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Smoking and Lung Function of Lung Health Study Participants after 11 years

ABSTRACT & COMMENTARY

Synopsis: *Continuing smokers from the Lung Health Study 1 followed for a period of 11 years demonstrated a greater decline in lung function when compared to sustained quitters.*

Source: Anthonisen NR, et al. *Am J Respir Crit Care Med*. 2002;166: 675-679.

THE LUNG HEALTH STUDY 3 (LHS 3) WAS DEVELOPED AS AN extension of the Lung Health Study 1 (LHS 1). The LHS 1 was a randomized, clinical trial of smoking cessation and regular administration of an inhaled bronchodilator (ipratropium bromide) conducted for a period of 5 years. The study was conducted in 5887 middle-aged smokers (35-60 years of age at study entry) who had airway obstruction (FEV_1/FVC ratio less than 70%), but who were otherwise healthy. The follow-up rate in LHS 1 was very high, with more than 90% of participants attending each of the 5 annual visits to evaluate pulmonary function, and thus an extension of the LHS 1 was thought to be feasible. The original participants were asked to return to their original clinical centers for reassessment approximately 11 years after their enrollment.

The objective of the LHS 3 was to assess whether differences in pulmonary function and smoking habits persisted between the 2 groups after 1 year and to determine if the profound effect of smoking cessation on lung function decline noted in LHS 1 persisted.

LHS 1 participants who were not deceased were enrolled in the LHS 3. They were asked to return for spirometry and to answer smoking questionnaires. Some participants were visited to obtain data. Smoking issues were addressed through questionnaires, which included the modified American Thoracic Society-Division of Lung Diseases questionnaire and a detailed smoking history. Smoking status was checked by measuring expired carbon monoxide. Results of 10 ppm or higher were considered indicative of smoking.

Spirometry was performed with the same type of spirometer used

VOLUME 24 • NUMBER 3 • FEBRUARY 15, 2003 • PAGES 17-24

in the LHS 1. FEV_1 and FVC were measured before and after 2 puffs (200 μg) of albuterol from a metered dose inhaler.

Patients continued to be grouped in the same 2 groups as in LHS 1. This consisted of usual care and smoking intervention. The smoking intervention group received smoking cessation counseling. They were also assigned to either active bronchodilator or placebo therapy during the original LHS 1. Smoking outcome was categorized as sustained quitter, intermittent quitter, or continuing smoker.

There were 4517 participants enrolled for LHS 3. Enrollment ranged from 77.1% to 91.0% at the various clinical centers. Younger, male patients who still continued to smoke were more likely to refuse enrollment in LHS 3. Nonenrollees were also less likely to be married. There were no significant differences in employment rate, alcohol consumption, and years of education between groups.

At LHS 3 enrollment, 16.7% of the participants were sustained quitters, 57.4% were intermittent quitters, and 25.9% were continuing smokers. There were major differences between treatment groups in smoking habit with 21.9% of the smoking intervention group being sustained quitters compared with 6.0% of the usual care group, and 23.4% of the smoking intervention group being continuous smokers in contrast to 31.3% of the usual care group ($P = 0.001$). At the LHS 3 visit, 48.8% of all participants were not smoking, with 51.7% of the smoking intervention group and 42.9% of the usual care group in this category.

For the 11 years, the FEV_1 of the usual care group declined by 587 mL (12.3% of predicted normal value), whereas that of the smoking intervention group declined by 502 mL (9.3% of predicted normal value). There was a strong relationship between smoking history and decline in pulmonary function. For smoking intervention and usual care participants combined, sustained quitters lost less than 27 mL/y (0.22% of predicted normal value), intermittent quitters lost approximately 48mL/year (approximately 0.91% of predicted normal), continuing smokers lost 60 mL/y (1.3% of predicted normal value). Over the 11 years of observation, the mean difference in FEV_1 between continuing smokers and sustained quitters was approximately 0.5 L, or 14% of the predicted normal value.

