

# CRITICAL CARE PHARMACOLOGY LITERATURE UPDATE

---

*JULY 2010*

**T**his 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**

Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility .....	2
Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomized, placebo-controlled trial.....	3
A prospective, randomized trial of intravenous prochlorperazine versus subcutaneous sumatriptan in acute migraine therapy in the emergency department. ....	3
Insufficient $\beta$ -lactam concentrations in the early phase of severe sepsis and septic shock .....	4
Concomitant ceftriaxone and high-concentration intravenous calcium therapy in adult critical care patients: a matched cohort study.....	5
Prolonged prothrombin time after recombinant activated factor VII therapy in critically bleeding trauma patients is associated with adverse outcomes .....	5
Identifying optimal initial infusion rates for unfractionated heparin in morbidly obese patients.....	6
Contributors.....	6

## **Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility a randomized trial**

**Russell D. Hull, MBBS; Sebastian M. Schellong, MD; Victor F. Tapson, MD; Manuel Monreal, MD; Meyer-Michel Samama, MD, PharmD; Philippe Nicol, PhD; Eric Vicaut, MD, PhD; Alexander G.G. Turpie, MD; and Roger D. Yusen, MD, MPH, for the EXCLAIM (Extended Prophylaxis for Venous ThromboEmbolism in Acutely Ill Medical Patients With Prolonged Immobilization) study\* *Ann Intern Med.* 2010;153:8-18**

The benefits of both short-term venous thromboembolism (VTE) prophylaxis in hospitalized acutely ill medical patients and extended-duration (4 week) prophylaxis in high-risk surgical patients have previously been established. This multicenter, randomized, placebo controlled trial seeks to assess the safety and efficacy of extended-duration VTE prophylaxis (with enoxaparin 40mg daily) in acutely ill medical patients, following a 6- to 14-day clinically proven regimen for VTE prophylaxis. The primary endpoints were VTE (the composite of symptomatic or asymptomatic proximal deep venous thrombosis (DVT), symptomatic pulmonary embolism (PE), or fatal PE) during the treatment period, and the incidence of major hemorrhagic complications during and up to 48 hours after the treatment period. Secondary endpoints were VTE incidence through 3 months, mortality (at 1 month, 3 months, and 6 months), and the incidence of major and minor hemorrhagic complications, serious adverse events, and thrombocytopenia. Final interim

efficacy analysis found lower-than-assumed VTE rates, with no statistical significance between treatment groups. Interim safety analysis also found statistically significant increase in the major hemorrhages associated with the enoxaparin group after unblinding. The data safety monitoring board (DSMB) terminated the study as originally designed, but allowed continuation in patients with level 1 immobility and patients with level 2 immobility and age older than 75 years, previous VTE, or active or previous cancer since these patients had VTE risk and event rates consistent with study design assumptions. Extended-duration enoxaparin significantly reduced VTE for the treatment period in the total population (absolute risk difference -1.53% [95.8% CI, -2.54% to -0.52%]). The VTE reduction was unchanged at 90 days. Major hemorrhage at 30 days was significantly greater in the enoxaparin group than in the placebo group (0.8% vs. 0.3%; absolute risk difference 0.51% [95% CI, 0.12% to 0.89%]). Total bleeding events were also significantly increased in the enoxaparin group versus placebo (absolute risk difference favoring placebo, 2.37% [95% CI, 1.26% to 3.48%]). No statistically significant increase was seen in serious adverse events that led to death with the enoxaparin group vs. placebo (1.3% vs. 1.5%). This article concludes that extended-duration prophylaxis with enoxaparin reduced the incidence of symptomatic or asymptomatic DVT, symptomatic PE, or fatal PE in acutely ill medical patients with level 1 immobility, those older than 75 years, and women, with an increased rate of major bleeding events. The use of extended-duration prophylaxis in patients with level 2 immobility is not supported unless they are older than 75 years, previous VTE, or active or previous cancer.

## **Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomized, placebo-controlled trial**

**CRASH-2 trial collaborators. *Lancet*. 2010;376:23-32.**

While the mechanisms of hyperfibrinolysis are thought to be similar between patients in the surgical and trauma populations, researchers have noted a relative paucity of data concerning antifibrinolytic drug use in the latter. The CRASH-2 trial collaborators set out to determine the efficacy of the lysine analogue tranexamic acid (Cyklokapron®), which works by inhibiting the conversion of plasminogen to plasmin and, by extension, clot breakdown. Investigators enrolled a robust, international sample of 20,211 adult trauma patients presenting within eight hours of injury who either had significant hemorrhage (bleeding plus: a systolic blood pressure < 90 mm Hg; a heart rate > 110 beats per minute; or both) or who were considered by their managing physician to be *at risk of* significant hemorrhage. The study randomized patients to either tranexamic acid – with a one gram loading dose followed by another gram administered over the following eight hours – or matching placebo. They found nine percent relative risk (RR) reduction in the primary outcome of all-cause mortality at 28 days' follow up (95% confidence interval [CI] 0.85-0.97), corresponding to an absolute 14.5% mortality rate in the *active* treatment group vs. 16% in the *placebo* group. Similarly, there was a fifteen percent relative risk reduction in

