INTERNAL MEDICINE ALERT

Evidence-based summaries of the latest research in internal medicine

Providing Evidence-based Clinical Information for 36 Years

AHC Media Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com
www.cmecity.com

AHC Media

INSIDE

Financial Disclosure:
Internal Medicine Alert's editor, Stephen Brunton, MD, is a retained consultant for Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Janssen, Lilly, Novartis, Novo Nordisk, Sanofi, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, and Teva. Peer reviewer Gerald Roberts, MD; executive editor Leslie Coplin; and managing editor Neill Kimball report no financial relationships relevant to this field of study.

Are Hospitalists Associated with Improvements in Quality of Care?

ABSTRACT & COMMENTARY

By Kenneth P. Steinberg, MD, FACP

Professor of Medicine, University of Washington School of Medicine, Seattle, WA

Dr. Steinberg reports no financial relationships relevant to this field of study. This article originally appeared in the February 2014 issue of Hospital Medicine Alert.

Synopsis: *This study demonstrates an association between the use of hospitalists by a hospital and a reduction in 30-day excess readmission rates for heart failure, acute myocardial infarction, and pneumonia.*

Source: Jungerwirth R, et al. Association of hospitalist presence and hospital-level outcome measures among medicare patients. *J Hosp Med* 2014;9:1-6.

THE NUMBER OF HOSPITALISTS IN THE UNITED STATES HAS GROWN RAPidly and it has been estimated that more than 80% of hospitals now employ hospitalists. Reasons for the rapidly increasing number of hospitalists include the need to increase efficiency and shorten length of stay, to cover for the decreased number of work hours now allowable for resident physicians, to allow primary care providers to spend more time in their offices, and to allow hospitalists to focus on the increasingly complex inpatient care environment. Hospitalists have been shown to increase efficiency and shorten length of stay, but the data that suggest hospitalists improve quality of care as measured by decreased mortality and readmission rates remain unclear. Many of the previous studies looking at this issue were single-institution studies with relatively small sample sizes.

Using two national databases, the authors of this current study were interested in examining the association between hospitals that utilize hospitalists and two measures of quality of care: 30-day all-cause mortality and 30-day readmission rates. They chose to study these variables in three patient conditions: heart failure (HF), acute myocardial

VOLUME 36 • NUMBER 6 • MARCH 29, 2014 • PAGES 41-48

INTERNAL MEDICINE ALERT IS AVAILABLE ONLINE
www.internalmedicinealert.com

infarction (AMI), and pneumonia (PNA). The investigators used 2008 data from the Centers for Medicare & Medicaid Services (CMS); these were hospital-level data of case mix-adjusted, risk-standardized, 30-day, all-cause predicted excess mortality and readmission rates, as measured from the first day of the index inpatient admission. Hospitals with fewer than 25 admissions for a given condition are excluded from the CMS database.

These CMS hospital-level data were then linked to data from the 2008 American Hospital Association Annual Survey Database that provides characteristics for approximately 6500 U.S. hospitals, including whether the hospitals employed hospitalists to provide care within the hospital. The primary independent variable was whether the hospital used hospitalists. Several other covariates were used, including other hospital demographic, geographic, and organizational data.

In the final analyses, there were 3029 U.S. hospitals of which 59.3% reported employing hospitalists. In the bivariate analyses, decreased mortality for all three conditions (HF, AMI, PNA) was associated with the presence of hospitalists and decreased readmission was seen with hospitalists for HF and AMI. However, in the multivariate regression analysis (taking into account other hospital characteristics), there was no statistically significant association between mortality and hospitalist care for any of the three conditions. In contrast, risk-standardized readmission rates were significantly lower for all three conditions in hospitals that employed hospitalists. Thus, the presence of hospitalists was not associated with a reduction in case mix-adjusted, risk standardized, 30-day all-cause predicted excess mortality. But hospitalists were associated with a decrease in adjusted and standardized 30-day excess readmissions for all three conditions: HF, AMI, and PNA.

