Providing Evidence-based Clinical Information for 27 Years

NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media LLC

INSIDE

Financial Disclosure:

Neurology Alert's physician editor, Matthew Fink, MD, reports no consultant, stockholder, speaker's bureau, research, or other relationships related to this field of study.
Peer reviewer M. Flint Beal, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company having ties to this field of study.

The Calcitonin Gene-Related Peptide Receptor: A New Source of Acute Migraine Relief

ABSTRACT & COMMENTARY

By Dara G. Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College, New York, NY

Dr. Jamieson reports she is a retained consultant for Boehringer Ingelheim, Merck, and Ortho-McNeil, and is on the speaker's bureau for Boehringer Ingelheim and Merck.

Synopsis: *Telcagepant, a new oral calcitonin gene-related peptide receptor antagonist, has similar efficacy and better tolerability for acute migraine headaches as compared to a triptan.*

Sources: Ho TW, Ferrari MD, et al. Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: A randomised, placebo-controlled, parallel-treatment trial. *Lancet* 2008;372:2115-2123; Edvinsson L.CGRP-receptor antagonism in migraine treatment. *Lancet* 2008;372:2089-2090.

KNOWLEDGE OF THE PATHOPHYSIOLOGY OF MIGRAINE HAS RESULTed in specific therapy for acute migraine headache attacks. Recognition of 5HT1B,1D receptors in the trigeminovascular system led to the development of 5HT1B,1D receptor agonists, triptans, with demonstrated therapeutic efficacy. For almost two decades, patients with migraines have used one of the seven triptan medications to relieve the pain of an acute migraine. As a migraine-specific alternative to over-the-counter medications or narcotics, triptans have improved the quality of life for millions of migraineurs who know that dependable headache relief is minutes to hours away. However, not all migraine patients experience tolerable pain relief with triptans, and the medications are not appropriate for use in patients with vascular disease or uncontrolled hypertension.

Calcitonin gene-related peptide (CGRP), an endogenous vasoactive neuropeptide, also has a key role in migraine pathophysiology. CGRP receptors are found on first- and second-order trigeminal neurons and on smooth muscle cells in meningeal vessels. Concen-

VOLUME 27 • NUMBER 7 • MARCH 2009 • PAGES 49-56

NOW AVAILABLE ONLINE
www.ahcmedia.com

trations of CGRP are increased in the blood of patients with migraines, and injection of CGRP can induce a migraine-like headache in migraineurs. While CGRP is a vasodilator, antagonism of CGRP receptors does not cause vasoconstriction, and CGRP antagonists may provide migraine relief without the vasoconstrictor effects of triptans.

With funding from Merck Research Laboratories, a randomized, parallel-treatment, placebo-controlled, double-blind trial, conducted at 81 sites in Europe and the United States, evaluated the clinical profile of MK-0974 (telcagepant), an orally bioavailable antagonist of the CGRP receptor. Patients age 18 years or older, without vascular disease or uncontrolled hypertension, with migraine diagnosed by International Headache Society criteria, treated moderate or severe migraine attacks with either oral telcagepant 150 mg or 300 mg, the oral triptan zolmitriptan 5 mg, or placebo. The five co-primary endpoints at two hours after treatment were pain freedom, pain relief, or absence of photophobia, phonophobia, or nausea. The 1,380 migraineurs were randomly assigned to receive telcagepant 150 mg (n=333) or 300 mg (354), zolmitriptan (345), or placebo (348). Telcagepant 300 mg was more effective than placebo for pain freedom (27% vs 10%, p<0.0001), pain relief (55% vs 28%, p<0.0001), and absences of phonophobia (58% of vs 37%, p<0.0001), photophobia (51% vs 29% of p<0.0001), and nausea (65% vs 55%, p=0.0061). Telcagepant 300 mg and zolmitriptan 5 mg had similar efficacy, and both were more effective than telcagepant 150 mg. Adverse events were noted for 31% or 37% of patients taking telcagepant 150 mg or 300 mg, respectively, 51% taking zolmitriptan 5 mg, and 32% taking placebo. The most common adverse events noted with the CGRP antagonist at 300 mg were dry mouth (6%), somnolence (5%), and dizziness (5%). The investigators concluded that telcagepant 300 mg had an efficacy for acute migraine comparable to that of zolmitriptan 5 mg, but with fewer associated adverse effects. The accompanying editorial by Lars Edvinsson noted that these results provide a new option for migraine treatment, even though the anti-migraine targets (e.g., peripheral sensory nerves or brainstem nuclei) of CGRP-receptor antagonists are still being explored.

■ COMMENTARY

With close to 30 million Americans suffering from chronic disabling headaches this new treatment option should bring relief to many headache sufferers. This large, phase III trial demonstrated that the benefit of telcagepant is comparable to that of a specific triptan. By extrapolation, these encouraging efficacy and tolerability results should be similar when telcagepant is compared with other triptans. Treatment of migraine headaches often necessitates multiple medications, and the safety profile of this CGRP antagonist should allow combination with over-the-counter medications and triptans, as well as daily preventative medications.

