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

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ABSTRACT & COMMENTARY

Delaying Intubation in Severe Alcohol Withdrawal

By Samuel Nadler, MD, PhD

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

SYNOPSIS: Delaying intubation until aspiration or cardiopulmonary decompensation did not affect mortality but increased the incidence of pneumonia and length of stay.

SOURCE: Stewart R, Perez R, Musial B, et al. Outcomes of patients with alcohol withdrawal syndrome treated with high-dose sedatives and deferred intubation. *Annals Am Thorac Soc* 2016;13:248-252.

Alcohol withdrawal is a very common cause of hospital admission and complicates many otherwise routine hospitalizations. Catecholamine storm and agitation that requires sedative medication administration characterize this syndrome. However, both the underlying withdrawal and sedative treatments may precipitate aspiration and cardiopulmonary compromise, necessitating endotracheal intubation. The timing of this inherently risky procedure often is based on clinicians' experiences alone. Both premature and delayed intubation may have significant effects on patient outcomes.

This study examined whether delaying intubation led to worsening outcomes. This was a single center, observational, cohort study of 188 patients admitted between 2008 and 2012 with alcohol withdrawal. Per protocol, all patients received continuous infusions of lorazepam (up to 1.2 mg/hour) then titrated to a Clinical Institute Withdrawal Assessment score of 6 or less. Patients could be admitted to either the ICU or floor-level care. The decision to intubate was deferred until clinically apparent aspiration or cardiopulmonary decompensation occurred. Patients were overwhelmingly male (92.6%) with a median age of 50.8 ± 9 years. Most were admitted to the ward (76.1%) with a mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 6.2 ± 3.4. In this cohort, 12.8% experienced seizures, 16% were diagnosed with pneumonia, and the mean length of stay was 9.6 ± 11.7 days.

Several variables were statistically different in intubated vs. non-intubated patients. Intubated patients had higher admission APACHE II scores (7.4 vs. 5.9; *P* =

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[INSIDE]

Hospital Medicine [ALERT]

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0.01), a higher rate of cirrhosis (10.5% vs. 2.7%; $P = 0.05$), and congestive heart failure (13.2% vs. 1.3%; $P = 0.004$). Interestingly, there was not a statistically significant difference in the history of delirium tremens, ICU admission, or seizure disorder between the two groups. Although there was no difference in overall mortality in intubated vs. non-intubated patients (2.6% vs. 0%), the rate of pneumonia was significantly higher in intubated patients (55.3% vs. 6%; $P < 0.0001$) as was length of stay (14.7 vs. 6 days; $P < 0.0001$). As would be expected, intubated patients required much higher total doses of benzodiazepines (761 vs. 229 mg lorazepam equivalents; $P < 0.001$) and daily doses of benzodiazepines (64.9 vs. 41.7 mg lorazepam equivalents; $P = 0.01$).

■ COMMENTARY

The authors concluded that deferring endotracheal intubation was not associated with excess morbidity or mortality. However, the data reported here paint a more complicated picture. Clearly, if earlier intubation could have prevented aspiration and the development of pneumonia, there would have been a benefit. This study showed certain variables retrospectively were associated with intubation, but these may not prospectively help clinicians understand the optimal timing of intubation. In the study, intubation was associated with pneumonia (odds radio [OR] = 23.54; 95% confidence interval [CI], 7.97-69.46; $P < 0.001$) and APACHE II > 10 (OR = 5.26; 95% CI, 1.79-15.5; $P = 0.003$). Length of stay was significantly longer in intubated patients. Age > 60 years, average benzodiazepine dose > 50 mg, and seizures did not have statistically significant ORs. It is unclear if this is intrinsic to intubation or related to delayed intubation leading to a more complicated hospitalization.

