CRITICAL CARE ALERT®

A monthly update of developments in critical care and intensive care medicine

Thomson American Health Consultants Home Page— www.ahcpub.com

CME for Physicians— www.cmeweb.com; CE for Nurses— www.ceweb.com

THOMSON AMERICAN HEALTH CONSULTANTS

INSIDE

Financial Disclosure: *Critical Care Alert*'s Editor, David J. Pierson, MD, nurse planner Leslie A. Hoffman, PhD, RN, and peer reviewer William Thompson report no financial relationships related to this field of study.

Forgotten Hazards of Sedatives

ABSTRACT & COMMENTARY

By Saadia R. Akhtar, MD, **MSc**

Idaho Pulmonary Associates, Boise

Dr. Akhtar reports no financial relationship to this field of study,

Synopsis: *This case series and prospective observational study describe propylene glycol toxicity in patients receiving IV benzodiazepines. The authors estimate the incidence of this important but unrecognized complication to be 19%.*

Source: Wilson KC, et al. *Chest*. 2005;128:1674-1681.

PROPYLENE GLYCOL IS USED AS THE CARRIER VEHICLE FOR A number of drugs including lorazepam and diazepam. It may cause metabolic abnormalities such as anion gap metabolic (usually lactic) acidosis and hyperosmolality. Case reports also describe it causing sepsis-like symptoms, cardiac arrhythmias, and neurological changes (agitation, seizures or coma).[1] Toxicity may be more common in patients with renal dysfunction.

A prospective, observational study was performed to determine incidence of propylene glycol toxicity in a single medical ICU. All admissions over a 3-month period were screened. Two groups of patients were enrolled: those receiving benzodiazepines with propylene glycol vehicle (lorazepam and diazepam, 21 patients) and those receiving an alternative benzodiazepine (midazolam, 23 patients). Usual clinical data were collected by medical record review. Propylene glycol toxicity was defined as hyperosmolality or anion gap metabolic acidosis not explained by another cause and reversed by cessation of the benzodiazepine. Standard statistical methods were used to compare the 2 groups.

Patients receiving benzodiazepines with propylene glycol vehicle were more likely to have a history of heavy alcohol intake. Otherwise there were no significant differences in age, gender, comorbid conditions, admitting diagnoses or clinical data between the 2 groups. Four (19%) of the 21 patients receiving the benzodiazepines with propylene glycol vehicle had evidence of propylene glycol toxicity. All did well after cessation of the infusions and were discharged from the ICU to the floor in stable condition.

Propylene glycol levels between 58 and 127 mg/L were measured in patients with only metabolic abnormalities. Based on their prior case reports, the authors note that levels ranging from 104 to 144 mg/dL were seen in patients with clinical deterioration felt to be secondary to propylene glycol toxicity. Toxicity almost always occurred in patients receiving greater than the usual recommended daily doses of lorazepam (0.01-0.1 mg/kg/hr) and diazepam (5-10 mg IV every 3-4 hours). However, there was at least 1 person with toxicity after as little as 68 mg of IV lorazepam by continuous infusion.

COMMENTARY

Wilson et al's report—the largest study of this topic in the published English literature—serves as an important reminder of a serious potential adverse effect of lorazepam or diazepam use in the ICU. It also suggests that at least metabolic evidence of propylene glycol toxicity may be much more common than previously realized.

The study clearly has numerous limitations. It is a small, single-center, unblinded observational study. Thus, considerable bias (in patient selection and management and data collection and interpretation) may exist, and certainly the incidence results may not be generalizable. It is unclear exactly what criteria were used to determine whether there was an alternate explanation for acidosis or hyperosmolality in patients classified as having propylene glycol toxicity. It is difficult from these data to define specific threshold levels of benzodiazepines that may lead to toxicity or to determine a threshold level of propylene glycol beyond which toxicity occurs. Further investigation is indicated to address these issues. More information is also needed to understand when and why propylene glycol toxicity may result in clinical deterioration. Long-term outcomes of toxicity (if any) ought to be investigated. Finally, the mechanism(s) of toxicity must be more clearly elucidated.

Despite its limitations, this remains an important report. Until the specifics of propylene glycol toxicity are better defined, at least awareness of and vigilance for this condition are warranted. Potential propylene glycol toxicity is yet another reason to consider limiting sedative use in the ICU. ■

References

1. Arroliga AC, et al. *Crit Care Med*. 2004;32:1709-1714.

Critical Care Alert, ISSN 1067-9502, is published monthly by Thomson American Health Consultants, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.

EDITORIAL GROUP HEAD: Lee Landenberger.

MANAGING EDITOR: Robert Kimball.

ASSOCIATE MANAGING EDITOR: Leslie Hamlin.

MARKETING PRODUCT MANAGER: Gerard Gernazian.

GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Critical Care Alert,*** P.O. Box 740059, Atlanta, GA 30374.