In this study, patients with vascular disease were excluded because of the possible randomization to a triptan. Further study is needed to determine the safety of telcagepant in patients with cerebrovascular and cardiovascular disease. However, if vascular safety is established, then migraineurs for whom triptans are prescribed should be able to enjoy relief with a migraine-specific acute pain medication. Triptans, and now CGRP antagonists, are the end result of years of laboratory and animal research into migraine pathophysiology, and are an affirmation of the benefits of time and money spent on basic science research and pharmaceutical development. ■

Neurology Alert, ISSN 0741-4234, is published monthly by AHC Media LLC, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

ASSOCIATE PUBLISHER: Coles McKagen.
MANAGING EDITOR: Allison Weaver
DIRECTOR OF MARKETING: Schandale Kornegay

GST Registration Number: R128870672.
Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

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

Back issues: $42. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

AHC Media LLC

Subscriber Information

Customer Service: 1-800-688-2421
Customer Service E-Mail Address:
customerservice@ahcmedia.com

Editorial E-Mail Address: allison.weaver@ahcmedia.com
World-Wide Web: www.ahcmedia.com

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $319
Add $17.95 for shipping & handling
Student/Resident rate: $125
Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.
Canada
Add 7% GST and $30 shipping.
Elsewhere
Add $30 shipping.

Accreditation

AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of *25 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the neurologist. It is in effect for 36 months from the date of the publication.

Questions & Comments
Please email **Allison Weaver**, Managing Editor, at allison.weaver@ahcmedia.com.

Stroke Is Associated with Central Periodic (Cheyne-Stokes) Breathing

ABSTRACT & COMMENTARY

By Charles P. Pollak, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Pollak reports no financial relationships relevant to this field of study.

Synopsis: *Sleep disordered breathing occurs in most acute stroke patients and may contribute to morbidity*

Source: Siccoli MM, Valko PO, Hermann DM, et. al. Central periodic breathing during sleep in 74 patients with acute ischemic stroke–Neurogenic and cardiogenic factors. *J Neurol* 2008;255:1687-1692.

CHEYNE-STOKES BREATHING (CSB) IS A TYPE OF PERIodic breathing that results from intracranial causes exacerbated by circulatory impairment (prolonged circulation time, congestive heart failure, hypoxia—see Plum and Posner, *The Diagnosis of Stupor and Coma*, 4th Ed, 2007). Respirographic tracings show alternating periods of hyperpnea, reflecting increased response to CO2, followed by apnea. The changes in depth of breathing are gradual, so the respirographic tracing has a spindle-like appearance. Unlike sleep apnea, CSB is not sleep dependent.

If the patient happens to be awake when respirations are normal or increased, he may lapse into sleep as they wane. Consciousness returns as respirations increase. The pathogenesis of CSB, then, involves overbreathing in response to CO2, alternating with posthyperventilation apnea. Arterial blood gases reflect mild overall hyperpnea. Classically, CSB implies bilateral dysfunction of the cerebral hemispheres or diencephalon, down to the upper pons. It is easy to see that circulatory impairments resulting in delayed feedback of CO2 or other blood gas information to the respiratory centers can cause or exacerbate respiratory instability such as periodic breathing.

Recently, Siccoli and colleagues at the University of Zurich investigated the brain lesions resulting from acute ischemic stroke that were responsible for CSB (termed "central periodic breathing," or CPB, in this report). Subjects were 74 patients admitted within 96 hours after first-ever stroke onset. Sleep-related breathing abnormalities assessed on the first night showed CPB in 53 patients (72%) during 10% of recording time. This may be compared with sleep apnea (obstructive or central), which was found in 41 (55%) patients. Of interest, the severity of CPB was strongly correlated with the severity of sleep apnea, suggesting that they may be pathogenetically related. CPB was much more frequent and severe in anterior circulation hemispheric strokes (six patients) and was milder in patients with strokes involving the left insula (n=5) and mesencephalon (n=5), as well as those with lower-left-ventricular ejection fraction.

■ **COMMENTARY**

Acute stroke is nearly always associated with a sleep-related breathing disorder, most often obstructive sleep apnea (OSA), which has been reported to occur in 69%–95% of patients. Because it is associated with transient ischemic attacks as often as completed stroke, CPB is more likely to be a predisposing condition rather than a cause of stroke. Risk factors that are shared by stroke and OSA include obesity, age, and hypertension. Furthermore, sleep fragmentation related to acute stroke may perpetuate and aggravate both central and obstructive sleep apnea.

Regardless of the mechanism, the astonishing frequency of OSA or CSB in stroke should make us wonder how much they may contribute to stroke morbidity and mortality and to what extent stroke burden might be lessened by treatment with continuous positive pressure ventilation (CPAP). Positive effects of CPAP have already been observed in individual patients, and a formal clinical trial of its potential benefits is warranted. ■

Congenital Myopathy 2009

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports that he receives grant/research support from Pfizer and is on the speaker's bureau of Athena Diagnostics.

Synopsis: *Great progress has been made in identifying the underlying genetic defects in congenital myopathies.*

Source: Sharma MC, Jain D, Sarkar C, et al. Congenital myopathies—A comprehensive update of recent advancements. *Acta Neurol Scand* 2008;Dec. 29 (E-pub ahead of print).

WITH AN INCIDENCE OF 6/100,000 LIVE BIRTHS AND comprising 10% of all neuromuscular disorders, congenital myopathies result from genetic abnormalities in the contractile apparatus of muscle. They demonstrate fixed, unique histochemical or ultrastructural changes on muscle biopsy, thus differentiating them from muscular dystrophies, which affect the stability of the sarcolemmal membrane and exhibit ongoing muscle degeneration and regeneration on muscle biopsy. Though congenital hypotonia with delayed motor milestones and slow progression is the usual presentation, adult onset and more rapid deterioration in childhood, may be seen. In the absence of any

pathognomonic symptom or syndrome for any congenital myopathy, research in other areas is advancing our understanding and classification of these diseases.

