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

Which is More Important, the Level of the LDL Cholesterol or the C-reactive Protein?

ABSTRACT & COMMENTARY

Synopsis: *The CRP and the LDL-C are independent predictors of cardiovascular risk.*

Source: Ridker PM, et al. *N Engl J Med*. 2005;352:20-28.

STATINS LOWER THE LEVELS OF C-REACTIVE PROTEIN (CRP) AS well as the levels of LDL cholesterol (LDL-C). Whether lowering the CRP affects the clinical outcomes of statin therapy has not previously been investigated.

The study population was derived from the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombosis in Myocardial Infarction 22 study (PROVE IT-TIMI 22), performed between November 2000 and February 2004; it involved 4162 patients who had been hospitalized in the preceding 10 days with acute coronary syndromes.

In this study, patients in whom statin therapy resulted in LDL-C levels of less than 70 mg/dL had lower event rates than those with higher levels (2.7 vs 4.0 event per 100 person years; $P = 0.008$). However, virtually an identical difference was observed between those who had CRP levels less than 2 mg/L after statin therapy and those who had higher levels (2.8 vs 3.9 events per 100 person-years; $P = 0.006$), an effect present in all levels of LDL-C achieved. For patients with post-treatment LDL-C levels of more than 70 mg/dL, the rates of recurrent events were 4.6 per 100 person-years among those with CRP levels of more than 2 mg/L and 3.2 events per 100 person-years among those with CRP levels of less than 2 mg/L. Although atorvastatin was more likely than pravastatin to result in low levels of LDL-C and CRP, meeting these targets was more important than the specific choice of therapy. Patients who had LDL-C levels of less than 70 mg/dL and CRP levels below 1 mg per liter after statin therapy had the lowest rate of recurrent events (1.9 per 100 person years).

Ridker and colleagues concluded that patients who have low CRP levels after statin therapy have better clinical outcomes than those

VOLUME 27 • NUMBER 2 • JANUARY 29, 2005 • PAGES 9-16

with higher CRP levels, regardless of the resultant level of LDL-C. Strategies to lower the cardiovascular risk with statins should include monitoring CRP as well as cholesterol.

COMMENT BY RALPH R. HALL, MD, FACP

In a second article in the same issue of *The New England Journal of Medicine*,[1] Nissen and associates add support to the individual contributions of lipid lowering and the CRP.

Nissen et al performed ultrasonography on 502 patients with angiographically documented coronary disease. Patients were randomly assigned to receive pravastatin 40 mg daily or atorvastatin 80 mg/d. Ultrasonography was repeated after 18 months to measure progression of atherosclerosis. Lipoprotein and CRP levels were measured at base line and at follow-up.

They found a reduced rate of progression of atherosclerosis associated with the more intense atorvastatin therapy than with pravastatin. These findings were significantly related to both the lower lipid levels and the CRP. They suggested that "the level of CRP may ultimately represent an important therapeutic target."

The relationship between CRP and lipid levels is complex. Treating inflammatory rheumatoid arthritis with prednisone or methotrexate results in improvement in the lipid profiles of the patients who have significant clinical improvement and who are not receiving lipid-lowering drugs. It has recently been reported that second-hand smoke will raise the CRP.[2]

A number of questions remain, as these are secondary prevention studies. What is the precise role of CRP levels in primary prevention? Is the age of the patient important when we prescribe intensive statin therapy? The mortality rate of older patients in intensive care units has been reported to be increased in those with lower lipid levels.[3] What is the role of exercise and diet in controlling CRP levels? Observational studies are conflicting as to the role of exercise in lowering the CRP.

The evidence is growing that we should add the CRP to our assessment of patients' risk. The evidence is at least as strong for intensive lipid lowering for patients with risk factors to control both the lipids and the CRP. ■

References

1. Nissen SE, et al. *N Engl J Med*. 2005;352:29-38.
2. Onder R. *Am J Med*. 2003;115:265-271.
3. Panageotakos DC. *Am J Med*. 2004;116:145-150.

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

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

EDITORIAL GROUP HEAD: Lee Landenberger.

