordial S waves; 5) relatively low voltage diffusely; 6) T wave inversion across much of the precordium consistent with right ventricular "strain." Taken together, the above findings in an adult with dyspnea suggest right ventricular hypertrophy (RVH) with a right ventricular "strain" pattern. Entities to consider include chronic pulmonary disease (emphysema, long-standing asthma) and primary pulmonary hypertension (which is most commonly seen in women the age of this patient). Rapid development of the above ECG picture would suggest acute pulmonary embolism. Admittedly, diffuse precordial T wave inversion as seen here could reflect an ischemic process — but the combination of findings described above is much more suggestive of a pulmonary diagnosis. This degree of RAD, the predominant R>S wave in lead V_1, the presence of RV "strain," and the arrhythmia shown above all strongly suggest marked severity of whatever the underlying pulmonary disorder turns out to be. ■

In Future Issues:

Effects of Dairy Compared with Soy on Oxidative and Inflammatory Stress

INTERNAL MEDICINE ALERT

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In an effort ensure *Internal Medicine Alert* is addressing the issues most important to you, we ask that you take a few minutes to complete and return this survey. The results will be used to ensure you are getting the information.

Instructions: Mark your answers by filling in the appropriate bubbles. Please write your answers to the open-ended questions in the space provided. Return the questionnaire in the enclosed postage-paid envelope by **July 1, 2010**.

In future issues of *Internal Medicine Alert*, would you like to see more or less coverage of the following topics?

	A. more coverage	B. less coverage	C. about the same
1. Endocrinology	O A	O B	O C
2. Pulmonology	O A	O B	O C
3. Cardiology	O A	O B	O C
4. Dermatology	O A	O B	O C
5. Neurology	O A	O B	O C
6. Gastroenterology	O A	O B	O C
7. Rheumatology	O A	O B	O C
8. Men's Health	O A	O B	O C
9. Women's Health	O A	O B	O C
10. Pediatrics	O A	O B	O C
11. Preventive Medicine	O A	O B	O C

12. What other topics would you like to see discussed in *Internal Medicine Alert*? _____

_____

13. Are the articles in *IMA* written about issues of importance and concern to you?

O A. always O B. most of the time O C. some of the time O D. rarely O E. never

14 Are the articles in *Internal Medicine Alert*

O A. Too short O B. Too long O C. About right

15. What type of information not currently provided in *Internal Medicine Alert* would you like to see added? _____

_____

Please rate your level of satisfaction with the the items listed: Please mark your answers in the following manner:

	A. excellent	B. good	C. fair	D. poor
16. quality of newsletter	O A	O B	O C	O D
17. article selections	O A	O B	O C	O D
18. timeliness	O A	O B	O C	O D
19. quality of commentary	O A	O B	O C	O D
20. clearness of abstracts	O A	O B	O C	O D
21. overall value	O A	O B	O C	O D
22. customer service	O A	O B	O C	O D

23. To what other publications or information sources about internal medicine do you subscribe?

_____

_____

24. Including *IMA*, which publication or information source do you find most useful, and why?

_____

_____

25. Please describe your work place:

O A. private practice O B. hospital O C. government institution O D. research

O E. Other_____

26. In the future, how do you plan to obtain your CME and CNE credits?

O A. travel to live conferences O B. subscription-based newsletters/journals O C. outside-sponsored teleconferences

O D. Internet-based activities O E. Other (please specify)_____

27. *Internal Medicine Alert* is currently accredited for a maximum of 24 hours of Prescribed credit by the American Academy of Family Physicians. If you participate in this CME activity for credits, how many hours do you spend in the activity each year?_____

28. List the top three challenges you face in your job today:

_____

_____

_____

Contact information_____

_____

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Hospital Medicine Alert, Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

Thiazolidinediones and Risk of Heart Failure

In this issue: FDA is reviewing safety of TZDs; SSRI use with tamoxifen; Metformin smells like fish; FDA Actions.

FDA reviews TZD safety

Thiazolidinediones (TZDs) have been under intense scrutiny in recent years after rosiglitazone (Avandia®) was linked to increased cardiovascular morbidity and mortality in several studies. In recent weeks, *The New York Times* has reported that some FDA staffers are recommending that rosiglitazone be removed from the market. According to the story in the *Times*, a "confidential government report" states that about 500 heart attacks and 300 cases of heart failure per month could be averted if patients were switched from rosiglitazone to pioglitazone (Actos®). Congress has even gotten involved, specifically the Senate's Committee on Finance, which in January issued a 350-page report on rosiglitazone, focusing on GlaxoSmithKline's handling of evidence of possible cardiac risks associated with use of the drug. Now the American Heart Association and the American College of Cardiology have weighed in on the issue suggesting there is insufficient evidence to support the use of pioglitazone over rosiglitazone and that both drugs increase the risk for heart failure and should not be initiated in patients with class III/IV heart failure. They further state that the drugs should not be used with an expectation of benefit with respect to ischemic heart disease events (*Circulation*, published on-line Feb. 23, 2010). Meanwhile, the FDA web site reports that the Agency is reviewing data on rosiglitazone and is planning a public meeting in July 2010 to present all known heart-related safety data on the drug and provide an updated assessment of the risks and benefits of rosiglitazone and the treatment of type 2 diabetes. ■