Back issues: $40.

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

Subscriber Information

Customer Service: 1-800-688-2421

Customer Service E-Mail Address: customerservice@ahcpub.com

Editorial E-Mail Address: robert.kimball@thomson.com

World Wide Web: http://www.ahcpub.com

Subscription Prices

United States

1 year *with* free AMA Category 1 credits: $289

(Student/Resident rate: $120)

Multiple Copies

Documents are available for multiple subscriptions. For pricing information, please call Steve Vance at (404) 262-5511.

Canada

Add GST and $30 shipping.

Elsewhere

Add $30 shipping.

Accreditation

Thomson American Health Consultants (AHC) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

AHC designates this educational activity for a maximum of 25 category 1 credits toward the AMA Physician's Recognition Award.

Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

AHC is accredited as a provider of continuing education by the American Nurses Credentialing Center's Nursing Commission on Accreditation. Provider approved by the California Board of Registered Nursing, Provider Number CEP 10864. This activity is approved for 16 nursing contact hours.

This educational activity is intended for critical care physicians and nurses. It is in effect for 36 months from the date of publication.

THOMSON AMERICAN HEALTH CONSULTANTS™

Questions & Comments

Please call **Robert Kimball,** Managing Editor, at (404) 262-5413 or e-mail at robert.kimball@thomson.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Aminophylline in COPD Exacerbations: Just Say No

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Professor, Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington, Seattle

Synopsis: *In a well-designed double-blind placebo-controlled clinical trial in COPD patients admitted with an exacerbation, aminophylline produced no clinically relevant benefit but increased the incidence of nausea.*

Source: Duffy N, et al. *Thorax*. 2005;60:713-717.

In this study from the University of Liverpool, Duffy and associates sought to determine whether the addition of intravenous aminophylline produced clinically important improvements in the rates of symptomatic recovery or increases in pulmonary function, and whether it shortened hospital stay, in comparison with standard therapy without aminophylline, among patients with COPD who were admitted with an exacerbation. The latter was strictly defined according to

accepted criteria, and patients with asthma, pneumonia, pneumothorax, malignancy, or serious cardiac disease were excluded. Because the use of noninvasive ventilation has become standard therapy for such patients if they are acidemic, and could have confounded the results, only patients with arterial pH > 7.32 were included.

All patients received nebulized albuterol and ipratropium every 6 hours, 30 mg of oral prednisolone every day, controlled oxygen therapy, and antibiotics as selected by their primary physicians. They were also randomized to receive either aminophylline (5 mg/kg loading dose followed by 0.5 mg/kg/hr maintenance infusion) or saline, intravenously, according to a carefully designed double-blind, double-dummy design involving adjustment and monitoring directed by individuals not involved in the patients' care. The patients and their primary physicians, who made all management and disposition decisions, did not know whether aminophylline or saline placebo was being given. In addition to arterial blood gases and spirometry, patients were assessed by 2 different standardized daily symptom scores and followed prospectively for nausea and other possible side effects of aminophylline.

During the study period, 320 patients were screened, of whom 132 were deemed eligible, and 80 agreed to be randomized into the study. The 39 aminophylline patients and 41 placebo patients were well-matched by all criteria. Eleven patients died and 10 refused eventual follow-up, with equivalent distribution in treatment and control groups, leaving 29 aminophylline and 30 placebo patients for complete evaluation at 6 weeks following hospital discharge.

Arterial blood gases measured after 2 hours of treatment showed a small but statistically significant fall in PCO_2 (mean difference of 1.25 mm Hg) and increase in pH (mean difference, 0.01 units) with aminophylline as compared to placebo. However, 46% of the aminophylline-treated patients complained of nausea, compared to 22% of the placebo-treated patients ($P < 0.05$). There were no statistically significant differences in the rates of change in dyspnea, post-bronchodilator spirometry, or length of hospital stay in the 2 groups. The authors conclude that, despite small but statistically significant alterations in acid-base balance, aminophylline produced no improvement in symptoms or clinical course and caused more nausea than placebo.

COMMENTARY

Aminophylline is included among the second-line therapies recommended by current clinical practice guidelines for COPD management.[1-3] However, this agent is a weak bronchodilator and its ratio of therapeutic-to-toxic effects is the worst of all currently available agents. Theophylline preparations are more likely to cause distressing symptoms and potentially life-threatening cardiovascular effects than any of the other current main-line therapies for asthma and COPD. Yet the use of aminophylline and its relatives remains widespread in the care of many patients, both for long-term maintenance and during exacerbations. This study is the largest, most rigorous examination of the effects of aminophylline on the course of exacerbations of COPD yet undertaken. Although aminophylline's initial effects on PCO_2 and pH were statistically significant, they were certainly not of a magnitude that could be important to either clinicians or patients. This statement is borne out by the lack of any demonstrable effect on symptoms of outcomes.

