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Hospital Medicine

Evidence-Based Information for Hospitalists Intensivists, and Acute Care Physicians [ALERT]

Vol. 8, Issue 2, April 2013
www.ahcmedia.com

ABSTRACT & COMMENTARY

Zolpidem Use Increases Fall Risk for Inpatients

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Dr. Best reports no financial relationships in this field of study.

SYNOPSIS: Zolpidem, a commonly utilized agent for sleep disturbance, is associated with increased fall risk in hospitalized, non-pregnant, non-critically ill patients. Its use for a given patient and its appropriateness within standard order sets should be carefully considered.

SOURCE: Kolla BP, Lovely JK, Mansukhani MP, Morgenthaler TI. Zolpidem Is Independently Associated With Increased Risk of Inpatient Falls. *J Hosp Med* 2013;8:1-6.

Sleep disturbance, a symptom frequently experienced by hospitalized patients, is often managed pharmacologically with hypnotic medications. In the United States, zolpidem is utilized most commonly because of its relative safety and lack of significant side effects. Of concern, however, are data suggesting that among the population of ambulatory community dwellers with hip fracture, rates of zolpidem use are higher than among the general population; this may suggest an association between zolpidem and fall risk. Falls in the hospital are associated with multiple adverse patient and system-related outcomes; hence, it would be important to know whether zolpidem use is associated with an increased fall risk amongst hospitalized patients.

In this IRB-approved retrospective, cohort study, Kolla and colleagues at the Mayo Clinic sought to determine whether zolpidem administration is associated with fall risk among inpatients. All subjects were adults, 18 years or older, admitted in 2010 to the Mayo Clinic (a large teaching hospital) in Rochester, Minnesota. Pregnant and critically ill patients in an intensive care unit were excluded. All subjects had an active prescription for zolpidem, either scheduled or "as needed" (PRN), as determined by an internal pharmacy database review. In analyzing outcomes, the cohort of hospitalized patients with a zolpidem prescription who received the medication was compared with a cohort with a prescription who did not receive the medication. Here, investigators intended to control for differential factors that would render a

Financial Disclosure: *Hospital Medicine Alert*'s physician editor, Kenneth P. Steinberg, MD, peer reviewer William Thompson, MD, executive editor Russ Underwood, and associate managing editor Jill Drachenberg have no relevant financial relationship related to the material presented in this issue.

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[ALERT]

Hospital Medicine Alert, ISSN 1931-9037, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305. Website: www.ahcmedia.com.

EXECUTIVE EDITOR:
Russ Underwood.

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

POSTMASTER: Send address changes to Hospital Medicine Alert, P.O. Box 105109, Atlanta, GA 30348.

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patient eligible (or ineligible) for zolpidem use.

The electronic medical record was reviewed for patient demographics as well as ICD-9 diagnostic codes for a number of conditions known to be associated with increased fall risk: visual impairment, gait instability, cognitive impairment/dementia, delirium and insomnia. Hospital length of stay (LOS), the Charlson comorbidity index (a score based on the number of patient medical conditions) and Hendrich's fall risk score as calculated by nursing on the admission date were also abstracted.

All falls occurring over the study period were identified from a central institutional reporting system through which all events are analyzed. For each fall event, the patient's medication administration record was accessed to determine all medications received within the prior 24 hours. Of note, medications in classes previously shown to increase fall risk (antidepressants, antipsychotics, antihistamines, sedative antidepressants, benzodiazepines and opioids) were included.

Statistical analysis consisted of the following: univariate analysis to calculate the odds ratio (OR) of inpatient falls for fixed variables: receipt of zolpidem, male sex, surgical admission, insomnia, visual, gait or cognitive impairment or delirium. Odds ratios were also calculated based on continuous variables: hospital LOS, zolpidem dose, Charlson index and fall risk score. Multivariate analysis was then performed to calculate the OR for fall following adjustment for all significantly associated fixed or continuous variable. Rates of use of other medication classes associated with falls were compared between the cohort who was administered and the cohort in whom it was only prescribed.

Over the study period, 16,320 patients were prescribed zolpidem, with 88% of prescriptions written as PRN. 30.4% (4962) of these patients received a dose of the medication. As compared with those with a prescription only, patients who received zolpidem were significantly older, more commonly male, more likely to have insomnia or delirium, had higher Charlson index scores and were more likely to be surgically admitted. No differences were observed between the two groups in admission fall risk scores, hospital LOS, or rates of visual, gait or cognitive impairment.

Within this study population, 672 falls occurred (among 609 unique patients). The OR for falls for patients administered zolpidem, as compared with those who did not receive it was 4.37 (95% CI = 3.33-5.74, P<0.001). The OR remained increased at 2.5 (95% CI 2.08-3.02; P<0.001) when compared with patients who did not receive zolpidem — with or without a prescription. Based on an absolute risk increase of 1.8%, the number needed to harm was 55.

The following variables were found to significantly increase fall risk: delirium (OR 4.96), zolpidem administration (OR 4.37), insomnia (OR 2.37), Henrich's fall score (OR 1.36), male sex (OR 1.36), Charlson index (OR 1.29), zolpidem dose (OR 1.21) and age (OR 1.01). After adjustment for these factors, the risk of falls associated with zolpidem administration remained elevated (OR 6.39; 95% CI = 3.07-14.49; P<0.001). Relative to their age or use of other medications increasing fall risk, patients sustaining a fall associated with zolpidem administration did not differ from inpatients sustaining a fall in absence of zolpidem.