bleeding-related mortality (95% CI: 0.85-0.97). There also was a trend favoring tranexamic acid in rates of vascular occlusion (RR 0.69; 95% CI 0.44-1.08; p-value 0.096), a composite endpoint that included myocardial infarction, stroke, and pulmonary embolism. A subgroup analysis suggested that benefit was derived only when the drug was started within three hours of injury. A weakness the authors noted was that the trial did little to explain the reason for reduced mortality, given that there ended up being *no difference in blood transfusion requirements* between groups. An accompanying commentary postulates a range of pleiotropic effects stemming from reduced plasmin activity, including inhibition of: monocyte, neutrophil, platelet, and endothelial cell response; cytokine and complement release; and proinflammatory gene activation. The authors say that their study raises a specter of hope for other traumatic injuries, such as intracranial hemorrhage. However, they correctly note that use in that population would be premature in the absence of clinical data. Likewise, success with tranexamic acid does not necessarily mean that other fibrinolytics are also effective in the trauma population. (The other commercially available antifibrinolytic widely available in the United States is aminocaproic acid [Amicar®].)

## **A prospective, randomized trial of intravenous prochlorperazine versus subcutaneous sumatriptan in acute migraine therapy in the emergency department.**

**Kostic MA, Gutierrez FJ, Rleg TS, et al. *Annals of Emerg Med*. 2010; 56(1): 1-6.**

Migraine is a significant debilitating condition commonly seen in the emergency department. Intravenous prochlorperazine (PRO) and subcutaneous sumatriptan (SUM) have been demonstrated as effective; however, there is a lack of evidence comparing the safety and efficacy of the two treatment options. This is a prospective, randomized, controlled, double-blind study comparing PRO 10 mg plus diphenhydramine 12.5 mg IV to SUM 6 mg for the treatment of migraine in the emergency department. Baseline characteristics, including pain scores and duration of headache, were similar at baseline. Overall, both treatment arms had a significant decrease in pain scores from baseline to 80 min (or discharge if sooner); however patients in the prochlorperazine group demonstrated a more profound improvement in pain control (73 mm reduction PRO vs 50 mm reduction SUM). Additionally, there was no difference in nausea and sedation reported between the treatment arms throughout the study. No patients in the sumatriptan group reported chest pain, although authors comment that the phraseology of the question to the patient may have contributed to this. Nine of the 32 subjects in the PRO group reported restlessness; however none of the patients requested additional anticholinergic treatment. Follow-up phone calls were made to assess recurrence of the migraine. Although there was a low response rate of 61%, fewer patients in the PRO group reported return of a headache compared to SUM (43% versus 63%, respectively). Overall, this study demonstrates the superiority of PRO plus diphenhydramine over SUM in the treatment of an acute migraine.

## **Insufficient $\beta$ -lactam concentrations in the early phase of severe sepsis and septic shock**

**Taccone FS, et.al. *Crit Care*. 2010; 14: R126.**

Antibiotic dosing strategies are commonly developed in healthy volunteers and rarely account for the altered pharmacokinetic (PK) parameters and physiologic abnormalities often seen in critically ill patients. In patients with severe sepsis and septic shock (SS/SS), increased volume of distribution and cardiac output, decreased protein binding and end organ dysfunction potentially affect serum drug concentrations. This prospective, multicenter, observational study (N=80) assessed first-dose beta-lactam concentrations in adult patients with SS/SS. All included patients received as a first dose ceftazidime 2g, cefepime 2g, piperacillin/tazobactam (P/T) 4.5g or meropenem 1g infused over 30 minutes. Exclusion criteria were age >85, pregnancy/lactation, previous administration of investigated drug, dialysis-dependence or beta-lactam allergy. Blood samples were drawn at 1, 1.5, 4.5 and 6 or 8 hours after the first dose and analyzed at a centralized reference laboratory. The primary outcome, percentage of time during the dosing interval that serum drug concentration was greater than 4 times the MIC of *Pseudomonas aeruginosa*, was 33% for P/T (optimal 50%), 45% of ceftazidime (optimal 70%), 34% for cefepime (optimal 70%) and 57% for meropenem (optimal 40%). This optimal bactericidal target was achieved in 44% patients who received P/T, 28% for ceftazidime, 16% for cefepime and 75% for meropenem. Notably, 41% of P/T patients had drug concentrations less than 4 times MIC only 90 minutes after dose administration. This study had well-

described methodology in an understudied patient population and suggests that initial dosing strategies for P/T, ceftazidime and cefepime may be suboptimal in patients with SS/SS. The impact on clinical endpoints, however, has not been established.

