CRITICAL CARE ALERT®

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

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INSIDE

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Methylprednisolone to Prevent Post-Extubation Laryngeal Edema

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *In a mixed population of adult ICU patients who had been intubated for at least 36 hours, administration of 80 mg of methylprednisolone over the 12 hours preceding extubation substantially reduced the incidence of post-extubation laryngeal edema and the need for re-intubation.*

Source: Francois B, et al. *Lancet.* 2007;369:1083-1089.

In this multicenter clinical trial from France, Francois and associates sought to determine whether methylprednisolone administered prior to extubation would prevent post-extubation laryngeal edema (PELE) and the need for re-intubation. They studied adult patients intubated for at least 36 hours for acute respiratory failure, in whom extubation was planned the following day. In a randomized, double-blind design, they gave such patients either methylprednisolone, 20 mg, or saline intravenously at 12, 8, and 4 hours prior to extubation, and also at the time the endotracheal tube was removed—for a total of 80 mg in the active treatment group. The investigators prospectively evaluated all patients for laryngeal edema (clinically defined as the acute development of upper respiratory obstruction) on 8 examinations over the 24 hours following extubation, and examined the cords visually at the time of reintubation when this was required.

The 2 patient groups were well matched, with 64% male and median age 66 years. Patients had similar frequencies of medical illness (62%), surgical conditions (19%), and trauma (19%). The median duration of intubation prior to randomization was 6 days. Of 761 patients entered into the study, data from 698 were included in the analysis. PELE developed in 76 of the 343 placebo-treated patients (22%) as compared to 11 of the 355 patients who received methylprednisolone (3%; $p < 0.001$). Re-intubation because of PELE occurred in 14 of 26 (54%) vs 1 of 13 (8%) of the patients on placebo vs methylprednisolone, respec-

tively ($P = 0.005$); overall rates of re-intubation were 26/343 (8%) vs 13/355 (4%), respectively ($p = 0.02$). By univariate analysis of the data, patients who developed PELE were more likely to be female, of shorter height, admitted for trauma, and intubated orally with larger endotracheal tubes for a shorter period of time.

COMMENTARY

This was a carefully planned, well carried out, rigorously described and reported study, and its results are impressive: administration of steroids for 12 hours prior to planned extubation in patients who had been intubated for 2 days or more reduced the incidence of PELE seven-fold, and also reduced the need for reintubation. Given the seriousness of PELE and the magnitude of the benefit shown in this study, does this mean that the regimen used in this study should become a standard of care in our ICUs? Maybe, and maybe not, as influenced by several considerations.

Are the patients in this study similar enough to my patients, and is the authors' experience with PELE and the need for reintubation consistent with what is encountered in my institution? The patient population is well-described, so that readers can judge how well they match up to the patients intubated and ventilated in their ICUs. The more dissimilar the populations (for example, for a neurocritical care unit or one that sees mainly postoperative patients), the more caution would seem appropriate. Although the authors cite a previous study that found a 22% incidence of PELE, as observed in their trial, this seems high to me. Perhaps it is related to the care with which this complication was deliberately sought, and an 8% reintubation rate is probably reasonable.

What happens in everyday clinical practice (clinical effectiveness) often does not replicate what is found in the rigorous, carefully-controlled circumstances of a clinical trial (efficacy). How effectively could the regimen used in this study be implemented in my ICU? Here there may be some problems with ventilatory management and extubation as typically practiced in the United States.

Francois et al evaluated their patients in the evening and determined that they would be extubated the next morning, permitting them to administer the 12 hours of steroids before extubation at the usual time. In this country decisions to extubate, particularly after several days of mechanical ventilation for acute respiratory failure as with the patients in this study, are typically made on morning rounds and carried out promptly. This is consistent with the current standard of care. According to the most-often cited weaning recommendations, the 2001 international consensus guidelines,[1] readiness for liberation from mechanical ventilation should be assessed using a spontaneous breathing trial; those who pass this trial should be extubated as soon as possible and not remain intubated any longer than is necessary. Numerous studies have confirmed the correlation between duration of intubation and the incidence of ventilator-associated pneumonia and other complications. The need to wait 12 hours in order to administer a course of methylprednisolone might lead to extubation during the night shift, when staffing may be less and observation for post-extubation difficulties harder to maintain, or holding the patient over until the next morning, essentially adding another day of intubation time.

