Providing Evidence-based Clinical Information for 26 Years

INTERNAL MEDICINE ALERT®

A twice-monthly update of developments in internal and family medicine

Thomson American Health Consultants Home Page—www.ahcpub.com

CME for Physicians—www.cmeweb.com

THOMSON
AMERICAN HEALTH CONSULTANTS

INSIDE

Ironing Out the Risk Factors for Diabetes

ABSTRACT & COMMENTARY

Synopsis: *Increased iron stores (eg, ferritin levels) are associated with an increased risk of type 2 diabetes in women.*

Source: Jiang R, et al. *JAMA*. 2004;291:711-717.

This paper comes from the Nurses' Health Study, a prospective evaluation of more than 120,000 registered nurses recruited between 1989 and 1990. This cohort has been described elsewhere;[1] in brief, it consists of healthy women, aged 30-55 years at baseline. The current study includes 698 women from the Nurse's Health Cohort who developed diabetes between 1990 and 2000. Controls were also drawn from the Nurses' Health Cohort, and were matched for age, race, fasting blood work results at study entry, and Body Mass Index (BMI). The definition of diabetes was in flux during this study. For cases identified prior to 1998, it was based on the National Diabetes Data Group criteria,[2] but beginning in 1998, it was based on the report of the American Diabetes Association.[3] Essentially, this resulted in a change in threshold of fasting glucose from 140 mg/dL to 126 mg/dL. Women with gestational or Type 1 diabetes were excluded. In addition to fasting, meticulously controlled blood work at study entry, participants completed voluminous questionnaires about family history, lifestyle factors, menopausal status, medication history, physical activity, and diet.

Compared with controls, the women who developed diabetes between 1990 and 2000 were heavier, more likely to have a family history of diabetes, and less likely to exercise and consume alcohol at study entry. Their diet was more likely to include higher amounts of heme iron, transfat, red and processed meats, and calories. They took in smaller amounts of dietary cereal fiber and magnesium. They also had higher plasma concentrations of C-Reactive Protein (CRP), fasting insulin, hemoglobin and A1C at baseline. At baseline, their mean serum ferritin levels were significantly higher than the controls (109 vs 71.5 ng/mL; $P < .001$), and their ratio of transferrin receptors to ferritin was significantly lower (102 vs 141; $P = .01$). The Relative Risk (RR) of developing diabetes rose linearly with ferritin levels; for those with the highest levels (> 107.2

VOLUME 26 • NUMBER 5 • MARCH 15, 2004 • PAGES 33-40

ng/mL), the RR was 3.2. Adjusting for important variables including BMI, age, race, family history, activity, caloric intake, menopausal status, CRP levels, and intake of iron supplements reduced the RR only modestly. The authors concluded that total body iron stores are an independent risk factor for type 2 diabetes.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

Hemachromatosis is a risk factor for diabetes, and iron has long been suspected of causing diabetes and/or cardiovascular disease because of its prooxidant properties.[4] Despite this suspected association, only one other small study (in men) has longitudinally evaluated the risk of diabetes in relationship to iron stores.[5] The current study is important because it tells us more about risk factors for diabetes (ferritin levels, transferrin to ferritin ratio, and CRP), and because it suggests that even menstruating women could be at risk with oversupplementation of iron.

The study particularly interested me because of the well-established relationship between iron stores and Restless Legs Syndrome (RLS). Individuals with ferritin levels below 45 ng/mL are at increased risk for RLS, and iron supplementation can reduce or eliminate RLS symptoms.[6,7] The current study by Jiang and colleagues reminds of us a common theme in medicine and nature: a little bit can be good, but more is not necessarily better!

References

1. Colditz GA, et al. *J Womens Health*. 1997;6:49-62.
2. National Diabetes Data Group. *Diabetes*. 1979;28:1039-1057.
3. American Diabetes Association. *Diabetes Care*. 1997;20:1183-1197.
4. Ford ES, Cogswell ME. *Diabetes Care*. 1999;22: 1978-1983.
5. Salonen JT, et al. *BMJ*. 1998;317-327.
6. Sun ER, et al. *Sleep*. 1998;21(4):371-377.
7. Hening W, et al. *Sleep*. 1999;22(7):970-999.

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.

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

EDITORIAL GROUP HEAD: Lee Landenberger.

MARKETING PRODUCT MANAGER: Schandale Kornegay.

ASSISTANT MANAGING EDITOR: Robert Kimball.

SENIOR COPY EDITOR: Christie Messina Petrone.

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.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

THOMSON™
AMERICAN HEALTH CONSULTANTS

Questions & Comments

Please call **Robert Kimball**, Assistant Managing Editor, at (404) 262-5413 (e-mail: robert.kimball@thomson.com) between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Subscriber Information

Customer Service: 1-800-688-2421.