Demonstrating significant clinical and histologic variability, central core myopathy, a calcium channel disorder and the first congenital myopathy to be identified, is associated with mutation of the ryanodine receptor gene (RYR1) on chromosome 19q13, also linked to malignant hyperthermia. Seen on oxidative stains as unstained areas, cores contain an antibody to the actin cross-linking protein, filamin C, and desmin, which may play a role in their formation. Multi-minicore disease demonstrates multiple cores on oxidative stains that, like the central cores they resemble ultrastructurally, are a non-specific finding on muscle biopsy. Selenoprotein N (SEPN1) and RYR1 gene mutations are both reported with multi-minicore disease, the latter with a severe neonatal form, but multi-minicore disease occurs with neither mutation, as well.

Rapidly fatal and affecting only newborn boys, X-linked myotubular myopathy (XLMTM) presents during pregnancy with polyhydramnios and decreased fetal movements, followed postpartum by hypotonia and respiratory insufficiency. It is associated with the XLMTM gene at Xq28 for myotubularin, which contains the consensus sequence for the active site of tyrosine phosphatases, a wide class of proteins involved in signal transduction. Immature muscle fibers fail to grow and differentiate, perhaps due to failure of myotubularin interaction with other proteins.

Mutation of either the myogenic factor-6 (MYF6) gene at chromosome 12q21 or the dynamin-2 (DNM2) gene at 19p13.2 is associated with the dominant form of centronuclear myopathy, while an amphiphysin 2 gene has recently been associated with the recessive form. All three proteins are involved in maintaining skeletal muscle fiber organization, including endocytosis, membrane trafficking, actin assembly, centrosome cohesion, and nuclear positioning.

Six genes, five related to thin filament proteins and one to sarcoplasmic reticulum protein, have thus far been shown to result in nemaline myopathy, the most common congenital myopathy, which may diversely present as a floppy infant; as childhood, adolescent, or adult onset myopathy; and be mild, moderate, or severe. Actin aggregate myopathy results from mutation of the skeletal muscle actin (ACTA1) gene at chromosome 1q42.1 and comprises three classes, based on muscle morphology demonstrating excess thin filamentous inclusions, intranuclear rod myopathy, or nemaline myopathy. Clinical symptomatology is similar to that seen with nemaline myopathy.

Accrual of desmin intermediate filaments characterize desmin related myopathies, presenting in the second to fourth decade of life as slowly progressive, distal, painless muscle weakness and atrophy, often associated with cardiac arrhythmia or cardiomyopathy. Primary desminopathies are associated with mutation of the desmin gene on chromosome 2q35, whereas secondary desminopathies, also designated as myofibrillar myopathies, may be caused by mutation of genes involving α-β-crystallin, selenoprotein N1, myotilin, or γ-filamin.

Hyaline body myopathy, a rare congenital myopathy localized to chromosome 3p22.2-p21.32, demonstrates subsarcolemmal hyalinized bodies rich in myofibrillary ATPase and myosin, and is classified among the so-called protein aggregate myopathies. Awaiting characterization and further classification are the congenital myopathies designated as reducing body myopathy, Zebra body myopathy, fingerprint myopathy, and cap disease.

■ **COMMENTARY**

No curative therapy currently exists for congenital myopathy, but prenatal genetic diagnosis is available for many forms, and physical and occupational therapy, respiratory care, orthopedic intervention, and feeding management can prolong life and improve its quality. Future prospects for potential therapy include genetic manipulation by allelic-specific knock down of mutant alleles, dilution of mutant protein by administration of the normal isoform, upregulating genes that may produce surrogates for the absent protein, and inducing muscle fiber hypertrophy (North K. What's new in congenital myopathies? *Neuromusc Disord* 2008;18;433-442). Much research remains to be done, but each advance is a step in the right direction. ■

Alzheimer Immunotherapy Can Alter Vascular Amyloid

ABSTRACT & COMMENTARY

By Norman R. Relkin, MD, PhD

Director, Memory Disorders Program, Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Relkin reports that he receives grant/research support from Baxter Bioscience, and is a consultant to Eisai, Pfizer, Myriad, and Smart Genetics.

Synopsis: *Although the active immunization trial was stopped because of severe side effects, autopsy studies*

revealed that soluble plaque amyloid moves to the perivascular spaces as an initial step before it is cleared from the brain.

Source: Boche D, Zotova E, Weller RO, et al, Consequence of Aβ immunization on the vasculature of human Alzheimer's disease brain. *Brain* 2008;131:3299-3310

BRAIN AUTOPSIES FROM PARTICIPANTS IN THE ILL-FATED AN-1792 Alzheimer's disease (AD) vaccine trial indicate that immunotherapy against beta amyloid (Aβ) can alter vascular amyloid deposits and potentially impact on congophilic amyloid angiopathy (CAA). AD patients in the Elan-sponsored AN-1792 trial were vaccinated with fibrillar Aβ-42 plus an immune adjuvant in a novel Phase II immunotherapy trial. The trial ended prematurely in 2002 when 6% of subjects developed meningo-encephalitis. Delphine Boche and colleagues from the University of Southampton studied the brains of nine patients who received AN-1792 and died between four months and five years after their first immunization. They also examined the brains of 11 AD patients who died at comparable stages of the disease but were unimmunized.

