AHC Media
A RELIAS LEARNING COMPANY

Hospital Medicine

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

Vol. 12, Issue 7, September 2017
AHCMedia.com

Cefazolin Leads to Better Outcomes for Methicillin-susceptible *Staphylococcus aureus* Bacteremia Than Nafcillin or Oxacillin

By Richard R. Watkins, MD, MS, FACP, FIDSA

Associate Professor of Internal Medicine, Northeast Ohio Medical University, Rootstown, OH; Division of Infectious Diseases, Cleveland Clinic Akron General, Akron, OH

Dr. Watkins reports that he has received research support from Allergan.

SYNOPSIS: A retrospective study that included patients from 119 Veterans Affairs hospitals found lower mortality and a similar recurrence rate for methicillin-susceptible *Staphylococcus aureus* bacteremia treated with cefazolin compared to nafcillin and oxacillin.

SOURCE: McDanel JS, Roghmann MC, Perencevich EN, et al. Comparative effectiveness of cefazolin versus nafcillin or oxacillin for treatment of methicillin-susceptible *Staphylococcus aureus* infections complicated by bacteremia: A nationwide cohort study. *Clin Infect Dis* 2017;65:100-106.

Beta-lactam antibiotics, most often nafcillin or cefazolin, are widely viewed as optimal therapy for methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia.[1] However, nafcillin is associated with more adverse events, including acute liver and kidney injury, rashes, cytopenias, and drug fever. Cefazolin often is used for MSSA infections in hemodialysis patients because of its convenient dosing regimen (i.e., at the end of dialysis). Therefore, McDanel et al compared outcomes for patients with MSSA bacteremia treated with nafcillin or oxacillin vs. cefazolin.

The study was a retrospective cohort that included medical and surgical patients admitted to one of 119 Veterans Affairs hospitals between 2003 and 2010 with at least one blood culture for MSSA and treated with cefazolin, nafcillin, or oxacillin. The primary outcome was all-cause mortality at 30 and 90 days. Recurrent MSSA infections were classified as MSSA-positive blood cultures between 45 and 365 days after the first positive blood culture. Definitive therapy was defined as starting a definitive antibiotic between days 4 and 14 after the first

Financial Disclosure: *Hospital Medicine Alert's Physician Editor, Kenneth P. Steinberg, MD, Peer Reviewer Rachael Safyan, MD, Editor Jill Drachenberg, Editor Dana Spector, and AHC Editorial Group Manager Terrey L. Hatcher report no relevant relationship related to the material presented in this issue.*

Hospital Medicine [ALERT]

Hospital Medicine Alert,
ISSN 1931-9037, is published monthly by
AHC Media, a Relias Learning company
111 Corning Road, Suite 250
Cary, North Carolina 27518.

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

POSTMASTER: Send address changes to
Hospital Medicine Alert,
AHC Media, LLC, a Relias Learning company
PO Box 74008694
Chicago, Il 60674-8694

SUBSCRIBER INFORMATION
(800) 688-2421
Customer.Service@AHCMedia.com
AHCMedia.com

Questions & Comments:
Please call Dana Spector
at (404) 262-5470 or email at
dspector@reliaslearning.com

Subscription Prices
United States:
Print: 1 year with free ***AMA PRA Category 1 Credits***™: $249
Add $19.99 for shipping & handling.
Online only: 1 year (Single user) with free ***AMA PRA Category 1 Credits***™: $199

MULTIPLE COPIES: Discounts are available for group subscriptions, multiple copies, site-licenses, or electronic distribution. For pricing information, please contact our Group Account Managers at
Email: Groups@AHCMedia.com
Phone: (866) 213-0844.
Back issues: $42
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION
Relias Learning is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Relias Learning designates this enduring material for a maximum of 2.25 ***AMA PRA Category 1 Credits***™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This CME activity is intended for hospitalists, intensivists, and acute care clinicians. It is in effect for 36 months from the date of the publication.

