

# INTERNAL MEDICINE ALERT<sup>®</sup>

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

Providing Evidence-based  
Clinical Information for 25 Years

Thomson American Health Consultants Home Page—<http://www.ahcpub.com>

CME for Physicians—<http://www.cmeweb.com>

THOMSON  
AMERICAN HEALTH  
CONSULTANTS

## INSIDE

Eat more  
protein and  
lower your  
blood glucose!  
page 154

'Si' for CT  
for PE  
page 155

Hospitaliza-  
tion for atrial  
fibrillation  
page 156

Chronic  
constipation  
page 157

## One-Day Quadruple Therapy Compared with 7-Day Triple Therapy for *H pylori* Infection

ABSTRACT & COMMENTARY

**Synopsis:** One-day quadruple therapy for eradication of *H pylori* seems effective.

**Source:** Lara L, et al. *Arch Intern Med.* 2003;163(17):2079-2084.

IN THIS STUDY FROM LARA AND ASSOCIATES, 160 PATIENTS WITH dyspepsia and *Helicobacter pylori* infection were identified by a positive <sup>14</sup>C urea breath test. Comparators were a 1-day treatment regimen of 2 tablets of 262 mg bismuth subsalicylate q.i.d., one 500-mg metronidazole tablet q.i.d., 2 grams of amoxicillin suspension q.i.d., and 2 capsules of 30-mg lansoprazole once daily vs a regimen of 7 days of clarithromycin 500 mg b.i.d., 1 gram of amoxicillin b.i.d., and lansoprazole 30 mg b.i.d. The 1-day therapy eradicated 95% of *H pylori* vs 90% with the 7-day treatment program. Adverse events were comparable, and no patient was non-compliant.

### COMMENT BY MALCOLM ROBINSON, MD, FACP, FACC

It is widely accepted that eradication of *H pylori* is effective in preventing the recurrence of many gastric and duodenal ulcers, although other benefits of eradication are more controversial. In particular, data in North America don't currently support *H pylori* eradication for the treatment of dyspepsia. However, it is known that eradication in ulcer disease patients positive for *H pylori* parallels that seen in patients who present with dyspepsia.

In this study, eradication rates with both tested regimens were quite high. As Lara et al point out, shorter therapies that achieve successful eradication rates would improve compliance. Previous studies have suggested less robust results for 1-day therapy than seen in the present study. As might have been expected, neither the 1-day regimen nor the 7-day program eliminated dyspepsia symptoms though declines in symptom severity were seen. Further verification of the applicability of ultra-short *H pylori* eradication regimens would be most welcome. ■

### EDITOR

Stephen A. Brunton, MD  
Clinical Professor,  
University of California Irvine

### ASSOCIATE EDITORS

James Chan, PharmD, PhD  
Pharmacy Quality and  
Outcomes Manager, Kaiser  
Permanente, Oakland, CA

William T. Elliott, MD, FACP

Chair, Formulary Committee,  
Northern California Kaiser  
Permanente; Asst. Clinical  
Professor of Medicine, University  
of California-San Francisco

Mary Elina Ferris, MD

Clinical Associate Professor  
University of Southern California

Ken Grauer, MD

Professor, Assistant Director,  
Family Practice Residency  
Program, University of Florida

Ralph R. Hall, MD, FACP

Emeritus Professor of Medicine  
University of Missouri-  
Kansas City School of Medicine

Harold L. Karpman, MD,

FACC, FACP  
Clinical Professor of Medicine,  
UCLA School of Medicine

Louis Kuritzky, MD

Clinical Assistant Professor,  
University of Florida,  
Gainesville

Martin Lipsky, MD

Professor and Chair,  
Department of Family Medicine,  
Northwestern University  
Medical School, Chicago, IL

David Ost, MD

Assistant Professor of Medicine,  
NYU School of Medicine,  
Director of Interventional  
Pulmonology, Division of  
Pulmonary and Critical Care  
Medicine, Northshore University  
Hospital, Manhasset, NY

Barbara A. Phillips, MD, MSPH

Professor of Medicine,  
University of Kentucky;  
Director, Sleep Disorders  
Center, Samaritan Hospital,  
Lexington, KY

Malcolm Robinson, MD,

FACP, FACC  
Medical Director, Oklahoma  
Foundation for Digestive  
Research; Clinical Professor of  
Medicine, University of Okla-  
homa College of Medicine  
Oklahoma City, OK

Jeff Wiese, MD

Chief of Medicine, Charity, and  
University Hospitals, Associate  
Chairman of Medicine,  
Tulane Health Sciences Center

Allan J. Wilke, MD

Assistant Professor of  
Family Medicine,  
Medical College of Ohio,  
Toledo, OH

VOLUME 25 • NUMBER 20 • OCTOBER 29, 2003 • PAGES 153-160

NOW AVAILABLE ONLINE!

