CRITICAL CARE ALERT®

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

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INSIDE

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

The One Thing Certain in the ICU Is Uncertainty

ABSTRACT & COMMENTARY

By Richard J. Wall, MD, MPH

Pulmonary Critical Care & Sleep Disorders Medicine, Southlake Clinic, Valley medical Center, Renton, WA

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

Synopsis: *This study showed that surrogate decision-makers with a loved one in the ICU want clinicians to discuss the patient's prognosis, even if it is uncertain.*

Source: Evans LR, et al. Surrogate decision-makers' perspectives on discussing prognosis in the face of uncertainty. *Am J Respir Crit Care Med* 2009;179:48-53.

WHILE ICU CLINICIANS UNDERSTAND THAT PROGNOSTIC UNCERtainty is a normal part of critical care, it is unclear if surrogates hold similar views. In this study, Evans et al conducted semi-structured face-to-face interviews with 179 surrogates who had an adult patient in the ICU. The study included patients from 4 tertiary academic ICUs (2 medical-surgical, 1 neurological, 1 cardiac). Patients were eligible if they had a high risk of dying (APACHE score ≥ 25). Interviews took place on days 3-5 of mechanical ventilation. Interviews were audiotaped, transcribed, and analyzed using a qualitative comparative methods framework. To improve validity, the conceptual framework was presented to a sample of study subjects and modified based upon their input.

Overall, most surrogates (87%) want physicians to discuss prognosis, even if it is uncertain. The researchers identified several reasons for this sentiment: 1) surrogates view prognostic uncertainty as unavoidable; 2) surrogates view physicians as the best source of prognostic information; 3) prognostic uncertainty leaves room for hope; 4) information exchange fosters trust in the physician; and 5) prognostic discussions allow families to prepare for the worst and make decisions.

VOLUME 17 • NUMBER 2 • MAY 2009 • PAGES 9-16

Although the researchers did not intentionally inquire about it, many surrogates offered unsolicited suggestions for physicians who must discuss an uncertain prognosis. One suggestion was to use language that clearly conveys uncertainty. For example, avoid making absolute predictions and instead use percentages or ranges. Also let families know that probabilities can change. Surrogates also stated that physicians should err on the side of "complete honesty" and disclose all available information. Of note, 12% of surrogates felt physicians should avoid discussing an uncertain prognosis. However, some of them stated such information might be discussed at a later date so long as it was presented in a certain way. Thus, the vast majority of surrogates want information even if it is uncertain.

■ COMMENTARY

Surrogate decision-makers are necessary in the ICU because many critically ill patients are unable to make their own decisions. Studies confirm that ICU surrogates want complete and honest communication, and clinician-family communication is perhaps the most important factor driving family satisfaction with care in the ICU.[1] For this reason, understanding the perspectives of surrogate decision-makers is an important undertaking for improving ICU quality.

Critical Care Alert, ISSN 1067-9502, is published monthly by AHC Media LLC, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

ASSOCIATE PUBLISHER: Coles McKagen
DIRECTOR OF MARKETING: Schandale Kornegay
SENIOR MANAGING EDITOR: Paula Cousins
GST Registration Number: R128870672.
Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

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

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

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1 year *with* free AMA Category 1 credits: $289
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(Student/Resident rate: $120)

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Questions & Comments

Please call **Paula Cousins,** Senior Managing Editor, at (404) 262-5468.

This study found that most (albeit not all) surrogates of critically ill patients want physicians to fully disclose prognostic estimates, even if they might be incorrect. Like physicians, most surrogates understand that prognostic uncertainty is unavoidable in the ICU. Unfortunately, I think many physicians avoid discussing uncertainty with families because it makes them feel clinically inadequate. Numerous studies support this notion, including the landmark SUPPORT trial which found that < 20% of physicians discuss prognostic information with seriously ill hospitalized patients.[2] Likewise, another study found that 80% of internists avoid discussing the patient's prognosis if the prognosis is not certain.[3]

Why do clinicians avoid discussing uncertainty? The authors posit that discussing uncertainty forces clinicians to acknowledge the limits of their medical knowledge. Another explanation is that clinicians want to avoid causing patients and families undue distress. Ironically, these clinician sentiments are misguided. Discussing uncertainty is viewed by surrogates as delivering *better* care because it increases trust between the family and physician and also gives families a chance to prepare for possible bereavement. The latter is especially important because lack of preparation for bereavement increases risk for adverse psychological outcomes such as depression.