AHC Media
A RELIAS LEARNING COMPANY

positive blood culture was collected.

Of the 11,154 patients with MSSA bacteremia identified, 3,167 (28%) met inclusion criteria for the study. Of these, 1,163 received cefazolin (37%) and 2,004 (63%) received nafcillin or oxacillin. At 90 days, 25% of those who received nafcillin or oxacillin had died vs. 20% who received cefazolin (P = 0.001). In a multivariate analysis, patients treated with cefazolin had a 37% reduction in 30-day mortality risk vs. patients treated with nafcillin or oxacillin (hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.51-0.78). Furthermore, 90-day mortality risk was 23% lower in those who received cefazolin compared to nafcillin or oxacillin (HR, 0.77; 95% CI, 0.66-0.90). The odds for developing recurrent MSSA bacteremia did not differ significantly between the two groups. The risk estimates for dialysis patients were not significantly different with cefazolin vs. nafcillin or oxacillin with respect to 30-day mortality, 90-day mortality, or recurrence of MSSA bacteremia.

■ COMMENTARY

This is an important study because it addresses a very frequent conundrum in clinical practice: whether cefazolin is as good as nafcillin for MSSA bacteremia. Indeed, cefazolin has a number of advantages compared to nafcillin, including a more convenient dosing schedule (especially for dialysis patients), fewer side effects, and lower cost. McDanel et al have provided solid evidence from their large observational study that many patients with MSSA bacteremia treated with cefazolin have outcomes just as good as or better than patients who receive nafcillin or oxacillin. However, as supported by a well-written editorial,[2] enthusiasm for treating all cases of MSSA bacteremia with cefazolin must be tempered by a more nuanced approach. One important concern is the recognition that a sizable minority of MSSA strains produce an inoculum effect, which is an increase in minimum inhibitory concentrations (MICs) due to high inoculum of MSSA (e.g., an MIC with an inoculum of 5×10^5 CFU/mL of 0.5 µg/mL increases to 128 µg/mL with an inoculum of 5×10^7 CFU/mL). This may become more pronounced when there is inadequate source control, such as an undrained abscess, resulting in high-grade bacteremia. The antistaphylococcal penicillins (e.g., nafcillin and oxacillin) seem to be less inhibited by the inoculum effect compared to cefazolin, making the latter drug a less attractive choice in infections where there is limited source control and high MSSA burden.

Despite the fact that the study by McDanel et al is the largest to date comparing cefazolin to nafcillin and oxacillin for MSSA bacteremia, several limitations must be mentioned. First, the observational design may have been influenced by confounding variables. Second, of all the patients with MSSA bacteremia who were screened, only 28% were included in the study. Thus, it is unknown how the remaining 72% of cases would have affected the results. In many of these cases, either an alternative agent (e.g., vancomycin) was used, the patient died, or the patient was discharged before receiving therapy. Third, important data were not reported, including source control; length and dose of therapy; cause of death; other sites of infection besides endocarditis, osteomyelitis, and skin and soft tissue infections; and adverse events from cefazolin vs. nafcillin or oxacillin.

So, what is the take-home message? Cefazolin is a reasonable and appropriate choice for most cases of uncomplicated MSSA bacteremia. However, the antistaphylococcal penicillins still have an important role, such as when source control is inadequate, bacterial burden is high, or the patient is critically ill. Once these conditions are mitigated, the antistaphylococcal penicillin can be switched to cefazolin to complete the course of treatment. Ideally, the issue of cefazolin vs. nafcillin or oxacillin for MSSA bacteremia needs to be addressed by a randomized clinical trial. Until then, clinicians must manage MSSA bacteremia based on careful consideration of the available data. ■

REFERENCES

1. Schweizer ML, Furuno JP, Harris AD, et al. Comparative effectiveness of nafcillin or cefazolin versus vancomycin in methicillin-susceptible *Staphylococcus aureus* bacteremia. *BMC Infect Dis* 2011;11:279.
2. Karchmer AW. Definitive treatment for methicillin-sensitive *Staphylococcus aureus* bacteremia: Data versus a definitive answer? *Clin Infect Dis* 2017;65:107-109.