Previous studies of the brains from the AN-1792 trial demonstrated removal of some or all of the plaque-associated amyloid deposits in cerebral cortex. The investigators hypothesized that after vaccination with AN-1792, soluble Aβ from brain plaques might drain into the brain's perivascular spaces and promote vascular amyloid deposition. To test this hypothesis, they paid particular attention in this study to amyloid in blood vessels. They found that AD patients immunized with AN-1792 had about 14 times as many blood vessels containing the 42-amino-acid form of Aβ (Aβ-42) in the cerebral cortex as unimmunized controls, and seven times more Aβ-42 in the leptomeninges. Levels of the 40-amino-acid form of beta amyloid (Aβ-40), more commonly associated with CAA, were also significantly increased. Patients who received AN-1792 had more cortical microhemorrhages and microvascular lesions than the unimmunized controls. However, none of the nine subjects studied had major CAA-related intracerebral hemorrhages. They did not find evidence that this form of immunotherapy otherwise altered structural proteins in the walls of cerebral blood vessels.

There was some indication that changes in vascular amyloid following AN-1792 immunization were time dependent. Most of the patients who died in the first three years after immunization had high levels of vascular amyloid compared to controls. However, two patients who survived four to five years after vaccination showed nearly complete clearance of brain plaques as well as vascular amyloid. The authors suggested that immunotherapy may initially deliver solubilized plaque amyloid to the vascular compartment resulting in an increase in vascular amyloid deposits. However, once the majority of amyloid in the brain substance is removed, the continued effect of antibodies against amyloid may reduce vascular amyloid burden, resulting in a long-term reduction.

■ **COMMENTARY**

This study by Boche and colleagues provides intriguing evidence that movement of amyloid from the brain parenchyma to the perivascular spaces may be a first step in the clearance of Aβ from the brain of AD patients who had active vaccination. It does not necessarily follow that all vaccines or other approaches to anti-amyloid therapy will lead to comparable changes in vascular amyloid. However, side effects relating to the brain vasculature, such as microhemorrhages, microvascular ischemic changes, and vasogenic brain edema, have now been reported following active vaccination and passive immunotherapy against Aβ. This study suggests why these side effects may occur, but also provides the interesting observation that sustained antibody exposure can actually reduce vascular amyloid deposits once the pool of parenchymal brain amyloid is sufficiently small. This raises the possibility that CAA itself could be a target for future immunotherapy interventions, perhaps using antibodies that more specifically target the vascular amyloid pool. ■

CNS Infections: An Indication for Continuous EEG Monitoring?

ABSTRACT AND COMMENTARY

By Padmaja Kandula, MD

Assistant Professor of Neurology and Neuroscience, Comprehensive Epilepsy Center, Weill Medical College

Dr. Kandula reports no financial relationships relevant to this field of study.

Synopsis: *In this retrospective study, the authors describe the prevalence and significance of both electrographic seizures and periodic discharges in critically ill patients with central nervous system infections.*

Sources: Carrera E, Claassen J, Oddo M, et al. Continuous electroencephalographic monitoring in critically ill patients with central nervous system infections. *Arch Neurol* 2008;65: 1612-1618.

ACUTE SYMPTOMATIC SEIZURES ARE A KNOWN COMPLICATION of central nervous system (CNS) infections. Traditionally, however, meningitides have been considered a medical and not neurological condition until focal neurologic signs or clinical seizures complicate the picture. In addition, use of continuous electroencephalography (cEEG) monitoring was not in wide practice until about a decade ago, when a landmark paper in 2000 by Towne and colleagues found an 8% incidence of nonconvulsive status epilepticus in a prospective study of patients with unexplained coma.[1] Since then, physicians have noted that both electrographic seizures and nonconvulsive status epilepticus are under-recognized causes of coma. Interest in critically ill subpopulations such as those with CNS infections has grown. However, the true prevalence of electrographic seizures remains largely a mystery in this patient population. Hence, the authors of this study define and characterize the EEG findings in these critically ill patients.

Over a one-year time period, all patients with CNS infections who underwent cEEG were retrospectively identified. Inclusion criteria were a diagnosis of primary CNS infection and accompanying elevation of the cerebrospinal fluid (CSF) white blood cell count (>4 /microliter) with or without characteristic imaging abnormalities. Exclusion criteria included postoperative neurosurgical infections and noninfectious causes of CSF pleocytosis. Infections were further subdivided into viral, bacterial, and fungal/parasitic based on appropriate CSF findings, including positive polymerase chain reaction (PCR), culture, antigen detection, and lymphocytic (viral infections) or neutrophilic (bacterial infections) pleocytosis. Imaging characteristics were used to help classify the cases.

A total of 1,078 patients with a diagnosis of primary CNS infection were retrospectively identified at the Columbia University Medical Center. Seventy-five patients (7%) underwent cEEG, and 42 patients met full criteria for the study.

In the study group, 64% of infections were viral, 8% bacterial, and 7% either fungal or parasitic. Fourteen of 42 patients had confirmed electrographic seizures, and 11 of these patients had accompanying periodic epileptiform discharges (PEDs). PEDs were recorded in 40% of patients. Overall, nearly half (48%) of patients had either electrographic seizures or PEDs. PEDs and viral etiology were independently associated with electrographic seizures.

Clinical outcome was assessed in nearly all study patients (40 of 42 patients). Twenty-one patients had poor neurological outcome as assessed by a Glasgow outcome scale of 1–3. After adjustment for neurologic status, both PEDs and electrographic seizures were associated with poor outcome.

■ COMMENTARY

This paper, like other retrospective studies, suffer from the same inherent limitations. Selection bias (only patients in whom cEEG was requested were included in the study) and small numbers make it difficult to extrapolate these findings to other patients with CNS infection. From a practical and neurophysiologic standpoint, it is not surprising that periodic discharges are often forerunners to potential clinical or electrographic seizures. However, to date there have been no prospective long-term data that address the outcome of patients treated for both PEDs and electrographic seizures.

