Providing Evidence-based Clinical Information for 25 Years

INTERNAL MEDICINE ALERT®

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

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

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

THOMSON
AMERICAN HEALTH CONSULTANTS

INSIDE

The case of the contaminated keyboard ***page 90***

Clinical outcomes and health care costs for physician-diagnosed peptic ulcer disease ***page 91***

Oregon's assisted suicide program ***page 92***

Effect of Lipid-Lowering Therapies on Stroke Prevention

ABSTRACT & COMMENTARY

Synopsis: *Lipid-lowering therapy reduces stroke incidence in coronary patients, especially when total cholesterol level is lowered to less than 232 mg/dL (6.0 mmol/L), which explains the best results being obtained with statins.*

Source: Corvol JC, et al. *Arch Intern Med*. 2003;163:669-676.

STROKE IS THE THIRD LEADING CAUSE OF MORTALITY IN THE United States after coronary heart disease and cancer and is the leading cause of disability.[1] Primary end points in clinical trials using lipid-lowering therapies have usually been coronary events and/or mortality and, in fact, as of this date no randomized trials with stroke as the primary end point have been completed. However, data from many randomized trials have clearly suggested that cholesterol lowering produced primarily by hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) effectively reduces stroke incidence.[2-6]

Corvol and associates carefully evaluated the effects of lipid-lowering therapy on stroke prevention in coronary patients by conducting a meta-analysis of the literature from 1966 through 2001 including randomized trials of primary and secondary coronary artery disease prevention using satins and nonstatin drugs, diet, and other interventions that provided data on stroke incidence. They analyzed 38 trials that studied 83,161 patients for an average follow-up of 4.7 years. The results of this literature search revealed that lipid-lowering therapy significantly reduced all (fatal plus nonfatal) stroke incidence by 17 percent. However, the best efficacy was obtained with statin therapy (ie, relative risk reduction of 24%) and secondary prevention (ie, relative risk reduction of 26%). Stroke incidence reduction was significantly correlated with cholesterol reduction, with the final cholesterol level proving to be the best value, which allowed a clear separation between absence or presence of stroke reduction with the best results noted to occur when the cholesterol level was less than 232 mg/dL.

COMMENT BY HAROLD L. KARPMAN, MD, FACC, FACP

The results of the meta-analysis conducted by Corvol et al pro-

VOLUME 25 • NUMBER 12 • JUNE 29, 2003 • PAGES 89-96

vide strong evidence in favor of the potential of lipid-lowering therapy to prevent stroke. The most convincing results were obtained using statin drugs—probably a reflection of the efficacy of these agents in their ability to lower blood lipid levels. However, since none of the published trials have had stroke as the primary end point, the incidence of stroke was very low, especially is the case of primary cardiovascular disease prevention, thereby reducing the power of the comparison. In fact, stroke reduction proved to be significant only in cardiovascular secondary prevention (19%) and not in primary prevention (5%) presumably because the ages included in the primary prevention studies were much lower. Controlled lipid-lowering trials that have stroke prevention as a primary end point are ongoing and will include a much more aged population who obviously are at a higher risk of stroke.

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 Kornegay.

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.

Back issues: $20. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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) 262-5480 (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: $289
(Student/Resident rate: $145).

Multiple Copies
1-9 additional copies: $215 each; 10 or more copies: $191each.

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.

In cardiovascular secondary prevention trials, statins reduced stroke incidence by 26%, which is close to the benefit obtained with antithrombotic drugs in secondary prevention of stroke.[7,8] The best effects were attained with statins because either stroke prevention with lipid-lowering therapy is related to cholesterol lowering (nonstatin therapies are less effective than statins are in this biochemical action) or because statins have other properties in addition to cholesterol lowering that may explain their ability to reduce stroke incidence. It appears to be critical to reduce the final cholesterol levels to less than 232 mg/dL with whatever drug is being used to reduce the cholesterol level.

