CRITICAL CARE PHARMACOLOGY LITERATURE UPDATE

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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 the selected articles in full for additional detail in order to fully interpret the study and its findings.

Contents

Predictors of Initial Nontherapeutic Anticoagulation with Unfractionated Heparin in ST-Segment Elevation Myocardial Infarction.

Cheng S, Morrow DA, Sloan S et al. Circulation 2009; 119: 1195-1202.

Unfractionated heparin (UFH) is the anticoagulant of choice in the treatment of ST segment elevated myocardial infarction (STEMI). Weight based dosing nomograms have improved the safety and efficacy, but there still exists a wide degree of variation in attaining therapeutic goals. Data from The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis in Myocardial Infarction (ExTRACT-TIMI) 25 trial evaluated which patient characteristics influence the achievement of a therapeutic aPTT as well as the associated risk of bleeding with a markedly high aPTT (aPTT > 2.75 times control) or a recurrent thrombotic event with a markedly low aPTT (aPTT < 1.25 times control). UFH was dosed according to the American College of Cardiology/American Heart Association (ACC/AHA) weight based algorithm and was administered for a least 48 hours. Significant variation in aPTT values were seen and were more likely to be elevated in lower weight elderly female patients with elevated creatinine. The increased risk of markedly high anticoagulation was 14% for each decade increase in age ($p=0.001$), 46% if the patient were female ($p<0.001$), 19% for each 10kg decrease in weight ($p<0.001$) and 8% for an increase of serum creatinine by 0.2mg/dl ($p=0.006$). Additionally, markedly low anticoagulation was independently associated with decreasing age and increasing weight. When high or low aPTT occurred there was a 2-fold increased risk of TIMI major or minor bleeding or fatal/nonfatal recurrent MI by 48 hours, respectively. These data suggest that additional factors in addition to weight should be considered when dosing UFH in STEMI patients.

The incidence and nature of adverse events during pediatric sedation/anesthesia with propofol for procedures outside the operating room: a report from the Pediatric Sedation Research Consortium

Cravero JP, Beach ML, Blike GT, et al. Anesth Analg 2009; 108(3): 795-804

The use of propofol for pediatric sedation outside of the operating room (OR), although controversial, has been embraced by emergency medicine specialists and pediatric intensivists due to its rapid onset, effectiveness, and short duration. To date, studies assessing use in the pediatric population have been underpowered to evaluate safety. To better study sedation in pediatric patients, the multicenter Pediatric Sedation Research Consortium, a prospective registry of pediatric sedation/anesthesia, was developed. The primary objective of the study was to evaluate registry data to determine the rate of adverse events and unplanned airway interventions with propofol use outside of the OR. 88,227 cases were eligible for evaluation, and of these 49,836 (56%) utilized propofol as the primary sedative. A majority of cases were supervised by a pediatric intensivist (48.8%) or an emergency medicine physician (36%) and the primary procedures

identified were radiology (60%), hematology/oncology (14%), and gastrointestinal (11%). The most frequently reported co-administered medications included opioids (10.2%) and midazolam (7.6%). There were 2,950 total complications reported (1,170 pulmonary complications). Desaturation (154.5/10,000 cases) was the most frequent complication, followed by airway obstruction (93.2/10,000 cases) and inadequate anesthesia (85/10,000 cases). There were no deaths and 2 cardiac arrest cases which responded quickly to treatment. Authors conclude the incidence of serious adverse events was low, but there is a significant risk of events with the potential of causing harm if timely intervention is not anticipated and available.

Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock

Russell JA, Walley KR, Gordon AC, et al. Crit Care Med 2009;37:811-818.

The answer to whether there is an interaction between corticosteroids and vasopressin is unclear, and the investigators of this trial set out to address this controversial subject. This is a post hoc analysis of patients enrolled in the Vasopressin in Septic Shock Trial (VASST, NEJM 2008; 358:877-87), comparing treatment with vasopressin (AVP) to norepinephrine (NE) in septic shock. Russell et al further classified patients into subgroups of corticosteroid treatment (defined as corticosteroid administration for a minimum of 1 day out of the 28-day study period) or no corticosteroid treatment. A *significant reduction in 28-day mortality*, the primary outcome, was found in the steroid plus AVP group (n = 295, 35.4%) when compared to the steroids plus NE group (n = 293, 44.7%, p = 0.03). Similarly, a trend to more days free of organ dysfunction was noted in the steroids plus AVP group. An opposing pattern of outcomes was seen in non-steroid treated patients, in which AVP-treated patients exhibited a trend toward *increased* mortality and *more* organ failures versus NE patients. As hypothesized, the response to AVP based on corticosteroid use (logistic regression interaction statistic) was statistically significant (p = 0.008). Although the exact mechanism of interaction is unclear, previous studies have suggested steroids may increase AVP mRNA, improve hemodynamic responsiveness, have no effect, or even decrease AVP gene expression. In the current study, AVP levels were nearly doubled in patients receiving steroids. In summary, because this is a post hoc substudy and steroid use was not controlled nor defined a priori, these results suggesting improved outcomes with corticosteroid administration with AVP are simply hypothesis-generating. Additional studies to delineate a potential cause/effect relationship and mechanism of interaction are warranted before applying the findings clinical practice.