■ COMMENTARY

This study demonstrates an association between the use of hospitalists by a hospital and a reduction in 30-day excess readmission rates (actual readmissions ÷ predicted readmissions; excess readmissions were calculated by looking at the difference in this ratio for a hospital compared to the national average of hospitals with similar case mix) for three important and common clinical conditions. The study only demonstrates an association and does not demonstrate causation between the presence of hospitalists and an effect on outcomes. In other words, there could be many other reasons why hospitals that employ hospitalists might have a lower excess predicted readmission rate unrelated specifically to the care provided by hospitalists. This study used hospital-level data from two large national databases and complex statistics to make these observations, and the authors do a good job of acknowledging the limitations of the study. The strengths, though, include the size and national bases of the study.

Hospitalists have extensive discharge experience and are uniquely situated to help affect the care, policies, and culture at institutions surrounding these transitions, even for patients for whom they do not provide direct care. I would be cautious about over-interpreting this study and hopefully these findings will be replicated in other studies. Demonstrating that hospitalists are associated with a reduction in hospital readmissions, an important quality metric, will be yet further evidence of the importance of utilizing physicians specializing in hospital medicine. I agree with the authors that although the use of hospitalists creates another hand-off in the transition between inpatient and outpatient settings, this risk might be overcome by the beneficial effects of hospitalists on the other various determinants of readmission, leading to an overall improvement in quality of care in this domain. ■

Internal Medicine Alert, ISSN 0195-315X, is published monthly by AHC Media, LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

EXECUTIVE EDITOR: Leslie Coplin.
MANAGING EDITOR: Neill L. Kimball.
EDITORIAL DIRECTOR: Lee Landenberger.

GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 550669, Atlanta, GA 30355.

Back Issues: $21.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: neill.kimball@ahcmedia.com
Online: www.ahcmedia.com

Subscription Prices

United States
1 year with free AMA Category 1 credits: $349
Add $19.99 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 is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 45 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This enduring material activity, *Internal Medicine Alert*, has been reviewed and is acceptable for up to 24 Prescribed credits by the American Academy of Family Physicians. AAFP certification begins January 1, 2014. Term of approval is for one year from this date with the option of yearly renewal. Each issue is approved for 1 Prescribed credits. Credit may be claimed for one year from the date of each issue. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Osteopathic Association has approved this continuing education activity for up to 48 AOA Category 2-B credits.

This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

AHC Media

Questions & Comments
Please call **Neill Kimball**, Managing Editor, at (404) 262-5404.

Inhaled Apomorphine as a Rescue Treatment in Parkinson's Disease

ABSTRACT & COMMENTARY

By Alexander Shtilbans, MD, PhD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Shtilbans reports no financial relationships relevant to this field of study. This article originally appeared in the February 2014 issue of Neurology Alert.

Synopsis: *Inhaled apomorphine, at doses up to 0.8 mg, appears safe and well tolerated by patients with Parkinson's disease, but does not result in significant improvement in wearing "off" periods, at the tested doses.*

Source: Grosset KA, et al. Phase IIa randomized double-blind, placebo-controlled study of inhaled apomorphine as acute challenge for rescuing "off" periods in patients with established Parkinson's disease. *Eur J Neurol* 2013;20:1445-1450.

Parkinson's disease causes severe motor symptoms — rigidity, bradykinesia, resting tremor, and postural instability. The motor symptoms respond to dopaminergic therapies such as dopamine agonists or levodopa. However, after several years of treatment, some patients develop motor fluctuations, such as dyskinesias and wearing "off" episodes. Young patients and those taking high doses of levodopa are more prone to developing dyskinesias. Wearing "off" is a troubling symptom that occurs at the end of the active period of a levodopa dose, and in some cases at any time. Presently, there are no safe and effective non-parenteral, FDA-approved, rapid-acting treatments to modify these episodes. Apomorphine, a potent dopamine agonist, has been studied as a rescue medication for wearing "off" episodes. When injected subcutaneously, however, it may cause severe nausea, vomiting, and skin reactions. Therefore, alternative routes of administration are being sought.