MARKETING PRODUCT MANAGER: Schandale Kornegay.

MANAGING EDITOR: Robert Kimball.

ASSOCIATE MANAGING EDITOR: Leslie Hamlin.

GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

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

Back issues: $21. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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: www.ahcpub.com

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $319
(Student/Resident rate: $125).

Multiple Copies
Documents are available for multiple subscriptions. For pricing information, please call Steve Vance at (404) 262-5511.

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, 2005. 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.

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.

THOMSON
AMERICAN HEALTH CONSULTANTS

Questions & Comments

Please call **Robert Kimball**, 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.

Abnormal Bleeding Risk with SSRIs

ABSTRACT & COMMENTARY

Synopsis: *Increased hospitalizations for abnormal bleeding were found in new users of selective serotonin reuptake inhibitor (SSRI) antidepressants, with more risk associated with SSRIs containing greater degrees of serotonin reuptake inhibition.*

Source: Meijer W, et al. *Arch Int Med*. 2004;164:2367-2370.

Using a prescription database of 69,000 new adult antidepressant users over 8 years in the

Netherlands, researchers identified all hospitalizations with a primary diagnosis of abnormal bleeding and linked them to use of antidepressants classified as high, intermediate or low serotonin reuptake inhibition activity. This classification was based on the drug's biochemical affinity for the serotonin transporter which is thought to cause higher inhibition of serotonin reuptake.[1]

Matched case-controls for age and sex were used, and 6.7% were excluded because they received only 1 prescription without refills. Mean age was 58 years. Follow-up ended when a refill gap of more than 30 days or a hospitalization for bleeding occurred; average follow-up was 229 days. Conditional logistic regression was used on the matched sets, with adjustments for the use of other medications.

In the users of the drugs with highest reuptake activity (fluoxetine, sertraline, clomipramine, paroxetine), there was a 2.6-fold increased risk of hospitalization for bleeding compared to users of drugs with lowest activity (trazadone, nortriptyline, doxepin, etc). For intermediate activity (amitriptyline, imipramine, citalopram, etc), there was a 1.9-fold increase.

Total hospitalizations for bleeding were 196 out of 64,647 in the study, giving an incidence of 4.9 per 1000 person-years. Forty-seven percent (47%) were for uterine bleeding (including menorrhagia and postmenopausal bleeding), 16% upper GI bleeding, and 11% cerebral bleeding. Most participants (73.5%) were women.

COMMENT BY MARY ELINA FERRIS, MD

Serotonin in platelets promotes aggregation and blood clotting, and it makes logical sense that SSRIs with the most inhibition of serotonin uptake would lead to more bleeding risk. This study from the Netherlands is intriguing because it differentiates between the numerous SSRIs on the basis of their presumed degree of reuptake inhibition activity and does find an association of more bleeding hospitalizations with more inhibition. This could lead to new research to help clinicians understand the differences among our myriad antidepressant choices.

Case reports and case-control studies have been published showing an association between SSRI use and various kinds of abnormal bleeding (upper GI bleeding, purpura, epistaxis, intracranial hemorrhage, vaginal bleeding, bleeding during surgery), with further increased risks shown when SSRIs are taken along with aspirin or NSAIDs.[2] Abnormal bleeding and altered platelet function are listed as potential side effects in the product literature for many SSRIs.

However, this association does not prove a cause-and-effect relationship, and actual platelet aggregation/coagulation studies have not shown measurable impaired hemostasis.[3] Unfortunately, there does not appear to be a benefit of SSRI use to prevent the development of first-time acute MI,[4] but that study did not differentiate SSRI's by level of activity. In the meantime, it would seem prudent to be cautious when using SSRIs with the highest reuptake activity in those patients with pre-existing bleeding risks. ■

References

1. van Walraven C, et al. *BMJ*. 1999; 319:1106-1109.
2. Dalton S, et al. *Arch Int Med*. 2003;163:59-64.
3. Alderman C, et al. *Ann Pharmacother*. 1996;30: 1232-1234.
4. Meier C, et al. *Br J Pharmacol*. 2001;52:179-184.