Early Diuretic Administration Associated With Improved Survival in Acute Heart Failure Patients

By Van Selby, MD

Assistant Professor of Medicine, University of California, San Francisco Cardiology Division, Advanced Heart Failure Section

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

SYNOPSIS: Among patients presenting to the ED with acute heart failure, those who received the first dose of intravenous furosemide within 60 minutes of arrival demonstrated lower in-hospital mortality compared to those receiving the first dose after 60 minutes.

SOURCE: Matsue Y, Damman K, Voors AA, et al. Time-to-furosemide treatment and mortality in patients hospitalized with acute heart failure. *J Am Coll Cardiol* 2017;69:3042-3051.

Acute heart failure (AHF) is a common reason for ED visits and hospitalizations. Clinical practice guidelines emphasize the importance of early diagnosis and treatment of patients presenting with AHF. However, no prospective study has demonstrated that prompt treatment is associated with improved patient outcomes.

To evaluate the relationship between time to treatment and outcome in AHF, the authors of the Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure (REALITY-AHF) trial enrolled patients presenting to one of 20 EDs in Japan for AHF who received IV furosemide within 24 hours of arrival. The primary metric of early care, the door-to-furosemide (D2F) time, was defined as the time from patient arrival to the ED to the first administration of IV furosemide. Patients who received the first dose of IV furosemide within 60 minutes were defined as the early treatment group, and those receiving the first dose after 60 minutes of arrival were defined as the non-early treatment group. The primary outcome was in-hospital mortality. The final cohort included 1,291 AHF patients. Median D2F was 90 minutes (interquartile range, 36-186 minutes), and 37.3% of patients met criteria for early treatment. Patients in the early treatment group were more congested, more likely to arrive by ambulance, and less likely to have a prior diagnosis of heart failure. Patients in the early treatment group had significantly lower in-hospital mortality compared to the non-early group (2.3% vs. 6.0%; $P = 0.00$). In multivariate analyses, early treatment was associated strongly with lower in-hospital mortality (odds ratio, 0.39; $P = 0.006$). Patients were stratified per baseline risk for adverse outcomes according to a risk prediction model. The association between D2F and mortality was observed regardless of the patient's baseline risk. The relationship between D2F and mortality was non-linear. Delaying D2F was associated with a steep increase in the risk of mortality over the first 100 minutes, but after that, the effect leveled off. The authors concluded that early treatment with IV loop diuretics is associated with lower in-hospital mortality among patients presenting to the ED with AHF.

■ COMMENTARY

Despite great efforts over the past decades, no novel treatment has been proved to meaningfully improve outcomes in patients with AHF. Therefore, providers must do the best they can using the available treatments, with IV loop diuretics as the primary therapy. Several retrospective studies have suggested a benefit associated with prompt initiation of treatment (vasodilators or diuretics), but none have prospectively studied the association between early administration of IV diuretics and outcomes.

Matsue et al demonstrated a clear association between early administration of IV furosemide and reduced in-hospital mortality in patients with AHF. This finding is not entirely surprising. Recent studies have shown that myocardial and end-organ damage begins early in AHF and progresses over time. Treating congestion earlier may minimize the damage, and recent studies have shown that AHF patients with decreased markers of congestion, myocardial injury, and end-organ damage demonstrate decreased mortality compared to those with ongoing evidence of organ dysfunction. Interestingly, the observed relationship between D2F and mortality was non-linear. Beyond 100 minutes, further increases in D2F did not increase mortality. If the benefits of early diuretic administration are primarily because of halting the process of ongoing myocardial and end-organ dysfunction, then it is difficult to explain why the benefits of early D2F end at 100 minutes. Alternatively, it is possible that patients who were treated quickly were those in whom the diagnosis was obvious at the time of ED arrival. This fits with the finding that

patients with early D2F were more likely to exhibit classic symptoms of congestion, including jugular venous distention and orthopnea. Diagnosing AHF in a patient presenting with dyspnea can be challenging when classic findings are absent. Multiple studies have shown that diagnostic delays are associated with longer time to medication administration, prolonged hospitalization, and even increased mortality.