Ian Town, in an editorial accompanying the Duffy study,[4] concluded the following: ". . . in considering the generalisability of the study, aminophylline might still be considered in the management of life threatening episodes of COPD by an experienced doctor in selected cases, together with other measures such as non-invasive ventilation. In such circumstances the benefits of respiratory stimulation and any effect on respiratory muscles may be more important than bronchodilation per se. However, for most clinical situations involving mild-to-moderate COPD exacerbations, we now have a clear answer to the question whether aminophylline should be used—and it is 'no.'"

Professor Town is more diplomatic than I can be on this issue. Aminophylline is a poor bronchodilator with potentially life-threatening side effects that require expensive and inconvenient monitoring. This study is the most carefully done to date, and, like the best-designed clinical studies preceding it and at least one meta-analysis, demonstrates no clinical benefit. Duffy et al excluded patients with initial arterial pH < 7.32, but there is no reason to believe that the therapeutic effect of aminophylline would be greater in more acidemic patients, and the likelihood of serious arrhythmias in such patients would be expected to be greater. We now have available much more effective, far safer bronchodilators. As far as I am concerned, the books should be closed on this antiquated and hazardous agent, at least in the acute setting. Just say no to aminophylline in exacerbations of COPD!

References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). www.goldcopd.com.
2. American Thoracic Society/European Respiratory Society Task Force.

Standards for the Diagnosis and Management of Patients with COPD [Internet]. Version 1.2. New York: American Thoracic Society; 2004 [updated 2005 September 8]. www.thoracic.org/copd

3. National Collaborating Centre for Chronic Conditions. Chronic obstructive pulmonary disease. *Thorax*. 2004;59(Suppl 1):1-232. www.thorax.bmjjournals.com/content/vol59/suppl_1

4. Town GI. *Thorax*. 2005;60:709.

Special Feature

Trouble-Shooting the Ventilated Patient

By David J. Pierson, MD, Editor

LATE IN THE EVENING YOU RECEIVE A PAGE ABOUT A patient who is "fighting the ventilator." You are cross-covering and do not know the patient. Your sign-out sheet says only that she is 68 years old, has severe COPD complicated by pneumonia, and has been in the ICU for the last 3 days. No specific problems are mentioned. The nurse tells you on the telephone that the patient was "fine" until about an hour ago, but has since become increasingly agitated. The ventilator's high-pressure alarm has been sounding frequently, and now the pulse oximeter's saturation readings have fallen from the mid-90s to the high-80s. What should you do?

This hypothetical scenario is familiar to everyone who cares for mechanically ventilated patients in the ICU. However, how to manage it most effectively, efficiently, and safely is not something that can be guided by high-level evidence from randomized clinical trials.[1-3] Nonetheless, a logical approach, an appreciation of the physiology involved, and an understanding of some of the basics of ventilatory support can help to demystify what can be not only an anxiety-provoking situation for the clinician but also a serious threat to the patient. This article discusses some of the potential causes for acute respiratory distress that develops in a patient who was previously tolerating mechanical ventilation. Based on these causes, it then presents a straightforward, step-by-step approach for approaching the problem and its correction.

Possible Causes: A Change in the Ventilator or Other Apparatus

Table 1 lists some of the more common processes that can cause a previously stable patient to start fighting the ventilator. The first thing that the clinician at the bedside should consider is some malfunction in the ventilator or circuit. Such malfunctions may either prevent the intended tidal volume from reaching the patient or cause distress by increasing the patient's work of breathing.[4-6] Although it is uncommon, ventilators do occasionally fail. Sometimes the ventilator circuit becomes disconnected from the endotracheal or tracheostomy tube, and falls on the bedding in such as way that the low-pressure alarm is not triggered. The circuit can also be interrupted where it connects to a filter, nebulizer, temperature probe, or humidifier, or at the connections to the ventilator itself.

Apparatus includes the artificial airway, and this may also be the source of patient distress. Malposition or kinking of the tube can increase inspiratory resistance, decreasing the delivered tidal volume, or cause an inspiratory leak such that the delivered volume does not

Table 1

Potential Causes for "Fighting the Ventilator"

A problem in the ventilator system
Ventilator failure (mechanical failure; FIO2)
Interruption in ventilator circuit (tubing, nebulizer, filters, etc)
Exhalation valve obstruction
A problem with the artificial airway
Obstruction (mucus, kinking)
Malposition
Cuff leak
Worsening of the primary process
COPD/asthma
Pneumonia
Congestive heart failure/pulmonary edema
Acute lung injury/ARDS
A new pulmonary complication
Pneumothorax
Dynamic hyperinflation and auto-PEEP
Bronchospasm
Pulmonary thromboembolism
Ventilator-associated pneumonia
Acute lung injury/ARDS
A non-pulmonary problem
Hypovolemia
Fluid overload
Cardiac ischemia; acute myocardial infarction
Primary central nervous system process
Sepsis
Drug-related problem (adverse effect; withdrawal)
Inappropriate ventilator settings
Tidal volume
Set rate
Positive end-expiratory pressure
Inspired oxygen fraction
Excessive triggering effort
Insufficient inspiratory flow
Inadequate sedation
Uncomfortable ventilator settings
ICU delirium

Key: ARDS—acute respiratory distress syndrome; COPD—chronic obstructive pulmonary disease; FIO_2—inspired oxygen fraction; PEEP—positive end-expiratory pressure

reach the patient's lungs. Development of a leak in the cuff, or in the pilot balloon or its connecting tube, is another common cause of a sudden decrease in delivered tidal volume.

