CRITICAL CARE PHARMACOTHERAPY LITERATURE UPDATE

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This is a monthly review of select articles in the medical literature pertaining to pharmacotherapy as applied in the critically ill patient population. The content below is for information purposes only and is intended to highlight recent articles that may be of interest those caring for patients in various critical or intensive care 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 and its findings.

CONTENTS

A Randomized Trial for the Treatment of Refractory Status Epilepticus

Rossetti AO, Milligan TA, Vulliémoz S, et al. Neurocrit Care. 2011;14:4-10.

Study Question: Is propofol as effective as barbiturates (thiopental or pentobarbital) in achieving control of refractory status epilepticus (RSE)?

Study Description: This article described a multicenter, prospective, randomized, single-blind trial of adult patients with RSE, defined as ongoing clinical or EEG seizure activity or repetitive seizures without return to baseline for 30 minutes despite treatment with benzodiazepines or an antiepileptic drug (AED). Exclusion criteria were seizure due to cerebral anoxia, pregnancy, study drug intolerance, mitochondrial disorders, egg allergy, serum triglyceride levels > 470 mg/dL or serum creatine kinase concentrations > 1500 units/L. Each study drug was administered as a bolus followed by continuous infusion and was titrated toward burst-suppression. Concomitant benzodiazepines and AEDs were administered as well. The primary outcome was RSE control after 36 to 48 hours of stable burst-suppression, defined as patient alive without clinical indication for titrating study drug higher during the first 7 days following the initial weaning and ≤ 1 discrete seizure per hour during the 2 hours after attainment of continuous, stable activity on electroencephalogram (EEG). Secondary outcomes included functional outcome at day 21 and after 3 months, length of mechanical ventilation, and safety outcomes.

Results: Due to low enrollment (n = 23), the study was terminated early. No differences in baseline characteristics were noted. The primary outcome of RSE control was not statistically different between the propofol and barbiturate arms (43% vs. 22%, p = 0.4). The duration of mechanical ventilation in survivors was *significantly* longer in the barbiturate arm (4 days vs. 13.5 days, p = 0.03) despite a similar duration of study-drug administration duration (2 days). No other differences in secondary outcomes were observed.

Conclusions: The authors concluded that use of barbiturates for RSE may be associated with longer duration of mechanical ventilation.

Comment: This study was significantly underpowered to develop conclusions about the relative efficacy of propofol and barbiturates for RSE. However, as it *is* the first prospective head-to-head trial comparing these agents for RSE, it *does* offer some insight into and guidance in the management of this infrequent neurological disorder.

A Randomized Active-Controlled Study Comparing the Efficacy and Safety of Vernakalant to Amiodarone in Recent-Onset Atrial Fibrillation

John Camm KA, Capucci A, Hohnloser SH, et al. JACC 2011; 57:313-321.

Study Question: Is intravenous vernakalant superior to amiodarone for the acute conversion of recent-onset atrial fibrillation (AF)?

Study Description: This was a phase III, multicenter, randomized, double-blind, double-dummy, comparator-controlled study of 232 patients with symptomatic, recent-onset AF (duration of 3 to 48 h), enrolled from April 2008 until November 2009. The study population included men and women between 18 and 85 years who were eligible for cardioversion, hemodynamically stable, and were taking adequate anticoagulation therapy. Patients were excluded if they had an uncorrected QT

interval > 440 ms; familial long QT syndrome; previous torsades de pointes, ventricular fibrillation, or sustained ventricular tachycardia; symptomatic bradycardia, known sick sinus syndrome, or ventricular rate < 50 beats/min; or QRS interval > 140 ms. Vernakalant group received a 10-minute infusion of 3mg/kg, followed by 15 minutes of observation and an additional 10-minute infusion of 2mg/kg if still in AF. The amiodarone group received 60 minutes of a 5 mg/kg infusion, followed by an additional 50 mg infusion over 60 minutes. Both groups received placebo injection in a separate line.

Results: A little under 52% of vernakalant patients converted from AF to sinus rhythm (SR) within 90 minutes of first exposure to the drug as compared to 5.2% of amiodarone patients ($p < 0.0001$). Around 53% of vernakalant patients were symptom-free at 90 minutes compared with 32.8% of amiodarone patients ($p = 0.0012$). SR was maintained for 98.3% of the vernakalant patients converted through 4 hours compared to 100% of amiodarone patients. There was a higher incidence of atrial flutter in vernakalant patients (8.6%) compared with amiodarone patients (0.9%) within 4 hours post-dose, although none of the atrial flutter events were considered to be serious.

Conclusions: Vernakalant was superior to amiodarone for the conversion of recent-onset AF. The low arrhythmic potential of vernakalant provides a rapid-acting therapeutic alternative to amiodarone for conversion of atrial fibrillation.

Comment: Limitations of this study include a short follow-up period for efficacy and a short infusion period for amiodarone.

Is Early Venous Thromboembolism Prophylaxis Safe In Trauma Patients With Intracranial Hemorrhage

Koehler DM, Shipman J, Davidson MA, et al. J Trauma. 2011;70:324-9.

