Famciclovir and Postherpetic Neuralgia

To the Editor: While appraising a study by Tyring and colleagues (1), we were struck, as we assumed were most readers, by the authors’ substantive efficacy claim: “The median times to resolution of postherpetic neuralgia were 63 days for the 500-mg famciclovir group, 61 days for the 750-mg famciclovir group, and 119 days for the placebo group.” However, before we accept this secondary end point as evidence that famciclovir provides clinically significant benefit to patients with herpes zoster, several important issues must be addressed.

The authors need to explain the higher percentage of patients with postherpetic neuralgia (PHN) in the famciclovir groups and provide data on the severity of pain in all three groups. The top line of their Table 4 provides the (intention to treat) numerator: 61 (500 mg of famciclovir), 68 (750 mg of famciclovir), and 56 (placebo) patients developed PHN. The top line of their Table 1 provides the denominator: 138 (500 mg), 135 (750 mg), and 146 (placebo) patients. The following are the percentages: placebo, 56/146 = 38% (>age 50, 31/70 = 44%); 500 mg, 61/138 = 44% (>age 50, 41/69 = 59%); 750 mg, 68/135 = 50% (>age 50, 47/69 = 68%). The calculation suggests, illogically, that famciclovir may have increased the percentage of patients with PHN and that the higher the famciclovir dose, the higher the percentage of patients developing PHN. The difference becomes statistically significant (P < 0.004) for the comparison of patients older than 50 years of age in the 750-mg group with those in the placebo group (arguably the age group of greatest clinical concern because of higher risk for severe PHN).

The authors reported pain intensity measurements for patients at trial onset, albeit measured by using a methodologically weak four-point scale. They did not report the intensity of PHN for the remainder of the study. Therefore, there is no way of knowing whether older patients in the famciclovir groups had increased intensity of PHN along with increased frequency.

Four years after publication Tyring and colleagues’ study, theirs is still the only published evidence that famciclovir treatment of herpes zoster benefits patients compared with placebo. Shortcomings in the methods and conclusions of this randomized clinical trial and evident omissions in the report indicate that the efficacy claim of these authors and subsequent analysis based on these data (2) are questionable (3).

The purpose of this letter is to draw attention to the limitation of the original trial report and to fuel debate as to whether currently published trial evidence is sufficient to support use of this drug for the treatment of herpes zoster.

Ken L. Bassett, MD, PhD
Carolyn J. Green, MSc
James M. Wright, MD, PhD, FRCP(C)
University of British Columbia
Vancouver, British Columbia V6T 1Z3, Canada

References
information presented in our paper, the authors have misinterpreted the information provided and arrived at an invalid conclusion.

Stephen Tyring, MD, PhD
University of Texas Medical Branch
Galveston, TX 77555

Robin L. Saltzman, MD
SmithKline Beecham Pharmaceuticals
Collegeville, PA

Robert Dworkin, PhD
University of Rochester School of Medicine and Dentistry
Rochester, NY

References

Theophylline Therapy for Near-Fatal Cheyne–Stokes Respiration

To the Editor: Pesek and colleagues (1) described abdication of near-fatal Cheyne–Stokes respiration by theophylline therapy. However, we believe that the use of the term “Cheyne–Stokes respiration” to describe their patient’s respiratory disorder was not consistent with the known pathophysiology and clinical description of this term. Thus, the authors’ findings are difficult to interpret.

As the authors note, Cheyne–Stokes respiration is characterized by periodic breathing in which apneas or hypopneas alternate with hyperventilation, occurring in a crescendo–decrescendo pattern of tidal volume (1). However, this pattern of respiration was not apparent in the figures that were presented. Moreover, the patient had hypercapnia while breathing room air (PCO2, 60 mm Hg) during these respiratory events. This is not consistent with Cheyne–Stokes respiration, which is associated with hypopcapnia (2). Indeed, hyperventilation, precipitating a decrease in PCO2, below the apneic threshold, is the key physiologic feature of Cheyne–Stokes respiration (2, 3). In addition, the patient had diabetic neuropathy but no evidence of heart failure. Cheyne–Stokes respiration usually occurs in patients with heart failure who have augmented chemosensitivity to CO2 and increased circulation time (4). Because diabetic patients with neuropathy are predisposed to blunted chemosensitivity (1), they are at increased risk for central alveolar hypventilation syndrome but not for Cheyne–Stokes respiration.