The authors of this paper conducted a single-center, randomized, double-blind, placebo-controlled study of the inhaled formulation of apomorphine for rescue treatment during "off" periods in patients with Parkinson's disease. The study aimed to find the minimum efficacious dose of inhaled apomorphine, as well as evaluate the safety, tolerability, and pharmacokinetics of this drug. Three different doses of apomorphine were compared to placebo. Parkinson's disease subjects had the disease for at least 3 years, complicated by motor fluctuations, and were in Hoehn and Yahr stage 2 to 2.5. Three dosage arms tested inhaled apomorphine doses of 0.2 mg, 0.5 mg, and 0.8 mg. Each arm included six patients receiving the drug and two receiving placebo. The primary endpoint was the proportion of patients who reported being in an "on" state at any time after dosing, and the time to improvement from "off" to "on." The secondary endpoint was the duration of the "on" state after dosing. Other outcomes measured were the change in the UPDRS 3 upper limb score, before and after dosing. Demographic characteristics of the patients within the three groups were comparable, except for the group receiving 0.8 mg of apomorphine, who were all males. The proportion of patients in the "on" state after receiving the drug was 0% at 0.2 mg, 50% at 0.5 mg, and 33.3% at 0.8 mg. One-sixth (16.7%) of patients receiving placebo achieved the "on" state ($P = 0.1311$). The mean duration of "on" time after dosing was 10 minutes for the 0.2 mg dose, and 40 minutes for 0.5 mg and 0.8 mg of apomorphine. Placebo was associated with 20 minute-mean duration of "on" time. The changes in UPDRS 3 were not significantly different between the active drug groups and placebo. Dyskinesias were not observed. Inhaled apomorphine was rapidly absorbed, achieving peak blood concentration at 1-3 minutes. The most common side effects for apomorphine and the placebo groups were headache and paresthesias.

The authors concluded that the inhaled formulation of apomorphine, at the doses studied, was well tolerated, but the small sample size limited the interpretation of the efficacy data of the study, which was not significantly different from placebo.

■ COMMENTARY

This is the first trial that evaluated the inhaled formulation of apomorphine and showed that it has high bioavailability, making it a potentially good rescue medication. However, the number of trial subjects was small and the group of patients receiving the highest dose of the drug was entirely male. There was a suggestion of efficacy at the highest dose of apomorphine tested (0.8 mg), but this was not significantly different from the placebo effects. Therefore, it will be important to test the drug in a larger group that includes women. The authors enrolled patients with a Hoehn and Yahr score of 2 to 2.5, which represents a moderate stage of disease, and would exclude some patients with more severe motor complications, including "off" periods. Only upper limbs were evaluated, limiting the assessment of patients with lower body-predominant Parkinson's disease.

The lack of significant adverse events or serious side effects, including nausea and vomiting, is encouraging and warrants further studies of inhaled apomorphine at higher doses and in a larger and more diverse group of patients. ■

Choosing Myeloma Maintenance Therapy: Patient Choice

ABSTRACT & COMMENTARY

By William B. Ershler, MD

INOVA Fairfax Hospital Cancer Center, Fairfax, VA; Director, Institute for Advanced Studies in Aging, Washington, DC

Dr. Ershler reports no financial relationships relevant to this field of study. This article originally appeared in the February 2014 issue of Clinical Oncology Alert.

Synopsis: *In a survey of consecutive myeloma patients from the Mayo Clinic on hypothetical constructs with varying expectations regarding overall survival benefit, toxicity, and financial burden, it was found that the majority of patients would not choose maintenance if toxicity was more than just mild and overall survival benefit was less than 1 year. Increasing financial burden (drug cost) also reduced the numbers that would choose maintenance therapy. Males were more likely than females to choose treatment in each of the scenarios presented.*

Source: Burnette BL, et al. Treatment trade-offs in myeloma. A survey of consecutive patients about contemporary maintenance strategies. *Cancer* 2013;119:4308-4315.

