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Critical Care [ALERT]

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

ABSTRACT & COMMENTARY

Is Pulmonary Oxygen Toxicity Still a Clinically Relevant Issue?

By Richard H. Kallet, MS, RRT, FAARC, FCCM
Director of Quality Assurance, Respiratory Care Services, San Francisco General Hospital
Dr. Kallet reports no financial relationships relevant to this field of study.

SYNOPSIS: This retrospective study examined pulse oximetry saturation and inspired oxygen fraction at 15-minute intervals in patients with acute lung injury. Using predetermined cutoff values for each variable, the authors determined that the duration of excessive oxygen administration was significantly related to worse oxygenation index at 48 hours of mechanical ventilation.

SOURCE: Rachmale S, et al. Practice of excessive inspired oxygen supplementation and effect on pulmonary outcomes in mechanically ventilated patients with acute lung injury. *Respir Care* 2012; May 15. [Epub ahead of print.]

Rachmale and colleagues retrospectively identified 210 patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS) undergoing mechanical ventilation for longer than 48 hours. They abstracted matched measurements of pulse oximetry saturation (SpO_2) and inspired oxygen fraction (FiO_2) at 15-minute intervals. Excessive O_2 exposure was defined a priori as an FiO_2 greater than 0.5 when the corresponding SpO_2 was greater than 92%. By institutional guidelines, tidal volumes ostensibly were kept between 6-8 mL/kg predicted body weight, whereas oxygenation goals were set by clinician discretion. Initially, both groups had comparable tidal volumes and positive end expiratory pressure (PEEP) levels, similar hemoglobin levels, and hemodynamic status.

In the first 48 hours of mechanical ventilation, 74% of patients had a SpO_2 greater than 92% with a corresponding FiO_2 greater than 0.5, whereas 53% had exceeded the SpO_2 threshold on an FiO_2

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greater than 0.70. The mean duration of excessive oxygen exposure was 17 hours (interquartile range, 7.5-33 hours). Compared to the cohort of patients defined as having appropriate FiO_2 exposure, those with an excessive FiO_2 exposure also had a significantly higher median oxygenation index (OI), which calculated as (O_2% × mean airway pressure/arterial oxygen tension [5.1 vs 13.3, respectively; $P = 0.0001$]), and also had a significantly greater change in OI from baseline to 48 hours (-1.5 vs 4.6, respectively; $P = 0.0001$).

It was determined that at least 12 hours of excessive FiO_2 exposure was required to produce a significant change in OI, after which further exposure had a linear relationship with OI found at 48 hours. The correlation between excessive FiO_2 and deterioration in OI remained despite adjusting for baseline OI and illness severity, as well as the degree of excessive exposure (i.e., $FiO_2 > 0.50$ or 0.70). Overall, 74% of patients had an excessive O_2 exposure representing approximately 20 hours of the first 48 hours of mechanical ventilation. Patients exposed to excessive O_2 had longer durations of mechanical ventilation, ICU, and hospital length of stay. Mortality was not different.

COMMENTARY

The severity of hyperoxic acute lung injury (HALI) is directly proportional to alveolar O_2 partial pressure (P_AO_2) and exposure duration. Across numerous species with normal lungs, inflammatory changes typically occur in a dose-dependent fashion only when P_AO_2 exceeds 450 mmHg (FiO_2 of 0.60) for several days.[1] Recently, it was found that mitochondrial production of reactive O_2 species increases at a substantially greater rate when FiO_2 is greater than 0.60.[2] HALI is both species-dependent and varies widely among individual animals. Susceptibility reflects a genetically determined response to injury through a balance between complex pro- and anti-inflammatory cellular mechanisms.[1] Humans appear to be *relatively* more resistant than other mammals to HALI.

From the late 1960s through the 1970s, the risk of HALI was exaggerated, in part because the pathogenesis of ARDS was poorly understood and its connection to ventilator-induced lung injury was unknown. In addition, all evidence used to support the clinical incidence of HALI was based on small, poorly controlled, retrospective studies. Moreover, as PEEP became a standard therapy for improving oxygenation in ARDS, most patients could be managed with a relatively non-toxic FiO_2, and consequently concern over HALI faded as a clinical priority.