If the decision to extubate is made based on the results of an early-morning assessment, could the protocol be abbreviated in order to get the tube out in the next several hours, administering only 2 or 3 doses of steroids beforehand? This question cannot be answered at present. And what if, on reassessment prior to extubation, the decision is made to defer extubation after the steroid course has already

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begun, as happened a few times during the study and is not uncommon in the unit? Continuing the regimen and extubating the patient the next day would mean giving 200 mg of methylprednisolone rather than 80 mg, the safety and expense of which might become problematic.

Certainly, patients with a history of PELE should receive methylprednisolone prior to planned extubation. Those patients whom the clinician suspects to be at especially high risk for PELE—which according to this study would include small women with large tubes, especially those admitted after trauma—would be good candidates as well. As to whether all other patients who will have been intubated for 2 days or more and do not have a specific contraindication should receive steroids prior to extubation—as is recommended in the editorial accompanying the Francois study[2]—I think the jury is still out. I am inclined to await further confirmation of this trial before introducing this regimen this broadly into my own ICU practice. ■

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Do Cellular Devices and 2-Way Radios Affect Ventilator Function?

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *Cellular telephones from 2 telecommunications systems and the 2-way radio used by local emergency services affected some of the ventilators tested (the older models), but only at close proximity, and no device tested had any effect on any ventilator beyond a distance of 1 meter.*

Source: Dang BP, et al. *J Crit Care.* 2007;22:137-141.

In this study, investigators at the University of Saskatchewan sought to determine whether current-technology cell phones and 2-way radios affected the function of the ventilator models in use in their province. The ventilators used were the Maquet Servo 300, the Puritan-Bennett 7200, the Draeger Babylog 8000, the Bird VIP GOLD Pediatric, the Pulmonetics LTV 1000 transport ventilator, the CPAP Sullivan III, and the Respironics BiPAP Synchrony. The mobile communication devices tested were cell phones from the 2 telecommunications systems serving Saskatchewan and the MRK/810-815 mHz/3w Ericsson GE walkie-talkie, which operated on the local system at a fixed power output of 3.0 w when in use.

Dang et al enlisted the technical assistance of the local provincial phone company, which provided the 2-way radio and one of the cell phones and helped to standardize and validate the testing procedures. The ventilators were placed in operation using a test lung in a basement room in the hospital. The cell phones and radio were tested under circumstances in which maximum power was used and the most interference with ventilator operation could be expected. They were placed at 0 m, 0.5 m, and 1.0 m, and farther from each ventilator if closer distances were associated with detectable changes in ventilator function.

The 2-way radio caused significant interference with the Puritan-Bennett 7200 at all distances up to 1.0 m, and with the pulmonetics LTV 1000, the Draeger Babylog 8000, and the Bird VIP GOLD at 0 m. The radio also caused the BiPAP Synchrony to shut down when placed at 0 m from the machine. The Motorola V300 cell phone, serviced by the more powerful of the 2 systems, caused interference with the Puritan-Bennett 7200 at 0 m only. None of the devices affected the Servo 300 or the CPAP Sullivan III, the 2 newest machines tested.

The authors point out that, with current technology, it is not the individual cell phone (of which there are a bewildering variety today) or the service provider (of which there are numerous, varying by region) that is relevant to potential influence with ICU devices, but rather the telecommunications system. The different systems vary, and it is the system to which a device is connected that determines its power output.

