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INSIDE

Diabetic Foot Infections: Culture Results from Bone Biopsy and Swab Specimens

ABSTRACT AND COMMENTARY

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This article originally appeared in the February 2006 issue of Infectious Disease Alert. *It was originally reviewed by the physician editor, Stan Deresinski, MD, FACP, and peer reviewed by Connie Price, MD. Dr. Deresinski is Clinical Professor of Medicine, Stanford University, and Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center. He serves on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. Dr. Price is Assistant Professor of Medicine, University of Colorado School of Medicine. She reports no relevant financial relationship related to this field of study.*

Synopsis: *Seventy-six patients with diabetic foot osteomyelitis underwent surgical bone biopsy for culture had bone culture results compared to swab culture results. The results of bone and swab cultures were identical in only 17% of patients and bone bacteria were isolated from swab cultures only 30% of the time.*

Source: Senneville E, et al. Culture of Percutaneous Bone Biopsy Specimens for Diagnosis of Diabetic Foot Osteomyelitis: Concordance with Ulcer Swab Cultures. *Clin Infect Dis*. 2006;42:57-62.

THIS STUDY FROM A SINGLE DIABETIC FOOT CLINIC IN FRANCE involved a retrospective chart review of patients who underwent surgical percutaneous bone biopsy with culture for microbiologic diagnosis of osteomyelitis. Patients included for study were those who had not received either local or systemic antibiotics for at least 4 weeks prior to cultures being obtained. Osteomyelitis was defined by a variety of reasonable criteria, which are detailed in the article. Swab specimens were obtained from foot ulcers after brief cleansing of the ulcer with sterile physiologic glucose solution applied with a sterile compress. Percutaneous bone biopsies were performed in the operating room using sterile technique with an 11-gauge biopsy needle inserted through a 5-10 mm skin incision made at least 20 mm from the periphery of the ulcer. When debridement was required, the biopsy was obtained prior to the foot being opened. Standard microbiological methods were employed to isolate and identify bacterial pathogens.

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Eighty-one bone biopsy samples and 69 swab samples were obtained from 76 patients. A mean of approximately 1.5-1.6 bacterial species were isolated from both culture sources. Interestingly, staphylococci were isolated much more frequently from bone samples (52%) than from swab samples (38%), but the isolation rate for *Staphylococcus aureus* was fairly similar (26% bone vs 33% swab). Somewhat counterintuitively, the difference is largely explained by the fact that coagulase negative staphylococci were isolated much more often from bone than from wound swabs (26% vs 5%). Streptococci were isolated from only 12% of bone biopsy specimens and 20% of ulcers. Gram negative bacilli were obtained from 18% of bone and 26% of swab samples. Anaerobes were isolated from 5% of bone and 3% of swab specimens. When looking at the proportion of pathogens isolated from cultures of bone biopsy and/or swab samples obtained from the 69 patients who had cultures from both sources, the concordance was poor. The percent concordance for *S. aureus* was 43%, for gram negative bacilli 29%, streptococci 26%, enterococci 7%, coagulase negative staphylococci 3%, and there was no concordance for corynebacteria and anaerobes.

COMMENTARY

This study serves as a good reminder of the historically poor reliability of superficial swab cultures in diagnosis of the etiologic agents causing diabetic foot infections in individual patients. Even the old saw I have been repeating for 30 years to fellows, residents, and students that, "only when one isolates *S. aureus* in pure culture from an ulcer can one assume that is the cause of the osteomyelitis," is proved false by this study. While surgical debridement is necessary in many cases, virtually all patients with osteomyelitis complicating diabetic foot infections will also require prolonged, often parenterally administered antibiotics. Because of the toxicities, expense, and potential inactivity of empirically chosen and excessively broad-spectrum antibiotics, it behooves us as hospital medicine clinicians to push our medical and surgical colleagues to obtain bone biopsies for culture so we can properly treat these serious infections. ■

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Toxic Shock Syndrome After Medical Abortion

ABSTRACT & COMMENTARY

By Leon Speroff, MD

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Dr. Speroff reports no relevant financial relationship related to this field of study.