However, whether excessive FiO_2 exposure might potentiate ALI/ARDS remains unknown. The few animal studies examining this issue have produced mixed results; likely because different animals and different methods of inducing ALI were used.[2] Currently, there is no compelling evidence supporting the findings of Rachmale et al. And as an initial impression, both the level of FiO_2 and the duration of excessive O_2 exposure in this study seem inadequate to substantially augment ALI/ARDS. The investigators also were appropriately cautious in their interpretation given the retrospective nature of their study, and, most importantly, noting that mathematical coupling necessarily biased their results (as inspired O_2% is a component of OI).

However, the statistical significance of their results is intriguing and deserves further study. Their findings would have been more convincing had they reported other measures associated with worsening ALI/ARDS (e.g., dead-space fraction and pulmonary compliance). But the authors' findings raise some important questions. First, should severe ARDS be managed more aggressively with higher PEEP and other lung recruitment strategies that might contribute to improved outcomes by reducing HALI? Recent meta-analyses of prospective randomized, controlled trials suggest that higher PEEP[3] and prone positioning[4] may confer a survival benefit in the subset of patients with very severe ARDS. Second, as advances

continue to be made in closed-loop mechanical ventilation, should automated control of FiO_2 be used to minimize periods of excessive O_2 exposure? As Rachmale et al have pointed out, clinicians are reluctant to maintain unstable patients at the brink of desaturation and prefer to maintain a "buffer zone" in O_2 saturation. This is particularly true when the acuity and census are high so that the response time to correct episodes of hypoxemia might be delayed.

Rachmale and colleagues have refocused attention on the possibility that HALI may contribute to morbidity in ALI/ARDS. It is possible that today the pendulum may have swung too far away from the excessive concern over HALI that existed in the 1970s. The critical care community at large has not enthusiastically embraced the routine use of high PEEP and other ancillary therapies that have been shown to improve oxygenation in ARDS. However, in severe ARDS, prolonged exposure to a FiO_2 of 0.80 or greater produces unambiguously toxic effects that may complicate patient management and prolong the need for mechanical ventilation. And in the subset of patients with severe ARDS in whom HALI is most likely to have a profound negative impact, we will likely never have convincing proof. For example, estimates are that it would take 20 randomizing centers approximately 15 years to provide confirmation of the recent meta-analysis that prone positioning improves mortality in very severe ARDS.[4] Therefore, the debate over how to balance PEEP and FiO_2 will continue, but perhaps in the near future with slightly more regard for the parsimonious use of O_2 therapy. ■

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ABSTRACT & COMMENTARY

Crystalloid Solutions Still Better than Colloid Solutions for Fluid Resuscitation

By Eric C. Walter, MD, MSc

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

SYNOPSIS: This blinded, randomized, controlled trial reports a higher risk of mortality, need for renal replacement therapy, and blood product transfusion in patients treated with the colloid solution hydroxyethyl starch compared to those treated with the crystalloid solution Ringer's acetate.

SOURCE: Perner A, et al; 6S Trial Group; Scandinavian Critical Care Trials Group. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012;367:124-134. Erratum: *N Engl J Med* 2012;367:481.

This blinded, randomized, multicenter trial compared the colloid solution low-molecular-weight hydroxyethyl starch (HES 130/0.42) with the crystalloid solution Ringer's acetate for the treatment of severe sepsis. Patients 18 years of age or older diagnosed with severe sepsis (a defined focus of infection and at least two systemic inflammatory response syndrome criteria and at least one new organ failure) who needed fluid resuscitation were included. Patients were randomized in a 1:1 ratio, stratified by the presence or absence of shock, active hematologic cancer, and admission to a university or non-university hospital. Just over 1200 patients were screened, 407 were excluded, and 804 underwent randomization. Most patients were excluded for having received more than 1000 mL of synthetic colloid (37%) or having undergone renal replacement therapy (34%) prior to randomization. The median age was 66 years and 60% were male. At randomization, 84% of patients were in shock, 35% had acute kidney injury, and 61% were mechanically ventilated. Treatment groups were well balanced.