Barrett's Esophagus Progression and Proton Pump Inhibitors

ABSTRACT & COMMENTARY

Synopsis: *Examining data from a 20-year time period, correlations were sought between antisecretory drug therapy and cumulative incidence of dysplasia. Incidence of dysplasia was significantly lower in patients who had received proton pump inhibitor (PPI) therapy vs no therapy or H2-receptor antagonists (H2RAs).*

Source: Alter MJ, et al. *Ann Intern Med*. 2004;141:715-717.

Chronic acid reflux is thought to underlie the pathogenesis of Barrett's esophagus (BE; (change from normal squamous mucosa to specialized columnar metaplasia). BE underlies most or all cases of esophageal adenocarcinoma, and it is believed by many that continued acid exposure increases adenocarcinoma risk. It has been speculated that acid suppression might alter cancer risk in this setting, but results of studies have not been conclusive one way or the other. This retrospective analysis of patients followed at the Tucson, Arizona, VA hospital between 1981 and 2000 attempts to compare patients with BE who received acid suppressive therapy with those who did not; 236 patients who initially presented without dysplasia were analyzed. Also, 155 patients (66%) received a PPI, and 149 patients got H2RAs, and 21 received neither. Fifty-six (56) patients developed dysplasia during a total follow-up of 1170 patient years creating an incidence rate of

4.7% per year. Dysplasia developed in 9 of 19 patients on neither medication, and in 25 of 64 patients taking H2RAs. PPI therapy given after diagnosis was associated with less dysplasia. At 5 years, dysplasia with PPI therapy was 11% vs 37%; at 10 years, results were 21% vs 58%. Time of diagnosis and length of Barrett's mucosa and grade of dysplasia did not alter these findings. The authors believe that these data strongly suggest that potent acid suppression can alter the progression from metaplasia to dysplasia.

COMMENT BY MALCOLM ROBINSON, MD, FACP, FACG

Alter and colleagues discuss some of the potential defects of the study. For example, prescriptions obtained outside of the VA system would not have been tracked. There were 2 cases of adenocarcinoma in patients who didn't demonstrate previous dysplasia. Both had received PPIs. Alter et al provide lots of useful information on the probable contributions of acid reflux and chronic inflammation to abnormal cellular proliferation. They mention the failure of prior studies of medical and surgical antireflux therapy to alter evolution to esophageal adenocarcinoma. Finally, they admit that prospective randomized data collection is necessary to confirm these findings.

An accompanying editorial by Dr. Thomas Schnell outlines other potential flaws to the conclusions of the Tucson VA study. He points out that acid suppression itself has been accused of promoting cancer, and he reiterates the considerable existing data that negate any protective effect of acid suppression on cancer progression in BE. Alter et al and the editorial both mention the fact that there is poor inter-observer agreement regarding the presence or absence of low-grade or indeterminate dysplasia (vs no dysplasia). There is of course no data on what happened to these patients prior to study entry, and many factors could impact later cancer risk (toxin exposure, diet, etc). The relatively brief exposure to PPIs in this study (only 1-2 years generally) was described by Dr. Schnell as terribly brief to have an effect on years of carcinogenesis. Nevertheless, on balance, this article is certainly ammunition for those who urge that all patients with BE be treated with PPIs (whether they have symptoms or not). I am not so sure about this conclusion, but I must admit that my doubt regarding PPI use in this setting has been shaken. We must all hope that well designed future prospective studies will provide an answer that all of us can accept in terms of the continued chronic and indefinitely prolonged use of expensive PPIs in any major subset of GERD patients. ■

Antiplatelet or Anticoagulant Therapy in Atrial Fibrillation

ABSTRACT & COMMENTARY

Synopsis: *The addition of antiplatelet therapy to reduced intensity anticoagulation in atrial fibrillation patients reduces death and embolic events without increasing bleeding.*

Source: Perez-Gomez F, et al. J Am Coll Cardiol. 2004;44: 1557-1566.

