CRITICAL CARE PHARMACOTHERAPY LITERATURE UPDATE

March 2012

This is a monthly review of select articles in the medical literature pertaining to pharmacotherapy used in critically ill patient populations. The content below is for information purposes only and is intended to highlight recent articles that may be of interest to those caring for patients in various intensive care or related settings. 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, its findings, and its applicability to practice.

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CONTRIBUTORS

Alia Anne Daghstani, Pharm.D. (Mercy St. Vincent); Sarah Day, Pharm.D. (Doctors Hospital); Erin Frazee, Pharm.D. (Mayo); Deanna McMahon Horner, Pharm.D., BCPS (UCSF); Emily Hutchison, Pharm.D., BCPS (IU Health – Methodist); Bridgette Kram, Pharm.D., BCPS (Wesley); Shawn Kram, Pharm.D., BCPS (Via Christi); Christine Lesch, Pharm.D. (NY Pres); Jessica Mercer, Pharm.D., BCPS (Bon Secours St. Francis); Kathy Nowicki, Pharm.D. (Wesley); Heather Personett, Pharm.D. (Mayo); Angela Plewa, Pharm.D., BCPS (Stroger)

Editors: Peter Herout, Pharm.D., BCPS (CardinalHealth); Charles J Turck, Pharm.D., BCPS (UMass)

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Linezolid in Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia: A Randomized, Controlled Study

Wunderink RG, Niederman MS, Kollef MH, et al. Clinical Infectious Diseases. February 2012: 1-9

Study Question: What is the efficacy and safety of fixed dosed linezolid compared to dose-optimized vancomycin for the treatment of MRSA nosocomial pneumonia?

Study Description: This is a phase IV, randomized, double blind, multicenter, international, comparator-controlled study. Patients were included in the study if they had documented hospital acquired or healthcare associated pneumonia (HAP/HCAP) and had a baseline sputum or respiratory sample positive for MRSA. Previous MRSA-active treatment within past 48 hours was reason for exclusion. Patients were then randomized to receive either linezolid 600 mg IV every 12 hours or vancomycin 15mg/kg IV every 12 hours for 7-14 days. Patients were assessed at baseline, at day 3, and every 3 days during treatment. Minimum inhibitory concentrations (MIC) for MRSA were also collected. The primary efficacy endpoint was clinical outcome (resolution of signs and symptoms of pneumonia, and no need for additional antibacterial agents) at the end of the study in per-protocol patients.

Results: A total of 1184 patients were included in the ITT population. After isolating MRSA pneumonia, the mITT population compromised n=224 in linezolid group and n=224 in the vancomycin group. Patient characteristics were similar between groups, however there was slightly more MRSA bacteremia in vancomycin group (10.8% vs 5.2%). At the end of study, 57.6% and 58.1% of linezolid group were considered to have achieved clinical cure and microbiologic success, respectively, compared to 46.6% and 47.1% in the vancomycin group. Nephrotoxicity was seen in 8.4% in the linezolid group compared to 18.2% in vancomycin group.

Conclusions: The investigators conclude that linezolid resulted in greater clinical efficacy compared to vancomycin for the treatment of MRSA pneumonia.

Perspective: Although no difference in response to vancomycin was seen in isolates with MIC of 2 mcg/mL compared to isolates with lower MICs, there was insufficient patient numbers to analyze this.

Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

Silbergleit R, Durkalski V, Lowenstein D, et al. N Engl J Med 2012;366:591-600

Study Question: Whether intramuscular (IM) midazolam is noninferior to intravenous (IV) lorazepam in prehospital status epilepticus (seizing for at least 5 minutes).

Study Description: This was a randomized, double blind, double dummy, noninferiority trial involving 79 receiving hospitals. Adults and children 13 kg or more were included and administered either 10mg midazolam (5mg for 13kg to 40kg) IM by autoinjector and placebo IV or placebo IM and 4mg lorazepam (2mg for 13kg to 40kg) IV. Patients with major trauma, hypoglycemia, cardiac arrest, or heart rate < 40 beats per minute were excluded.

Results: The primary outcome was termination of seizures prior to arrival without the need for rescue therapy. IM midazolam was noninferior to IV lorazepam (73.4% vs 63.4%, p < 0.001), and superior in a secondary analysis (p<0.001). Additional secondary outcomes revealed decreased hospitalization (57% vs. 65%) and ICU admission (28.6% vs 36.2%) for the IM midazolam group.

