CRITICAL CARE PHARMACOLOGY LITERATURE UPDATE

JUNE 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

β-Blockers for chest pain associated with recent cocaine use.

Rangel C, Shu RG, Lazar LD, Vittinghoff E, Hsue PY, Marcu GM. *Arch Intern Med* 2010;170:874-879.

The use of β-blockers in the setting of chest pain associated with recent cocaine use continues to be controversial. Although in theory use of non-selective β-blockers could lead to unopposed α-adrenergic stimulation and cocaine induced vasoconstriction, coronary vasospasm and increase in oxygen demand, β-blockers are known to produce improved outcomes following acute myocardial infarction. A retrospective study of 331 patients identified as being admitted through the ER with symptomatic chest pain and a toxicological screen positive for cocaine was conducted. Of those, 151 patients received a β-blocker in the ER. Compared to those not receiving a β-blocker they were older, had a higher admission blood pressure, and more likely to be on aspirin, statins, and ACEI as an outpatient. During hospitalization there were no significant differences in initial ECG findings or changes, or number of subjects with positive troponin level, MI, intubation, death, LOS, or ventricular arrhythmia requiring intervention between the groups. Significantly more patients in the non-β-blocker group required vasopressors in the first 24 hours of admission. Follow-up mortality information from the National Death Index on 317 study subjects showed no significant difference in death following β-blocker use in the ER or after discharge, nor was β-blocker use found to be associated with death following logistic regression analysis. Discharge on a β-blocker regimen was associated with a 70% reduction in the risk of cardiovascular death after adjusting for potential confounders. Despite the study limitations the authors conclude that the administration of β-blockers is safe in patients with recent cocaine use, and continued use on an outpatient basis may offer long term cardiovascular mortality benefits.

Argatroban therapy for heparin-induced thrombocytopenia in ICU patients with multiple organ dysfunction syndrome: a retrospective study.

Saugel B, Phillip V, Moessmer G, Schmid RM, Huber W. Crit Care 2010 14:R90.

Heparin-induced thrombocytopenia (HIT) is an immune-mediated process, which can lead to thrombocytopenia, hypercoagulability, and thrombosis. Questions have been raised about the appropriate starting dose of argatroban, one of the backbones of HIT therapy. Evidence suggests that the recommended 2 mcg/kg/min in normal adults is likely excessive in those with organ dysfunction, particularly hepatic dysfunction, as this is the primary mechanism of clearance. The primary objective of this retrospective single-center case series of twelve critically ill individuals was to demonstrate dosing difficulties of argatroban in the setting of multiple organ dysfunction syndrome (MODS). Mean argatroban starting dose was conservative at 0.32 ± 0.25 mcg/kg/min, but there was wide variability (0.04-0.83mcg/kg/min). Despite the conservative initial dose, 50% of patients required dose reduction to achieve goal aPTT. Multivariate analyses revealed hepatic insufficiency, present in 33% of patients, was the only variable assessed that was independently associated with difference in mean argatroban dose (r=0.676, P=0.016). Neither bleeding nor

thromboembolic complications were appreciated in these patients. Of note, in 50% of patients, the suspicion of HIT was confirmed with the heparin-induced platelet activation assay. The authors conclude that argatroban is reasonable for MODS patients with HIT and that the 50-75% dose reduction currently recommended for critically ill patients with hepatic dysfunction may not be enough. Despite the fact that this study was small, highly variable, and included patients with chronic and end-stage liver disease who may not often receive argatroban for HIT, it further adds to the minimal available literature for this drug in critically ill patients.

Early anticoagulation is associated with reduced mortality for acute pulmonary embolism

Smith SB, Geske JB, Maguire JM et al. CHEST 2010;137:1382-90.

Acute pulmonary embolism (PE) is often fatal, though treatment with IV heparin can improve overall survival. Guidelines recommend anticoagulation for suspected PE, but the effect of time to initiation on mortality has yet to be elucidated. This retrospective review examined 400 patients admitted to an Emergency Department (ED) with a confirmed diagnosis of PE, treated with IV heparin. Timing of heparin initiation and time to therapeutic aPTT were evaluated. Primary outcomes were 30-day and in-hospital mortality. Sixty-five percent of patients began heparin in the ED, at a median time of 10.8 hours from arrival. Those receiving heparin in the ED had lower in-hospital mortality (1.4% vs. 6.7%; OR 0.20, CI 0.06-0.69; p= 0.009) and 30-day mortality (4.4% vs. 15.3%; OR 0.25, CI 0.12-0.55; p <0.001). Therapeutic aPTT within 24 hours was also associated with lower 30 day-mortality (5.6% vs. 14.8%; OR 0.34, CI 0.14-0.84; p= 0.037). After accounting for morbidities that might confound this relationship, authors identified COPD and positive troponin as concomitant conditions associated with delayed anticoagulation and increased mortality. They theorize this relates to delayed diagnosis given the similar presentation of PE and COPD exacerbation or myocardial ischemia. These results reinforce the importance of heparin therapy for acute PE and suggest that early initiation and achievement of therapeutic aPTT may be preferable and should be considered during treatment in the ED. It also identifies specific patients in whom a broad array of differential diagnoses may lead to delays in therapy.