Will D2F become a quality of care measure similar to the door-to-balloon time for ST-segment elevation myocardial infarction? Not based on the results of this study alone. The findings will need to be replicated in larger, more diverse cohorts, and the optimal D2F needs to be identified. It also will be important to further clarify whether it is in fact D2F, and not the delay in diagnosis, that leads to worse outcomes. For now, it seems reasonable for clinicians treating AHF patients to strive for both earlier diagnosis and initiation of IV diuretic therapy in patients presenting to the ED with possible AHF. This may include increased use of serum B-type natriuretic peptide measurement or other tests to promptly diagnose AHF and prompt initiation of IV diuretics once AHF is determined to be the most likely diagnosis. Until new therapies are identified to improve outcomes in AHF, we must use the tools we have as effectively as possible. ■

Requiem for Beta-blockers Post-Myocardial Infarction?

By Michael H. Crawford, MD, Editor

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

SYNOPSIS: A propensity score analysis of all hospital survivors of acute myocardial infarction in the United Kingdom from 2007-2013 showed that one-year survival in hospital patients without heart failure or left ventricular dysfunction treated with beta-blockers did not differ from survival in those patients not so treated.

SOURCES: Dondo TB, Hall M, West RM, et al. Beta-blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. *J Am Coll Cardiol* 2017;69:2710-2720.

Ibáñez B, Raposeiras-Roubin S, García-Ruiz JM. The swing of beta-blockers: Time for a system reboot. *J Am Coll Cardiol* 2017;69: 2721-2724.

Controversy exists regarding the benefits of routine beta-blockers post-myocardial infarction (MI) in patients without heart failure or reduced left ventricular ejection fraction (LVEF) in the modern reperfusion era. Thus, investigators used the United Kingdom national heart attack register to determine their effect on one-year mortality for survivors of acute MI who were hospitalized and did not have LV systolic dysfunction (LVEF < 30%) or heart failure. This analysis involved 531,282 patients admitted to one of 247 hospitals between 2007 and 2013. After excluding those > 100 years of age, hospital deaths, those with prior MI, percutaneous coronary intervention, or coronary artery bypass grafting, heart failure, and those on a beta-blocker or loop diuretics, 179,810 remained. A propensity score analysis using a 24-variable model was used to adjust for potential confounders. Of the 91,895 with an ST segment elevation myocardial infarction (STEMI) and 87,915 with a non-STEMI, 95% were treated with beta-blockers. Patients given beta-blockers tended to be younger men, and those not receiving them more often were diabetic, asthmatic, or had chronic renal and cerebrovascular disease. In the total population during a maximum one-year follow-up, the mortality rate was 5%. This unadjusted rate was lower in those who received beta-blockers compared to those that did not (5% vs. 11%; $P < 0.001$). After propensity weighting and adjustment, there was no mortality difference between those on beta-blockers and those not at one month, six months, and one year. Also, this result was the same for STEMI and non-STEMI patients. The authors concluded that among hospital survivors of acute MI without heart failure or LVEF < 30%, one-year mortality was not different for those on beta-blockers vs. those who were not.

■ COMMENTARY

When the Beta-Blocker Heart Attack Trial (BHAT) first was published in 1982, I remember noting that in the subgroup analyses, the mortality benefit was strongest in those with evident heart failure on admission or a large anterior MI. Of course, subgroup analyses are not always accurate, and beta-blockers post-MI, supported by other studies, went on to be universally recommended. This even became a Medicare quality measure, but it was retired a few years ago when data emerged noting that the universal use of beta-blockers post-MI increased the risk of cardiogenic shock. Thus, over the years, we have chipped away at the recommendation, holding beta-blockers if the patient was bradycardic, hypotensive, or in acute heart failure.