Go to [www.internalmedicinealert.com](http://www.internalmedicinealert.com) for access.

# Eat More Protein and Lower Your Blood Glucose!

ABSTRACT & COMMENTARY

**Synopsis:** A high-protein diet lowers the blood glucose postprandially in persons with type 2 diabetes and improves overall glucose control. However, longer-term studies are necessary to determine the total magnitude of response, possible adverse effects, and long-term acceptability of the diet.

**Source:** Gannon MC, et al. *Am J Clin Nutr.* 2003;78:734-739.

THE FOCUS OF THE TYPE AND AMOUNT OF DIETARY protein recommended for diabetics is usually to pro-

**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:** Glen Harris.  
**MARKETING PRODUCT MANAGER:**

Schandale Komegay.

**MANAGING EDITOR:** Robin Mason.

**ASSISTANT MANAGING EDITOR:** Robert Kimball.

**SENIOR COPY EDITOR:** Christie Messina.

**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.

Copyright © 2003 by Thomson American Health Consultants. All rights reserved. No part of this newsletter may be reproduced in any form or incorporated into any information-retrieval system without the written permission of the copyright owner.

**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 **Robin Mason**, Managing Editor, at (404) 262-5517 (e-mail: robin.mason@ahcpub.com) or **Robert Kimball**, Assistant Managing Editor, at (404) 262-5413 (e-mail: robert.kimball@ahcpub.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@ahcpub.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, 2003. 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.

## 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. Lipsky is a consultant for and is on the speaker's bureau of Aventis and AstraZeneca. 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, Ferris, 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.

vide adequate protein for the maintenance of lean body mass. There are apparently no reports considering the role of protein in the management of hyperglycemia.

The object of this study was to compare the metabolic effects of a high-protein diet with those of a control diet that is currently recommended by several scientific organizations.

The metabolic effects of both diets, consumed for 5 weeks each, (separated by a 2-5 week washout period), were studied in 12 subjects with untreated type 2 diabetes. The ratio of protein to carbohydrate to fat was 30:40:30 in the high-protein diet and 15:55:30 in the control diet. The subjects remained weight stable during the study. All food was provided by Gannon and associates.

With fasting glucose concentration used as a baseline from which to determine the area under the curve, the high-protein diet resulted in a 40% decrease in the mean 24-hour integrated glucose area response. Glycated hemoglobin decreased 0.8% and 0.3% after 5 weeks on the high-protein and control diets, respectively. The difference was significant ( $P < .05$ ). Fasting triacylglycerol was significantly lower after the high-protein diet than after the control diet ( $P < .001$ ) Insulin, C-peptide, and free fatty acid concentrations were not significantly different after the 2 diets.

A high-protein diet lowers the blood glucose postprandially in persons with type 2 diabetes and improves overall glucose control. However, longer-term studies are necessary to determine the total magnitude of response, possible adverse effects, and long-term acceptability of the diet.

## COMMENT BY RALPH R. HALL, MD, FACP

In the accompanying editorial Eckel notes that typical glycemic studies involve "the examination of the effect of a single meal of added protein compared with that of other macronutrients on postingestion glucose and insulin concentrations."<sup>1</sup> Although the sample size was small, the design of the study, which involved the patients having all their meals provided by the study group, was excellent.

More information is needed before we assign patients to this diet. Although recent studies continue to show short-term benefits by increasing protein in the diet, there are no long-term studies to examine the effects on atherosclerosis. Will diets low in saturated and trans fat and high in protein and mono and polyunsaturated fat accelerate the development of vascular disease? The primary concern regarding most new-onset type 2 diabetes is weight loss. How will patients respond to increased protein and a low-caloric diet for prolonged periods of time? What will be the effects of oral hypoglycemic medication on such a diet?