Use of dexmedetomidine as a sedative and analgesic agent in critically ill adult patients: a meta-analysis

Tan JA, Ho KM. Intensive Care Med 2010;36:926-939.

The objective of this meta-analysis was to assess the effects of dexmedetomidine as a sedative and analgesic agent. Twenty-four randomized controlled trials were included in the meta-analysis. Trials compared dexmedetomidine to placebo, or an alternative sedative agent in critically ill adults, outside of the operating room setting. Overall, 2419 patients from 11 countries were included. There was significant heterogeneity between the included studies in length of ICU stay (I^2 = 83.1%) and mechanical ventilation (I^2 = 74.6%). Dexmedetomidine was associated with an overall reduction in length of ICU stay [weighted mean difference (WMD) -0.48 days, p

= 0.002]. There was no significant difference in duration of mechanical ventilation. There was no significant difference in occurrence of bradycardia between the dexmedetomidine group and the group receiving placebo or alternative sedative agents; however, there was a significantly higher rate of bradycardia in patients receiving dexmedetomidine loading doses and higher maintenance doses (> 0.7 mcg/kg/h) (5.8% versus 0.4%, p = 0.007). There was no significant difference in occurrence of hypotension requiring intervention (p = 0.25), or delirium (p = 0.18), atrial fibrillation (p = 0.77), nausea and vomiting (p = 0.90), myocardial infarction (p = 0.67), hyperglycemia (p = 0.85), self-extubation (p = 0.68), or mortality (p = 0.26). In this meta-analysis, patients receiving dexmedetomidine had statistically shorter ICU length of stay but the clinical significance of this difference is questionable. Further studies of dexmedetomidine may be useful to provide insight on the specific critically ill patient population that will benefit most from dexmedetomidine administration.

Prothrombin Complex Concentrates (PCC) for Oral Anticoagulant Therapy-Related Intracranial Hemorrhage: A Review of the Literature.

Bershad EM, Suarez JI. NCC 2010; 12: 403-413.

Patients with intracranial hemorrhage (ICH) have a higher mortality when the bleed is associated with warfarin or other anticoagulant therapy. Currently the strategies to reverse the INR in these patients differ widely among physicians. This review discussed some of the advantages and disadvantages of PCC when compared to other agents. Vitamin K therapy is essential for reversal as it provides a lasting effect on the INR; however the effect is quite delayed requiring the administration of other fast acting reversal agents. PCC is a heterogenous mixture of clotting factors II, IX, and X. In addition, there are other components depending on the preparation including protein C and S, antithrombin III, and even heparin. In some preparations unavailable in the US, factor VII is even included. It is supplied as a lyophilized powder available for reconstitution and can be given in small volumes. Fresh frozen plasma is also a fast acting agent that can be given. Disadvantages of this product are that it comes in large volumes that may be problematic in patients with heart and kidney disease; also, it is stored frozen and takes up to 60 minutes to thaw. Recombinant factor VIIa is another fast acting reversal agent which is available in a small volume without the thaw-time delay. Advantages of PCC over this product would be that it provides more complete reversal of anticoagulation since it would correct multiple factors. The data to support one intervention over another is limited.

Articles of Interest

Consensus Summary of Aerosolized Antimicrobial Agents: Application of Guideline Criteria Insights from the Society of Infectious Diseases Pharmacists. Le J, Ashley E, Neuhauser M, Brown J, Gentry C, Klepser M, Marr A, Schiller D, Schwiesow J, Tice S, VandenBussche H, Wood GC, and the Society of Infectious Diseases Pharmacists Aerosolized Antimicrobials Task Force. *Pharmacother* 2010;30(6):562–584.

Clinical Outbreak of Linezolid-Resistant Staphylococcus aureus in an Intensive Care Unit. Sánchez García M, De la Torre MA, Morales G, et al. *JAMA*. 2010;303(22):2260-2264.

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