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INSIDE

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Steroids to Prevent Extubation Failure?

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *This meta-analysis of studies examining the efficacy of systemic corticosteroids for preventing laryngeal edema following extubation concludes that this treatment is effective. This result differs from those of several previous meta-analyses, and raises practical issues such as whether extubation should be delayed for at least 12 hours after a patient passes a spontaneous breathing trial and qualifies for extubation so that a course of steroids can be given.*

Source: Fan T, et al. Prophylactic administration of parenteral steroids for preventing airway complications after extubation in adults: Meta-analysis of randomised placebo controlled trials. *BMJ* 2008;337:a1841; doi: 10.1136/bmj.a1841.

POST-EXTUBATION LARYNGEAL EDEMA, ALTHOUGH INFREQUENT, can necessitate reintubation and lead to other complications. The administration of a course of parenteral corticosteroids prior to extubation to reduce the likelihood of laryngeal edema has been advocated for many years, although the studies published to date have been small and several meta-analyses of their aggregate findings have failed to show this treatment to be effective. Fan and colleagues at Sichuan University in Chengdu, China, performed a new meta-analysis of those studies, including an additional recently published series and different selection criteria for the data to use in the meta-analysis, and concluded that steroid treatment is effective in preventing post-extubation laryngeal edema and the need for reintubation.

Using PubMed, the Cochrane Controlled Trials Register, and several other databases, the authors searched for randomized controlled trials comparing parenterally administered corticosteroids to placebo for the prevention of laryngeal edema following extubation. Their search produced 6 eligible trials, reporting a total of 1923 patients. They reasoned that, because laryngeal edema was the condition targeted by corticosteroid treatment and hence the outcome variable of interest, only those patients with this cause for respiratory distress

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and reintubation following extubation needed to be included in the meta-analysis. Using data selected in this manner where possible, and including 80 patients from a recently reported study from Taiwan that was not available for the previous meta-analyses, Fan and associates found the following results: Compared with placebo, steroids given in multiple doses over 12-24 hours prior to planned extubation decreased the odds ratio for laryngeal edema (0.38; 95% confidence interval [CI], 0.17-0.85) and subsequent reintubation (0.29; 95% CI, 0.15-0.58). A single dose of steroids immediately prior to extubation had no significant effect. The authors found no adverse effects of steroids as used in the studies examined.

■ COMMENTARY

By the tenets of evidence-based medicine, the only evidence more authoritative than the results of a randomized controlled trial is a meta-analysis of multiple such trials. Thus, the current study by Fan et al ought to be pretty much the last word on whether corticosteroids are beneficial for preventing post-extubation laryngeal edema and the need for reintubation. But what happens when more than one meta-analysis is available, based on pretty much the same evidence, and they come to different conclusions? Such is the case here. A Cochrane review, also published in 2008, concluded that corticosteroids had not been shown to be effective for preventing either laryngeal edema or reintubation.[1] As pointed out in the editorial accompanying the Fan meta-analysis, methodological differences likely explain the disparate results: "The difference in results comes from a combination of the new data, and a careful selection of the "most appropriate" data from the five other studies. Where possible, Fan and colleagues included only patients who needed reintubation for laryngeal edema and excluded those who were reintubated for other reasons, who would not respond to corticosteroids and who would dilute any effect. This selection allowed them to use a less conservative (fixed effects) model than that used in the previous review."[2]

Patients fail extubation for a number of reasons, including inability to protect the upper airway because of altered neurological status, the inadequate clearance of lower respiratory tract secretions, and insufficient recovery of ventilatory muscle and airway function after acute respiratory failure to sustain the required work of spontaneous breathing, in addition to laryngeal edema. Only the last of these would be expected to be prevented by a course of systemic corticosteroids. This fact partly justifies the Fan et al strategy of excluding other causes for reintubation in their meta-analysis. However, there are two problems. First, when patients do not do well after extubation and the managing clinician decides that reintubation is necessary, the specific reason is often unclear, and, while a few such patients have clear-cut laryngeal edema, most do not. This makes it unlikely that any post-hoc procedure for classifying reintubation into various causes would be completely accurate, and raises doubts about the appropriateness of selectively omitting some patients in the published studies from analysis. And, second, if laryngeal edema is the only one of several potential reasons for reintubation for which steroids can help, a large number of patients would have to receive the preventive therapy for those with laryngeal edema to benefit.