Conclusions: IM midazoloam is at least as safe and effective as IV lorazepam for prehospital seizure cessation.

Perspective: The difficulty of gaining IV access for patients in status epilepticus and the refrigeration requirement make injectable lorazepam less than desirable in an out of hospital situation. This study suggests IM midazolam is a therapeutic alternative and possibly a superior therapy in this situation. Important to note is that the study used an autoinjector, which may have decreased time to administration but is not available commercially.

Phenytoin, Levetiracetam, and Pregabalin in the Acute Management of Refractory Status Epilepticus in Patients with Brain Tumors

Swisher CB, Doreswamy M, Gingrich KJ, et al. Neurocrit Care. 2012;16:109-113.

Study Question: Can we provide evidence for a treatment regimen for refractory status epilepticus (RSE) in patients with brain tumors that does not require intubation?

Study Description: This study used the DEDUCE (Duke enterprise data unified content explorer) database to retrospectively identify patients meeting three criteria: brain tumors, presenting with complex partial status epilepticus (SE), and receiving phenytoin (PHT), levetiracetam (LEV), and pregabalin (PGB) – also referred to as the Trifecta. A clinical response to the Trifecta was defined as complete resolution of clinical seizures and/or cessation of repetitive epileptiform discharges on EEG, if no other AEDs were added during hospitalization, and if SE did not recur during hospitalization. The electronic medical record was used to collect data on 1 year outcomes.

Results: A total of 23 patients met all three study inclusion criteria. Sixteen (70%) had a prior history of seizures and 26% had tumor progression at time of RSE diagnosis. At the time of SE onset, 21 (91%) were on an anti-convulsant with most patients being on LEV at baseline (61%). The most common tumor type was glioblastoma multiforme (52%). There was a trend towards the presence of peritumoral edema on MRI and response to the Trifecta, however, this was not significant (p=0.12). Of patients in the responder group (n=16), more were on an AED at baseline (100%) as compared to non-responders (p=0.03).

PGB was typically used as third line treatment and 16/23 (70%) had cessation of RSE after the addition of this third component of the Trifecta. Serum PHT levels were therapeutic at the time of SE cessation with an average of 18.8 mcg/mL. The mean time to response was 3.5 days and it took 2.3 days to administer the third AED in the responder group vs. 4.2 days and 2.1 days in the non-responders, respectively. In the non-responders, 5/7 had SE cessation with the addition of a fourth AED.

Conclusion(s): The use of the Trifecta (PHT, LEV, PGB) is safe and highly effective.

Perspective: The Trifecta offers an attractive alternative in managing patients with brain tumors who experience RSE. One important condition must

be met for this regimen to be feasible: the patient must be able to take oral medication since PGB does not have an IV formulation. The mean doses reported in the study were acceptable, however, no information was presented regarding side effects and therefore conferring safety of this regimen. The regimen studied appears to be effective for this specific patient population, although the results must be interpreted cautiously due to the small size and retrospective nature.

HALOPERIDOL PROPHYLAXIS DECREASES DELIRIUM INCIDENCE IN ELDERLY PATIENTS AFTER NONCARDIAC SURGERY: A RANDOMIZED CONTROLLED TRIAL

Wang W, Hong-Liang L, Dong-Xin W, et al. Crit Care Med. 2012; 40:731-739

Study Question: Is the short-term use of low dose intravenous haloperidol safe and effective in preventing post-operative delirium in critically ill elderly patients after noncardiac surgery?

Study Description: This prospective, double-blind, placebo controlled, multicenter trial (n=457) randomized patients > 65 years old admitted to the ICU after noncardiac surgery to receive haloperidol 0.5 mg IV bolus followed by continuous infusion of 0.1 mg/hr for 12 hours or placebo. The primary endpoint was incidence of delirium during the first seven days after surgery. Secondary endpoints included time to delirium onset, open-label haloperidol usage, delirium-free days, ICU and hospital length of stay, post-operative complications and 28-day mortality.