Treatment recommendations for patients with multiple myeloma (MM) have evolved over the past 5 decades. Novel agents and combinations have led to patients living longer, and more effective initial therapy, including high-dose chemotherapy followed by autologous stem cell reconstitution, has more than doubled life expectancy for newly diagnosed patients compared to 2 decades ago. Despite this demonstrably greater success with initial therapy, the role of maintenance therapy has remained controversial. Early efforts using primarily a continuation of alkylating agent therapy showed little, if any, benefit.[1,2] Subsequently, maintenance strategies incorporating interferon demonstrated prolongation in progression-free survival (PFS) by meta-analysis.[3,4] The more recent use of novel agents such as thalidomide, lenalidomide, and bortezimib have proven effective and with less toxicity. Two randomized trials have demonstrated improved PFS with lenalidomide maintenance after autologous transplantation for MM.[5,6] Yet, enhancement of overall survival (OS) remains to be conclusively demonstrated, and quality-of-life (QOL) data are lacking.

Although current myeloma maintenance strategies generally involve less toxic agents (lenalidomide, bortezimib) than their predecessors such as thalidomide and interferon, they are not without side effects and are very expensive. For example, a monthly supply of lenalidomide costs an estimated $10,000.

With the currently available information including effects on PFS, OS, and cost, investigators at Mayo Clinic conducted a systematic survey of MM patients regarding what constitutes a meaningful benefit that would make burdens of maintenance treatments (toxicity and cost) acceptable.

A self-administered survey was mailed to 1159 consecutive, living patients who had been evaluated at Mayo Clinic; 886 responded and 736 (64%) returned a completed questionnaire. The survey provided background information on the standard of care for MM and existing data on the effectiveness of maintenance.

Among responders, the most worrisome potential toxicity was identified as peripheral neuropathy by 27%, cytopenias by 24%, deep vein thrombosis by 20%, fatigue by 15%, nausea by 8%, and diarrhea/constipation by 7%. If treatment were to be provided free of cost, had no toxicity, and the OS benefit was ≤ 1 year, then 49% of patients indicated they would choose maintenance. In comparison, if treatment were associated with moderate toxicity, this proportion decreased to 42%. Adding a treatment cost of $25 per month decreased the proportion that would choose maintenance to 39% of patients. A moderate increase in cost to $250 per month did not affect the proportion choosing maintenance. However, with a marked increase in cost to $10,000 per month, the proportion who would choose maintenance with mild or moderate toxicity decreased to 32%. Across the different scenarios, male patients were more likely than female to choose maintenance therapy and older patients required a smaller increment in improved survival to opt for maintenance when compared to younger patients.

■ COMMENTARY

The current results indicated that willingness to receive maintenance treatment declined when actual benefits were provided in concrete numeric terms compared with a general statement of PFS benefit. The authors also observed that the magnitude of benefit required to consider maintenance was affected by cost and toxicity. The findings are sobering, but not all that surprising in light of the real but modest data on efficacy as honestly presented to study participants and the clear discussion of potential toxicity and costs. The findings should also be interpreted in the appropriate context. All of the patients had been evaluated at the Mayo Clinic, many of whom travelled great distances for consultation, if not treatment. Despite this common thread, responses came from patients at all

stages, including those recently diagnosed and those who were in the terminal phase of illness. Nonetheless, it is important to recognize that patient choice is an essential element in the selection of treatment, and what might be considered standard therapy could be less desirable when quality of remaining life or financial considerations are factored in. This, of course, is relevant to all aspects of the physician/patient relationship. However, in the context of choosing maintenance therapy for patients with myeloma, this report provides current and relevant parameters. Although maintenance therapy is commonly selected, future research will hopefully define those who are most likely to benefit. For example, as suggested by the authors, those patients who had experienced an excellent response to initial intervention might be just the population for whom maintenance therapy is of limited benefit and should be withheld.[7,8] ■

