CRITICAL CARE ALERT®

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

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INSIDE

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Do Silver-coated Endotracheal Tubes Affect VAP Mortality?

ABSTRACT & COMMENTARY

By Richard 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 exploratory analysis of patients with VAP in a previous trial showed an association between lower mortality and use of a silver-coated tube.*

Source: Afessa B, et al. Association between a silver-coated endotracheal tube and reduced mortality in patients with ventilator-associated pneumonia. *Chest* 2009 Dec 28; Epub ahead of print.

ENDOTRACHEAL TUBES (ETTs) COATED WITH ANTIMICROBIAL SUBSTANCES can reduce bacterial adhesion on the tube, block biofilm formation, and reduce bacterial burden in tracheal secretions. Various antimicrobial agents have been employed for this purpose. One tube has silver ions in a polymer on both the inner and outer lumens. The ions migrate to the surface and provide a sustained antimicrobial effect. Recently, the North American Silver-Coated Endotracheal Tube (NASCENT) study showed that a silver coating prevents ventilator-associated pneumonia (VAP).[1]

The NASCENT study was a prospective, randomized controlled trial conducted in 54 North American centers between 2002 and 2006. Adults expected to require mechanical ventilation with an ETT for at least 24 hours were randomly assigned to intubation with either a silver-coated tube or a non-coated tube. VAP diagnosis was based on quantitative cultures of bronchoalveolar lavage fluid. Overall, VAP rates were lower in patients intubated with coated tubes (4.8% vs 7.5%; $P = 0.03$), with a 36% relative risk reduction in VAP incidence. No significant differences were observed in the duration of intubation, ICU stay, hospital stay, mortality, or adverse events.

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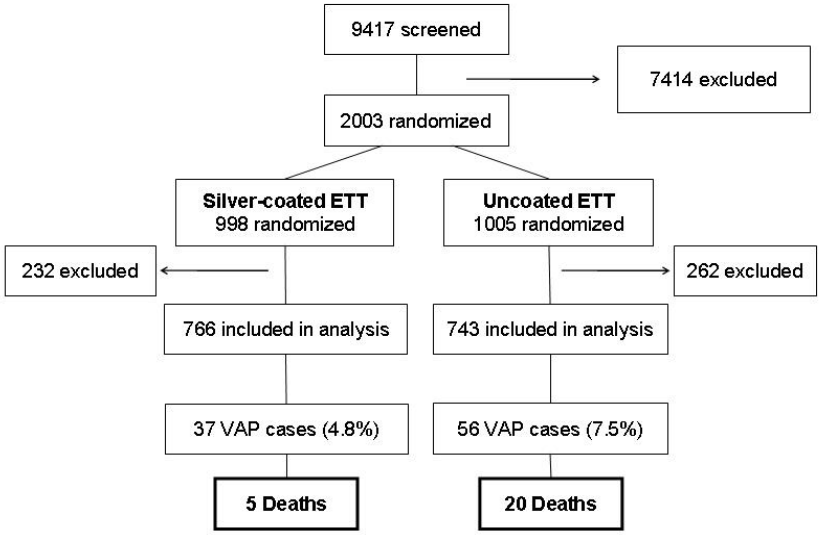
Figure. Flow chart of patients in the North American Silver-Coated Endotracheal Tube (NASCENT) study,[1] showing the sources and numbers of patients used in this exploratory analysis of mortality in ventilator-associated pneumonia



In the current paper, the NASCENT data set was re-examined to explore various subsets of patients. First, the authors looked at the subset of 93 patients who were diagnosed with VAP. Next, they looked at the tiny subset of 25 VAP patients who died. They then looked at the subset of 406 patients who died without VAP. Finally, the authors reviewed microbiology and identified VAP cases with potentially multidrug-resistant bacteria. All of this information was entered into a series of multivariate analyses to evaluate the influence of ETT type and other variables on mortality.

After displaying the various analyses in several somewhat confusing tables, the authors focus most of their discussion (and the title of the paper) on the subset of 25 VAP patients that died *(see Figure, above)*. Their conclusion: A silver-coated ETT is associated with lower risk of mortality in patients with VAP.

COMMENTARY

This study is an exploratory analysis, pure and simple. The authors took subsets of data from a prior randomized trial and performed new multivariate analyses to see if they could uncover any associations. Such post-hoc analyses are frequently performed to generate new hypotheses for future studies. Information gleaned from an exploratory analysis, however, should never impact clinical practice.