COMMENT BY DAVID OST, MD, AND NAJMA USMANI, MD

Chronic obstructive pulmonary disease (COPD) is a major and growing health problem throughout the world. The principal etiologic factor, and by far the most potent one, cigarette smoking, has been associated with this disease for decades. Classic studies by Fletcher and associates[1] have shown that smoking cessation usually mitigates the rate of decline of lung function. The LHS 1, which was a landmark study in COPD research, documented the decline in lung function related to smoking.[2]

The LHS 3 documents and further emphasizes the deleterious effect that smoking has on lung function. Differences in lung function between participants who quit smoking and those who did not increased progressively over 11 years, resulting in substantial differences in FEV_1 values.

Sustained quitters had a rate of decline in lung function similar to never smokers, which were significantly lower than in continuing smokers. LHS 3 also demonstrated that loss of lung function in continuing smokers is similar between the sexes as has been noted in other

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

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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: $20. 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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1 year *with* free AMA Category 1 credits: $289
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The program is also approved by the American Osteopathic Association for 40 Category 2B credit hours.

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studies.[3] This emphasizes that smoking cessation is the first and most important clinical intervention in smokers with mild airway obstruction. ■

Dr. Usmani is a Fellow, Pulmonary and Critical Care, North Shore University Hospital and Nassau University Medical Center, East Meadow, NY.

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Use of Selective Serotonin Reuptake Inhibitors and Risk of Upper Gastrointestinal Tract Bleeding

ABSTRACT & COMMENTARY

Synopsis: *SSRIs increase the risk of upper gastrointestinal bleeding, and this effect is potentiated by concomitant NSAID or aspirin use.*

Source: Dalton S, et al. *Arch Intern Med*. 2003;163:59-64.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) have become extremely popular in the past 2 decades due to efficacy along with absence of significant toxicity. This Scandinavian study involved 26,005 users of antidepressants in the county of North Jutland, Denmark (total population of 490,000). SSRIs produced a 3.6-fold increase in the risk of upper GI hemorrhage (55 hospitalizations vs the expected 15.3), and their use along with NSAIDs increased risk to 12.2 fold. There were no increased risks of upper GI bleeding associated with use of antidepressants without effects on serotonin receptors. Dalton and colleagues speculate that this effect relates to the critical role of serotonin release by platelets in the overall hemostatic process and to the inability of platelets to resynthesize depleted serotonin stores.

■ COMMENT BY MALCOLM ROBINSON, MD, FACP, FACG

This interesting report provides data on a previously generally unsuspected linkage between use of SSRIs and GI hemorrhage—as well as a reasonable pathophysiologic explanation for the observation. The investigation was undertaken because of an earlier case-control study of 1651 cases of GI bleeding and 10,000 matched controls that also described a 3-fold increased risk of upper GI bleeding among users of all types of SSRIs vs nonusers.[1] These 2 studies seem to provide compelling evidence of a relationship between this commonly used type of antidepressant medication and clinically important upper GI bleeding. Careful studies of platelet function should be undertaken to elucidate any measurable abnormality due to SSRI use. SSRIs are valuable drugs, but they may have this newly recognized and reported significant drawback. Further information is awaited with great interest. ■

Reference

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Fluoroquinolones and Tendinopathies

ABSTRACT & COMMENTARY

Synopsis: *The excess risk of Achilles tendon disorders attributable to fluoroquinolone use was estimated to be 3.2 cases per 1000 patient-years, with most of that increase accounted for by patients 60 years of age and older who concomitantly receive corticosteroids.*

Source: van der Linden PD, et al. Fluoroquinolones and risk of Achilles tendon disorders: Case-control study. *BMJ*. 2002; 324:1306-1307.

THE IMS DATABASE CONTAINING INFORMATION from UK general practices covering 1 million to 2 million inhabitants was queried in order to perform a nested case control study designed to examine risk factors for the development of Achilles tendon disorders (ATD) related to fluoroquinolone use. The cohort included 47,776 adults who had received a fluoroquinolone, of whom 704 (1.4%) had Achilles tendonitis and 38 (.08%) had Achilles tendon rupture.