In summary, although Pesek and colleagues’ report was very interesting, we believe that the use of the term “Cheyne–Stokes respiration” is misleading. The patient’s clinical presentation, laboratory data, and polysomnographic data are more consistent with a diagnosis of central alveolar hypventilation syndrome, whose pathophysiology is different from that of Cheyne–Stokes respiration (3). Because respiratory stimulants are well-recognized therapy for central alveolar hypoventilation syndrome (3), it is not surprising that theophylline would be effective in this patient. On the other hand, it may not be appropriate to use theophylline for Cheyne–Stokes respiration in patients with heart failure because phosphodiesterase inhibitors have been shown to increase mortality rates in such patients (5).

Don D. Sin, MD, MPH
T. Douglas Bradley, MD
University of Toronto
Toronto, Ontario M5G 2C4, Canada

References

To the Editor: Pesek and colleagues (1) reported a very interesting case of periodic central apneas responding acutely to theophylline. However, we take exception to using the term “Cheyne–Stokes respiration” to describe the pattern of breathing in this case. Cheyne–Stokes respiration is a form of periodic breathing in which hyperpnea and hypopnea oscillate cyclically. Apnea can accompany the hypopneic phase of the disorder (2, 3). In contrast to other patterns of periodic breathing, the transition between hyperpnea and hypopnea are gradual and have a crescendo–decrscendo appearance (2). Cheyne–Stokes respiration is found most often in patients with congestive heart failure, where it is normally regulated by changes in PCO2 (2, 4, 5).

The respiratory pattern illustrated in Pesek and colleagues’ Figures 1 and 2A is not characteristic of Cheyne–Stokes respiration because it lacks the typical crescendo–decrscendo oscillatory pattern of tidal volume changes seen in this disorder. In addition, the presence of diurnal hypercarbia in Pesek and co-workers’ patient suggests a more global deficiency in central respiratory control rather than typical Cheyne–Stokes respiration, in which the arterial CO2 tension is usually low or normal (2, 4, 5). The authors correctly point out several important confounding factors, such as diazepam, chronic renal failure, and dialysis, all of which may contribute to destabilizing the central respira-
tory centers. Therefore, we caution against using this case to generalize on the efficacy of theophylline to treat Cheyne–Stokes respiration.

Edgar I. Geigel, MD
Alejandro D. Chediak, MD
Mount Sinai Medical Center
Miami Beach, FL 33140

References

In response: Sin and Bradley and Geigel and Chediak point out that the respiratory tracings do not represent classic Cheyne–Stokes respiration (CSR). Qualitative monitoring of chest wall movements depends on the gain and nonlinear transfer characteristics of the respiratory monitor used and may not always reflect CSR. Part A of the Figure shows a respiratory tracing in of the chest movements in a patient having the typical pattern of CSR (1), evident on simultaneous, more sensitive measures of breathing. Compare this figure to one of those to which the correspondents object (Figure, part B). There is little difference between these two tracings. Other considerations are that breathing disorder patterns are not mutually exclusive but rather frequently coexist and that breathing patterns are labile and are easily affected by apprehension, laboratory environment, and instrumentation. Part C of the Figure shows a tracing from our index patient, which better reflects CSR. We chose the tracings not to illustrate CSR but rather to highlight other, more novel aspects of the report.