In summary, lipid-lowering therapy appears to reduce stroke incidence in coronary artery disease patients, and the benefit appears to relate to the ability of drugs to lower the blood cholesterol level adequately. Therefore, it would appear that statin drug therapy may be extended to the higher-risk stroke population both for primary and secondary prevention, especially if ongoing randomized clinical trials confirm the findings of the meta- analysis performed by Corvol et al. ■

References

1. Williams GR, et al. *Stroke*. 1999;30:2523-2528.
2. Blauw GJ, et al. *Stroke*. 1997;28:946-950.
3. Hebert PR, et al. *JAMA*. 1997;278:313-321.
4. Hebert PR, et al. *Arch Intern Med*. 1995;155:50-55.
5. Di Mascio R, et al. *Cerebrovasc Dis*. 2000;10:85-92.
6. Atkins D, et al. *Ann Intern Med*. 1993;119:136-145.
7. The ESPS Group. *Lancet*. 1987;2:1351-1354.
8. Bousser MG, et al. *Stroke*. 1983;14:5-14.

The Case of the Contaminated Keyboard: Does It Compute?

ABSTRACT & COMMENTARY

Synopsis: *Computer keyboards may serve as reservoirs for serious nosocomial pathogens.*

Source: Schultz M, et al. *Infect Control Hosp Epidemiol*. 2003;24:302-303.

Investigators at an urban tertiary care medical center obtained microbial cultures from computer keyboards to determine whether bacterial and fungal organisms contaminated their surfaces.

One hundred samples were taken from keyboards close to patients in high-use areas of the facility. Just

over half of the samples were taken from ambulatory care locations such as hemodialysis and emergency units, while the remainder were selected from acute care medical and surgical units and a long-term care facility.

The researchers found that only 5% of the cultures were negative; the other 95% contained 1 or more organisms. Coagulase-negative staphylococci and *Bacillus* spp. predominated (representing 128 of the total 175 isolates). *Staphylococcus aureus*, Gram-negative bacilli, and enterococcus—more traditional nosocomial pathogens—were isolated 11 times. Interestingly, 3 of the 5 cultures taken from operating room computer keyboards were negative.

Schultz and associates noted that routine cleaning of computer keyboards was not a standard practice in their institution. Given their observation that bacterial contamination of keyboards with potential nosocomial pathogens was common, they strongly recommended that cleaning of keyboards be routine or that other options (such as use of easily sanitized plastic keyboard covers) be considered.

COMMENT BY JERRY D. SMILACK, MD

Computers in patient care areas of hospitals and other medical facilities are now commonplace. Data entry and retrieval before, during, and after patient contact offers the possibility of transmitting microorganisms from patient A to keyboard to patient B. Does this actually happen, and if so how commonly? The answers are not yet known, but this study suggests that there is the potential.

This report is not the first to show that contamination of computer keyboards may be the rule, rather than the exception. Neely et al provided evidence that plastic covers over keyboards served as a reservoir for *Acinetobacter baumannii* in a pediatric burn unit.[1] Bures et al found that 24% of computer keyboards in patient rooms, a nurses' station, and a physicians' station were contaminated with such pathogens as methicillin-resistant *S aureus* (MRSA), enterococci, and a variety of Gram-negative bacilli.[2] They extended their findings to show that environmental and patient MRSA isolates were indistinguishable by pulsed-field gel electrophoresis, suggesting that transmission from patient to environment to patient could indeed occur. They, too, recommended policies of daily cleaning of plastic keyboard covers and intensified handwashing. Others have found similar rates of keyboard contamination as well.[3, 4]

What do these studies tell us? They further document evidence that bacterial contamination occurs on a variety of medical equipment and environmental surfaces and may serve as a source for nosocomial infection. Adherence to routine cleaning and disinfection practices and increased emphasis on, and compliance with, hand hygiene recommendations[5] are critical elements in providing optimal patient care. ■

References

1. Neely AN, et al. *Clin Infect Dis*. 1999;29:1358-1360.
2. Bures S, et al. *Am J Infect Control*. 2000;28:465-471.
3. Devine J, et al. *J Hosp Infect*. 2001;48:72-75.
4. Man GS, et al. *J Hosp Infect*. 2002;52:314-315.
5. Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep*. 2002;51(No. RR16):1-44.

Dr. Smilack is Infectious Disease Consultant, Mayo Clinic, Scottsdale, Scottsdale, Ariz.