This represented an overall excess risk of 3.2 cases per 1000 patient-years. The adjusted relative risk (RR) of ATD was 1.9 (95% CI, 1.3-2.6) for current fluoroquinolone use; there was no increased risk associated with recent (but not current) or remote past use. While there was no increased risk associated with current use among those younger than 60 years

of age, for those 60 years of age or older, the RR was 3.2 (2.1-4.9) and for those in this latter age group who were also receiving corticosteroids, the RR was 6.2 (3.0-12.8). Those with both risk factors, age older than 60 years and corticosteroid use, accounted for 87% of cases of ATD.

COMMENT BY STAN DERESINSKI, MD, FACP

A large increase in both fluoroquinolone use and nontraumatic tendon ruptures were observed in The Netherlands between 1991 and 1996.[1] It was concluded, however, that less than 7% of the increase in tendon ruptures could be attributed to the increase in fluoroquinolone use. Nonetheless, the epidemiologic and laboratory evidence demonstrates a strong causal relationship.

Fluoroquinolones are known to cause cartilaginous abnormalities in immature animals, such as beagle pups. Histologic changes in tenocytes of experimental animals exposed to fluoroquinolones include vacuolation of tenocytes and decrease in fibril diameter with an increase in the distance between individual collagenous fibrils. In vitro experiments indicate that fluoroquinolones stimulate matrix-degrading protease activity of fibroblasts while inhibiting fibroblast metabolism.

Much evidence supports the hypothesis that tendinopathy is the consequence of chelation of magnesium ions by fluoroquinolones—a class effect and the reason why simultaneous oral administration of magnesium-containing antacids and fluoroquinolones results in markedly impaired gastrointestinal absorption of the latter. Thus, both magnesium deficiency and ciprofloxacin administration can each cause similar biochemical changes in the Achilles tendons of immature dogs.

Fluoroquinolones remain highly effective antibiotics in most regions. The low incidence of tendon disorders should not preclude their use, especially when only a tiny fraction of these complications involve actual tendon rupture. Nonetheless, the recognition that patients older than age 60 years, especially those receiving corticosteroids, comprise those at significant risk should alert the clinician. An evaluation in The Netherlands in 1998 found that the median time from initiation of fluoroquinolone use to onset of tendon symptoms was 6 days.[2] It is unfortunate, of course, that these risk factors describe a large number of patients with underlying chronic obstructive lung disease who are at risk of acute bacterial exacerbations and who might benefit, on occasion, from fluoroquinolone therapy. Thus, if a fluoroquinolone is the treatment of choice in such a patient, it might be beneficial, albeit unproven, to correct any magnesium deficiency that might be present, with the hope that this would reduce the potential for development of a tendinopathy. ■

Dr. Deresinski is Clinical Professor of Medicine, Stanford University, Palo Alto, Calif.

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Pharmacology Update

Adalimumab—Humira

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

THE FDA HAS APPROVED A NEW ANTI-TUMOR NECROsis factor alpha (TNF alpha) drug for the treatment of rheumatoid arthritis (RA). Adalimumab, produced by recombinant DNA technology using a mammalian cell system, is a monoclonal antibody (IgG1) specific for human TNF alpha. It is a fully human antibody compared to infliximab, which is a chimeric antibody (75% human and 25% mouse). Adalimumab, which is administered as a subcutaneous injection every other week, is marketed by Abbott as "Humira."

Indications

Adalimumab is indicated for reducing the signs and symptoms and inhibiting the progression of structural damage in adults with moderately to severely active RA who have not adequately responded to one or more disease-modifying antirheumatic drugs (DMARDs). In may be used alone or in combination with methotrexate or other DMARDs.[1]

Dosage

The recommended dose is 40 mg given subcutaneously every other week. For those not taking methotrexate, dosing every week may be needed to achieve optimal effect.[1]

Adalimumab is supplied as a single-use prefilled syringe or single-use vial for patient or institutional use. The product should be refrigerated but not frozen.[1]

Potential Advantages

Adalimumab has been shown to inhibit the progression of structural damage in adults with moderately severely active RA with inadequate response to methotrexate. This study (n = 407) was assessed radiographically at 1 year and was expressed as change in erosion, joint space narrowing, and total score (erosion plus narrowing).[1] Significant differences were detected between patients on adalimumab and methotrexate compared to methotrexate and placebo. In a small, open label study of adalimumab monotherapy (n = 36), 42% showed no radiographic progression.[2] Adalimumab is given by subcutaneous injection every 2 weeks compared to twice weekly subcutaneous injections for etanercept and every 8-week intravenous infusions for infliximab.