Study Question: In traumatic brain injury (TBI) patients with evidence of intracranial hemorrhage injury (IHI), are rates of IHI progression different in patients who receive early (< 72 hours) vs. late (> 72 hours) venous thromboembolism prophylaxis (VTE px)?

Study Description: This article described a retrospective cohort study in a Level 1 trauma center from July 1, 2004, to June 30, 2008, comparing two years before and after a VTE px practice management change that emphasized VTE px beginning 48 hours post admission with enoxaparin 30 mg SQ q 12 hours. The study looked primarily at IHI progression events, which included subarachnoid hemorrhages, subdural hematomas, epidural hematomas, axonal shear injuries, intraparenchymal contusions, and intraventricular hemorrhages. The study also reported VTE outcomes.

Results: Six hundred sixty-nine patients were enrolled. The time from admission to first dose of enoxaparin was 2.77 + 0.49 days and 5.31 + 1.97 days in the early (n = 268, 40%) vs. late (n = 401, 60%) groups, respectively. At baseline, patients in the late group had more severe head and neck abbreviated injury scores ($p = 0.003$), indicating an *elevated* risk of VTE. IHI progression events before VTE px were 9.38% vs. 17.41% in the early vs. late groups, respectively ($p < 0.001$). IHI progression events after VTE px were 1.46% vs. 1.54% ($p = 0.912$). There was no statistically significant difference in rates of deep venous thrombosis (1.5% vs. 3.5%, $p = 0.117$) or pulmonary embolism (1.5% vs. 2.2%, $p = 0.49$) between early and late groups,

respectively, although there were some trends toward higher VTE rates in the *late* group.

Conclusions: Early VTE px *does not* increase rates of IHI progression in hemodynamically stable patients with TBI.

Comment: This study was limited by lack of power and possible selection bias as trauma physicians could delay VTE px if they felt uncomfortable with earlier initiation of therapy. It *is* worth noting that the IHI progression rates observed in *this* study were consistent with those of previous studies. This study suggests that it is safe to start VTE px at 48 hours postadmission in selected patients with TBI.

Ticagrelor Versus Clopidogrel in Patients With Acute Coronary Syndromes Undergoing Coronary Artery Bypass Surgery: Results From the PLATO (Platelet Inhibition and Patient Outcomes) Trial

Held C, Åsenblad N, Bassand JP, et al. J Am Coll Cardiol. 2011;57;672-84.

Study Question: What is the efficacy and safety of ticagrelor compared to clopidogrel in the subset of patients in the PLATO trial who underwent a coronary artery bypass graft procedure (CABG)?

Study Description: This article describes a post-hoc analysis of the PLATO trial, which was a multicenter, international, prospective, randomized, double-blind, clinical trial comparing ticagrelor to clopidogrel within 24 hours of ischemic symptom onset in addition to aspirin. For patients with acute coronary syndromes (ACS) being considered for CABG, clopidogrel and ticagrelor were held pre-operatively for 5 and 1 to 3 days, respectively. Included patients underwent a CABG with last intake of study drug within 7 days preceding surgery. The primary efficacy endpoint was the time from CABG to first occurrence of the composite of death from vascular causes, and the primary safety measure was time from CABG to the first occurrence of any major bleeding event.

Results: The analysis included 1,261 patients from the PLATO trial having undergone CABG within 7 days of last study drug intake (6.8% of original study's population). The ticagrelor patients discontinued their study drug 2 (30.1%), 3 to 5 (43.8%) and > 5 (26.1%) days prior to the CABG, whereas the corresponding numbers for patients taking clopidogrel were 27.7%, 37.9%, and 34.5%. The primary end point of composite death from vascular causes was 10.6% in ticagrelor and 13.1% in clopidogrel ($p = 0.29$) with a reduction in cardiovascular death favoring ticagrelor ($p < 0.01$). There were no statistically significant differences in bleeding events among groups.

Conclusions: In ACS patients requiring CABG, ticagrelor with aspirin was associated with reductions in cardiovascular deaths without increased risk of bleeding when compared to aspirin and *clopidogrel*.

Comment: Primary endpoint was a composite outcome in which a subgroup suggested benefit; ticagrelor is not currently FDA approved.

Fidaxomicin versus vancomycin for Clostridium difficile infection

Louie TJ, Miller MA, Mullane KM, et al. N Engl J Med. 2011;364:422-31.

Study Question: Is fidaxomicin non-inferior to vancomycin for the treatment of patients with C. difficile infection?

Study Description: This prospective, double-blind, randomized controlled trial included patients with a positive stool sample for C. difficile obtained within 48 hours of randomization and the presence of diarrhea. Patients were excluded if they received more than 4 doses of metronidazole or vancomycin or any other treatment for C. difficile within the 24 hours preceding randomization or if they had life-threatening or fulminant disease or a concurrent diagnosis of ulcerative colitis or Crohn's disease. Patients were randomized to either fidaxomicin 200 mg PO BID or vancomycin 125 mg PO QID, each for 10 days. The primary endpoint was clinical cure (< 4 unformed stools for 2 consecutive days maintained for the remainder of the treatment course and without requirement of further therapy for the 2 days following the end of treatment).