Customer Service E-Mail: customerservice@ahcpub.com

Editorial E-Mail: robert.kimball@thomson.com

World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $249
(Student/Resident rate: $125).

Multiple Copies
1-9 additional copies: $224 each; 10 or more copies: $199 each.

Canada
Add 7% GST and $30 shipping

Elsewhere
Add $30 shipping

Accreditation

Thomson American Health Consultants (AHC) designates this continuing medical education (CME) activity for up to 45 hours in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.
AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.
This CME activity was planned and produced in accordance with the ACCME Essentials.
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.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Brunton is a consultant for Andrx, Reliant, and AstraZeneca and serves on the speaker's bureau of Janssen, Schering, Aventis and AstraZeneca. Dr. Hall is a consultant for Aventis. Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3-M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim. Dr. Ost is on the speaker's bureau of Merck, Roche, and Boehringer Ingelheim and does research for the American Lung Association. Dr. Phillips serves on the speaker's bureau of Cephalon, Boehringer Ingelheim, Merck, Res Med, and GlaxoSmithKline and is a consultant for Boehringer Ingelheim, Wyeth-Ayerst, and Res Med. Dr. Robinson serves as a consultant for TAP, Pfizer, Janssen, Eisai, J&J-Merck, and Procter & Gamble, is on the speaker's bureau of Janssen, Eli Lilly, Solvay, TAP, and Aventis, and does research for Forest Labs, Wyeth-Ayerst, AstraZeneca,and Centocor. Drs. Chan, Elliott, Grauer, Karpman, Wiese, and Wilke report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

Thomson American Health Consultants accepts pharmaceutical sponsorship of some programs but only in the form of unrestricted educational grants that must meet all ACCME and ANCC requirements.

Assessment of Esophageal Motor Function in Patients with Dysphagia or Chest Pain

ABSTRACT & COMMENTARY

Synopsis: *Contrary to expectations, the most common esophageal motility abnormality in patients with noncardiac chest pain is hypotensive lower esophageal sphincter (LES), and the most common motor abnormality in dysphagia is ineffective peristalsis. If chest pain and dysphagia are both present, the most common motility finding is achalasia.*

Source: Dekel R, et al. *Aliment Pharmacol Ther*. 2003;18: 1083-1089.

FEW PROSPECTIVE DATA EXIST ON SPECIFIC esophageal motor abnormalities in patients who present with noncardiac chest pain or dysphagia. How-

ever, at least in the past, many gastroenterologists would have predicted a high prevalence of esophagospastic disorders (eg, esophageal spasm or nutcracker esophagus) in patients with these complaints. This report from multiple cooperating centers describes findings in 403 patients who presented with dysphagia and 140 patients with noncardiac chest pain and 44 patients with both symptoms on presentation. Sixty one percent (61%) of patients with noncardiac chest pain were found to have hypotensive LES pressure. Only 10% each were found to have nutcracker esophagus (high pressure peristalsis > 180 mm Hg) or nonspecific esophageal motor abnormalities. If patients presented with dysphagia, 27% had ineffective peristalsis followed by 18% with achalasia and 14% with nonspecific motor abnormalities. Also, 35% and 25% of patients with both dysphagia and noncardiac chest pain had achalasia and nonspecific motor abnormalities, respectively. Previous studies have suggested that reflux plays an important role noncardiac chest pain (60%); and motility disturbances have been historically implicated in 30% of such patients. Only 2% of patients with noncardiac chest pain had diffuse esophageal spasm in this prospective study, 7% in dysphagia, and 10% of patients with both of these symptoms; 10% or less had nutcracker esophagus in any of these groups.

COMMENT BY MALCOLM ROBINSON, MD, FACP, FACG

On balance, manometric testing was not really helpful in patients with either noncardiac chest pain or dysphagia alone. Many of these patients would have responded to a therapeutic trial of acid suppression. Dysphagia was the most common reason for referral for manometry (70%), but a relatively small minority had any clinically relevant motor abnormality found. Indeed, normal motility testing was found in 53-70% of these patients regardless of the indication for testing. Dysphagia patients had more abnormal manometric findings than noncardiac chest pain (47% vs 30%; $P < .0001$). Overall, manometry could have led to a beneficial therapeutic intervention in only 16.4% of patients with dysphagia. The patients most likely to benefit from motility studies are those with both dysphagia and chest pain (eg, 35% achalasia). On balance, relatively few patients need esophageal motility studies for their management in most situations. However, availability of motility testing remains critical for the diagnosis of achalasia and, in more general terms, for the preoperative assessment of patients considered for anti-reflux procedures. ■

Overview of Newer Antiepileptic Drugs for Neuropathic Pain and Migraine

ABSTRACT & COMMENTARY

Synopsis: *The newer AEDs possess the potential advantages of better tolerability and fewer drug-drug interactions compared with standard treatments such as tricyclic antidepressants or established AEDs. However, with the exception of data supporting the efficacy of gabapentin in PHS and PDN, there is currently insufficient evidence to determine whether the newer AEDs have equal or superior efficacy relative to proven pharmacotherapies.*

Source: Pappagallo M. *Clin Ther*. 2003;25:2506-2538.

