
CRITICAL CARE PHARMACOLOGY LITERATURE UPDATE

November/December 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

A Comparison of the Effects of Etomidate and Midazolam on Hospital Length of Stay in Patients With Suspected Sepsis: A Prospective, Randomized Study	2
Outcomes of etomidate in severe sepsis and septic shock	2
Steady-state pharmacokinetics and BAL concentration of colistin in critically ill patients after iv colistin methanesulfonate administration	3
Aerosolized plus intravenous colistin versus intravenous colistin alone for the treatment of ventilator-associated pneumonia: a matched case-control study	3
Hyperoncotic colloids and acute kidney injury: a meta-analysis of randomized trials	4
Loss of protein, immunoglobulins, and electrolytes in exudates from negative pressure wound therapy	4
Safety of recombinant activated factor VII in randomized clinical trials.....	5
Ventilator-associated pneumonia is more common and of less consequence in trauma patients compared with other critically ill patients.	6
Other Articles of Interest	6
Contributors	6

A COMPARISON OF THE EFFECTS OF ETOMIDATE AND MIDAZOLAM ON HOSPITAL LENGTH OF STAY IN PATIENTS WITH SUSPECTED SEPSIS: A PROSPECTIVE, RANDOMIZED STUDY

Tekwani KL, Watts HF, Sweis RT, et al. *Annals of Emergency Medicine* 2010;56:481-489.

Over the past several years, the use of etomidate to induce sedation in patients with sepsis has raised concerns regarding its effects on adrenocortical function. Etomidate exerts its effects by blocking the conversion of cholesterol to cortisol as soon as 30 minutes after administration and up to 48 hours. The clinical significance of this has been a subject of debate. Authors of this prospective, double-blind, randomized study sought to determine the effect of a single dose of etomidate on hospital length of stay in patients with suspected sepsis compared to those who received midazolam during rapid sequence intubation (RSI). Patients (N=122) were randomized to receive one dose of either 0.3mg/kg of etomidate or 0.1mg/kg of midazolam as part of RSI if they had a suspected infectious cause for their illness and exhibited 2 of 4 SIRS criteria. Results showed no statistically significant difference in hospital length of stay or any of the secondary outcomes (in-hospital mortality, ICU length of stay, length of mechanical intubation). Authors did take into account use of steroid supplementation, which was used at the discretion of treating physician. No difference in mortality was observed between the two groups. A secondary analysis was done with those patients with confirmed sepsis, and results were similar. There was a numerically greater death rate in patients receiving etomidate, and this may have affected results by making it appear as though these patients had a shorter length of hospital stay. However, subgroup analysis of survivors also showed no difference. (AP)

OUTCOMES OF ETOMIDATE IN SEVERE SEPSIS AND SEPTIC SHOCK

Dmello D, Taylor S, O'Brien J, Matuschak GM. *CHEST* 2010; 138:1327-1332.

The beneficial and predictable pharmacodynamic properties of etomidate make it a favorable choice in hypotensive patients to induce sedation during rapid-sequence intubation (RSI). This retrospective cohort study sought to determine the effects of single-dose etomidate as well as the impact of adrenal suppression on mortality and outcomes in 224 consecutive patients with severe sepsis or septic shock who required intubation and mechanical ventilation within 48 hours of admission. Patients were categorized as having received etomidate during RSI or non-etomidate patients. Adrenal insufficiency was defined as a baseline cortisol level of $<15 \mu\text{g/dL}$ or a failure of $\geq 9 \mu\text{g/dL}$ response to a $250 \mu\text{g}$ IV bolus of ACTH. Of the 66 etomidate and 58 non-etomidate patients who were tested within 72 hours of intubation, 24% and 22%, respectively, were diagnosed with adrenal insufficiency. Total hospital mortality rate for all patients was 40%. The relative risk of mortality with etomidate was 0.92 (CI, 0.74-1.14; $p=0.51$). A correlation with etomidate and mortality was not seen when adjusted for demographics (OR, 0.9; CI, 0.45-1.83; $p=0.78$). A trend toward a greater risk for vasopressors use following etomidate was observed (RR, 1.16; CI, 0.9-1.51; $p=0.31$), but ICU length of stay and number of ventilator days was similar between the groups. The authors concluded that hospital mortality and outcomes were not altered with the use of single-dose etomidate during RSI in critically ill patients. Authors suggest conducting studies to determine if the use of steroids prior to or during RSI alters outcomes, and the effects of etomidate on adrenal function must be better understood. (MH)

STEADY-STATE PHARMACOKINETICS AND BAL CONCENTRATION OF COLISTIN IN CRITICALLY ILL PATIENTS AFTER IV COLISTIN METHANESULFONATE ADMINISTRATION

Imberti R, Cusato M, Villani P, Carnevale L, Iotti GA, et al. *CHEST* 2010;138:1333-39.