Although no statistical difference occurred for mortality, this study was not powered to detect such a change. Other studies of alcohol withdrawal show similar or higher mortality rates.[1] This study adds to the knowledge base regarding alcohol withdrawal. It remains a prevalent cause of hospital admission and develops during many routine hospital admissions. Treatment of alcohol withdrawal via a protocol with infusions of benzodiazepines even up to 20 mg/hour without intubation until aspiration or cardiopulmonary compromise did not show excess mortality when compared with other studies. However, it is debatable whether there is not excess morbidity in waiting until aspiration occurs before intubation. A prospective, randomized trial of this protocol would better address this question. Furthermore, understanding prospectively the factors associated with intubation may enable higher vigilance in these patients and prompt earlier intubation that may reduce excess morbidity shown in this trial. ■

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ABSTRACT & COMMENTARY

Rivaroxaban in the Real World

By Michael Crawford, MD, Editor

SYNOPSIS: A large Phase IV registry study shows that rivaroxaban is associated with a very low incidence of major bleeding, death, or stroke. Also, adherence to therapy was much higher than observed in other studies with vitamin K antagonists.

SOURCE: Camm AJ, Amarenco P, Haas S, et al. XANTUS: A real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur Heart J* 2016;37:1145-1153.

Although approved for stroke prevention in non-valvular atrial fibrillation (NVAF), there has been controversy regarding the safety of rivaroxaban. Investigators in Europe conducted a prospective, observational outcome study of rivaroxaban use, which assessed its safety and efficacy in NVAF. The treating physician made decisions as to the dose of rivaroxaban. Follow-up was for one year or 30 days after the last dose of rivaroxaban if it ended earlier. The primary outcome was related to safety and included major bleeding and all-cause death. Secondary outcomes included thromboembolic (TE) events and non-major bleeding. Intracranial bleeding was included in TE and major bleeding events. A central committee adjudicated all endpoints. From 311

centers largely in Europe, Israel, and Canada, 6,784 patients were included, of whom 79% took rivaroxaban 20 mg/day, 21% 15mg/day, and 0.5% other doses. Mean patient age was 72 years, with 37% aged older than 75 years. Comorbidities were common, and 18% had new atrial fibrillation, 41% had paroxysmal atrial fibrillation, and 41% had persistent or permanent atrial fibrillation. Ninety-six percent of patients did not experience any major adverse events (death, stroke, bleeding). There were 2.1 major bleeding events per 100 patient-years; 1.9 died and 0.7 experienced a stroke. Adverse events were more common in patients with more comorbidities, especially reduced renal function despite rivaroxaban dose reduction. Major bleeding usually was treated conservatively, with few receiving non-specific reversal agents. At the end of the observation period, 20% had discontinued treatment mainly for apparent adverse events. The authors concluded that rate of stroke and major bleeding was low in a broad NVAF population treated with rivaroxaban.

■ COMMENTARY

Randomized, controlled trials (RCTs) are expensive, but necessary for new drug approval. They also are highly selective in patient enrollment to minimize the effects of other patient variables on the results. However, once a drug is approved, there is a need for real-world, less selective data to more clearly define the safety and efficacy of new drugs. Such studies are mandated by the European Medicines Agency and generally take two forms. Large administrative database studies often involve entire European countries. Denmark recently has conducted many such studies. They are very large and less expensive, but they are often retrospective and provide less detailed information. Registry studies provide more detailed information on smaller, more select populations. Also, registry studies require patient consent, so there are fewer cognitively impaired subjects as compared to administrative databases. This study of rivaroxaban is a registry study and is the first such study conducted on the new oral anticoagulants.

Patients in this registry study were lower risk than those in the Phase III ROCKET-AF trial that secured FDA approval for rivaroxaban; the mean $CHADS_2$ score for this study was 2 and was 3.5 for ROCKET-AF. This is not unusual for registry studies. RCTs want to include patients more likely to experience events so researchers can detect differences more readily. This registry study featured several strengths. First, it was prospective. Second, it used uniform definitions of events. Third, there was an independent event adjudication committee. However, since patients have to agree to participate, there may be residual confounding. Of interest, two-thirds of patients screened enrolled, suggesting this was a fairly representative sample.