Potential Disadvantages

The drug may affect the host defense against infections and malignancies. Active tuberculosis has been associated with TNF-alpha therapy including adalimumab.[1,5] Patients should be tested for latent tuberculosis and treated if needed before initiating anti-TNF therapy. A higher incidence of lymphomas and development of autoantibodies have also been observed. Forty-eight cases of malignancies and 10 cases of lymphoma were observed in 2468 patients treated with adalimumab for a median of 24 months. In controlled trials, 17% of patients developed antinuclear antibodies (ANA) compared to 7% of placebo-treated patients. One patient (out of 2334) developed lupus-like syndrome.[1] Adalimumab should be prescribed with caution in patients with preexisting or recent-onset CNS demyelinating disorders. Neutralizing antibody formation was more common with monotherapy (12%) than in combination with methotrexate (1%). The rate was also higher with every other week therapy compared with weekly therapy. Efficacy was lower in patients with neutralizing antibodies.[1] Injection site reaction (20%) is the most common side effect.

Comments

Adalimumab is a fully human monoclonal antibody with high and specific affinity for TNF-alpha thus preventing binding to its receptors. TNF-alpha is a proinflammatory cytokine believed to play an essential role in articular matrix degradation and progression of inflammatory synovitis.[3,4] Adalimumab produces a rapid decrease in acute phase reactants of inflammation (eg, C-reactive protein and erythrocyte sedimentation rate) and modulates cartilage and synovium turnover as measured by biological markers (eg, metalloproteinase, cartilage oligomeric matrix protein).[1,2,6] The efficacy and safety of adalimumab was assessed in 4 randomized, double-blind studies in adult RA patients. Efficacy was based on American College of Rheumatology (ACR20, ACR50, or ACR70). This represents a 20%, 50%, or 70% improvement in patient's tender joint count and swollen joint count plus the same percentage improvement or greater in at least 3 of the following criteria: 1) patient's pain assessment; 2) patient's global assessment; 3) physician's global assessment; 4) patient's self-assessed disability; and 5) acute-phase reactant (ESR or CRP). In placebo-controlled trials, ACR20 was 46% (vs 19%) for monotherapy at 6 months and 63% (vs 30%) and 59% (vs 34%) for combined therapy with methotrexate at 6 and 12 months, respectively.[1] These are similar to those reported for etanercept and infliximab.[4] Radiographic evaluation of disease progression was an additional primary end point in one of the randomized trial. This study demonstrated that patients who received adalimumab/methotrexate had less joint deterioration than those who received methotrexate alone. The effect of inhibition of TNF-alpha is an ongoing concern. Opportunistic infections, malignancies, autoantibodies, and demyelinating disease have been associated with anti-TNF-alpha therapy. The wholesale cost of adalimumab is about $1300 per month, which is similar to that of etanercept.

Clinical Implications

Adalimumab is the latest of the TNF-alpha inhibitors joining infliximab (chimeric monoclonal antibody) and etanercept (a soluble receptor). There are currently no published comparative trials among these agents. Efficacy as assessed by ACR criteria across studies appears to be similar among the 3 drugs. Whether there are true differences in efficacy (ACR and/or disease progression) and/or side effects remain to be determined. ■

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6. The findings of the Lung Health Study 3 include all of the following statements *except*:

a. Smoking cessation has a profound benefit on lung function.
b. Loss of lung function in continuing smokers is the same between the sexes.
c. Bronchodilators improved the rate of FEV_1 decline in smokers only.
d. Sustained quitters had a rate of decline in lung function similar to never smokers.