The problem with BHAT and other similar randomized, controlled trials conducted in the 1980s is that they were conducted before we had available reperfusion therapy, statins, angiotensin-altering drugs, or antithrombotics other than aspirin. New trials in the current therapeutic milieu have not been performed, but we know that today there is less heart failure, reduced ejection fraction, and ventricular arrhythmias post-MI compared to the 1980s. Recent smaller observational studies have failed to demonstrate a survival benefit of routine beta-blocker use post-MI. This has occasioned the European Society of Cardiology guidelines to reduce this recommendation to class IIa. The American guidelines still list it as a class I recommendation.

This study from the United Kingdom was very large, involved current therapy at high levels, and used an unbiased source (all MIs). It demonstrated in propensity-matched patients that there is no difference in survival at any time over one year post-hospital discharge in all post-MI patients without heart failure or LVEF < 30% who received beta-blockers vs. those who did not. Despite the strengths of this study, there are weaknesses beyond the issue of residual conforming in any observational study. Since only hospital survivors were studied, the study did not address the acute in-hospital use of beta-blockers. Because of the potential for inducing cardiogenic shock, the American guideline no longer recommends routine acute intravenous beta-blockers. Also, heart failure and LVEF only were determined in the hospital, and we don't know if beta-blockers were prescribed later. Additionally, we have no information on adherence to therapy or drug doses post-discharge. Another issue brought up by the editorialists from Spain is that the LVEF exclusion of < 30% is lower than the < 40% used in most other studies. It could be that patients with EFs between 30% and 40-45% could benefit from beta-blockers. Thus, they suggested that a randomized trial be conducted using an LVEF cutoff of 40%.

The authors emphasized that recommending pharmacologic therapy that is not beneficial risks adverse effects, increases costs, and reduces the likelihood that patients will be compliant with other, more effective medications. They suggested that the American guidelines should be rewritten. The editorialists, on the other hand, recommended "extreme caution" in enacting such a recommendation until a randomized trial is performed. Clearly, beta-blockers are indicated for selected patients in the hospital with acute MI, such as those with arrhythmias and hypertension, but should be given intravenously infrequently. At discharge, those with evidence of heart failure or a low EF will benefit from beta-blockers if there are no contraindications. The controversy surrounds those without heart failure, with preserved EF, normal blood pressure, and no arrhythmias. The European guidelines, supported by this paper, would say no. The U.S. guidelines would say yes. Since this is no longer a performance measure for Medicare, we are free to use our own judgment. ■

Maternal Mortality, Postpartum Hemorrhage, and Tranexamic Acid: The WOMAN Study

By John C. Hobbins, MD

Professor, Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Aurora

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

SYNOPSIS: A multicenter study involving patients in 193 countries has shown a decrease in maternal mortality in women with postpartum hemorrhage who were given tranexamic acid once the diagnosis was made.

SOURCE: WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with postpartum hemorrhage (WOMAN): An international, randomized, double-blind, placebo-controlled trial. *Lancet* 2017; Apr 26. doi: 10.1016/S0140-6736(17)30638-4.

Tranexamic acid has been used successfully to reduce blood loss after surgery and trauma by its ability to counter the conversion of plasminogen to plasmin, the active ingredient in the fibrinolysis that often accompanies excessive blood loss.[1] Postpartum hemorrhage is the leading cause of maternal death, especially in undeveloped countries. This has led a consortium of investigators to undertake a multicenter, randomized, clinical trial in 21 countries to assess the efficacy of using tranexamic acid to diminish maternal mortality and morbidity in patients with postpartum hemorrhage.