Results: Patients in the haloperidol group had significantly longer durations of anesthesia and surgery. The use of fentanyl, midazolam and propofol were similar between groups. In the haloperidol group, incidence of postoperative delirium was significantly lower (15.3 vs 23.2%, p = 0.031) and time to delirium onset was longer (6.2 vs 5.7 d, p = 0.021). Delirium-free days and length of ICU stay were statistically significantly shorter in the haloperidol group (6.8 vs 6.7 d, p = 0.027; 21.3 vs 23 hrs, p = 0.024, respectively), but length of hospital stay and 28-day mortality did not differ. Use of open-label haloperidol, adverse events and postoperative complications were similar between groups.

Conclusions: Prophylactic, low-dose intravenous haloperidol significantly decreases the incidence of post-operative delirium with limited adverse effects in elderly patients admitted to the ICU after noncardiac surgery.

Perspective: While prophylactic haloperidol appears safe and effective in decreasing post-operative delirium, its effect on ICU and hospital length of stay are not clinically significant. Also, 75% of patients were post-operative intra-abdominal surgery which limits generalizeability.

TOTAL EPINEPHRINE DOSE DURING ASYSTOLE AND PULSELESS ELECTRICAL ACTIVITY CARDIAC ARRESTS IS ASSOCIATED WITH UNFAVORABLE FUNCTIONAL OUTCOME AND INCREASED IN-HOSPITAL MORTALITY

Arrich J, Sterz F, Herkner H, et al. Resuscitation 2012;83:333-7

Study Question: Do increasing cumulative doses of epinephrine correlate with unfavorable functional

outcome and in-hospital mortality in patients with asystole or PEA who are successfully resuscitated?

Study Description: Retrospective cohort study of patients who presented to Vienna General Hospital after witnessed in- or out-of hospital asystole or PEA arrest who were successfully resuscitated. Total cumulative epinephrine dose was recorded. Patients were considered to have an unfavorable functional outcome if they did not achieve a Cerebral Performance Category (CPC) score of 1 or 2 during the observation period. To adjust for confounding, all available variables that could be associated with outcome were also collected and multivariable regression was performed.

Results: Nine hundred forty six patients were included in the study. The median dose of epinephrine was 2 mg. Patients receiving higher doses had significantly longer low flow times and higher in-hospital mortality ($p<0.001$). In both univariable and multivariable regression, increasing doses of epinephrine were associated with an increased risk of unfavorable functional outcome and in-hospital mortality. The multivariable regression model suggested that the influence of effect of epinephrine dose on outcome is independent of the length of cardiac arrest.

Conclusion(s): Two hypotheses may explain the results: 1) epinephrine is potent at resuscitating patients with severe organ hypoxia who subsequently die in the hospital or 2) epinephrine has deleterious effects in the post-resuscitation period. Based on the results, the authors concluded that the increasing cumulative dose of epinephrine is an independent risk factor for unfavorable functional outcome or in-hospital mortality.

Perspective: This is a hypothesis generating retrospective study. Based on the results researching different treatment strategies, epinephrine dosage limits, or adjunctive agents for asystole and PEA patients may be warranted.

Other Recent Publications of Interest

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Crit Care Med. 2012 Mar;40(3):823-828. Analysis of risk factors for adverse drug events in critically ill patients* Kane-Gill SL, Kirisci L, Verrico MM, Rothschild JM.

Advanced Hemodynamic Monitoring: Principles and Practice in Neurocritical Care Christos Lazaridis Published online: 16 June 2011 Springer Science+Business Media, LLC 2011

Haloperidol Dosing Strategies in the Treatment of Delirium in the Critically-Ill Erica H. Z. Wang • Vincent H. Mabasa Gabriel W. Loh • Mary H. H. Ensom Published online: 26 October 2011 _ Springer Science+Business Media, LLC 2011

Incidence and Management of Ischemic Stroke and Intracerebral Hemorrhage in Patients on Dabigatran Etexilate Treatment Masaki Watanabe • Fazeel M. Siddiqui •Adnan I. Qureshi Published online: 12 July 2011_ Springer Science+Business Media, LLC 2011

Gastrointestinal Prophylaxis in Neurocritical Care Clemens M. Schirmer • Joshua Kornbluth •Carl B. Heilman • Anish Bhardwaj Published online: 12 July 2011 _ Springer Science+Business Media, LLC 2011