The observations by Cheyne in 1818 and Stokes in 1854 made no reference to CO₂ or other pathophysiologic features as pathognomonic characteristics. Although patients with congestive heart failure (CHF) and CSR often have transcutaneous PCO₂ measurements indicating hypocapnia, Sin and Bradley overstate the universality of this observation and overlook important pathophysiologic information. Arterial blood gas measurements by Dowell and colleagues (2) showed peak CO₂ levels of 45 to 73 mm Hg in 4 of 10 patients with CSR (1 with lung disease). Massumi and Nutter (3) described peak CO₂ levels of 52 to 62 mm Hg during CSR in 3 of 7 patients with CSR who also had profound dyshrhythmias unquestionably related to CSR (a clinical picture similar to our patient’s).

We are perplexed at Sin and Bradley’s assertions that respiratory stimulants are well-recognized for treating central alveolar hypoventilation syndrome and that theophylline’s effectiveness in our patient is unsurprising. They cite Bradley and Phillips, who stated that in their experience theophylline “does not provide long-term improvement in adults with hypercapnic CSA.” The absence of a ventilatory response to aminophylline has even been suggested as a possible aid to diagnosis of central alveolar hypoventilation syndrome (CAH) (4). Pulmonary texts that address theophylline therapy for CAH do so simply to dismiss theophylline as seldom beneficial in CAH. Our patient’s swift, absolute, and long-term response to theophylline is not easily reconciled with a diagnosis of CAH.

Many studies have demonstrated CSR resolution with theophylline. With regard to use of theophylline for treating CSR in CHF, our report should have no direct relevance to changing patient care in general. Indeed, we emphasized that an interesting feature of our patient was the absence of CHF. Any potential effect of theophylline on CSR in CHF has been addressed more thoroughly elsewhere. However, theophylline at maximal therapeutic concentrations has minimal phosphodiesterase inhibitory activity (5). Thus, although we cannot speak to the long-term effects of theophylline for treating CSR in patients with CHF, Sin and Bradley’s reasoning is inconsistent with current knowledge and is unlikely to be germane to the question.

Virend K. Somers, MD, PhD
Catherine Pesek, DO
University of Iowa College of Medicine
Iowa City, IA 52242

Improving Preventive Care Guidelines

To the Editor: Although preventive care guidelines are useful and may serve to increase preventive care maneuvers, I believe that Dr. Weingarten (1) misses an important point: Physicians must know the primary literature in order to tailor preventive services to their patients. In the most controversial subset of the example chosen by Dr. Weingarten, mammographic screening in women 40 to 50 years of age, none of the 10 recommendations given tell the physician or patient the information needed to make an informed decision. The primary literature tells us that there is a benefit to screening (2), with a number needed to screen to save one life of 769. There is also a harm to screening—23.8% of women between 40 and 50 years of age who are screened annually have at least one false-positive mammogram (3), with its attendant risks of anxiety and disruption of life (4). By discussing the benefit (a small chance of finding a curable cancer) and the risk (a substantial risk for a false-positive test result), a physician can help a woman make an informed choice and can reduce the anxiety provoked when a test result does turn positive.

I believe that general internists can and should know the primary literature on prevention. In areas of controversy, that knowledge is especially important. An understanding of the risks and benefits of any preventive care maneuver, whether counseling, chemoprophylaxis, vaccines, or screening tests, is essential to giving one’s patient appropriate advice.

References

Figure. Chest wall movements. A. In patient with Cheyne–Stokes respiration, as reported by Naughton et al. (1). The tracing is similar to the one in question from Pesek et al. (3). B. A tracing from the index patient that is more representative of Cheyne–Stokes respiration.

A

B

C

Figure. Chest wall movements. A. In patient with Cheyne–Stokes respiration, as reported by Naughton et al. (1). The tracing is similar to the one in question from Pesek et al. (3). B. A tracing from the index patient that is more representative of Cheyne–Stokes respiration.