Shared pathophysiologic mechanisms for migraine, neuropathic pain, and epilepsy underscore the notion that antiepileptic drugs (AED) should be standard treatment for the former. Five new AEDs and their use in these nonepileptic painful disorders are summarized. Each shares one or more of several mechanisms of action, including sodium or calcium channel blockade, inhibition of glutamate transmission or nitric oxide formation, enhanced GABAergic or serotonergic transmission, or free-radical scavenging.

Gabapentin, in controlled clinical trials, has been demonstrably efficacious for post-herpetic neuralgia, painful diabetic neuropathy, and migraine prophylaxis. Preliminary reports in the noncontrolled setting suggest it may also be beneficial in trigeminal neuralgia and for dysesthetic limb pain and painful spasms in multiple sclerosis.

Lamotrigine was beneficial, in controlled trials, for painful HIV neuropathy, painful diabetic neuropathy, and central post-stroke pain. Results in the latter were not dramatic, and 10% (3/30) withdrew due to adverse effects, but other studies showed that tolerability was comparable to gabapentin. Open-label use of lamotrigine, in combination with other agents for migraine prophylaxis, resulted in approximately a 50% improvement, 66% in those with aura, and case reports indicate it may be useful in SUNCT—short-lasting, unilateral, neuralgiform headache with conjunctival injection and tearing.

Oxcarbazepine has no controlled trials to its credit. Open-label use has reportedly been beneficial in carbamazepine-refractory trigeminal neuralgia and gabapentin-refractory painful radiculopathy. Tolerability

was comparable to carbamazepine in the former and not problematic in the latter. Its use in migraine prophylaxis has yet to be examined.

Topiramate was efficacious in the controlled setting in painful diabetic neuropathy, with 36% reporting a > 50% decrease in pain as measured by a visual analog score, compared to 21% with placebo (P = .005). Intercostal neuralgia and trigeminal neuralgia are other reported instances where it may be useful, although a recent controlled, crossover study in 3 patients with tic showed no benefit. Large, well-performed, controlled studies have demonstrated statistically significant benefit in migraine prophylaxis.

Zonisamide, in open-label study, has shown promise for refractory cervical or lumbar radiculopathy and, in retrospective review, in painful diabetic neuropathy (n = 30), fibromyalgia (n = 19), and pelvic pain (n = 7). Only 7% overall (n = 10) discontinued medication due to side effects. Migraine prophylaxis, in open-label study, showed an approximately 40% improvement and an even more striking 50% improvement in chronic daily headache.

Dizziness and somnolence are seen with all the newer AEDs but are dose related, and tolerance generally develops over time. Other adverse effects include fatigue, cognitive dysfunction, diplopia, nausea/vomiting, weight loss, and rash. Generally, these improve once steady-state levels are reached and do not lead to discontinuation of medication. Lamotrigine has the highest incidence of rash at 10%, less so when it is begun at a low dose and increased slowly. Although serious in only 3%, immediate medication withdrawal is necessary in all instances of rash. Overall, oxcarbazepine has the highest rate of reported adverse effects among the newer AEDs, but rash is rare, hepatic and hematologic toxicity is not a serious concern, and it is better tolerated as monotherapy. Topiramate has the highest rate of cognitive side effects (10%), again less so if started low and slow. Weight loss is an often-desired side effect, averaging 5.9 kg at 1 year and 10.9 kg in patients obese at baseline. As a sulfonamide, zonisamide has an inherent risk of rash and hematologic toxicity, but in practice this has not been a significant problem (rash incidence, 2%). It has also been used uneventfully in sulfa-allergic patients. Drug interactions are generally not a problem with 2 notable exceptions. Oral contraceptives should not be used with topiramate or oxcarbazepine due to their induction of the cytochrome P enzyme family, and lamotrigine dosage should be lowered when combined with valproic acid due to decreased clearance induced on the former by the latter. ■

COMMENT BY MICHAEL RUBIN, MD

Lamotrigine's initial dose and subsequent titration may be increased more rapidly in the absence of concurrent valproate use. If no valproate is on board, lamotrigine may be initiated at 50 mg/d (25 b.i.d.) and then increased by 25-50 mg/d on a weekly basis. When lamotrigine is added to valproate for migraine prophylaxis, the dosages are reasonable.

