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INSIDE

What Do We Really Know About Adiponectin?

ABSTRACT & COMMENTARY

Synopsis: *Measures that increase adiponectin levels might be valuable targets for decreasing the risk of atherosclerosis present in patients with diabetes.*

Source: Schulze MB, et al. *Diabetes Care*. 2004;27:1680-1687.

Patients with diabetes have a markedly increased risk of fatal coronary artery disease. This risk has mainly been attributed to hyperglycemia, dyslipidemia, and inflammatory mechanisms. Adiponectin, which is synthesized in adipose tissue, appears to play a role in all of these pathways. It has been found to be a major modulator of insulin action and resistance, have inflammatory properties, and influence lipid metabolism. Previous studies, however, have not evaluated the relationship between adiponectin and an array of complex metabolic abnormalities observed in diabetes.

This study examined the association between plasma levels of adiponectin and HbA1c, blood lipids, and inflammatory markers. Blood samples were obtained from 741 participants in the Health Professionals Follow-up Study with a diagnosis of type 2 diabetes.

Plasma adiponectin levels were positively correlated with HDL cholesterol and negatively correlated with triglycerides, apoprotein-B100, C-reactive protein (CRP), and fibrinogen. These associations were not appreciably altered after controlling for lifestyle exposures, and obesity associated variables. A 10 mg/mL higher level of adiponectin was associated with significantly lower level of HbA1c, triglycerides, apoB-100, CRP, and fibrinogen and higher HDL cholesterol. Associations between adiponectin and inflammatory markers were independent of HbA1c and HDL cholesterol suggesting that the inflammatory properties are not mediated by effects of glycemic control and blood lipids. The results were consistent among obese and non-obese men.

The study supports the hypothesis that increased adiponectin levels might be associated with better glycemic control, better lipid profiles, and reduced inflammation in diabetic subjects. Further, measures that increase adiponectin levels might be valuable targets for

VOLUME 26 • NUMBER 15 • AUGUST 15, 2004 • PAGES 113-120

decreasing the atherosclerotic risks in patients with diabetes.

COMMENT BY RALPH R HALL, MD, FACP

In a comprehensive review of "Adipose Tissue as an Endocrine Organ" Kershaw and Flier note that, in the past, we viewed adipose tissue as a depot for the storage of energy.[1] Subsequently we found that fat was a major site for steroid metabolism and in 1994, the identification and characterization of leptin established adipose tissue as an endocrine organ. We now know that adipose tissue expresses and secretes a variety of bioactive peptides that act at both local and systemic sites. Excesses and as well as deficiencies in adipose tissue stores, like those seen in HIV patients after treatment with antiviral therapy, have harmful and metabolic consequences.[1]

Kershaw's and Flier's review points out that besides adipocytes, adipose tissue contains connective tissue matrix, nerve tissue, stromovascular cells and immune cells. Many of the peptides that are secreted by adipose tissue are derived from the non-adipocyte fraction. There are at least 18 adipocyte-derived proteins with endocrine function. In addition there are receptors for the traditional endocrine hormones such as insulin, glucagon, growth hormone, thyroid hormone, androgens, estrogens, etc.

Adiponectin is present in different isoforms and has different receptors in muscle and liver. The effects are modified by the plasma concentrations, and by the different isoforms and tissue-specific receptors.

Administration of adiponectin to primates corrects insulin resistance, improves dyslipidemia, and decreases inflammatory markers. Blood levels increase with weight loss and the administration of insulin sensitizing drugs.

Plasma adiponectin levels decline before the onset of obesity and insulin resistance. This suggests that adiponectin contributes to the pathogenesis of these conditions.

As the study by Schultz and colleagues suggests, modulating adiponectin levels is a promising approach to the management of the complications of type 2 diabetes and the metabolic syndrome. ■

Reference

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Internal Medicine Alert, ISSN 0195-315X, is published twice monthly by American Health Consultants, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

EDITORIAL GROUP HEAD: Lee Landenberger.

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ASSOCIATE MANAGING EDITOR: Leslie Hamlin.

GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

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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United States
1 year *with* free AMA Category 1 credits: $299
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Internal Medicine Alert has been approved by the American Academy of Family Physicians as having educational content acceptable for prescribed credit hours. Term of approval covers issues published within one year from the beginning distribution date of January 1, 2004. This volume has been approved for up to 45 prescribed credit hours. Credit may be claimed for one year from the date of this issue.
The program is also approved by the American Osteopathic Association for 40 Category 2B credit hours.
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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Herbal Medications and Surgery: How Much Do Patients Tell Us?