Patients judged to need fluid resuscitation by ICU clinicians were provided trial fluid up to a maximum of 33 mL/Kg of ideal body weight per day. This value was chosen to try to ensure that no patients received more HES than the manufacturer's recommended daily dose of 50 mL/Kg. If additional fluid was required, unblinded

Ringer's acetate was used for all patients. Trial fluid was provided free of charge in identical bags prepared by the manufacturer. The manufacturer had no role in the protocol, trial conduct, data analysis, or reporting.

The composite primary outcome was either death or dependence on dialysis at 90 days and occurred more often in patients who received HES (51%) than in patients who received Ringer's acetate ([43%] relative risk, 1.17; 95% confidence interval [CI] 1.01 to 1.36; $P = 0.03$]. Since only one patient in each group was dependent on dialysis at 90 days, the primary difference in outcome was due to higher mortality among patients given HES. Many secondary outcome measures were also worse among patients given HES. More patients required renal replacement therapy (relative risk, 1.35; 95% CI, 1.01 to 1.80; $P = 0.04$) and blood transfusions (relative risk, 1.20; 95% CI, 1.07 to 1.36).

COMMENTARY

Strengths of this study include a large, heterogeneous patient population from both university and community hospitals in several countries with few exclusion criteria. Thus, the study is well generalizable. The trial was well blinded, minimizing bias. The authors had excellent follow-up with 798 of 804 patients contributing data at 90 days.

There seems to be an endless debate over the use of colloids and crystalloids for fluid resuscitation. Colloids are generally believed to raise oncotic pressure better than crystalloids, allowing for greater plasma volume expansion with less overall fluid requirements. For example, the natural colloid albumin may expand plasma volume 40% more than crystalloid. In the Saline vs Albumin Fluid Evaluation (SAFE) Study, a randomized controlled trial of albumin vs saline in an intensive care unit, patients given saline had a greater net fluid balance compared to those who received albumin.[1] However, the plasma volume expansion properties may differ among colloid solutions. There were no significant differences in fluid volume balance between patients who received HES and Ringer's Lactate in this study.

Those in favor of colloids argue that increased plasma volume expansion leads to a more rapidly improved blood pressure with less overall volume delivered. Despite these arguments, multiple trials have failed to show a benefit over crystalloids with respect to mortality. In the SAFE trial, 28-day mortality did not differ between the two groups. A recent Cochrane review of 66 randomized, controlled trials of various colloid solutions compared to crystalloids also found no difference in mortality.[2] We now have evidence of increased mortality with the use of HES compared to Ringer's acetate.

In summary, the use of HES compared to Ringer's acetate was associated with increased mortality, need for renal replacement therapy, and blood product transfusion. These data, coupled with numerous previous studies and the increased expense of colloids, argue that crystalloids should be used preferentially for most patients requiring fluid resuscitation. ■

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ABSTRACT & COMMENTARY

ICU Admission or General Ward for Diabetic Ketoacidosis? The Answer Varies Dramatically in Different Hospitals

By David J. Pierson, MD, Editor

SYNOPSIS: In a large cohort of patients admitted to New York hospitals with diabetic ketoacidosis, about half were admitted to the ICU, with a range of 2% to 88% among individual hospitals. This large practice variation was unassociated with mortality or length of stay, and more than half of it remained unaccounted for after extensive adjustments for patient and institutional characteristics.

SOURCE: Gershengorn HB, et al. Variation in use of intensive care for adults with diabetic ketoacidosis. *Crit Care Med* 2012;40:2009-2015.

Using a statewide administrative database and other sources, Gershengorn and colleagues examined data on all adult patients with a primary diagnosis of diabetic ketoacidosis (DKA) who were admitted to hospitals in the state of New York from 2005-2007. The investigators sought to determine what proportion of these patients were admitted to the ICU, and what associations with patient or hospital characteristics or other identifiable aspects of care might explain any observed differences.