This article originally appeared in the February 2006 issue of OBGYN Alert. *It was peer reviewed by Catherine Leclair, MD. Dr. Leclair is Assistant Professor, Obstetrics and Gynecology, Oregon Health and Sciences University, Portland. She reports no relevant financial relationship related to this field of study.*

Synopsis: *Rare cases of fatal toxic shock syndrome associated with* Clostridium sordellii *have been reported; clinicians are urged to be aware of warning signals.*

Source: Fischer M, et al. Fatal Toxic Shock Syndrome Associated with *Clostridium sordellii* After Medical Abortion. *N Engl J Med.* 2005;353:2352-2360.

THE CDC REPORTED 4 CASES OF FATAL TOXIC SHOCK syndrome in California associated with *Clostridium sordellii* that occurred within one week after medical abortions (induced with 200 mg of oral mifepristone and 800 µg of vaginal misoprostol).[1]

Patient 1: A healthy 18-year-old woman underwent medical abortion at 47 days gestation, and 4 days later was seen in an emergency ward with abdominal cramping. She was afebrile and there was no tenderness on physical examination. No laboratory studies or cultures were obtained. Three days later, the patient returned with nausea, vomiting, and weakness. She was again afebrile, but now had tachycardia, hypotension, an extremely elevated white count, blood cultures that later were negative, and bilateral infiltrates on chest X-ray. She still had no positive findings on physical examination. Despite treatment with antibiotics, the patient rapidly developed respiratory distress and died 10 hours after admission.

Patient 2: A healthy 21-year-old woman underwent medical abortion at 43 days gestation and became unresponsive 6 days later. Resuscitation was unsuccessful. No laboratory studies or cultures were performed.

Patient 3: A healthy 22-year-old woman underwent medical abortion at 53 days gestation and presented to an emergency ward 5 days later with nausea, vomiting, diarrhea, and abdominal pain. The patient had normal vital signs except for mild tachycardia. The patient was admitted to rule out an ectopic pregnancy, and the next day developed hypotension, diffuse abdominal tenderness, a white count of 120,200 cells/μL, and metabolic acidosis. Blood cultures before antibiotic treatment were negative. Within a few hours, the patient had a cardiopulmonary arrest. Emergency laparotomy revealed a large amount of serous peritoneal fluid that failed to grow aerobic or anaerobic bacteria. The patient died during surgery, 23 hours after coming to the hospital.

Patient 4: This healthy 34-year-old woman had her medical abortion at 45 days gestation and presented to an emergency ward 4 days later with nausea, vomiting, and abdominal pain. Vital signs were normal, and the only finding on physical examination was abdominal tenderness. Her white count was elevated, and cultures of blood and urine were later negative. Despite antibiotic treatment, the patient went into refractory hypotension and died 12 hours after presenting to the hospital.

The autopsies revealed pleural, pericardial, and peritoneal effusions, inflammation of endometrium and myometrium with multiple small abscesses, necrosis, and hemorrhage without gas formation. There were no retained fetal or placental tissues. Formalin-fixed tissues were obtained by the CDC, and *Clostridium sordellii* was identified in uterine tissues by a nonspecific polyclonal anti-clostridium antibody, followed by specific polymerase-chain-reaction assays on extracted DNA.

COMMENTARY

Clostridium sordellii is a Gram-positive anaerobic bacillus that has been previously identified as a cause of fatal toxic shock syndrome in 10 cases in the United States, 8 within 1 week after delivery of live-born infants, one within a week after a medical abortion, and one not associated with pregnancy (and one more case in Canada following medical abortion). The clinical and pathological findings (responses to exotoxins) in the 4 new cases and the 10 previous cases were similar. Clostridium species are known to colonize the vagina and to be associated with postpartum endometritis and septic abortion. Recognized infections with *Clostridium sordellii*, however, are very rare, although this rare prevalence may be partly due to the difficulty in the isolation and identification of this organism. The usual anaerobic culture techniques seem to be insufficient for timely diagnosis. The FDA has reported that testing the manufacturing lots of mifepristone and misoprostol has indicated no evidence of bacterial contamination.