The authors conclude that interference from mobile communications devices is less of a problem with newer ventilators than with older models, and that even with the older, more vulnerable machines, such devices are safe to use if they are not operated within 1 m of the ventilator.

■ **COMMENTARY**

Personal cellular devices and 2-way communications

systems have become indispensable to health care professionals and are ubiquitous today. Despite their usefulness and their penetration into many aspects of hospital and ICU operation, such devices have the potential to interfere with ventilators and their vital electronic equipment. Because life support is involved, the stakes are high, and as a result the use of cell phones and other mobile communication devices has been banned in many ICUs. However, as this article illustrates, this area is evolving rapidly and the issue might need to be revisited. Given the value of the devices and the advances in recent equipment design, it may not be desirable to keep mobile communication units out of the ICU.

Dang et al point out that their study was targeted at the ventilators and communication systems in use in Saskatchewan, and that caution should be used in generalizing their findings beyond this context. It would seem advisable for individual hospitals to find out about their local telecommunication systems and the characteristics of the ventilators in use in their ICUs and elsewhere in their institutions. In any event, it is reassuring to note that the likelihood of interference with ventilator operation seems low if cell phones and other devices are kept at least 1 m away. ■

Preoperative Anemia and Postoperative Outcomes in the Elderly

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *In this study of 310,311 veterans aged 65 or older who underwent major noncardiac surgical procedures, 30-day mortality increased 1.6% for every percentage-point decrease in preoperative hematocrit below 39%.*

Source: Wu WC, et al. *JAMA.* 2007:297(22):2481-2488.

Using data from 132 US veterans hospitals collected in the National Surgical Quality Improvement Program, Wu et al performed a retrospective cohort study of patients aged 65 or older who underwent major non-cardiac surgery between 1997 and 2004. Major surgery included all procedures, elective and emergency, performed in the operating room under general, spinal, or epidural anesthesia. Postoperative mortality and cardiac events (cardiac arrest or Q-wave myocardial infarction) were correlated with preoperative hematocrit values. The latter were divided into 14 groups, from < 18% to ‡ 54%, and referenced to a normal range of 39% to 53.9%.

The study cohort was comprised of 310,311 veterans (98% male, 80% white). Of these, 42.8% had preoperative anemia, defined as hematocrit < 39%, and 0.2% had polycythemia (hematocrit ‡ 54%). Anemic patients had significantly ($p < 0.001$) more diabetes, cardiac disease, neurologic disorders, renal disease, long-term corticosteroid use, and cancer than non-anemic patients. They also tended to be older, inpatients rather than outpatients before surgery, and non-independent in functional status, and to have higher American Association of Anesthesiologists class.

For the entire study population, 30-day postoperative mortality was 3.9% and the cardiac event rate was 1.8%. Both of these outcomes rose monotonically for patients with progressively lower and higher hematocrit levels than normal. For example, the mortality rates were 1.5% for patients with hematocrits of 45.0 to 47.9%, 5.8% with values of 33.0 to 35.9%, 14.9% with values of 24.0 to 26.9%, and 35.4% with values < 18%. There was a 1.6% (95% confidence interval, 1.1%-2.2%) increase in 30-day postoperative mortality associated with every percentage-point decrease in hematocrit level from the normal range. This increase was not just observed in patients with very low hematocrits, and began when the level fell below 39%.

COMMENTARY

In this study, elderly patients with preoperative hematocrits below the lower limit of normal had worse outcomes, and mortality increased progressively with lower and lower hematocrits. This does not necessarily mean that the anemia was the cause of the worse outcomes, or, that raising the hematocrit into the normal range in these patients would have improved their outcomes. The authors acknowledge both of these points. In fact, the anemic patients were substantially different from their non-anemic counterparts in a lot of ways that would be expected to push the findings in the direction observed, including being older, having more comorbidities, and being less functional prior to surgery. This suggests that preoperative anemia is a marker for, rather than an independent cause of, worse postoperative outcomes.