These authors conclude that zolpidem use in hospitalized patients is associated with an increased risk of falls, even when this risk is adjusted for other factors which are known to increase fall risk. To date, this is the largest study of its kind and the only one which has utilized multivariate analysis. Several study limitations are apparent. First, results cannot be generalized to pregnant patients or those in the ICU. Second, the study utilized administrative data for identification of comorbidities. Next, investigators did not account for the severity of visual, gait or cognitive impairment which may have ramifications for the results. Furthermore, this study does not account for changes in fall risk over a hospitalization, as it utilizes only a baseline fall risk score. More practically, we are provided no additional data with which to weigh the relative fall risks of alternative hypnotic agents, such as trazodone. It is interesting to consider that although insomnia is the most common indication for a zolpidem prescription, insomnia itself was again shown here to increase fall risk and hence

the risk of zolpidem may be additive, particularly in patients for whom the medication is ineffective in inducing sleep.

In summary, hospitalists should be aware of the risks of zolpidem use, and as with any medication, weigh cautiously the risks and benefits of use. As no medication is without some risk, nonpharmacologic therapies for sleep should be utilized and prioritized. Providers should monitor the effects of zolpidem on an ongoing basis so as not to continue the medication in patients gaining no benefit. From a systems standpoint, the decision as to whether zolpidem should be included as standard option within templated admission order sets should be carefully considered. Finally, other contributors to fall risk in the hospital should be identified and remedied. ■

ABSTRACT & COMMENTARY

Risk of Bleeding with Warfarin Therapy for Atrial Fibrillation

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Dr. DiMarco does research for Medtronic, is a consultant for Medtronic, Novartis, and St. Jude, and is a speaker for Boston Scientific.

This article originally appeared in the January 2013 issue of Clinical Cardiology Alert. *It was edited by Michael H. Crawford, MD, Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco, and peer reviewed by Ethan Weiss, MD, Assistant Professor of Medicine, Division of Cardiology and CVRI, University of California, San Francisco. Dr. Crawford reports no financial relationships relevant to this field of study, and Dr. Weiss is a scientific advisory board member for Bionovo.*

SOURCE: Gomes T, et al. Rates of hemorrhage during warfarin therapy for atrial fibrillation. *CMAJ* 2013; 185:E121-E127.

This paper details the result of a population-based cohort study of all Ontario, Canada, residents older than 66 years of age who began warfarin therapy for atrial fibrillation over an 11-year period. Patients were identified by the authors from data in the Ontario Health Insurance Plan. Patients were included if they had a hospital or office visit diagnosis of atrial fibrillation and began warfarin during this time period. Medical records were then surveyed for the occurrence of major hemorrhages. This was defined as a visit to an emergency department or admission to a hospital for hemorrhage during warfarin therapy. Patients were followed for up to 5 years after starting warfarin. Hemorrhage was classified by anatomic site using standard definitions. If patients had more than one admission for hemorrhage, only the first event was included.

During the 13-year study period, there were 125,195 patients who began therapy with warfarin in the setting of a diagnosis of atrial fibrillation. This was 47% of all new users of warfarin in this age group during this time period. Of these patients, 69% had an estimated CHADS2 score ≥ 2. In this inception cohort, the cumulative incidence of hemorrhage was 1.0% at 30 days, 4.1% at 1 year, and 8.7% at 5 years. During the study, the overall risk of hemorrhage was 3.8% per patient year. The annualized risk was highest during the first 30 days of therapy (11.8%) and 3.4% during the follow-up period. Hemorrhage was more common as the CHADS2 score increased. Patients with a CHADS2 score ≥ 4 had a 16.7% hemorrhage rate per person year in the first 30 days and 6.0% per year afterwards. By contrast, those with CHADS2 scores < 2 had hemorrhage rates of 1.8% per person year with a score of 0 and 2.5% per person year with a score of 1. Hemorrhage rates were higher among patients older than 75 years (4.6% in older patients vs 2.9% in younger patients). Upper and lower gastrointestinal hemorrhage accounted for 63% of the hemorrhage-related hospitalizations, intracranial hemorrhage for 5%, and other sites, mostly genitourinary, for 39%. There were 1963 deaths due to hemorrhage in the hospital or within 7 days after discharge. Intracranial hemorrhage had the highest mortality (41.7%) compared to gastrointestinal hemorrhage (14.7%) and other sites of hemorrhage (12.6%).

The authors conclude that in a large inception cohort of patients with atrial fibrillation, hemorrhage is common during both the first 30 days and subsequent months of warfarin therapy and is related to risk factors in the CHADS2 score and also to age. The risk of hemorrhage is higher than has been seen in recent published randomized trials of anticoagulation therapy. The mortality rate associated with hemorrhage, particularly intracranial hemorrhage, is extremely high.