Long-term nutritional studies in which patients receive all their nutrients require dedicated subjects and are expensive to carry out. The potential benefits of these nutritional studies are so great, however, that the funds for this research must be provided. ■

## Reference

1. Eckel RH. *Am J Clin Nutr.* 2003;78:671-672.

## 'Si' for CT for PE

ABSTRACT & COMMENTARY

**Synopsis:** *Helical CT scan is a definitive way to rule out significant pulmonary embolism.*

**Source:** Donato AA, et al. *Arch Intern Med.* 2003;163:2033-2038.

THIS WAS A PROSPECTIVE, OBSERVATIONAL STUDY OF outcomes of patients who underwent helical computed tomography (CT) scans when they were suspected of having pulmonary emboli. The aim was to determine the outcome of those patients with negative scans who did not receive anticoagulation. There were 433 sequential patients enrolled. Patients were excluded from follow-up analysis for many reasons, including indeterminate CT (14 patients), positive studies with anticoagulation initiated (119 patients), anticoagulation begun or continued without respect to scan results (57 patients), and high-probability V/Q scan with negative CT (2 patients). Thus, there were 243 patients who had negative helical CT results for pulmonary embolus (PE) who were not anticoagulated. Follow-up at 3 months was accomplished for 239 of them. Their mean age was 59 years, and 98 of them (41%) had one or more risk factors for PE. Their pretest probability<sup>1</sup> for PE was low probability for 65%, moderate probability for 27%, and high probability for 8%.

Follow-up was accomplished by phone (63%), direct encounter (17%), or review of subsequent hospital records (19%). A total of 33 patients died in the follow-up period; one of these deaths was felt by reviewers to be suspicious for PE. The causes of death in this group were lung cancer (5 patients), sepsis (5 patients), pneumonia (4 patients), disseminated carcinoma (5 patients), leukemia/lymphoma (4 patients), COPD (2 patients), and a variety of other causes for one case each.

Four patients who had a negative CT and did not receive anticoagulation had venous thromboembolic events (1.7%). Two had DVT, 2 had PE. One of those

with PE died, and it is worth examining this death in some detail. This patient was admitted with *Proteus mirabilis* sepsis and developed Doppler-documented venous thrombosis associated with an indwelling catheter 5 days after her admission and negative CT. Conservative care was undertaken as requested by her family, and she died on hospital day 11. Sepsis was listed as the cause of death.

## ■ COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

Everything about venous thromboembolic (VTE) disease and its workup is risky and complicated. The entity itself can kill, the diagnostic modality of choice (pulmonary angiogram) is morbid and fallible, and treatment (anticoagulation) is arduous. PE is estimated to occur somewhere between 50,000 to 175,000 times annually in the United States,<sup>2</sup> but the condition is suspected 3 or 4 times more frequently than it is proven to occur. Pulmonary angiography, long considered the diagnostic gold standard, is difficult to interpret and expensive. It is associated with a complication rate of 6.5% and a death rate of 0.5% and often requires getting a radiologist out of bed. Clinicians have long searched for a better diagnostic test, and clinical prediction formulae, radionuclide scans, Doppler's, and d-dimer blood assays all have some promise and usefulness in the diagnosis of VTE.

Helical CT has reasonable sensitivity (86-96%) for central emboli,<sup>3,4</sup> but there has been concern about its ability to detect subsegmental emboli.<sup>5</sup> The current paper is important because it indicates that the detection of subsegmental emboli may not matter much in a real-world situation. What is important is the clinical outcome of the patient. Not anticoagulating those patients with negative CTs in this study resulted in a 0.4% death rate, which is actually similar to the death rate associated with pulmonary angiography itself. Several other studies have reported similar findings, including follow-up of 6 or more months.<sup>6,7</sup> The current study is notable in that it is the first such study to be conducted at a community hospital without full-time academic thoracic radiologists, and thus, most likely represents a "real life" condition. Donato and associates compare the result of this and other studies of helical CT with outcomes for V/Q scans and note that low-probability V/Q scans are associated with a 2.7-3.7% of patients with subsequently documented VTE if anticoagulation is withheld,<sup>6,8</sup> they also note high interobserver variability for low- and intermediate-probability V/Q scans, which is much less troublesome with helical CT.