In general, the results showed a low incidence of adverse events in patients treated with rivaroxaban. Compared to ROCKET-AF, there were fewer strokes (0.7 vs. 1.7 per 100 patient-years), major bleeds (2.1 vs. 3.6), and major gastrointestinal bleeds (0.9 vs. 2.0). Fatal bleeds (0.2 vs. 0.2) and intracranial hemorrhage were similar (0.4 vs. 0.5). Also, persistence of therapy was quite good (80% at one year compared to 62% in similar studies with vitamin K antagonists). It is important to use drugs that patients will actually take to prevent strokes.

One concerning finding was a systematic under-dosing in the study; 15% of patients were on a lower-than-recommended dose of rivaroxaban for no apparent reason. This is not unique to this study and has occurred in studies with dabigatran and apixaban. This doesn't surprise me as I have been tempted to use a lower dose in very old, frailer patients because I am afraid of bleeding but don't have the courage to withhold anticoagulants. Also, I have seen patients lower their dose after the first bruise on their arm appears. Many have been scared by the commercials on television, both from pharmaceutical companies and trial lawyers. Clinicians must use this encouraging data to counter these forces and make sure appropriate patients with NVAF take these drugs at appropriate doses. ■

ABSTRACT & COMMENTARY

Communication Facilitators Potentially Can Improve Care for the Sickest ICU Patients

By Elaine Chen, MD

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

SYNOPSIS: Highly trained communication facilitators who counseled families and met with physicians and nurses were shown to decrease symptoms of depression in family members at six months and decreased ICU length of stay without affecting mortality.

SOURCE: Curtis JR, Treece PD, Nielsen EL, et al. Randomized trial of communication facilitators to reduce family distress and intensity of end-of-life care. *Am J Respir Crit Care Med* 2016;193:154-162.

Studies have shown that interventions designed to improve clinician-family communication in the ICU can lead to better care. This study was a parallel-group, randomized trial of a "communication facilitator" intervention. Researchers trained a nurse and a social worker to act as communication facilitators to improve goals of care discussions in the ICU and improve communication between ICU team and families of critically ill patients.

The study included five ICUs in two hospitals, an academic level I trauma center, and a community-based hospital. Over five years, researchers screened 2,209 patients, of which 488 met eligibility criteria that included such parameters as mechanically ventilated and high Sequential Organ Failure Assessment scores. Additionally, 168 subjects underwent randomization to either intervention or control in a 1:1 ratio. The final analysis included 86 control patients with 137 family members (51%) and 82 intervention patients with 131 family members (49%).

Facilitators received extensive, evidence-based training in clinician-family communication in the ICU. Facilitators interviewed families and summarized concerns to physicians and nurses. Facilitators participated in family conferences and followed up with family after the patient was discharged to acute care.

Symptoms of depression were assessed using Patient Health Questionnaire-9 at baseline, three months, and six months. Symptoms of anxiety were assessed using the Generalized Anxiety Disorder-7 at baseline, three months, and six months. Symptoms of post-traumatic stress disorder (PTSD) were assessed using the PTSD Checklist Civilian Version (PCL) at three and six months.

There were no statistically significant differences in symptoms of anxiety or PTSD between controls or interventions, although at six months the PTSD difference was just short of statistical significance ($P = 0.056$) in favor of the intervention group demonstrating lower PCL scores. There was a statistically significant decrease in symptoms of depression at six months in the intervention group compared with the control group ($P = 0.017$), but not at three months.

There were no differences in ICU mortality (29% in control group vs. 26% in intervention group; $P = 0.615$) or withdrawal of life support among those who died (71.4% in control group vs. 80% in intervention group; $P = 0.737$). However, time to withdrawal of life support was significantly shorter in the intervention group (16.5 days in control group vs. 7.2 days in intervention group; $P = 0.001$). Among survivors, ICU and hospital length of stay (LOS) were similar. Among decedents, both ICU LOS (28.5 days in control group vs. 7.7 days in intervention group; $P = 0.001$) and hospital LOS (31.8 days in control group vs. 8 days in intervention group; $P = 0.001$) were shorter in the intervention group. Total ICU costs were significantly reduced in the intervention group, but only in decedents. However, average ICU costs per day also decreased in the intervention group among both survivors and decedents.