An exploratory analysis is handicapped from the start. It inherits all of the problems from its parent trial including imbalances in enrollment, errors in measurement, missing data, unmeasured confounding, biases, and random bad luck. Then it asks new unblinded questions which the data were not originally designed to answer. Using a traditional *P*-value of 0.05 means that researchers only need to ask 20 exploratory questions before they will uncover a new false-positive "truth."

The original NASCENT study tested a specific intervention (silver-coated ETT) and looked at a specific outcome (VAP incidence). It was a sophisticated and challenging multicenter study, with large numbers of patients

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Questions & Comments

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

excluded for various reasons. The incidence of the primary outcome was low in both the intervention and control arms. Despite randomizing 2003 patients, there were only 93 VAP cases *(see Figure)*.

The current article claims to look at "mortality in patients with VAP." In the NASCENT trial, however, mortality was a secondary outcome, and there were only 25 deaths in the two arms combined. Thus, any death analyses in the current paper are based on comparisons between a group of five and a group of 20. Did I mention that the current study was funded by the manufacturer of the silver-coated tube (Bard; Covington, GA)? Reader beware.

Don't get me wrong. I have enormous respect for the authors of the current paper. They are fantastic clinical researchers and world-class experts on VAP. Given their clinical acumen, their implications may indeed be true. However, this study is merely hypothesis-generating. These analyses are conducted in a subset of a subgroup of a narrowly selected study population. The study provides little useful information for a practicing clinician.

So what do we know? From the NASCENT trial, we know that silver-coated tubes lower the risk of VAP by approximately 35% and also delay the onset of VAP. However, the trial never suggested that silver-coated tubes reduce mortality. Quite the contrary. In the NASCENT trial, mortality rates were higher in the silver-coated group (31% vs 27%; $P = 0.08$). But yes, I suppose we know one other thing — the authors will certainly be back with a larger more rigorous study looking at some of these newly uncovered "truths." Stay tuned.

Reference

1. Kollef MH, et al. Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia. *JAMA* 2008;300:805-813.

Can We Make Intubation a Safer Procedure for Patients?

ABSTRACT & COMMENTARY

By Andrew M. Luks, MD

Pulmonary and Critical Care Medicine, University of Washington, Seattle

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

Synopsis: *This two-phase, prospective, multicenter study demonstrated that implementation of an intubation management protocol reduced the incidence of severe hypoxemia and cardiovascular collapse during endotracheal intubation when compared to standard practice, but did not improve other patient outcomes such as ICU mortality or duration of mechanical ventilation.*

Source: Jaber S, et al. An intervention to decrease complications related to endotracheal intubation in the intensive care unit: A prospective, multiple-center study. *Intensive Care Med* 2010;36:248-255.

Endotracheal intubation is a procedure fraught with multiple, potentially life-threatening complications. Given that "care bundles" have been associated with improved management of various critical care problems including severe sepsis and ventilator sedation and weaning, Jaber and colleagues sought to determine whether implementation of an intubation management protocol would decrease the incidence of intubation-related complications.

To investigate this question, they conducted a two-phase intervention study involving all ICU endotracheal intubation procedures, except those performed for cardiac arrest, at three different hospitals. During a 6-month control phase, intubation was performed by the clinician caring for the patient without use of a protocol. This was followed by a 4-month lead-in period during which an intubation management bundle was developed and all ICU staff received training in the bundle practices and a 6-month intervention period during which all intubations were performed using the management bundle. The bundle comprised a total of 10 interventions including the presence of two operators, fluid administration prior to intubation (500 mL normal saline or 250 mL of hydroxyethyl starch), preparation of long-term sedation, preoxygenation for 3 minutes using non-invasive positive pressure ventilation (NIPPV), rapid sequence intubation using etomidate or ketamine with succinylcholine, cricoid pressure, confirmation of tube placement by capnography, norepinephrine for low diastolic pressure post-intubation, initiation of long-term sedation and selection of initial ventilator settings (tidal volume 6-8 mL/kg IBW; F_IO_2 1.0; PEEP < 5 cm H_2O; and respiratory rate 10-20 breaths/min). During each study period, they recorded the number of severe life-threatening complications (death, cardiac arrest, hypotension that persisted > 30 minute or required vasopressor support, severe hypoxemia) and mild-to-moderate complications (intubation requiring > 3 attempts, > 10 minutes, or need for another operator; esophageal intubation, gastric aspiration, arrhythmia requiring intervention, severe agitation, or dental injury). Other outcome measures included the duration of mechanical ventilation, the number of ventilator-free ICU days, ICU length of stay, and vital status

upon ICU discharge.