References

1. Medical Research Council's Working Party on Leukaemia in Adults. *Br J Cancer* 1980;42:823-830.
2. Cohen HJ, et al. *J Clin Oncol* 1986;4:888-899.
3. Myeloma Trialists' Collaborative Group. *Br J Haematol* 2001;113:1020-1034.
4. Fritz E, Ludwig H. *Ann Oncol* 2000;11:1427-1436.
5. Attal M, et al. *N Engl J Med* 2012;366:1782-1791.
6. McCarthy PL, et al. *N Engl J Med* 2012;366:1770-1781.
7. Kyle RA. *Mayo Clin Proc* 2011;86:419-420.
8. Rajkumar SV. *Nat Rev Clin Oncol* 2012;9:372-374.

Brief Reports

Curcumin Comparable to Fluoxetine for Treatment of Major Depressive Disorder

By Carrie Decker, ND

Founder and Medical Director, Blessed Thistle, Madison, WI

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

This article originally appeared in the February 2014 issue of Integrative Medicine Alert.

Source: Sanmukhani J, et al. Efficacy and safety of curcumin in major depressive disorder: A randomized controlled trial. *Phytother Res* 2013; Jul 6 [Epub ahead of print].

Curcumin, the primary active constituent of *Curcuma longa*, is well known for its antioxidative and anti-inflammatory actions, but also has been used traditionally for conditions including depression and anxiety in Chinese and Ayurvedic medicine. Animal studies have shown curcumin to have an antidepressive effect by promoting neurogenesies in the hippocampus as well as acting as a monoamine oxidase inhibitor. This study is the first known clinical trial of curcumin for the treatment of major depressive disorder (MDD).

Sixty individuals diagnosed with MDD (not having other psychiatric disorders or other uncontrolled organic disease) were randomized to treatments with 20 mg of fluoxetine, 1000 mg of curcumin (500 mg twice daily), or these treatments in combination for a period of 6 weeks. There was not a placebo group. The study was observer-masked but participants were not blinded to their treatment regimen. Efficacy of treatment was measured by the Hamilton Depression Rating Scale, 17-item version (HAM-D17). Forty-five individuals completed the study, with no significant difference in each group. The mean change in HAM-D17 score was comparable in all three groups (P = 0.77) with a mean change of -14.0 in the fluoxetine group, -12.6 in the curcumin group, and -14.8 in the combination group. A slightly lower tolerability was found in the combination treatment group, but the difference was not significant, with only mild side effects reported. ■

Religious Deterrence?

By Carol A. Kemper, MD, FACP

Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center

Dr. Kemper does research for Abbott Laboratories and Merck.

The article originally appeared in the February 2014 issue of Infectious Disease Alert.

Source: Van Wagoner N, et al. Church attendance in men who have sex with men diagnosed with HIV is associated with later presentation for HIV care. *Clin Infect Dis* 2014;58:295-299.

A cross-sectional analysis of persons newly presenting for HIV care was performed at a university HIV clinic in Birmingham, Alabama, examining risk factors for delayed presentation. Part of the initial intake was an assessment of church attendance, which was compared with self-reported sexual behavior (including men who have sex with men [MSM], men who have sex with women [MSW], and women who have sex with men [WSM] — men who have sex with both were included in MSM). A total of 508 people were included in the survey (60% MSM, 21% MSW, and 18%WSM). The median age was 33 years; and 62% were African American. More than half (56%) attended church on a regular basis. One-third had a CD4 count < 200 cells/mm^3 (AIDS by CD4 count) at presentation.

There was a statistically significant correlation ob-

served between church attendance and presentation with AIDS (P = 0.02). Church-going MSM were statistically more likely to present with more advanced disease, as defined by CD4 count < 200 cells/mm^3, than non-church goers (34% vs 20%; adjusted odds ratio, 2.2; P = 0.01). Church-going MSM were also statistically less likely to have been previously HIV tested (79% vs 88%; P = 0.041). The opposite was observed in WSM. Non-church going women were less likely to report prior HIV testing than church-going women (41% vs 68%; P = 0.01).