Regarding the concurrent use of oral contraceptives with topiramate or oxcarbazepine, there is some evidence to suggest that the cytochrome P isoenzyme involved is not induced until one reaches a topiramate blood level > 200/d and an oxcarbazepine blood level > 1200/d. Furthermore, no relative or absolute contraindication to contraceptive use exists for topiramate or oxcarbazepine because the induced cytochrome P increases estrogen metabolism, not progesterone. Breakthrough bleeding can be a problem, however, and an oral contraceptive with more estrogen might be warranted. Consult your gynecologist.

Lastly, topiramate and zonisamide inhibit carbonic anhydrase and thus, should be avoided when using other carbonic anhydrase inhibitors as the combination may increase the risk of clinically significant hyperchloremic metabolic acidosis leading to osteomalacia or nephrolithiasis. ■

Dr. Rubin is Professor of Clinical Neurology, New York Presbyterian Hospital-Cornell Campus, New York, NY.

Can We Reduce the Incidence of Diabetes by Increasing the Intake of Dietary Magnesium?

ABSTRACTS & COMMENTARY

Synopsis: *Plasma fasting insulin levels are higher and the risk for developing type 2 diabetes is greatest in those with the lowest intake of magnesium (Mg).*

Sources: Song Y, et al. *Diabetes Care*. 2004;27:59-65;Lopez-Ridaura R, et al. *Diabetes Care*. 2004;27:134-140.

THE REPORT BY SONG AND COLLEAGUES USED A VALIdated food frequency questionnaire in 39,345 women from the Womens' Health Study. The relative risks of type 2 diabetes occurring across quintiles of Mg intake were determined over a 6-year period.

There was a significant inverse relationship between Mg intake from both food and supplements, and the development of type 2 diabetes. Although there was a trend ($P = 0.05$) between Mg intake and the occurrence of diabetes in those women with a Body Mass Index (BMI) of less than 25 kg/m^2 there was a significant increase in the relationship in those women with a BMI of 25 kg/m^2 or greater.

In a sample of 349 subjects from this study they measured fasting plasma insulin levels to examine their relationship to Mg intake. The mean insulin levels for overweight women in the lowest quintile was 53.5 compared to 41.5 pmol/L among those at the highest quintile.

The report of Lopez-Ridaura and colleagues followed 85,060 women and 42,872 men. Mg intake was evaluated using a validated food frequency questionnaire every 2-4 years. The follow up period in women was 18 years and 12 years in men. After adjusting for family history, age, BMI, physical activity, smoking, alcohol consumption, hypertension, and hypercholesterolemia the relative risk for type 2 diabetes was 0.67 ($P < 0.001$) in men and 0.66 for women ($P < .001$) comparing the highest and lowest quintile of total Mg intake.

These finding suggest a significant inverse association between Mg intake and diabetes risk. It also supports the recommendation to increase consumption of major food sources of magnesium such as whole grains, nuts, and green leafy vegetables.

COMMENT BY RALPH R. HALL MD, FACP

Nadler[1] in an accompanying editorial reviewed previous reports from the Iowa Womens' Health Study[2] and the Honolulu Heart Program[3] in which increased intake of Mg and whole grains reduced the incidence of cardiovascular disease as well as diabetes.

There is sufficient evidence to support a trial of diets such as whole grains nuts, and leafy green vegetables in patients at risk for type 2 diabetes. This diet is consistent with current dietary recommendation for the prevention of cardiovascular disease as well.

The benefits of lifestyles with appropriate exercise and nutrition are tremendous in terms of morbidity, quality of life, and financial gain. It seems so simple—why can't we do more? ■

References

1. Nadler JA, et al. *Diabetes Care.* 2004;27:270-271.
2. Meyer KA, et al. *Am J Clin Nutr*. 2000:71;921-930.
3. Abbott RD, et al. *Am J Cardiol.* 2003;92:665-669.

Pharmacology Update

Estradiol/Levonorgestrel Transdermal System (Climara Pro™)

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

THE FDA HAS APPROVED THE FIRST ONCE-A-WEEK combined hormone therapy for postmenopausal symptoms. This transdermal system delivers estradiol and the progestin levonorgestrel, which until now has only been used in contraceptive combinations. Berlex markets transdermal estradiol/levonorgestrel as Climara Pro™.

Indications

Estradiol/levonorgestrel (E2/LNG) is indicated for the treatment of moderate-to-severe vasomotor symptoms associated with menopause.[1]

Dosage

One transdermal system is applied to a smooth, clean area of the skin on the lower abdomen. The system should be replaced weekly. The sites should be rotated with an interval of at least 1 week between applications to the same site. If the system falls off it can be reapplied to another site on the lower abdomen. If a new system is needed the original treatment schedule should be maintained.[1] Each system delivers 45 µg/d of estradiol and 15 µg/d of levonorgestrel.