This was not an ICU study, and the proportions of patients in the cohort who were critically ill prior to surgery or managed in the ICU postoperatively are not given. Only about 8% of the operations were classified as emergent. The authors found essentially no relation-

ship between hematocrit and outcomes in this subset of patients. This may have been because of the overriding effects of comorbidities in these patients, or because the preoperative hematocrit values in the database did not reflect the patients' status at the time of surgery: 21% of the total patient population had no hematocrit recorded within 30 days of the operation. Another interesting finding was that patients who received more than 4 units of transfused blood preoperatively had a *reduced* rate of postoperative death: the odds ratio was 0.88, with a 95% confidence interval of 0.79-0.98. This supports the notion that recognition and management of serious anemia prior to a scheduled major operation is a good idea.

What should ICU clinicians make of this study's findings in the context of the recent attention focused on hematocrit levels and outcomes in critically ill patients? Studies using large databases have shown associations between lower hematocrits and increased mortality in patients with acute myocardial infarction. However, prospective studies randomizing ICU patients to lower vs higher transfusion thresholds have found that a more liberal transfusion strategy does not improve outcome. It may be that, in general, the presence and severity of anemia are markers for poor prognosis from a multiplicity of disease processes, and that treating the marker per se may not affect the factors responsible for that poorer prognosis. Nonetheless, the present study may prove useful to clinicians in helping to identify patients at increased risk for unfavorable outcomes after elective major noncardiac surgery, so that such patients can be monitored closely if they are in the ICU. ■

Special Feature

Burnout Syndrome in the ICU

By James E. McFeely MD

Medical Director Critical Care Units, Alta Bates Summit Medical Center, Berkeley, CA

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

BURNOUT SYNDROME (BOS) IS A CONDITION IN which professionals lose concern and emotional feeling for the people they work with, and come to treat them in a detached or even dehumanizing manner. Burnout in the context of the Intensive Care Unit (ICU) is a psychological response to chronic interpersonal stress on the job. We are all aware of colleagues who appear burned out. The syndrome is so pervasive in the ICU that it almost has become a part of the background noise. In the last few years, several studies have documented the severity and extent of burnout in both intensivists and critical care nursing staff.

Burnout syndrome is described as an inability to cope with emotional stress at work or as an excessive use of energy and resources leading to feelings of failure and exhaustion. While objective study of BOS takes intensivists into less familiar disciplines such as psychology and anthropology, research in these fields shows the vast extent of burnout in our work environment and points to institutional factors as those most associated with the phenomenon.

How Can Burnout Be Detected and Quantitated?

A simple measurement tool called the Maslach Burnout Inventory (MBI) has been developed and well validated for detecting and measuring the severity of BOS. The scale evaluates three domains: emotional exhaustion, depersonalization (negative or cynical attitudes towards patients), and loss of feeling of personal accomplishment at the work site. This tool has been applied in several different studies, all of which point to an epidemic of burnout in the ICU.[1-3]

How Common Is It, And Who is Most Likely To Get It?

Embriaco and colleagues sent the MBI questionnaire to directors of 318 ICUs in France in early 2004.[1] Practicing physicians returned 978 surveys. As measured by the MBI, a high level of burnout was identified in 47% of the responding intensivists, while a moderate level of burnout was identified in a further 30%. Depersonalization was observed in 37% of the respondents, with a high level of emotional exhaustion in 19% and a low level of personal accomplishment in a further 39%. In all, 40% of the respondents indicated that they wanted to leave their current jobs. Of those intensivists exhibiting high levels of burnout on the MBI scale, 51% indicated they wanted to change careers.

In univariate analysis of the same data, certain groups showed higher levels of burnout than others. These included female intensivists; younger intensivists and those who were unmarried or childless; and physicians reporting conflicts with nurses, colleagues, or patient families during the seven days prior to taking the survey (in contrast, good quality relationships with chief nurses and nursing staff were associated with a lower score on the survey). Higher degrees of burnout were also associated with organizational factors such as increased workload (working hours per week, number of night shifts per month, compensation for overtime and recent vacations). Interestingly, the severity of illness of patients (as

quantified using the SAPS II score) and mortality rates did not correlate with the rate of burnout.