I suspect very different results might be observed if this analysis were performed in a part of the country other than the South, and the type of religion may have some bearing on the results. Nonetheless, I have heard many times from several of my black HIV+ MSM their concerns about being ostracized from their community, should their HIV+ status be revealed. ■

Average Survival Time of Chocolate: 55 minutes

By Carol A. Kemper, MD, FACP

Dr. Kemper does research for Abbott Laboratories and Merck. The article originally appeared in the February 2014 issue of Infectious Disease Alert.

Source: Gajendragadkar PR, et al. The survival time of chocolates on hospital wards: Covert observational study. *BMJ* 2013; 347:f7198.

I LOVE BEING ON CALL FOR THE HOLIDAYS — IT'S NOT SO BUSY, and there are goodies and boxes of See's chocolate at every nursing station (despite our infection control provision against having food at the nursing station, which is largely ignored, especially at the holidays). It's no wonder Warren Buffet bought See's candies in 1972.

These rascals in the department of cardiology at Bedford Hospital in the United Kingdom surveyed the rate of chocolate consumption on nursing units at three different hospitals. Two different types of boxed chocolates were deployed (a total of 8 boxes, 2 per unit, with a total of 258 chocolates). The boxes were "kept under covert surveillance," and the time to consumption recorded. Three-fourths of the chocolates were observed being eaten.

The medium time to opening the first box of chocolate, once it arrived at the nursing station, was 12 minutes (range, 0-25 minutes). The average survival time of chocolate was 55 minutes. Chocolate consumption was non-linear, with a burst of chocolate eating activity followed by slower ingestion. Using an exponential decay model, the survival half-life for a box of chocolates was 99 minutes. One brand of chocolates survived longer than the other. Nurses and health care assistants consumed most of the chocolates, while only 15% fell victim to physicians. ■

Pharmacology Update

Droxidopa Capsules (Northera™)

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

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

A NEW DRUG FOR THE TREATMENT OF NEUROGENIC ORTHOstatic hypotension (NOH) has been approved by the FDA under its accelerated approval program. Droxidopa is a prodrug to norepinephrine. It is the second drug to be approved for this indication after midodrine. Droxidopa is marketed by Chelsea Therapeutics, Inc., as Northera. The drug has been approved and used in Japan since 1989.

Indications

Droxidopa is indicated for the treatment of orthostatic dizziness, lightheadness, or the "feeling that you are to black out" in adults with symptomatic NOH caused by primary autonomic failure and pure autonomic failure.[1] Primary autonomic failure includes Parkinson's disease and multiple system atrophy, and pure failure includes dopamine beta-hydroxylase deficiency and non-diabetic autonomic neuropathy.[1]

Dosage

The recommended starting dose is 100 mg three times daily and may be titrated by 100 mg three times daily (every 24-48 hours) up to a maximum dose of 600 mg three times daily.[1] The capsules should be taken consistently with or without food. The last daily dose should be taken at least 3 hours before bedtime and the head of the bed should be elevated to reduce supine hypertension.[1] Droxidopa is available as 100 mg, 200 mg, and 300 mg capsules.

Potential Advantages

Droxidopa is only the second drug approved for NOH and is an alternative to midodrine. The latter appears to have a stronger warning for elevation of supine blood pressure.

Potential Disadvantages

The product was approved with limited evidence of efficacy.[2] Droxidopa's effectiveness beyond 2 weeks is

uncertain.[1] The drug may cause or exacerbate supine hypertension and may exacerbate ischemic heart disease, arrhythmias, and congestive heart failure.[1] Neuroleptic malignant syndrome-like symptoms have been reported during postmarketing surveillance in Japan.[1] Patients on dopa-decarboxylase inhibitors (e.g., carbidopa) may need dose adjustment for droxidopa. The capsules contain FD&C yellow #5 (tartrazine). This dye may cause allergic-type reaction in susceptible individuals (e.g., those with aspirin hypersensitivity).