Currently, there is no consensus among neurologists or intensivists on if, when, and how to treat this subpopulation. For now, based on current retrospective evidence, cEEG should be considered in comatose patients with CNS infections, particularly viral infections, who fail to improve despite appropriate medical management. In our center, periodic discharges in high-risk patients, such as those with CNS infections, are treated with an anti-epileptic agent and continuously monitored for possible evolution of periodic discharges into electrographic seizures. Evolution of electroencephalographic activity then warrants additional treatment. A definitive prospective treatment trial of subclinical seizures and PEDs and long-term outcome is needed to determine appropriate treatment. ■

Reference

1. Towne AR, Waterhouse EJ, Boggs JG, et al. Prevalence of nonconvulsive status epilepticus in comatose patients. *Neurology* 2000;54:340-345.

Decreased Size of Acute Ischemic Stroke: An Additional Benefit from Chronic Warfarin Therapy?

ABSTRACT & COMMENTARY

By Dana Leifer, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Leifer reports no financial relationships relevant to this field of study.

Synopsis: *Chronic treatment with warfarin, prior to presentation with an ischemic stroke, is associated with a significant decrease in infarct size.*

Source: Ay H, Arsava EM, Gungor L, et al. Admission international normalized ratio and acute infarct volume in ischemic stroke. *Ann Neurol* 2008;64:499-506.

WARFARIN IS WELL KNOWN TO DECREASE THE INCIdence of ischemic stroke in patients with atrial fibrillation, and guidelines published by the American Heart Association (*Stroke* 2006;37:577-617) and other groups strongly recommend its use. Nevertheless, studies have repeatedly shown that many appropriate candidates for warfarin are not treated because of fears about its hemorrhagic complications and the need for monitoring of the international normalized ratio (INR).

Ay and colleagues have now found an additional reason for treating appropriate patients with warfarin. Not only does warfarin reduce the risk of stroke, but, according to their study, it also appears to reduce the size of infarcts, and therefore, the disability associated with the stroke. Ay and colleagues retrospectively examined a series of 93 patients who were taking warfarin at the time of admission for an acute ischemic stroke.

The primary finding of the study was that for patients taking warfarin, there is an inverse correlation between the admission INR and the admission infarct volume as measured by diffusion-weighted imaging ($r = -0.38$; $p < 0.001$). This association remained significant after controlling for other predictors of lesion volume, including a history of atrial fibrillation, prior transient ischemic attack or stroke, stroke etiology, warfarin use for cardiac source of embolism, and intravenous thrombolytic treatment for the acute stroke ($p = 0.014$ for the multivariate analysis).

Additional analysis showed that the median lesion volume was significantly smaller in patients with an admission INR ≥ 2, compared to those with an INR < 2 (3.4 mL compared to 13.1 mL, $p < 0.001$). Significant effects were found both for strokes considered to be the result of cardiogenic embolism and for strokes thought to have other mechanisms.

The authors also compared patients on warfarin at stroke onset to a group of control patients matched for etiology of stroke who were not taking warfarin. Infarct volume tended to be smaller in the group on warfarin ($p = 0.72$), and was significantly smaller in the group on warfarin with INR ≥ 2 compared to patients not taking warfarin ($p = 0.001$). Multivariate analysis confirmed that the difference remained significant after controlling for other predictors of lesion volume ($p = 0.048$).

The authors confirmed the results with several additional analyses that suggest that the effect is a robust one. Admission INR had significant inverse correlations with the volume of hypoperfused areas on perfusion MRI on admission, with final infarct size on follow-up imaging, with initial clinical severity, as measured by the National Institutes of Health Stroke Scale, and by clinical disability at discharge, measured by the modified Rankin Scale.

■ COMMENTARY

As the authors point out, there are several possible explanations for the results. Therapeutic anticoagulation may reduce the size of emboli or make them more fragile so that they are more likely to break up spontaneously. In addition, inhibition of the thrombotic system may decrease thrombus propagation and tend to allow the fibrinolytic system to prevail, or prevent microvascular thrombosis in regions of slow flow.

In any case, the finding that treatment with warfarin at therapeutic levels can reduce the size of ischemic strokes and thereby reduce the disability that they cause, provides an additional compelling reason to treat appropriate patients with warfarin and to adjust warfarin doses carefully to maximize the percentage of time during which patients have a therapeutic INR. ■

CME Questions

34. Which of the following statements about telcagepant is *false*?

a. Telcagepant is an antagonist of the CGRP receptor.
b. Telcagepant causes vasoconstriction.
c. Telcagepant has fewer side effects than zolmatriptan.
d. Telcagepant and zolmatriptan have equal efficacy in relieving migraine.

35. Sleep-disordered breathing after stroke is characterized by:

a. obstructive sleep apnea.
b. central periodic breathing.
c. Cheyne-Stokes respiration.
d. central sleep apnea.
e. All of the above

36. Potential future therapies for congenital myopathy may include:

a. genetic manipulation by allelic-specific knock down of mutant alleles.
b. dilution of mutant protein by administering the normal isoform.
c. upregulating genes that may produce surrogates for the absent protein.
d. inducing muscle fiber hypertrophy.
e. All the above

37. Which effect did the AN-1792 vaccine NOT exert in the brain of immunized Alzheimer's disease patients?

a. Increased vascular amyloid
b. Decreased vascular amyloid
c. Increased microhemorrhages
d. Increased major hemorrhages