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Elevated Estradiol and Testosterone Levels and Risk for Breast Cancer

To the Editor: Cauley and colleagues (1) reported that breast cancer risk was elevated not only in white postmenopausal women with high estrogen levels but also in those with high androgen levels. The association between breast cancer risk and androgen has been seen in many epidemiologic studies (2–4), but the mechanism by which androgens contribute to the cause of breast cancer is poorly understood. The relation between androgen and breast cancer is believed to be confounded by the strong correlation between estrogen and androgen because androgen is a precursor of estrogen in its metabolic pathway. Cauley and coworkers found that free testosterone was linked to breast cancer risk after adjustment for estrogen, suggesting that the association of androgen with breast cancer is independent of estrogen.

In a recent study by our group (5), we also found evidence supporting the notion that androgen may play a role in breast cancer. In breast cancer tissue, we analyzed DNA sequence from exon 1 of the androgen receptor gene that contained the variable length of CAG repeat known to inversely affect transcription according to its length. Our study showed that with longer CAG repeats, shorter CAG repeats were associated with aggressive disease and poor survival. This finding suggests that enhanced transcriptional activity of the androgen receptor gene might promote breast cancer progression.

Androgen receptor is expressed more frequently in breast cancer tissue than the estrogen or progesterone receptor is. This indicates that a subset of breast tumors may express androgen receptor only. However, the actual role of androgen receptor in breast cancer remains unclear. Considering the relatively consistent finding of hyperandrogenism in breast cancer, the impact of androgen on breast cancer warrants further investigation.

References


2. Mauss and colleagues (1) presented retrospective data on serum glucose levels in HIV-infected patients and concluded that protease inhibitors, male sex, and older age are risk factors for impaired glucose tolerance in such patients. Al-

Delayed Treatment of Bacterial Meningitis

To the Editor: Aronin and colleagues (1) purport to show that a delay in institution of antimicrobial therapy for patients with acute bacterial meningitis after initial presentation to the emergency department is associated with disease progression and worsened clinical outcomes. However, such evidence is absent from their report. Their Table 6 shows that patients whose clinical status deteriorated between presentation and institution of antimicrobial therapy did have worse ultimate outcomes than patients whose level of illness remained stable until antimicrobial therapy began, but no data associating worsening clinical status with delayed antimicrobial therapy are presented.

For all one can glean from the table, the patients with worsening clinical status might even have received earlier institution of antimicrobial therapy. It seems possible that rapidly worsening clinical status was a marker for fulminating disease, which might have led to worse clinical outcomes independent of the timing of initiation of antibiotics. Without data showing that antibiotic therapy was delayed to a greater extent in patients whose clinical status worsened before initiation of therapy, no conclusion can be made about the effect of the timing of antimicrobial therapy on either early disease progression or late sequelae. An analysis similar to that shown in the authors’ Table 5 for patients with stable disease status before antimicrobial therapy would be useful for patients with clinical deterioration before therapy.

James R. Johnson, MD
University of Minnesota
Veterans Affairs Medical Center
Minneapolis, MN 55417

Reference


Improved Glucose Tolerance in HIV-Infected Patients

To the Editor: Mauss and colleagues (1) presented retrospective data on serum glucose levels in HIV-infected patients and concluded that protease inhibitors, male sex, and older age are risk factors for impaired glucose tolerance in such patients. Al-

References

though the data were of interest, the study did not address the potential contribution of many drugs known to impair glucose metabolism, such as glucocorticoids and megesterol acetate (2). Similarly, in the reverse-transcriptase inhibitor group, the authors failed to account for the effect of didanosine alone, which is known to cause abnormalities in glucose homeostasis (2). Use of another drug known to cause abnormalities in glucose metabolism, acetylsalicylic acid, was not considered among the three different groups (2, 3). The possibility that more than one inciting drug may have been used was addressed only in the group that received protease inhibitors. It is believed that impaired glucose tolerance is often associated with insulin resistance, compensatory hyperinsulinemia, obesity, hypertension, and dyslipidemia caused by high triglyceride or low high-density lipoprotein cholesterol levels. Mauss and colleagues failed to address the contributions of these well-established risk factors. It would be reasonable to postulate that such common risk factors as obesity, duration of diabetes, and lipid profile were also the main risk factors for impaired glycemia in this patient sample (4).