Move over, angiograms. Helical CT is here! ■

## References

1. Wells PS, et al. *Ann Intern Med.* 1998;129:997-1005.
2. Silverstein MD, et al. *Arch Intern Med.* 1998;158:585-593.
3. Remy-Jardin M, et al. *Radiology.* 1992;185:381-387.
4. Van Rossum AB, et al. *Thorax.* 1996;51:23-28.
5. Goodman LR, Lipchik RJ. *Radiology.* 1996;199:25-27.
6. Garg K, et al. *AJR Am J Roentgenol.* 1999;172:1627-1631.
7. Lomis NNT, et al. *J Vasc Interv Radiol.* 1999;10:707-712.
8. Hull RD, et al. *Arch Intern Med.* 1994;154:289-297.

# Hospitalization for Atrial Fibrillation

## ABSTRACT & COMMENTARY

**Synopsis:** *The frequency with which patients are hospitalized for atrial fibrillation is increasing dramatically with a large proportion of the increase due to an increased number of elderly patients in the population. Part of this increase may also be due to changes in management strategies for atrial fibrillation. Inpatient observation for initiation of antiarrhythmic therapy or for anticoagulation is now commonly recommended, particularly in elderly patients.*

**Source:** Wattigney WA, et al. *Circulation.* 2003;108:711-716.

WATTIGNEY AND ASSOCIATES FROM THE CENTERS for Disease Control conducted a survey of hospitalizations related to atrial fibrillation during the period of 1985-1999. Wattigney et al use the National Hospital Discharge Survey (NHDS), which includes demographic and medical information abstracted from medical records of inpatients selected from a nationally representative sample of nonfederal, short-stay hospitals in the United States. Records were limited to patients 35 years of age or older with atrial fibrillation recorded as 1 of up to 7 discharge diagnoses. Data for patients with atrial fibrillation reported as both a primary diagnosis and as a secondary diagnosis were included in this analysis. These data were combined with census bureau estimates to calculate age- and sex-specific prevalence of hospitalization for atrial fibrillation per 10,000 members of the US population.

The estimated number of hospitalizations and unadjusted prevalence with atrial fibrillation as the principle diagnosis increased from 154,086 in 1985 to 376,487 in

1999. This was a 144% relative increase. In the same period, hospitalization that listed atrial fibrillation as any of the 7 diagnoses increased from 787,750 to 2,283,673 (a 190% relative change). Although women outnumbered men in the absolute numbers of atrial fibrillation hospitalizations, the age-standardized prevalence of hospitalizations for atrial fibrillation was consistently higher among men than women. Analysis for the data using age-specific prevalence showed an increase in atrial fibrillation hospitalization with increasing age. There was only a minor increase over time among patients aged 35 to 54 years but a striking increase in patient groups older than 75 years of age. Most patients with atrial fibrillation during the course of the study were discharged home. However, over time, the percentage of patients discharged home decreased slightly with a corresponding increase in discharges to a long-term care institution. However, Wattigney et al could not determine how many of these patients originated in a long-term care institution and were discharged back to their prior residence. Death was uncommon for discharges in which atrial fibrillation was the primary diagnosis. However, atrial fibrillation as a secondary diagnosis was commonly associated with either stroke, acute myocardial infarction, or congestive heart failure, and case fatality rates were high among patients with these conditions. Particularly among elderly patients, pneumonia was the most common noncardiac principle diagnosis seen in association with atrial fibrillation.

Essential hypertension, ischemic heart disease, and congestive heart failure were the most commonly associated cardiac co-morbidities.

Wattigney et al conclude that the frequency with which patients are hospitalized for atrial fibrillation is increasing dramatically with a large proportion of the increase due to an increased number of elderly patients in the population. Part of this increase may also be due to changes in management strategies for atrial fibrillation. Inpatient observation for initiation of antiarrhythmic therapy or for anticoagulation is now commonly recommended, particularly in elderly patients. Wattigney et al argue that better techniques for maintaining sinus rhythm are necessary to counter this trend.

### ■ COMMENT BY JOHN DiMARCO, MD, PhD

This paper presents interesting data showing the effect of atrial fibrillation on hospitalizations in the US population. It is well known that atrial fibrillation becomes increasingly frequent as patients become older. The data presented here confirm that this aging of the population is reflected in an increase in hospitalization of patients with this arrhythmia.