ABSTRACT & COMMENTARY

Synopsis: *Herbal medication use is quite common among surgical patients. This pattern is consistent with the recent substantial increase in the use of alternative medical therapies.*

Source: Adusumilli PS, et al. *J Am Coll Surg*. 2004;198: 583-590.

THIS STUDY WAS AIMED AT IDENTIFYING THE PATterns of use of herbal medications in patients undergoing surgery. It was designed as a prospective study

using a simple questionnaire in surgical patients 18 years or older, presenting for elective surgery to a New York City hospital over a 10-week period. The survey utilized was developed on the basis of a literature search aimed at determining the types of herbal medicines commonly used in the United States that had been documented to have interactions in the perioperative period in surgical patients.

A total of 3362 eligible participants were approached preoperatively to complete the questionnaire with a response rate of 65%. Fifty-seven percent were women, 73% college educated, 72% non-smokers and 58% belonged to the higher income group. Fifty-seven percent of respondents admitted using herbal medications at some point in their life; 38% had consumed herbal preparations in the 2 years prior to the procedure and 16% continued to use herbal medicine during the month of their surgery.

Herbal medicines were more commonly consumed by those patients undergoing gynecological surgery (52%) and the lowest (10%) in those undergoing vascular surgery procedures. An important observation was the fact that a significantly higher number of patients who used herbal medications did not have a primary care physician ($P = 0.005$). Those patients that had a good perception of their health status were more likely to take herbal medications than those who had a poor or average self-rating of their health.

Among those patients taking herbal medication, only 7% volunteered their herbal medicine consumption history to their health care providers. A good number of patients (17%) preferred taking herbal medications because of their dissatisfaction with conventional health care. The prevalence of alternative therapies was ascertained in those patients that answered the survey demonstrating chiropractic, acupuncture, hypnosis, homeopathy, and spiritual healing practices among others.

COMMENT BY JOSEPH VARON, MD, FACP, FCCP, FCCM

Complementary and alternative medicines (CAM) are gaining increased interest among American patients.[1] It is not surprising that many illnesses, including those requiring surgery, might lead patients to seek alternative and complimentary medicine therapeutics.

The practice of CAM in its traditional form requires individualized therapy. In the paper by Adusumulli and associates, an attempt to identify the patterns of utilization of herbal medicines as a form of CAM is accomplished. It is surprising to find out that a large number of patients presenting for elective surgery either were currently consuming herbal medications or had done so in the 2 years prior to the surgical procedure.

What is probably more important for the primary care clinician is the fact that most patients did not "volunteer" the information to their health care providers. Many herbal medications have been shown to interfere with the pharmacokinetics of a variety of medications and anesthetic agents.[2] In addition, many herbal medications have been associated to a variety of potentially lethal reactions.[3]

This paper is also important because it reinforces the concept of self-medication. Many patients in this survey did not have a primary care provider. Clearly, CAM and the use of herbal medications probably have a role in modern medicine. However, clinicians must be astute and inquire about the use of these agents due to their potential toxicity. ■

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Dr. Varon is Professor at the University of Texas Health Science Center in Houston.

Laparoscopy for Primary Colorectal Cancer Resection

ABSTRACT & COMMENTARY

Synopsis: *In a prospective, randomized trial, primary excision of colorectal carcinomas by laparoscopic surgery was compared with laparotomy. Disease recurrence and 5-year survival were not significantly different in the 2 groups. Operative time was greater for those receiving laparoscopic approach but post-operative recovery and hospital stays were shorter.*

Source: Leung KL, et al. *Lancet*. 2004;363:1187-1192.

The primary surgical approach to colorectal carcinoma remains the single greatest chance of cure. Laparoscopic resection of this disease has been used since 1991 and it has been shown to improve postoperative recovery and reduce surgical stress. However, due to concerns regarding the adequacy of disease control and long-term survival, this procedure is only recommended for colorectal cancer as part of a clinical trial. Leung and colleagues from the Department of

Surgery at the Chinese University of Hong Kong conducted a randomized controlled clinical trial with the goal of demonstrating that the survival rates are similar after laparoscopic and open resection for rectosigmoid carcinoma. Between 1993 and 2002, 403 patients with rectosigmoid cancer seen at the Prince of Wales Hospital and the United Christian Hospital in Hong Kong, were randomized to receive either laparoscopic assisted (n = 203) or conventional open (n = 200) sigmoid colectomy. Disease-free interval and overall survival were analyzed post-operatively.