Several underlying assumptions in this field remain untested. For example, it is unknown if surrogates truly comprehend the complicated concepts of probability, comorbidity, and prognostic uncertainty. Regardless, I think the message from the current study is straightforward: Talk to patients and their families. There is an enormous desire for information exchange among families in the ICU. When performed properly, the act of communication (which involves listening and not just talking) is sometimes the most potent therapy we deliver. ■

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Non-invasive Ventilation in Acute Respiratory Failure: Importance of the Interface

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *When 4 different interfaces with varying internal dead space were randomly applied during non-invasive ventilation in 14 patients with acute respiratory failure, there were no significant differences in gas exchange, minute ventilation, or work of breathing, but patient tolerance of the different devices varied substantially.*

Source: Fraticelli AT, et al. Physiological effects of different interfaces during noninvasive ventilation for acute respiratory failure. *Crit Care Med* 2009;37:939-945.

In the application of non-invasive ventilation (NIV) in the management of patients with acute respiratory failure, Fraticelli and colleagues at Henri Mondor Hospital in Créteil, France, sought to determine the clinical effects of using interfaces with varying dead space and other features. They randomly applied 4 different interfaces for periods of 20 minutes each (with intervening 15-minute rest periods). The interfaces were a whole-face mask with internal volume of approximately 1000 mL, an oronasal mask with an internal volume of 163 mL, a second oronasal mask with a smaller internal volume (84 mL), and a mouthpiece with essentially no internal volume. Pressure-targeted NIV was administered according to usual clinical practice in the authors' institution, with slightly higher pressures used with the largest-volume mask to account for greater gas compression, and slightly lower pressures with the mouthpiece to minimize leaks. Measured variables with the different interfaces were minute ventilation, arterial blood gases, patient-ventilator synchrony, inspiratory work of breathing (using an esophageal probe), air leaks, and patient comfort (using a visual analog scale).

Fourteen alert and cooperative patients were studied, 7 each with hypoxemic and hypercapnic acute respiratory failure. The pressures used during NIV were a pressure support of 11 ± 3 cm H_2O above the positive end-expiratory pressure (PEEP); PEEP was 6 ± 2 cm H_2O in the hypoxemic patients and 4 ± 3 cm H_2O in the hypercapnic patients. NIV was effective in reducing the pressure-time product of the respiratory muscles (an index of the work of breathing) using all 4 interfaces, with no differences among them. Arterial PO_2 improved in all patients but there were no differences in minute ventilation or in PCO_2 or pH with any of the interfaces. Air leaks and patient-ventilator asynchrony were higher with the mouthpiece, but there were no other differences among the interfaces. Using the visual analog scale, comfort was significantly less with the mouthpiece, with no other differences. The authors concluded that the internal volume of the masks had no apparent short-term dead-space effect, and that the different interfaces were essentially interchangeable in clinical practice.

■ COMMENTARY

Used effectively and in the right patients who present with acute respiratory failure, NIV reduces mortality, avoids the need for intubation in many instances, prevents hospital-acquired pneumonia, shortens ICU length of stay, and saves money.[1] However, NIV is not like some new antibiotic that the patient's physician simply needs to know when to prescribe. To implement NIV effectively, and achieve improved outcomes, requires that a whole program be set up in the institution, involving not only new policies and procedures, but also increased staff knowledge and training, the right equipment, and availability in every area of the hospital in which the need may exist.[2]