During the study period, there were 15,994 patient admissions for DKA to 159 hospitals. Most of the hospitals were in urban settings and about half of them were teaching hospitals. Median hospital size was 190 beds with 9.4% of these being ICU beds. The DKA admissions represented 0.4% of all hospital and 1.4% of all ICU admissions to the study hospitals during the 3-year study period. Median reliability- and risk-adjusted hospital mortality was 0.7% (range, 0.4% to 3.4%), and median hospital length of stay was 3 days (range, 1 to 6 days).

Of the admissions for DKA, 52.6% were admitted to an ICU. These patients tended to be younger, white, privately insured, from a higher-income zip code, and admitted on the weekend, with all these differences being statistically significant. They were also more likely to have chronic illnesses and be admitted emergently. The proportion of DKA admissions receiving intensive care varied dramatically across hospitals, with an adjusted range of 2.1% to 87.7%. However, this variation was not associated with mortality or hospital length of stay. ICU admission occurred less often in hospitals that admitted larger numbers of patients with DKA (highest quartile vs lowest, odds ratio 0.40, $P = 0.002$), but more often in hospitals with higher rates of ICU admission for non-DKA admissions (odds ratio 1.31, $P = 0.001$, for each additional 10% increase). Using multilevel modeling to account for individual patient and hospital factors, the authors were able to explain less than half of the observed variation in ICU utilization for patients with DKA: 58% of the variability attributable to hospitals could not be explained.

COMMENTARY

Like acute gastrointestinal bleeding without hypotension, DKA is a common reason for ICU admission that carries a low risk for mortality, and also has a thoroughly studied and highly protocolized management approach. The fact that this study found no differences in mortality or hospital length of stay in nearly 16,000 DKA admissions, only half of which included care in an ICU, reinforces the concept that a large proportion of such admissions can be handled safely and effectively on the acute-care wards. Despite the large number of patients included, this retrospective study based on administrative data cannot determine the reasons for the differences in ICU admission rates among the various hospitals. However, Gershengorn et al nicely demonstrate that the issue of where to manage DKA patients is currently being approached very differently in different institutions, with a rate of ICU admission varying from 1 in 50 to more than 4 out of every 5 such patients.

As the authors point out, their findings can be interpreted in various ways. It may be that patients admitted with DKA can be managed just fine without ICU admission. However, it is also possible that such patients are already being triaged appropriately at all the study hospitals, such that those who really need ICU care (and are thus having their outcomes improved accordingly) are getting it. The latter interpretation, while possible, seems less likely to me in view of the enormous practice variation documented across the 159 hospitals. I suspect that much of the observed variation relates to traditional practice patterns and other aspects of institutional culture in the different hospitals.

Practice variation has been identified as an important problem in health care,[1] and its reduction is currently a major target for many quality and safety initiatives. However, as recently emphasized in a tri-society statement on the appropriate use of clinical research data and other types of knowledge in critical care, practice variation is inevitable in a high-stakes field with an incomplete and sometimes contradictory database.[2] How much this assertion applies to DKA is uncertain. As the authors of the current study caution, further research is needed to clarify the most effective and cost-efficient use of the ICU for patients admitted with DKA. ■

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ABSTRACT & COMMENTARY

Let There be Light — In the ICU!

By Linda L. Chlan, RN, PhD
School of Nursing, University of Minnesota

Dr. Chlan reports that she receives grant/research support from the National Institutes of Health.

SYNOPSIS: While national guidelines direct new critical care units to ensure natural lighting, the results of this study did not find any association with greater ambient light levels and better patient outcomes, suggesting further work is needed in this area.

SOURCE: Verceles AC, et al. Ambient light levels and critical care outcomes. *J Crit Care* 2012; Jul 2. [Epub ahead of print.]