■ COMMENTARY

Since the new oral anticoagulants, dabigatran and rivaroxaban, were approved for stroke prevention in

patients with atrial fibrillation, concerns have been raised about bleeding problems with these agents that had not been prominent in the randomized clinical trials. Reports in both the medical literature and the lay press have complained that the level of anticoagulation cannot be monitored with standard tests and that there is no available rapid antidote. Although these statements about the new oral anticoagulants are true, this paper points out that bleeding with warfarin is also a major concern. Particularly striking are the very high rates of bleeding with warfarin during the first month of therapy and the shockingly high mortality rates seen during hospitalizations for hemorrhage. We have scoring systems for both stroke risk and bleeding risk in patients on anticoagulant therapy. The data in this paper indicate that applying these risk scores in clinical practice is still problematic. ■

ABSTRACT & COMMENTARY

Physicians' Own Beliefs on Goals of Care Influence Presentation of Comfort Care Option to Patient Surrogates

By Betty Tran, MD, MS

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

This article originally appeared in the January 2013 issue of Critical Care Alert. *It was edited by David J. Pierson, MD, and peer reviewed by William Thompson, MD. Dr. Pierson is Professor Emeritus, Pulmonary and Critical Care Medicine, University of Washington, Seattle, and Dr. Thompson is Associate Professor of Medicine, University of Washington, Seattle. Drs. Pierson and Thompson report no financial relationships relevant to this field of study.*

SYNOPSIS: During family discussions, physicians who believe more strongly that life support should be withdrawn are more likely to present the option of comfort care and describe its benefits.

SOURCE: Schenker Y, et al. Association between physicians' beliefs and the option of comfort care for critically ill patients. *Intensive Care Med* 2012;38:1607-1615.

This study conducted in five ICUs at two academic hospitals in San Francisco sought to describe how comfort care is presented to surrogates and if physicians' beliefs on whether life support should be withdrawn are associated with the option of comfort care being presented. One hundred and five physician-family conferences were identified through the ICU nurses, but only 72 were included in the final analysis after excluding conferences in which the physician and/or family declined participation. Each conference was audiotaped and subsequently transcribed verbatim for analysis. The study team coded whether comfort care was presented as an option by the physician, what risks and benefits of comfort care were presented, and what other treatment options (unlimited intensive care or limited intensive care) were offered. Demographic information was collected on patients, surrogates, and physicians. Physicians were also asked immediately after the conference to grade how strongly they believed life support should be withheld or withdrawn prior to the family conference on a scale of 0 (not strongly at all) to 10 (extremely strongly). Coders were blinded to all the participants' questionnaire responses.

The physician-family conferences occurred a mean of 10 days after ICU admission; on average, 60% of the ICU stay had elapsed at the time of the conference. Patients had a mean APACHE II score of 29 on the day of the conference, with the overall inpatient mortality rate being 72% (all due to withdrawal of life support). Comfort care was not presented as an option in 32 of 72 (44%) of the conferences; of these, 78% included only discussion of continued unlimited intensive care. In multivariate analyses, the only variable associated with the presentation of comfort care was the strength of the physicians' belief that life support should be withdrawn (odds ratio [OR] 1.38, 95% confidence interval [CI] 1.14-1.66; $P = 0.01$). In the 40 (56%) of 72 conferences in which comfort care was presented, there was an association between the strength of the physician's belief that life support should be withdrawn and the number of unique benefits of comfort care that were discussed (OR 1.12, 95% CI 1.01-1.25; $P = 0.04$).

■ COMMENTARY

In their clinical policy and consensus statements, the American College of Critical Care Medicine and American Thoracic Society support a shared decision-making model that includes surrogates, family members, and the health care team when the patient

lacks full decision-making capacity. For example, for technical decisions regarding choice of antibiotics, surrogates overwhelmingly prefer physicians to make the final decision, but when it comes to life-sustaining treatment decisions, the extent to which the physician is involved is variable and can depend not only on surrogate preferences, but also the physician's own professional judgment and ethics.[1-3]

Thus, depending on the context, although the authors cite their findings as surprising, their results can be viewed as fairly predictable. Physicians may be more likely to present and promote comfort care as an option in cases where they believe no other medical treatment is available or for patients who have a dismal prognosis from a prior underlying condition, such as metastatic cancer or chronic lung disease. On the other hand, physicians may be less likely to present comfort care options in situations they perceive to be potentially reversible. Alternatively, if patients or surrogates have previously expressed their wishes to continue aggressive care, physicians may be more reluctant to raise the option of comfort care. In these situations, the omission of comfort care as an option is not necessarily an oversight on the part of the physician, but may be a conscientious decision based on the clinical scenario. As the authors duly note, the context surrounding the decision not to present comfort care as an option is an important area for future research.

Furthermore, although the authors rightly argue that failure to present comfort care as an option based purely on physicians' beliefs is problematic, the issue of how and when best to present this alternative to surrogates has yet to be answered. The notion that comfort care is "giving up" or "doing less" as opposed to "doing everything" will have to be quelled, and continual, open communication between physicians and surrogates will be necessary to foster trust in the families of critically ill patients and to understand their preferences in the decision-making process. These aims, in addition to improving clinician communication skills in discussing life-sustaining treatment decisions, will enhance the extent to which physicians can support and advise surrogates in the decision-making process. ■

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ABSTRACT & COMMENTARY

Parenteral Iron for Cancer-Associated Anemia

By William B. Ershler, MD

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This article originally appeared in the March 2013 issue of Clinical Oncology Alert. *It was peer reviewed by V.R. Veerapalli, MD. Dr. Veerapalli is Staff Clinician, INOVA Fairfax Cancer Center, Falls Church, VA. Drs. Ershler and Veerapalli report no financial relationships relevant to this field of study.*

SYNOPSIS: In an observational study conducted in Germany of more than 600 anemic cancer patients receiving parenteral iron (ferric carboxymaltose), hemoglobin levels were shown to rise significantly. The iron treatment was well tolerated. Randomized interventional studies are warranted to demonstrate efficacy in terms of physical function and quality of life and safety in this population.