This study has two important findings that relate to the effective implementation of NIV in treating patients with acute respiratory failure. First, although there are a number of key considerations with respect to the interface,[3] the effects of varying mask dead space do not seem to be clinically important. Second, different interfaces may vary considerably with respect to patient tolerance and comfort. This latter finding is consistent with clinical experience at institutions where NIV is done really well. There is no "one-size-fits-all" with respect to NIV masks. Application of NIV according to a fixed protocol that applies the same brand and size of mask to all patients is sure to fail in many patients who would be successfully managed with appropriate individualization of the interface. The successful implementation and clinical application of NIV in treating patients with acute respiratory failure has a solid scientific underpinning but remains an art as well. This modality of respiratory care illustrates the importance of interdisciplinary collaboration and institutional systems integration in achieving the best patient outcomes. ■

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Pro-Con Perspective

Dexmedetomidine vs Midazolam for Sedating Mechanically Ventilated ICU Patients

By James E. McFeely, MD, and Andrew Luks, MD

Dr. McFeely is Medical Director Critical Care Units, Alta Bates Summit Medical Center, Berkeley, CA; Dr. Luks is with Pulmonary and Critical Care Medicine, University of Washington, Seattle. They report no financial relationship to this field of medicine.

Editor's Note: The alpha2-receptor agonist dexmedetomidine (Precedex®), introduced for perioperative and procedural sedation and other short-term applications, is approved by the FDA for use in the ICU, although the package insert emphasizes that this approved use is for not more than 24 hours. This study by Riker et al investigated whether dexmedetomidine, which has several potential advantages over benzodiazepines and opioids for more prolonged ICU sedation, was superior to midazolam for this use in mechanically ventilated patients. Its results appear quite positive, yet the article has provoked controversy, with experienced, critical care clinicians interpreting it quite differently. Editorial Board members James McFeely, MD, and Andrew Luks, MD, independently evaluated the Riker paper, and provide divergent perspectives on its findings and implications for the use of dexmedetomidine for sedating mechanically ventilated ICU patients.

Synopsis: *This prospective, double-blind, multicenter, randomized trial found that dexmedetomidine sedated patients as well as midazolam and resulted in a shorter duration of mechanical ventilation, with fewer patients experiencing delirium.*

Source: Riker RR, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: A randomized trial. *JAMA* 2009;301:489-499.

MIDAZOLAM IS COMMONLY USED FOR SEDATION IN critically ill patients but concerns persist as to whether it induces delirium, and also prolongs mechanical ventilation and ICU stay, due to its accumulation in lipid stores with prolonged administration. Riker and colleagues sought to determine whether dexmedetomidine could serve as a suitable alternative to midazolam, achieving similar levels of sedation with fewer adverse consequences. To investigate this question, dexmedetomidine was frequently used at a dose higher than the limits approved by the FDA and well beyond the 24-hour time limit listed on the drug label.

The authors conducted a prospective, double-blind, randomized trial at 68 centers in 5 countries over a 2.5-year period. Patients were included if they were ≥ 18 years of age, had been on mechanical ventilation for ≤ 4 days, and had an anticipated duration of mechanical ventilation of ≥ 3 days. Exclusion criteria included hypotension requiring the use of 2 or more vasopressors; admission diagnoses of trauma, burns, acute myocardial infarction, or severe neurologic injury; dialysis; acute hepatitis; and severe chronic liver disease. Included patients were taken off their pre-existing sedative medications and randomized to receive either dexmedetomidine (0.8 μg/kg/hr) or midazolam (0.06 mg/kg/hr), intravenously, with adjustments as needed to achieve sedation as assessed by the Richmond Agitation and Sedation Scale (RASS) with a score between -2 and +1. Patients who were not adequately sedated by the study drug could receive open-label midazolam boluses of 0.01-0.05 mg/kg every 10-15 minutes until adequate sedation was achieved. Fentanyl and haloperidol boluses could also be administered for pain and delirium, respectively, and every patient had a daily sedation vacation. The primary endpoint was the percentage of time within the target sedation range (RASS score, -2 to +1). Secondary endpoints included prevalence and duration of delirium, as assessed by the Confusion Assessment Method for the ICU (CAM-ICU) protocol, use of fentanyl and open-label midazolam, the duration of mechanical ventilation, and length of ICU stay.

