CRITICAL CARE PHARMACOLOGY LITERATURE UPDATE

October 2010

This monthly review of select articles has been compiled and prepared as a service to the members of the Clinical Pharmacy and Pharmacology (CPP) Section of the Society of Critical Care Medicine (SCCM). The content below is for information purposes only and is intended to highlight recent articles that may be of interest to the CPP membership. Though some core content from the publications is presented, the reader is encouraged to review each article in full for additional detail in order to fully interpret the study and its findings.

CONTENTS

RANDOMIZED CONTROLLED TRIAL OF INTRAMUSCULAR DROPERIDOL VERSUS MIDAZOLAM FOR VIOLENCE AND ACUTE BEHAVIORAL DISTURBANCE: THE DORM STUDY.

Isbister GK, Calver LA, Page CB, et al. *Ann of Emerg Med*. 2010; 56(4): 392-401.

Violence and acute agitation is a significant burden in the emergency department. Treatment of patients with this condition is often times complicated by alcohol intoxication and drug abuse. Two drug classes, benzodiazepines and antipsychotics have been studied for stabilization of patients with acute behavioral disturbances in the ED. Oftentimes, patients have a tolerance to the effects of benzodiazepines and large doses are necessary. This may result in over-sedation. Use of antipsychotics, such as droperidol and haloperidol, has fallen out of favor in some institutions due to the reported risk of arrhythmias and QTc prolongation. This study is a prospective, randomized controlled trial comparing intramuscular droperidol (10 mg), midazolam (10 mg), and a combination droperidol (5 mg) with midazolam (5 mg) for the treatment of acute behavioral disturbance in adult ED patients. Additional sedation could be ordered at the discretion of the treating physician. Overall (N=91), there was no significant difference in the duration of acutely agitated behavior (p = 0.66). Droperidol resulted in a more consistent level of moderate sedation, while sedation with the combination and midazolam alone was highly variable and unpredictable. In general, over sedation was more common in the midazolam group. Furthermore, most cases of over sedation with droperidol or the combination groups occurred after the administration of a supplemental benzodiazepine. The combination of alcohol and benzodiazepine use also increased the risk of over-sedation and respiratory depression. There was no significant difference in rates of QTc prolongation between the groups. Based on results of this study, authors recommend the use of droperidol over midazolam for the treatment of acute behavioral disturbances in the ED.

NEUROMUSCULAR BLOCKERS IN EARLY ACUTE RESPIRATORY DISTRESS SYNDROME.

Papazian L, Forel J, Gacouin A, et al. *N Engl J Med*. 2010;363:1107-16.

Neuromuscular blockings agents (NMBAs) have been associated with improved oxygenation in patients with ventilator dyssynchrony secondary to acute respiratory distress syndrome (ARDS). This multicenter, randomized, placebo-controlled, double-blinded study was designed to evaluate whether NMBAs, in conjunction with lung-protective mechanical ventilation settings, would improve mortality in patients with early ARDS. Patients (N=340) meeting the following criteria were enrolled from 20 ICUs in France: endotracheal mechanical ventilation with a PaO2:FiO2 ratio < 150 on a PEEP of ≥ 5 cm of water and V_T 6-8 mL/kg with bilateral infiltrates consistent with edema for ≤ 48 hours prior to enrollment. The primary outcome, 90-day mortality, was improved in patients receiving cisatracurium when adjusted for baseline PaO2:FiO2 ratio, SAPS II, and plateau pressure (p=0.04). The intervention group also had more ventilator-free days for the first 28 days (10.6 vs 8.5, p=0.04) and 90 days (53.1 vs 44.6, p=0.03), more days outside of the ICU during the first 90 days (47.7 vs 39.5, p=0.03), and more days without organ failure excluding respiratory failure (15.8 vs 12.2, p=0.01). Muscle strength, evaluated based on the Medical Research Council scale, did not differ significantly between groups at day 28 or at ICU discharge. Due to the blinded nature of the study, significant deviations from current ICU NMBA practice were made including the use of a non-weight based, non-titratable cisatracurium regimen and the absence of peripheral nerve stimulator monitoring. Based on this study, adjunct NMBAs may be useful in improving clinical outcomes in patients with early ARDS.