Feasibility of implementing a reduced fasting protocol for critically ill trauma patients undergoing operative and nonoperative procedures

Pousman RM et al. J Parenter Enteral Nutr. 2009; 33:176-80.

In the ongoing effort to reduce time to target attainment of post-procedure nutrition goals, an observational study conducted at Vanderbilt University has demonstrated that reducing fasting times *prior* to selected procedures in trauma patients is associated with a trend toward faster achievement of nutrition goals. Researchers compared a group of 41 mechanically ventilated trauma patients prior to the implementation of a reduced fasting protocol (control) to 34 patients *post*-implementation (intervention). Control patients went through fasting periods of at least eight hours pre-procedure; the protocol called for *small bowel* feeds up until the procedure or *gastric* feeds halted 45 minutes prior. Patients were eligible for participation if they were undergoing: orthopedic surgery of an extremity that did not require prone positioning; tracheostomy; percutaneous feeding tube placement; otolaryngeal or ophthalmologic surgery; or invasive, non-operative procedures like bronchoscopies and inferior venacaval filter placement. Intervention patients went a median of 29.5 hours without nutrition as compared to 38 hours in the control group ($p = 0.07$). Protocol patients reached nutrition goals in a median of 4.5 days versus 7 days in the control group ($p = 0.20$). While they had not conducted a formal power analysis prior to the study, the study's authors determined that they would have needed a total sample of 700 patients to detect the difference they observed in the study's primary outcome, total volume of enteral nutrition post-procedure, with 80% power. There were two episodes of hypoglycemia (blood glucose < 70 mg/dL) in the intervention group and none in the control group ($p = 0.03$); otherwise, there were no differences between groups in complication rates. The study's place in the literature is one of hypothesis generation, and the authors caution against applying their findings in the absence of controlled clinical trials.

Abbreviated Infusion of Eptifibatide after Successful Coronary Intervention: The BRIEF-PCI (Brief Infusion of Eptifibatide Following Percutaneous Coronary Intervention) Randomized Trial

Fung AY, Saw J, Starovoytov A, et al. JACC 2009; 53(10): 837-848

Eptifibatide given as a bolus dose followed by an 18 hour infusion was shown in the ESPRIT trial to decrease the composite endpoint of death, myocardial infarction (MI) and target vessel revascularization at 6 months. The BRIEF-PCI study was designed to compare the usual extended infusion with an abbreviated two hour infusion. Both groups received the standard bolus dose. After randomizing 624 patients with acute coronary syndromes who were undergoing non-emergent PCI, the two hour infusion was found to be non-inferior in terms of the incidence periprocedural ischemic myonecrosis and a 30 day composite outcome of MI, death, and target vessel revascularization. In addition, the

18 hour infusion was found to be associated with a higher risk of major bleeding (1% vs 4.2%). The investigators concluded that patients who undergo non-emergent successful PCI, and who do not have certain risk factors (recent STEMI, visible thrombus, unprotected left main intervention, or unsuccessful PCI), do not benefit from an eptifibatide infusion beyond 2 hours after PCI. In addition, the use of the shorter infusion minimizes risk of bleeding and reduces costs associated with eptifibatide treatment. The authors comment that the abbreviated infusion may allow for shorter hospital stay as well. Because this abbreviated infusion is limited to non-emergent PCI, it is unlikely to have a large impact in the critical care environment.

Methemoglobinemia related to local anesthetics: A summary of 242 episodes

Guay J. Anesth Analg. 2009; 108:837-45.