There is another important matter that influences my decision whether to give steroids to all my patients to prevent laryngeal edema: I am not used to deciding that a patient is ready to be extubated 12-24 hours in advance. We make rounds in the morning, assess the patient's status including the results of a spontaneous breathing trial, and decide on extubation right then based on that information. Waiting until that evening — or the next morning — to carry out the extubation so that several timed doses of steroids could be administered would prolong the period of intubation for a large number of patients who would not benefit from that

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Questions & Comments

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therapy. Given that a single bolus of steroids immediately prior to extubation does not seem to be effective, the regimen used in the studies included in the meta-analyses (which is either effective or ineffective, depending on which of the latter you prefer) seems ill-suited to current ICU practice.

The use of corticosteroids prior to a second extubation attempt in a patient who had stridor during an earlier failed extubation makes sense. So does their administration to patients who had difficult intubations, who have unusually large endotracheal tubes for their size (particularly women), who have sustained airway injuries or trauma to the head and neck, or who have no cuff leak on repeated measurements — although the required delay while several doses of steroids are administered needs to be factored into the clinical decision. However, I remain unconvinced that more liberal administration of steroids to intubated patients to diminish the likelihood of post-extubation stridor is currently justified by the available evidence. ■

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Should Patients at Increased Risk of Bleeding Receive Activated Protein C?

ABSTRACT & COMMENTARY

By Andrew M. Luks, MD

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Dr. Luks reports no financial relationship to this field of study.

Synopsis: *This retrospective medical record review demonstrated that patients with severe sepsis who received recombinant activated protein C in the face of bleeding precautions had higher rates of bleeding and death compared to those without bleeding precautions.*

Source: Gentry CA, et al. Adverse outcomes associated with the use of drotrecogin alfa (activated) in patients with severe sepsis and baseline bleeding precautions. *Crit Care Med* 2009;37:19-25.

DESPITE CONCERNS THAT RECOMBINANT HUMAN Activated Protein C (rhAPC) is associated with an increased risk of bleeding, the FDA failed to list several of the bleeding-related exclusion criteria used in the PROWESS trial as contraindications to use of this agent.[1] Instead, criteria such as presence of an intracranial aneurysm, use of aspirin within the preceding 7 days, or ischemic stroke within 3 months were labeled as "precautions" and use of the medication under such conditions is still permitted. Gentry and colleagues sought to determine whether the use of rhAPC in patients with such precautions was, in fact, associated with an increased risk of bleeding and other adverse events.

To investigate this issue, the authors conducted a retrospective review of all adult patients who received rhAPC at 2 tertiary medical centers over a 4-year period. For each identified patient, the authors reviewed whether the patients had baseline contraindications and precautions for use of the medication based on the official product labeling. Patients were labeled as having "baseline bleeding precautions" if they had either a contraindication or a precaution for use of rhAPC that would have excluded them from the PROWESS trial. The authors then compared outcomes between patients with and without baseline bleeding precautions with the primary outcomes being the incidence of serious bleeding events and mortality at 30-days post-discharge. Serious bleeding events were defined as an acute fall > 2 g/dL in hemoglobin concentration (except for intracranial bleeding), a need to transfuse > 4 units of packed red blood cells in 48 hours, objective evidence of bleeding that led to prolonged hospitalization or death, and a progress note documenting a diagnosis relevant to bleeding.

Complete data were available for a total of 73 patients who received rhAPC at the 2 institutions during the study period. Twenty (27%) of these patients had baseline bleeding precautions that would have excluded them from the PROWESS trial. Serious bleeding events occurred in 7 of the 20 patients with baseline bleeding precautions (35%) vs only 2 of the 53 patients who lacked such precautions (3.8%; $P < 0.0001$) The bleeding events included gastrointestinal bleeds (6), hemothorax (1), hemorrhagic stroke (1), and subarachnoid hemorrhage (1). An additional 5 gastrointestinal bleeds, 4 of which occurred in the group with baseline bleeding precautions, occurred but did not meet criteria for serious bleeding events, thereby bringing the total bleeding

rate to 55% in the group with baseline bleeding precautions and 5.6% in the group without such precautions.