While these equipment-related problems tend to be easy to identify, picking up the fact that something in the circuit has increased the patient's work of breathing can be more difficult. The increase in breathing effort can originate in either the inspiratory or the expiratory limb of the circuit. Simple observation of the patient's breathing pattern can help here, although this is not always the case. If the agitation and distress began when the ventilator or circuit was changed, inappropriate assembly or malfunction of a component is suggested. However, these problems can develop more slowly, and valves may suddenly become dysfunctional during use.

Possible Causes: A Change in the Patient

Worsening of the Primary Process

A common cause for increasing intolerance of ventilatory support is worsening of the primary process that caused the patient to require intubation and mechanical ventilation. Table 1 lists what I consider to be the most common primary causes of acute respiratory failure that tend to do this. Exacerbations of COPD or asthma may worsen after admission, particularly if treatment with inhaled bronchodilators and systemic corticosteroids has been delayed or is suboptimally aggressive. Hypoxemic respiratory failure caused by community-acquired pneumonia can worsen in the initial 24 hours, particularly if the number of lobes involved turns out to be more than initially appreciated or if the patient was dehydrated on admission. Acute lung injury and the acute respiratory distress syndrome (ARDS) frequently worsen during the first 2 or 3 days after criteria for these diagnoses are first met.

There is also a difference between *sudden development* and *sudden discovery*. Sometimes a patient is perceived to have developed acute distress when in fact the worsening has been progressive but this has not been fully appreciated. Whatever acute illness caused the patient to require ventilatory support in the first place may have been more severe than initially appreciated, or it may have progressed unnoticed since admission. This is more likely to be the cause for fighting the ventilator that is noted within the first day or two after intubation. In this instance the problem may simply be that the initial ventilator settings are no longer adequate in the face of increased demands for oxygenation, ventilation, or mechanical support.

A New Pulmonary Process

Barotrauma is always a possibility during invasive mechanical ventilation, and it may not become clinically evident for many hours after intubation. Pneumothorax, the most potentially lethal of the forms of extra-alveolar air encountered during ventilatory support, can quickly become physiologically important, so having this complication first on the list of possibilities is appropriate. Another, more subtle complication of positive-pressure ventilation is dynamic hyperinflation and auto-PEEP.[7,8] Auto-PEEP is especially common in patients with obstructive lung disease, but it may occur in others as well and should always be thought of when patients appear to be struggling to breathe. Circumstances in which dynamic hyperinflation and auto-PEEP are especially likely are listed in Table 2.[9] The use of ventilator graphics monitoring can be helpful in identifying the presence of auto-PEEP, particularly when the patient is triggering the ventilator, preventing assessment by end-expiratory airway occlusion.[10,11]

The appearance or worsening of wheezing should prompt consideration of bronchospasm as a potential cause for fighting the ventilator. However, wheezing is a sign of airway obstruction, not necessarily of bronchospasm. It can be produced by secretions or other causes of airway obstruction, and is likely to worsen whenever there is increased expiratory effort. Pulmonary thromboembolism should always be on the list of possible causes for new hypoxemia or other deterioration in a ventilated patient. However, other causes are much more common, and a computed tomographic angiogram should seldom be the first procedure undertaken in evaluating the problem. Thromboembolism is more likely if the patient has obvious predisposing conditions such as a history of thrombosis, vascular injury, or malignancy, or if deep-venous thrombosis prophylaxis has not been given, and also if a search for other likely explanations for the respiratory distress is negative.

After the first 2 or 3 days, the likelihood of developing ventilator-associated pneumonia increases the longer a patient has been intubated. This serious com-

Table 2

When to Suspect Dynamic Hyperinflation and Auto-PEEP in the Ventilated Patient

- Unexplained tachycardia, hypotension, or pulseless electrical activity develop, especially soon after initiation of ventilatory support
- The patient appears to be working very hard to **initiate** breaths from the ventilator circuit
- The patient's inspiratory efforts do not trigger the ventilator every time
- Expiratory flow continues to the start of the next inspiration
- The patient has known or suspected COPD or asthma
- Large-volume intravenous fluid resuscitation has been required

plication is suggested when respiratory secretions increase in quantity or become more purulent, when the patient develops fever and/or new leukocytosis, and there is a new and persistent area of opacification on the chest radiograph. Finally, patient agitation is a frequent finding when acute lung injury or ARDS develops during the course of mechanical ventilation. Even when the risk factor associated with ARDS was present on admission, meeting the criteria for the syndrome often takes 2 or 3 days, or even longer.