Reductions in ICU and hospital LOS among patients who died suggest that LOS reduction was due to an earlier decision to withdraw life-sustaining treatments. Mortality did not change; withdrawing life support earlier did not lead to increased mortality. In this study, reduced LOS in the intervention group was associated with reduced costs for patients who died, suggesting that reduced intensity of end-of-life care occurred with no worsening, but instead possibly a reduction in family distress.

This study showed that a communication facilitator trained to improve communication between the ICU team and family may be associated with reduced symptoms of depression for family members six months after a patient's ICU stay. There were no significant differences at three months or in symptoms of anxiety or PTSD. The authors concluded that differences in symptoms of depression only can be viewed as exploratory, and further study is warranted. Overall goals of future studies should be to identify the most beneficial and cost-effective interventions to support families of critically ill patients and reduce intensity of non-beneficial care at the end of life.

■ COMMENTARY

There is no doubt that improved communication with families of critically ill patients with a high risk of mortality is beneficial. But how exactly is it beneficial? And how is it best delivered? This study suggests that it improves family distress at six months, but only in depressive symptoms. An earlier study showed that improving communication decreased levels of depression, anxiety, and PTSD three months after a patient died in the ICU.[1]

This study was limited by a small sample size, difficulty recruiting patients, and loss of follow-up. The results in this study may not be generalizable, given that the intervention involved only two facilitators who were highly skilled and extensively trained and took place in two hospitals that have been the venue for multiple palliative care interventions by perhaps the most well-known U.S. research group on palliative care in the critical care setting. The likely pre-existing high level of communication skills in these ICUs may bias the outcome, decreasing the likelihood of a positive result. Variability in the model of intensive care delivery can also significantly affect communication. Factors such as location, referral base, availability of palliative care, resident or mid-level provider support, number of beds,

and whether the unit is open or closed may all contribute, and the level of significance is difficult to measure. Additionally, this study population was relatively racially homogeneous, with more than 80% of family members classified as Caucasian. Racial issues in trust and withdrawal of life support have been controversial, but data from a more heterogeneous population would be interesting and perhaps more generalizable.

Compassionate and thorough communication is an integral part of the practice of medicine, an art that drew many to medicine in the first place. Clinicians should strive to be excellent communicators with families of critically ill patients, knowing that words can make a difference. But if someone else (e.g., a facilitator) is a better communicator or has more time available to discuss complex issues, why not use one? Additionally, cost of care, LOS, and intensity of non-beneficial treatments at the end of life are issues hospital administrators and payors value highly. If interventions can simultaneously improve family outcomes as well as control costs, shouldn't clinicians pursue this solution aggressively? I look forward to future research in this direction. ■

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ABSTRACT & COMMENTARY

New Analysis of COGENT Data Supports Proton Pump Inhibitor Benefit with Low and High Aspirin Doses

By Jeffrey Zimmet, MD, PhD

Associate Professor of Medicine, University of California, San Francisco; Director, Cardiac Catheterization Laboratory, San Francisco VA Medical Center

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

SYNOPSIS: A dedicated analysis of the COGENT trial involving coronary artery disease patients on dual antiplatelet therapy shows comparable risks of gastrointestinal and cardiovascular events between low- and high-dose aspirin, and similar benefits of prophylactic proton pump inhibitor therapy.

SOURCE: Vaduganathan M, Bhatt DL, Cryer BL, et al. Proton-pump inhibitors reduce gastrointestinal events regardless of aspirin dose in patients requiring dual antiplatelet therapy. *J Am Coll Cardiol* 2016;67:1661-1671.

Much of cardiology therapeutics deal with balancing the benefits of antiplatelet and antithrombotic agents against the risks of bleeding. Dual antiplatelet therapy (DAPT) is the normal course of treatment for patients who present with acute coronary syndromes or post percutaneous coronary intervention (PCI), but it exposes patients to well-recognized risks of gastrointestinal (GI) bleeding. Although available data support a protective effect of proton pump inhibitors (PPIs) in this arena, these agents are generally underused, at least in part due to an underestimation of risk posed by low-dose aspirin.