There were 121 intubations during the control period and 123 intubations in the intervention period, with the two groups being well matched in terms of reasons for intubation and other clinical factors. Among those patients intubated during the intervention period, 75% of the total recommended number of procedures was followed by practitioners. Intubation during the intervention phase was associated with a lower incidence of life-threatening (21% vs 34%; $P = 0.03$) and mild-to-moderate (9% vs 21%; $P = 0.01$) complications. This result appears to be driven by a large decrease (~ 50%) in the incidence of severe hypoxemia ($SpO_2 < 80\%$ during intubation attempts) and cardiovascular collapse during the intervention phase, as there were no statistically significant differences in the incidence of other complications, including cardiac arrest or death, esophageal intubation, aspiration, agitation, or dental injury. With regard to the other outcome measures, there were no differences in the duration of mechanical ventilation or ICU stay, the number of ventilator-free days, or ICU mortality between the two patient groups.

COMMENTARY

Care bundles are becoming an increasingly prevalent part of ICU practice as we now have bundles for a large number of processes including ventilator management, ventilator weaning, sedation, and treatment of sepsis, pneumonia, and myocardial infarction. Given the risks associated with endotracheal intubation and the potential for life-threatening complications, any practice that decreased such risk would be a worthwhile intervention and the study by Jaber and colleagues suggests there may be opportunities for improvement on this front. Although the incidence of many types of complications (e.g., esophageal intubation, gastric aspiration) was not decreased, they did show a significant decrease in the incidence of severe hypoxemia and hemodynamic instability, two important outcomes.

One of the interesting phenomena of evidence-based practice in critical care and other aspects of medicine is that when a study demonstrates a positive result, the practices used in that study are often adopted wholesale with little modification. An excellent example of this is the positive end-expiratory pressure-inspired oxygen fraction "ladder" that is frequently used in management of hypoxemia in patients with the acute respiratory distress syndrome. Although there is no physiologic basis for the ladder, it has been widely adopted at many institutions because it was the procedure used in the original ARDS Network study. While the study by Jaber and colleagues supports the notion of having an intubation bundle, there are aspects of their procedures that may not be ideal and should be re-evaluated before adoption of such a bundle at other institutions. Their protocol, for example, called for starting individuals on a tidal volume of 6-8 mL/kg predicted body weight, even though there is no evidence to support these tidal volumes in all individuals and such low tidal volumes at the initiation of mechanical ventilation may lead to atelectasis and worsening oxygenation beyond the short time frame analyzed in this study. They also call for a respiratory rate of 10-20 breaths/min, a number that is likely adequate for many patients but would lead to severe hypoventilation in patients with severe metabolic acidosis, particularly in light of the low tidal volumes in the protocol. In addition, there were items that were omitted from the protocol that might be of benefit. One could imagine, for example, adding an element to the protocol about airway assessment and mandating the availability of Eschmann stylets or ultrasound-guided laryngoscopy for any patients with unfavorable airway characteristics.

Given these concerns about the particular protocol elements, it is best to view the study by Jaber and colleagues as establishing "proof of concept" rather than providing a detailed roadmap we should all follow. What is needed prior to widespread adoption of these protocols is to refine the procedures contained within the protocol to ensure we are delivering optimal care.

Daily Multidisciplinary ICU Rounds Improve Patient Outcomes

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *In this large retrospective cohort study of more than 100,000 patients in 112 hospitals, after correction for illness severity and other factors, daily rounds by a multidisciplinary care team were associated with lower mortality in the ICU, regardless of whether an intensivist model of physician staffing was in use.*

Source: Kim MM, et al. The effect of multidisciplinary care teams on intensive care unit mortality. *Arch Intern Med* 2010;170:369-376.