Overall, 26 of the 73 patients (35.6%) died within 30 days of discharge with mortality being significantly higher (65% vs 24.5%; $P = 0.015$) in the group with baseline bleeding precautions. Among patients with APACHE II scores > 25, mortality was 73% in the group with baseline bleeding precautions vs 33% in the group without bleeding precautions. In multivariate analysis, the presence of a baseline bleeding precaution was the only variable associated with serious bleeding events but was one of several variables, along with APACHE II score and the presence of bloodstream infection, associated with an increased mortality risk.

■ COMMENTARY

Aside from its high cost, the primary concern regarding the use of rhAPC in patients with severe sepsis has been the increased risk of significant bleeding. Given this concern, one would expect that substantial effort would be made to avoid the use of this agent in patients thought to be at increased risk for bleeding complications. Although the original PROWESS investigators employed strict criteria limiting use of rhAPC in these situations, the FDA failed to list many of these criteria as explicit contraindications. Instead, they labeled many study exclusion criteria as warnings, thereby permitting physicians to use the medication in these situations if the benefits were thought to outweigh the risks. The data from Gentry and colleagues clearly show an increased risk of bleeding events and mortality in patients with such baseline bleeding precautions and, as a result, suggest we may be doing our patients harm by using the more liberal FDA criteria.

The data in this study must be viewed with some degree of caution, as the number of patients in each group was very small. Data were also collected in a retrospective manner and, as a result, the two groups are likely not as well matched as if the data had been collected prospectively. If Gentry and colleagues' results differed widely from those of other studies, these issues would severely limit the applicability of the study's findings. However, multiple other studies using the package labeling as entry and exclusion criteria have also shown an increased risk of bleeding compared to trials that used the more strict PROWESS criteria.[2,3] This growing body of data suggests that it may be time to review our hospital protocols for the use of this medication. In addition to limiting its use to those patients at high risk of death (APACHE II > 25), we should be adhering to the bleeding-related exclusion criteria in the original trials and not to the more liberal FDA specifications. ■

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Volume of Clinical Information Generated in the ICU

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *This 6-year study of the volume of clinical information documented in the medical record during the care of patients in the pediatric ICU of a university-affiliated hospital found that a median of 1348 separate items were generated each day, and that the amount increased by 26% from 2000 to 2005.*

Source: Manor-Shulman O, et al. Quantifying the volume of documented clinical information in critical illness. *J Crit Care* 2008;23:245-250.

THIS STUDY FROM THE UNIVERSITY OF TORONTO sought to quantify the number of individual pieces of clinical information entered into the medical record on each patient in the ICU each day. The authors performed a 6-year retrospective cohort study in the pediatric ICU of a university-affiliated hospital, and included data from every patient who was admitted to the ICU for at least 24 hours between January 2000 and December 2005. The same computerized health record system was used throughout the study period. Additional information in handwritten notes by physicians, nurses, and pharmacists, verbally communicated information, and records of medication orders and administration were not included.

During the 6-year study period, 10,533 patients were admitted to the ICU for a total of 61,450 patient-days. A total of 5623 admissions with at least one complete 24-hour patient-day was analyzed. The median number of documented clinical data for each complete 24-hour

ICU day was 1348 (interquartile range, 1018-1664; mean, 1341), which represented an average of 56 items per patient-hour. This information was composed of items from fluid balance (34%), respiratory and ventilation (21%), vital signs (17%), nursing care (15%), laboratory results (6%), neurologic assessment (4%), and dialysis or ECMO (0.7%). Significantly more information was documented on patients who received conventional mechanical ventilation, high-frequency oscillatory ventilation, inotropes or vasoactive medications, hemodialysis, or ECMO, as compared to patients who did not receive these interventions.

There was a 26% increase in the number of items documented per day during the 6-year observation period, from 1165 in 2000 to 1471 in 2005 ($P < 0.0001$). A median of 24 patients were discussed on clinical rounds each day, and a median of 27,559 items were documented in the medical record each day. A 20-minute handover between nurses on 1:1 assignments would have included discussion summarizing an average of 674 items documented during the previous 12-hour shift.