A total of 366 patients received the study drugs (244 dexmedetomidine and 122 midazolam) and baseline characteristics were evenly matched in the two groups. Despite the multinational study design, the overwhelming majority of study patients were from the United States. The mean maintenance infusion doses were 0.056 mg/kg/hr for midazolam (4.4 mg for an 80 kg patient) and 0.83 μg/kg/hr for dexmedetomidine.

There was no difference in time within the target RASS range between dexmedetomidine (77.3%) and

midazolam (75.1%). Fifty-four percent of the dexmedetomidine patients experienced delirium compared to 76.6% of the midazolam-treated patients, a result that held up regardless of whether the patients had delirium at the time of study enrollment. Open-label midazolam use was more common in the dexmedetomidine group (63% vs. 49%; $P = 0.02$) while fentanyl and haloperidol use were the same in the two groups. The median time to extubation was shorter by 1.9 days in the dexmedetomidine group (3.7 vs 5.6 days; $P = 0.01$), but there were no significant differences in the length of ICU stay (5.9 vs 7.6 days; $P = 0.24$). Forty-two percent of the dexmedetomidine patients developed bradycardia, compared to only 20% of the midazolam patients, and 11% of patients experiencing bradycardia required treatment such as decreasing or stopping the study drug or administering atropine.

■ COMMENTARY BY JAMES E. McFEELY, MD

This article provides compelling evidence that dexmedetomidine is safe for prolonged use and at higher doses than currently recommended by the package insert. The study was well grounded, using treatment methodologies common in clinical practice and a patient group of appropriate interest for prolonged mechanical ventilation. The daily arousal assessment and use of bolus sedatives and narcotics are also consistent with current clinical practice. The trial was of a robust size and the outcome measures were important.

Dexmedetomidine appears to be at least as good as midazolam in maintaining sedation within a goal range. It appears superior, however, in a number of other areas. In particular, it is associated with a significant decrease in frequency of delirium. Midazolam is noted to be associated with delirium, which has negative short-term as well as long-term effects on patient outcome. Dexmedetomidine was also associated with an almost 2-day reduction in ventilator days, at least partially due to its lack of respiratory-depressant effect.

Complications of dexmedetomidine included a modest increase in frequency of hyperglycemia and an increased frequency of bradycardia. The reduction in heart rate was probably related to sympatholytic blunting. Of note, only 12 of 244 patients required intervention for bradycardia.

This paper should provoke a reassessment of the role of dexmedetomidine in all our ICUs. Those unfamiliar with the drug should become familiar with it and get it on formulary. Those who have it but are not using it should reassess its role, particularly in patients belonging to the same cohort as the subjects of this clinical trial.

■ COMMENTARY BY ANDREW M. LUKS, MD

On the surface, the results of this study would seem to suggest that dexmedetomidine is an ideal sedative for the ICU. It achieved levels of sedation comparable to one of our standard agents while causing less delirium and decreasing the duration of mechanical ventilation. Aside from the concerns about bradycardia, a problem we have seen at our institution when using drug levels high enough to achieve adequate sedation, there are some important limitations in this study that warrant attention and should dampen the enthusiasm for this medication that is sure to arise from this study.

The most important limitation is the protean list of study exclusion criteria that was actually much longer than the abbreviated list described above. The study population was also not very ill, with mean APACHE II scores of 18-19 in the two study groups. Given these issues, a sizeable majority of the patients at many of the institutions where we practice, particularly tertiary medical centers, would never have been included in this study and we are left to wonder whether these results would hold up in a broader population of critically ill patients.

There is also reason to question the data regarding the duration of mechanical ventilation, one of the important secondary study endpoints that will be used to justify the use of the medication. The study did not include explicit extubation criteria, nor did the investigators appear to use protocols for initiating spontaneous breathing trials, a tactic previously demonstrated to shorten the duration of mechanical ventilation compared to physician-driven decision making. To the extent that extubation practices differed across institutions and countries in the study, this might have had an impact on the study results in this regard.