In this study, Perez-Gomez and colleagues report the results of the National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF) trial. The hypothesis for this trial was that the addition of an antiplatelet agent to a moderate intensity anticoagulant regimen would improve mortality and embolic events in atrial fibrillation patients at intermediate or high risk for such events. Patients were eligible for the study if they had either intermittent or persistent atrial fibrillation and were either older than age 60 or had other risk factors for embolic events. The high-risk group consisted of 495 patients with a history of prior embolism and/or mitral stenosis. The intermediate group consisted of 714 patients without mitral stenosis or prior embolism. Patients with prosthetic valves, a stroke in the previous 6 months, renal insufficiency, uncontrolled hypertension, or other indications for nonsteroidal, inflammatory, antiplatelet drugs or anticoagulants were excluded.

The antiplatelet agent used in the study was triflusal, a drug structurally similar to acetylsalicylic acid. Triflusal was administered at a dose of 600 mg per day, the equivalent of 300 mg of aspirin per day. The anticoagulant used was acenocumarol, the coumarin derivative most commonly used in Spain. In the intermediate risk group, patients were randomized between antiplatelet therapy only, anticoagulant therapy with a target INR of 2-3, and combination therapy with triflusal and acenocumarol, with a target INR of 1.25-2. In the high-risk group, patients were randomized to either anticoagulant therapy with a target INR of 2-3 or combination therapy with triflusal and an INR range of 1.4-2.4.

The primary outcome was a composite of vascular death, transient ischemic attack, nonfatal stroke, and systemic embolism. Secondary end points were severe bleeding, myocardial infarction, nonvascular

death, and minor bleeding.

In the intermediate risk group, the annual event rates for the combined primary end points were 3.82% in the triflusal group, 2.70% in the anticoagulant group, and 0.92% in the combined therapy group. In the high-risk group, the annual event rates for the composite end point were 4.76% in the anticoagulant only group and 2.44% in the combined triflusal-anticoagulant group. Among the intermediate risk patients, the annual rates for severe bleeding were 0.35% in the triflusal group, 1.8% in the anticoagulant group, and 0.9% in the combined therapy group. In the high-risk group, the annual rate for severe bleeding was 2.1% in the anticoagulant group and 2.1% in the combined therapy group. Actuarial analysis of the primary composite end point showed that combined therapy was superior to the other treatment modalities in both the intermediate and high-risk patients.

Perez-Gomez et al concluded that addition of antiplatelet therapy to reduced intensity anticoagulation in atrial fibrillation patients reduces death and embolic events without increasing bleeding.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Numerous studies have established the value of warfarin anticoagulation in patients with valvular and nonvalvular atrial fibrillation. When warfarin is used alone, the optimal target INR appears to be 2-3. Attempts to use warfarin at a dose that would produce only minimal or no changes in the INR in combination with antiplatelet therapy have been unsuccessful. In this paper, Perez-Gomez et al attempted to use a moderate reduction in target INR in association with antiplatelet therapy in both a very high risk group and an intermediate risk group. Although the study group is relatively small, the data do suggest that this approach may be effective. The key difference between this and prior studies is that the reduction in anticoagulation target intensity was only moderate.

In the intermediate group, the median INR was 1.93 vs 2.47 in the anticoagulant group. Adherence to this target was quite good. Two-thirds of the INR values were within the prescribed range in both groups. In the high-risk group, the median INR in the combined therapy group was 2.17 and in the anticoagulant group it was 2.50. By lowering the target INR, Perez-Gomez et al were able to add an antiplatelet agent without increasing bleeding or losing the benefits of anticoagulation.

These data suggest that very careful monitoring of INR during warfarin therapy, plus the addition of an antiplatelet agent, can allow lower targets to be used without detrimental effects. This approach may be of benefit for patients who have a perceived increased risk for bleeding, in whom physicians might otherwise be reluctant to use standard anticoagulant therapy, despite the presence of atrial fibrillation. ■

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

Statin Metabolism Interactions

ABSTRACT & COMMENTARY

Synopsis: *Pravastatin is the statin with the least interactions with cytochrome P450-(CYP) 3A4 inhibitors.*

Source: Jacobson TA. *Am J Cardiol*. 2004;94:1140-1146.