Prospective, Randomized Comparison of Lansoprazole Suspension, and Intermittent Intravenous Famotidine on Gastric pH and Acid Production in Critically Ill Neurosurgical Patients

Gretchen M. Brophy, Marcia L. Brackbill, Katherine L. Bidwell, Donald F. Brophy. *Neurocrit Care* (2010) 13:176-181

Neurosurgical critical care patients are at increased risk of stress-related mucosal disease (SRMD) due to the possibility of gastric acid hypersecretion, mechanical ventilation, and hemodynamic instability. Prophylactic pharmacotherapy is a mainstay of stress ulcer prophylaxis (SUP). This single-center randomized, prospective trial compared the effects of lansoprazole (LAN) 30mg per nasogastric (NG) tube once daily with famotidine (FAM) 20mg IV every 12 hours for SUP. Patients with active GI hemorrhage, prior use of anti-secretory agent during admission, history of gastric or duodenal ulcers, gastric pH > 4 prior to first dose of medication, allergy to study drugs, pregnancy, or renal compromise were excluded. Investigation of the primary outcome, time to gastric pH > 4, found that 17 (74%) of the FAM patients and 10 (36%) of the LAN patients had a pH > 4 on day one. There was no difference in pH at day two or three. Additionally, there was no difference in the percent of time gastric residual volumes were < 28mL in either group on any day. More patients in the FAM group had heme-positive gastric aspirates on day one, but this difference was not associated with worse outcomes such as GI ulceration and/or overt bleeding. This difference was not evident for days two or three. There was no difference in the secondary outcome of clinically significant bleeding between the groups, but an increased rate of thrombocytopenia was noted in the FAM group (17% for FAM vs. 4% for LAN). For this small prospective trial (n = 51), LAN and FAM appear to be equally effective at increasing gastric pH, but the delay seen with LAN suggests a loading dose may be required.

Beta-adrenergic blockade and traumatic brain injury: protective?

Schroeppel TJ, Fischer PE, Zarzaur BL, Magnotti, et al. *J Trauma* 2010; 69(4): 776-782.

Sympathetic storm, a condition usually manifested by fevers, tachycardia, hypotension or hypertension, hypoventilation and rigidity, is a phenomenon that frequently complicates the care of traumatic brain injured patients. Beta blockers (BB), along with other therapies such as bromocriptine and opioid narcotics, are used to control this excessive sympathetic drive. The current study compared a retrospective cohort of trauma patients that received BB (n=506) as a part of their care to those patients who received no BB (n=2095). Patients in the BB group were generally older (51 vs 38 years; $p<0.0001$) and had higher injury severity scores (30 vs 25; $p<0.0001$). Patients in the BB group also had significantly higher head abbreviated injury scale and lower Glasgow Coma Scale (GCS) at baseline. In spite of these differences at baseline, there was no difference in the unadjusted mortality of the entire population. In addition, when mortality was analyzed and adjusted for confounders including age, admission GCS and injury severity score, the BB group had a significantly lower odds of dying (OR 0.347; CI 0.246-0.490). This study was retrospective and non-interventional; therefore the results must be interpreted with caution. Regardless, this adds to the existing body of literature which suggests beta-adrenergic blockade is protective in the traumatic brain injury population. Randomized controlled trials are needed.

Nationwide implementation of adjunctive dexamethasone therapy for pneumococcal meningitis

Brouwer MC, et al. *Neurology* 2010;75:1-7.

Some data exist suggesting patients with bacterial meningitis, particularly from *Streptococcus pneumoniae*, may benefit from receipt of dexamethasone therapy; however its use remains controversial. This multicenter, prospective, cohort study conducted in the Netherlands sought to assess the impact of routine dexamethasone therapy on Glasgow Outcome Score (GOS) compared to historical controls who did not routinely receive corticosteroids. The cohort included 357 patients who were > 16 years of age with pneumococcal meningitis, 92% of whom received dexamethasone therapy. Excluded patients had culture-negative cerebrospinal fluid or hospital-acquired meningitis. The control sample was made up of 352 patients of whom 17% received dexamethasone therapy. The primary endpoint of favorable outcome according to GOS occurred in 61% of routine corticosteroid patients and 50% of controls (p=0.002). Other significant findings included a reduction in mortality (20% vs 30%; p=0.001), neurological complications (60% vs 75%; p<0.001), cranial nerve palsy at discharge (17% vs 28%; p=0.003) and hearing impairment at discharge (12% vs 22%; p=0.001) in the routine dexamethasone group compared to the controls. Although this study demonstrates that the impact of corticosteroids in pneumococcal meningitis has the potential to improve outcomes, it is a purely observational analysis with variable time to administration relative to the antimicrobials. Unfortunately, the prospective identification of individuals with pneumococcal meningitis for whom this therapy might be beneficial continues to be challenging. Furthermore, the potential adverse consequences of corticosteroids in non-pneumococcal meningitis have not been well-defined.