Results: Six hundred twenty-nine patients were included; groups were similar at baseline with respect to previous treatment failure and C. difficile infection and incidence of NAP1/BI/027 strain. The rate of clinical cure was non-inferior with fidaxomicin at 88.2% vs. 85.8% with vancomycin in the modified intention-to-treat analysis. Fewer patients in the fidaxomicin group had a recurrence of infection (15.4% vs. 25.3%; p = 0.005), although this difference was only observed for *non*-NAP1/BI/027 strains.

Conclusions: Fidaxomicin is not inferior to vancomycin in achieving clinical cure of C. difficile and may lead to lower rates of recurrence in non-North American Pulsed Field type 1 strains.

Comment: The results of this study are only applicable in patients with mild or moderate disease, as fulminant disease was excluded.

Transdermal Nicotine Replacement Therapy in Cigarette Smokers with Acute Subarachnoid Hemorrhage

Seder DB, Schmidt JM, Fernandez L, et al. Neurocrit Care. 2011;14:77-83.

Study Question: In active smokers who develop aneurysmal subarachnoid hemorrhage (SAH), does nicotine replacement therapy (NRT) increase mortality or worsen other outcomes like cerebral ischemia due to vasospasm, imaging evidence of vasospasm, or delirium?

Study Description: This article described a retrospective study that utilized a prospectively collected database from patients admitted to a single-center ICU after a non-traumatic SAH. Patients who were active smokers prior to admission and who survived for > 3 days were included. Patients were started on a 21-mg transdermal nicotine patch daily at the discretion of the neurointensivist. Standard medical management of *all* patients was directed by one of four neurointensivists.

Results: Six hundred five patients were included in the database, of which 569 patients met inclusion criteria and 55% received NRT. Baseline demographics were similar between the two groups, with the exceptions of a higher percent of patients in the NRT group being identified as: heavy smokers (> 10 cigarettes/day); patients with diabetes; heavy drinkers; and those with cerebral edema present on admission CT. Multivariate analysis revealed that, in smokers, NRT was strongly associated with 3 month survival. There were no significant differences in

most other medical complications or vascular events, including vasospasm and myocardial infarction. However, delirium was *more frequent* in the *NRT* group. Also, as compared to the NRT group and non-smokers, smokers who did *not* receive NRT had lower rates of pneumonia, pulmonary edema, fever, and seizures.

Conclusions: NRT is safe in active smokers who develop aneurismal SAH.

Comment: As NRT was prescribed in a non-randomized method, significant selection bias may in part account for the results. Furthermore, although there was an increase in survival in patients who received NRT compared to both non-NRT smokers and non-smokers, the number of deaths was small. This difference could therefore be due to chance, a confounder not taken into account, *or* the authors' hypothesized neuroprotective effects of nicotine.

Effect of Oral Beta-Blocker On Short and Long-Term Mortality in Patients with Acute Respiratory Failure: Results from the BASEL II-ICU Study

Noveanu M, Breidthardt T, Reichlin T, et al. Crit Care. 2010;14:R198.

Study Question: Do beta-blockers affect in-hospital and one-year mortality rates in patients with acute respiratory failure?

Study Description: A post-hoc analysis was conducted on data from a prospective, randomized, controlled, single-blinded multicenter study (B-type natriuretic peptide for Acute Shortness of Breath Evaluation, or BASEL II-ICU trial), performed between 12/04 and 3/07 in seven intensive care units in Switzerland. Outcomes included in-hospital mortality and one-year mortality.

Results: Data from 314 patients with acute respiratory failure were reviewed. At baseline, beta-blocker use was more frequent in both the in-hospital ($p = 0.001$) and one-year ($p<0.0001$) survivors vs. non-survivors. A multivariate analysis found that in-hospital (HR 0.33, $p = 0.007$) and one-year (HR 0.29, $p = 0.0003$) mortality rates independently favored patients who were taking beta-blockers on admission as compared to those who were *not*.

Conclusions: The authors conclude that beta-blocker therapy is associated with decreased mortality rates in patients with acute respiratory failure.

Comment: The data presented were observational in nature and based on a post-hoc analysis of a randomized controlled trial. It is unclear whether a compliance bias, rather than beta-blocker use itself, was responsible for the differences observed between survivors and non-survivors. Based on a univariate analysis, survivors were more likely to take beta-blockers, in addition to statins, aspirin, clopidogrel, and ACE inhibitors or ARBs at admission. Compliance with the medication management of *comorbidities*, such as heart failure, coronary artery disease, and hypertension, likely *also* influenced the outcome of mortality in a compliant vs. non-compliant group.

Contributors

Marcus Costner, PharmD, BCPS (VA); 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, BCPS (MUSC); Erin Nystrom, PharmD, BCNSP (Mayo); Heather Personett, PharmD (Mayo); Angela Plewa, PharmD, BCPS (Stroger); Bridgette Kram, PharmD (Wesley); Charles J Turck, PharmD, BCPS (UMass); Peter Herout, PharmD, BCPS (CardinalHealth).