7. Antidepressants associated with increased risk of upper GI bleeding include which of the following types?

a. All antidepressants, regardless of their mechanism of action
b. GI bleeding is more common in depressed patients, whether they take any antidepressants
c. Antidepressants with a selective inhibitory action on norepinephrine uptake (eg, nortriptyline)
d. SSRI antidepressants
e. SSRI antidepressants plus antidepressants with a balanced action on serotonin and norepinephrine reuptake mechanisms

Answers: 6(d); 7(d)

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Internal Medicine Alert	0 1 9 5 - 3 1 5 X	10/14/02
4. Issue Frequency	**5. Number of Issues Published Annually**	**6. Annual Subscription Price**
Bi-Weekly	24	$239.00

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305 — Contact Person: Willie Redmond; Telephone: 404/262-5448

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*

Publisher *(Name and Complete Mailing Address)*: Donald R. Johnston, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

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Publication required. Will be printed in the February issue of this publication. ☐ Publication not required.

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By Louis Kuritzky, MD

Prostate Cancer Screening

In contrast to screening for breast and colon cancer, both of which have been demonstrated to reduce mortality, prostate cancer screening (PCS) has not yet been proven to favorably affect overall mortality, although some trials have found that PCS screening reduces prostate cancer-related mortality. Hence PCS has not met the same standard as other commonly used screening tools. Because of the discordance between the relative lack of supportive data to provide justification for PCS and the very high frequency of PCS testing, Ransohoff and colleagues sought to evaluate what factors promote PCS. That PCS can result in harm (eg, postsurgical impotence, incontinence) is clear; whether PCS can provide benefit (ie, reduction in mortality) remains to be demonstrated.

Ransohoff et al describe the PCS model as "lacking negative feedback:" a patient who undergoes PCS and has no cancer-suggestive findings feels reassured by these findings and is happy to have participated; a patient who has an elevated PSA often undergoes medical or surgical intervention. Even in the face of postintervention sequelae, the screened patient may feel that, ultimately, the intervention has spared his life, and he too may be grateful for the PCS.

Currently, whether PCS is mortality-effective is uncertain. Nonetheless, public satisfaction and enthusiasm for PCS remains high. It is conceivable that, in the long run, harm from PCS-stimulated intervention may outweigh benefit. Until the relative risks and benefits of PCS are more clearly defined, clinicians are well advised to review the decision path of PCS with patients *before* the process is embarked upon, in order that fully informed consent, dispassionately, may be attained. ■

Ransohoff DF, et al. Am J Med. 2002; 113:663-667.

Can We Trust Home BP Measurement?

The window of observation of blood pressure as obtained in the typical office setting has important limitations, with both exaggerations (ie, "white-coat" hypertension), and underestimates (ie, "masked hypertension") of hypertension burden being well documented. Abnormal circadian BP patterns, such as failure to experience the normal nocturnal decline in blood pressure, predict higher cardiovascular risk yet are not discerned by simple office measurement. Twenty-four-hour Ambulatory Blood Pressure Monitoring (ABPM) can resolve all 3 of these issues but is not without significant expense, and despite the endorsement of ABPM by the JNC VI report and the WHO guidelines, this technique remains only rarely used. Whether home blood pressure measurement, perhaps an intermediate step between office measurement and ABPM, is reliable is the subject of this report.

Bachmann and colleagues included 48 hypertensive patients from a single practice, who had been referred for 24-Hour ABPM. Subjects were randomly assigned to either a group which was asked to keep a personal log of the BP measurements recorded by the ABPM, and advised that their log would be checked for accuracy against that registered by the ABPM device, or a group who were also advised to periodically record BP measurements as registered by the ABPM device, but who were unaware that the ABPM automatically records and stores BP measurements. Discrepant results occurred when patient-recorded records either had an incorrect time, an incorrect BP value, or a BP was entered as recorded when the ABPM device had not performed such a measurement. Although patients unaware of the ABPM recording capacity were found to have more "fictional" registrations than the "informed" group (10/728 vs 29/616), ultimately these discrepant recordings did not confound the overall mean accuracy of averaged home blood pressure readings. ■

Bachmann LM, et al. J Clin Hypertens. 2002;4:405-407,412.