Kim and associates conducted a population-based, retrospective cohort study of medical patients admitted to acute care hospitals throughout the state of Pennsylvania between July 2004 and June 2006. They linked a statewide hospital organizational survey with hospital

discharge data, and used multivariate logistic regression to look for independent relationships between daily multidisciplinary ICU rounds and 30-day patient mortality. They used data from each hospital's ICU that treated the largest number of adult, noncardiac, nonsurgical patients, and thus excluded pediatric ICUs and patients with primary cardiac, neurological, or surgical diagnoses. ICUs were classified according to whether physician staffing was by primary intensivist management, mandatory intensivist consultation, optional intensivist consultation, or absence of any intensivist. Whether a given hospital had multidisciplinary ICU rounds was determined by a yes or no answer to the question, "Does the ICU have daily multidisciplinary ICU rounds consisting of the physician, nurse, and other health care professionals (e.g., social worker, respiratory therapist, pharmacist)?" Based on the responses, hospitals were classified into four categories: 1) low-intensity staffing without multidisciplinary care teams; 2) low-intensity staffing with multidisciplinary care teams; 3) high-intensity staffing with multidisciplinary care teams; and 4) high-intensity staffing without multidisciplinary care teams.

Altogether, 471,112 patients were admitted to ICUs in 169 Pennsylvania hospitals during the study period. Kim et al excluded 55 hospitals (135,923 patients) that did not provide complete survey data, and also, because of their small number, the two hospitals (7699 patients) in category 4 above (high-intensity staffing but no multidisciplinary care teams). Further exclusion of patients with nonmedical diagnoses left 107,324 patients in 112 hospitals as the study cohort. Of these, 54 hospitals (48%) were in category 1, 36 (32%) were in category 2, and 22 (20%) were in category 3.

There was considerable heterogeneity among the hospitals, with those in category 3 (high-intensity staffing with multidisciplinary care teams) tending to be larger, teaching hospitals caring for sicker patients with more comorbidities. Accordingly, unadjusted in-hospital mortality was highest (16.4%) in those hospitals. However, after adjusting for patient and hospital characteristics, multidisciplinary care was associated with significant reductions in the odds of death (odds ratio [OR], 0.84; 95% confidence interval [CI], 0.76-0.93; $P = 0.001$). Stratified by intensivist physician staffing, the lowest odds of death were in high-intensity units with multidisciplinary care teams (OR, 0.78; 95% CI, 0.68-0.89; $P < 0.001$), followed by ICUs with low-intensity staffing and multidisciplinary care teams (OR, 0.88; 95% CI, 0.79-0.97; $P = 0.01$), as compared to low-intensity hospitals without multidisciplinary care teams. These findings persisted with examination of different patient subgroups, including those with sepsis, the requirement for mechanical ventilation, and the greatest severity of illness.

COMMENTARY

Numerous studies have shown that the presence of trained intensivists is associated with improved ICU outcomes, including mortality. This study shows that this benefit is at least in part due to multidisciplinary ICU teams in units where this model of patient care is present. That is, for medical ICU patients, all other factors being equal (e.g., primary diagnosis, severity of acute illness, and comorbidities), the likelihood of survival is better if they are managed in a unit in which the physician rounds daily with the nurse and others such as a clinical pharmacist, respiratory therapist, and/or social worker.

As the authors point out, the reasons for this association are uncertain. However, there are a number of likely explanations. Multidisciplinary rounds may reduce practice variation among individual physicians, facilitate management according to accepted best practices, and foster the implementation of evidence-based treatments (such as lung-protective ventilation for acute lung injury), the use of checklists (such as for central line insertion), and the use of protocols (such as for sedation and ventilator weaning). Pharmacist participation in rounds reduces medication errors and other drug-related adverse events. And rounding together on a daily basis undoubtedly improves communication among the different members of the ICU team.

Although the continuous presence of a trained intensivist is accepted as an ideal for ICU care, fewer than half of all units in the United States currently have such staffing. The present study demonstrates that, regardless of whether the high-intensity intensivist staffing model is in effect, daily multidisciplinary care rounds are associated with better patient outcomes. It thus suggests that implementing multidisciplinary ICU care could reduce mortality in units that do not currently use it.

Can We Ventilate Patients Without Sedation?

ABSTRACT & COMMENTARY

By Andrew M. Luks, MD

Pulmonary and Critical Care Medicine,
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Dr. Luks reports no financial relationship to this field of study.

Synopsis: *This single-center randomized trial demonstrated that when compared with standard sedation*

practices and daily sedation vacations, a protocol of no sedation was associated with a shorter duration of mechanical ventilation in critically ill patients.