38. Epileptiform discharges are common in patients with CNS infections.

a. True
b. False

39. Periodic epileptiform discharges are associated with poor outcome.

a. True
b. False

40. Admission INR correlates inversely with which of the following?

a. Initial DWI lesion volume
b. NIHSS on admission
c. Modified Rankin Scale at discharge
d. Final infarct volume
e. Initial perfusion defect
f. All of the above

Answers: 34. b; 35. e; 36. e; 37. d; 38. a; 39. a; 40. f

CME Objectives

The objectives of *Neurology Alert* are:

• To present the current scientific data regarding diagnosis and treatment of neurological disease, including stroke, Alzheimer's disease, transient ischemic attack, and coma;

• To discuss the pathogenesis and treatment of pain;

• To present basic science lessons in brain function;

• To discuss information regarding new drugs for commonly diagnosed diseases and new uses for traditional drugs;

• To discuss nonclinical issues of importance to neurologists, such as the right to die and the physician's legal obligation to patients with terminal illness. ■

CME Instructions

Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

In Future Issues:

Magnesium as a Neuroprotective Agent

Clinical Briefs in
Primary Care
The essential monthly primary care update
By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

VOLUME 14, NUMBER 3 PAGES 5-6 MARCH 2009

Liraglutide: Promise of the Incretin Class

Source: Nauck M, et al. *Diabetes Care* 2009;32:84-90.

GLUCAGON-LIKE PEPTIDE-1 (GLP) IS A recently "rediscovered" endogenous hormone of the incretin class. GLP has diverse favorable metabolic effects that modulate excess glucose excursions, including enhancement of glucose-dependent insulin secretion, slowing of gastric emptying, blunting of glucagon, and increased satiety. "Natural" GLP has a fleeting (2 minutes or less) half-life, precluding its utility as a pharmacotherapeutic tool. Recently, we have captured some of the valuable activity of the incretins by employing agents that block the degradation enzyme of GLP, DPP-4. Subcutaneous liraglutide (LIR) is a synthetic GLP analogue with a half-life of 13 hours, allowing once-daily dosing.

Nauck et al performed a double-blind, controlled trial of LIR vs glimepiride or placebo added to maximum-dose metformin in more than 1000 Type 2 diabetics. Subjects were followed for approximately 6 months.

At the end of treatment, A1c reductions (about 1%) were similar for 2 different doses of LIR or glimepiride. Important differences, however, included changes in body weight and incidence of hypoglycemia. For instance, minor hypoglycemia was seen in only about 3% of LIR subjects, but 17% of glimepiride subjects. LIR was associated with modest weight loss (average 2.3 kg) compared to a 1 kg weight gain in glimepiride subjects. The most common adverse effect noted with LIR was nausea (11-19%), which has been commonly reported with another injectible member of the incretin class, exenatide. ■

Low-glycemic Index Diet in Type 2 Diabetics

Source: Jenkins DJ, et al. *JAMA* 2008; 300:2742-2753.

THE KNOWLEDGE THAT NOT ALL CARbohydrate sources provide a similar rate of glucose rise has been captured with the glycemic index metric; high-glycemic index foods (e.g., bread, potatoes, simple sugars) produce very prompt glucose rise compared with low-glycemic index items (e.g., beans, complex carbohydrate sources like cruciferous vegetables). In Type 2 diabetics, in whom first-phase insulin secretion (that component of insulin secretion intended to respond to prompt glucose rise) is lost, low-glycemic index foods are intuitively preferred. Unfortunately, confirming meaningful benefits from consumption of a low-glycemic index diet has been difficult.

In this trial, Jenkins et al studied Type 2 diabetics (n = 210) assigned to 6 months of a low-glycemic index diet or a high-cereal fiber diet. Both diets achieved A1c reduction, but the low-glycemic index diet was superior (0.5% vs 0.18%). An additional favorable effect of the low-glycemic index diet was a modest HDL increase.

Whether patients can and will sustain a low-glycemic index diet, and whether such A1c reductions will reduce diabetes-related endpoints, remains to be determined. In the meantime, there is no suspicion of any detrimental effect of the low-glycemic index diet: Most short and intermediate term data suggest salutary effects. ■

Glucose Control and Macrovascular Disease

Source: Duckworth W, et al. *N Engl J Med* 2009;360:129-139.

MOST CLINICIANS MAINTAIN A FAIRLY glucose-centric view of diabetes. That is, we have made the assumption that the most visible derangement in diabetes, hyperglycemia, is the culprit producing vascular disease. The next intuitive step is that if glucose is pathogenetic in the development of vascular disease, then glucose modulation should reduce it. Despite consistent favorable clinical trial data confirming the benefits of glucose control upon microvascular disease (retinopathy, nephropathy, neuropathy), no clinical trial (except a single trial with acarbose) has shown reduction in macrovascular risk (myocardial infarction or stroke).

The VA Diabetes Trial (VADT) follows close on the heels of the ACCORD and ADVANCE trials, which not only failed to show reductions in macrovascular disease, but in one trial (ACCORD) demonstrated increased mortality in persons with very tightly controlled diabetes.

The VADT enrolled almost 2000 veterans with Type 2 diabetes and randomly assigned them to standard vs intensive therapy. Since almost half had already sustained a CV event, other tools to reduce CV risk were already widely employed in both groups.

At the 5.6 year endpoint of the trial, the intensive therapy group attained a substantially lower A1c than the standard therapy group: 6.9% vs 8.4%. Disappointingly, there was no discernible reduction in CV risk or microvascular endpoints in this group. There was a reassuring contrast between VADT and ACCORD: No increase in mortality with tight control was seen, despite a greater incidence of hypoglycemia. Clinicians will have to rely upon diet, exercise, smoking cessation, lipid modulation, and blood pressure control to reduce CV endpoints in Type 2 diabetics. ■

Risks Associated with the Morning BP Surge

Source: Kario K, White WB. *J Am Soc Hypertens* 2008;2:397-402.