Systolic and Diastolic Dysfunction

Congestive heart failure (CHF) is typically classified as systolic (ie, reduced ejection fraction), diastolic (normal ejection fraction, with impaired ventricular filling), or both. Indeed, though CHF may have been generally conceptualized solely as "inadequate pumping," some degree of diastolic dysfunction accompanies almost all patients suffering systolic dysfunction. Additionally, isolated diastolic dysfunction, which may present with identical clinical symptoms as systolic dysfunction, has recently been recognized to be approximately as common as systolic dysfunction in patients with manifest CHF. Redfield and associates evaluated with doppler echocardiography adults older than 45 years of age participating in the Rochester (Minnesota) Epidemiology Project (n = 2042), none of whom entered the study with a diagnosis of CHF.

In this asymptomatic (for CHF) group, validated CHF prevalence was 2.2%, approximately equally divided between systolic and diastolic dysfunction. Diastolic dysfunction, whether mild, moderate, or severe, was found by multivariate analysis to be predictive of all-cause mortality. This trial indicates that diastolic dysfunction, previously regarded as more "benign" than systolic dysfunction, portends significant adverse health outcomes. ■

Redfield MM, et al. JAMA. 2003;289: 194-202.

A Special Wave

By Ken Grauer, MD

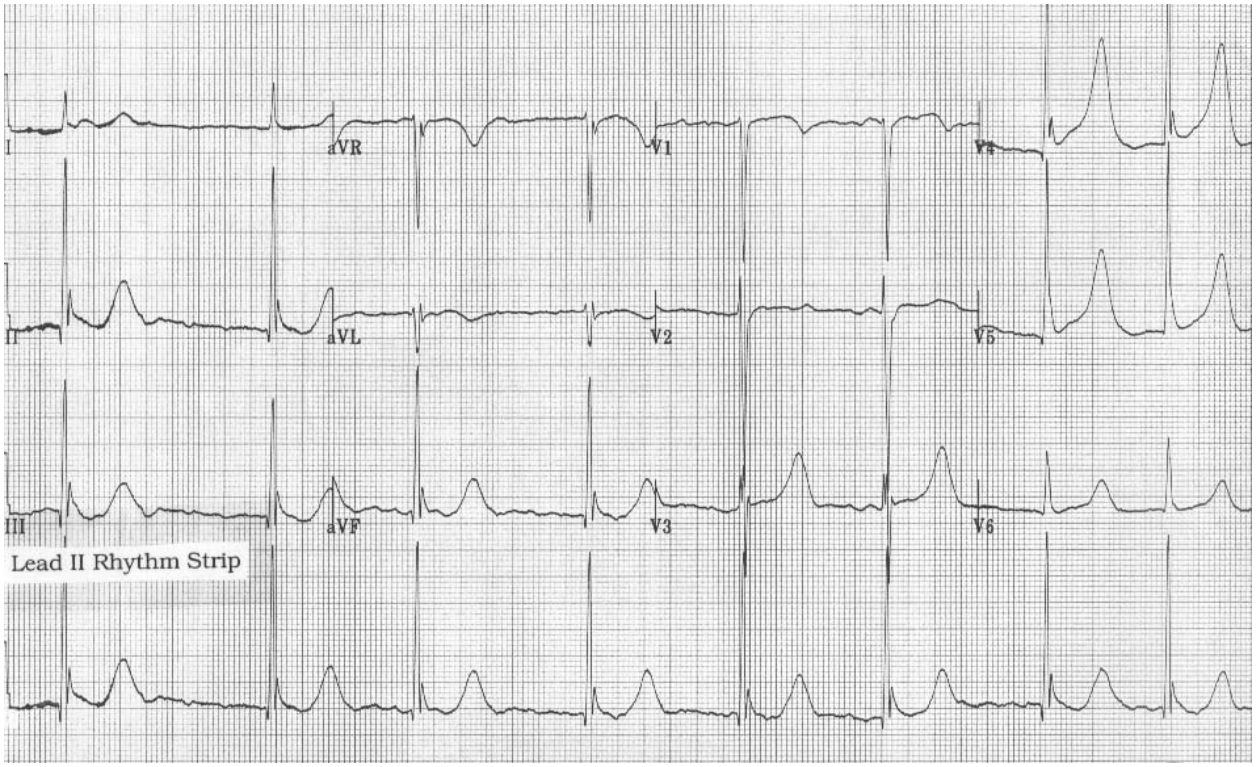

Figure. 12-lead ECG and accompanying rhythm strip obtained from a 68-year-old man admitted following a drug overdose.