■ COMMENTARY

It will come as no surprise to anyone who works in today's ICU environment that the quantity of clinical information generated and documented for each patient over the course of a day is enormous — although the sheer numbers revealed by this study are staggering, they do not include data from continuous oximetry, electrocardiography, vascular pressure tracings, and numerous other forms of information that clinicians use. Of note, substantially more information was documented for patients receiving pressors, ventilatory support, and other high-tech interventions. This study's findings support the general impression that the overall workload for clinicians in the ICU is high and increasing, and the implications of the avalanche of data it documents with respect to hand-offs and the potential for clinical error should be obvious. ■

Special Feature

Severe Pulmonary Hypertension in the ICU

By Richard J. Wall, MD, MPH

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Dr. Wall reports no financial relationship to this field of study.

PULMONARY HYPERTENSION (PH) IS COMMON AMONG patients in the intensive care unit (ICU). In fact, many ICU clinicians simply view PH the same way they view leukocytosis — as an expected finding caused by the "bigger problems" of sepsis, respiratory failure, congestive heart failure, volume overload, and myocardial infarction. In severe cases of PH, however, the hemodynamic consequences of the PH itself can be devastating: hypotension, low cardiac output, hypoxemia, cor pulmonale, liver congestion, renal failure, and death.

In the current review, the general approach to managing ICU patients with severe life-threatening PH will be addressed. By definition, this refers to critically ill patients with (or at risk of) hemodynamic instability. After briefly discussing the physiology and diagnosis of PH, this article will review current treatments.

Definition of PH

PH is defined as right ventricular (RV) systolic pressure > 40 mm Hg, or mean resting pulmonary arterial (PA) pressure > 25 mm Hg (> 30 mm Hg with exercise).[1] Additional criteria include pulmonary vascular resistance (PVR) > 3 Wood Units and pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg. In ICU patients, the diagnosis is commonly suspected based upon typical signs and symptoms or made with echocardiography. With the growing availability of bedside echocardiography, ICU clinicians are increasingly diagnosing this entity. In many cases, the diagnosis is already established prior to ICU admission.

In healthy individuals, PA pressure is ~20% of the systemic arterial system. In fact, the pulmonary vascular system has an incredible ability to handle changes in flow and pressure through its vasodilator reserve. When these compensatory mechanisms are overwhelmed, however, the pulmonary vasculature's response can result in a cascade of events that leads to irreversible cardiogenic shock and multi-organ failure.

PA systolic pressure is determined by RV stroke volume and the compliance of the main PA and its branches. PA diastolic pressure is determined by the tone of the pulmonary arterioles, the size of the pulmonary vascular bed, and PCWP. The latter is determined by the pulmonary venous pressure, left atrial pressure, mitral valve integrity, and left ventricular diastolic pressure.

In 2003, an international symposium outlined a 5-category classification system for PH *(see Table, page 94)*.[2] In this system, patients are grouped based on the underlying pathophysiology of their condition. Although one should ideally determine the classification of every patient with PH, this is often impossible when a patient with severe PH is intubated and on vasopressors with

multi-organ failure. Those interested in learning more about the pathogenesis of PH are referred to Gaine's excellent review.[3]

Diagnosis

When PH is diagnosed, it is essential that the PH is adequately characterized through the measurement of mixed venous oxygen saturations, cardiac output, and assessment of RV function. The latter is especially important because the ultimate determinant of hemodynamic stability is RV function. In ICU patients, the etiology of PH is often multifactorial. Common contributors include pulmonary emboli, hypoxemia, anemia, acidosis, sepsis, and left-sided heart failure. Many ICU patients have mild-to-moderate underlying PH prior to the acute event that lands them in the ICU.

An ICU patient with acute, severe PH may be mistakenly thought to have "septic shock" because such patients have similar findings of hypotension, lactic acidosis, and renal failure. Furthermore, infections can precipitate an abrupt deterioration of underlying chronic PH. Other common causes for rapid deterioration of underlying PH include pulmonary embolism, pneumothorax, RV infarction, gastrointestinal bleeding, pancreatitis, anemia, thyroid disease, atrial arrhythmias, ischemic bowel, hyponatremia, hypokalemia, subdural hematoma, and acute renal failure.[4] Thus, clinicians must maintain an index of suspicion for PH even when an alternative diagnosis seems plausible.