Clinical Outcomes and Health Care Costs for Physician-Diagnosed Peptic Ulcer Disease

ABSTRACT & COMMENTARY

Synopsis: *Even in physician-diagnosed peptic ulcer disease, test-and-treat strategy for* H pylori *did not reduce costs, and use of acid-reducing medications remained very high.*

Source: Allison JE, et al. *Arch Intern Med*. 2003;163: 1165-1171.

It has been proposed that peptic ulcer disease (PUD) should lead to treatment for *Helicobacter pylori* (HP) if present. It has been assumed that such HP eradication would eliminate any requirement for future therapy, thus reducing health care costs. In this study by Allison and colleagues, 650 patients on long-term acid suppression for PUD specifically diagnosed by physicians were randomized to test-and-treat (T&T) for HP or usual care. Mean age was 57, 48% of patients were male, and 63% were non-Hispanic whites. Diagnosis of PUD was either based on endoscopy or x-ray or on a typical ulcer history (eg, epigastric pain relieved by food, antacids, H2 receptor antagonists, or PPIs). GERD in the absence of PUD was specifically excluded as was chronic NSAID use. A total of 321 patients were randomized to T&T, and the other 329 were continued on usual management. Only 17% of all study participants had

PUD documented by endoscopy or radiography. Only 38% of all patients had a positive test for HP. Although ulcer-like dyspepsia and use of acid-reducing medications were less likely to be present after 12 months in the T&T subset, 75% of the T&T group continued to use acid blockers. Overall costs were higher in the T&T group than in those receiving usual care, mostly attributable to urea breath testing and to the HP treatment. HP was successfully eradicated in 84% of those found to be positive as analyzed per protocol.

COMMENT BY MALCOLM ROBINSON MD, FACP, FACG

Physician diagnosis of PUD seems to be woefully inadequate, and most patients thought to have this diagnosis prove to have nonulcer dyspepsia. It is clear that HP eradication does not benefit nonulcer dyspepsia. Even in the HP-positive group that was successfully eradicated, 41% still had dyspepsia at the 12-month follow-up. Most patients diagnosed with PUD in this large managed care setting had neither PUD nor HP. Possibly unlike other geographic settings, there seems to be little benefit in the T&T strategy in the United States.

It is possible that results would have been different if only patients with documented PUD were included. However, the increasing incidence of PUD in the absence of HP suggests that even this group might not benefit from HP testing. Nevertheless, most authorities still agree that HP eradication is appropriate with documented infection in the presence of unequivocal gastric or duodenal ulcer or malt lymphoma of the stomach. ■

Oregon's Assisted Suicide Program

ABSTRACT & COMMENTARY

Synopsis: *An update on Oregon's assisted suicide program since it became legal in 1997.*

Source: Hedberg K, et al. *N Engl J Med.* 2003;348:961-964.

Physician-assisted suicide has been legal for terminally ill patients in Oregon since October 1997. Since then, 129 patients have chosen to participate in the program and died after ingestion of lethal medication. More than 90% died at home, and about half died in the presence of their physician. The number of patients participating in the program has steadily increased from 24 people during the first year of the program to 58 people in 2002. Interestingly, not all patients who received prescriptions for lethal medications used them. Eight patients receiving such prescriptions in 2001 and 2002 are still alive.

Of the 129 who died following ingestion of lethal medication, 79% had terminal cancer, 8% had ALS, 6% had COPD, and 7% had AIDS, scleroderma, or other heart and lung disease. Rates of physician-assisted suicide were significantly higher for patients with ALS and terminal cancer than other terminal diseases. Compared with Oregon residents who died of the same underlying disease, rates of physician-assisted suicide were higher among those who were divorced, or had higher levels of education, and they tended to be younger.

COMMENT BY CAROL A. KEMPER, MD, FACP

These data suggest that younger, better-educated people may be more accepting of physician-assisted suicide. Although relatively few people chose to participate, the program appears to be slowly gaining in acceptance. ■

Dr. Kemper is Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases; Santa Clara Valley Medical Center, Santa Clara.Calif.

Iontophoresis for Tennis Elbow

ABSTRACT & COMMENTARY

Synopsis: *Iontophoresis was more effective than placebo in relieving tennis elbow symptoms in the short term.*

Source: Nirschl RP, et al. Iontophoretic administration of dexamethasone sodium phosphate for acute epicondylitis: A randomized, double-blinded, placebo-controlled study. *Am J Sports Med*. 2003;31(2):189-195.