AMBULATORY MONITORING OF BLOOD pressure (BP) has demonstrated a pattern of BP change typified by an overnight reduction in BP of 10-20% and a "morning surge" in BP beginning closely around the time of awakening. Even in patients with hypertension, morning surge in BP is seen. And it's not only BP that surges in the morning: Blood coagulability, plaque vulnerability, platelet aggregability, and blood viscosity also increase at this time. Because CV events (MI, stroke, arrhythmia) also cluster disproportionately around this circadian phenomenon, experts have opined that modulation of the morning BP surge might provide benefits in clinical outcomes.

The relationship between the morning BP surge and CV risk is strengthened by the observation that it correlates with arterial wall stiffness, left ventricular hypertrophy, and carotid intima-media thickness.

Office blood pressure is typically measured several hours after the morning surge. Encouraging more widespread use of at-home BP self-monitoring is a reasonable first step to obtain more information about morning BP. Since we have not yet learned which, if any, antihypertensives might hold special benefits on morning BP, and we do not have a major clinical trial confirming risk reduction through morning BP control, we lack sufficient evidence to mandate control of morning BP surge as a specific entity at this time. ■

Simplifying Dosing for Actinic Keratoses

Source: Zeichner JA, et al. *J Am Acad Dermatol* 2009;60:59-62.

ACTINIC KERATOSES (AK) ARE AT BEST precancerous skin lesions, and at worst (a belief held by many leaders in the skin cancer field) skin carcinoma in situ. In either case, the combination of cosmetic burden, troublesome symptoms, and association with squamous cell cancer motivates their destruction. Although it is commonplace to utilize simple local destructive measures (e.g., cryotherapy) to destroy an individual lesion, it is becoming increasingly clear that field therapy (i.e., treating an entire region to include both evident and subclinical AK lesions) provides a better and more lasting service to the patient.

Imiquimod is an immune system upregulator that has shown excellent efficacy in eradication of AK. As with all other topical agents employed for this purpose, local adverse effects and complexity of dosing regimen are limitations for some patients. Typical dose regimens for imiquimod rely upon 2-3 times weekly application of 5% cream for 8-16 weeks. Less frequent dosing, if effective, would reduce cost, enhance compliance, and possibly be better tolerated.

In this small study (n = 20), subjects applied imiquimod 5% cream once weekly for 16 weeks to half of the face, and placebo to the other half. At 16 weeks, 47% of imiquimod recipients showed marked improvement or better. In contrast to 2-3 times weekly dosing regimens, local adverse effects were essentially absent.

Total clearance rates with more frequent dosing are much higher, but so are intolerance and adverse effect rates. The authors suggest that these favorable results should be stimulus for larger, longer-duration studies. ■

Aerobic and Resistance Training Effects in PAD

Source: McDermott MM, et al. *JAMA* 2009;301:165-174.

THE PRESENCE OF PERIPHERAL ARTERIal disease (PAD), confirmed by an ankle-brachial index of < 0.95, is often manifest by limitation in ability to walk, pain with walking, and limitation in performance of normal daily activities. For most patients, smoking cessation is the most important intervention. Pharmacotherapy is of limited value. Exercise training has been suggested as a method to improve oxygen utilization by the tissues and functional ability.

McDermott et al studied PAD patients (n = 156) who were randomized to aerobic training (treadmill), resistance training (weight training), or control. The treadmill group exercised 3 times weekly, beginning at a 2 mph walking speed for 15 minutes, working up to 40 minutes (with increases in treadmill speed and grade as tolerated). The resistance training group exercised 3 times weekly with knee extensions, leg presses, and leg curls. Both groups were followed for 6 months. The primary outcome was distance on the 6-minute walk.

Treadmill exercise improved the primary endpoint, but the control and resistance training groups did not significantly differ. Treadmill exercise also improved distant vascular health, as demonstrated by improvements in brachial artery flow-mediated dilation (no improvement was seen in the control or resistance training groups). ■

Clinical Briefs in Primary Care is published monthly by AHC Media LLC.

Associate Publisher: Coles McKagen. **Editor:** Stephen Brunton, MD. **Senior Managing Editor:** Paula Cousins. This is an educational publication designed to present scientific information and opinion to health professionals, stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for the layman.

Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: paula.cousins@ahcmedia.com
World Wide Web: www.ahcmedia.com
Address Correspondence to: AHC Media LLC
3525 Piedmont Road, Building Six, Suite 400
Atlanta, GA 30305.

AHC Media LLC

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

Warning Regarding Topical Anesthetics

In this issue: FDA warning on topical anesthetics; antipsychotics increase sudden cardiac death; the step up vs step down debate; treating pain, fatigue, mood, and sleep in fibromyalgia; FDA Actions.

Something for your pain?