Initial workup should include physical examination, chest radiograph, and an electrocardiogram (ECG). The ECG should be examined for RV or left ventricular (LV) hypertrophy, atrial arrhythmias, and ischemia. This may provide important clues to the etiology. Keep in mind that automated computerized interpretations on ECG machines often erroneously label RV hypertrophy/strain as "anterior ischemia" or "inferior MI."[5]

If there are no signs of left-sided failure in a patient with elevated jugular venous pressure, hypoxemia, and clear lungs, then pulmonary embolism (PE) must be excluded. The differential diagnosis for such a patient also includes cardiac tamponade, RV infarction, pericardial constriction, and acute worsening of chronic PH. Because hypoxemia is common in PH regardless of the etiology, it is not useful in the diagnosis of PE.

Although multiple strategies exist for excluding PE,[6] many of these traditional approaches are impractical in ICU patients. For example, D-dimer has very limited utility in the ICU due to the high prevalence of comorbidities that cause false-positives. In the hemodynamically unstable patient, bedside echo-doppler is a useful first test. In more stable patients, computer tomographic angiography (CTA), ventilation-perfusion scanning, or conventional angiography are reasonable options. Although multidetector CTA has become the most popular first-line test, there are surprisingly few prospective data on its predictive value. In fact, a study of ICU patients found that 25% of CTA examinations were non-diagnostic, usually due to poor contrast bolus or artifact from motion and hardware.[7] Intensivists should also remember that critically ill patients were excluded from the recent PIOPED II study.

Table

Classification of pulmonary hypertension

Category 1: Pulmonary arterial hypertension
- Idiopathic/familial
- Related to another identifiable process: Collagen vascular disease (especially scleroderma and lupus)
- Portal hypertension
- HIV infection
- Congenital heart disease with left-to-right shunting
- Drugs, toxins, anorexigens, cocaine
- Other, including hemoglobinopathies, hereditary hemorrhagic telangiectasia, myeloproliferative disorders, splenectomy, hemolytic anemia, Gaucher disease
- Persistent PH of the newborn

Category 2: Pulmonary venous hypertension
- Left-sided heart disease
- Veno-occlusive diseases

Category 3: Disorders of the respiratory system
- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic high altitude exposure
- Neonatal lung disease, alveolar capillary dysplasia

Category 4: Chronic thrombotic/embolic disease
- Thromboembolic obstruction of pulmonary arteries
- Nonthrombotic pulmonary emboli (e.g., parasites, schistosomiasis, tumor)
- In situ thrombotic diseases, sickle cell disease

Category 5: Miscellaneous
- Sarcoidosis, histiocytosis X, lymphangioleiomyomatosis

Source: Simonneau G, et al. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2004;43(12 Suppl S):5S-12S.

Treatment of PH

In patients with suspected PE, heparin therapy should be started promptly. Recent meta-analyses suggest low-molecular-weight heparin (LMWH) is preferable to unfractionated heparin because it has lesser risk of

recurrence or bleeding, but these studies did not include patients with hemodynamically unstable PE.[8,9] Oral anticoagulation with warfarin should be continued for at least 6 months after the event, and longer if there is a non-reversible risk factor.

In hemodynamically unstable ICU patients with RV failure and no underlying cardiopulmonary disease, empiric thrombolytic therapy may be given without confirming the diagnosis of PE.[4] Surgical embolectomy and catheter-based interventions are other options, but such modalities have not been rigorously studied in large randomized trials. Further, no trials have compared thrombolytics against surgical or catheter-based approaches. In general, surgical and catheter-based interventions should only be performed in experienced centers because the reported favorable outcomes likely have as much to do with treatment protocols at these sites as with the procedures themselves.[10]

Hypotension in severe PH should be managed aggressively, promptly, and intelligently. In general, hypotension is rarely due to intravascular volume depletion. Rather, hypotension is usually due to deteriorating RV failure. Determining volume status in such patients is notoriously difficult. Although intravascular volume can be low in PH patients with edema and ascites, administering fluids to patient with RV pressure overload will further dilate and compromise RV function, thereby decreasing LV stroke volume and causing downstream systemic hypotension. The imprudent administration of fluids can potentially result in a fatal cardiovascular spiral. When volume status is not clear, carefully administer a small volume challenge (250 mL saline over 10 minutes), and assess the effect on systemic pressure.