SOURCE: Steinmetz T, et al. Clinical experience with ferric carboxymaltose in the treatment of cancer- and chemotherapy-associated anemia. *Ann Oncol* 2013;24:475-482.

Anemia is common in cancer patients for a number of reasons, including iron deficiency, inflammation, and chemotherapy,[1] and its presence negatively influences performance, quality of life, and even the effectiveness of tumor-directed therapy.[2,3] In fact, iron deficiency even in the absence of anemia is associated with impaired physical function, weakness, and fatigue,[4,5] all of which have been demonstrated to improve with iron supplementation.[6,7]

Iron deficiency can be recognized as either an absolute deficiency in total iron stores (low serum iron and ferritin levels) or by a reduction in utilizable iron in an individual with adequate stores (low transferrin saturation). Inasmuch as ferritin is upregulated during inflammation, the reliance on this measure may be misleading in patients with malignancy.

Anemia associated with cancer and cancer chemotherapy has been treated with erythropoiesis-stimulating agents (ESA) or red cell transfusions, but not infrequent adverse consequences have been reported and alternative approaches are under active investigation. In this light, intravenous iron, known to improve response to ESAs, may alone be an effec-

tive means of improving cancer-associated anemia, although the data on its use without coadministration of ESA are lacking. To address this, Steinmetz and colleagues evaluated effectiveness and tolerability of a commonly used (in Europe) parenteral iron preparation, ferric carboxymaltose (FCM), in the routine treatment of anemic cancer patients.

For the purposes of this observational review, data on 639 patients enrolled in 68 hematology/oncology practices throughout Germany were analyzed. Of the 639 patients, 619 received FCM at the oncologist's discretion, 420 had eligible baseline hemoglobin (Hb) measurements, and 364 had at least one follow-up Hb measurement. Data of transfused patients were censored from analysis before transfusion.

The median total iron dose was 1000 mg per patient (interquartile range 600-1500 mg). The median Hb increase was comparable in patients receiving FCM alone (1.4 g/dL [0.2-2.3 g/dL; n = 233]) or FCM + ESA (1.6 g/dL [0.7-2.4 g/dL; n = 46]). Patients with baseline Hb up to 11.0 g/dL and serum ferritin up to 500 ng/mL benefited from FCM treatment (stable Hb ≥ 11.0 g/dL). Also, patients with ferritin > 500 ng/mL but low transferrin saturation benefited from FCM treatment. FCM was well tolerated; 2.3% of patients reported putative drug-related adverse events and these were mainly gastrointestinal. Only one serious adverse drug reaction occurred and this was in a heavily pretreated man with a head/neck tumor and pulmonary metastases who experienced respiratory failure on the same day he received his second FCM injection.

■ COMMENTARY

Fatigue is a common occurrence among cancer patients, particularly those who are undergoing chemotherapy or radiation therapy. Although anemia is commonly observed, clinicians have been less aggressive about treating with ESAs or transfusion in patients with moderate anemia for fear of accelerating disease or shortening survival.[8,9]

Yet, there are studies now demonstrating efficacy of parenteral iron in improving hemoglobin levels and reducing transfusion requirements,[10,11] and this, with the current observational analysis indicating both safety and efficacy of such an approach on a larger scale and in a variety of practice settings, provides rationale for more extensive investigation. In this regard, an interventional trial in cancer patients with mild-to-moderate anemia in which outcomes other than hemoglobin level, such as physical function (e.g., 6-minute walk test) and quality of life, would be very instructive. ■

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Stroke Alert: A Review of Current Clinical Stroke Literature

By Matthew E. Fink, MD

Professor and Chairman, Department of Neurology, Weill Cornell Medical College, and Neurologist-in-Chief, New York Presbyterian Hospital

This article originally appeared in the March 2013 issue of Neurology Alert. *It was peer reviewed by M. Flint Beal, MD. Dr. Beal is Anne Parrish Titzel Professor, Department of Neurology and Neuroscience, Weill Cornell Medical Center. Dr. Fink is a retained consultant for MAQUET and Dr. Beal reports no financial relationships relevant to this field of study.*

SYNOPSIS: Special Report from the International Stroke Conference: Current Endovascular Interventions for Acute Ischemic Stroke Do Not Result in Better Clinical Outcomes than Intravenous Thrombolysis

Attendees of the international stroke meeting in Hawaii in February 2013 were astonished by three reports of long-awaited trials comparing endovascular therapies with intravenous thrombolysis — IMS III,[1] SYNTHESIS,[2] and MR RESCUE.[3] In all three studies, the clinical outcomes were not statistically different between the intra-arterial interventional groups and the intravenous-medical groups.