The purpose of this study was to measure light levels in patient rooms, and also to determine if there were any relationships between greater light levels and mortality, length of stay, ventilator-free days, and amount of medication. A retrospective, observational design was used to evaluate 3799 consecutive first- and single-patient admissions to the medical intensive care unit (MICU) at the University of Maryland Medical Center from April 2006 to June 2009. The MICU is a 29-bed, closed unit with 24/7 intensivist staffing. Of note, the MICU did not have any protocols in place for environmental regulation (noise, light, interactions with patients) or designated quiet-time hours during the conduct of the study. Each patient room contained a window with retractable shades to allow entry of ambient light. Light measurements were obtained using the Actitrac actigraph/luxmeter (IM Systems, Baltimore, MD) for 10-minute periods between 1100 and 1330 to coincide with solar noon. Patient rooms were categorized based on their orientation: north, south, east, west. Patient data were abstracted from the hospital's electronic medical record and administrative record systems. The primary study outcome was MICU length of stay. Secondary outcomes were in-hospital and MICU mortality, 28-day ICU-free days, 28-day ventilator-free days, and medications received (percent of patients receiving sedative and opioid medications and dose received). Patient variables were also assessed, including Charlson co-morbidity index, Case Mix Index, age, gender, and race; none of these were significantly different based on light levels or room orientation.

South-facing rooms were found to receive the highest level of light and also had the widest range of light exposure. There were no significant differences reported between room orientation and any of the patient outcomes. The only difference in medications received was in the south-facing rooms where patients received a 25 mcg higher median daily dose of fentanyl. The results of this study did not support the researchers' hypothesis that room orientations with higher-intensity light levels would be associated with better patient outcomes.

COMMENTARY

For several years, design requirements have been in existence that stipulate ICU patient rooms need to have direct, ambient light. However, there is no agreement as to what constitutes "healthy" light levels for ICU patients. The findings from Verceles and colleagues further add to this conundrum, as the results from this study do not add any strong evidence in support of these design recommendations: Higher levels of light did not lead to any positive patient outcomes. Clearly, additional research is needed in this area using accurate measurements of light levels and salient patient outcomes. Levels of ambient light are only one aspect of the environmental milieu requiring careful attention for ICU patient healing and beneficial, salient outcomes.

While this was not part of the design or aims of the study conducted by Verceles et al, it is not known how alert patients were, if patients were even awake, or if patients were aware of light levels in their room during the study light measurement periods. Likewise, we do not know what the night-time environment was like in the MICU over the lengthy study period, and how that may have contributed to the reported outcomes. As articulated by the researchers, activity and noise levels were not reported or accounted for in this study nor were there any environmental enhancements in place in the form of protocols during the study period. Activity regulation and noise reduction strategies may be equally important when designing studies on environmental manipulation for promoting positive outcomes for ICU patients. Natural, ambient light may be important, but probably is not the only essential component for promoting a healing milieu in the ICU. ■

ABSTRACT & COMMENTARY

Monitoring Hemoglobin by Pulse Oximetry in the ICU: Is it Accurate and Safe?

By David J. Pierson, MD, Editor

SYNOPSIS: This study of ICU patients with acute gastrointestinal bleeding found that total hemoglobin as measured by pulse oximetry could not be determined in a substantial proportion of instances, and was inaccurate more than half the time when available, as compared to co-oximeter measurements on venous blood.

SOURCE: Coquin J, et al. Precision of noninvasive hemoglobin-level measurement by pulse co-oximetry in patients admitted to intensive care units for severe gastrointestinal bleeds. *Crit Care Med* 2012; Jun 22. [Epub ahead of print.]