Little is known about the pharmacokinetics of colistin following intravenous administration in critically ill patients. Due to the recent availability of highly reliable HPLC based assays, the investigators aimed to evaluate plasma pharmacokinetics and BAL concentrations of IV colistin at steady state in critically ill patients. Thirteen adult patients with ventilator associated pneumonia caused by multidrug-resistant organisms were given 2 million IU (174 mg) of colistin methanesulfonate (CMS) IV every 8 hours via 30 minute infusion. Blood samples and BAL were obtained after at least 2 days of therapy. Patients with CrCl < 80 ml/min were excluded. Details of the individual pharmacokinetic parameters are available in the manuscript, and it was noted that there was significant interindividual variation. The mean plasma C_{max} was 2.21 ± 1.08 $\mu\text{g/mL}$ and the C_{trough} 1.03 ± 0.69 $\mu\text{g/mL}$. Two hours after the colistin infusion concentrations were undetectable in BAL, though in one patient receiving colistin via aerosol had a concentration on 0.48 $\mu\text{g/mL}$. The authors believe that the every 8 hour dosing is preferable to other regimens (Q12 or Q24h dosing) as the AUC/MIC ratio appears to be more important than achievement of high peak concentrations. Another important pharmacodynamic issue may be that, despite low concentrations, clinical cures are realized. This may be due to the tissue binding properties of colistin rather than tissue penetration. (PH)

AEROSOLIZED PLUS INTRAVENOUS COLISTIN VERSUS INTRAVENOUS COLISTIN ALONE FOR THE TREATMENT OF VENTILATOR-ASSOCIATED PNEUMONIA: A MATCHED CASE-CONTROL STUDY

Kofteridis et al. *Clinical Infectious Diseases* 2010; 51(11):1238-1244.

Ventilator-associated pneumonia (VAP) has been associated with increased morbidity and mortality in patients in the intensive care unit (ICU). The incidence of infections, such as VAP, continues to increase in ICUs due to multidrug-resistant pathogens such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. Polymyxin antibiotics, such as colistin, are being prescribed at an increased rate to treat these infections. This single center, retrospective matched case-control study was designed to compare the efficacy and safety of intravenous (IV) colistin to aerosolized (AS) plus IV colistin in patients diagnosed with multidrug resistant (MDR) gram-negative VAP. Patients included in this trial were admitted to the ICU with a culture-documented, monobacterial, colistin only sensitive VAP due to *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, or *Klebsiella pneumoniae*. Eligible patients (n=86) received either ≥ 6 doses of AS and ≥ 3 days of IV therapy (the AS-IV colistin group) or IV colistin for ≥ 3 days without AS colistin (the IV colistin group). The end point of clinical success (comprised of clinical cure or clinical improvement) of the treatment of VAP was not statistically significant amongst the two groups (60% IV and 74% AS-IV; $P = 0.10$), however the rate of clinical cure favored the AS-IV colistin group (32.5% IV and 54% AS-IV; $P = 0.05$). The secondary endpoints of mortality rate in the ICU ($p = 0.066$) and VAP mortality rate ($p = 0.289$) were not statistically significantly different. No difference in adverse effects was observed in patients who received AS-IV or IV colistin. Nephrotoxicity

occurred in 8 patients in each group (19%) and neurotoxicity was not observed in any patients in this study. Based upon these results, the authors concluded that the addition of AS colistin did not increase the efficacy of IV colistin in treating VAP due to MDR gram negative bacteria. (NT)

HYPERONCOTIC COLLOIDS AND ACUTE KIDNEY INJURY: A META-ANALYSIS OF RANDOMIZED TRIALS

Wiedermann CJ, Dunzendorfer S, Gaioni LU, Zaraca F, Joannidis M. *Crit Care* 2010;14(5):R191.