After curative resection, the 5-year survival rate for the laparoscopic group was slightly greater than that of the open resection group (76.1% vs 72.9%). However, patients in the laparoscopic resection group had a slightly lower probability of being disease free at 5 years than those in the open resection group (75.3% vs 78.3%), but neither of these findings was significant. The postoperative recovery for the laparoscopic group was significantly better, but the operative time for the laparoscopic procedure was significantly longer and the direct cost was greater. The overall morbidity and operative mortality was the same between the 2 groups.

COMMENT BY WILLIAM B. ERSHLER, MD

Laparoscopic surgical procedures have evolved dramatically over the past decade and, at many sites, have supplanted the need for open surgeries and the inherent associated costs in terms of postoperative morbidity and lengthy recovery. The concern that appropriate wide excision and regional node sampling would be compromised by the procedure has delayed its widespread use for primary colon cancer surgery. In the current randomized clinical trial the results of laparoscopic excision were analogous to open laparotomy in terms of disease recurrence and overall survival. Thus, it would seem perfectly reasonable to recommend this approach.

However, when it comes to changing standing surgical approaches in oncology, the pace is very slow. Take for example how long it took for surgeons to abandon the radical mastectomy in favor of the modified mastectomy or even lumpectomy (with axillary node sampling). Thus, despite this relatively large trial published in a first-line journal, it would be surprising to see surgeons abandon their standard approach. Furthermore, the results from this single institution at which the participating surgeons obviously have extensive experience in laparoscopic techniques cannot readily be translated to community practice where the experience may be limited. Thus, the report is of great interest. Hopefully, surgical oncology training programs will evolve in such a way that this methodology will be familiar to a greater number of practicing surgeons and laparoscopic procedures will be considered for patients in whom such an approach is considered appropriate. ■

Dr. Ershler is Director, Institute for advanced Studies in Aging, Washington, DC.

Risk of *Clostridium difficile* Diarrhea Among Hospital Inpatients Prescribed Proton Pump Inhibitors

ABSTRACT & COMMENTARY

Synopsis: *Although PPIs are considered to be among the safest of drugs, these studies suggest that PPIs increase the risk for hospitalized patients to develop C.* difficile*-related diarrhea.*

Source: Dial S, et al. *CMAJ*. 2004;171:33-38.

DIAL AND COLLEAGUES POINT OUT THAT *Clostridium difficile* is the most common form of nosocomial infectious diarrhea in the Western world, apparently increasing in frequency, severity, and consequential health care costs (more than 1 billion dollars in the United States annually). In general, pathogenesis of *C. difficile* is closely related to antibiotic-related changes in normal flora followed by overgrowth of the *C. difficile.* Decreased gastric acidity is known to be a risk factor for various infectious diarrheal illnesses, and this may also be true for *C. difficile* colitis. The first part of Dial et al's studies identified all patients at the Montreal Royal Victoria Hospital who received antibiotics over 9 months. *C. difficile*-related diarrhea developed in 6.8% of the patients, 9.3% of 591 patients who received PPIs, and 4.4% of 596 patients who did not receive these drugs. Since there was apparently more severe concomitant disease in the patient cohort that received PPIs, a second study was done at a separate teaching hospital where all patients with *C. difficile* and diarrhea were identified and matched by antibiotic class taken and age and inpatient ward with a general group of patients who had received antibiotics. Development of *C. difficile*-related diarrhea was associated with female sex (OR, 2.1; 95% CI 1.2-3.5), prior renal failure (OR, 4.3), previous recent hospitalization (OR, 2.6) and use of PPIs (OR, 2.7; CI 1.4-5.2).