Hypotension must be reversed quickly or the "PH spiral" will overwhelm your efforts. If too much time elapses, chances are slim that you will reverse the vicious sequence of events: Systemic hypotension causes low oxygen delivery, hypoxemia and decreased blood pressure compromise coronary blood flow, ventricular ischemia causes worsening pump failure, hypoxemia and acidosis exacerbate pulmonary vasoconstriction, worsening RV function leads to decreased LV filling, and so on. Eventually, the patient will deteriorate into electromechanical dissociation or ventricular fibrillation.

In patients unable to maintain a mean systemic arterial pressure of at least 60 mm Hg, α-1 adrenergic agents (e.g., phenylephrine, norepinephrine, high-dose dopamine) should be used. The α-1 receptor increases systemic pressure, coronary perfusion, systemic resistance, and LV afterload. At the same time, it reduces RV compression of the LV outflow tract, thereby improving LV stroke volume. In patients with a decent systemic arterial pressure, inotropes such as dobutamine and milrinone can improve cardiac output. Once systemic pressure is reasonable, IV epoprostenol can be used to further increase cardiac output and reduce pulmonary pressures.

Some have successfully used inhaled nitric oxide (iNO) as a selective pulmonary vasodilator to reduce pulmonary artery pressure, improve cardiac output, and reverse hypotension.[4] It should be noted, however, that this indication has not been approved by the FDA. Others have used inhaled epoprostenol in a similar manner. For the hemodynamically unstable patient in the ICU, iNO has the advantage of increasing pulmonary perfusion only in ventilated areas. As a result, iNO improves gas exchange and decreases PVR without increasing intrapulmonary shunting, as might occur when IV epoprostenol vasodilates unventilated lung segments. Another advantage is that inhaled NO is rapidly inactivated in the alveolar capillaries, thereby minimizing systemic hypotensive effects. Patients stabilized with iNO can be later converted to IV epoprostenol for long-term use.

A prompt infectious workup with cultures and broad-spectrum antibiotics should be performed. Oxygen should be titrated to keep saturations above 92%. Mechanical ventilation (either non-invasive or via intubation) may be necessary to maintain adequate oxygenation, especially if the patient has pneumonia. As mentioned previously, hypoxemia causes pulmonary vasoconstriction and worsens ventricular function, which is the last thing you want. Blood transfusions can be used to improve oxygen delivery: [(Hgb × 1.34 × SaO_2%) × cardiac output]. However, the potential risks of immune suppression and volume overload must be carefully considered.

Atrial fibrillation and atrial flutter are common tachyarrhythmias that lead to rapid clinical deterioration. Treatment should follow typical ACLS algorithms, with DC cardioversion of unstable patients. Avoid IV diltiazem or adenosine in hemodynamically unstable patients. Short-acting beta blockers, IV digoxin, and amiodarone are useful agents. The latter is especially useful for maintaining sinus rhythm. Ventricular arrhythmias are usually an ominous sign that things have gone too far. Cardiopulmonary resuscitation is almost never successful in PH patients with severe right heart failure.[11]

Other adjunctive vasodilator agents are available, but their use in the ICU is largely anecdotal. Sildenafil, a potent phosphodiesterase-5 inhibitor, has been shown to augment and prolong the hemodynamic effects of iNO. Although maximal effects are not seen for 3-6 months,

some effects are noted within hours. In addition, sildenafil prolongs the effect of NO by preventing breakdown of its second messenger (cGMP), and thus may lessen the rebound seen after discontinuation of iNO. Endothelin antagonists (e.g., bosentan, sitaxsentan) do not exhibit any effects for at least 2 weeks and have no role in acute ICU management of PH. If a patient is already on an endothelin antagonist, it is reasonable to continue it. However, one must remain aware of the risk of liver toxicity and various drug interactions with this class.