The COGENT trial, originally published in 2010, randomized patients with an acute indication for DAPT to concurrent therapy with omeprazole or placebo. Although the study ended prematurely due to loss of funding, it showed that omeprazole reduced the risk of composite upper GI events (1.1% vs. 2.9%; $P < 0.001$) as well as symptoms of dyspepsia at 180 days, without increasing ischemic events. Researchers examined whether the protective effect of PPIs was consistent across different doses of aspirin, and to determine the cardiovascular safety and GI efficacy of PPI therapy in patients on low-dose vs. high-dose aspirin.

COGENT was a multinational trial that randomized 3,761 patients from 393 sites across 15 countries. Based on available aspirin dosing data from 99.8% of the intention-to-treat cohort, patients were divided into low-dose (< 100 mg, most commonly 81 mg; n = 2,480; 66.1%) and high-dose (> 100 mg, most commonly 325 mg; n = 1,272; 33.9%) aspirin groups. Low-dose aspirin users were more likely to be older and female, and to present with a history of hypertension, stroke, and established peripheral artery disease. Unsurprisingly, high-dose aspirin users were more likely, compared with the low-dose group, to have undergone recent PCI (91.3% vs. 61.6%) and to be enrolled from U.S. sites (80.4% vs. 39.8%).

At a mean follow-up of 110 days, PPI use reduced the incidence of the primary GI endpoint significantly in both the low-dose (1.2% vs. 3.1%; $P = 0.003$) and high-dose (0.9% vs. 2.6%; $P = 0.05$) aspirin groups. There was no apparent effect of aspirin dose on PPI efficacy in reducing the primary GI endpoint (P for interaction = 0.80). PPI use did not significantly increase

the incidence of major adverse cardiovascular events in low-dose (5.6% vs. 5.5%; $P = 0.95$) or high-dose (4.2% vs. 5.5%; $P = 0.92$; interaction $P = 0.91$) aspirin groups. After adjustment for baseline risk, high-dose aspirin did not influence the risk for adjudicated composite upper GI events, gastroesophageal reflux disease, or major adverse cardiac events compared with low-dose aspirin.

In this large randomized trial of PPI use in cardiac patients on DAPT, the authors concluded that low-dose aspirin was associated with similar risks of GI and cardiovascular events compared with high-dose aspirin, and that prophylactic PPI therapy consistently reduced the rates of GI events and GI symptoms out to 180 days.

■ COMMENTARY

PPI therapy has long demonstrated efficacy in reducing GI events and symptoms, so why is it so consistently underused in treatment of coronary artery disease (CAD) patients on DAPT? One answer is that clinicians underestimate the risk of bleeding when using low-dose aspirin. In the COGENT trial, approximately two-thirds of the 3,752 patients were treated with low-dose aspirin. The trial confirmed that patients on low-dose aspirin did not have an increased risk of cardiovascular events, but conversely demonstrated that adverse GI events were similar between low- and high-dose groups. Notably, this second point is in contrast to data from the HORIZONS AMI and CURRENT-OASIS 7 trials, which previously reported elevated GI event rates with high-dose aspirin. Moreover, in this trial the magnitude of the measured benefit of prophylactic PPI use was similar regardless of aspirin dose. In the low-dose aspirin group, PPI use was associated with a nearly 2% absolute risk reduction (number needed to treat = just over 50) in primary upper GI events at 180 days. The limited follow-up of the COGENT trial is clearly a weakness, and yet one might have predicted an even greater degree of benefit with more time.

The other issue is the persistent debate over potential adverse interactions between PPIs and clopidogrel. COGENT is by far the largest randomized, clinical trial of PPI therapy in patients with CAD on aspirin and clopidogrel, and very clearly demonstrated no adverse effect of omeprazole on cardiac endpoints. Here again, the limited term of follow-up is of some concern, and yet ischemic event rates are consistently highest in the early months post acute coronary syndrome and post PCI. A recent meta-analysis of 10 randomized trials similarly showed that PPIs decrease the risk of low-dose aspirin–associated upper GI bleeding in patients treated with DAPT without an increase in the risk of major cardiovascular events. Notably, the newer and more-potent P2Y12 agents were not used in COGENT and are lacking data on PPI efficacy.