How great is the risk? The 4 patients in this report and the one previous case (whose death was attributed to a ruptured ectopic pregnancy) represent the only fatal cases recognized after nearly 500,000 uses of medical abortion in the United States since mifepristone was approved in 2000. The mortality rate is estimated to be from 1.0 to 1.5 per 100,000; a rate that would be higher than that associated with legal surgical abortions. The number of American women reported as dying from abortion declined from nearly 300 deaths in 1961, to only 6 in 1985, 10 in 1992, and 4 in 1999, or about 0.6 deaths for every 100,000 legal abortions.[2,3] The risk of death from any cause associated with pregnancy is higher. For comparison, in 1990, the maternal death rate for childbirth in the United States was 10 per 100,000 births, and for ectopic pregnancy, approximately 50 per 100,000 cases,[4-6] and, in 1992, 17 deaths were associated with spontaneous miscarriage.[2]

Why haven't similar cases been reported in Europe? Philip Darney has speculated regarding the possibilities.[7] Because of equivalent efficacy and safety, the currently accepted method of medical abortion, supported by the recommendation of the World Health Organization, uses 200 mg mifepristone orally, followed the next day by 800 μg misoprostol vaginally; this differs from the FDA-approved regimen of 600 mg mifepristone orally, followed by 400 μg misoprostol also given orally. Thus, one might suspect different American and European experiences to reflect the different dose of mifepristone; however, American clinicians have not followed the FDA-approved regimen, but instead, used the European lower-dose regimen that has solid clinical trial support. The use of self-administered vaginal misoprostol in America is different compared with the European practice of administering misoprostol by health care personnel in a clinic setting. Darney questions whether the misoprostol oral route with its equivalent pharmacokinetic behavior might be preferable.

Is there an alteration in immunity secondary to one of the drugs. McGregor and Equiles suggest that mifepristone may impair stress responses by blocking both progesterone and glucocorticoid receptors.[8] On the other hand, Grimes points out that infection with Clostridium sordellii has occurred without exposure to mifepristone.[9]

At this point in time, no changes have been suggested in the regimen used for medical abortion. The best prevention of fatal toxic shock with this rare infection is awareness of the possibility and early recognition. Abdominal cramping as a presenting complaint makes the diagnosis difficult because this is a common symptom following medical abortion. Unique characteristics include: the absence of fever, markedly elevated white counts, fluid effusions sufficient to produce hemoconcentration, and eventually tachycardia and hypotension. Specific antibiotics with demonstrated efficacy against *Clostridium sordellii* have not been identified. Early recognition of this rare infection would mandate consideration of aggressive surgery with hysterectomy, a lesson learned from the experience with septic abortions in the years before legalized abortion. ■

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Forgotten Hazards of Sedatives

ABSTRACT & COMMENTARY

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

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

This article originally appeared in the February 2006 issue of Critical Care Alert. *It was reviewed by the physician editor, David J. Pierson, MD, and peer reviewed by William Thompson, MD. Dr. Pierson is Professor, Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington. He reports no relevant financial relationship related to this field of study. Dr. Thompson is Board Certified in Critical Care Medicine, Pulmonary Medicine, and Internal Medicine, VA Medical Center, Boise, Idaho. He reports no relevant financial relationship related to this field of study.*

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

Source: Wilson KC, et al. Propylene Glycol Toxicity: A Severe Iatrogenic Illness in ICU Patients Receiving IV Benzodiazepines: A Case Series and Prospective, Observational Pilot Study. *Chest*. 2005;128:1674-1681.

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

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

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

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

COMMENTARY

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

The study clearly has numerous limitations. It is a small, single-center, unblinded observational study. Thus, considerable bias (in patient selection and management and data collection and interpretation) may exist, and certainly the incidence results may not be generalizable. It is unclear exactly what criteria were used to determine whether there was an alternate explanation for acidosis or hyperosmolality in patients classified as having propylene glycol toxicity. It is difficult from these data to define specific threshold levels of benzodiazepines that may lead to toxicity or to

determine a threshold level of propylene glycol beyond which toxicity occurs. Further investigation is indicated to address these issues. More information is also needed to understand when and why propylene glycol toxicity may result in clinical deterioration. Long-term outcomes of toxicity (if any) ought to be investigated. Finally, the mechanism(s) of toxicity must be more clearly elucidated.

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

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Anticoagulation for Atrial Fibrillation in Acute MI

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

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Dr. Crawford is on the speaker's bureau for Pfizer.