Coquin and colleagues evaluated the accuracy of noninvasive total hemoglobin measurement using a widely marketed pulse oximeter in patients admitted to the ICU with acute gastrointestinal (GI) hemorrhage. Non-moribund patients with GI bleeding and symptoms or signs of active hemorrhage within 12 hours of ICU admission were connected via fingertip sensor to a self-calibrating pulse oximeter (Masimo Rainbow SET, Irvine, CA) for continuous monitoring of total hemoglobin for the first 24 hours in the unit. Simultaneously every 8 hours during this period, hemoglobin concentrations were determined from the oximeter, from capillary blood using a portable photometer (HemoCue Hb 201, Meaux, France), and from venous blood using a laboratory co-oximeter (LH-780, Beckman Coulter, La Brea, CA). The authors used Bland-Altman analysis to assess the bias and precision of the pulse oximeter and capillary-blood hemoglobin measurements as compared to the co-oximeter readings. The primary study endpoint was the percentage of inaccurate measurements (defined as > 15% difference from the co-oximeter) by the other two devices.

During the 5-month study period, 75 patients were admitted to the ICU with acute GI bleeding. Of these, 31 were excluded for a priori study design reasons, 10 were admitted to attending physicians uninvolved in the study, and one refused, leaving 33 patients from whom data were reported. The patients received a median of four units of red blood cell transfusion (range, 0 to 36 units) during the 24-hour study period, and six of them (18%) received a norepinephrine infusion for hypotension. A reading for hemoglobin concentration could not be obtained from the pulse oximeter in 25 (19%) of the scheduled measurements. When readings could be obtained, they had a bias of 1.0 ± 1.9 g/dL, which was significantly greater than that for the capillary measurements (0.4 ± 1.0 g/dL, $P < 0.05$) in comparison to those in venous blood. Measurements with the pulse oximeter were inaccurate by the authors' criteria 56% of the time as compared to 15% for the capillary measurements ($P < 0.05$). Concordance was unaffected by norepinephrine infusion, although unavailability of readings by pulse oximetry was more frequent (42% vs 15%, $P < 0.05$).

Data from the pulse oximeter and the capillary-blood photometer were not used in managing the patients in this study. However, using the unit's transfusion thresholds based on hemoglobin concentration, the authors determined that erroneous decisions would have been made more often using the pulse oximetry readings, typically in the form of administering blood unnecessarily. Because of this possibility of unnecessary transfusion based on the pulse oximeter's readings, the authors conclude that the use of this device to guide transfusion in patients with acute GI bleeding may be hazardous.

COMMENTARY

Over the last 20 or 30 years, there have been numerous instances where monitoring devices were introduced clinically into the ICU prior to rigorous study of their accuracy and clinical utility in that setting. Often such devices have been evaluated in normal volunteers, and then studied short-term in the controlled environment of the operating room, after which they have been promoted by their manufacturers or other advocates for use in critical care before clinical studies in critically ill patients have been done. The accuracy of the new pulse oximeters that measure total hemoglobin concentration has been evaluated in normal volunteers undergoing controlled hemodilution.[1] However, patients with acute GI hemorrhage are typically vasoconstricted and their hemoglobin levels may change rapidly and unpredictably. The present

study suggests that in this context these devices may be considerably less accurate.

Other studies should be done, both to confirm these findings and to assess the appropriateness of noninvasive hemoglobin monitoring in other types of critically ill patients. For now, the authors' conclusions seem reasonable: "Determination of pulse co-oximetry-based hemoglobin in patients presenting with severe gastrointestinal bleeds can be inaccurate, which renders its use to guide transfusions potentially hazardous. The unavailability of measurements, especially during vasopressor infusion, represents another serious limitation for hemorrhagic patients." ■

REFERENCE

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CME/CNE Questions

1. In the study by Rachmale et al, how much excessive O_2 exposure was required to produce a worse oxygenation index?

a. At least 48 hours
b. 24 hours
c. 36 hours
d. At least 12 hours
e. None of the above

2. Compared to patients who received Ringer's acetate, patients randomized to receive hydroxyethyl starch were found to have:

a. reduced mortality.
b. no difference in mortality.
c. increased mortality.
d. a decreased risk of renal replacement therapy.
e. less blood product transfusion.