Summary

When a critically ill patient experiences acute and hemodynamically unstable PH, there is a limited amount of time to intervene. Otherwise, the patient will irreversibly spiral into biventricular failure, followed by systemic shock and death. Even among patients with chronic PH, acute PE must be excluded as the precipitant for deterioration. Prompt empiric treatment with heparin or thrombolytics should be considered in such cases, even if the diagnostic workup is still underway. Fluids should be cautiously administered, and an adequate assessment of RV function is essential at the onset. Several different medications are now available to the ICU clinician for managing this serious condition. ■

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CME / CNE Questions

45. Which of the following regimens has been used in the studies supporting the administration of corticosteroids prior to extubation to prevent laryngeal edema?

a. Multiple doses administered systemically over a 12- to 24-hour period
b. Multiple doses administered by aerosol down the tube over 12 to 24 hours
c. A single dose administered systemically immediately prior to extubation
d. A single dose administered by aerosol down the tube immediately prior to extubation

46. Which of the following outcomes is associated with the use of rhAPC in patients with baseline bleeding precautions as defined by product labeling?

a. Decreased risk of gastrointestinal bleeding
b. Decreased 30-day mortality
c. Increased risk of severe bleeding events
d. Increased risk of acute lung injury

47. Pulmonary hypertension is defined by which of the following?

a. Right ventricular systolic pressure > 40 mm Hg
b. Pulmonary arterial mean pressure > 25 mm Hg at rest
c. Pulmonary arterial mean pressure > 30 mm Hg with exercise
d. All of the above

Answers: 45. a, 46. c, 47. d.

CME / CNE Objectives

After reading each issue of *Critical Care Alert*, readers will be able to do the following:

- Identify the particular clinical, legal, or scientific issues related to critical care.
- Describe how those issues affect nurses, health care workers, hospitals, or the health care industry in general.
- Cite solutions to the problems associated with those issues.

PHARMACOLOGY WATCH

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

Warning Regarding Topical Anesthetics

In this issue: FDA warning on topical anesthetics; antipsychotics increase sudden cardiac death; the step up vs step down debate; treating pain, fatigue, mood, and sleep in fibromyalgia; FDA Actions.

Something for your pain?

The FDA has issued a warning regarding topical anesthetics and the risk of life-threatening side effects. This is the second warning in 2 years regarding this issue, the first coming in February 2007 following the deaths of two women who used extensive topical anesthetics in preparation for cosmetic procedures. The latest warning was prompted by a study published in *Radiology*, which compared oral acetaminophen or ibuprofen vs lidocaine gel applied to the skin of the breasts to reduce discomfort during mammography. In the study, 4% lidocaine gel was applied by a nurse from the clavicles to the inferior costal margins and laterally to the mid axillary lines and then covered with plastic wrap to ensure consistency of application. Discomfort from mammograms was significantly lower in the lidocaine gel group and the authors postulate that decreased discomfort may improve the likelihood of future mammographic screening (Lambertz CK, et al. *Radiology* 2008;248:765-772). The FDA's previous warning in 2007 followed on the heels of two reports of young women undergoing laser hair removal who applied either lidocaine or tetracaine topical preparations to the lower extremities and then covered the application with plastic wrap. Both women developed seizures, fell into a coma, and eventually died due to excessive blood levels of the topical anesthetic. Many of these topical products are available over the counter. The FDA strongly advises consumers not to: make heavy application of topical anesthetics over large areas of skin, use concentrated formulas, apply to broken or irritated skin, wrap the treated skin with plastic wrap or other dressings, or apply heat to skin treated with these products.