Finally, the study did not address another important issue with this medication — its high cost. At our institution, dexmedetomidine administered at a rate of 0.7 µg/kg/hr to a 70 kg patient costs $370/day, more than 10 times the daily cost of midazolam and 90 times more than that of fentanyl. It is true that the higher cost may be offset by the decreased costs associated with a shorter duration of mechanical ventilation (e.g., less ventilator-associated pneumonia), but until we have data suggesting that target levels of sedation, less delirium, and shorter duration of mechanical ventilation can actually be achieved in a range of critically ill patients substantially broader than those examined in this study and more reflective of what we see in our daily practice, we should not be committing to this expensive alternative. ■

Special Feature

Acute Coronary Syndrome: A Concise Summary for the Non-cardiologist

By James E. McFeely, MD

PATIENTS WITH ACUTE CORONARY SYNDROME PRESENT one of the most common admission diagnoses in the intensive care unit. For non-cardiology intensivists, the ever-evolving treatment algorithms present a challenging body of literature on which to remain current. Nevertheless, because of the frequent need to assist with the management of these patients, it behooves us to stay as current as possible with this literature. Fortunately, our cardiology colleagues have done an excellent job of designing large, well-controlled (and cleverly named) clinical trials that are published in readily accessible journals. In addition, they frequently update practice guidelines incorporating the most recent findings and recommendations.[1,2]

ST-Elevation Myocardial Infarction (STEMI)

The main goal of management of STEMI is localizing and then opening the occluded coronary artery as quickly as possible. The availability of 12-lead ECG recordings in the field has decreased the time from initial diagnosis to intervention by allowing earlier activation of the cardiac catheterization laboratory team and emergency room staff prior to patients' arrival. Any emergency management system without this capacity should be addressing this deficiency now.

Once the diagnosis of STEMI is made, percutaneous coronary intervention (PCI) remains the treatment of choice if it can be accomplished within 90 minutes (preferably significantly sooner) by a competent angiographer (level of evidence A, Class I recommendation).[3] If patients present to a hospital without PCI capability and cannot be transferred to a PCI center within 90 minutes of first medical contact, they should be treated with fibrinolytic therapy within 30 minutes of hospital presentation (level of evidence B, Class I recommendation).

Other elements of acute medical management involve multidrug anticoagulant therapy, including enoxaparin or other heparin-like drug, as well as clopidogrel bisulfate (Plavix®) and potentially eptifibatide (Integrilin®) or tirofiban (Aggrastat®). All patients should receive aspirin unless there is a well-documented intolerance. The most recent guideline recommends coronary artery bypass grafting (CABG) only for patients who fail PCI or have unsuitable anatomy with ongoing pain or hemodynamic instability. Successful reperfusion is defined as at least a 50% reduction in ST-elevation in the lead initially showing the greatest elevation. The presence or absence of chest pain is unreliable for identifying failed reperfusion and should not be used as an indicator. Meta-analysis of rescue trials of PCI following failed thrombolytic therapy has shown a decrease in adverse clinical events compared with medical therapy alone.[4]

A strategy of planned immediate PCI following fibrinolytic therapy ("facilitated PCI") has been shown to result in worse outcomes than primary PCI alone. The mortality rate was significantly higher when there was a very short time between thrombolytic administration and PCI. This approach is now considered harmful.