Potential Advantages

E2/LNG provides a convenient once-weekly hormone treatment for menopausal symptoms (ie, hot flushes) with a progestin to protect against endometrial hyperplasia.

Potential Disadvantages

E2/LNG is not approved for the treatment of vulvar and vaginal atrophy. Application site reactions are the most common adverse effects (40.6%). In controlled clinical trials, 2.1% of participants withdrew from treatment at 12 weeks and 8.5% at 1 year. Other side effects include vaginal bleeding (36.8%) and breast pain (18.9%).[1]

Comments

E2/LNG has been shown to reduce the number and

severity of moderate-to-severe hot flushes compared to placebo.[1,2] In addition, over a 1-year period, E2/LNG did not show any significant endometrial hyperplasia. In contrast, 17% of subjects on E2 alone (Climara™) showed hyperplasia.[1,2] The cumulative proportion of patients with uterine bleeding or spotting was lower with E2/LNG compared to E2 alone.[2] Triglyceride levels declined compared to E2 alone. Application site reactions, vaginal bleeding, and breast pain were the most common side effects. The wholesale cost of Climara Pro™ is $30.50 per month which is higher than Climara™ ($28).

Clinical Implications

E2/LNG is the first once-weekly patch for treating moderate-to-severe vasomotor symptoms. Another product, estradiol/norethindrone acetate (CombiPatch®) is applied twice weekly. As a result of the WHI study, estrogen or estrogen/progestin products may be considered for moderate-to-severe vasomotor symptoms and should be used at the lowest dose for the shortest duration possible. E2/LNG provides another option for this use. Transdermal estrogen appears to be associated with a more favorable risk/benefit ratio compared to oral estrogen in regards to thrombotic, hemodynamic, and endothelial effects.[3,4] ■

References

1. Climara Pro™ Product Information. Berlex. December 2003.
2. Shulman LP, et al. *Menopause*. 2002;9(3):195-207.
3. Girdler SS, et al. *Obstet Gynecol*. 2004;103(1):169-180.
4. Scarabin PY, et al. *Lancet*. 2003;362:428-432.

CME Questions

10. Which of the following groups of variables are associated with an increased risk of developing diabetes in healthy women?

a. Increased serum ferritin levels, reduced cereal intake, higher CRP levels.
b. Increased serum ferritin levels, reduced physical activity, lower CRP levels.
c. Reduced serum ferritin levels, reduced cereal intake, lower fasting insulin levels.
d. Increased serum ferritin levels, increased dietary transfat, alcohol abstinence
e. Reduced serum ferritin levels, increased dietary heme intake, chronic alcohol ingestion.

11. Which of the following questions are true?

a. There was a significant correlation between Mg intake and the occurrence of type 2 diabetes in women with BMIs of < 25.
b. The plasma fasting insulin levels are higher in women with low Mg intake.
c. These are the first studies to recognize the significance of an adequate Mg intake relative to glucose metabolism.

12. Patients most likely to benefit from esophageal motility assessment are those with:

a. Heartburn alone.
b. Dysphagia alone
c. Heartburn and dysphagia concomitantly
d. Dysphagia and noncardiac chest pain concomitantly
e. Noncardiac chest pain alone

Answers: 10 (a); 11 (b); 12 (d)

Use of B-Type Natriuretic Peptide in the Evaluation and Management of Acute Dyspnea

By Louis Kuritzky, MD

THE ETIOLOGY OF ACUTE DYSPNEA (DSP) can be diverse, and it is often especially difficult to separate pulmonary from cardiac causes. Recently, brain natriuretic peptide (BNP)—so called because of its original identification in porcine brain—has become recognized as a valuable diagnostic tool because it promptly rises in response to pathologic cardiac ventricular wall stress (eg, heart failure), and its levels are proportional to the degree of cardiac dysfunction. BNP is not affected by pulmonary conditions such as COPD, unless COPD has been of sufficient severity to result in right ventricular failure.

Whether standard clinical evaluation or BNP-based diagnosis provides more effective management for acute DSP was studied in this trial (n = 452) Primary end points were time to discharge and cost, both of which would be presumed to be adversely affected by inaccurate initial diagnosis.

Evaluation for all patients in the emergency department included an initial history and physical, EKG, oximetry, blood chemistry, chest X-ray and (for half of the group) point-of-contact BNP testing (15 minute on-site results). A BNP level > 100 pg/mL was considered sufficiently elevated to be consistent with heart failure.