Comments

Droxidopa is converted by two enzymes (catechol-O-methyltransferase and DOPA decarboxylase) to norepinephrine. The approval of the drug was based mainly on two enriched studies, one with a short-term treatment period of 1 week and the other with an 8-week treatment period.[1,2] In the first study, subjects with symptomatic NOH (n = 263) were titrated up to 600 mg droxidopa three times a day and only responders were then randomized to droxidopa (n = 82) or placebo (n = 80). The primary endpoint was based on the composite Orthostatic Hypotension Questionnaire (OHQ) 7 days after randomization. OHQ is comprised of two questionnaires, the Orthostatic Hypotension Symptom Assessment (OHSA), a six-item questionnaire pertaining to symptoms, and the Orthostatic Hypotension Daily Activity Scale, which is four items pertaining to ability to stand and walk. Statistically significant treatment effect was not demonstrated with OHQ. Item 1 of OHSA (symptoms of dizziness, lightheadedness, feeling faint, and feeling like you might black out) barely missed statistical significance (P = 0.06). In the 8-week study, subjects with symptomatic NOH and Parkinson's disease and a decrease of at least 20 mmHg (systolic blood pressure [SBP]) or 10 mmHg (diastolic blood pressure [DBP]) were titrated up to 600 mg three times a day with droxidopa (n = 87) or placebo (n = 84). Those intolerant of droxidopa at the lowest dose were discontinued from the study. Others were continued for an 8-week treatment period. The primary endpoint was item #1 on OHSA assessed at weeks 1, 2, 4, and 8 of the treatment period. Statistical significance was achieved at week 1 (P = 0.028) but not beyond. There was high intra-individual variability. Two other studies, one lasting 2 weeks and another lasting 3 months, were followed with a withdrawal phase. Neither study showed statistical difference between droxidopa and placebo.[1,2] There are no data on mortality or morbidity.

Clinical Implications

NOH can be a severely disabling condition due to reduction of SBP of at least 20 mmHg or DBP of 10 mmHg within 3 minutes of standing. This is believed to be due to the failure of the autonomic nervous system to respond to the change in position.[2] Current approved pharmacological treatment includes midodrine, with droxidopa being the latest approval for NOH. The approval, however, was based on limited efficacy data as well as limited duration of action. In addition, the enrichment design of the trials makes it difficult to have a true placebo group to compare relative adverse reaction profiles. Twenty-nine cases of neuroleptic malignant syndrome were reported from Japan's postmarketing surveillance data.[2] The cost of droxidopa was not available at the time of this review. ■

References

1. Northera Prescribing Information. Charlotte, NC: Chelsea Therapeutics, Inc.; February 2014.
2. http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/cardiovascularandrenaldrugsadvisorycommittee/ucm381154.pdf. Accessed March 12, 2014.

CME Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Scan the QR code to the right or log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. ■

CME Questions

1. In the multivariate analysis by Jungerwirth et al, what outcomes were found to be statistically associated with the presence of hospitalists in Medicare patients admitted with either heart failure, acute myocardial infarction, or pneumonia?

a. Reduction in 30-day mortality
b. Reduction in 30-day readmission rates
c. Reduction in both 30-day mortality and 30-day readmission rates
d. No impact on either 30-day mortality or 30-day readmission rates

2. Curcumin, dosed at 500 mg, twice daily:

a. is well tolerated and may improve symptoms of major depressive disorder.
b. is poorly tolerated but may improve symptoms of major depressive disorder.
c. is poorly tolerated and does not improve symptoms of major depressive disorder.
d. is well tolerated but does not improve symptoms of major depressive disorder.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is a retained consultant for Boehringer Ingelheim, Daiichi Sankyo, Forest Pharmaceuticals, Janssen, Lilly, Novo Nordisk, Pfizer, and Sanofi.

GERD Medications and B12 Deficiency

Source: Lam JR, et al. *JAMA* 2014;310:2435-2442.

The consequences of vitamin B12 (B12) deficiency most commonly include neurologic (CNS and peripheral nervous system) and hematologic (megaloblastic anemia). Because the progression of symptoms and signs related to B12 deficiency can be subtle, yet extremely burdensome to patients, clinicians must maintain a high level of vigilance for circumstances in which B12 deficiency can predictably occur, such as alcoholism and malnutrition.