COMMENT BY MALCOLM ROBINSON MD, FACP, FACG

Do PPIs directly cause what we have considered to be "antibiotic colitis" that has been associated with *Clostridium difficile*? There was one case identified in these patient populations who in fact did develop *C. difficile*-related diarrhea without any prior antibiotic administration. However, this scenario is clearly not common. On the other hand, it is certainly possible that *C. difficile*, like other intestinal pathogens, may be sensitive to inhibition by an acidic milieu. If so, potent gastric inhibition could facilitate successful GI colonization by exogenous *C. difficile*. Ten percent of patients who received antibiotics in the cohort segment of the study were receiving H2-receptor antagonists (vs 50% on PPIs). H2-receptor antagonist therapy did not increase risk for the development of *C. difficile*-related diarrhea. Since a great many hospitalized patients receive PPIs with little or no therapeutic justification, hospitals should consider the advisability of attempting to educate physicians to administer these agents only when clearly indicated. Additional studies should be done, including direct assessment of pH on viability of oral *C. difficile* inocula. ■

Pharmacology Update

Tinidazole Tablets (Tindamax™)

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

THE FDA HAS APPROVED A 5-NITROIMIDAZOLE FOR the treatment of trichomoniasis, giardiasis, and amebiasis. Tinidazole, a second-generation nitroimidazole antiprotozoal agent, is marketed as Tindamax™ by Presutti Laboratories.

Indications

Tinidazole is indicated for the treatment of trichomoniasis caused by *Trichomonas vaginalis* in both females and males. It is also indicated for the treatment of giardiasis and amebiasis (intestinal and amebic liver abscess) caused by *E. histolytica*. It is not indicated for the treatment of asymptomatic cyst passage.[1]

Dosage

For the treatment of trichomoniasis the recommended dose is a single 2 g dose taken with food. The sexual partner should be treated with the same dose at the same time.

For giardiasis the adult dose is a single 2 g dose taken with food. In pediatric patients (older than 3 years of age) the dose is a single 50 mg/kg dose (up to 2 g).

For intestinal amebiasis the adult dose is 2 g daily for 3 days with food, and for pediatric patients, 50 mg/kg/d (up to 2 g) for 3 days. For amebic liver abscess the recommended dose is 50 mg/kg/d with food (up to 2 g) for 3-5 days.

Alcoholic beverages should be avoided while on tinidazole and for 3 days thereafter.

Tinidazole is available as 250 mg and 500 mg tablets. The tablets can be ground to a fine powder and made into a suspension with artificial cherry syrup for pediatric use.[1]

Potential Advantages

Tinidazole has good in vitro activity against both metronidazole and metronidazole-resistant *T. vaginalis* and shown effectiveness against metronidazole-refractory vaginal trichomoniasis.[2,3] The elimination half-life of tinidazole is 12-14 hours, about twice that of metronidazole (6-7 hours), and may be better tolerated.[4]

Potential Disadvantages

As with metronidazole, tinidazole is contraindicated during the first trimester of pregnancy. Convulsive seizures and peripheral neuropathy has also been reported with these drugs. Approximately 38% of *T. vaginalis* isolates showed cross-resistance to metronidazole. Drugs that may interact with metronidazole may also interact with tinidazole (eg, alcohol, lithium, phenytoin, fosphenytoin, cyclosporine, tacrolimus fluorouracil, rifampin, phenobarbital, cholestyramine). Similar to metronidazole, tinidazole may produce transient leucopenia and neutropenia although no persistent hematological abnormalities have been observed in clinical trials. Total and differential leukocyte counts are recommended if retreatment is needed.[1] Common side effects include metallic/bitter taste, dyspepsia, weakness/fatigue/malaise, and vomiting.[1]

Comments

Tinidazole is a second generation 5-nitroimidazole similar to metronidazole. It has been established as an effective drug against trichomoniasis, giardiasis, and amebiasis. The cure rate for trichomoniasis for a single 2-g dose ranged from 80% to 100%.[1,5-8] The cure rate for tinidazole ranged from 80% to 100% for giardiasis, 86% to 93% for

intestinal amebiasis, and 81% to 100% for amebic liver abscess.[1,9,10] In general, tinidazole was equal to, or more effective than, metronidazole. In addition, these agents share similar side effects although some studies suggest that tinidazole is better tolerated.[4,8] The average wholesale cost for a 2-g dose of tinidazole is $18.24 which is significantly more expensive than generic metronidazole.