In IMS III, the study was stopped, for futility, after 656 patients with moderate-to-severe ischemic stroke were randomized to either intravenous tPA alone or endovascular therapy after IV tPA. The primary outcome measure, a modified Rankin score of 2 or less at 90 days, did not differ significantly between the two groups (40.8% for endovascular and 38.7% with intravenous tPA), and there were no subgroups based on clinical severity that showed any differences in outcome. Mortality was similar between the groups (19.1% vs 21.6%) as was symptomatic intracerebral hemorrhage (6.2% vs 5.9%). The trial showed similar safety profiles and outcomes. Of note, there was variability in the devices used for endovascular therapy at the discretion of the operators — Merci retreiver, Penumbra system, Solitaire device, or intra-arterial tPA. Angiography had to begin within 5 hours of symptom onset and be completed within 7 hours.

In the SYNTHESIS trial, 362 patients with acute ischemic stroke were randomly assigned, within 4.5 hours of symptom onset, to intravenous thrombolysis with tPA or intra-arterial endovascular therapy using a combination of thrombolysis or clot retrieval, or both. The median time from stroke onset to start of treatment was 3.75 hours for endovascular therapy and 2.75 hours for intravenous tPA. The primary outcome was survival free of disability (Rankin score of 0 or 1) at 3 months, and there was no significant difference between the groups (30.4% for endovascular and 34.8% for intravenous). Odds ratios were adjusted for age, sex, stroke severity, and atrial fibrillation at baseline. Symptomatic intracranial hemorrhage occurred in 6% of each group and there were no significant differences in other serious adverse events or death rates.

The MR RESCUE trial used imaging in an attempt to select patients for treatment and predict outcome based on CT or MR measurements of potentially reversible ischemic penumbra. The study randomly assigned 118 eligible patients within 8 hours after onset of large-vessel, anterior-circulation ischemic strokes to undergo mechanical embolectomy with Merci retriever or Penumbra system, or receive standard care, which might include intravenous tPA. All patients underwent CT or MRI studies to determine infarct core and penumbra, and were stratified to favorable penumbra group or a non-penumbra pattern. For all patients, the mean time to enrollment was 5.5 hours, and 58% had a favorable penumbra pattern. Revascularization was successful in 67% of the embolectomy group. Mortality at 90 days was 21%, and the rate of symptomatic hemorrhage was 4%, without any significant differences between the two groups. Mean scores in the modified Rankin score did not differ between the groups, and there were no differences between the favorable penumbra pattern or the nonpenumbral pattern group. A favorable penumbra pattern did not predict a better outcome, and there was no difference between embolectomy vs standard care.

We congratulate the investigators of all three of these studies for their herculean efforts to complete this work, but we are disappointed by the results. How can we explain the findings, and what should be our next steps?

First, the methodology for clot extraction in all three studies used a first generation of devices, and the newer devices that are becoming available are technically superior at performing clot extraction. So, it is expected that use of these newer devices will result in better outcomes. But second and more importantly, the time windows allowed for these studies had a negative impact on the results. The IMS III study allowed angiography to begin as long as 5 hours after onset of symptoms and was completed by 7 hours. In the SYNTHESIS trial, the intravenous tPA group was treated on average 1 hour faster than the endovascular intervention group. In MR RESCUE, mean time to enrollment was 5.5 hours and extended up to 8 hours.

We know from experimental studies in animals as well as humans that speed and time to revascularization has a profound impact on outcome. We constantly state that "time is brain" and urge our physicians to institute thrombolysis as fast as possible. Yet, these studies all had delays in the institution of treatment, often due to the extensive diagnostic studies that were part of the protocols. In this situation "perfect is the enemy of good." The future studies must have protocols that limit the diagnostic studies to only what is absolutely necessary to make a triage decision — intravenous thrombolysis or intra-arterial clot extraction. Then we will need to repeat these studies using the newest devices in the shortest time window possible. Imaging studies will have to follow treatment and not delay it. Time is still the enemy, and remains the single most important variable that influences the results of therapies. Although it is certainly important and intellectually interesting to evaluate the penumbra and the

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collaterals, we cannot allow those studies to slow us down in our attempts to treat patients. New trials must reflect real-world practice issues, or we will not make the progress we are seeking. I would propose a simple clinical scale and rapid CT or MRI as we are currently performing it, and then an immediate decision to go to the angiography suite for interventional clot retrieval or standard therapy. Any further delays will result in worse outcomes. I am optimistic that future studies, if properly designed, will show that new interventional techniques will improve the clinical outcomes for patients with acute ischemic stroke. ■

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4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.

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CME QUESTIONS

1. Which patient factor is associated with fall risk in hospitalized patients?
a. Zolpidem administration
b. Delirium
c. Insomnia
d. All of the above

2. In the prospective observational study by Schenker et al., the only variable associated with the presentation of comfort care as an option during a family conference was:
a. The age of the patient.
b. The strength of the physician's belief that life support should be withdrawn.
c. The presence of multiple organ failure at the time of the conference.
d. A history of metastatic cancer.

3. The observational report of parenteral iron use in cancer patients in Germany supports the conclusion that:
a. Treatment is associated with higher hemoglobin levels.
b. Physical function is improved in those who were shown to have a rise in hemoglobin level.c. Quality of life is improved in those who were shown to have a rise in hemoglobin level.
d. Physical function is improved by treatment in all recipients whether there was a rise in hemoglobin level or not.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss pertinent safety, infection control and quality improvement practices;
- explain diagnosis and treatment of acute illness in the hospital setting; and;
- discuss current data on diagnostic and therapeutic modalities for common inpatient problems.