3. Of the patients hospitalized with diabetic ketoacidosis in the study of Gershengorn et al, which of the following is closest to the range in the proportions admitted to the ICUs in the various hospitals?

a. 40% to 50%
b. 30% to 60%
c. 20% to 70%
d. 10% to 80%
e. 2% to 90%

4. In the study by Verceles et al, the main benefits of natural light on MICU patient outcomes were:

a. less mortality with higher levels of natural light.
b. less sedation administered to patients with higher levels of natural light.
c. shorter ICU stay associated with higher levels of natural light.
d. shorter length of ventilatory support with higher levels of natural light.
e. None of the above

5. In the study of noninvasive hemoglobin measurement by pulse co-oximetry in patients with acute gastrointestinal bleeding, measurements with the pulse oximeter were inaccurate by the authors' criteria what percentage of the time?

a. 25%
b. 44%
c. 56%
d. 78%
e. 92%

6. What was the effect of norepinephrine infusion on noninvasive hemoglobin measurements by pulse co-oximetry?

a. The value was overestimated by 40%.
b. The value was overestimated by 20%
c. The value was underestimated by 20%
d. The value was underestimated by 40%
e. No valid reading could be obtained a higher percentage of the time

CME/CNE Objectives

Upon completion of this educational activity, participants should be able to:

- identify the particular clinical, legal, or scientific issues related to critical care;
- describe how those issues affect physicians, nurses, health care workers, hospitals, or the health care industry; and
- cite solutions to the problems associated with those issues.

[IN FUTURE ISSUES]

Is ICU telemedicine cost-effective?

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.*

Does Finasteride Cause Permanent Sexual Side Effects?

In this issue: Side effects of finasteride; new ruling on pharmaceutical companies paying generic manufacturers; and FDA actions.

Sexual side effects of finasteride

Finasteride — the popular drug used to treat male pattern baldness and symptomatic benign prostatic hypertrophy — may cause long-term sexual dysfunction, according to a new study. Several recent studies have shown that the drug, which is marketed as 1 mg (Propecia) and 5 mg (Proscar), can cause sexual side effects that persist after stopping the drug in as many as 20% of men. In April, the FDA required new labeling for both strengths regarding libido, ejaculation, orgasm disorders, and even infertility that may persist after treatment ends. The new study looked at 54 men, with an average age of 31, who reported ≥ 3 months of sexual side effects after taking the 1 mg strength for male pattern baldness. All men were previously healthy without previous history of sexual dysfunction, medical conditions, psychiatric conditions, or prescription medication use. After 9-16 months of follow-up, 96% of subjects reported persistent sexual side effects (based on the Arizona Sexual Experience Scale). The duration of finasteride use did not correlate with changes in sexual dysfunction scores. The authors urge prescribers of finasteride to warn men of potential adverse effects (*J Sex Med* published online July 12, 2012). ■

Pharmaceutical company ruling

Is it legal for pharmaceutical companies to pay generic manufacturers to keep their products off the market? Until now it has been. Brand-name manufacturers have written enormous checks to keep their low-cost generic competitors off the market. That may change, however, after a federal appeals court in Philadelphia ruled that the practice is anticompetitive, a decision that is counter to three previous federal circuit courts rulings. *The New York Times* cites the example of Bayer Pharmaceuticals which paid generic drug maker Barr Laboratories and other generic houses $400 million to withhold their generic version of ciprofloxacin, their $1 billion a year blockbuster antibiotic. The case could eventually end up at the Supreme Court. At stake is billions of dollars in lost profits for pharmaceutical manufacturers, but an equal amount of savings for Medicare/Medicaid, health plans, and consumers. ■

FDA actions

The FDA has approved the second new weight-loss medication within a month. The new product combines phentermine along with topiramate in an extended-release product. Phentermine has been marketed since 1959 and was part of the infamous "fen-phen" combination that was popular in the 1990s (fenfluramine was eventually banned due to cardiac valvulopathy in 1997). Topiramate is currently marketed as an anticonvulsant and for migraine prophylaxis as Topamax. The combination was rejected by the