Over a six-year period (2010-2016), 20,060 women with postpartum hemorrhage (defined as blood loss of > 500 mL after vaginal delivery or > 1,000 mL following a cesarean delivery) were enrolled from 193 hospitals. One

group was randomized to receive a 1 g (10 mL) dose of tranexamic acid intravenously over a 10-minute therapeutic window. The control group received placebo in the same manner.

Initially, the primary outcomes were the need for hysterectomy up to 42 days after delivery and death from all causes. A total of 10,051 women received tranexamic acid vs. 10,009 who received placebo. There were 483 deaths in the study, 374 of which occurred within 24 hours of randomization and 43 within one hour of randomization. Most importantly, 346 (72%) were due to maternal hemorrhage.

The risk of death from bleeding was significantly less in the tranexamic group vs. placebo group (1.5% vs. 1.9%; relative risk [RR], 0.81; 95% confidence interval [CI], 0.65-1.00). After adjusting for baseline risk, the RR was 0.78 (95% CI, 0.62-0.98). Deaths from reasons other than hemorrhage were no different between groups.

The timing of when the drug was given appeared to be important. If administered within three hours, the RR of death was significantly reduced (1.2% vs. 1.7%; RR, 0.69; 95% CI, 0.52-0.91) compared with after three hours (2.6% vs. 2.5%). The need for hysterectomy to stem bleeding or to prevent death was no different between groups, but there was a significant reduction in the need for laparotomy to control bleeding (1.3% vs. 0.8%; RR, 0.64; 95% CI, 0.49-0.845).

■ COMMENTARY

This study, which was funded by the London School of Hygiene & Tropical Medicine and the Gates Foundation, represented a gargantuan undertaking. The hospitals involved were mostly in underdeveloped areas with limited resources. The authors originally powered their study on the hypothesis that the drug would decrease the need for hysterectomy, but since many of these operations occurred within one hour of randomization, the authors focused on death as a primary outcome measure and increased their enrollment from 15,000 to 20,000 patients.

The results suggested that giving tranexamic acid within three hours of the diagnosis of postpartum hemorrhage resulted in more than a 20% reduction in maternal death and a 40% decrease in the need for laparotomy. The logical conclusion of this tour de force investigation is that the relatively inexpensive drug can diminish maternal mortality in many areas of the world with limited resources. However, higher maternal mortality is not limited to underdeveloped areas. The U.S. maternal mortality rate is nothing to brag about, having risen from 7.2/100,000 in 1987 to 17.8/100,000 in 2011.[2] In fact, the national media has picked up on the fact that the maternal mortality rate in the United States is two times higher than Canada and six times higher than Sweden.[3] Also, it is very likely that we do far more laparotomies for postpartum hemorrhage than the countries involved in the above multicenter study. For these reasons, we should pay attention to the implicit message in the study: Tranexamic acid given within three hours of diagnosis of postpartum hemorrhage can save lives and decrease the need for laparotomies.

The WHO has recommended its use in postpartum hemorrhage if uterotonics fail or if there is evidence of trauma.[4] Given that the common increase in fibrinolytic activity noted postpartum occurs within one hour of delivery and based on the results of the multicenter study, the authors suggested that waiting too long for an oxytocic to work could limit its effectiveness significantly. Therefore, since the drug has not been associated with side effects, such as thromboembolic events,[5] and is relatively inexpensive (average $130 per 10 mL dose in the United States), one might consider giving this potentially life-saving drug to all patients once the objective diagnosis of postpartum hemorrhage is made.

Hopefully, the price of the drug will not follow the same historical course as the EpiPen. ■

REFERENCES

1. CRASH-2 Collaborators, Roberts I, Shakur H, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: An exploratory analysis of the CRASH-2 randomized controlled trial. *Lancet* 2011;377:1096-1101.
2. Osterman MJ, Kochanek KD, MacDorman MF, et al. Annual summary of vital statistics: 2012-2013. *Pediatrics* 2015;135:1115-1125.
3. Ingraham C. Our maternal mortality rate is a national embarrassment. The Washington Post. Available at: http://wapo.st/2rRp1mt. Accessed May 20, 2017.
4. WHO recommendations for prevention and treatment of postpartum haemorrhage. Geneva: World Health Organization; 2012. Available at: https://www.ncbi.nlm.nih.gov/books/NBK131942/. Accessed May 20, 2017.
5. Crash-2 Collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage (CRASH-2): A randomized placebo-controlled trial. *Lancet* 2010;376:23-32.