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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, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

Volume 18, Number 4 Pages 7-8 April 2013

A Relationship Between Nocturia and Hypertension

Source: Feldstein CA. *J Am Soc Hypertens* 2013;7:75-84.

Nocturia could easily be misconstrued as a "nuisance" symptom since, after all, nobody dies from nocturia … or do they? Indeed, urinary frequency and nocturia have been associated with greater risk for nocturnal falls and hip fracture; hence, nocturia can be much more than just a nuisance.

Clinicians are used to identifying nocturia as a symptom associated with benign prostatic hyperplasia, overactive bladder, uncontrolled diabetes, uncontrolled congestive heart failure, use of diuretics, and (less commonly) interstitial cystitis. What is only minimally recognized, however, is the emerging observation that hypertension is associated with nocturia.

Several plausible mechanisms can explain the nocturia/hypertension relationship: hypertension-induced alterations in glomerular filtration or tubular transport, activation of atrial natriuretic peptide from ventricular wall stress induced by hypertension, and resetting of the pressure-natriuresis relationship in the kidney, to name a few.

Feldstein indicates that the prevalence of nocturia in untreated hypertension patients may be as high as 33%. Since nocturia can be both a burdensome symptom and lead to significant morbidity (and mortality), clinicians may wish to specifically inquire about nocturia when encountering hypertension patients. ■

Peripheral Artery Disease: Helping Patients to Walk the Walk

Source: Ahimastos AA, et al. *JAMA* 2013; 309:453-460.

Currently available treatments for peripheral artery disease (PAD) are only modestly effective. PAD portends increased risk of cardiovascular disease; hence, most PAD patients should be receiving pharmacotherapy with a statin and an antiplatelet agent (usually clopidogrel).

Because one of the quality-of-life limiting factors in advanced PAD is disease-mediated diminution in walking distance and walking time, incorporation of pharmacotherapy to improve these limitations is also considered important. Unfortunately, the two FDA-approved treatments (pentoxifylline and cilostazol) for symptoms of PAD provide only a modest increase in walking distance (25% or less). Smoking cessation and exercise advice remain critically important, but are too often not heeded.

Ramipril is an angiotensin-converting enzyme (ACE) inhibitor that has been used in numerous major clinical trials, including the HOPE trial, ONTARGET trial, REIN trial, and others. Use of ramipril is usually predicated on 1) its ability to lower blood pressure, 2) its ability to improve outcomes in congestive heart failure, or 3) its ability to improve albuminuria.

Based on results seen in a small pilot trial that suggested favorable results of ramipril on treadmill time in subjects with PAD, Ahimastos et al performed a larger randomized clinical trial (n = 212).

At the conclusion of the 6-month trial of ramipril 10 mg/day vs placebo, pain-free walking time had increased by more than 50% in the ramipril group, but only 10% in the placebo group.

Although the mechanism for improved function is speculative, it has been noted that ACE inhibitors increase skeletal muscle blood flow; indeed, this has been the mechanism to which improved insulin sensitivity in diabetics has been attributed. Ramipril may offer a new avenue to improve functionality in patients with PAD. ■

Long-Term Functional Outcomes After Localized Prostate Cancer Treatment

Source: Resnick MJ, et al. *N Engl J Med* 2013;368:436-445.

When prostate cancer is localized, either radical prostatectomy (RPT) or external beam radiation (EBR) can often be curative. The adverse effect profile of these two interventions, however, may be meaningfully different and such differences might also be time-dependent.

Resnick et al studied men (n = 1164) from the Prostate Cancer Outcomes Study who had been enrolled between the ages of 55-74 and had localized prostate cancer. More than 80% of the men had a Gleason score of 7 or less. The prevalence of urinary incontinence (UI) and erectile dysfunction (ED) were compared among these men at years 2, 5, and 15.

Prostatectomy subjects were five to six times more likely to have incontinence at

2 years and 5 years than EBR subjects. Similar disadvantage was seen in the prevalence of ED (two- to four-fold increased incidence in the RPT group). At the 15-year conclusion of their observations, no differences between groups remained. However, one would anticipate, for instance, a substantial incremental increase in ED as men age *with or without intervention*; hence, the fact that between-group differences are eliminated by 15 years provides little solace for the men who suffer the adverse effects in the interim! ■

The Word 'GPR40 Modulator' May Soon be Entering Our Vocabulary

Source: Basu A, et al. *Diabetes Care* 2013;36:185-187.

The search for safe and effective agents to treat type 2 diabetes (DM2) continues, with hypoglycemia often being a limiting adverse effect of otherwise highly efficacious agents.

It has been observed that free fatty acids (FFA) play a role in glucose homeostasis, although the story line is complex. Acutely, elevations of FFA *stimulate* beta cell secretion of insulin. *Chronic* FFA elevations result in an impaired insulin response to high glucose levels, a phenomenon known as lipotoxicity.

The mechanism by which FFA impacts insulin secretion has been elegantly worked out and includes the G-protein-coupled receptor (GPR40). Because GPR is involved not only in insulin secretion, but also plays a role in obesity and dyslipidemia, its potential as a multimodal intervention has looked promising.