Zuhayr T. Madhun, MD
Baha M. Arafah, MD
Grace A. McCamney, MD
University Hospitals of Cleveland
Cleveland, OH 44106

References

Treatment of Chronic Lead Intoxication

To the Editor: We read with interest Lin and colleagues’ article (1). In a study of approximately 300 patients, our team showed that a high percentage of patients with gout, hypertension, and chronic renal failure had an excessive body lead burden (2). Six patients with EDTA were treated until urine lead excretion decreased below 150 μg/d. All treated patients progressed to end-stage renal disease, and 3 patients subsequently received kidney transplants. The EDTA mobilization test was done on patients who received transplants, and values greater than 1000 μg of lead per 72-hour urine collection were recorded.

An article suggesting that treatment in lead-intoxicated rats could increase lead deposition in the brain (3) led us to refrain from treating the remaining patients who had received a diagnosis of lead intoxication. We then conducted an experimental trial in which 30 rats were intoxicated with low doses of lead. Fifteen rats were subsequently treated with EDTA. The chelating agent reduced levels of lead in the kidney (4.0 ± 0.5 compared with 19.5 ± 2.0 μg/g; P < 0.001), although bone lead deposits were unaffected (39.7 ± 1.9 compared with 40.0 ± 2.5 μg/g; P > 0.2). Several studies have shown that most of the body’s lead is deposited in the bone. Lead may be released during normal bone remodeling by the osteoclasts. In addition, any situation that may lead to an upset in bone metabolism in intoxicated patients (for example, steroid therapy, osteoporosis, or immobilization) may provoke the extensive release of lead from bone and its subsequent deposition in other tissues (a “reintoxication”).

We believe that the short treatment period in Lin and colleagues’ study would achieve scarce elimination of the body lead burden. Given that appreciable amounts of lead in the bone must be continuously lost to the bloodstream in patients with long-term exposure, it is surprising that such treatment slowed progression of renal insufficiency. We conclude that chelation therapy is not curative and, if given, should not be administered for prolonged periods.

Ana I. Sanchez-Fructuoso, MD, PhD
Dolores Prats, MD
Alberto Barrientos, MD, PhD
Hospital Clínico Universitario S. Carlos
28008 Madrid, Spain

Hepatitis B Virus Genotypic Resistance to Lamivudine

To the Editor: Lamivudine is a potent inhibitor of HIV reverse transcriptase and of hepatitis B virus (HBV) DNA polymerase (1). Its long-term efficacy in chronic HBV infection is limited by relapse after discontinuation and breakthrough during therapy by genotypic resistance. Hepatitis B virus breakthrough has been described in immunocompetent patients and patients who have received liver transplants. We report the first cases of HBV lamivudine resistance in HIV-infected patients.

Nineteen patients with HIV and HBV were treated with lamivudine (300 mg/d) for a median of 16 months (range, 4 to 34 months). All patients were negative for hepatitis C and delta virus markers. All patients were men (median age, 37 years [range, 32 to 52 years]) who underwent liver biopsy before treatment; 53% were cirrhotic, and the median Knodell score was 11 (range, 2 to 18). At the beginning of treatment, all patients were HBV DNA positive by liquid-phase hybridization (Murex Diagnostic, Chatenay–Malabry, France), with a median viremia level of 3736 pg/mL (range, 6 to 85 000 pg/mL). All 19 patients became HBV DNA negative after initiation of lamivudine therapy, and 7 developed a breakthrough—as defined by reappearance of detectable serum HBV DNA—after 8, 10, 11, 19, 23, 28, and 34 months of therapy. The rate of breakthrough increased with the duration of treatment, and the breakthroughs (6 of 7) occurred after 10 months; the percentage of breakthrough occurrence was 36.8% after a median treatment duration of 16 months. No histologic or virologic differences were seen between the 7 patients with breakthrough and the 12 patients without breakthrough (23 months compared with 12 months; P < 0.05). In 1 patient, breakthrough occurred despite hepatitis B e antigen (HBeAg)/anti-HBeAg seroconversion; anti-HBeAg antibodies disappeared, and the patient became positive for HBeAg after breakthrough.