Increase in sudden cardiac death

Antipsychotics, both typical and atypical, are associated with a dose-related increase in sudden cardiac death according to a new study. Typical antipsychotics such as thioridazine (Mellaril®) and haloperidol (Haldol®) block repolarizing potassium currents and prolong QT intervals. Multiple studies have shown a dose-related increased risk of sudden cardiac death associated with these drugs. Less is known about the atypical antipsychotic drugs although many have similar cardiovascular effects. Researchers from Nashville reviewed the records of Medicaid enrollees in Tennessee including the records of 44,218 and 46,089 baseline users of a single typical and atypical antipsychotic, respectively. These were matched with 186,600 nonusers of antipsychotic drugs. Thioridazine and haloperidol were

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the most frequently prescribed typical agents, while clozapine (Clozaril®), quetiapine (Seroquel®), olanzapine (Zyprexa®), and risperidone (Risperdal®) were the most commonly used atypical agents. Both users of typical and atypical antipsychotic drugs had higher rates of sudden cardiac death than nonusers with adjusted incident rate ratios of 1.99 (95% CI, 1.68-2.34) and 2.26 (95% CI, 1.8-2.72), respectively. There was a higher rate for users of atypical antipsychotic drugs vs typical antipsychotics with an incident rate of 1.14 for the comparison (95% CI, 0.93-1.39). For both classes of drugs, the risk for current users increased significantly with increasing dose. The authors conclude that current users of typical and of atypical antipsychotic drugs had similar, dose-related increased risk of sudden cardiac death and that atypical antipsychotic drugs are no safer than the older drugs (Ray WA, et al. *N Engl J Med* 2009;360:225-235). An accompanying editorial suggests that children and the elderly are particularly vulnerable to these drugs and their use in these populations should be "sharply reduced" (Schneeweiss S, Avorn J. *N Engl J Med* 2009;360:294-296).

Step up vs step down

Which is more effective for treating dyspepsia: Starting with aggressive therapy and tapering down, or starting with antacids and progressing to more aggressive therapy depending on symptoms? The so called step-up vs step-down debate has raged for years, particularly in managed-care settings. In a new study from the Netherlands, patients with dyspepsia were randomized to treatment with an antacid, H2-receptor antagonist, and proton pump inhibitor (step up) vs the same drugs in reverse order (step down), with each step lasting 4 weeks. Primary outcome was symptom relief and cost-effectiveness of initial management at 6 months. Treatment success after 6 months was achieved in 72% of patients in the step-up group and 70% of patients with step-down group. The average medical costs were lower for patients in the step-up group (€228 vs €245; P = 0.0008) mainly because of the cost of medication. The rate of adverse effects was the same in both groups and were generally mild. The authors suggest that treatment success is similar in both groups but the step-up strategy was more cost-effective for patients with new onset dyspeptic symptoms (van Marrewijk CJ, et al. *Lancet* 2009;373:215-225). An accompanying editorial suggests that the degree of cost difference between the two groups was overestimated because costs were based on brand name drugs and generics are now available. It furthers suggested that the study may not change practice in primary care as the author recommends a 4-8 week course of a proton pump inhibitor for patients with symptoms of the upper gastrointestinal tract with discontinuation of treatment if patients remain asymptomatic (van Zanten SV. *Lancet* 2009;373:187-189).

Pain, fatigue, mood, sleep and fibromyalgia

Tricyclics work better than other antidepressants for the treatment of fibromyalgia according to new study from Germany. In a meta-analysis of 18 randomized controlled trials of antidepressants for the treatment of fibromyalgia, researchers reviewed studies utilizing tricyclic and tetracyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAO). All antidepressants were associated with a reduction in pain, fatigue, depressed mood, and sleep disturbances. Pain reduction was particularly good for tricyclic antidepressants, while MAO inhibitors showed modest effect and SSRIs and SNRIs showed a small effect. TCAs were effective in low doses of 12.5-50 mg, far below the doses commonly employed to treat depression, and were very effective for reducing pain, fatigue, and sleep disturbance (*JAMA* 2009;301:198-209). Currently duloxetine (Cymbalta®), pregablin (Lyrica®), and milnacipran (Savella™) are the only FDA-approved drugs for the treatment of fibromyalgia.

FDA Actions

The FDA is launching a program to improve the safety of imported drugs to the United States. The pilot program would allow manufacturers of drugs outside United States to apply for 1 of 100 certifications, which would require that companies have a secure supply chain for their product. Criteria would include holding an FDA-approved drug application, guaranteeing that active pharmaceutical ingredients would be imported only to make FDA-approved drugs, complying with Good Manufacturing Practices, and guaranteeing that their drug products use a secure supply chain. This program is in response to concerns about manufacturing processes outside the United States and the embargoing of several foreign manufactured drugs in the last year. ■

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