Wattigney et al are convinced, however, that more

aggressive therapy to restore and maintain sinus rhythm in patients with atrial fibrillation, using either ablation, device-based, or pharmacologic approaches, may counter this trend, but this opinion is not supported by recent clinical trials. In fact, in both the AFFIRM trial and the RACE trial, increased rates of hospitalization were seen in patients in whom a rhythm control strategy was used as the primary approach. Part of the reason for this was related to the need for hospitalizations to initiate antiarrhythmic drug therapy, but it is also likely that the common failures of antiarrhythmic therapy led to an acute presentation that required a hospital stay for stabilization. A need for hospitalization might not have been seen if patients had just been maintained on a stable rate control regimen. Unless antiarrhythmic therapy is highly successful and safe, the need for frequent hospitalizations will likely persist. Unfortunately, there have been no major recent breakthroughs in drug therapy for atrial fibrillation, and ablation approaches, though more promising, have not been shown to be highly effective in the elderly patients with advanced disease who account for the majority of hospitalization.

This paper does provide important epidemiologic data about the magnitude of atrial fibrillation in the United States today. What we need now are better solutions. ■

*Dr. DiMarco is Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville, Va.*

## Chronic Constipation: Current Concepts

ABSTRACT & COMMENTARY

**Synopsis:** *This review article sums up the symptoms and treatment of chronic constipation.*

**Source:** Lembo A, Camilleri M. *N Engl J Med.* 2003;349:1360-1368.

CHRONIC CONSTIPATION MAY AFFECT UP TO 27% OF the population, resulting in 2.5 million physician visits, 92,000 hospitalizations, and laxative sales in the hundreds of millions of dollars. This syndrome is most common in women, Caucasians, and the elderly. Risk factors include sedentary lifestyle, lower educational and socioeconomic status, history of sexual abuse, and depression.

Constipation is arbitrarily described as less than 3

stools/week associated with straining and inability to completely evacuate stools. This excellent review divides constipation by normal vs slow transit vs disorders of rectal evacuation.

Normal-transit constipation is most common and is often relieved with administration of supplementary fiber or administration of an osmotic laxative. Defecatory disorders include pelvic floor dyssynergia, anismus, and other less common pelvic neuromuscular defects. Slow-transit constipation seems most common in young women, often associated with bowel movements once a week or less frequently. Poor responses to diet changes and laxatives are common in this group, and there have been subtle-to-marked changes in enteric neural networks in these patients. Evaluation of constipation must include careful physical examination, including rectal examination (described nicely in the article).

Laboratory tests might include measures of calcium, glucose, blood count, and electrolytes. Any “alarm” symptoms mandate anatomic examination of the colon. Colonoscopy should always be done in patients older than 50 years. Physiological examinations such as anal-rectal manometry, defecography, and colon transit times are only needed in patients found to be refractory to simple therapeutic maneuvers. Contrary to the opinions held by some, there is no role of increased fluid intake in patients who are not dehydrated. Fiber supplements up to 25 g/d are appropriate in patients with normal or slow-transit constipation. If fiber therapy fails, options include osmotic laxatives such as milk of magnesia, polyethylene glycol, or Lactulose. Tegaserod has been useful in patients with constipation-predominant irritable bowel syndrome. Biofeedback can be very helpful in correction of defecatory disorders. Botulinum toxin injection into the puborectalis muscle has been suggested, but controlled trials are absent. Colectomy and ileorectostomy have been effective for some truly refractory cases of constipation, but complications may be severe after this procedure.

### ■ COMMENT BY MALCOLM ROBINSON MD, FACP, FACG

This article is a very helpful review of a common and often vexing problem for physicians and their patients. In my view, it should be read by all physicians likely to see such patients (and that includes almost all of us). There have been some very important advances in the differential diagnosis and management of chronic constipation since most of us were trained, and it would be wise to take this opportunity for a well-prepared and highly readable update. ■

# Levonorgestrel/Ethinyl Estradiol Tablets (Seasonale)

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

THE FDA HAS APPROVED THE FIRST 91-DAY ORAL CONTRACEPTIVE. The product is taken for 12 weeks (84 days), followed by 1 week of inactive tablets, resulting in 1 menstrual period every 3 months. This new oral contraceptive contains a common estrogen (ethinyl estradiol) and progestin (levonorgestrel) and is marketed by Duramed Pharmaceuticals Inc as Seasonale.