A Non-Pulmonary Problem

Although manifested by respiratory distress, fighting the ventilator may be caused by a new, non-pulmonary problem, as listed in Table 1. The latter includes changes in volume status. Volume depletion in a patient receiving positive-pressure ventilation most often causes tachycardia and hypotension. However, central hypovolemia can be subtle, particularly when high levels of PEEP are used, and it should be considered in the assessment of newly-recognized agitation and respiratory distress. More commonly, respiratory deterioration is associated with volume overload. Pulmonary congestion and early pulmonary edema can cause tachypnea, air hunger, and increased oxygen requirements, which may be interpreted as fighting the ventilator. Hypervolemia is particularly a threat in patients who initially require volume resuscitation and subsequently have infusions of isotonic fluid continued for one or more days thereafter. Volume overload may be associated with wheezing and the development of auto-PEEP as well as with the other signs mentioned.

Cardiac ischemia or myocardial infarction should be considered, particularly in patients with known heart disease. An intracranial hemorrhage or other cerebrovascular event may announce itself by a change in breathing pattern or respiratory rate, and decreased responsiveness or other new neurological findings may initially be overlooked. The onset of sepsis may produce restlessness and tachypnea before other signs appear.

Drugs can cause patients to fight the ventilator in 2 general ways. The first of these is an adverse drug reaction. Many drugs administered to mechanically ventilated patients can cause delirium, hallucinations, and other alterations in perception, and these things are often manifested by agitation and distress. Other drugs such as central-nervous system stimulants and methylxanthines increase ventilatory drive and the sensation of air hunger. Recovery from the effects of muscle relaxants may be delayed, leading to respiratory distress in patients receiving only partial ventilatory support. Corticosteroids, especially when given in conjunction with muscle relaxants or for prolonged periods, are associated with muscle weakness and inability to wean from ventilatory support. Less often, idiosyncratic reactions to aminoglycosides and some other drugs can produce ventilatory muscle weakness.

The second general mechanism by which drugs can contribute to fighting the ventilator is withdrawal. Agitation and respiratory distress developing 2 to 5 days after admission may be caused by withdrawal from alcohol, opioids, or other agents the patient may have been taking regularly prior to hospitalization. In patients with prolonged critical illness, withdrawal from drugs administered in the hospital should also be considered a possibility.

Possible Causes: Inappropriate Ventilator Settings

The ventilator settings chosen by the clinician may not match the patient's desired breathing pattern, although this is typically evident from the beginning. However, patients who are obtunded or heavily sedated when admitted to the ICU may become more alert and first show signs of respiratory distress hours later. In addition, ventilator settings may be altered either inadvertently or during procedures, causing subsequent patient distress.

Table 1 lists several of the ventilator settings that may affect a patient's perception of the ease or adequacy of breathing. The use of lung-protective ventilation in the management of acute lung injury or ARDS[12] involves tidal volumes much smaller than what many patients want.[13] Because the proven mortality benefit of lung-protective ventilation[14,15] is believed to be related to both tidal volume and airway pressure, respiratory distress associated with this approach must be managed by means other than increasing ventilation volumes and pressures. Patients in respiratory distress are tachypneic, and lung-protective ventilation allows the rate to be increased, but only up to a point. Respiratory rates above 35 breaths/min tend to be associated with increasing auto-PEEP, which should be avoided.[12]

Triggering sensitivity should be maintained at 1.0 to 1.5 cm H_2O. When the threshold for initiation of inspiratory flow exceeds this range effort increases, and this is uncomfortable for most patients. For patients who are awake and acutely aware of their breathing, the inspiratory flows commonly used in ventilatory support may be inadequate. Although peak inspiratory flow during quiet normal breathing is about 50 L/min, normal inspiratory flows during activity are typically 2 to 4 times greater than this, and peak inspiratory flow in healthy

individuals exceeds 400-500 L/min. Thus, dyspneic patients may be further distressed if inspiratory flow is less than 70-80 L/min. One potential advantage of pressure-targeted over volume-targeted ventilation is the higher peak inspiratory flows achievable with the former—as high as 200 L/min in some instances.

Possible Causes: Inadequate Sedation

The need for administration of more sedatives is an important cause of respiratory distress and patient-ventilator dyssynchrony. As mentioned, the low tidal volumes associated with lung-protective ventilation may require more sedation in some patients than would otherwise be the case. However, to assume that fighting the ventilator is simply a sign of the need for increased doses of sedatives, particularly when respiratory distress develops in a patient who previously tolerated ventilatory support, is a potentially dangerous mistake. Such development should be approached as a diagnostic problem as well as a management challenge. Inadequate sedation and ICU delirium should always be diagnoses of exclusion, and the processes discussed above should be considered and excluded. A patient should never be paralyzed just to achieve synchrony with the ventilator; such an approach does nothing either to clarify the cause of the distress or to relieve it.