The FDA has issued a warning regarding topical anesthetics and the risk of life-threatening side effects. This is the second warning in 2 years regarding this issue, the first coming in February 2007 following the deaths of two women who used extensive topical anesthetics in preparation for cosmetic procedures. The latest warning was prompted by a study published in *Radiology*, which compared oral acetaminophen or ibuprofen vs lidocaine gel applied to the skin of the breasts to reduce discomfort during mammography. In the study, 4% lidocaine gel was applied by a nurse from the clavicles to the inferior costal margins and laterally to the mid axillary lines and then covered with plastic wrap to ensure consistency of application. Discomfort from mammograms was significantly lower in the lidocaine gel group and the authors postulate that decreased discomfort may improve the likelihood of future mammographic screening (Lambertz CK, et al. *Radiology* 2008;248:765-772). The FDA's previous warning in 2007 followed on the heels of two reports of young women undergoing laser hair removal who applied either lidocaine or tetracaine topical preparations to the lower extremities and then covered the application with plastic wrap. Both women developed seizures, fell into a coma, and eventually died due to excessive blood levels of the topical anesthetic. Many of these topical products are available over the counter. The FDA strongly advises consumers not to: make heavy application of topical anesthetics over large areas of skin, use concentrated formulas, apply to broken or irritated skin, wrap the treated skin with plastic wrap or other dressings, or apply heat to skin treated with these products.

Increase in sudden cardiac death

Antipsychotics, both typical and atypical, are associated with a dose-related increase in sudden cardiac death according to a new study. Typical antipsychotics such as thioridazine (Mellaril®) and haloperidol (Haldol®) block repolarizing potassium currents and prolong QT intervals. Multiple studies have shown a dose-related increased risk of sudden cardiac death associated with these drugs. Less is known about the atypical antipsychotic drugs although many have similar cardiovascular effects. Researchers from Nashville reviewed the records of Medicaid enrollees in Tennessee including the records of 44,218 and 46,089 baseline users of a single typical and atypical antipsychotic, respectively. These were matched with 186,600 nonusers of antipsychotic drugs. Thioridazine and haloperidol were

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

the most frequently prescribed typical agents, while clozapine (Clozaril®), quetiapine (Seroquel®), olanzapine (Zyprexa®), and risperidone (Risperdal®) were the most commonly used atypical agents. Both users of typical and atypical antipsychotic drugs had higher rates of sudden cardiac death than nonusers with adjusted incident rate ratios of 1.99 (95% CI, 1.68-2.34) and 2.26 (95% CI, 1.8-2.72), respectively. There was a higher rate for users of atypical antipsychotic drugs vs typical antipsychotics with an incident rate of 1.14 for the comparison (95% CI, 0.93-1.39). For both classes of drugs, the risk for current users increased significantly with increasing dose. The authors conclude that current users of typical and of atypical antipsychotic drugs had similar, dose-related increased risk of sudden cardiac death and that atypical antipsychotic drugs are no safer than the older drugs (Ray WA, et al. *N Engl J Med* 2009;360:225-235). An accompanying editorial suggests that children and the elderly are particularly vulnerable to these drugs and their use in these populations should be "sharply reduced" (Schneeweiss S, Avorn J. *N Engl J Med* 2009;360:294-296).

Step up vs step down

Which is more effective for treating dyspepsia: Starting with aggressive therapy and tapering down, or starting with antacids and progressing to more aggressive therapy depending on symptoms? The so called step-up vs step-down debate has raged for years, particularly in managed-care settings. In a new study from the Netherlands, patients with dyspepsia were randomized to treatment with an antacid, H2-receptor antagonist, and proton pump inhibitor (step up) vs the same drugs in reverse order (step down), with each step lasting 4 weeks. Primary outcome was symptom relief and cost-effectiveness of initial management at 6 months. Treatment success after 6 months was achieved in 72% of patients in the step-up group and 70% of patients with step-down group. The average medical costs were lower for patients in the step-up group (€228 vs €245; P = 0.0008) mainly because of the cost of medication. The rate of adverse effects was the same in both groups and were generally mild. The authors suggest that treatment success is similar in both groups but the step-up strategy was more cost-effective for patients with new onset dyspeptic symptoms (van Marrewijk CJ, et al. *Lancet* 2009;373:215-225). An accompanying editorial suggests that the degree of cost difference between the two groups was overestimated because costs were based on brand name drugs and generics are now available. It furthers suggested that the study may not change practice in primary care as the author recommends a 4-8 week course of a proton pump inhibitor for patients with symptoms of the upper gastrointestinal tract with discontinuation of treatment if patients remain asymptomatic (van Zanten SV. *Lancet* 2009;373:187-189).

Pain, fatigue, mood, sleep and fibromyalgia

Tricyclics work better than other antidepressants for the treatment of fibromyalgia according to new study from Germany. In a meta-analysis of 18 randomized controlled trials of antidepressants for the treatment of fibromyalgia, researchers reviewed studies utilizing tricyclic and tetracyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAO). All antidepressants were associated with a reduction in pain, fatigue, depressed mood, and sleep disturbances. Pain reduction was particularly good for tricyclic antidepressants, while MAO inhibitors showed modest effect and SSRIs and SNRIs showed a small effect. TCAs were effective in low doses of 12.5-50 mg, far below the doses commonly employed to treat depression, and were very effective for reducing pain, fatigue, and sleep disturbance (*JAMA* 2009;301:198-209). Currently duloxetine (Cymbalta®), pregablin (Lyrica®), and milnacipran (Savella™) are the only FDA-approved drugs for the treatment of fibromyalgia.

FDA Actions

The FDA is launching a program to improve the safety of imported drugs to the United States. The pilot program would allow manufacturers of drugs outside United States to apply for 1 of 100 certifications, which would require that companies have a secure supply chain for their product. Criteria would include holding an FDA-approved drug application, guaranteeing that active pharmaceutical ingredients would be imported only to make FDA-approved drugs, complying with Good Manufacturing Practices, and guaranteeing that their drug products use a secure supply chain. This program is in response to concerns about manufacturing processes outside the United States and the embargoing of several foreign manufactured drugs in the last year. ■