Source: Strom T, et al. A protocol of no sedation for critically ill patients receiving mechanical ventilation: A randomised trial. *Lancet* 2010;375:475-480.

While intravenous infusion of sedative medications and daily sedation vacations have become standard practice in most ICUs, an institution in Denmark has actually been ventilating patients without intravenous sedatives for several years. Strom and colleagues sought to determine if this strategy was associated with shorter duration of mechanical ventilation than the more standard approach of sedative infusions and daily interruption of sedation.

The authors conducted a single-center, randomized, non-blinded study of critically ill patients who were expected to need mechanical ventilation > 24 hours. Patients were excluded if they had elevated intracranial pressure, had medical indications for sedative infusions (e.g., status epilepticus), were pregnant, or met criteria for ventilator weaning. Patients in the intervention group received bolus sedation with morphine (2.5 or 5 mg) on an as-needed basis. Physical restraints were not used and patients suspected of having delirium were treated with haloperidol. Patients who were still uncomfortable despite haloperidol received propofol for 6 hours after which time a trial off sedation was restarted. In addition to bolus morphine administration, patients in the control group received a propofol infusion before being transitioned to midazolam after 48 hours and received daily interruptions of their sedative infusion. All patients were ventilated using pressure support and once ventilator settings for patients in the control group reached an inspired oxygen fraction of 0.4 and positive end-expiratory pressure of 5 cm H_2O, sedation was discontinued unless their ventilator requirements worsened. The primary outcome measure was the number of days without mechanical ventilation in the 28 days following intubation. Secondary outcomes included total length of stay in the ICU, ICU and hospital mortality, need for brain imaging, unplanned extubation, and ventilator-associated pneumonia.

A total of 140 patients were enrolled in the study (67% male; 33% female) but 27 were excluded from the analysis because mechanical ventilation was stopped within 48 hours. Ten of the 55 patients (18%) in the no-sedation group required continuous sedation with propofol on more than two occasions, usually due to oxygenation problems in the setting of severe acute respiratory distress syndrome (ARDS). Patients in the intervention group spent 4.2 fewer days (95% confidence interval, 0.3-8.1) on the ventilator than patients in the control group and had a shorter length of ICU stay (13.1 vs 22.8 days) and hospital stay (34 vs 58 days). Morphine use was not different between the two groups (0.0048 mg/kg/hr of mechanical ventilation in the intervention group vs 0.0045 mg/kg/hr in the control group). There were no statistically significant differences in ICU or in-hospital mortality, need for brain imaging, unplanned extubation, ventilator-associated pneumonia, or a need for reintubation within 24 hours. Delirium was more common in the intervention group (20% vs 7%) and haloperidol was used more frequently in that group (19 vs 8 patients).

COMMENTARY

Strom and colleagues demonstrate that it may be possible to move beyond the benefits of daily interruption of sedative medications and achieve further gains with a no-sedative strategy for many but not all, critically ill patients. In fairness, this was not truly a "no-sedation" strategy as all patients received bolus doses of morphine, a medication with sedative effects, but they did manage most of the patients without the need for propofol or midazolam. Of particular note was the fact that they were able to do so without seeing an increase in complication rates such as unplanned extubation or ventilator-associated pneumonia.

Before we rush to turn off the propofol and midazolam drips on all of our patients, however, there are several key issues that must be addressed. The first, and most obvious, issue is that this was a single-center study with a limited number of patients. More importantly, the protocol was implemented at an institution that already had almost 8 years of experience with the no-sedation strategy at the time the trial was conducted. As a result, both physician and nursing staffs were likely comfortable and facile with the approach, a situation that might not exist at other institutions where the use of sedation is strongly ingrained in ICU practice. For this reason, we will clearly need larger, multicenter trials to establish that this approach can be adopted safely at institutions with a tradition of different sedation practices. It is not difficult to imagine the culture shift that such a strategy will require and more data will be necessary to encourage such a shift.

Other aspects of the protocol also warrant attention and may limit attempts at implementation. The ICU in this study maintained a 1:1 patient-nurse ratio for all study participants and the investigators also used extra people to help calm the patients when they developed agitation. These are resource-intensive measures that may not be feasible at many institutions and it remains to be seen whether the cost savings associated with shorter duration of mechanical ventilation and ICU stay offset the costs of

these resources.