Clinical Implications

Trichomoniasis is a common sexually transmitted disease. It is estimated that there are about 7.4 million cases annually. Current treatment is metronidazole as a single 2 g dose. For patients that are not responsive, options have included an increase in the dose of metronidazole or multiple doses of the drug (eg, 500 mg twice daily × 7 days or 2 g for 3-5 days).[11] Tinidazole provides an effective alternative for patient intolerant of or not responsive to metronidazole. Tinidazole is also a convenient single dose alternative to metronidazole and furazolidone for giardiasis. ■

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CME Questions

4. **Which one of the following statements is *false*?**
   a. Adiponectin levels decrease prior to the development of insulin resistance.
   b. Adiponectin influences immune mechanisms through its action on lipoprotein metabolism.
   c. Adiponectin levels increase with weight loss and insulin sensitizers.
   d. Fat is the source of many hormones and the cells have receptors for other hormones such as thyroid, insulin, and glucagons.

5. **PPIs are most likely to increase the predisposition for the development of *Clostridium difficile*-related diarrhea in hospitalized patients by:**
   a. Stimulating the growth of endogenous *C. difficile* in the colon.
   b. Increasing the secretion of mucus and bicarbonate in the stomach, thus protecting orally acquired GI pathogens.
   c. Removing an effective acid barrier in the stomach that would ordinarily protect against successful inoculation of the gut with *C. difficile*.
   d. Improving antibiotic absorption, thus worsening disruptions of normal bowel flora
   e. Leading to fungal overgrowth, a co-factor for successful C. *difficile* proliferation.

6. **When comparing laparoscopic surgery to open resection of colorectal carcinoma, which of the following statements is not true?**
   a. Operative time was less for the laparoscopic group.
   b. Hospital stay was shorter for the laparoscopic group.
   c. Disease-free survival was comparable in both groups.
   d. Overall 5-year survival was comparable in both groups.

Answers: 4 (b); 5 (c); 6 (a)

By Louis Kuritzky, MD

Multivitamin Supplements and HIV Disease Progression and Mortality

The greatest burden of the HIV epidemic resides outside the United States. Especially in economically lesser-privileged nations, not all individuals who might benefit from antiretroviral (ARV) treatment can obtain it. Observational studies have suggested that micronutrient supplementation (MNS) might be a favorable immunomodulator in HIV, perhaps delaying disease progression. If this were confirmed with interventional studies, a delay in onset of advanced disease would reduce the number of individuals needing ARV. Of course, MNS is also markedly less costly than ARV.

HIV-infected pregnant women (n = 1078) were enrolled beginning in 1995. Women were assigned to vitamin A (30 mg beta carotene + 5000 IU preformed vitamin A), multivitamins excluding vitamin A (20 mg B1, 20 mg B2, 25 mg B6, 100 mg niacin, 50 µg B12, 500 mg vitamin C, 30 mg vitamin E, 0.8 mg folic acid), the combination of both, or placebo.

Investigators measured CD4, CD8, and CD3 counts, and viral load; typical symptoms and signs of HIV disease such as diarrhea, wasting, thrush, and angular cheilitis were also followed.

The primary outcome (death or stage 4 HIV disease) was statistically reduced by multivitamins (relative risk = 0.71), as were many of the individual HIV-related complications (eg, thrush, cheilitis). Vitamin A alone produced no measurable benefit, and the addition of extra vitamin A to the multivitamin regimen actually appeared to reduce some of the benefits of multivitamins alone. ■

Fawzi WW, et al. N Engl J Med. 2004;351:23-32.

The Long-term Outcomes of Sibutramine Effectiveness on Weight (LOSE Weight) Study

Clinical trials in research settings may not reflect accurately what clinicians in a non-academic milieu may anticipate, despite using the same fundamental pharmacologic tools. Drug efficacy is sometimes distinguished from drug effectiveness by defining the former as data from randomized trials, and the latter as results in the typical practitioner's settings.

The United States Preventive Services Task Force has encouraged diet, behavioral interventions, and pharmacologic treatment as reasonable evidence-based management choices for obesity. Sibutramine (SIB) is an FDA approved tool for adjunctive pharmacotherapy of obesity, and clinical trials confirm its durable efficacy (2 years duration). Porter and colleagues studied the effectiveness of SIB in a group-model HMO.

All of the participants (total n = 588) participated in an educational program for weight management, including seminars and visits with prevention specialists. Half of the group also received SIB, beginning with 10 mg daily, increased to 15 mg daily if the patient had not lost at least 4 pounds at the and of the first month of treatment. Sibutramine dose was decreased to 5 mg if adverse effects on pulse or BP occurred.