An Approach to Ventilator Trouble-Shooting

Given the possible causes for fighting the ventilator and the potential seriousness of several of them, it is important to approach the problem in a logical and systematic fashion. Table 3 outlines such an approach.

To exclude equipment malfunction and to assure that the artificial airway is patent, the patient should first be disconnected from the circuit and manually ventilated with supplemental oxygen. This maneuver may instantly relieve the patient's distress and reveal its likely cause. Whether the patient is easy or difficult to hand-ventilate is also an important observation. Especially if inspiratory obstruction is suggested during manual ventilation, the airway should next be suctioned, both to assure its patency and to assess any change in secretions. The respiratory therapist should then perform a quick inspection of the ventilator and its circuit to make sure that there are no obvious failures or defects.

Once these initial, potentially life-saving maneuvers have been completed, the responding clinician should quickly gather information available at the bedside that may point to the cause of the problem. Taking report from the patient's nurse and respiratory therapist may provide clear indications of the nature of the problem. Was the onset of respiratory distress abrupt or gradual? What happened first? Is it intermittent? The clinical setting for ventilatory support is also important. Is this *routine* ventilation after surgery, or is the patient ventilated because of primary respiratory failure due to pneumonia, obstructive lung disease, or ARDS? Does the patient have severe underlying pulmonary or cardiac disease? In addition, it is important to know whether the patient is receiving full or partial ventilatory support, and volume- vs pressure-targeted ventilation.[9]

The clinician should then undertake a brief physical examination, targeted at the manifestations of respiratory distress and their most likely causes. The amount of inspiratory effort being expended by the patient with every breath should specifically be assessed, as should the symmetry of chest expansion, air movement, and lung sounds. To the visual and auscultatory impression of breathing effort can be added evidence from ventilator graphics, if this type of monitoring display is available.[16] Other recent monitoring data should be examined next, looking for trends in vital signs, inspiratory and expiratory airway pressures, and minute ventilation over the last few hours. The respiratory therapists at my

Table 3

A Clinical Approach to the Patient Who Is Fighting the Ventilator

- Disconnect patient from ventilator circuit and ventilate manually with 100% oxygen
- Assess airway patency and suction airway
- Get report from the bedside nurse and/or respiratory therapist
  - Circumstances and timing of respiratory distress
  - Reason for ventilatory support
  - Underlying medical status
  - Recent events and trends
  - Type of ventilatory support being used
- Perform brief, targeted physical examination
  - Overall appearance
  - Vital signs
  - Amount of effort to initiate inspiration
  - Symmetry of chest excursion
  - Air movement; lung sounds
- Check recent monitoring data
  - Trends in vital signs
  - Trends in peak and plateau airway pressure
  - Auto-PEEP
  - Minute ventilation
  - Intake and output volumes
- Review recent laboratory data
  - Arterial blood gases
  - Leukocyte count and hematocrit
  - Acid-base status
- Review most recent chest radiograph.
- If above measures fail to clarify situation, obtain a new bedside chest radiograph.
- Sedate patient as indicated and tolerated, if necessary, depending on results of above steps.
- Proceed with further diagnostic studies and treatment as clinically indicated.

institution monitor every ventilated patient for auto-PEEP at least once each shift, and this important assessment should be done if not already recorded.

Pertinent recent laboratory data—especially oxygenation and acid-base status as revealed by arterial blood gases, and complete blood count to look for signs of new infection or blood loss—should next be examined. To complete the initial assessment, the patient's most recent chest X-ray should be reviewed, and a new one obtained at the bedside if none has been done recently or the cause for the problem is still not apparent. This last step is especially important, as most of the potentially life-threatening problems in Table 1 are identified or at least suggested by radiographic findings.

As the clinician proceeds through the assessment algorithm, the likely cause of the patient's acute distress should become more apparent—or, at least, the most life-threatening possibilities should be able to be excluded. At this point, the patient's level of sedation can be increased with less likelihood of overlooking or obscuring important findings. It may also be justifiable, if the preceding measures have not revealed the reason for distress or relieved it, to try modifying the mode, inspiratory flow, or other ventilator settings in an attempt to achieve better patient comfort.