Studies in humans have shown that GPR40 agonists live up to the expectation that they lower glucose, with a very low risk of hypoglycemia. For instance, a head-to-head comparison with the sulfonylurea glimepiride found hypoglycemic episodes to be six-fold lower with the GRP40 agonist.

In an era of a burgeoning population of DM2 patients, we look forward to the addition of pharmacotherapies that safely complement our current options. ■

A More Effective Regimen for *H. pylori* Eradication

Source: Liou JM, et al. *Lancet* 2013;381: 205-213.

In the United States, peptic ulcer disease is caused primarily by two culprits: nonsteroidal anti-inflammatory drugs and *Helicobacter pylori* (and their combination). Evolution of pharmacotherapy for *H. pylori* currently employs combinations of amoxicillin (AMOX), metronidazole (METR), clarithromycin (CLAR), and a proton pump inhibitor (PPI). Unfortunately, over time *H. pylori* eradication rates with such regimens have fallen to as low as 80% or less. Is there a better way?

Liou at al randomized *H. pylori*-positive Taiwanese adults (n = 900) to one of three regimens — 1) Sequential 10 days: PPI + AMOX for 5 days followed by PPI + CLAR + METR for 5 days; 2) Sequential 14 days: PPI + AMOX for 7 days followed by PPI + CLAR + METR for 7 days; or 3) Standard 14 days: PPI + AMOX + CLAR for 14 days. The PPI used in this clinical trial was lansoprazole.

Adverse effect profiles of the three regimens were similar. Eradication rates were statistically significantly higher using sequential regimens (10 days = 87%, 14 days = 91%) than in standard regimens (82%).

Reflecting an increased recognition of problematic CLAR resistance at the end of the initial comparison trial, treatment failures from each regimen were assigned to receive an additional 14-day sequential course of treatment in which levofloxacin was substituted for CLAR. Eradication rates from this "rescue" population (regardless of which initial regimen they had received) were 80%.

Based on this large dataset, the authors suggest that sequential treatment regimens should become first line. ■

Uric Acid: How Much of a Bad Guy?

Source: Rosendorff C, et al. *J Clin Hypertens* 2013;15:5-6.

Uric acid (URA) has become the object of intense scrutiny of late, with more than its share of accusations linking it to hypertension and heart disease. The relationship between URA and gout is incontrovertible, though not necessarily universal. That is, in persons who develop gout, risk of future attacks is definitely related to absolute URA plasma levels. However, among persons without gout, elevations of URA appear to be well tolerated without evident toxicity in most: In asymptomatic adults with URA levels > 9.0 mg/dL, only about 5% per year go on to manifest acute gout.

The association of URA with hypertension, myocardial infarction, and even congestive heart failure is acknowledged. Whether this relationship is *causal*, and if a causal relationship is determined, whether lowering of URA will be beneficial remains to be determined. Remember the enthusiasm attendant to the recognition that homocysteine was associated with cardiovascular disease, heightened by the assurance that lowering homocysteine was simple and safe (B vitamins and folate), soon thereafter torpedoed by the interventional trials that failed to show improved outcomes in subjects whose homocysteine levels were reduced?

Despite the growing enthusiasm for criminalizing URA, we still do not have a large randomized, controlled trial indicating that modulation of URA improves hard endpoints. Until then, since all medications that reduce URA have their own bundle of potential misadventure to consider, we should watch and wait. ■

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PHARMACOLOGY WATCH

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

Is This the End of the Road for Calcium Supplementation?

In this issue: Calcium supplementation in women; type 2 diabetes treatments and pancreatitis risk; treating chronic idiopathic urticaria; rivaroxaban and VTE; and FDA actions.

High calcium intakes in women

Another study suggests that calcium supplementation may lead to excess all-cause mortality and cardiovascular disease in otherwise healthy women. Researchers studied more than 61,000 Swedish women for 19 years. Diet and calcium intake, including calcium supplementation, were assessed with the primary outcome being death from all causes and cause-specific cardiovascular disease, ischemic heart disease, and stroke. Higher *dietary* intake of calcium (> 1400 mg/day) was associated with a higher death rate from all causes compared to intake between 600-1000 mg/day (hazard ratio [HR], 1.40; 95% confidence interval [CI], 1.17-1.67). Higher calcium intake was also linked to increased risk of cardiovascular disease (HR, 1.49; CI, 1.09-2.02) and ischemic heart disease (HR, 2.14; CI, 1.48-3.09). There was no higher risk of stroke. Intake of calcium in tablet form > 1400 mg/day was associated with 2.5 times greater risk of death from all causes (HR, 2.57; CI, 1.19-5.55). The authors conclude that higher intakes of calcium in women are associated with higher death rates from all causes as well as increased rates of cardiovascular disease but not stroke (*BMJ* published online Feb. 13, 2013. DOI: org/10.1136/bmj.f228). Previous studies have focused more on stroke risk associated with calcium showing mixed results. This well-done study, along with previously published data from the Women's Health Initiative, provides ample evidence to rethink calcium supplementation for the 60% of middle-aged and older American women who are regular users of calcium supplements. The U.S. Preventive Services Task Force came to the same conclusion (even before this study was published) with publication of updated guidelines in February stating that "current evidence is insufficient to assess the balance of the benefits and harms of combined vitamin D and calcium supplements for the primary prevention of fractures in postmenopausal women or men." They further state there is no evidence to support use of more than 1000 mg of calcium and 400 mcg of vitamin D per day and recommends against using doses lower than 1000 mg of calcium and 400 mcg of vitamin D. Their rationale is that supplementation does not reduce fracture risk but does increase the risk of renal stones in otherwise healthy women. This does not apply to women with osteoporosis or vitamin D deficiency (*Ann Intern Med*, published online Feb. 26, 2013). ■