Utility of ampicillin-sulbactam for empiric treatment of ventilator-associated pneumonia in a trauma population.

McMillian WD, Bednarik JL, Aloi JJ, Ahern JW, Crookes BA. *J Trauma*. 2010;69:861-5.

The 2005 ATS/IDSA guidelines on the treatment of ventilator-associated pneumonia (VAP) make the distinction between treatment regimens for patients who *are* versus *are not* thought to be at risk of infection with multidrug-resistant pathogens (MDRPs). While patients with MDRP risk factors and suspected VAP should receive combinations of broad-spectrum agents empirically, the ATS/IDSA guidelines recommend a leaner, more narrow-spectrum approach to early VAP cases *without* MDRP risk factors, specifically monotherapy with: ampicillin/sulbactam (AMP/SUL); ceftriaxone; a quinolone; or ertapenem. Citing past studies demonstrating better than 85% sensitivity of early-onset VAP pathogens to AMP/SUL, the present study's authors set out to verify the results in their own rural trauma population. They enrolled 121 adult patients who had been on mechanical ventilation (MV) for at least two days, were treated with IV antibiotics, and had at least one of the following: a clinical diagnosis of VAP; an endotracheal tube aspirate culture; or a positive bronchoalveolar lavage. Researchers found that the three most prevalent bugs were MSSA (23.9%), *H. influenza* (20.9%), and *P. aeruginosa* (11.7%) and, from days 3 through 7, the prevalence of AMP/SUL *resistance* among isolates ranged from 26% to 50%, with the number of resistant isolates *past* day 7 exceeding 60%. On the basis of their results, the study's authors conclude that, contrary to guideline recommendations and past studies, AMP/SUL *is not* a good choice for empiric treatment of early-onset VAP. They reasonably urge other institutions that use AMP/SUL for empiric early VAP treatment to conduct similar studies in-house.

OTHER ARTICLES OF INTEREST

A CRITICAL APPRAISAL OF THE QUALITY OF CRITICAL CARE PHARMACOTHERAPY CLINICAL PRACTICE GUIDELINES AND THEIR STRENGTH OF RECOMMENDATIONS

Gorman SK, Chung MH, Slavik RS, et al. *Intensive Care Med* 2010;36:1636-1643.

Clinical practice guidelines focused on pharmacotherapy in the critically ill play an important part in day to day bedside care, yet they are limited by a lack of quality supporting evidence. The purpose of this study was to systematically evaluate published guidelines and the scientific basis behind the recommendations. Using a tool called AGREE (Appraisal of Guidelines, REsearch, and Evaluation), which consists of 6 weighted domains, appraisers reviewed 24 guidelines published in the peer-reviewed literature in order to classify them into 3 categories: strongly recommend; recommend with alterations; or, not recommended. Of the 24 guidelines reviewed, 25% were strongly recommended, 37.5% were recommended with alterations, and 37.5% were not recommended. Those resulting as strongly recommended included guidelines on: management of severe traumatic brain injury; prevention of ventilator associated pneumonia; management of community acquired pneumonia; the Surviving Sepsis Campaign; cardiopulmonary resuscitation and emergency cardiovascular care; and stress ulcer prophylaxis. Only 36% of 248 reviewed guideline recommendations were deemed to be supported by quality evidence.

CONTINUOUS RENAL REPLACEMENT THERAPIES: A BRIEF PRIMER FOR THE NEUROINTENSIVIST
Patel P, Nandwani V, McCarthy PJ, Conrad SA, Scott LK. *Neurocrit Care* 2010;12:286-294.

ALCOHOL-USE DISORDERS IN THE CRITICALLY ILL PATIENT
de Wit M, Jones DG, Sessler CN, Zilberberg MD, Weaver MF. *Chest* 2010;138:994-1003.

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