Safe Treatment Recommendations for Benzodiazepine Dependence

By Tim Drake, PharmD, MBA, BCPS, and Martin S. Lipsky, MD

Dr. Drake is Assistant Professor of Pharmacy, College of Pharmacy, Roseman University of Health Sciences.
Dr. Lipsky is Chancellor, South Jordan Campus, Roseman University of Health Sciences, South Jordan, UT.

Drs. Drake and Lipsky report no financial relationships relevant to this field of study.

SYNOPSIS: There are clear, evidence-based treatment withdrawal regimens for benzodiazepine-dependent patients.

SOURCE: Soyka M. Treatment of benzodiazepine dependence. *N Engl J Med* 2017;376:1147-1157.

Benzodiazepines bind to the gamma-aminobutyric acid type A receptor, increasing the receptor's affinity for gamma-aminobutyric acid, which causes an inhibitory effect in the central nervous system. They have been used since the 1960s for their anxiolytic, hypnotic, anticonvulsant, amnesic, and muscle-relaxant effects. Benzodiazepines by themselves are fairly safe, especially when used for less than two to four weeks. Dependence can develop in patients who use them for longer than one month. Common side effects include drowsiness, lethargy, fatigue, stupor, and disturbances in concentration and attention. Contraindications include myasthenia gravis, ataxia, sleep apnea, chronic respiratory insufficiency, and angle closure glaucoma. Because of the increase in falls, fractures, and cognitive decline, benzodiazepines should be avoided in the elderly. Physical and mental dependence can occur with benzodiazepine use, even if tolerance does not develop. Common signs of dependence include doctor or pharmacy shopping and/or early refills or overlapping prescriptions. Characteristics of long-term benzodiazepine use include: age > 65 years, prescribed by a psychiatrist, regular use, use of a high dose, and use of other psychotropic medications. Physical withdrawal symptoms include muscle tension, weakness, spasms, pain, flu-like symptoms, and a "pins and needles" sensation. Psychological withdrawal symptoms include anxiety or panic disorders, agitation, depression, mood swings, tremor, reduced concentration, and sleep disturbances. The most serious withdrawal complication is seizures, which can develop with abrupt withdrawal.[1]

To avoid withdrawal, benzodiazepines should be tapered over four to six weeks or more for higher doses (> 30 mg per day of diazepam). The taper rate should be based on the patient's ability to tolerate symptoms and can be done by decreasing the dose by 50% each week or by a 10-25% overall reduction every one to two weeks. A withdrawal schedule with precise dosing recommendations, along with medications to treat symptoms or coexisting conditions, can be helpful. For depression or chronic anxiety, a serotonin reuptake inhibitor is recommended. Trazodone or doxepin can be used to treat insomnia. Pregabalin, gabapentin, and beta-blockers can be tried as alternative anxiolytic agents, but caution is advised with pregabalin because of abuse potential. Switching from a short-acting benzodiazepine to a long-acting agent makes sense, but has not been proven useful clinically. Additionally, the use of the benzodiazepine antagonist flumazenil has not shown benefit and may induce seizures.[1]

Psychotherapy should be included in the plan to support the withdrawal process, to facilitate further abstinence, and to treat the underlying disorder. Cognitive behavioral therapy has the most evidence supporting its use and is the most widely used treatment for benzodiazepine withdrawal. Components of this therapy should include social competence training, relaxation techniques, training to overcome anxiety, and other behavioral therapy approaches. Other approaches include motivational interviewing, although the evidence is insufficient to support its use on an outpatient basis. Motivational techniques are more useful for inpatient treatment, whereas group or individual psychotherapeutic techniques are more useful on an outpatient basis.[1]

■ COMMENTARY

Benzodiazepine use has substantially increased in the past 10 years. Consequently, it is not surprising that deaths from overdose also increased from 0.58 in 1996 to 3.07 deaths per 100,000 adults in 2013.[2] Additionally, 46-71% of patients receiving opioid maintenance therapy use benzodiazepines,[3] which is concerning since the combination increases the risk of respiratory depression.