At 6 months, weight loss in the SIB group was substantially greater than the comparator group (6.87 kg vs 3.1 kg); this disparate success was evidenced at 1 year, with maintenance of weight loss still superior in recipients of SIB. These results closely reflect data generated by academic clinical trials. The efficacy and effectiveness of SIB appear comparable. ■

Porter JA, et al. Am J Manag Care. 2004;10:369-376.

Trial of Atorvastatin in Rheumatoid Arthritis (TARA)

Modulation of lipid levels appears to be the primary mechanism for beneficial effects of statins upon cardiovascular disease. At the same time, statins have been demonstrated in-vitro to impact on numerous aspects of inflammatory pathways, such as adhesion molecule expression and leukocyte cytokine release; similarly, vascular effects including smooth muscle apoptosis and endothelial cell function have been shown.

It has been suggested that the exaggerated cardiovascular risk associated with rheumatoid arthritis (RA) might be mediated to some degree by inflammatory pathways common to both rheumatoid arthritis and the vasculopathy. Based upon promising animal data, a study in human RA (n = 116) was undertaken to specifically examine the effects of atorvastatin (vs placebo) upon 1) a rheumatoid disease activity score (primary outcome), and 2) various secondary outcomes, including laboratory data (CRP and ESR), swollen joint count, and others. Atorvastatin was administered in a dose of 40 mg daily, in addition to traditional RA disease-modifying therapy.

After 6-months treatment there was a statistically significant improvement in the RA disease actvity score, CRP, ESR and swollen joint count. There was no adverse event signal amongst atorvastatin subjects greater than placebo. Statins may have a role in attenuating cardiovascular risks in RA through both modulation of inflammatory processes and dyslipidemia. ■

McCarey DW, et al. Lancet. 2004;363:2015-2021.

The P Holds the Key

By Ken Grauer, MD

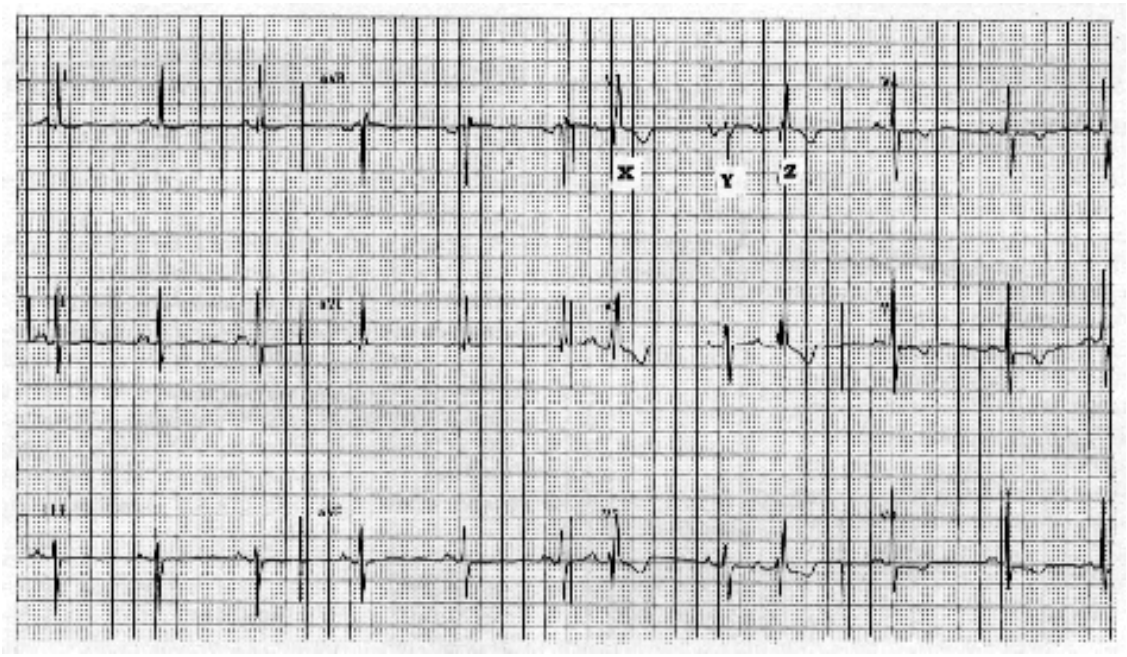

Figure. 12-lead ECG obtained from a 79-year-old woman with "skipped beats."