A similar study was performed using the same MBI instrument to measure burnout in critical care nurses in France.[2] Of the 2,392 respondents, 33% of these nurses had severe BOS as measured by the MBI. In multivariate analysis of this data, four groups of characteristics were associated with severe burnout: personal characteristics such as younger age; organizational factors such as the ability to control one's schedule and participate in clinical research; quality of working relationships, including those with patients, head nurses and physicians; and end-of-life variables such as caring for a dying patient or decision-making regarding life-sustaining treatments within the week prior to taking the inventory.

A separate study performed across the European Union found that burnout tended to cluster in ICUs.[4] Multilevel analysis showed that burnout complaints among colleagues made a statistically significant and unique contribution in predicting variance in burnout rates between units. This suggests burnout may be communicated within a unit from one nurse to another—exemplifying the phenomenon of "emotional contagion" substantiated by a wide-range of disciplines.

Burnout, Post-traumatic Stress Disorder and Moral Distress

Critical care nurses were also recently given survey instruments to determine the prevalence of symptoms of post-traumatic stress disorder (PTSD), anxiety, and depression.[5] Of 230 ICU nurses who completed the surveys, 21% recalled having nightmares and 17% had severe anxiety and panic related to experiences working in the ICU. The most frequent symptoms among these nurses were sleep problems, irritability, agitation, anger, and muscle tension. These ICU nurses with positive symptoms consistent with PTSD were more likely to work evening or night shifts and were less likely to have taken on the role of charge nurse. While PTSD may be the upper end of a stress response continuum rather than a distinct pathologic entity, the majority of these nurses would meet diagnostic criteria for sub-threshold PTSD, a rate of subclinical PTSD similar to those found in female Vietnam veterans.

The development of moral distress, which results when a person perceives that the right course of action cannot be implemented because of outside constraints, has also been studied. In a survey of 60 critical care nurses, moral distress accounted for 10% of the variance of the emotional exhaustion subscale of the MBI.[6]

What Can Be Done about Burnout Syndrome?

The first step in attempting to control work stress is for an organization to understand that work stress is an organization-level problem, not an individual employee's problem, and that prevention and treatment of burnout requires an integrated response from the institution as well as the individuals working in the ICU.[7-10] Where work stress exists, hospital administrators must recognize it and provide resources in order to mitigate it. Helpful measures include more flexible shift scheduling (which is associated with decreased frequency of burnout among nurses); training in communication between hospital staff and patient families as well as between doctors and nurses; and mutual support and debriefing (perhaps with the assistance of an outside party) after a difficult case or acute crisis.

Of course, some variables associated with increased rates of burnout are difficult to control, such as work flow (random rapid increases in census, lack of staff) and unreasonable or difficult families. But even in those situations, contingency plans can be developed. Flexible staffing and a coordinated response to triage between the physicians and nursing administration can help with workflow problems. Social workers, case managers, ethics committees and the availability of a palliative care service can occasionally help in dealing with patient families.

Role of The Medical Director and Nurse Manager

Medical directors and nurse managers have a particularly important role in countering the contagion of burnout. They can do this by creating an overall supportive environment in the unit, with an emphasis on peer group support and positive socialization within the unit. They must discourage bullying or negative comments and promote positive feedback to colleagues when they perform well, as well as make staff feel that their leaders empathize with the tasks they are trying to accomplish. In general, medical directors and nurse managers must attempt, and staff must perceive them making every possible attempt, to minimize stress in what is a physically, cognitively and emotionally demanding work environment. ■

For readers interested in measuring the amount of burnout in their own units, the Maslach Burnout Inventory can be purchased at this website:

http://www.cpp-db.com/detail/detailprod.asp?pc35

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Noninvasive Ventilation with ICU Ventilators: A Note of Caution

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *When noninvasive ventilation is administered using ICU ventilators that offer this feature, air leaks in the circuit cause triggering delay, increased patient work, and delayed cycling. Activating the special noninvasive ventilation feature improves these problems on some of the ventilators tested (but variably so), and actually made them worse on others.*

Source: Vignaux L, et al. *Intensive Care Med.* 2007 (e-pub prior to print): DOI 10.1007/s00134-007-0713-0.