This article originally appeared in the February 2006 issue of Clinical Cardiology Alert. *It was peer reviewed by Rakesh Mishra, MD, FACC. Dr. Mishra is Assistant Professor of Medicine, Weill Medical College, Cornell University, Assistant Attending Physician, NewYork-Presbyterian Hospital. He reports no relevant financial relationship related to this field of study.*

Synopsis: *In daily clinical practice, OAC was only given to a minority (30%) of AMI patients with AF, despite the fact that OAC was associated with a 29% relative and 7% absolute reduction in 1-year mortality after adjustment for confounding variables. The results emphasize the importance of OAC treatment for AF after AMI.*

Source: Stenestrand U, et al. Anticoagulation Therapy in Atrial Fibrillation in Combination with Acute Myocardial Infarction Influences Long-Term Outcome: A Prospective Cohort Study from the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA). *Circulation*. 2005;112:3225-3231.

ALTHOUGH THE ACC/AHA GUIDELINES RECOMMEND oral anticoagulants for atrial fibrillation (AF) complicating myocardial infarction (MI), it is not always given. Thus, Stenestrand and colleagues from the Register of Information and Knowledge about the Swedish Heart Intensive Care Admissions studied oral anticoagulation (OAC) usage in post-MI patients with AF, and evaluated its effect on mortality at one year. Patients admitted to Swedish hospitals with acute MI discharged alive between 1995 and 2002 were assessed. There were 6182 patients with acute MI and AF on the discharge ECG (7.6% of the total MI population). The incidence of AF increased with age. Most (78%) had AF on admission. In 29%, OAC was prescribed at discharge, 60% were given aspirin or thienopyridine, and 11% received no antiplatelet or anticoagulant therapy. Mortality at one year was highest for those on nothing (45%), as compared to those on platelet inhibitors only (31%) and those on OAC (22%). Of those on OACs at discharge, 46% were taking it on admission. There was no difference between the treatment groups with regard to reperfusion therapy and heart failure. OAC use reduced one-year mortality (RR .73) primarily due to reduced ischemic cardiac death (55.6 vs 62%). Fatal stroke was reduced from 7.5 to 5.7% in the OAC group. No subgroup benefited more than others. Stenestrand et al concluded that OAC use in post-MI AF patients was associated with a significant reduction in one-year mortality.

■ COMMENTARY

Although this is an observational study, there are no prospective trials of therapy for AF complicating acute MI. The AF trials excluded acute MI patients. Yet this is an important issue since about 10% of acute MI patients have AF. In this cohort, about one-third were treated with OACs and all the rest received antiplatelet drugs. Those treated with OACs clearly did better in terms of one-year mortality.

Prior studies of aspirin plus fixed low-dose OAC (CARS, CHAMP) in post acute MI patients showed no benefit. However, INR > 2.0 adjusted OAC plus aspirin in 2 trials in post MI patients did show a reduction in the combined end point of death, reinfarction, and stroke (ASPECT-2, WARIS-2). However, bleeding rates doubled. In this study, bleeding rates were not higher on OAC.

Although deaths due to vascular causes were reduced in this study by OACs, other causes of death were increased on OACs from 21.9% to 27.6%. Most patients died of the acute MI or other ischemic complications. Stroke deaths were in the 6-7% range and were reduced by OAC. Nonfatal strokes were also reduced from 10% to 8%. Thus, the usual recommendation for oral anticoagulants for AF in any setting would seem to apply to acute MI patients. In this group, like any other, aspirin and other antiplatelet drugs are not as effective. This study supports the general conclusions of the AF OAC studies. What is surprising is that only one-third of post MI patients with AF got OAC. Some may have had contradictions to their use, but more likely physicians were afraid to load up the drugs that can cause bleeding in this patient group. This fear seems unfounded in this observational study. The benefits of OAC exceeded the risks. ■

Prophylactic Amiodarone After Heart Surgery

ABSTRACT & COMMENTARY

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This article originally appeared in the February 2006 issue of Clinical Cardiology Alert. *It was originally reviewed by the physician editor, Michael H. Crawford, MD, and peer reviewed by Rakesh Mishra, MD, FACC. Dr. Crawford is Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco. He is on the speaker's bureau of Pfizer. Dr. Mishra is Assistant Professor of Medicine, Weill Medical College, Cornell University, Assistant Attending Physician, NewYork-Presbyterian Hospital. He reports no relevant financial relationship related to this field of study.*

Synopsis: *Oral amiodarone prophylaxis of atrial tachyarrhythmias after cardiac surgery is effective and well tolerated.*

Source: Mitchell LB, et al. Prophylactic Oral Amiodarone for the Prevention of Arrhythmias That Begin Early After Revascularization, Valve Replacement, or Repair: PAPABEAR: A Randomized Controlled Trial. *JAMA*. 2005;294:3093-3100.