Finally, it is worth noting that while the strategy was successfully implemented in many patients, 18% of those patients randomized to the no-sedation group ultimately required infusions of sedative medications. This tended to be in the patients with severe ARDS and indicates that the strategy might not be suitable for all individuals. Interestingly, the mean APACHE II scores were fairly high in the intervention and control groups (average score, 26 in both groups), suggesting that severity of illness alone may not predict the need for sedation. In fact, the more severely ill patients may be more encephalopathic and, as a result, may need less sedation than less ill patients who are more alert and, as a result, more uncomfortable with the endotracheal tube and other interventions. Follow-up studies of the no-sedation approach will need to address the question of which groups are appropriate for this particular strategy.

Acetazolamide Does Not Facilitate Weaning in Patients with COPD

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *This case-control study of 26 mechanically ventilated patients with severe COPD and metabolic alkalosis demonstrated that daily doses of acetazolamide caused a modest decrease in serum bicarbonate levels but had no effect on the duration of weaning or any other examined outcome.*

Source: Faisy C, et al. Effectiveness of acetazolamide for reversal of metabolic alkalosis in weaning COPD patients from mechanical ventilation. *Intensive Care Med* 2010 Mar 9; Epub ahead of print.

This clinical study was carried out to test the hypothesis that acetazolamide (Diamox®) would correct metabolic alkalosis and facilitate weaning in intubated patients with severe chronic obstructive pulmonary disease (COPD) who had elevated serum bicarbonate and were alkalemic. The authors enrolled 26 patients with COPD and acute respiratory failure (causes not stated) who had been hypercapnic (PCO_2, 77 ± 22 mmHg) and acidemic (pH, 7.25 ± 0.10) at the time of intubation. They were considered to be ready to wean from ventilatory support when there had been resolution of the acute process for which the patient was intubated, were receiving no sedation and had a Glasgow Coma Scale Score > 12, had an adequate cough and absence of excessive secretions, were afebrile and hemodynamically stable, and had no significant abnormalities in plasma electrolytes and serum glucose levels. For weaning, the patients were also required to have a respiratory rate ≤ 35 breaths/min, to be on ≤ 50% oxygen and ≤ 8 cm H_2O of positive end-expiratory pressure with $PaO_2/F_IO_2 \geq 150$ mmHg, and to have "no significant respiratory acidosis" (not further defined).

Once these criteria were met the patients received a single daily intravenous infusion of acetazolamide, 500 mg. Weaning was carried out via progressive reduction of pressure support and/or daily T-piece trials. Weaning success as well as bicarbonate levels and arterial blood gas values were recorded and compared with those of a 1:1 historical control group managed in the same ICU using the same protocols who were matched for demographics, pulmonary function, and other factors but did not receive acetazolamide.

There were no statistically significant differences between the acetazolamide patients and the controls with respect to age, gender, BMI, FEV1 (35% and 37% of predicted, respectively), baseline COPD management, ventilator management, arterial blood gases (pH 7.45 and 7.44; PCO_2 48 and 50 mmHg), or serum bicarbonate (34.5 and 32.5 mmol/L) at the time of readiness to wean. Acetazolamide was administered for a mean of 4 days (range, 1-11 days) in the experimental group, whose serum bicarbonate values decreased significantly (mean, 3.8 mmol/L; $P = 0.01$) by the time of extubation. However, serum bicarbonate, PCO_2, and pH were no different between the experimental and control patients at the time of extubation. There were no significant differences in any other evaluated outcome variable — duration of weaning, total number of days ventilated, extubation success, use of non-invasive ventilation as rescue, or re-intubation rate — between the acetazolamide and historical control groups.

COMMENTARY

This case-control study showed that the administration of acetazolamide to patients with severe COPD who were recovering from acute respiratory failure and who were alkalemic but otherwise considered ready for weaning had no effect on outcome except for a somewhat lower serum bicarbonate level. Acetazolamide (Diamox) is a carbonic anyhdrase inhibitor that essentially causes metabolic acidosis. It has been used for many years to stimulate respiratory drive and to counter elevated bicarbonate levels, and it continues to be administered to patients with COPD in an attempt to facilitate ventilator weaning by reducing alkalemia. However, even theoretically the rationale is shaky. Patients with severe COPD and underlying chronic hypercapnia need their compensatory metabolic

alkalosis in order to ameliorate the acidemia that would exist without the elevated serum bicarbonate. If such patients were to maintain a normal pH in the face of a "normal" bicarbonate, they would also have to normalize alveolar ventilation and PCO_2, something that may not be feasible physiologically, at least during recovery from acute respiratory failure.