The objective of this meta-analysis was to assess whether infusion of hyperoncotic albumin (hALB) or hyperoncotic hydroxyethyl starch (hHES) solutions to prevent or correct hypovolemia increased the risk of acute kidney injury (AKI). Parallel-group randomized controlled trials were included if they evaluated the incidence of AKI in patients receiving 20-25% albumin or 10% hydroxyethyl starch versus control groups receiving crystalloid, 4-5% albumin, or no fluid. Of 109 identified clinical trials, 11 were included. There were a total of 1220 patients; hALB was evaluated in 7 trials and hHES evaluated in 4 trials. Control groups consisted of no fluid (7 trials), crystalloid (3 trials), and hypo-oncotic colloid (1 trial). Overall 199 (16%) patients developed AKI. hALB *decreased* the odds of AKI by 76% (OR 0.24, CI 0.12 to 0.48). hHES *increased* the odds of AKI by 92% (OR 1.92, CI 1.31 to 2.81). No evidence of heterogeneity or publication bias was noted with respect to the AKI endpoint for trials evaluating either hALB or hHES. There was 23% overall mortality within the 10 trials that reported at least 1 death. Odds of mortality were reduced by 48% with hALB (OR 0.52, CI 0.28 to 0.95). Alternatively, hHES raised the odds of mortality by 41% (OR 0.41, CI 1.01 to 1.96). Mortality data for hALB and hHES did not display heterogeneity or publication bias. Limitations of this meta-analysis include nonstandard criteria for diagnosing AKI and largely different populations between studies evaluating hALB (cirrhotic patients) and hHES (surgical population/sepsis). (JM)

LOSS OF PROTEIN, IMMUNOGLOBULINS, AND ELECTROLYTES IN EXUDATES FROM NEGATIVE PRESSURE WOUND THERAPY

Wade C, Wolf SE, Salinas R, et al. *Nutr Clin Pract* 2010; 25:510-6.

Estimating protein needs in critically ill patients presents challenges in patients with unusual losses in which protein content can not be quantified. In this study, authors measured total protein concentrations in wound exudate collected via negative pressure wound therapy (NWPT) from open abdominal wounds and soft tissue wounds in surgical/trauma ICU patients. A total of 26 20-ml exudate samples were collected from 8 open abdomens in 8 patients and 29 samples from 12 soft tissue wounds in 11 patients. The total protein concentration was similar between open abdomen and soft tissue wound exudate, 2.9 ± 0.9 g/dL and 2.59 ± 0.6 g/dL, respectively. In addition, authors assessed electrolyte concentration of wound exudate, which closely resembled serum electrolyte concentrations, e.g., mean sodium concentration in open abdomen wound and soft tissue wound exudate was 141.1 ± 7.6 mEq/L and 142.3 ± 9.8 mEq/L, respectively; potassium in exudate was 4.3 ± 0.57 mEq/L and 4.5 ± 0.5 mEq/L, respectively. Although the study was limited to a small number of patients, the results provide a basis for quantification of protein and electrolyte losses in wound exudate collected with NWPT. In this small sample of surgical/trauma critically ill patients, protein content of wound fluid totaled 29 grams per liter, and electrolyte content was similar to that of serum. (EN)

SAFETY OF RECOMBINANT ACTIVATED FACTOR VII IN RANDOMIZED CLINICAL TRIALS.

Levi M, Levy JH, Andersen HF, Truloff D. *New Engl J Med.* 2010;363:1791-800.

The use of recombinant activated coagulation factor VII (rFVIIa) has been used off-label with some frequency in recent years for the treatment of severe uncontrolled hemorrhage. Concerns remain about the safety of rFVIIa when used for this indication, as it theoretically increases the risk for thrombotic events. Indications for rFVIIa currently include prevention and treatment of bleeding in patients with congenital or acquired hemophilia, factor VII deficiency, or Glanzmann's thrombasthenia (the latter approved only in the European Union). The present study's authors set out to investigate the frequency of thrombotic complications when rFVIIa is used for off-label indications. They conducted a meta-analysis of 35 randomized controlled trials with 4,468 participants, including hemorrhaging patients (4,119 patients) and healthy volunteers (349). Rates of thrombotic events *overall* were *not* significantly different between those who had received *rFVIIa* (10.2%) and those who had received *placebo* (8.7%) for either actively hemorrhaging patients or volunteers. (Note: mortality rates *were not* examined in great detail in this meta-analysis.) When thrombotic events were separated into arterial or venous events, arterial thrombotic events *were* more common in patients treated with rFVIIa (5.5% versus 3.2%, $P=0.003$), although this finding was limited to the subgroup of patients over age 65 (specifically those above *age* 75). The majority of arterial thrombotic events were coronary (53.9%) and occurred more frequently in elderly patients. Higher rates of arterial thrombosis were also associated with noncompressible, spontaneous central nervous system (CNS) bleeds. In the subgroup of patients with spontaneous CNS bleeding, higher doses of rFVIIa correlated with higher rates of thrombosis: placebo (5.4%); rFVIIa < 80 mcg/kg (6%); 80 to 120 mcg/kg (10.3%); and