The question of whether to invasively study patients who are successfully treated with fibrinolytic therapy remains in evolution. Angiography with possible revascularization is needed in the setting of symptoms of ischemia following STEMI. The question remains what to do with patients who have no ischemic symptoms. Two studies addressed this issue, randomizing patients to angiography or conservative management. A modest improvement in long-term survival was seen in patients who underwent routine angiography. Patients with an angiographically documented total occlusion of the STEMI artery should not have PCI of that lesion, as they had less favorable long-term outcomes with PCI than with treatment by medical management alone.[5]

Unstable Angina or Non-ST-Elevation Myocardial Infarction (UA/NSTEMI)

The first line of therapy for the other acute coronary syndrome, UA/NSTEMI, is anticoagulation.[6] Without significant contraindications, all patients should be given aspirin, heparin, and potentially a glycoprotein IIb/IIIa receptor blocker, in anticipation that coronary revascularization will occur shortly thereafter. An analysis of 7 randomized trials found better long-term survival with routine early invasive strategy compared to a conservative medical approach. Currently, PCI strategies have a Class I recommendation for high-risk asymptomatic patients with a recent acute coronary syndrome and no serious comorbidities and amenable lesions. There are 11 risk factors that can identify the patient as high-risk, including abnormal troponin and/or new ST-segment depression. As these are part of the diagnosis of UA/NSTEMI, essentially all patients with this syndrome should undergo angiography.

CABG is currently recommended for any left main coronary artery disease, three-vessel disease, or two-vessel disease with proximal left anterior descending (LAD) involvement. Two-vessel disease with a large area of myocardium at risk is also an indication for CABG. Over the last several years, PCI has been used with increasing frequency relative to CABG for UA/NSTEMI.

Remaining questions in the treatment of UA/NSTEMI include when to perform the angiography and how complete the revascularization should be. On the basis of 1 randomized trial, early revascularization within 6 hours would be optimal. Beyond that, outcomes show little change as the time to angiography lengthens.

In patients with UA/NSTEMI it can be difficult at angiography to identify the culprit lesion. This may result in the need to perform PCI on several lesions when there are multiple possible candidates. By contrast, in the case of STEMI it is recommended that elective PCI not be performed in a non-infarct-related artery at the time of the primary PCI.

Beyond the revascularization procedures, medical management of both groups of patients is similar. Beta blockade is strongly recommended within the first few hours (contraindications include signs of heart failure, high risk for cardiogenic shock, heart block, or active reactive airways disease). Early use of angiotensin-converting enzyme (ACE) inhibitors is recommended in patients with ejection fractions less than 40% in the absence of shock. In non-PCI patients, clopidogrel should be added to aspirin and administered for at least 1 month and preferably up to 1 year. PCI patients may need to take antiplatelet therapy much longer.

As intensivists, we frequently see bleeding complications related to antiplatelet therapy.[7] With aspirin therapy there is a low but persistent and relatively constant rate of bleeding. When clopidogrel is added to aspirin, there is an increased risk of bleeding in the first 9-12 months, which then plateaus. Patients who have their clopidogrel stopped prior to 1 year, particularly patients with drug-eluting stents, are at significantly increased risk of late stent thrombosis.

In terms of general medical management, maintenance of normal potassium and magnesium levels is recommended. Maintenance of normal blood sugar may be beneficial, but hypoglycemia needs to be carefully avoided. Use of a proton pump inhibitor is recommended in hospitalized patients on dual antiplatelet therapy who are at high risk for gastrointestinal bleeding, such as those older than age 60 or with a previous history of bleeding, steroid use, or prolonged hospital or ICU stay.

The clearest trend to emerge from the literature on the management of acute coronary syndrome is improved outcomes with rapid revascularization and with prolonged use of anticoagulant and antiplatelet therapy. However, given the pace of change in treating this disorder, intensivists are well advised to review this literature annually. ■

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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.

CME / CNE Questions

4. **Which of the following is *true* about surrogate decision-makers in the ICU?**
   a. Most surrogates think prognostic uncertainty is rare in the ICU.
   b. Most surrogates want physicians to avoid discussions about prognosis unless the physicians is very certain.
   c. Physician communication is a key determinant of surrogate satisfaction with care in the ICU.
   d. When a physician states that a patient's prognosis is "uncertain," this will commonly erode the surrogate's trust in the physician.
   e. None of the above