Clinical Scenario: The ECG in the Figure was obtained from a 68-year-old man admitted to the intensive care unit (ICU) for a drug overdose. In view of his ECG, what vital sign needs to be checked? How many ECG findings consistent with this patient's clinical condition can you identify?

Interpretation: The ECG in the Figure manifests many of the features of hypothermia. The most commonly cited ECG finding of this condition is the elevated and very prominent J wave (also called the Osborne wave or camel-hump sign) that is especially well seen in the inferior leads and lead V4 of this tracing. The etiology of the Osborne wave is uncertain; it is most often seen when hypothermia is moderate to severe (core temperature less than 86°F or 30°C). In addition to the prominent J wave, three other features characteristic of hypothermia are also seen here: 1) bradycardia; 2) atrial fibrillation with a slow ventricular response; and 3) fine undulations in the baseline (attributable to muscle tremor). The patient in this case had a core temperature of 90°F on admission, though it was thought to be lower before his arrival to the Emergency Department. He had been found unresponsive in the street during the cold weather months after ingestion of unknown drugs the evening before. All ECG manifestations of hypothermia resolved following core rewarming. ■

In Future Issues: NSAIDs and GI Bleeding

PHARMACOLOGY WATCH

FDA Issues 'Black Box' Warning Based on WHI Study

The FDA has mandated a "Black Box" warning for all estrogen and estrogen/progestin products for use by postmenopausal women. The new warnings are based on analysis of data from the Women's Health Initiative (WHI) study that was published July 2002. The box warning emphasizes that these drugs have been associated with increased risks for heart disease, heart attacks, strokes, and breast cancer and that they are not approved for heart disease prevention. Wyeth Pharmaceuticals, the manufacturer of Premarin, Prempro, and Premphase, products that were used in the WHI study, are also required to change their indications to: treatment of severe vasomotor symptoms, vulvar and vaginal atrophy associated with menopause, prevention of postmenopausal osteoporosis, and should only be used when the benefit clearly outweighs the risk. The labeling will also be required to include consideration of other therapies for the atrophy and osteoporosis indications, and to recommend use of the lowest dose for the shortest duration possible. While Wyeth's products are the focus of this initial press release and FDA action, all estrogen products will be subject to new labeling. The FDA is also recommending future research to answer questions regarding the risks of lower-dose estrogen products and if other types of estrogens and progestins are associated with lower risk of CVD and breast cancer. The complete press release can be viewed at www.fda.gov.

ALLHAT: Thiazide for Hypertension Treatment

Thiazide diuretics should be considered first-line therapy for hypertension, according to the authors of the ALLHAT study published in December. In a finding that surprised nearly everyone (especially the sponsors of the study) in patients with hypertension and at least one other cardiovascular risk factor, the diuretic chlorthalidone was associated with better cardiovascular outcomes at less cost and with equal tolerability compared to a calcium channel blocker or an ACE inhibitor. ALLHAT enrolled more than 33,000 patients from 623 centers in the United States, Canada, and the US Virgin Islands. Patients were randomized to the calcium channel blocker amlodipine, the angiotensin-converting enzyme inhibitor lisinopril, or chlorthalidone. Mean follow-up was 4.9 years with the primary outcome being combined fatal CHD or nonfatal MI. Secondary outcomes included all-cause mortality, stroke, combined CHD, and combined cardiovascular disease (CVD). The 6-year rate of the primary outcome and all-cause mortality was virtually identical for all 3 drugs. Chlorthalidone was superior to amlodipine in preventing heart failure (10.2% vs 7.7%, RR, 1.38, 95% CI, 1.25-1.52) and was superior to lisinopril for lowering blood pressure and in 6-year rates of combined cardiovascular disease including stroke (6.3% vs 5.6%) and heart failure (8.7% vs 7.7%). With improved cardiovas-

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cular outcomes, lower cost, and equal tolerability, the study concludes that thiazide-type diuretics are superior in preventing one or more forms of CVD and that they should be the preferred agent in antihypertensive therapy, and should be included in all multidrug regimens (*JAMA*. 2002;288:2981-2997). An accompanying editorial calls ALLHAT "one of the most important trials of antihypertensive therapy" and suggests that national guidelines should be changed to emphasize use of thiazide diuretics as initial therapy (*JAMA*. 2002;288:3039-3042).