Vignaux and colleagues at the University Hospital in Geneva performed a laboratory study of the performance of ICU ventilators featuring a noninvasive ventilation (NIV) mode, with and without an induced air leak. As a model representing a patient being ventilated with NIV, they used a PVC head equipped with upper airways and a trachea, the latter connected to a 2-chamber lung model. A driving ventilator ventilated one chamber using airway pressure release mode, while the other chamber mimicked spontaneous breathing and was connected to the model's trachea. The investigators applied NIV via a standard oronasal mask, and produced a controlled air leak using a 3-way stopcock placed between the NIV ventilator circuit's Y-piece and the mask.

Eight ICU ventilators currently available in Europe that feature NIV mode and are marketed for this use were tested under similar conditions. Triggering and pressurization were tested under conditions of normal mechanics in the test lung, and cycling was tested under conditions of normal, obstructive, and restrictive mechanics. The tests were performed using pressure support mode with no leak, pressure support plus leak, and pressure support mode plus leak with the NIV feature activated. With the experimental setup used, the leaked volume under the latter two conditions was essentially 100% of the baseline tidal volume and "patient" minute ventilation.

With most of the ventilators tested, leaks led to an increase in trigger delay and workload, a decrease in pressurization, and delayed cycling. The NIV mode partially or totally corrected these problems—with most but not all of the ventilators—with marked differences between the different machines. On some of the ventilators the NIV mode actually made the leak-induced dysfunction worse.

COMMENTARY

Air leaks around the mask are a major problem with NIV. They are unpleasant for patients and can lead to poor acceptance of this life-saving therapy, and they can interfere with its effectiveness even when tolerated by the patient. Ventilators such as the Respironics BiPAP and others of similar design that were developed for home care and other non-ICU use compensate well for leaks, as several studies have demonstrated. However, these and other studies have also shown that standard ICU ventilators, which were designed for closed-circuit use with intubated patients who have no or minimal leaks, are poorly suited for NIV because of their lack of leak compensation and can be dangerous in this application, especially in pressure support mode.

Thus, the availability of better leak compensa-

tion via the new NIV mode features on an increasing number of ICU ventilators (most of these still not available in the US) would seem to be a real advance. But not so fast: this study shows that—at least with the NIV simulation model used and under the conditions applied—these ventilators vary a great deal in their ability to deliver on what they promise.

One additional point made by Vignaux et al in their discussion is worthy of repeating. The use of new modes and other ventilator features tends to expand beyond their intended specific applications into clinical circumstances in which they have not been investigated and may be dangerous. Using the new NIV mode in intubated patients could be hazardous, in two respects. First, if an intubated patient were switched to NIV mode from another mode in which the ventilator had performed its automated self-tests of circuit resistance and compliance in order to determine correction factors for its flow and pressure sensors, its function might be altered. Second, because NIV modes are designed to deal with large system leaks and to compensate for them, the ventilator may not alarm in the presence of such leaks as it does in other modes that assume a closed circuit with minimal leak; in such circumstances an intubated patient could develop a clinically important air leak that would not trigger the intended alarm. ■

CME Questions

21. What was the effect of a 12-hour course of methylprednisolone prior to planned extubation on the incidence of post-extubation laryngeal edema?
a. a 7-fold reduction
b. a 2-fold reduction
c. no significant change
d. a 2-fold increase
e. a 7-fold increase

22. Which of the following is the primary determinant of whether a cell phone will cause interference with the operation of a ventilator?
a. The brand of cell phone
b. The cellular service provider
c. The telecommunication system in the region
d. Whether the cell phone is in "talk" mode or "search" mode
e. How recently the cell phone was manufactured

23. In the study of preoperative anemia and postoperative outcomes in elderly VA patients:
a. Anemic patients undergoing emergency operations had worse outcomes.
b. All the patients had hematocrits drawn immediately prior to surgery.
c. Patients who received > 4 units of transfusion preoperatively had higher mortality.
d. All of the above.
e. None of the above.