Methemoglobin is produced when the iron bound to hemoglobin is oxidized, converting it from its ferrous (Fe2+) to ferric form (Fe3+), making it incapable of oxygen transport. Typically, methemoglobin levels are maintained around 1 to 2% by reduction to hemoglobin with cytochrome b5 methemoglobin reductase and its cofactor, NADH. In the presence of direct or indirect oxidizers, such as local anesthetics, production of methemoglobin overwhelms the cytochrome reductase enzymatic system, leading to accumulation and associated toxicities of methemoglobinemia, such as cyanosis, altered mental status, respiratory distress, coma, and even death. This article reviewed 242 individual cases of local anesthetic-induced methemoglobinemia found in Pub Med from 1949 through 2007. Patient cases were included if the total dose of local anesthetic utilized was 10 mg/kg of lidocaine using the following conversion factors: lidocaine = 1, bupivacaine = 4, cocaine = 4, mepivacaine = 0.8, prilocaine =0.9, tetracaine = 4. The main local anesthetics implicated in reported cases were benzocaine (66%), prilocaine (28%), and lidocaine (5%). The wide inter-patient variability of response to the local anesthetics makes cases of methemoglobin difficult to predict. The author recommends avoiding benzocaine use in all patients due to the risk of methemoglobinemia induction with as little as one spray. Avoidance of prilocaine may be necessary in infants less than 6 months-old, pregnant women, those with glucose-6-phosphate dehydrogenase (G6PD) deficiency and patients receiving oxidizing drugs to reduce the incidence of methemoglobinemia. Finally, lidocaine should be restricted to patients who are not concomitantly receiving other oxidizing agents.

Continuous Infusion of Pantoprazole with Octreotide Does Not Improve Management of Variceal Hemorrhage

Alaniz C, Mohammad RA, Welage LS. Pharmacotherapy 2009; 29(3):248-254

Hemorrhage is a major, life-threatening complication of gastroesophageal varices. As such, this study proposed to assess the effectiveness of continuous infusion pantoprazole on patient outcomes with the recommended therapy for control of active variceal bleeding, octreotide. This was a retrospective cohort study which included 130 patients with documented variceal hemorrhage, determined by EGD, between January 2002 and

June 2005. Patients were assigned to 1 of 2 groups; a continuous infusion (pantoprazole n=53) > 24 hours or a control group (octreotide alone n=3, octreotide with <24 hours pantoprazole n=24, or octreotide with intermittent acid suppression n=50). The primary outcome was the number of packed RBC's transfused during hospitalization. Other outcomes included number of FFP, platelets, and cryoprecipitate transfused, endoscopic interventions, frequency of rebleeding, length of ICU stay, length of hospitalization and mortality rate. Authors found no significant difference in any outcome measures with the exception of FFP transfusion which was higher in the continuous infusion group (p=0.05). Patients most likely to benefit from pantoprazole infusion include those with bleeding from gastric varices, whereas most bleeding episodes in study patients were due to esophageal varices. Although no benefit was observed with continuous infusion of pantoprazole with octreotide in the treatment of varices, prospective studies are needed to better evaluate their role in this setting.

A clinical evaluation committee assessment of recombinant human tissue factor pathway inhibitor (Tifacogin) in patients with severe community-acquired pneumonia

Laterre P-F, Opal SM, Abraham E, et al. Critical Care 2009, 13:R36.

The coagulation-inflammation pathway continues to be a research target. The Phase III OPTIMIST Trial determined that the inhibition of tissue factor pathway with tifacogin resulted in no difference in 28 day all-cause mortality. Treatment benefit was found, however, in a subset of patients with pneumonia and who did not receive heparin. The purpose of the present study was to retrospectively determine the validity and categorization (HAP or CAP) of the subgroup pneumonia cases from the OPTIMIST Trial. Patients with CAP treated with tifacogin had lower 28-day all-cause mortality compared to placebo (27.9% versus 32.7%, p=0.25). In a subset of patients with microbiologic evidence of infection and no heparin administration, the difference widened (29.3% versus 51.9%, p=0.02). Tifacogin treated patients had more bleeding events, especially those on heparin. Results of this study reflect the high mortality associated with severe CAP and the potential importance of the coagulation-inflammation pathway, much like that seen in the PROWESS trial. This subgroup analysis is limited by its retrospective nature, and that diagnosis of pneumonia could be made with subjective evidence. This study is promising in that it specifies a subpopulation of sepsis, details that the current drotrecogin alfa data lack. Until followup studies are performed, FDA approval of tifacogin is unlikely based on the available data.

Recent Guidelines and Reviews of Interest

American Society for Parenteral and Enteral Nutrition. Enteral Nutrition Practice Recommendations.
J Parent Enteral Nutr 2009; 33(2):122-167

2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.
Circulation 2009; 119: DOI 10.1161/CIRCULATIONAHA.109.192064

Antimicrobial Stewardship in the Intensive Care Unit.
Lawrence KL, Kollef MH. Am J Resp Crit Care Med 2009; 179:434-438

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