Use of BNP testing provided an advantage for time-to-discharge from the ED (63 minutes vs 90 minutes), need for hospitalization (75% vs 85%), time to hospital discharge (8 days vs 11 days), and intensive care costs ($874 vs $1516)

Use of BNP testing, in concert with traditional diagnostic tools, shortens the time to initiation of specific and appropriate treatment, and hospitalizations. Overall, use of the BNP test reduced total treatment cost by more than 25%. ■

Mueller C, et al. N Eng J Med. 2004; 350:647-654.

Association Between C-Reactive Protein and Age-Related Macular Degeneration

By Louis Kuritzky, MD

AGE-RELATED MACULAR DEGENERATION (AMD) is an important cause of loss of visual acuity, and because there are few effective treatments, enhanced prevention is paramount. The association between some cardiovascular risk factors (eg, smoking, dyslipidemia, obesity) and AMD has not gone unnoticed. Since C-reactive protein (CRP) has been associated with cardiovascular risk, it has become an item of interest whether CRP is similarly associated with AMD.

Study subjects (n = 4757) comprised persons with mild (n = 1063), intermediate (n = 1621), and advanced (n = 956) AMD, and controls (n = 1117). Subjects were followed every 6 months with tests of visual acuity and fundoscopy.

CRP levels were particularly discordant in persons with advanced AMD compared to those with no AMD. Even after statistical adjustment for age, sex, smoking, and obesity, CRP levels maintained a relationship with AMD. Persons in the 90th percentile for CRP had almost a 2-fold increased odds ratio for AMD. Seddon and colleagues suggest that CRP elevation is an independent risk factor for AMD. Since this is the first evidence to implicate inflammation (as manifest by CRP) etiologically in AMD, it remains to be shown whether modulation of CRP might have favorable effects on this end point. ■

Seddon JM, et al. JAMA. 2004;291: 704-710.

VZV Reactivation in Astronauts

By Carol Kemper, MD, FACP

STRESS IS A KNOWN TRIGGER FOR reactivation of herpes viruses. Just the physical and psychological trauma of swapping alpha-male mice between 2 mouse colonies and the resultant battle for new alpha-male-dom has been shown to trigger reactivation of HSV in about half the mice. Herpes zoster can also reactivate after stress, including the stress of surgery.

After a 47-year-old healthy astronaut developed herpes zoster 2 days before a space flight, Mehta and associates decided to examine whether the stress of space flight can result in the reactivation of VZV. A total of 312 saliva samples, obtained from 8 astronauts before, during, and after space flight were examined by PCR. Amazingly, 61 of 200 (30%) specimens obtained during and after space flight were positive, compared with 1 of 112 (< 1%) obtained in a 234-265 day period before flying. No VZV was detected in 88 samples from 10 control subjects, who did not fly. Seven of 8 astronauts had at least 1 positive specimen during flight (2-12 days), while all 8 had anywhere from 1-8 positive specimens within 15 days of returning to earth. ■

Mehta SM, et al. J Med Virol. 2004; 72:174-179.

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

What Would You Ask the Technician?

By Ken Grauer, MD

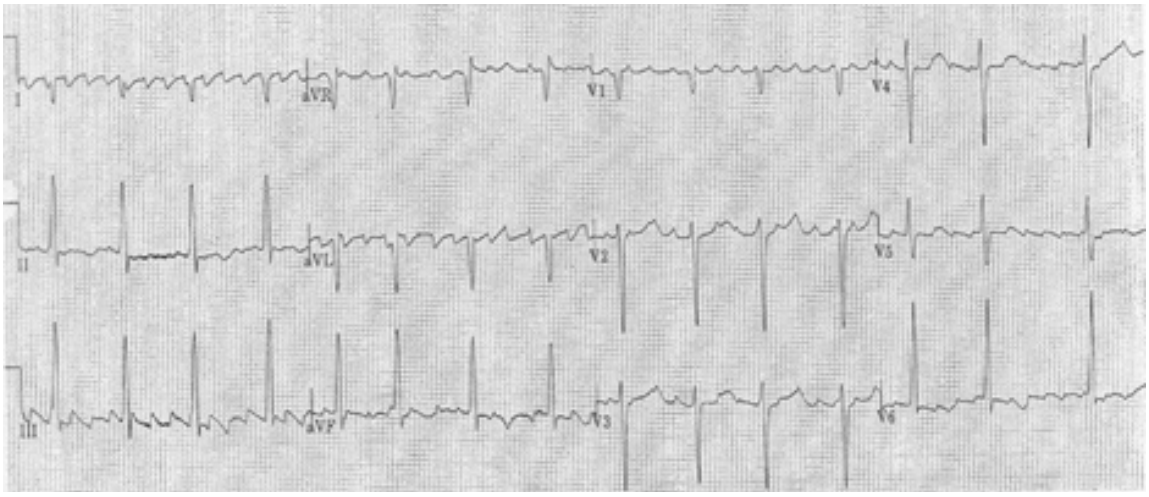

Figure. 12-lead ECG recorded from a 67-year-old woman with heart failure.