Atrial fibrillation remains a common and vexing problem after cardiac surgery. In this report, we find the results of the Prophylactic Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valve Replacement, or Repair (PAPABEAR) trial. This was a randomized, controlled study of patients undergoing non-emergent CABG surgery and/or valve surgery. Patients scheduled for elective cardiac surgery were randomized to receive amiodarone or matching placebo in a double-blind fashion with stratification for age, type of surgical procedure, and preoperative beta blocker treatment. Treatment with amiodarone or placebo was begun 6 days prior to surgery, and continued through the first 6 days after surgery. The amiodarone dose was 10 mg/kg daily divided into 2 doses. Patients were treated before surgery as outpatients. Continuous telemetry ECG monitoring was then begun during their operation and continued for the subsequent 6 days. The primary outcome event was documentation of an atrial tachyarrhythmia during the first 6 days after surgery. The atrial tachyarrhythmia had to last for 5 minutes or longer, and require treatment by the attending physician.

Over a 4-year period, a total of 601 patients were randomized into the PAPABEAR trial. The groups were well matched. The mean age of the patients was 61.6 years, and 82% were male. Sixty-five percent had CABG surgery only. Thirty-five percent had valve replacement or repair with or without associated bypass surgery.

Postoperative atrial tachyarrhythmias occurred in 48 of 299 amiodarone patients (16.1%) vs 89 out of 302 (29.5%) placebo patients. Among the patients with arrhythmias, atrial fibrillation was observed in 128 patients and atrial flutter in 9. The peak occurrence in both groups was between day 2 and day 5 after surgery. The hazard ratio for atrial arrhythmias on amiodarone vs placebo was 0.52, and the absolute reduction was 13.4%. Similar hazard ratios in favor of amiodarone were observed when patients were stratified by age, type of surgery, and preoperative beta blocker use.

The durations of postoperative intensive care unit stays were equivalent in the amiodarone and placebo groups, with a slight decrease in total post-hospital stay for the amiodarone patients (8.2 vs 8.9 days, $P = 0.11$). There were 7 deaths in the placebo group vs 5 in the amiodarone group. Sustained ventricular arrhythmias were less common in the amiodarone group than in the placebo group (0.3% vs 2.6%, $P =$ O.04). Adverse events that led to discontinuation of study drug or dosage reduction were more common in the amiodarone group than in the placebo group. The most common reasons for stopping or reducing therapy were: bradycardia requiring temporary pacing (5.7% vs 2.0%), QT prolongation over 650 m/sec (1.3% vs 0%), and rash (1% vs 0%). Other perioperative complications did not differ between the groups. There were no differences in either readmission to the hospital within 6 months or in one year mortality between the 2 groups.

Mitchell and colleagues conclude that perioperative or oral amiodarone is an effective and well tolerated approach for reducing postoperative atrial tachyarrhythmias after cardiac surgery.

COMMENTARY

The PAPABEAR trial is the largest study reported to date involving the use of perioperative oral amiodarone in patients scheduled for elective cardiac surgery. Prior studies have indicated that beta adrenergic blockers are also effective in reducing postoperative AF. This study shows that oral amiodarone can be safely begun as an outpatient before surgery and can be used with benefit both alone and in addition to beta blockers. Although no significant changes were observed in the duration of hospital stay, there was a trend towards a favorable decrease in length of stay.

Also noted were slight decreases in the frequency of ventricular arrhythmia and in postoperative mortality.