The argument for PPI use in a majority of CAD patients on DAPT is strong, particularly insofar as these patients typically present with other risk factors for GI bleeding, which brings this recommendation in accordance with current guidelines. This study demonstrates that the shift toward low-dose aspirin in the DAPT equation should not provide a false sense of security, and that these patients benefit significantly from GI prophylaxis with PPIs. ■

ABSTRACT & COMMENTARY

Acetazolamide in Mechanically Ventilated Patients with COPD: Is There a Benefit?

By Kathryn Radigan, MD

Attending Physician, Division of Pulmonary and Critical Care, Stroger Hospital of Cook County, Chicago

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

SYNOPSIS: Compared to placebo, the use of acetazolamide in mechanically ventilated patients with COPD does not significantly reduce the duration of mechanical ventilation.

SOURCE: Faisy C, Meziani F, Planquette B, et al. Effect of acetazolamide vs placebo on duration of invasive mechanical ventilation among patients with chronic obstructive pulmonary disease: A randomized clinical trial. *JAMA* 2016;315:480-488.

Although there are no randomized, controlled trials to support its use, acetazolamide is used frequently as a respiratory stimulant in mechanically ventilated patients suffering from COPD and metabolic alkalosis. To determine whether acetazolamide shortens duration of mechanical ventilation in patients with COPD, Faisy et al conducted the DIABOLO study, a randomized, double-blind, multicenter trial from October 2011 to July 2014. Throughout 15 ICUs in France, 382 patients with COPD who were expected to be mechanically ventilated for > 24 hours were randomized to acetazolamide or placebo. Within 48 hours of ICU admission, patients with pure or mixed metabolic alkalosis received IV acetazolamide 500-1000 mg twice daily or placebo for the duration of their ICU stay. The primary outcome was duration of mechanical ventilation. Secondary outcomes were changes in arterial blood gas and respiratory parameters, weaning duration, adverse events, use of noninvasive ventilation after extubation, successful weaning, duration of ICU stay, and ICU mortality.

Of the 382 randomized patients, 380 completed the study. There were no significant differences between the acetazolamide group (n = 187) and the placebo group (n = 193) in median duration of mechanical ventilation (-16.0 hours; 95% confidence interval [CI], -36.5 to 4 hours; *P* = 0.17), duration of weaning off mechanical ventilation (-0.9 hours; 95% CI, -4.3 to 1.3 hours; *P* = 0.36), daily changes of minute ventilation (-0.0 L/min; 95% CI, -0.2 to 0.2 L/min; *P* = 0.72), or partial carbon dioxide pressure in arterial blood (-0.3 mmHg; 95% CI, -0.8 to 0.2 mmHg; *P* = 0.25). Compared to placebo, daily changes of serum bicarbonate (between-group difference, -0.8 mEq/L; 95% CI, -1.2 to -0.5 mEq/L; *P* < 0.001) and number of days with metabolic alkalosis (between-group difference, -1; 95% CI, -2 to -1 days; *P* < 0.001) were decreased significantly in the acetazolamide group. Although there is concern that the study may have been underpowered, the use of acetazolamide in mechanically ventilated COPD patients does not reduce the duration of mechanical ventilation.

■ COMMENTARY

The principal acid-base disturbances in mechanically ventilated COPD patients are often respiratory acidosis and metabolic alkalosis. Although the causes of metabolic alkalosis in these patients often are multifactorial, there is concern that alkalosis may depress cardiac output and/or respiratory drive, alter oxyhemoglobin dissociation, and favor the development of hypokalemia and hypophosphatemia. These factors may lead to prolonged weaning and duration of mechanical ventilation.[1,2]