Clinical Scenario: How would you interpret the 12-lead ECG shown in the Figure? What is distinctly unusual about this tracing? What would you ask the technician who recorded this tracing?

Interpretation/Answer: There are a number of interesting findings on the 12-lead ECG shown in the Figure. Although the variation from beat to beat is not great, the rhythm is irregularly irregular. QRS duration is upper normal, suggesting a supraventricular mechanism for the rhythm. No P waves are seen in lead II. Instead, a sawtooth pattern of atrial activity is noted in a number of other leads at a rate of approximately 300/minute. This strongly suggests that atrial flutter is the rhythm, seen here with a variable but controlled ventricular response. Marked RAD (right axis deviation) is present. There is voltage for LVH (left ventricular hypertrophy). Assessment of ST segment morphology is difficult to ascertain because of baseline artifact and the effect of flutter activity, however acute ST-T wave changes do not appear to be present.

There are two distinctly unusual features about this tracing. The first relates to the cardiac rhythm. Despite the baseline artifact that is present, identification of repetitive atrial activity at a rate of approximately 300/minute in several leads (especially leads I, II, and V1) defines the rhythm as atrial flutter. The most common type of atrial flutter manifests a characteristic sawtooth patten that is generally best seen in all three of the inferior leads. However, there is no indication at all of flutter activity in lead II of this tracing. Instead, the lead that is most suggestive of flutter activity is lead I, a lead which often shows no trace at all of flutter activity on a 12-lead ECG. The second unusual finding is also noted in lead I, which shows a predominantly (if not totally) negative QRS complex. While this finding may be indicative of lateral infarction, there is no suggestion of lateral infarction in the precordial leads. The most common type of lead reversal (ie, mixing up left and right arm electrodes) is also unlikely because lead aVR is predominantly negative as it should be (lead aVR shows a Qr pattern, instead of manifesting a positive QRS complex as would be expected if the arm leads were reversed). Thus, some technical mishap other than lead reversal should be suspected as a possible cause of the unusual appearance of the QRS complex in lead I and the unexpected presence of characteristic flutter activity in lead I instead of in lead II.

The patient in question was a 67-year-old woman with severe mental retardation, who was admitted to the hospital for an exacerbation of heart failure. She could not understand instructions, and would only allow an ECG to be recorded while she was lying on her right side. The importance of verifying proper body position during ECG recording is essential for understanding potential alterations in ECG complex morphology from what is normally expected. While this case is admittedly a more extreme example, it is important to appreciate that recording an ECG with a patient supine but with elevation of the bed even by a small amount may produce surprising changes in QRST morphology compared to ECG recordings made with the bed flat. Asking your technician to always indicate in writing on the ECG such alterations in body position during ECG recording would obviate many problems with interpretation. ■

In Future Issues:

Tough Love for Low Back Pain

PHARMACOLOGY WATCH

Sinus and Allergy Health Partnership Releases New Guidelines for Treatment of Bacterial Rhinosinusitis

New guidelines for the treatment of bacterial rhinosinusitis were published in the January supplement of *Otolaryngology- Head and Neck Surgery* by the Sinus and Allergy Health Partnership. The goal of the guidelines is to reduce the use of antibiotics for viral infections and to use the most appropriate antibiotic for bacterial infections. The guidelines recommend antibiotics if patients are getting worse after 5-7 days or if they are not better after 10-14 days. Patients with mild disease should be treated with cefpodoxime (Vantin), cefuroxime (Ceftin), amoxicillin, amoxicillin/clavulanate (Augmentin), or cefdinir (Omnicef). Patients with moderate disease or those with recent antibiotic exposure should receive amoxicillin/clavulanate, ceftriaxone, or one of the respiratory fluoroquinolones including gatifloxacin (Tequin), moxifloxacin (Avelox), or levofloxacin (Levaquin). The respiratory quinolones do not include ciprofloxacin. This is a follow-up to the group's first guidelines, which were published in 2000 (*Otolaryngol Head Neck Surg*. Supplement. 2004;130:1).