STATINS HAVE BECOME THE MAINSTAY OF PREVEN-tive cardiology. However, concern continues regarding the potential for rhabdomyolysis, especially at higher doses of these agents. Thus, Jacobson studied 4 groups of healthy subjects to assess the pharmacokinetics of: 1) 40 mg pravastatin or 40 mg simvastatin coadministered with 480 mg verapamil; 2) 40 mg pravastatin or 80 mg of atorvastatin plus 100 mg mibefradil; 3) 40 mg pravastatin or 80 mg atorvastatin plus 200 mg itraconazole; and 4) 40 mg pravastatin, 40 mg simvastatin, or 80 atorvastatin plus 500 mg clarithromycin.

When compared to pravastatin alone, coadministration of verapamil, mibefradil, or itraconazole with pravastatin did not alter pravastatin pharmacokinetics. Clarithromycin did increase the area under the curve (AUC) of plasma pravastatin (100% $P < .001$), but increased the AUC of simvastatin 219% and atorvastatin 343%. Verapamil increased simvastatin AUC 4-fold. Mibefradil increased atorvastatin AUC > 4-fold, and itraconazole increased atorvastatin AUC 47%. Clarithromycin increased the AUC of all 3 statins; simvastatin 10 fold, atorvastatin > 4-fold, and pravastatin almost 2-fold. Jacobson concluded that

pravastatin is the statin with the least interactions with cytochrome P450-(CYP) 3A4 inhibitors.

COMMENT BY MICHAEL H. CRAWFORD, MD

The withdrawal of cervastatin from the market, and the recent physician notification that the starting dose of rosuvastatin is 10 mg, underscores the concern about anything that may increase the incidence of the rare but serious adverse reaction of rhabdomyolysis, which is dose related. Coadministration of other agents that share the CYP receptor may lead to increased serum levels of certain statins for prolonged periods. These agents include gemfibrozil, calcium channel blockers, immunosuppressives, macrolide antibiotics, certain antifungal agents, protease inhibitors of HIV, amiodarone, and grapefruit juice.

Some have estimated that more than half the rhabdomyolysis cases reported to the FDA involved coadministration of other CYP inhibitors. In fact, the package insert for simvastatin recommends a daily dose no higher than 20 mg with the coadministration of verapamil or amiodarone. Simvastatin and atorvastatin are lipophilic statins which demonstrate profound increases in drug levels over time when given with CYP inhibitors. Pravastatin is hydrophilic and is not a CYP substrate. Mibefradil is a T-channel calcium blocker, which is a strong CYP inhibitor and was withdrawn from the US market because of numerous serious drug interactions. However, in this study, it did not interact with pravastatin. Other studies have shown an overall extremely low incidence of rhabdomyolysis with pravastatin, 0.04 per million prescriptions vs 0.12 for simvastatin, 0.10 for lovastatin and 3.2 for cerivastatin.

The down side of pravastatin is that it is not a particularly potent statin and may require concomitant lipid-lowering agents to get the desired effect. This may be the reason that Merck came out with Vytorin™, which combines lower doses of simvastatin with ezetimibe. Thus, when using more potent statins, one must weigh the tiny risk of rhabdomyolysis against the major benefits of effective lipid-lowering in patients with vascular disease. However, care must be taken when the coadministration of CYP inhibitors is necessary. In these situations, pravastatin may be an alternative if lipid targets can be met. ■

Dr. Crawford is Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco

Pharmacology Update

Eszopiclone Tablets (Lunesta™)

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

A NEW NONBENZODIAZEPINE HYPNOTIC HAS BEEN approved by the FDA for the treatment of insomnia. Eszopiclone is the active (S)-isomer of zopiclone that is available outside of the United States. It shares pharmacological characteristics with other nonbenzodiazepine agents such as zolpidem and zaleplon. Eszopiclone is marketed by Sepracor as Lunesta™.

Indications

Eszopiclone is indicated for the treatment of insomnia.[1]

Dosage

The recommended starting dose is 2 mg immediately before bedtime for those with difficulty in falling asleep. The dose may be increased to 3 mg for sleep maintenance. For elderly patients the recommended dose is 1 mg and 2 mg respectively.[1]

Eszopiclone is available as 1 mg, 2 mg, and 3 mg tablets.