Clinical Scenario: The ECG in the Figure was interpreted as showing PVCs (premature ventricular contractions) and chamber enlargement. Do you agree? Can you identify at least four findings "keyed by the P" in this ECG?

Interpretation/Answer: The underlying rhythm on this tracing is sinus, as indicated by the presence of an upright P wave preceding each QRS complex in lead II. There are two widened and abnormal appearing beats seen in simultaneously recorded in leads V_1, V_2, V_3 (labeled X and Z). Sandwiched between these two beats is a normal, sinus conducted impulse (beat y). The two abnormal appearing beats are *not* PVCs. Instead they are PACs (premature atrial contractions) conducted with RBBB (right bundle branch block) aberration. Premature P waves precede beats X and Z, and hold the key for this definite diagnosis.

P wave morphology in this tracing suggests other findings. Distinct notching and slight prolongation of the P wave in lead II, as well as the deep negative component to the P wave of the normal sinus conducted beat in lead V_1 (beat y) is strongly suggestive of LAE (left atrial enlargement). The prominent point to the small amplitude initial positive deflection of this P wave preceding beat y also suggests the possibility of clearly also suggests the possibility of RAE (right atrial enlargement), although this much more subtle finding is clearly a less reliable indicator of RAE than would be the finding of tall peaked P waves in the inferior leads (which is not seen here).

The other noteworthy finding on this tracing is shallow symmetric T wave inversion in leads V4 through V6, which may indicate ischemia. Note that T wave inversion is *not* seen in the normally conducted beats (under y) in leads V_1, V_2, and V_3. Here again, the "P holds the key" because the PAC preceding beats X and Z tells us that these QRS complexes are aberrantly conducted, which means that the deep T wave inversion following these beats can not be interpreted as indicative of ischemia. Thus, there is evidence of ischemic T wave inversion, but only in the lateral precordial leads (V_4-V_6), and not in leads V_1, V_2, and V_3. ■

In Future Issues:

Treatment of Depression: When Do Symptoms Go Away?

PHARMACOLOGY WATCH

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The Importance of Publishing Negative Clinical Studies

Sources of funding for pharmaceutical research has come under scrutiny in the last decade as academic and government sources of funding have become increasingly scarce and the pharmaceutical industry has become the main source of research dollars. But the issue of objectivity has been raised, and some have even suggested that negative studies, that is studies that show a drug in an unfavorable light, may never be published. The American Medical Association has recently tackled this issue and has asked the department of Health and Human Services to establish a public registry of all clinical trials in United States. The registry would include information regarding the design of the study and the questions to be addressed. The registry would also contain data about the study results, both positive and negative. Some members of Congress have indicated interest in pursuing legislation to create such a registry, and even large pharmaceutical companies such as Merck and GlaxoSmithKline support the concept. But despite the AMA's valid concerns, several negative studies have been newsworthy in the last 2 months. This issue of *PharmWatch* highlights a few of those.

Cognitive Effects of Estrogen Therapy

Two studies in the *Journal of the American Medical Association* suggest that estrogen alone therapy may be associated with a decline in cognitive function in post-menopausal women and may increase the risk of dementia. Both studies are follow-ups from the Women's Health Initiative Memory Study (WHIMS) which had previously shown that estrogen plus progesterone therapy increases the risk of dementia in postmenopausal women. The first study was a follow-up of nearly 3000 women randomized in a double-blind fashion to conjugated estrogen, conjugated estrogen plus progesterone, or placebo. In the estrogen alone wing, 28 women taking estrogen developed probable dementia vs 19 assigned to placebo (HR, 1.49; 95% CI, 0.83-2.66). Similar rates were noted in the estrogen plus progesterone wing. When data were pooled for both estrogen and estrogen plus progesterone, the overall hazard ratio for dementia was 1.76 (95% CI, 1.19-2.60; P = .005). Increased risk of mild cognitive impairment was also noted in the estrogen alone group and the estrogen plus progesterone group. When the data were pooled, the hazard ratio for mild cognitive impairment was 1.25 (95% CI, 0.97-1.60). This study showed that there is no difference between estrogen alone vs estrogen plus progesterone therapy in the risk of dementia or mild cognitive impairment, and in fact, both therapies increase the risk of both these end points (*JAMA*. 2004;291:2947-2958). The second study asked whether estrogen alone alters global cognitive function in postmenopausal