### Indications

Levonorgestrel/ethinyl estradiol (Seasonale) is indicated for the prevention of pregnancy in women.<sup>1</sup>

### Dosage

One active tablet is taken daily for 84 consecutive days followed by 7 days of inactive tablets. The tablets should be taken at the same time of the day each day. The first cycle should begin on the first Sunday after the onset of menstruation or if menstruation begins on a Sunday.<sup>1</sup>

### Potential Advantages

The number of scheduled menstrual cycles is reduced from once monthly to once every 3 months.

### Potential Disadvantages

There is a higher frequency of intermenstrual bleeding and/or spotting compared to 28-day cycle regimens, although these tend to decrease with each successive cycle.<sup>1,2</sup> More subjects discontinue Seasonale compared to a 28-day regimen due to unacceptable intermenstrual bleeding/spotting, 7.7% vs 1.8%.<sup>1</sup> Also, unintentional pregnancies may go undetected for longer periods of time due to the longer interval between menstrual cycles.

### Comments

Seasonale is the first 91-day oral contraceptive. The active ingredients, ethinyl estradiol and levonorgestrel, are the same and contain the same daily doses as the commonly used contraceptives Levlen and Nordette. In the case of Seasonale, women take 3 uninterrupted cycles of active drug. In a 1-year study, 4 pregnancies

occurred over 809 completed 91-day cycles. This represents an overall use-efficacy (typical user efficacy) pregnancy rate of 1.98 per 100 women-years of use.<sup>1</sup> When Seasonale (4 cycles) was compared to a 28-day regimen Nordette (13 cycles), the Pearl Index based in method failure was 0.55 per 100 women compared to 1.45 for Nordette.<sup>2</sup> The primary advantages for women are fewer scheduled menstrual cycles compared to a 28-day regimen. The primary disadvantage is higher frequency of intermenstrual bleeding and/or spotting, particularly in the first cycle. Percent of subjects with 7 or more days of bleeding and/or spotting in the first cycle of Seasonale was 65% compared to 38% in users of the first 4 cycles of a 28-day regimen.<sup>1</sup> Similarly, the percentage of patients with 20 or more days of bleeding and/or spotting was 35% and 6%, respectively. However, over 1 year of use the total days (withdrawal and intermenstrual) were similar.<sup>1</sup> Seasonale is priced comparably to other branded oral contraceptives. Its wholesale cost is about \$96 for a 91-day cycle compared to about \$89 for 3 28-day cycles of Nordette. The company is expected to seek FDA approval of a low-dose formulation of Seasonale in 2004.<sup>3</sup>

### Clinical Implications

Seasonale provides an option for women who elect to have a fewer number of scheduled menstrual cycles. However, some may find the higher frequency of intermenstrual bleeding and/or spotting unacceptable. ■

### References

1. Seasonale Product Information. Barr Laboratories, Inc. September 2003.
2. Anderson FD, et al. *Contraception*. 2003;68(2):89-96.
3. FDC Report. *The Pink Sheet*. 2003;65(37):38-39.

## CME Questions

### 19. Chronic constipation can be managed by which of the following modalities?

- a. Osmotic laxatives such as milk of magnesia, Lactulose, and polyethylene glycol
- b. Subtotal colectomy and ileorectal anastomosis
- c. Biofeedback for pelvic floor and anorectal motor dysfunction
- d. Substantial supplementation of dietary fiber
- e. All of the above

### 20. Which of the following statements is false?

- a. A change in fat intake was important in lowering the glucose in the patients on the high protein diet.
- b. The plasma C-peptide and insulin levels were unchanged in the high protein diet.
- c. The glycosylated hemoglobin levels were decreased during a high protein euglycemic diet.

**21. *H. pylori* eradication was obtained in what percentage of patients treated with a done-day quadruple therapy regimen?**

- a. 15%
- b. 35%
- c. 55%
- d. 95%
- e. 100%

**Answers: 19 (e); 20 (a); 21 (d)**

*Readers are Invited. . .*

Readers are invited to submit questions or comments on material seen in or relevant to *Internal Medicine Alert*. Send your questions to: Robert Kimball, *Internal Medicine Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *Internal Medicine Alert* via the internet by sending e-mail to robert.kimball@ahcpub.com. We look forward to hearing from you. ■

**AHC Online**  
**Your One-Stop Resource on the Web**

More than 60 titles available.  
Visit our Web site for a complete listing.