Potential Advantages

Zolpiclone appears to have greater anxiolytic activity than zolpidem or zaleplon.[2] Eszopiclone may provide better relief of anxiety with less sedation compared to zopiclone.[3,4] Unlike zolpidem or zaleplon, eszopiclone is not limited to short-term use by FDA-approved labeling.

Potential Disadvantages

Eszopiclone has an elimination half-life of approximately 6 hours. It may be less effective in reducing sleep latency than agents with shorter half-lives (eg, zaleplon), and it may be more likely to have residual next day effects.[5] The racemic form of zopiclone has been associated with residual effects on driving, divided attention, and memory compared to zaleplon and more rebound on discontinuation than zolpidem.[6,7] Most common adverse events associated with eszopiclone are headache (17-21% vs 13% for placebo) and unpleasant taste (17-34% vs 3%).[1]

Comments

Eszopiclone is the pure (S)-isomer of zopiclone one

of the 3 nonbenzodiazepine hypnosedatives. They offer some advantages over benzodiazepines in terms of tolerance, dependence, and withdrawal.[2] In a randomized, double-blind, placebo-controlled study eszopiclone significantly improved sleep latency, wake time after sleep onset, number of awakenings, sleep time, and quality of sleep compared to placebo.[8] No evidence of tolerance was reported. After 6-weeks of use, discontinuation-emergent effect appeared to be mild and, while sleep efficiency was reduced, it appeared to be resolved by the second night after discontinuation.[1] There are currently no published comparative trials with other nonbenzodiazepine agents as comparative trials have been with the racemic form. Zopiclone is associated with more cognitive and memory affect than zaleplon and with more withdrawal effects than zaleplon and zolpidem.[9] The group has a whole has been associated with a low incidence of dependence compared to benzodiazepine.[10] The wholesale cost of eszopiclone ranges from $2.80 to $3 per day and is about 50 cents to $1 higher than zolpidem or zaleplon.

Clinical Implications

Eszopiclone does not appear to offer any clear clinical advantages over available nonbenzodiazepine drugs such as zaleplon and zolpidem. ■

References

1. Lunesta Product Information. Sepracor Inc. December 2004.
2. Drover DR. *Clin Pharmacokinet*. 2004;43(4):227-238.
3. Carlson JN, et al. *Eur J Pharmacol*. 2001;415(2-3): 181-189.
4. Georgiev V. *Curr Opin Investig Drugs*. 2001;2:271-273.
5. Nakajima T, et al. *Psychiatry Clin Neurosci*. 2000; 54(1):37-40.
6. Vermeeren A, et al. *Sleep*. 2002;15:25(2):224-231.
7. Tsutusi S, et al. *J Int Med Res*. 2001;29(3):163-177.
8. Krystal AD, et al. *Sleep*. 2003;26(7):793-799.
9. Terzano MG, et al. *Drug Safety*. 2003;26(4):261-282.
10. Hajak G, et al. *Addiction*. 2003;98(10):1371-1378.

CME Questions

3. **The Tucson VA study describes a population of patients with Barrett's esophagus who were treated with PPIs, H2RAs, or neither. What was the risk of developing dysplasia or adenocarcinoma of the esophagus in PPI recipients over 10 years of follow-up?**
   a. 5% of patients developed adenocarcinoma of the esophagus.
   b. 2 patients developed adenocarcinoma of the esophagus.
   c. 75% of Barrett's esophagus patients got cancer over 10 years.
   d. 21% of patients developed dysplasia.
   e. 11% of patients developed dysplasia.
4. **Which of the following adverse effects have been associated with SSRI antidepressants?**
   a. Decreased platelet aggregation
   b. Increased first-time acute MI
   c. Increased risk of all hospitalizations
   d. Increased abnormal bleeding
   e. Variable results depending on gender
5. **Which of the following is true?**
   a. The CRP and the LDL-C independently predict risk.
   b. The CRP levels do not fall with intensive lipid therapy.
   c. Second hand smoke does not affect CRP levels.