Acetazolamide, a carbonic anhydrase inhibitor, frequently has been used as a respiratory stimulant in patients with COPD and metabolic alkalosis. The inhibition of renal carbonic anhydrase enzyme leads to decreased serum bicarbonate and arterial pH and increased minute ventilation as a result of stimulation of peripheral and central chemoreceptors.[3] As the drug is relatively safe, with rare occurrences of undesirable effects, it is used often as a respiratory stimulant in mechanically ventilated patients presenting with COPD and metabolic alkalosis but has not been well-studied. Faisy et al showed that despite achieving significant decreases in serum bicarbonate and fewer days of metabolic alkalosis in patients who were randomized to acetazolamide compared to placebo, there was no significant difference in duration of mechanical ventilation. Although there was no statistically significant decrease in length of mechanical ventilation in patients who received acetazolamide, the between-group difference in median duration of mechanical ventilation may be clinically relevant at 16 hours. Unfortunately, the study was powered to detect a 15% difference in invasive mechanical ventilation duration, and the observed median duration of mechanical ventilation was lower in both groups than anticipated for statistical power. If the study was designed to detect a 10% reduction in mechanical ventilation, it is plausible that the study would have reached statistical significance.

Although a difference in ventilator time may have been missed due to unfortunate statistics, it also must be noted that acetazolamide is a drug that features a complex mechanism of action and that its use is often even more complicated in the ICU setting. Although the acetazolamide dose was maximized at 500-1000 mg IV twice daily, it is possible that the dose remained inadequate. To appreciate a clinically relevant respiratory effect, a decrease in serum bicarbonate of at least 5 mEq/L is often necessary. Although serum bicarbonate decreased significantly, it did not affect respiratory parameters. It is unclear whether this decrease in bicarbonate was insufficient to affect respiratory parameters or whether the lack of response was due to tissue compartmentalization of carbonic anhydrase isozymes and low acetazolamide selectivity. Despite the obvious benefit higher doses may have on respiratory drive, it is also important to be wary of increased respiratory drive, especially in patients with COPD, as increased respiratory drive may also lead to increased work of breathing, respiratory muscle fatigue, decreased exhalation time, and possibly placing the patient at increased risk of auto-positive end-expiratory pressure. Furthermore, the authors noted that the PaO_2/FiO_2 ratio of the acetazolamide group was significantly higher than control. It is plausible that if there was a benefit, it may be due to its diuretic effect or the increased oxygen saturation of hemoglobin.

In review of this study, it remains unclear whether acetazolamide is of benefit in mechanically ventilated patients with COPD. Although there was no statistically significant decrease in duration of mechanical ventilation, there was no harm, and patients treated with acetazolamide were found to have increased daily PaO_2/FiO_2 ratio, with a trend toward shorter duration of mechanical ventilation. Therefore, it is the responsibility of clinicians to remain thoughtful regarding the use of acetazolamide in mechanically ventilated patients with COPD and consider its use on a case-by-case basis. ■

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CME QUESTIONS

1. The study by Stewart and colleagues demonstrated the following outcome(s) when intubation was delayed in severe alcohol withdrawal until clinical apparent aspiration or cardiopulmonary compromise:

a. No difference in mortality between intubated and non-intubated patients

b. No difference in pneumonia between intubated and non-intubated patients

c. No difference in length of stay between intubated and non-intubated patients

d. An increased risk of ventricular tachycardia in non-intubated patients

e. All of the above

2. When compared to the ROCKET-AF randomized clinical trial, the Camm, et al., registry study of real-world usage of rivaroxaban for non-valvular atrial fibrillation demonstrated:

a. Increased risk of intracranial bleeding

b. Increased risk of gastrointestinal bleeding

c. Decreased risk of stroke

d. Decreased risk of major adverse events

e. C and D

3. In the analysis of the COGENT trial of dual antiplatelet therapy after percutaneous coronary intervention, the use of a proton-pump inhibitor was associated with:

a. An increased risk of pneumonia

b. A decreased risk of gastrointestinal bleeding

c. An increased risk of subsequent coronary events

d. A decreased risk of gastrointestinal bleeding only for patients on low-dose aspirin

e. A decreased risk of mortality

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.

[IN FUTURE ISSUES]

More original, peer-reviewed content by and for hospitalists