24. Standard ICU ventilators are poorly suited to noninvasive ventilation because they:
a. cannot generate high enough airway pressures
b. lack appropriate volume and pressure monitors
c. do not compensate well for air leaks
d. cannot generate large enough minute volumes
e. cannot connect properly to masks as opposed to endotracheal tubes

Answers: 21 (a); 22 (c); 23 (e); 24 (c)

CME / CE Objectives

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

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

In Future Issues: **Geriatric Trauma and End-of-Life Issues**

PHARMACOLOGY WATCH

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

SSRIs Associated With Low Rate of Birth Defects, Studies Show

In this issue: *SSRIs are safer in pregnancy than previously thought; Estrogen therapy in younger women may be of benefit in preventing cardiovascular disease; Warfarin is substantially better than antiplatelet therapy in preventing stroke in patients with atrial fibrillation; The FDA tightens regulations regarding dietary supplements, Lyrica is approved for treatment of fibromyalgia.*

SSRIs are associated with a low rate of birth defects according to 2 new studies in the *New England Journal of Medicine*. SSRIs are often taken by women in their childbearing years, but the risk of birth defects has been unclear. Paroxetine (Paxil) specifically has been associated with omphalocele and heart defects, but there is little data on the risk of other SSRIs. In the first study from Boston University and Harvard, researchers assessed the association between first-trimester maternal use of SSRI and birth defects among nearly 10,000 infants with and over 5,800 infants without birth defects who participated in the Sloan Epidemiology Center Birth Defects Study. Use of SSRIs was not associated with significantly increased risk of craniosynostosis (odds ratio 0.8), omphalocele (odds ratio 1.4), or heart defects overall (odds ratio 1.2). Analysis of specific SSRIs and specific deficits showed significant associations between use of sertraline (Zoloft) and omphalocele (odds ratio 5.7) and septal defects (odds ratio 2.0) and between use of paroxetine and right ventricular outflow tract obstruction defects (odds ratio 3.3). There were no significant associations with other defects with other SSRIs or non-SSRI antidepressants. In the other study, researchers from the CDC and University of British Columbia looked at data obtained on 9,622 infants with major birth defects and 4,092 control infants born between 1997 and 2002. Records were obtained from birth defects surveillance systems in 8 U.S. states and controls were selected randomly from the same geographic areas. Mothers were interviewed regarding exposure to potential risk factors including medications before and during pregnancy. No significant associations were found between maternal use of SSRIs overall during early pregnancy and congenital heart defects or most other categories or subcategories categories of birth defects. Maternal SSRI use was associated with amencephaly (odds ratio 2.4), craniosynostosis (odds ratio 2.5) and omphalocele (odds ratio 2.8). Their conclusion was that maternal use of SSRIs during early pregnancy was not associated with significantly increased risk of congenital heart defects or most other categories or birth defects. There was an association with SSRI use and 3 types of birth defects, but the absolute risk was small and further studies are warranted (*N Engl J Med* 2007; 356:2675- 2683, 2684-2692). An accompanying editorial points out that 2 previous stud-

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ies had suggested a relationship between paroxetine and cardiac malformations including ventricular septal defects, an association that was not found in these current studies. Although a small rate of congenital heart malformations, including right ventricular outflow tract lesions, were found the rate was still low, less than 1%. The editorialists, Dr. Michael Green from Massachusetts General states, "The 2 reports in this issue of the Journal, together with other available information, do suggest that any increased risks of these malformations in association with the use of SSRIs are likely to be small in terms of absolute risks." (*N Engl J Med* 2007; 356:2732-2733). ■