Lateral epicondylitis (tennis elbow) and medial epicondylitis (golfer's elbow) are common complaints for both working and athletically active adults. Inflammation at the common tendon origin due to overuse can lead to degenerative changes, tendinosis, microtears, and amorphous fibrous tissue. Although surgery can be effective at relieving symptoms, there is a

high recurrence rate of at least 15%. Therefore, nonoperative methods for treatment continue to be explored. Iontophoresis is a method to deliver steroid locally with the assistance of a small, external electric current to drive water-soluble drugs through the skin to the target area. Locally high concentrations of drug can be achieved with few systemic side effects.

Nirschl and colleagues performed a randomized, double-blinded, placebo-controlled study of 199 patients with either medial or lateral epicondylitis. Patients received either active drug or placebo on 6 separate occasions 1-3 days apart for a 15-day period of time. They found that the active treatment group that received dexamethasone improved significantly on visual analogue scale ratings (23-mm improvement compared to 14 mm for placebo). The improvement was most notable in the short term with differences becoming less distinct at 1-month follow-up. Other primary variables measured included an investigator's global evaluation scale and a patient's global evaluation scale, both of which were significantly improved for the treatment group in the short term.

Secondary variables included assessment by the investigator of the patient's level of severity. All measures showed improvement for the treatment group regarding pain, tenderness, and assessment of disease severity. Again, differences were more pronounced at short-term follow-up with less distinction at 1 month from treatment. Nirschl et al found on more careful analysis of their data that those patients who received their 6 treatments over fewer total days tended to have more pronounced improvements. Their conclusion was that iontophoresis with dexamethasone was both safe and effective, especially if treatments are condensed over fewer days (10 days or fewer).

COMMENT BY DAVID R. DIDUCH, MS, MD

Tennis elbow or golfer's elbow are very common complaints. Repetitive activities are often the inciting event, but continued use in the work or home environment perpetuates the process. Surgery can be effective but has a high recurrence rate so is often avoided until nonoperative measures have failed. This paper is by Robert Nirschl, probably the leading authority on tennis elbow surgery, and other authors in a multicenter study that was IRB approved and extremely well designed. That the champions for surgery of tennis elbow are presenting this nonoperative treatment underscores the importance of treating these patients without surgery initially.

They found that iontophoresis with dexamethasone was indeed effective. The placebo-controlled, double-blinded design of the study adds credibility to their findings. They were very astute to analyze their data more carefully and determine that condensing the treatments over fewer days was more effective. Although the differences between treatment and control groups were less distinct with longer follow-up, Nirschl et al are encouraged to perform further studies with a more condensed administration of the drug and the addition of therapeutic exercises. None of these patients underwent physical therapy or other modalities to keep the study design as clean as possible. It is likely that in combination we will see even more pronounced effects.

It is also important to note that iontophoresis was found to be a very safe drug delivery method. This provides local delivery of a relatively high concentration of agent without many of the side effects, such as subcutaneous fat necrosis, skin depigmentation, and pain associated with steroid injections. Studies like this that validate safe, effective, nonoperative treatment for common problems are a welcome addition to the literature. ■

Dr. Diduch is Associate Professor, Department of Orthopaedic Surgery, University of Virginia School of Medicine, Charlottesville, Va.

Rapid Parkinsonism Follows 20% of Cirrhosis

ABSTRACT & COMMENTARY

Synopsis: *Cirrhosis-related parkinsonism may represent a unique, consistent, and common subset of acquired hepatocerebral degeneration, whose features are permanent and entirely different from acute hepatic encephalopathy episodes.*

Source: Burkhard PR, et al. *Arch Neurol*. 2003;60:521-528.

THE NEUROLOGICAL MANIFESTATIONS OF CHRONIC cirrhosis and hepatic failure are protean. Myoclonus (often negative), chorea, and dystonia may occur in these patients, often accompanied by pyramidal dysfunction and dementia. More than three-quarters of patients with chronic cirrhosis have abnormalities in the basal ganglia on MRI, typically bilateral pallidal hyperintensity on T1 images. Other studies have shown that patients with cirrhosis develop manganese deposits in the basal ganglia. The density of D2-receptors is depressed as well.