Diabetes therapies and pancreatitis risk

Glucagonlike peptide 1 (GLP-1) mimetics (e.g., analogs of GLP-1 and dipeptidyl peptidase IV inhibitors) used for the treatment of type 2 diabetes might increase the risk of pancreatitis, according to a recent population-based, case-control study. Using a large population database of

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type 2 diabetics, 1269 cases of acute pancreatitis were identified and those patients were matched with 1269 controls with similar risk factors (age, sex, diabetes mellitus complications, etc). After adjusting for available confounders, current use of GLP-1 based therapies (exenatide [Byetta] and sitagliptin [Januvia]) more than doubled the risk for acute pancreatitis (adjusted odds ratio 2.24, 95% CI, 1.36-3.68). The authors state that "Our findings suggest a significantly increased risk of hospitalization for acute pancreatitis associated with the use of sitagliptin or exenatide among adult patients with type 2 diabetes mellitus" (*JAMA Intern Med* published online Feb. 25, 2013. DOI: 10.1001/jamainternmed.2013.2720). Both drugs already carry a boxed warning regarding pancreatitis. ■

Omalizumab for idiopathic urticaria

Chronic idiopathic urticaria is one of the most frustrating entities to treat as many patients do not respond to antihistamines, even in high doses. Now, a new study suggests that omalizumab (Xolair), an IgE monoclonal antibody used to treat asthma, may be effective in these patients. Patients with moderate-to-severe chronic idiopathic urticaria (n = 323) were randomized to SQ injections of omalizumab every 4 weeks for three total injections at doses of 75 mg, 150 mg, 300 mg, or placebo. The primary outcome was itch-severity score. The 75 mg dose was no better than placebo, but the two higher doses showed significant reductions in itching, with the 300 mg dose being the most effective. The higher dose was also associated with the highest risk of side effects, however, at about 6%. The authors conclude that omalizumab was effective in these patients who were previously symptomatic despite antihistamines. The study was sponsored by the drug manufacturers Genentech and Novartis Pharma (*N Engl J Med* published online Feb. 24, 2013. DOI: 10.1056/NEJMoa1215372). ■

Rivaroxaban for VTE prevention

Rivaroxaban, the oral Xa inhibitor, is as effective as enoxaparin in preventing venous thromboembolism (VTE) in patients with acute medical illnesses, but with a higher risk of bleeding, according to a new study. More than 8100 acutely ill hospitalized patients were randomized to 10 days of enoxaparin 40 mg SQ daily or 35 days of rivaroxaban 40 mg orally with matching placebos. The primary outcome of asymptomatic or symptomatic VTE occurred in 2.7% of patients in both groups by day 10. By day 35, the rates were 4.4% for rivaroxaban and 5.7% for enoxaparin ($P = 0.02$). However, the bleeding rate was more than double in the rivaroxaban group at day 10 (2.8% vs 1.2%, $P < 0.001$) and even higher at day 35 (4.1% vs 1.7%, $P < 0.001$). The authors conclude that rivaroxaban was noninferior to enoxaparin for standard duration thromboprophylaxis (10 days) and reduced the risk of VTE at 35 days with an increased risk of bleeding (*N Engl J Med* 2013;368:513-523). ■

FDA actions

A new selective estrogen receptor modulator (SERM) has been approved for the treatment of dyspareunia due to vulvar and vaginal atrophy in postmenopausal women. Ospemifene appears to benefit vaginal epithelium without significant effect on the endometrium. The drug's safety and efficacy was established in three clinical trials of nearly 1900 postmenopausal women with vulvar and vaginal atrophy who were randomly assigned to ospemifene or placebo. After 12 weeks, the first two trials showed statistically significant improvement in dyspareunia while the third trial supported the long-term safety of the drug. The drug is contraindicated in women with genital bleeding, estrogen-dependent cancer, or thromboembolic disease. The risk of stroke and VTE was higher than baseline but lower than the rates seen with estrogen replacement therapy. Ospemifene comes with a boxed warning regarding endometrial hyperplasia and abnormal vaginal bleeding. Common side effects include hot flashes, vaginal discharge, muscle spasms, and sweating. It will be marketed by Shionogi Inc. as Osphena.

The FDA has approved ado-trastuzumab emtansine for use as a single agent in patients with late-stage, HER2-positive breast cancer. The drug is approved for patients who have already been treated with trastuzumab and taxane separately or in combination. Approval was based on a study of nearly 1000 women with metastatic breast cancer in which progression-free survival was about 3 months longer with the drug compared to lapatinib plus capecitabine, and overall survival was about 6 months longer. Ado-trastuzumab emtansine is marketed by Genentech as Kadcyla. ■