5. **Which of the following statements is *true* about the interface (mask or mouthpiece) used for non-invasive ventilation in acute respiratory failure?**
   a. There are no clinically important differences for any interface.
   b. Masks with higher internal dead space are less well tolerated by patients.
   c. They impose markedly different levels of inspiratory work of breathing.
   d. They vary markedly with respect to patient comfort and tolerance.
   e. None of the above

6. **Dexmedetomidine decreased the rate of delirium in this trial by:**
   a. 12%
   b. 23%
   c. 32%
   d. 48%
   e. 60%

7. **The use of dexmedetomidine for sedation of critically ill patients is associated with which of the following side effects?**
   a. Adrenal insufficiency
   b. Bradycardia
   c. Gastrointestinal hemorrhage
   d. Hyponatremia
   e. Ileus

8. **Percutaneous coronary intervention should *not* be performed in which of the following situations?**
   a. STEMI within 60 min of onset of pain
   b. STEMI with recurrent pain
   c. NSTEMI with amenable lesions
   d. Total occlusion of the STEMI artery
   e. Two target lesions are identified in a patient with UA

Answers: 4. c, 5. d, 6. b, 7. b, 8. d.

In Future Issues:

Errors in Parenteral Drug Administration in the ICU

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*.

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In this issue: Aspirin dose and cardioprotection; uncovering modafinil's abuse potential; proton-pump inhibitors and clopidogrel; FDA actions.

Finding pharmaceuticals in natural products

Some natural products are not so "natural" after all. The FDA has warned consumers for several months that a number of weight-loss products contain undeclared pharmaceutical ingredients. The newest products to join the list are Herbal Xenicol which contains cetilistat (a drug similar to orlistat that is not approved in this country), as well as Slimbionic and Xsvelten, both of which contain sibutramine (the prescription medication also known as Meridia®). The FDA's list of over-the-counter weight-loss agents that contain undeclared active pharmaceutical ingredients now includes 72 products. Some of the other undeclared pharmaceutical ingredients found in these products include fenproporex (an amphetamine derivative no longer available in this country), fluoxetine (Prozac®, an SSRI), furosemide (Lasix®, a loop diuretic), and even phenytoin (Dilantin®, an antiseizure medication). The FDA is seeking recalls on many of these products; however, some are available only online and previous recall efforts have proved inadequate.

In a related story, the FDA has announced a voluntary recall of Zencore Plus, the heavily marketed product for "natural male enhancement," which has been found to contain benzamidenafil, a new PDE5 inhibitor not yet available in this country. Benzamidenafil is similar in action to sildenafil (Viagra®) and tadalafil (Cialis®). PDE5 inhibitors are noted to have a drug interaction with nitrates, leading to potential life-threatening risk of sudden and profound drop in blood pressure. Zencore Plus is distributed by Hi-Tech Pharmaceuticals in Norcross, GA, and is widely sold in health food stores, by mail order, and by Internet sales.

Aspirin dose and cardioprotection

What is the best dose of aspirin for patients taking dual therapy with clopidogrel to prevent cardiovascular events? Investigators looked at 15,595 patients with cardiovascular disease or multiple risk factors in an observational analysis from a double-blind, placebo-controlled randomized trial. Patients were randomized to doses of aspirin less than 100 mg (75 mg or 81 mg), 100 mg, or greater than 100 mg (150 mg or 162 mg) with or without clopidogrel. The primary efficacy outcome was the composite of myocardial infarction, stroke, or cardiovascular death and the primary safety endpoint was severe life-threatening bleeding. In patients given aspirin alone, the hazard ratio for the efficacy and safety endpoints were the same regardless of aspirin dose. In patients given aspirin with clopidogrel, there was a statistically nonsignificant associated reduction in efficacy with aspirin doses over 100 mg, and a

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significantly higher increase in harm (hazard ratio, 1.30 with clopidogrel plus aspirin greater than 100 mg). The authors conclude that daily doses of aspirin greater than 100 mg were not associated with benefit and may be associated with harm in patients also taking clopidogrel. Therefore, daily doses of aspirin 75-81 mg optimize efficacy and safety in patients requiring long-term aspirin therapy, especially in patients receiving dual antiplatelet therapy (*Ann Intern Med* 2009;150:379-386). This is especially important given the recent U.S. Preventive Services Task Force recommendation that encourages men ages 45-79 years to take aspirin preventively when the potential benefit of a reduction of myocardial infarction outweighs the potential harm of an increase in gastrointestinal hemorrhage. Women ages 55-79 years are also encouraged to use aspirin when the potential benefit of a reduction in ischemic stroke outweighs the potential harm of increased gastrointestinal hemorrhage (*Ann Intern Med* 2009;150:396-404).