greater than 120 mcg/kg (11.9%; $P=0.02$). On the basis of these results, it seems that continued use of rFVIIa off-label for severe, uncontrolled, life-threatening hemorrhage should not be ruled out in most patients strictly on the grounds of safety. In certain patient subgroups, like the elderly and those experiencing spontaneous CNS bleeds, the risk-benefit calculus becomes more complicated, and clinicians should understand that rFVIIa *is* associated with significantly higher rates of arterial thromboembolic events in these patients. (KE)

VENTILATOR-ASSOCIATED PNEUMONIA IS MORE COMMON AND OF LESS CONSEQUENCE IN TRAUMA PATIENTS COMPARED WITH OTHER CRITICALLY ILL PATIENTS.

Cook et al. *J Trauma*. 2010;69:1083-91.

Ventilator-associated pneumonia (VAP) is a common infection in trauma patients and has been shown to be more prevalent in these patients compared to other critically ill patients. VAP rates in trauma patients continue to be high, despite the adoption of VAP prevention strategies. The authors studied whether it was true that VAP rates were higher in trauma patients at East Texas Medical Center (ETMC). This was a retrospective cohort study of all intubated adult patients (N=2591) admitted to ETMC during the period from January 1, 2007 through December 31, 2008. Patients were considered to have VAP if the following criteria were met: radiographic evidence of a new or progressive and persistent pulmonary infiltrate and clinical signs and symptoms of pneumonia, such as fever, leukocytosis or leucopenia, purulent sputum, worsening gas exchange ($PAO_2/FIO_2 \leq 240$), and/or positive quantitative bronchoalveolar lavage (BAL) specimen occurring in a patient requiring mechanical ventilation. Of the 161 patients diagnosed with VAP, 71 were nontrauma and 91 were trauma. The VAP incidence rate (per thousand ventilator days) observed in trauma patients was four times higher than in nontrauma patients (24.3 to 6.1, $p < 0.001$). Incidence rate in the trauma patients was higher at 17.8%, compared to the results from the National Healthcare Safety Network (NHSN) reports ranging from 8.1%-15.9%. There were more deaths in the non-trauma group (31.4% vs 11.0%, $p = 0.002$), and this can be partially explained by differences in measured comorbidities and age. (VB)

OTHER ARTICLES OF INTEREST

International recommendations for glucose control in adult non diabetic critically ill patients
Ichai et al. *Critical Care* 2010, 14:R166.

Immediate β -Blockade in Patients With Myocardial Infarctions: Is There Evidence of Benefit?
Sinert R et al. *Ann Emerg Med*. 2010;56:571-577.

Patterns of Antihypertensive Treatment in Patients with Acute Severe Hypertension from a Nonneurologic Cause: Studying the Treatment of Acute Hypertension (STAT) Registry
Devlin JW et al. *Pharmacotherapy* 2010;30:1087-1096.

CONTRIBUTORS

Marcus Costner, PharmD, BCPS (VA); Karly Erickson, PharmD Candidate, (UMASS); Erin Frazee, PharmD (Mayo); Haley Goodwin, PharmD (Johns Hopkins); Deanna McMahon Horner, PharmD, BCPS (UCSF); Emily Hutchison, PharmD, BCPS (Clarian Methodist); Shawn Kram, PharmD, BCPS (Via Christi); Jessica Mercer, PharmD (MUSC); Erin Nystrom, PharmD, BCNSP (Mayo); Heather Personett, PharmD (Mayo); Angela Plewa, PharmD, BCPS (Stroger); Bridgette Therriault, PharmD (Wesley); Nicholas Tinsley, PharmD; Charles J Turck, PharmD, BCPS (UMass); Peter Herout, PharmD, BCPS (EPI-Q, Inc.). Editorial Assistance: Deepali Dixit, PharmD; Christine Lesch, PharmD