Burkhard and colleagues have studied all consecutive

patients with cirrhosis who were evaluated as candidates for liver transplantation over a 1-year period in the University Hospital of Switzerland. A total of 51 patients were evaluated, and 11 were found to have clinical parkinsonism with extrapyramidal symptoms and signs. Those 11 were then carefully examined using a battery of tests that included the Unified Parkinson's Disease Rating Scale (UPDRS), a neuropsychological exam, an MRI (interpreted by a neuroradiologist blinded to patients' status), and measurements of copper and whole blood manganese. Cerebrospinal fluid levels of manganese were determined in 3 patients.

The clinical picture of cirrhosis-induced parkinsonism was very uniform. In the 11 patients, symptoms of parkinsonism began slowly and progressed rapidly over an average of 7 months. Symptoms and signs were symmetric, with generalized bradykinesia, dysarthria, postural instability, and prominent action tremor (not rest tremor). Six patients exhibited dystonia, typically involving the face and/or the feet. Mental status was reasonably preserved, but frontal lobe dysfunction developed on neuropsychological testing. Two patients were treated with levodopa, with significant improvement in parkinsonism as measured by the UPDRS. In all 11 patients, whole-blood manganese levels were elevated above normal. Cerebrospinal fluid manganese levels were also elevated in the 3 patients in whom it was measured. All patients had an abnormal MRI, with bilateral symmetric T1 hyperintensities in the substantia nigra and globus pallidus.

COMMENT BY STEVEN FRUCHT, MD

In this careful study, Burkhard et al have defined the clinical and radiologic features of parkinsonism associated with cirrhosis. The disorder is common and probably under-recognized. The clinical presentation is one of a rapid, progressive, symmetric parkinsonian state, unaccompanied by pyramidal dysfunction, cerebellar signs, or cognitive decline. Involvement of the substantia nigra on MRI contributes a partial presynaptic deficit in these patients, as does the response to treatment with levodopa.

The etiology of cirrhosis-induced parkinsonism is unknown, but Burkhard et al's results argue that the role of abnormal manganese deposition may be a critical factor. Unlike patients with acute manganism, neuropsychiatric features were absent in this cohort, save for evidence of frontal lobe dysfunction. Manganese deposition in the substantia nigra and globus pallidus has been previously demonstrated in patients with acute manganism. Liver transplantation in cirrhotic patients reverses the abnormalities seen on MRI. These factors suggest that manganese deposition causes cirrhotic parkinsonism. For patients who might not qualify for liver transplant, chelating agents might provide an alternate treatment to help slow this process. It certainly seems worthwhile treating these patients with levodopa. This disorder thus provides a compelling example of an extrapyramidal syndrome resulting indirectly from a serious medical illness. ■

Dr. Frucht is Assistant Professor of Neurology, New York Presbyterian Hospital-Cornell Campus, New York, NY.

Pharmacology Update

Aripiprazole Tablets (Abilify—Bristol-Myers Squibb)

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

ARIPIPRAZOLE IS A NEW ANTIPSYCHOTIC AGENT approved for the treatment of schizophrenia. This atypical agent is a quinolinone that has partial agonist activity at dopamine D2 receptors. The drug will be marketed as being better tolerated and safer than other atypical agents, as well as being dosed once a day. Aripiprazole is manufactured by Otsuka Pharmaceutical Company in Japan and is marketed by Bristol-Myers Squibb and Otsuka America Pharmaceutical Inc. under the rather unique tradename "Abilify."

Indications

Aripiprazole is indicated for the treatment of schizophrenia.[1]

Dosage

The recommended starting dose and target dose is 10 or 15 mg once daily. The drug may be taken without regard to meals, and dosage adjustments are not needed for renal or hepatic impairment. The dose should be reduced by 50% if administered concomitantly with drugs that inhibit 2D6 or 3A4 isoenzymes. The dose should be doubled if administered concomitantly with 3A4 inducers.[1]

Aripiprazole is available as 2-mg, 5-mg, 10-mg, 15-mg, 20-mg, and 30-mg tablets.