PPIs and clopidogrel

Increasing evidence suggests that proton pump inhibitors (PPIs) may attenuate the effect of clopidogrel on platelet aggregation. PPIs are often used prophylactically in patients with acute coronary syndrome (ACS), as patients on clopidogrel and aspirin may be at higher risk for GI bleeding. A new study from VA researchers was set up to determine if there are clinical implications from the interaction between PPIs and clopidogrel.

In a retrospective cohort study of 8205 patients with ACS taking clopidogrel, 63.9% were also prescribed a PPI at discharge, during follow-up, or both. Death or rehospitalization for ACS occurred in 20.8% of patients taking clopidogrel without a PPI and 29.8% patients taking clopidogrel with a PPI. Use of clopidogrel plus a PPI was associated with an increased risk of death or rehospitalization for ACS compared with use of clopidogrel without a PPI (adjusted odds ratio, 1.25; 95% confidence interval, 1.11-1.41). Patients taking a combination of the two drugs were at higher risk for hospitalizations for ACS and revascularization procedures, but not for all-cause mortality. Patients taking a PPI without clopidogrel were not at higher risk for rehospitalization. The authors conclude that concomitant use of clopidogrel and a PPI after hospital discharge for ACS is associated with an increase risk of adverse outcomes, suggesting that PPIs may attenuate the benefits of clopidogrel, and that PPIs should only be used with clopidogrel if there is a clear indication, and not for routine prophylaxis (*JAMA* 2009;301:937-944).

Modafinil's abuse potential

Modafinil (Provigil®) is a wake-promoting medication used to treat narcolepsy and other sleep disorders. Recently, the drug has be used off-label to enhance cognition in psychiatric patients and even in healthy patients seeking a memory boost. Modafinil has been touted as having a low abuse potential; however, a new study questions that assumption. Most stimulant medications, such as methylphenidate and amphetamine, increase brain dopamine levels. Modafinil was thought to exert its effect in the brain on pathways other than dopamine, but now there is evidence that dopamine is involved. Researchers from the National Institute on Drug Abuse looked at 10 healthy male volunteers to measure the effects of modafinil at therapeutic dosing of 200 mg and 400 mg given orally. PET scans were used to measure the effect of modafinil on extracellular dopamine and dopamine transporters. Modafinil increased extracellular dopamine and showed evidence of occupancy of dopamine transporters, effects similar to drugs with the potential for abuse. The authors conclude that, considering the increasing use of modafinil, there needs to be heightened awareness for potential abuse of and dependence on modafinil in vulnerable populations (*JAMA* 2009;301:1148-1154).

FDA Actions

The FDA is requiring the manufacturers of metoclopramide (Reglan®) include a boxed warning on their labeling regarding the risk of long-term or high-dose use and tardive dyskinesia. Manufacturers will also be required to implement a risk evaluation and medication strategy (REMS) to ensure patients are provided with a medication guide that discusses the risk. Metoclopramide is approved for the treatment of gastric motility problems associated with GERD, diabetic gastroparesis, and nausea and vomiting.

A new proton pump inhibitor has been approved by the FDA, bringing the number of PPIs on the market to six. Dexlansoprazole is the purified active isomer of lansoprazole (Pepcid®). The drug has a delayed-release formulation designed to provide two separate releases of the medication. It is approved for the treatment of GERD and erosive esophagitis. Takeda Pharmaceuticals will market dexlansoprazole as Kapidex™. ■