Estrogen for Younger Postmenopausal Women

Another follow-up study from the Women's Health Initiative suggests that estrogen therapy in younger postmenopausal women may be of benefit in preventing cardiovascular disease. Analysis was done on the "estrogen-only" wing of WHI in women who had undergone hysterectomy prior to enrolling in the study and were not treated with progesterone. Women age 50 to 59 were treated with 0.625 mg per day of conjugated equine estrogens or placebo. CT heart scanning was done at entry to the study and after a mean of 7.4 years of treatment and 1.3 years after the trial was completed. The endpoint of mean coronary-artery calcium scores was lower among women receiving estrogen (83.1) than those receiving placebo (123.1) (P = 0.02 by rank test). After adjusting for coronary risk factors, the odds ratios for coronary-artery calcium scores of more than 0, 10 or more, and 100 or more in the group receiving estrogen as compared to placebo were respectively 0.78, 0.74, and 0.69. The corresponding odds ratios among women with at least 80% adherence to the study estrogen or placebo were 0.64 (P = 0.01), 0.55 (P < 0.001), and 0.46 (P = 0.001). For women who had calcium scores greater than 300 the multivariate odds ratio was 0.58 (P = 0.03) in an intention-to-treat analysis and 0.39 (P = 0.004) among women with at least 80% adherence. The authors conclude that in women age 50 to 59 years old at enrollment, estrogen treatment resulted in a lower calcified plaque burden in the coronary arteries compared to placebo. They also point out that estrogen has complex biological effects and may influence the risk of cardiovascular events and other outcomes through multiple pathways (*N Engl J Med* 2007; 356:2591-2602). An accompanying editorial points out that not only did women in this analysis who were treated with estrogen have lower calcium scores, women in whom hormone replacement therapy was initiated at a younger age also had a 30% reduction in total mortality and did not have significant increases in any adverse outcomes examined. This supports the "timing hypothesis" for hormone replacement therapy that suggests that the cardiovascular benefits of hormone replacement are only evident if treatment is started before atherosclerosis develops. (*N Engl J Med* 2007;356:2639-2641). ■

Warfarin Better for Atrial Fibrillation Patients

Recent meta-analysis has confirmed the value of warfarin in preventing stroke in patients with nonvalvular atrial fibrillation. Twenty-nine trials involving more than 28,000 patients were reviewed. Compared with control, warfarin and antiplatelet agents reduce stroke by 64% (95% CI, 49% to 74%) and 22% (CI, 6% to 35%) respectively. Adjusted-dose warfarin was substantially more efficacious than antiplatelet therapy, and increases in extracranial hemorrhage assisted with warfarin were small. The authors conclude that warfarin is substantially more efficacious at preventing stroke in patients with a fibrillation than is antiplatelet therapy (by approximately 40%). (*Ann Int Med* 2007; 146: 857-867). ■

FDA Actions

The FDA has strengthened its regulations regarding dietary supplements, issuing a "final rule" requiring current good manufacturing practices for dietary supplements. The rule ensures the supplements are produced in a quality manner, do not contain contaminants or impurities, and are accurately labeled. Manufacturers will also be required to report all serious dietary supplement-related adverse events to the FDA by the end of the year.

Pregabalin (Lyrica-Pfizer) has been approved for the treatment of fibromyalgia, the first drug approved for this indication. Fibromyalgia, which is characterized by pain, fatigue, and sleep problems, affects up to 6 million people in United States. Approval was based on 2 double-blind, controlled trials involving 1,800 patients that showed improvement in pain symptoms at doses of 300 mg or 450 mg per day. The drug has already been approved for partial seizures, postherpetic neuralgia, and diabetic neuropathy. ■