Use of proton pump inhibitors (PPIs) and histamine-type 2-receptor antagonists (H2RA) is widespread in the United States. In 2012, more than 150 million prescriptions were written for PPIs alone. These numbers underestimate use since OTC versions of PPIs are also available.

Absorption of B12 requires that it first be cleaved from its food protein source on entering the GI tract. Gastric acid is required to release B12 from food. Since PPIs and H2RAs reduce gastric acidity, it should come as no surprise that they might be associated with greater risk for B12 deficiency.

A case-control study using the population of the Kaiser Permanente Northern California Healthcare system provided the opportunity to compare PPI/H2RA use among persons confirmed to have B12 deficiency (n = 25,956) vs controls (n = 184,199).

Receiving a PPI prescription for ≥ 2 years was associated with a 65% increased odds ratio of B12 deficiency. Similarly, receipt of H2RA treatment for that same interval was associated with a 25% increased risk.

The benefits of PPI and H2RA treatment are often substantial. That B12 deficiency is more likely to occur when using long-term GERD treatments should not discourage their use, but rather, increase clinician vigilance for the possibility of B12 insufficiency, especially when potentially appropriate symptoms or signs appear. ■

Dietary Fish Intake and New Onset Diabetes

Source: Virtanen JK, et al. *Diabetes Care* 2014;37:189-196.

The cornerstones of diabetes prevention are healthy diet and maintenance of desirable weight. The most focus of diet has been the role of caloric restriction to improve glycemia in overweight and obese individuals. The Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) provides an opportunity to evaluate the potential role of diet and new onset diabetes in Finnish men.

The observational data from KIHD included measurement of omega-3 polyunsaturated fatty acids (PUFAs) by dietary history. Long-chain omega-3 PUFA levels are considered to be a reliable indicator of the level of fish consumption in the diet.

Over an interval of almost 20 years, there was a linear inverse relationship between omega-3 PUFAs and incident type 2 diabetes. Men in the highest quartile of omega-3 PUFA enjoyed a 33% lesser likelihood of incident diabetes, adjusted for other risk factors. The mechanisms by which omega-3 PUFAs exert a protective effect on incident diabetes are not fully understood, especially since studies that examine fish (or fish oil supplements) have not detected any direct impact on glucose metabolism. On the other hand, because higher fish intake is associated with lesser adiposity, avoiding the diabetogenic effects of obesity may be an important contributor. ■

The Metabolic Impact of Low-Dose Thiazide Diuretics

Source: Mukete BN, Rosendorff C. *J Am Soc Hypertens* 2013;7:454-466.

Hyperglycemia and hypokalemia are well-recognized consequences of thiazide diuretic (TZD) therapy. Both adversities appear to be dose-related, and since we currently generally use low-dose TZD for treatment of hypertension (the most common indication for TZD therapy), it is useful to identify its impact on metabolic parameters.

Mukete and Rosendorff performed a meta-analysis on clinical trial data of 17,947 subjects in whom potassium (K+) and glucose measurements were taken. Overall, the mean changes in both parameters compared to other treatments were modest: an increase of glucose of only 1.4 mg/dL and a decrease in K+ of 0.27 mEq/L.

The largest hypertension trial ever performed was the ALLHAT trial, which found that compared to the calcium channel blocker amlodipine or the ACE inhibitor lisinopril, diuretic therapy was associated with a small but statistically significant increased risk for new onset diabetes (8.1% vs 9.8% vs 11.6%, respectively). Although looking at mean changes of metabolic parameters, especially restricting the view to only low-dose thiazides, looks relatively reassuring, the fact that some outliers will still experience clinically relevant hypokalemia or hyperglycemia mandates our continued vigilance for both consequences during the course of long-term treatment. ■

In Future Issues:

Antibiotic Prescription Strategies for Acute Sore Throat: A Prospective Observational Cohort Study