A fundamental aspect of managing patients with severe COPD who require intubation and mechanical ventilation is to avoid over-ventilation and alkalemia. When the latter occurs, the depressant effect of alkalosis on ventilatory drive is often cited as a rationale for using acetazolamide to decrease serum bicarbonate. However, patients with COPD who fail weaning nearly always manifest rapid shallow breathing and respiratory distress, signs of inadequate mechanical capabilities rather than diminished drive to breathe. In any event, although its case-control design is problematic, this study failed to demonstrate any clinically relevant effect of acetazolamide on weaning. This agent does not appear to be helpful in weaning patients with COPD from mechanical ventilation.

CME / CNE Questions

3. **Which of the following statements is *true* about silver-coated endotracheal tubes, ventilator-associated pneumonia, and mortality?**
   a. Silver-coated endotracheal tubes reduced mortality in a randomized controlled study, as compared with non-coated tubes.
   b. Silver-coated endotracheal tubes reduced VAP incidence in a randomized controlled study, as compared with non-coated tubes.
   c. The NASCENT trial was an exploratory analysis.
   d. None of the above
   e. All of the above

4. **Adoption of an endotracheal intubation bundle was associated with improvement in which of the following outcomes?**
   a. Incidence of severe hypoxemia (SpO_2 < 80%) during the intubation attempt
   b. Incidence of severe hypoxemia (SpO_2 < 80%) two hours following intubation
   c. Esophageal intubation
   d. Aspiration of gastric contents
   e. Dental complications

5. **Which of the following statements is *true* about the use of acetazolamide to facilitate weaning in patients with severe COPD?**
   a. It shortens the weaning process.
   b. It decreases ventilatory drive.
   c. It worsens metabolic alkalosis.
   d. It increases arterial PCO_2.
   e. None of the above

Answers: 3. b, 4. a, 5. e.

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.

In Future Issues: **Reducing Pain on Chest Tube Removal**

PHARMACOLOGY WATCH

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

Finding ACCORD in the Management of Type 2 Diabetes?

In this issue: Examining the three arms of the ACCORD trial; and FDA Actions: clopidogrel, dexlansoprazole, and tamsulosin.

ACCORD and type 2 diabetes

Every once in a while a medical study comes along that turns medical dogma on its ear. The Multiple Risk Factor Intervention Trial (MRFIT), published in 1982, was such a study, so was the Women's Health Initiative (WHI), published in 2002. Both studies challenged conventional wisdom and changed practice. MRFIT caused us to take a hard look at risk factor intervention especially hypertensive treatment, while WHI established that combination hormone therapy in postmenopausal women should no longer be routinely recommended because of the risk of breast cancer and heart disease.

The Action to Control Cardiovascular Risk in Diabetics (ACCORD) trial, published in March in the *New England Journal of Medicine*, is also such a study, and is destined to change medical practice in the treatment of type 2 diabetes. ACCORD looked at three aspects of care in type 2 diabetes, the first was the effects of intensive glucose lowering, the second was the effect of intensive blood pressure control, and the third was the effect of combination lipid therapy.

The intensive glucose lowering study was published early in 2008 when it was found that the intensive therapy group (targeting hemoglobin A1c < 6.0%) reported a higher mortality than the standard therapy group (targeting A1c 7.0%-7.9%). At the same time, intensive therapy did not significantly reduce major cardiovascular events (*N Engl J Med* 2008;358:2545-2559).

The second and third wings of the ACCORD trial were published on-line March 14, and the results were similarly discouraging for aggressive care. A total of 4733 participants with type 2 diabetes were enrolled in the intensive blood pressure control wing and were randomized to intensive therapy, targeting a systolic pressure < 120 mmHg, or standard therapy targeting a systolic blood pressure < 140 mmHg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After a mean follow-up of 4.7 years, mean target blood pressures were met in both groups. The annual rate of the primary outcome was 1.87% in the intensive therapy group and 2.09% in the standard therapy group (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.73-1.06; P = 0.20). The annual rates of death from any cause were 1.28% in the intensive therapy group and 1.19% in the standard therapy group (HR, 1.07; 95% CI, 0.85-1.35; P = 0.55). There was a slightly reduced risk of stroke in the intensive therapy group (0.32% vs 0.53%; P = 0.01); however, serious adverse events were more than double in the intensive therapy group. The authors conclude