Two words of caution are in order here, however. First, the volume and pressure targets of lung-protective ventilation should not be altered if the patient has acute lung injury or ARDS, as these have been proven to save lives.[14,15] And, finally, current ICU ventilators have new mode combinations and variations that are unfamiliar to many clinicians, and empirically switching to some unfamiliar ventilatory approach should be avoided unless everyone who will be involved in the patient's management has been thoroughly instructed in its use and potential complications. ■

References

1. Tobin MJ. *Respir Care.* 1992;37:1081-1096.
2. Keith RL, Pierson DJ. *Clin Chest Med*. 1996;17:439-451.
3. Hess DR, Thompson BT. *Crit Care Med*. 2006;34:231-233.
4. Austin PN, et al. *Respir Care.* 2002;47:667-674.
5. Younes M, et al. *Am J Respir Crit Care Med*. 2002;166:21-30.
6. Racca F, et al. *Respir Care Clin N Am*. 2005;11:225-245.
7. Brochard L. *Intensive Care Med*. 2002;28:1552-1554.
8. Ranieri VM, et al. *Clin Chest Med*. 1996;17:379-394.
9. Pierson DJ. Invasive mechanical ventilation. In: Albert RK, Spiro SG, Jett JR, eds. *Clinical Respiratory Medicine*. London/Philadelphia, Elsevier Health Sciences, 2nd edition, 2004:189-209.
10. Blanch L, et al. *Respir Care*. 2005;50:110-123.
11. Dhand R. *Respir Care*. 2005;50:246-261.
12. Kallet RH, et al. *Respir Care*. 2001;46:1024-1037.
13. Kallet RH, Luce JM. *Respir Care*. 2002;47:183-185.
14. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342:1301-1308.
15. Kallet RH, et al. *Crit Care Med*. 2005;33:925-929.
16. Nilsestuen JO, Hargett KD. *Respir Care.* 2005;50:202-234.

CME Questions

16. What was the incidence of propylene glycol toxicity in patients receiving IV diazepam or lorazepam in Wilson et al's study?

a. 4%
b. 19%
c. 23%
d. 41%
e. 100%

17. Reported manifestations of propylene glycol toxicity include all except:

a. elevated anion gap
b. hyperosmolality
c. elevated liver function tests
d. seizures
e. sepsis-like syndrome

18. When added to other aspects of standard therapy for COPD exacerbations requiring hospitalization, and compared with placebo infusion, intravenous aminophylline:

a. improved mortality, length of stay, pulmonary function, arterial blood gases, and symptoms.
b. improved length of stay, pulmonary function, arterial blood gases, and symptoms, but had no effect on mortality.
c. improved pulmonary function, arterial blood gases, and symptoms, but had no effect on hospital length of stay or mortality.
d. improved pulmonary function and symptoms only.
e. improved arterial blood gases but to a degree that was not clinically important.

Answers: 16 (b); 17 (c); 18 (e)

CME / CE 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.

In Future Issues: ICU Intensivist-to-Bed Ratio

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.

Letrozole for Postmenopausal Women with Breast Cancer

Letrozole (Femara) is a potent aromatase inhibitor that is used to treat women with metastatic breast cancer and, in a neoadjuvant role, for women who have failed tamoxifen. Aromatase inhibitors exert their effect by blocking the conversion of androgens to estrogens and reducing estrogen levels in tissue and plasma. Recently, letrozole was compared with tamoxifen for adjuvant therapy in postmenopausal women with steroid-hormone-receptor-positive breast cancer.

A total of 8010 women were randomized to 5 years of letrozole (4003) or tamoxifen (4007). After a median follow-up of 25.8 months, there were 351 events (local or distant recurrence) in the letrozole group and 428 events in the tamoxifen group, with 5-year disease-free survival estimates of 84% and 81.4%, respectively. Adverse effects of the drugs were different with tamoxifen, resulting in a higher rate of thromboembolism, endometrial cancer, and vaginal bleeding, while letrozole was associated with a higher incidence of skeletal and cardiac events and hypercholesterolemia.

The authors suggest that in women with endocrine-responsive breast cancer, adjuvant treatment with letrozole, as compared with tamoxifen, reduced the risk of recurrent disease (Thurlimann B, et al. A Comparison of Letrozole and Tamoxifen in Postmenopausal Women with Early Breast Cancer. *N Engl J Med*. 2005;353:2747-2757). In an accompanying editorial Sandra Swain, MD, from the National Cancer Institute, states that "all the evidence points to aromatase inhibitors as critically important for improving the outcome among postmenopausal women with breast cancer who have positive or negative lymph nodes and who are at a substantial risk for recurrent disease." (Swain SM, et al. Aromatase Inhibitors—A Triumph of Translational Oncology. *N Engl J Med*. 2005;353:2807-2809). Based on this study, the FDA has recently approved letrozole for adjuvant treatment (immediately after surgery) in postmenopausal women with hormone sense of breast cancer.

Do Antidepressants Increase Risk of Suicide?

An article in the January issue of the *American Journal of Psychiatry* asks "Is the FDA Warning About Antidepressants Wrong?" Researchers from Group Health Cooperative in the Pacific Northwest used population-based data to evaluate the risk of suicide death and serious suicide attempt in relation to the initiation of antidepressant treatment.