Candesartan Effective Against Migraines

The angiotensin II receptor blocker candesartan is effective in preventing migraine headaches, according to a new study. Norwegian researchers looked at 60 patients age 18-65 with 2-6 migraines per month. Patients were randomized in a double-blind placebo-controlled crossover study with the main outcome being number of days with headache. Secondary outcomes included use of pain medications and triptans, hours with headache, headache severity, and days lost from work. During the 12-week study, the mean number of days with headache was 18.5 with placebo vs 13.6 with candesartan (P = .001) in the intention to treat analysis (n = 57). Patients were considered a candesartan responder if they noted a reduction of 50% or more of days with headache (18 of 57 patients, 31.6%) or days with migraine (23 of 57 patients, 40.4%). Although this represented a minority of patients, those who did respond benefited from effective migraine prophylaxis. Candesartan's tolerability profile was comparable with placebo (*JAMA*. 2003;289:65-69).

Cough! No Cold Relief from Echinacea

Echinacea offers no benefit in treating the common cold according to a study from the University of Wisconsin. A total of 148 college students with recent onset colds were randomized to an encapsulated mixture of unrefined Echinacea (*E purpurea* herb and root and *E angustifolia* root) 6 times a day on the first day of illness and 3 times a day on the subsequent days up to a total of 10 days. The main outcome was the severity and duration of self-reported symptoms of URI. No statistically significant differences were detected between Echinacea and placebo groups for any of the measured outcomes, which included trajectories of severity over time or mean cold duration. No significant side effects were noted with Echinacea. The study concludes that no detectable benefit or harm could be found with Echinacea treatment for the common cold (*Ann Intern Med*. 2002;137:939-946).

COX-2 Inhibitors and GI Benefits Could Be Overrated

Could the GI benefits of COX-2 inhibitors be overrated? A new study suggests that the COX-2 inhibitor celecoxib is no safer than a combination of diclofenac plus omeprazole with regard to ulcer risk in patients with a history of peptic ulcer disease and arthritis. Researchers from Hong Kong recruited patients with arthritis and NSAID-related bleeding ulcers. After their ulcers had healed, 287 patients who were negative for *Helicobacter pylori*, were randomly assigned to receive celecoxib 200 mg twice a day plus placebo, or diclofenac 75 mg twice a day plus 20 mg of omeprazole for 6 months. Recurrent bleeding ulcer occurred in 7 patients receiving celecoxib and 9 receiving diclofenac/omeprazole (4.9% vs 6.4%). Renal adverse events including hypertension, peripheral edema, and renal failure occurred in 24.3% of patients receiving celecoxib and 30.8% of those receiving diclofenac/omeprazole. The authors suggest that neither regimen offered effective protection against recurrent ulcer complications or renal adverse effects (*N Engl J Med*. 2002;347:2104- 2110).

FDA Actions

Pfizer's new anti-migraine drug, eletriptan (Relpax) has been approved by the FDA for marketing. The drug that is available in 20-mg and 40-mg tablets has been shown to be effective in aborting migraine headaches within 2 hours. The company is marketing a 80-mg tablet in Europe, but the FDA refused to approve the higher dose due to an increase in adverse events.

Montelukast (Singulair), Merck's leukotriene inhibitor, has been approved by the FDA for the treatment of seasonal allergic rhinitis. The drug has been on the market since 1998 for the treatment of asthma in adults and children. This new indication is the first for a leukotriene inhibitor, and creates a new, nonantihistamine treatment modality for this indication. Montelukast was approved for symptoms of seasonal allergic rhinitis in adults and children aged 2 years and older. It is available in 10 mg strength for adults, and a chewable 4 mg or 5 mg strength for children. ■