Answers: 3 (d); 4 (d); 5 (a)

By Louis Kuritzky, MD

Treatment of Recent-Onset AF with the Pill-in-the-Pocket

ALTHOUGH CHRONIC ORAL ANTIARrhythmic prophylaxis and catheter ablation both enjoy great success for preventing recurrences of atrial fibrillation (AF), some patients are not appropriate candidates for either method, especially patients with infrequent recurrences of AF. Oral flecainide (FLEC) and propafenone (PRO) are highly efficacious in restoring sinus rhythm as demonstrated for hospitalized patients with recent onset AF.

Alboni and colleagues studied the feasibility of patient-administered FLEC or PRO for patients (n = 210) who had successfully responded to emergency room treatment of recent onset AF (< 48 hours). Study participants who experienced symptomatic recurrences presumed to be AF (n = 165) were advised to self-administer PRO or FLEC within 5 minutes of onset of new palpitations. Mean followup was 15 months.

Drug self-administration was effective in resolving symptoms in 94% of episodes, with a mean time to resolution of approximately 2 hours. There was a concomitant dramatic decline in the need for emergency room visits compared with the year prior to the study.

These results show promise for self-administration of PRO or FLEC for persons with recent onset of AF who have previously responded in the emergency room to antiarrhythmic treatment. Because the list of exclusions in this trial was long, clinicians will want to familiarize themselves with the full details of appropriate inclusion and exclusion before considering such methodology for their own patients in non-research settings. ■

Alboni P, et al. N Engl J Med 2004;351: 2384-2391.

Antibody Responses after Intradermal Flu Vaccination

THE YEAR 2004 WAS UNUSUAL IN REFerence to problematic shortages of influenza vaccine (FLUVAX), resulting in vaccine rationing. One of the methods that might reduce the actual volume of vaccine needed in any season would be intradermal vaccination, as opposed to the traditional IM route currently advocated for FLUVAX administration. Support for this method is predicated upon the observation that intradermal vaccine provides greater exposure to macrophages and dendritic cells than IM, and hence induces a similar serum antibody response, using less vaccine.

Belshe and associates studied the immunogenicity of intradermal FLUVAX in 2 groups of adults: age 18-60, and age older than 60. The intradermal formulation they studied was 40% of the strength of standard IM vaccine, and was administered by a tuberculin syringe.

Amongst younger subjects, the immune responses of IM and intradermal administrations were essentially equivalent. In subjects older than 60 years, antibody titers were significantly lower than achieved by IM methodology, but were still sufficient to meet the criteria of the European Committee for Proprietary Medicinal Products that ensure vaccine adequacy. Conceivably, during times of vaccine shortage, administration of smaller volumes of FLUVAX intradermally, especially to younger recipients, would be a rational choice. ■

Belshe RB, et al. N Engl J Med. 2004;351:2286-2294.

Isosorbide Dinitrate and Hydralazine in Blacks with HF

NEUROHUMORAL MODULATORS SUCH as ACE inhibitors, angiotensin receptor blockers, beta blockers, and aldosterone have all shown meaningful benefit for patients with chronic heart failure (CHF). Retrospective analyses of trials including significant populations of black patients have suggested that this group, which appears to have less intense activation of the renin-angiotensin-aldosterone system in CHF than non-black comparators, enjoys a significant responsivity to administration of nitrates and hydralazine.

This trial was performed to investigate the impact of nitrates (specifically, isosorbide dinitrate titrated to 40 mg t.i.d.) and hydralazine (titrated to 75 mg t.i.d.) in patients with NYHA Class II-IV CHF already receiving standard therapy, which includes ACE inhibitors, angiotensin receptor blockers, beta blockers, spironolactone, and digoxin. The primary efficacy end point was a composite of death from any cause, first hospitalization for heart failure, and quality of life.

The study was terminated early because of a statistically significant favorable impact of active intervention, including a 43% relative reduction in death from any cause, 33% reduction in first hospitalization, and improvement in quality of life. Black patients already receiving standard therapy for CHF may benefit from the addition of both hydralazine and nitrates. ■

Taylor AL, et al. N Engl J Med. 2004;351:2049-2057.

In Future Issues: Colonoscopy for Young Patients with Hematochezia