Computerized health plan records for over 65,000 patients with over 82,000 episodes of antidepressant treatment between 1992 and 2003 were reviewed. In the 6 months after initiation of antidepressant treatment, the risk of suicide was found be no higher than at any other time during treatment. The risk of suicide attempt was highest in the month before starting treatment, and declined progressively after starting medication. When newer drugs were compared to older drugs, an increase in suicidality was

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

only seen with the older drugs.

The authors conclude that the risk of suicide during acute-phase antidepressant treatment is approximately 1 in 3000 treatment episodes, and the risk of serious suicide attempt is approximately one in 1000. Available data do not indicate significant increase in risk of suicide or serious suicide attempt after starting treatment with newer antidepressant drugs (Simon GE, et al. Suicide Risk During Antidepressant Treatment. *Am J Psychiatry*. 2006;163:41-47, available free at ajp.psychiatryonline.org). The study calls into question the March 2004 FDA public health advisory regarding worsening depression and suicidality in pediatric and adult patients being treated with 10 newer antidepressants (bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, escitalopram, and venlafaxine).

Can Viagra Improve Heart Function?

Concern still lingers regarding the safety of erectile dysfunction drugs in patients with heart failure. A new study from Australia suggests that sildenafil (Viagra) actually improves heart function in patients with systolic dysfunction. In a randomized, placebo-controlled, double-blind, 2-way crossover study, 20 patients with controlled left ventricular failure and ejection fractions < 35% received sildenafil 50 mg or matching placebo. Cardiac output was determined by Doppler echocardiography, aortic pressure waveform, and aortic and femoral arterial stiffness was also evaluated. With a peak effect at 60 minutes after administration, sildenafil resulted in an increase in cardiac index of 0.37 L/min, decrease in total systemic resistance, decreased aortic and lower limb pulse-wave velocity, and decreased wave reflection (all significant at $P < .0001$). The authors conclude that sildenafil improved cardiac performance by decreasing LV load, resulting in increased cardiac output and increase in exercise capacity in heart failure patients (Hirata K, et al. Effect of Sildenafil on Cardiac Performance in Patients with Heart Failure. *Am J Cardiol*. 2005;96:1436-1440).

Can Tamoxifen Increase Your Height?

Tamoxifen may increase height potential in short pubertal periods, according to new study in the journal *Pediatrics*. The study was a retrospective chart review of 7 boys with a mean age of 15 who took tamoxifen 10-20 mg twice a day for a mean of 26 months. Six of the boys were also receiving growth hormone. Tamoxifen significantly decreased the rate of skeletal maturation and improved predicted adult height without negative effects on sexual maturation. Skeletal maturation was determined by review of bone radiographs by independent endocrinologists. The authors state that "additional evaluation of this therapy is now required to determine if the increase in predicted adult height results in a clinically significant increase in final adult height." (Kreher NC, et al. The Use of Tamoxifen to Improve Height Potential in Short Pubertal Boys. *Pediatrics*. 2005;116:1513-1515).

A Dramatic Increase of Clostridium difficile

Clostridium difficile is increasing in frequency and severity in both hospital and community settings. Widespread use of acid suppressing proton pump inhibitors (PPIs) and H2 receptor agonists (H2RAs) may be a contributing factor, according to new study. Two population-based, case-control studies from England reviewed all 1672 cases of *C. difficile* reported between 1994 and 2004, while a second study looked at cases defined as community acquired. All cases were matched 10 controls. The incidence of *C. difficile* increased dramatically between 1994 and 2004. The adjusted rate ratio of *C. difficile* associated disease with current use of PPIs was 2.9 (95% CI, 2.4-3.4) and, with H2RAs, the rate ratio was 2.0 (95% CI, 1.6-2.7). The authors conclude that the use of acid-suppressive therapy is associated with an increase risk of community-acquired *C. difficile*. Parenthetically, they also found an increased risk associated with use of nonsteroidal anti-inflammatory drugs (*JAMA*. 2005;294:2943-3048).

FDA Actions

The FDA has approved Bristol-Myers Squibb's abatacept (Orencia) for the treatment of rheumatoid arthritis. The drug, which is produced by recombinant DNA technology, is a T cell costimulation modulator. It is approved for patients with moderately-to-severely active rheumatoid arthritis who had an inadequate response to one or more DMARDs, including TNF antagonists. It may be used as monotherapy or with other non-TNF inhibitor DMARD. Abatacept is administered as a 30-minute IV infusion at 0, 2, and 4 weeks, then every 4 weeks thereafter.

The FDA and GlaxoSmithKline have issued a "Dear Doctor" letter regarding rare reports of macular edema in patients receiving rosiglitazone (Avandia). The majority of the cases involved concurrent peripheral edema and, in the majority of cases, macular edema improved with discontinuation of the drug. Macular edema presents as blurred or distorted vision, decrease color sensitivity, and decreased dark adaptation. ■