Potential Advantages

Aripiprazole does not appear to cause prolactino-

ma, extrapyramidal effects, or prolongation of QT interval.[2,3] It also has minimal effect on weight gain and no effects on plasma triglyceride and glucose levels.[4] Aripiprazole also has the lowest affinity among the atypical antipsychotics alpha-1 adrenergic receptors, histamine-1 and muscarinic receptors.[5]

Potential Disadvantages

Common side effects of nausea, postural dizziness, and somnolence were moderate in severity.[2] Aripiprazole is extensively metabolized by cytochrome P450 isoenzymes 2D6 and 3A4. Dosage adjustment is recommended when aripiprazole is co-administered with inhibitors of 2D6 or 3A4 or inducers of 3A4.[1]

Comments

Aripiprazole's pharmacology differs from other atypical antipsychotics. It is a partial agonist at dopamine D2 and serotonin 5-HT1A receptors and may be considered as the first dopamine-serotonin system stabilizer.[8,9] It is also an antagonist at 5-HT2A.[4] Efficacy was demonstrated in 3 out of 4 short-term studies (4-6 weeks) involving patients with a primary diagnosis of schizophrenia or schizoeffective disorder.

The efficacy measures include the Positive and Negative Syndrome Scale (PANSS) total, PANSS-positive subscale, PANSS negative subscale, PANSS-derived Brief Psychiatric Rating Scale (BPRS) score, and clinical global impression (CGI). In general, aripiprazole was superior to placebo in PANSS total and PANSS positive and negative subscales in all 3 studies and CGI in 2 of 3.[1,6] In the 4th study (n = 103) aripiprazole was superior to placebo in the BPRS. Two of the studies had an active control (haloperidol 10 mg/d or risperidone 6 mg/d) but these studies were not designed to compare active treatments. Aripiprazole appears to be well tolerated. In an unpublished 52-week study, aripiprazole 30 mg appeared to be comparable to haloperidol in patients with an acute relapse of chronic schizophrenia.[4,7] In this study, 8% of patients had a weight gain of ≥ 7% of body weight. The weight gains were related to BMI with 30% weight gain of those with BMI < 23 and 19% in those with BMI between 23 and 27.[1] The wholesale cost for aripiprazole (10 mg or 15 mg per day) is about $250 per month.

Clinical Implications

Aripiprazole offers another atypical antipsychotic that appears to be effective and well tolerated. Currently available drugs have some drawbacks. Clozaril requires periodic blood testing for agranulocytosis, ziprasidone increases QT interval, olanzapine causes weight gain, and risperidone causes prolactinoma.[10-12] Broader clinical experience or comparative studies between aripiprazole and other atypical antipsychotics will determine the future role of this agent. ■

References

1. Abilify Product Information. Bristol-Myers Squibb. November 2002.
2. Kelleher JP, et al. *CNS Drugs*. 2002;16(4):249-261.
3. Taylor DM. *Int J Clin Pract*. 2003;57(1):49-54.
4. Anonymous. *Med Lett Drugs Ther*. 2003;45:15-16.
5. Goodnick PJ, Jerry JM. *Expert Opin Pharmacother*. 2002;2(12):1773-1781.
6. Kane JM, et al. *J Clin Psychiatry*. 2002;63(9): 763-771.
7. McGavin JK, Goa KL. *CNS Drugs*. 2002;16(11): 779-786.
8. Jordan S, et al. *Eur J Pharmacol*. 2002;441(3): 137-140.
9. Burris KD, et al. *J Pharmacol Exp Ther*. 2002; 302(1):381-339.
10. Taylor D. *CNS Drugs*. 2003;17(6):423-430.
11. Bobes J, et al. *Schizophr Res*. 2003;62(1-2):77-88.
12. Goodnick PJ et al. *Expert Opin Pharmacother*. 2002; 3(10):1381-1391.

CME Questions

28. When comparing the 5-mg and 10-mg warfarin-dosing nomograms,

a. patients in the 10-mg group, on average, reached a therapeutic INR 1.4 days sooner than patients in the 5-mg group.
b. a higher percentage of patients in the 5-mg group were at a therapeutic INR at day 5.
c. patients in the 5-mg group had fewer INR determinations.
d. there were more major bleeding episodes in the 10-mg group.
e. there were more deaths in the 5-mg group.