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FDA in 2010 due to safety concerns, but Vivus Pharmaceuticals submitted additional data to the agency and recently won approval in July. In the process, the company changed the brand name from Qnexa to Qsymia. Similar to the recently approved lorcaserin (Belviq), phentermine/topiramate is approved as an addition to a reduced-calorie diet and exercise for weight management in adults with a BMI of 30 or greater, or with a BMI of 27 or greater with at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia. In two placebo-controlled trials, 3700 obese and overweight patients lost an average of 6.7-8.9% of their body weight, depending on the recommended or higher dose therapy (slightly better results than those seen with lorcaserin). Patients who have not lost at least 3% of their body weight by week 12 should discontinue the drug. Because of continued safety concerns, the drug was approved with a Risk Evaluation and Mitigation Strategy (REMS), which consists of a medication guide, prescriber training, and pharmacy certification. The drug cannot be used during pregnancy or in patients with recent stroke or heart disease, and patients should have their heart rates monitored during therapy. Vivus will market Qsymia immediately, but will be required to conduct 10 postmarketing studies to assess safety.

The FDA has approved aclidinium bromide, a dry powder inhaler for long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). Aclidinium is a long-acting antimuscarinic agent that works primarily on the M3 receptor causing sustained bronchodilation. The approval was based on three studies of nearly 1300 patients with COPD. The drug may cause anticholinergic side effects, including worsening narrowing-angle glaucoma and urinary retention. It should not be used as a rescue inhaler and is not recommended for those 18 years of age or younger. It is dosed twice a day. Aclidinium inhaler is the second anticholinergic inhaler to be approved after tiotropium (Spiriva), which was approved in 2004. Aclidinium will be distributed by Forest Laboratories and will be marketed as Tudorza Pressair.

The FDA has approved mirabegron to treat adults with overactive bladder. The drug is a novel, once-daily beta-3 adrenergic agonist that works by enhancing storage function and relaxing the urinary bladder, a unique effect and distinct from currently marketed antimuscarinics that inhibit bladder contraction. The once-a-day medication will be available in 25 mg pills. The dose can be increased to 50 mg after 2 months if needed. The approval was based on three placebo-controlled trials that showed statistically significant improvement in incontinence episodes and number of urinations per 24 hours. The most common adverse effects were hypertension, nasopharyngitis, urinary tract infection, and headache. Mirabegron will be marketed by Astellas Pharma as Myrbetriq.

The FDA has approved a new colon cleansing agent for colonoscopy prep. The new prep is sodium picosulfate, magnesium oxide, and citric acid in powder form that is dissolved in water and taken in two doses the night before and the morning of the procedure. It may also be taken the afternoon and the evening before the procedure (Day-Before regimen). The safety and efficacy of the new agent was studied in two studies of about 1200 patients undergoing colonoscopy in which standard PEG plus electrolytes was used as a comparator, and the new prep was found to be at least as effective as the standard prep. Ferring Pharmaceuticals will market the new two-dose prep as Prepopik.

The FDA has approved icosapent ethyl, a new fish oil preparation for the treatment of hypertriglyceridemia. It is approved as an adjunct to diet to treat patients with triglyceride levels greater than 500 mg/dL. The drug contains ultra purified ethyl EPA, an omega-3 fatty acid. The new product follows GlaxoSmithKline's Lovaza, another fish oil that is currently marketed for the same indication and generates more than $1 billion in annual sales. The new product is manufactured by Amarin Corporation and will be marketed as Vascepa. Fish oils are effective at lowering triglycerides but evidence is lacking that they are effective for secondary prevention of cardiovascular disease (*Arch Intern Med* 2012;172:686-694).

An FDA advisory committee has recommended an new indication for Genentech's ranibizumab (Lucentis) for the treatment of diabetic macular edema, an indication for which there is currently no approved therapy. The drug is approved to treat neovascular age-related macular degeneration and macular edema following retinal vein occlusion. Diabetic macular edema is commonly treated with laser therapy, a procedure that has the potential side effect of some vision loss. The FDA generally follows its advisory committee's recommendations and should make a final recommendation later this year. ■