1. Point your Web browser to:  
<http://www.ahcpub.com/online.html>
2. Select the link for "AHC Online's Home page."
3. Click on "Sign On" at the bottom of the page.
4. Click on "Register now." (It costs nothing to register!)
5. Create your own user name and password.
6. Sign on.
7. Click on "Search" at the bottom of the page.
8. Perform a search and view the results.

If you had a subscription to a product, the price next to the search results for that product would say "FREE." Otherwise, the pay-per-view cost per article is displayed. To take a look at a sample article, click on "Content" at the bottom of the screen. Select Clinical Cardiology Alert, Archives, 1997, January 1, and the first article, "More Good News About Beta Blockers." We've made this article free so you can see some sample content. You can read it online or print it out on your laser printer.

**Test Drive AHC Online Today!**

**Annual Statement of Ownership, Management, and Circulation**

1. Publication Title <b>Internal Medicine Alert</b>		2. Publication No. 0 1 9 5 - 3 1 5 X		3. Filing Date 10/01/03	
4. Issue Frequency Bi-Weekly		5. Number of Issues Published Annually 24		6. Annual Subscription Price \$249.00	
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 Robin Salet Telephone 404/262-5489	
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)  
Brenda Mooney, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

Editor (Name and Complete Mailing Address)  
Rob Kimball, same as above

Managing Editor (Name and Complete Mailing Address)  
Glen Harris, same as above

10. Owner (Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual. If the publication is published by a nonprofit organization, give its name and address.)

Full Name	Complete Mailing Address
Thomson American Health Consultants	3525 Piedmont Road, Bldg. 6, Ste 400 Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box  None

Full Name	Complete Mailing Address
Thomson Healthcare, Inc.	Five Paragon Drive Montvale, NJ 07645

12. Tax Status (For completion by nonprofit organizations authorized to mail at nonprofit rates.) (Check one)  
 The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes.  
 Has Not Changed During Preceding 12 Months  
 Has Changed During Preceding 12 Months (Publisher must submit explanation of change with this statement)

13. Publication Name  
**Internal Medicine Alert**

14. Issue Date for Circulation Data Below  
September 15 2003

15. Extent and Nature of Circulation	Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies (Net Press Run)	4341	3785
(1) Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. (Include advertiser's proof and exchange copies)	3463	3201
b. Paid and/or Requested Circulation	12	10
(2) Paid In-County Subscriptions (include advertiser's proof and exchange copies)	61	55
(3) Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	69	69
(4) Other Classes Mailed Through the USPS	3605	3335
c. Total Paid and/or Requested Circulation (Sum of 15b(1) and 15b(2))	24	27
(1) Outside-County as Stated on Form 3541	1	1
d. Free Distribution by Mail (Samples, Complimentary and Other Free)	0	0
(2) In-County as Stated on Form 3541	25	25
(3) Other Classes Mailed Through the USPS	50	53
e. Free Distribution Outside the Mail (Carriers or Other Means)	3655	3388
f. Total Free Distribution (Sum of 15d and 15e)	686	397
g. Total Distribution (Sum of 15c and 15f)	4341	3785
h. Copies Not Distributed	99	98
i. Total (Sum of 15g, and h.)	99	98

Percent Paid and/or Requested Circulation (15c divided by 15g times 100)  
 16. Publication of Statement of Ownership  
 Publication required. Will be printed in the **October 2003** issue of this publication.  Publication not required.

17. Signature of Editor, Publisher, Business Manager, or Owner  
 Signature: *Brenda L. Mooney*  
 Title: **Publisher**  
 Date: **9/30/03**

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

- Instructions to Publishers**
1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
  2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
  3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
  4. Item 15h, Copies Not Distributed, must include (1) newstand copies originally stated on Form 3541, and returned to the publisher, (2) estimated returns from news agents, and (3) copies for office use, leftovers, spoiled, and all other copies not distributed.
  5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or if the publication is not published during October, the first issue printed after October.
  6. In item 16, indicate date of the issue in which this Statement of Ownership will be published.
  7. Item 17 must be signed.  
**Failure to file or publish a statement of ownership may lead to suspension of second-class authorization.**

By Louis Kuritzky, MD

## Weight Loss in Type 2 Diabetes

**M**OST SUBJECTS WITH TYPE 2 DIABETES (DM2) are overweight. There is abundant support for the diverse benefits of weight loss in DM2, including improved insulin resistance, lipid profiles, and blood pressure, to name but a few. Unfortunately, weight loss is a very daunting challenge for most DM2 patients, often complicated by the fact that some hypoglycemic pharmacotherapies tend to induce weight gain.