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that in patients with type 2 diabetes targeting systolic blood pressure < 120 mm Hg as compared to < 140 mm Hg did not reduce the rate of the composite outcome of fatal and nonfatal major cardiovascular events (*N Engl J Med* published on-line March 14, 2010). While these results are somewhat surprising, they may not change the general recommendation for more aggressive blood pressure management in type 2 diabetes to systolic blood pressure ≤ 130/80 mm Hg, which is consistent with most current guidelines (including JNC VII).

In the third wing of ACCORD, 5518 patients with type 2 diabetes who were being treated with the statin simvastatin were randomized also to receive fenofibrate or placebo. The primary outcome was first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After a mean follow-up of 4.7 years, the annual rate of primary outcome was 2.2% in the fenofibrate group and 2.4% in the placebo group (HR 0.92; 95% CI, 0.79-1.08; P = 0.32). There were also no significant differences between the two study groups with respect to any secondary outcomes or death rate. Subgroup analysis suggested slightly higher benefit for men vs women and perhaps a benefit for those with high baseline triglycerides (> 204 mg/dL) and low HDL (≤ 34 mg/dL). The authors conclude that the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke compared with simvastatin alone (*N Engl J Med* published on-line March 14, 2010). This study does not in any way diminish the known benefit from aggressive statin therapy in type 2 diabetics, but does suggest that targeted treatment of triglycerides with fenofibrate is of no value. The FDA is reviewing the ACCORD data, but as of this time they have "made no new conclusions or recommendations regarding the use of simvastatin or other statin drugs and fenofibrate."

Do statins increase the risk of type 2 diabetes? It has been suggested that lipophilic statins may cause unfavorable metabolic side effects such as reduction of insulin secretion and worsening of insulin resistance. In a small single-blind, placebo-controlled parallel study, 40 to 44 patients were randomized to receive placebo, or atorvastatin 10, 20, 40, and 80 mg during a 2-month period. While atorvastatin significantly reduced LDL and apolipoprotein B levels, the drug was also associated with significantly increased fasting plasma insulin levels, as well as hemoglobin A1c levels (mean changes in fasting insulin levels, 25%, 42%, 31%, and 45%, respectively, for increasing dose; A1c increases of 2%, 5%, 5%, and 5%, respectively; P < 0.05 by paired t-test). Atorvastatin also decreased insulin sensitivity in a dose-responsive fashion. The authors conclude that atorvastatin resulted in significant increases in fasting insulin, hemoglobin A1c consistent with increased insulin resistance (*J Am Coll Cardiol* 2010;55:1209-1216). Previous studies have shown similar results with lipophilic statins including atorvastatin, rosuvastatin, and simvastatin, while pravastatin seems to reduce the risk of diabetes.

FDA Actions

The FDA has issued a warning to health care providers regarding the antiplatelet drug clopidogrel (Plavix®). It is recently been found that up to 14% of the population did not metabolize the drug effectively and may not fully convert the drug to its active form. Clopidogrel is dependent on CYP2C19 and those that genetically lack the enzyme may not convert the drug to its active form. Recent studies have suggested that reduced CYP2C19 activity was associated with higher risk for cardiovascular outcomes. A test is available to identify genetic differences in CYP2C19 function and the FDA is recommending that health care professionals consider use of other antiplatelet medications or use alternative dosing if patients are poor metabolizers. The manufacturer of Plavix is being asked to add a black box warning to the drug labeling to this effect. Previously, it was discovered that some proton pump inhibitors including omeprazole may also inhibit metabolism to the active drug. Meanwhile Eli Lilly's prasugrel (Effient®), a direct competitor to clopidogrel, is not affected by CYP genetic variants.

The FDA has approved Takeda Pharmaceutical's request to change the name of its proton pump inhibitor dexlansoprazole from Kapidex® to Dexilant™. The change is being made due to several dispensing errors that occurred between Kapidex and the prostate cancer drug Casodex® (bicalutamide) and the analgesic Kadian® (morphine).

The FDA has approved a generic version of Boeringer Ingelheim's tamsulosin (Flomax®) for the treatment of benign prostatic hyperplasia in men. Generic tamsulosin should be available later in 2010.