29. Eradication of *Helicobacter pylori* should always be undertaken in patients with:

a. Duodenal ulcer disease
b. Gastric ulcer disease
c. MALT lymphoma of the stomach
d. All of the above
e. None of the above

Answers: 28 (a); 29 (d)

Clinical Briefs

By Louis Kuritzky, MD

Increase in Blood Glucose Concentration During Antihypertensive Treatment as a Predictor of Myocardial Infarction

RELEASE OF THE ALLHAT TRIAL, THE largest antihypertensive trial ever performed, has suggested that chlorthalidone, amlodipine, and lisinopril all provide favorable cardiovascular risk reduction. Additionally, this trial demonstrated that chlorthalidone, in addition to being less expensive, has a slightly more favorable cardiovascular risk reduction than its comparators. On the other hand, even modest doses of chlorthalidone were associated with an increase in glucose.

The Uppsala longitudinal study of men began in 1970-1974, and included 2322 men younger than age 50 at that time. In this population, Dunder and colleagues studied men (n = 1860) who were seen at baseline and 10 years later, and grouped them into participants who had or had not received antihypertensive treatment. Hypertensive treatments include beta blockers, thiazides, or both, with a small subset of individuals having been treated with hydralazine also. Subjects were evaluated for incidence of myocardial infarction, metabolic syndrome, and glucose derangements.

Subjects with an MI had a significantly higher fasting blood sugar than those who did not suffer an MI but only in the group receiving antihypertensive treatment. Whether the metabolic effect of antihypertensive therapy upon glucose mitigates some of the beneficial effects upon cardiovascular mortality remains uncertain, given the favorable results of studies like the ALLHAT trial. ■

Dunder K, et al. BMJ. 2003;326: 681-684.

Adverse Drug Events in Ambulatory Care

ADVERSE EVENTS (AE) FROM MEDications have been well studied among hospital inpatients. It has been reported that as many as 6.5% of hospitalized patients have one or more AE, of which more than one-fourth are considered preventable. AE in the ambulatory setting have been less studied, but have been estimated to occur 5-35% of the time.

Gandhi and colleagues prospectively studied patients (n = 661) from Boston-area primary care practices. Any person older than age 18 who received a prescription was eligible. Telephone survey at 10, 14, and 90 days, chart review, and patient input were used to discern possible AE.

Twenty-five percent of patients experienced AE, of which approximately half were rated 'serious,' including symptomatic bradycardia, symptomatic hypotension, and GI bleeding. Eleven percent of AE were considered preventable, and more than twice that number were "ameliorable" (ie, steps could have been taken to mitigate or reverse the AE).

AE are common in the outpatient setting and offer substantial room for clinicians to obviate (or mitigate) burden to our patients. ■

Gandhi TK, et al. N Engl J Med. 2003;348:1556-1564.

Prevention of Hip Fracture by External Hip Protectors

IN THE YEAR FOLLOWING A HIP FRACture (HIP), as many as one-third of persons die, and an equal number suffer inability to walk, or severe disability. One of the interventions intended to reduce HIP is use of external hip protectors (EHP), cushion-like devices worn during daily activity, which are intended to diminish the effect of a fall. Based upon the 10 randomized trials published to date, clinicians may be left with some degree of uncertainty concerning the efficacy of HIP, since 5 studies showed a statistically significant HIP impact, 2 studies found a favorable trend, and 3 studies showed no effect.

Van Schoor and associates enrolled 561 persons older than age 70 who resided in nursing homes or other assisted living facilities. Subjects wore hip protectors for approximately 15 months.

Two different varieties of hip protector were used: the Safehip and the Tytex devices.

Time to first hip fracture did not differ between those who wore an EHP and the control group. Compliance (monitored by unannounced visit) with EHP was imperfect: 61% at 1 month, 45% at 6 months, and 37% at 1 year. Whether greater compliance with EHP might have altered the outcome is unknown, but Van Schoor et al also mention that protectors with greater impact-effectiveness are to be desired, since 4 of 18 fractures in the intervention group occurred while the subject was wearing the protective device. ■

Van Schoor NM, et al. JAMA. 2003;289:1957-1962.

In Future Issues: **Choosing the Right Starting Dose of Warfarin**