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women. During a mean 5.4 years of follow-up, nearly 3000 women were randomized to 0.625 mg of conjugated estrogen or matching placebo per day. The women were assessed annually with the Modified Mini-Mental State Examination. The data showed that testing scores were 0.26 units lower among women assigned to conjugated estrogen compared to placebo (P = .04). When the data for estrogen alone was pooled with estrogen plus progesterone, the decrease was 0.21 (P = .006). The adverse effect of hormone therapy was more pronounced in women with low baseline cognitive function. The authors conclude that for women age 65 and older, hormone therapy, including estrogen alone therapy, had an adverse effect on cognition (*JAMA*. 2004;291:2959-2968). As pointed out in the accompanying editorial (*JAMA.* 2004;291:3005-3007), this study did not look at women who took estrogen in the years immediately following menopause. Previous observational data have suggested that there is a critical period just after menopause during which estrogen may be neuro-protective (*JAMA*. 2002;288:2123-2129). However, these current studies seem to conclusively show that neither estrogen nor estrogen plus progesterone are neuroprotective for older women.

Vitamin Therapy and Restenosis

Vitamin therapy to lower homocysteine levels has been touted as an effective way to prevent restenosis after coronary angioplasty. A new study, however, suggests that vitamin combination may actually increase the risk of restenosis in these patients. In a double-blind, placebo-controlled study from Germany and the Netherlands, 636 patients who had undergone successful coronary stenting were randomized to a combination of 1 mg of folic acid, 5 mg of vitamin B, and 1 mg of vitamin B12 intravenously, followed by daily oral doses of the 3 vitamins for 6 months; or to placebo. In a follow-up, the mean luminal diameter was significantly smaller in the vitamin group and placebo group (P = .008), and the extent of luminal loss was greater (P = .004). The restenosis rate was also higher in the vitamin group than the placebo group (34.5% vs 26.5%, P = .05). A higher percentage of patients in the vitamin group also required target vessel revascularization (P = .05). The authors conclude that contrary to previous findings, the administration of folate, vitamin B-6, and vitamin B12 after coronary stenting, may increase the risk of in-stent stenosis (*NEJM*. 2004;350:2673-2681).

Echinacea and the Common Cold

Echinacea purpurea, the commonly prescribed herbal remedy, may have no effect on the common cold, according to a new study. In this randomized, double-blind, placebo-controlled trial, 128 patients with early symptoms of the common cold were randomized to 1 mg of Echinacea or lactose placebo 3 times per day for 14 days or until cold symptoms were resolved, whichever came first. No statistically significant difference was observed between treatment groups for either a total symptom score (P range for symptoms = .29-.90) or mean individual symptom scores (P range = .09-.93). The time toward resolution of symptoms is not statistically significant between the 2 groups (*Arch Intern Med.* 2004;164:1237-1241). The authors admit, however, that testing different preparations and dosing ranges of Echinacea may be needed to confirm these findings.

Effects of Paxil in Children Under 18

GlaxoSmithKline has been accused of suppressing negative data about its antidepressant paroxetine (Paxil), showing that it is broadly ineffective in children and adolescents, and could increase the risk of suicidal behavior. The accusation comes in the form of a lawsuit from New York Attorney General Eliot Spitzer, who filed the suit in early June accusing the company of fraudulently suppressing the data. In response, Glaxo has published several studies on its web site, and states that these studies had previously been published in journals or presented at scientific meetings. The company also reiterates that paroxetine is not approved for treatment of patients 18 years or younger, and states that they do not promote off-label use of their products. The British firm has released data from 9 pediatric trials, as well as the bibliography of public communications derived from the studies, and letters to United States physicians summarizing the data. As mentioned earlier, GlaxoSmithKline, has stated publicly, it's support of the American Medical Association's proposal to create a national registry of all proposed pharmaceutical studies. More information is available at www.gsk.com/media.

FDA Actions

Schering has received approval from the FDA to market a new low dose estrogen patch for the treatment of osteoporosis. The patch, which is dime sized, is applied once a week, and delivers 14 micrograms per day of estradiol. It will be marketed this summer under the trade name Menostar. ■