SSRI use with tamoxifen

The SSRI paroxetine (Paxil®) reduces the effect of tamoxifen in women with breast cancer leading to higher breast cancer mortality according to a new study in the *British Medical Journal*. Concern about SSRIs interfering with the metabolism of tamoxifen was raised last June at the American Society of Clinical Oncology meeting. Tamoxifen is converted from its prodrug to the active metabolite via the cytochrome P450 pathway, specifically CYP2D6. Paroxetine is an exceptionally strong inhibitor of CYP2D6, the strongest inhibitor of all the SSRIs. In the study, Canadian researchers looked at more than 2400 women from Ontario treated with tamoxifen for breast cancer along with a single SSRI. After adjustment for confounders, absolute increases of 25%, 50%, and 75% in the proportion of time on tamoxifen with overlapping use of paroxetine were associated with 24%, 54%, and 91% increases in the risk

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of death from breast cancer, respectively ($P < 0.05$, for each comparison). No such risk was seen with any other antidepressant. The authors conclude that paroxetine use during tamoxifen treatments is associated with an increased risk of death from breast cancer, supporting the hypothesis that paroxetine can reduce or abolish the benefit of tamoxifen in women with breast cancer (*BMJ* 2010;340:c693). The study is important because up to one-quarter of women diagnosed with breast cancer experience a depressive disorder, and antidepressants are commonly used during tamoxifen treatment for not only depression, but also for treatment of hot flashes and other symptoms. It is evident that paroxetine should never be prescribed to women taking tamoxifen for treatment of breast cancer and that preference should be given to antidepressants that show little or no inhibition of CYP2D6. Among the SSRIs, the strongest inhibitors of CYP2D6 besides paroxetine are fluoxetine (Prozac®), duloxetine (Cymbalta®), and to a lesser extent sertraline (Zoloft®). Among non-SSRI antidepressants, bupropion (Wellbutrin®) also is a strong CYP2D6 inhibitor. Drugs that are not inhibitors of the enzyme include citalopram (Celexa®) and venlafaxine (Effexor®). ■

Generic metformin smells fishy?

If your patients tell you their pills smell like fish, they may be taking generic metformin. A letter to the *Annals of Internal Medicine* describes two patients who stopped taking generic metformin because of a fishy taste that caused nausea. The fishy smell is a property of metformin and is well known to pharmacists. Apparently the film-coated extended-release formulations have less smell and may be better tolerated (*Ann Intern Med* 2010;152:267-268). ■

FDA actions

A new FDA warning states that **long-acting beta agonists** (LABAs) should never be used alone in the treatment of asthma in children or adults. The LABAs salmeterol (Serevent®) and formoterol (Foradil®) have been associated with severe worsening of symptoms when used without a controller medication such as an inhaled corticosteroid. Both products will be required to include warnings on the product label that states:

- Use of LABAs is contraindicated without the use of an asthma controller medication;
- LABAs should only be used long term in patients whose asthma cannot be adequately controlled on asthma controller medications;
- LABAs should be used for the shortest duration of time required to achieve control, and should be discontinued once asthma control is achieved;
- Pediatric and adolescent patients who require an LABA in addition to an inhaled corticosteroid should use a combination product containing both an inhaled steroid and a LABA to ensure compliance with both medications.

The FDA has approved **rosuvastatin (Crestor®)** for primary prevention in patients without elevated LDL-cholesterol but who have an elevated C-reactive protein (2 mg/L or higher) and at least one additional cardiovascular risk factors such as low HDL, hypertension, or family history of premature heart disease. The approval was based on the JUPITER trial, which showed a 44% reduced relative risk of cardiovascular events in patients with normal LDL cholesterol but elevated CRP.

The FDA has approved a new **pneumococcal vaccine** for infants and children. Wyeth Pharmaceuticals' **Prevnar 13™** is a 13-valent conjugate vaccine that will replace the currently available 7-valent Prevnar®. It is approved for the prevention of invasive disease caused by 13 different serotypes of *S. pneumoniae*.

The FDA has approved the **monoclonal antibody rituximab (Rituxan®)** to treat certain patients with chronic lymphocytic leukemia (CLL). Rituximab is approved for CLL patients who are starting chemotherapy for the first time and also for those who have not responded to other CLL therapies. It is administered with fludarabine and cyclophosphamide for the treatment of CLL. Rituximab is manufactured by Genentech.

The FDA is initiating a risk-management program for **erythropoiesis-stimulating agents** (ESAs) for the treatment of chemotherapy-related anemia. The drugs, which include epoetin alfa (Procrit®, Epogen®) and darbepoetin alfa (Aranesp®), have been associated with accelerated tumor growth and higher mortality rates in some cancer patients. The Risk Evaluation and Medication Strategy (REMS) requires that patients receive a medication guide on safety issues associated with the drugs and requires training and certification of health care professionals who administer chemotherapy to patients with cancer and counseling of patient regarding the risks of the drugs. The REMS does not currently apply to patients being treated with an ESA for anemia due to other conditions, specifically renal failure. ■