The FDA recently released a statement that the prescribing information for opioid analgesics and benzodiazepines will be changed to include the following statement: "Concomitant use of opioid pain or cough medicines and benzodiazepines, other central nervous system depressants, or alcohol may result in profound sedation, respiratory depression, coma, and/or death."[4] Also, the combination of opioids and benzodiazepines should be reserved for patients who have failed alternative treatments. This change will result in the need for many patients to either taper off their opioids or benzodiazepines. Tapering one agent, either the opioid or

Continued on back cover

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.

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log onto AHCMedia.com, then select "My Account" to take a post-test. First-time users must register on the site.
3. Pass the online test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After completing the test, a credit letter will be emailed to you instantly.
5. Twice yearly after the test, your browser will be directed to an activity evaluation form, which must be completed to receive your credit letter.

the benzodiazepine, should be accomplished before beginning to taper the other agent. Because of the possible dependence, benzodiazepines should be used with caution to treat the side effects of opioid withdrawal.

"There is a striking discrepancy between the high prevalence of benzodiazepine dependence and the very low treatment rates, especially in addiction service centers."[5] Although there have been many advertisements, health statements, and political statements about the opioid epidemic, there is little marketing on the use or abuse of benzodiazepines. Many opioid-related deaths involve the concomitant use of alcohol or benzodiazepines. Maybe a portion of the funds used to educate the public about the appropriate use of opioids also should be used to educate about the potential problems associated with the long-term use of benzodiazepines. ■

REFERENCES

1. Soyka M. Treatment of benzodiazepine dependence. *N Engl J Med* 2017;376:1147-1157.
2. Bachhuber MA, Hennessy S, Cunningham CO, Starrels JL. Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996-2013. *Am J Public Health* 2016;106:686-688.
3. Jones JD, Mogali S, Comer SD. Polydrug abuse: A review of opioid and benzodiazepine combination use. *Drug Alcohol Depend* 2012;125: 8-18.
4. FDA Drug Safety Communication. FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. Available at: http://bit.ly/2ruAV39. Accessed May 18, 2017.
5. Soyka M, Queri S, Küfner H, Rösner S. Where are the 1.9 million patients dependent on legal drugs hiding? [In German] *Nervenarzt* 2005;76:72-77.

CME QUESTIONS

1. In the retrospective cohort study by McDanel and colleagues looking at outcomes of patients with MSSA bacteremia, compared to nafcillin and oxacillin, cefazolin was associated with:

a. More acute kidney injury and skin rash.

b. Fewer side effects but higher mortality at both 30 and 90 days.

c. Lower mortality at both 30 and 90 days.

d. A higher rate of recurrent bacteremia.

2. According to the study conducted by Matsue, et al., giving furosemide to patients with acute heart failure within the first 60 minutes of arrival to the hospital led to which of the following outcomes:

a. Decreased in-hospital mortality

b. Decreased risk of being admitted to an ICU or CCU

c. Increased risk of acute kidney injury

d. Increased of developing cardiogenic shock.

3. In the registry study by Dondo and co-investigators, what was the effect of beta-blockers on post-MI patients who did not have clinical heart failure or an LV ejection fraction less than 30%?

a. Improved event-free survival

b. Increased risk of cardiogenic shock

c. Increased risk of significant arrhythmias

d. No difference in mortality at one year

[IN FUTURE ISSUES]

More original, peer-reviewed content by and for hospitalists