Toxicity is always a question with amiodarone. In PAPABEAR, patients with preoperative bradycardia, QT prolongation, thyroid or hepatic disease, and interstitial pulmonary disease were excluded to minimize the potential for toxicity. After these precautions, the major adverse effect reported was the need for temporary pacing after operation. We are not told if this was confined to the early postoperative phase and, could therefore, be easily treated using epicardial pacing wires. If pacing was needed only in the first 24 to 48 hours after operation, as seems likely, this should not be a major problem. If, however, the bradycardia occurred later in the hospital stay, this would prolong ICU admission and probably require insertion of another transvenous temporary pacing wire, increasing costs, and subjecting the patient to an additional procedure. As expected, other adverse events were minor since the course of therapy was quite short.

The outcome of the PAPABEAR trial and earlier studies indicate that there are significant advantages to a short perioperative course of amiodarone in patients undergoing elective cardiac surgery. Routine use of this approach, particularly in patients at high risk for atrial arrhythmias, should be considered by cardiologists and cardiac surgeons. ■

Aminophylline in COPD Exacerbations: Just Say No

ABSTRACT & COMMENTARY

By David J. Pierson, MD

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Dr. Pierson reports no relevant financial relationship related to this field of study.

This article originally appeared in the February 2006 issue of Critical Care Alert. *It was peer reviewed by William Thompson, MD. Dr. Thompson is Staff Pulmonologist, VA Medical Center, Associate Professor of Medicine, University of Washington. He reports no relevant financial relationship related to this field of study.*

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

Source: Duffy N, et al. Intravenous Aminophylline in Patients Admitted to Hospital with Non-Acidotic Exacerbations of Chronic Obstructive Pulmonary Disease: A Prospective Randomised Controlled Trial. *Thorax*. 2005;60:713-717.

In this study from the University of Liverpool, Duffy and colleagues sought to determine whether the addition of intravenous aminophylline produced clinically important improvements in the rates of symptomatic recovery or increases in pulmonary function, and whether it shortened hospital stay, in comparison with standard therapy without aminophylline, among patients with COPD who were admitted with an exacerbation. The latter was strictly defined according to accepted criteria, and patients with asthma, pneumonia, pneumothorax, malignancy, or serious cardiac disease were excluded. Because the use of noninvasive ventilation has become standard therapy for such patients if they are acidemic, and could have confounded the results, only patients with arterial pH > 7.32 were included.

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

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

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

cally significant alterations in acid-base balance, aminophylline produced no improvement in symptoms or clinical course and caused more nausea than placebo.

COMMENTARY

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

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

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

References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). www.goldcopd.com.
2. American Thoracic Society/European Respiratory Society Task Force. Standards for the Diagnosis and Management of Patients with COPD [Internet]. Version 1.2. New York: American Thoracic Society; 2004 [updated 2005 September 8].www.thoracic.org/copd
3. National Collaborating Centre for Chronic Conditions. Chronic Obstructive Pulmonary Disease. *Thorax*. 2004;59(Suppl 1):1-232. www.thorax.bmjjournals.com/content/vol59/suppl_1
4. Town GI. Aminophylline for COPD Exacerbations? Not Usually. *Thorax*. 2005;60:709.

CME Questions

1. In patients with atrial fibrillation as a complication of myocardial infarction:
a. treatment with antiplatelet agents or oral anticoagulants does not affect outcome in this subgroup of patients with atrial fibrillation.
b. oral anticoagulation reduced 1 year mortality.
c. the incidence is higher in younger patients.
d. antiplatelet agents were equal in efficacy to oral anticoagulants in improving survival.

2. Compared to placebo in patients hospitalized for acute exacerbations of COPD, intravenous aminophylline:
a. did not cause an increase in adverse symptoms.
b. led to a more rapid improvement in dyspnea.
c. had no appreciable beneficial effects on the clinical course of the exacerbation.
d. led to a more rapid improvement in spirometry.

3. In patients with diabetic foot infections and osteomyelitis who underwent bone biopsy:
a. the concordance between bone biopsy and wound swab cultures was poor.
b. coagulase-negative staphylococci were not isolated from bone biopsy despite being present on wound swab cultures.
c. the concordance between bone biopsy and wound swab cultures was excellent thus negating the need for bone biopsy.
d. gram-negative rods were not a cause of osteomyelitis.

Answers: 1. (b); 2. (c); 3. (a)