### **Concomitant ceftriaxone and high-concentration intravenous calcium therapy in adult critical care patients: a matched cohort study**

**Dalton BR, Zuege DJ, Shahpori R, Laupland KB. *Ann Pharmacother.* 2010;44:1158-63.**

In 2007 the US Food and Drug Administration issued a warning advising against the use of concomitant ceftriaxone and intravenous calcium after precipitation of these co-administered drugs was linked with 9 cases of neonatal or infant cardiorespiratory decompensation and/or death. In order to evaluate whether this warning is applicable in an adult setting, this retrospective, matched-cohort study was performed. Patients hospitalized in the adult ICU between 1/1/03 and 12/31/08 were included in the study if they had undergone continuous renal replacement therapy (CRRT) with a citrate anticoagulation protocol including a calcium chloride infusion (8 mg/ml). Subjects were matched based on operating room status, age, baseline APACHE II, time from ICU admission to CRRT initiation, and CRRT duration. Exposure was defined as at least one day of overlapping treatment of ceftriaxone with intravenous calcium. Respiratory events in addition to ICU/hospital mortality were compared between the exposed cohort (n=142) and a matched, unexposed

group (n=350). None of the outcome parameters were statistically significant indicating that adult patients may be minimally affected by this drug interaction.

Unfortunately, a small sample size limits the power of the study to completely rule out the risk of concomitant exposure of both of these agents.

### **Prolonged prothrombin time after recombinant activated factor VII therapy in critically bleeding trauma patients is associated with adverse outcomes**

**McMullin NR, Wade CE, Holcomb JB, et al. *The Journal of Trauma Injury, Infection, and Critical Care* 2010;69(1):60-69**

This paper consists of a post hoc analysis of data taken from two randomized clinical trials using recombinant activated factor VII (rFVIIa) in trauma patients. Observations of these two trials suggested that persistent coagulation parameter abnormalities, specifically prothrombin time (PT), may be associated with more resuscitative efforts post dosing of rFVIIa. For this analysis, authors chose a PT cutoff value of 18 seconds or longer (providing an optimal combination of sensitivity and specificity in 24 hour mortality and massive transfusion data sets), in which outcome measures were then compared between 1 hour post-dose PT $\geq$  18 seconds group versus 1 hour post-dose PT $<$ 18 seconds group. Two hundred seventy seven patients from the previous studies were eligible for analysis, of which 169 patients were included. Results of the analysis showed that PT and aPTT values at baseline were

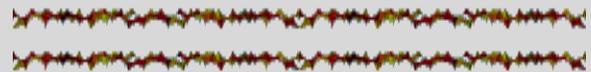
significantly higher in the groups of patients with 1 hour PT values  $\geq 18$  seconds compared to patients with 1 hour post dose PT value  $<18$  seconds for both rFVIIa and placebo. There were no significant differences between groups in amount of blood product administered before dosing of study drug. However, patients in the PT  $\geq 18$  seconds 1 hour post-dose group had a 23 fold higher 24 hour mortality rate, higher 30-day mortality rate, higher massive transfusion rate, fewer ICU-free days, and fewer hospital-free days. Although there were several limitations of this study, this post-hoc analysis suggests utility of PT values in identifying patients who may benefit from additional blood product administration regardless of the use of rFVIIa to prevent trauma-related morbidity and mortality.

## Identifying optimal initial infusion rates for unfractionated heparin in morbidly obese patients

J N Riney, Hollands JM, Smith JR, and Deal EN  
*Ann Pharmacother* 2010;44:1141-51.

With the growing percentage of obese and morbidly obese patients, dosing of anticoagulation is increasingly difficult. In this single-center observational cohort study, morbidly obese (WHO class III, BMI  $\geq 40$ ) patients receiving therapeutic unfractionated heparin (UFH) infusions for at least 24 hours were matched to WHO class I/II/overweight (BMI 25-39.9) and under/normal weight groups (BMI  $<25$ ). The primary outcome of mean heparin infusion rates (calculated using actual body weight) was significantly different between groups with the morbidly obese group requiring 11.5 units/kg/h, the BMI 25-39.9

group requiring 12.5 units/kg/h, and the BMI  $<25$  group requiring 13.5 units/kg/h ( $p < 0.001$ ). A difference was not detected between groups when a bolus was administered. The morbidly obese group had a significantly higher number of aPTT values considered therapeutic at 32% versus 29.8% in the BMI 25-39.9 group and 21.9% in the BMI  $<25$  group ( $p = 0.08$ ). The authors suggested applying a strategy by which UFH infusion protocols be changed to reflect initial dosing by BMI category. This study noted strengths in its large cohort relative to previous studies and the results were generally concordant with those prior studies. This study is limited by the constrained number of confounding variables abstracted, the institution-specific nature of the results, and the use of data prior to the change of heparin potency nationwide.



## Contributors

Marcus Costner, PharmD, BCPS (VA); Erin Frazee, PharmD (Mayo); Haley Goodwin, PharmD (Johns Hopkins); Deanna McMahon Horner, PharmD, BCPS (UCSF); Emily Hutchinson, PharmD, BCPS (Methodist); Erin Koopman, PharmD, BCNSP (Mayo); Shawn Kram, PharmD, BCPS (Via Christi); Jessica Mercer, PharmD (MUSC); Heather Personett, PharmD (Mayo); Angela Plewa, PharmD, BCPS (Stroger); Bridgette Therriault, PharmD (Mayo); Charles J Turck, PharmD, BCPS (UMass); Peter Herout, PharmD, BCPS (EPI-Q, Inc.). Reviewed by: Deepali Dixit, Pharm.D.