The genotypic analysis of the HBV polymerase gene (including the YMDD domain) identified a mutation in the YMDD motif in the 7 patients with breakthrough: In 6 cases, methionine in position 532 was replaced by valine (YMDD), and in 1 case it was replaced by isoleucine (YIDD). Other mutations previously described in residues 521, 528, and 533 were noted (3). These results show that lamivudine-resistant strains of HBV may emerge in HIV-infected patients despite high-dose therapy (300 mg/d) and HBeAg and anti-HBeAg seroconversion; such strains usually appear after 10 months of therapy. Physicians are aware of this risk in patients infected with both HBV and HIV who are waiting for new treatments to control lamivudine-resistant strains of HBV. Even if breakthrough mutations are less able to replicate than wild-type mutations, risk for liver deterioration, which may cause substantial morbidity or death, is associated with breakthrough.
A 34-year-old woman with no family history of ischemic heart disease, smoking, diabetes mellitus, hypertension, or hyperlipidemia had effort-induced, atypical chest pain for 6 months. Resting electrocardiography showed minor, nonspecific T-wave changes in the precordial leads, but the treadmill test revealed 2-mm downward-sloping ST-segment depression in the anteroseptal and anterolateral leads at 50 W. Coronary angiography showed severe left coronary ostial stenosis estimated at 98% with no evidence of irregularities in the other coronary arteries (Figure). Arteriographic evaluation showed no abnormality of the aorta and its branches. Studies for collagen and autoimmune diseases and results of serologic tests for syphilis were negative. On surgery, the ascending aorta was macroscopically normal. A circumferential area of white fibrosis, regular in outline, was found in the left coronary ostium, leaving a lumen of only 1 mm in diameter. The left coronary ostium was enlarged by using a saphenous vein patch (Figure). Histopathologic examination showed only intimal fibrosis at the left ostial level with no cholesterol clefts, inflammatory cells, muck, or calcium. The media and the adventitia did not seem to be involved. The patient's recovery was uneventful.

Diseases that especially affect the coronary ostia are atherosclerosis, syphilitic aortitis, Takayasu disease, rheumatoid arthritis, and aortic valve disease. Iatrogenic complications, such as mediastinal irradiation or cardiac surgery, can also affect the coronary ostia (1). Focal fibromuscular hyperplasia, more common in young or middle-aged women, is a rare cause of ostial and large coronary arterial lesions (1). The predominant involvement of the intima (intimal fibroplasia) has been described in fibromuscular dysplasia; some researchers, however, consider it a secondary event preceding advanced medial changes characterized by severe disorganization, disruption, and replacement of smooth-muscle layers by focal proliferation of myofibroblastic cells (2). Solitary coronary ostial involvement in a young patient with no known risk factors for ischemic heart disease does not usually indicate atherosclerosis in the absence of stenosis in the other coronary arteries. However, an advanced degree of isolated intimal fibrosis without associated lipid or calcium deposits, which was the only pathologic process involving the left anterior descending coronary artery, was seen in three young persons and was considered the early phase of coronary atherosclerosis despite the patients' lack of risk factors (3–5). Despite its rarity, this condition must be included in the differential diagnosis of identifiable causes of angina pectoris and atypical chest pain in young persons with no evident risk factors for atherosclerosis.

**Left Coronary Ostial Stenosis Caused by Focal Intimal Fibrosis**

*To the Editor:* A 34-year-old woman with no family history of ischemic heart disease, smoking, diabetes mellitus, hypertension, or hyperlipidemia had effort-induced, atypical chest pain for 6 months. Resting electrocardiography showed minor, nonspecific T-wave changes in the precordial leads, but the treadmill test revealed 2-mm downward-sloping ST-segment depression in the...