In DM2, besides traditional weight loss programs, little information has been shared regarding novel dietary approaches, such as meal replacement programs (MRP) or repetitive low-calorie diets, especially in combination with pharmacotherapy.

This trial involved overweight or obese DM2 subjects (n = 61), all of whom, after calculation of daily basal energy requirement, received advice on a traditional reduced calorie diet (500-1000 Kcal reduction daily) plus exercise (recommended 30 minutes thrice weekly). Those randomized to the combination therapy received, in addition, sibutramine 10-15 mg/d and replacement meals (consisting of 900-1300 Kcal/d of meal shakes or bars, administered as 220 Kcal 4-6 times daily). Subjects were instructed to use meal replacements as their sole nutrition for 1 week every 2 months, and use the meal replacement products (calories = 340) to substitute for a single meal each day during the non-low-calorie MRP weeks.

At 1 year, weight loss in the combined treatment group was greater than the standard treatment group, including a 6.4% decline from baseline body weight. This intensive regimen provided greater effect upon weight loss and

A1C than some prior trials. Long-term maintenance of weight reduction has remained an elusive goal, and whether study subjects could maintain these favorable changes for a greater duration is unknown. ■

*Redmon JB, et al. Diabetes Care. 2003;26:2505-2511.*

## Dalteparin and Chronic Foot Ulcers in Diabetics with PAD

**T**HE INCREASING PREVALENCE OF type 2 diabetes (DM2) will be likely accompanied by an increase of late-onset diabetic complications, such as chronic foot ulcers (CFU). One of the limiting factors in healing CFU is the microcirculatory impairment found in DM2.

Consecutive DM2 patients with CFU (n = 87) were randomly assigned in a double-blind fashion to dalteparin 5000 units SQ daily (or a similar volume of saline). Treatment continued until the ulcer healed, or up to 6 months. Traditional ulcer care by appropriate consultants was provided to all patients.

There were 2 patients withdrawn from the study, one because of a bleeding event and one because of superficial skin necrosis at the injection sites (although concomitant insulin administration at the same sites complicates attributing etiology).

The number of patients with completely healed ulcers or markedly reduced ulcer size was much superior in the dalteparin group (29 vs 20 patients). The number of amputations in the dalteparin group was also substantially lower (2 vs 8). Dalteparin may be considered in addition to traditional therapies for foot ulcers in DM2 patients with peripheral arterial occlusive disease. ■

*Kalani M, et al. Diabetes Care. 2003;26:2575-2580.*

## Pioglitazone and LDL in Nondiabetic Hypertensives

**T**HE ROLE OF LDL IN DEVELOPMENT of arteriosclerotic disease is well established. In some patient groups, especially diabetics, the type of LDL appears to be as (or more) important than the absolute amount of LDL. That is, small dense LDL (SDLDL), which is disproportionately present in type 2 diabetics (and especially when diabetes control is poor), is associated with a marked increased cardiovascular risk.

Hypertension is sometimes described as a syndrome, rather than a single physical finding, because of its frequent concomitance with dyslipidemia, insulin resistance, and obesity. As among diabetics, SDLDL is disproportionately present in hypertension. Although pioglitazone (PIO) is typically considered as a hypoglycemic agent, it has previously been shown to reduce SDLDL levels as well. Whether this beneficial effect might also occur with hypertensive, nondiabetic subjects was the object of inquiry in this trial.

Patients with hypertension (n = 60) were randomized to PIO 45 mg/d or placebo for 16 weeks. At the end of that time, patients on PIO enjoyed a decline of 22% in SDLDL levels, with no demonstrable effect on total triglycerides, LDL, or HDL. Glitazones appear to act through the peroxisome proliferators-activated receptor-gamma (PPAR-gamma) and may ultimately have a role in correcting or improving dyslipidemia associated with both diabetes and hypertension. ■

*Winkler K, et al. Diabetes Care. 2003;26:2588-2594.*

## In Future Issues:

Exercise, Breast Cancer, and Menopause