Steroids Not Linked to Risk of Fractures

Long-term use of inhaled steroids for the treatment of respiratory diseases or nasal steroids for the treatment of allergic rhinitis are not associated with an increased risk of fractures if they are used in normal doses, according to a study from Canada. Researchers conducted a case-control study of all elderly Québec residents who were dispensed respiratory medications and could be followed for at least 4 years from 1988 to 2001. The rate of hip or upper extremity fractures was not increased in those patients who used daily inhaled corticosteroids (RR, 0.97). The rate of upper extremity fractures increased by 12% with every 1000 µg increase in the daily inhaled corticosteroid, but the rate of hip fractures did not increase. The rate of hip fractures was only elevated with very high doses (more than 2000 µg per day) of inhaled corticosteroid. Nasal steroids did not increase the risk at any dose. The authors conclude that long-term use of inhaled and nasal corticosteroids at usual recommended doses is not associated with the risk of fracture (*Am J Resp Crit Care Med*. 2004;169:83-88).

ADT Puts Men at Risk for Osteoporosis

Men treated for prostate cancer with androgen deprivation therapy (ADT) are at risk for osteoporosis and fractures, according to a new study. One year of ADT resulted in 2-8% bone loss in the lumbar spine and 1.8-6.5% bone loss

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5413. E-mail: christie.petrone@ thomson.com. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

in the femoral neck. The study was a meta-analysis of 9 studies that included a total of 208 patients. The authors suggest that men starting ADT should be considered for bone mineral density measurement, and men at high risk should be offered a bisphosphonate (published online January 19, 2004. *Cancer*).

Study Shows Valsartan May Improve Sexual Function in Postmenopausal Women

A new study suggests that valsartan may improve sexual function in hypertensive postmenopausal women. Researchers randomized 120 postmenopausal women aged 51-55 with mild-to-moderate hypertension to valsartan 80 mg daily or atenolol 50 mg daily for 16 weeks. Doses were doubled if diastolic blood pressures remained above 90 mm Hg. The end point was a questionnaire that self-evaluated various aspects of sexual desire, orgasmic response, and coital activity. The drugs lowered blood pressure equally effectively. Women in the valsartan group noted significantly improved sexual desire (38% increase, $P < .01$), changes in behavior (45% increase, $P < .001$), and sexual fantasies (51% increase, $P < .001$). In the atenolol group, scores for sexual desire and sexual fantasies significantly worsened (18% decrease, $P < .01$, and 23% decrease, $P < .001$, respectively). The authors conclude that in the study group, hypertensive postmenopausal women in their 50s, valsartan improved some aspects of sexual function, whereas atenolol worsened it. They further speculate the drugs may have differential effects on serum hormone levels, specifically testosterone (*Am J Hyperten*. 2004;14:77-81).

New Direct-to-Consumer Pharma Advertising Rules Considered

Anyone who watched the Super Bowl can verify that direct-to-consumer advertising of prescription pharmaceuticals is big business. Now the FDA is considering tighter restrictions on the content of these ads, requiring pharmaceutical companies to highlight key risks associated with the drugs rather than listing the large number of potential side effects in small print. The guidelines encourage companies to use less cluttered formats for print ads, perhaps even using bullet points to set the import risks apart. Print ads currently contain an extensive list of side effects similar to the package insert, often in a similarly small font, frequently on a separate page from the main advertisement. The FDA is also considering changing the criteria for "reminder" ads that simply name the drug without giving the indication for its use. Currently, these ads do not require information on adverse effects and often run close to disease awareness campaigns also paid for by the drug company. These new FDA restrictions have not been finalized and are sure to be opposed by Pharma.

FDA Actions

Boehringer Ingelheim Pharmaceuticals has received FDA approval to market tiotropium bromide inhalation powder (Spiriva) for the treatment of COPD. Tiotropium, a once-daily anticholinergic agent, is indicated for the long-term maintenance treatment of bronchospasm associated with COPD.

Modafinil (Provigil) has been approved for improving wakefulness in patients with excessive sleepiness due to obstructive sleep apnea/hypopnea syndrome and shift work sleep disorder. The drug is currently approved for improving wakefulness in patients with narcolepsy.

The FDA has approved a 3-day course of azithromycin (Zithromax) for the treatment of acute bacterial sinusitis. The drug, which is dosed at 500 mg once a day, is the only 3-day regimen approved for this indication. Azithromycin is currently approved for the treatment of community-acquired respiratory infections and skin infections, as well as otitis media.

Olanzapine (Zyprexa) has been approved for maintenance treatment of bipolar disorder. The drug appears to be effective in delaying relapse into either mania or depression in bipolar patients. Olanzapine was approved in 2000 for the short-term treatment of acute mixed or manic episodes associated with bipolar disorder.

The FDA has also approved a combination of olanzapine and fluoxetine (Prozac) for the treatment of bipolar depression. The combination drug will be marketed under the trade name Symbyax. Quetiapine fumarate (Seroquel) was also recently approved for monotherapy and adjunct therapy with lithium and divalproex, for the short-term treatment of acute manic episodes associate with bipolar I disorder. ■