

## **August 2009 Journal Club Synopsis**

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**Topic: New I.V. Anti-hypertensive medications in the ED**

### **Clinical Scenario:**

CC: “not acting right”

HPI: Mr. Jones, a 39 year old male is brought in by his family with a chief complaint of “not acting right.” As described by the family, the patient was complaining of intermittent headaches over the last month, and over the last 2days he has become inappropriate verbally, with bouts of nausea, vomiting, blurred vision, and confusion. He is now poorly responsive with a GCS of 10. His family states he had increased his Motrin use at home to control headaches.

PMHx: DM2, moderate HTN (medications recently adjusted)

Meds: Metformin, Lisinopril, Motrin prescribed by the NP he sees at the local clinic.

Surg. Hx. None

Allergies: None

Vitals: RR 20, BP 250/135 in both arms, HR 117, Temp 98.3, Accucheck 107

PE: Patient is A&O x 1. Prominent papilledema, Otherwise normal.

\*What medication would you like to use to control this patient’s BP in the acute setting?

Initial workup shows:

Cr 7, BUN 50, K+ 5.8, CT head negative, ++proteinuria, EKG shows signs of LVH only

\*\*After initial labs are back, any desire to change your choice of BP medication?

### **Articles Selected & Synopsis:**

Article 1:

Pollack CV, et al., Clevidipine, an Intravenous Dihydropyridine Calcium Channel Blocker, Is Safe and Effective for the Treatment of Patients With Acute Severe Hypertension, *Annals of Emergency Medicine*, Volume 53, No. 3 : March 2009, p 329-338. (The VELOCITY Trial).

The VELOCITY Trial was performed as an open label uncontrolled clinical study. The study was intended to assess the safety and efficacy of intravenous clevidipine in patients with acute severe increase in blood pressure by using prespecified, non-weight-based titration dosing, with continuous maintenance infusion for 18 hours or longer.

Patients aged 18 years or older and presenting in the emergency department or ICU with severe hypertension (systolic blood pressure 180 mm Hg and/or diastolic blood pressure 115 mm Hg) were treated with clevidipine to achieve a predetermined, patient-specific (determined by clinician) systolic blood pressure target range. Clevidipine was initiated at 2 mg per hour and titrated as needed in doubling increments every 3 minutes to a maximum of 32 mg per hour, during 30 minutes, and then continued for a total duration of 18 to 96 hours. Patients commonly presented with both acute hypertension and end-organ injury; 81% (102/126) had demonstrable end-organ injury at baseline. Within 30 minutes of starting clevidipine, 88.9% (104/117) of patients achieved target range. Median time to target range was 10.9 minutes. No concomitant intravenous antihypertensives were needed in 92.3% (108/117) of patients receiving 18 hours or more of clevidipine infusion. Clevidipine was well tolerated with successful transition to oral antihypertensive therapy after infusion to a defined blood pressure target in 91.3% (115/126) of patients.

Clevidipine, dosed in a non-weight-based manner, was safe and effective in a cohort of patients with severe hypertension at a starting dose of 2 mg per hour, followed by simple titration during 18 hours or more of continuous infusion. Patients were effectively managed via simple blood pressure cuff monitoring without requirement for an arterial line.

Article 2:

Aronson S., et al, The ECLIPSE Trials: Comparative Studies of Clevidipine to Nitroglycerin, Sodium Nitroprusside, and Nicardipine for Acute Hypertension Treatment in Cardiac Surgery Patients, Cardiovascular Anesthesiology, Vol 107, No. 4, October 2008, p. 1110-1121.

Acute hypertension during cardiac surgery can be difficult to manage and may adversely affect patient outcomes. Clevidipine is a novel, rapidly acting dihydropyridine L-type calcium channel blocker with an ultrashort half-life that decreases arterial blood pressure (BP). The Evaluation of Clevidipine In the Perioperative Treatment of Hypertension Assessing Safety Events trial (ECLIPSE) was performed to compare the safety and efficacy of clevidipine (CLV) with nitroglycerin (NTG), sodium nitroprusside (SNP), and nicardipine (NIC) in the treatment of perioperative acute hypertension in patients undergoing cardiac surgery.

The study analyzed data from three prospective, randomized, open-label, parallel comparison studies of CLV to NTG or SNP perioperatively, or NIC postoperatively in patients undergoing cardiac surgery at 61 medical centers. Of the 1964 patients enrolled, 1512 met postrandomization inclusion criteria of requiring acute treatment of hypertension based on clinical criteria. The patients were randomized 1:1 for each of the three parallel comparator treatment groups. The primary outcome was the incidence of death, myocardial infarction, stroke or renal dysfunction at 30 days. Adequacy and precision of BP control was evaluated and is reported as a secondary outcome.

There was no difference in the incidence of myocardial infarction, stroke or renal dysfunction for CLV-treated patients compared with the other treatment groups. There was no difference in mortality rates between the CLV, NTG or NIC groups. Mortality was significantly higher, though, for SNP-treated patients compared with CLV-treated patients ( $P = 0.04$ ). CLV was more effective compared with NTG ( $P = 0.0006$ ) or SNP ( $P = 0.003$ ) in maintaining BP within the prespecified BP range. CLV was equivalent to NIC in keeping patients within a prespecified BP range; however, when BP range was narrowed, CLV was associated with fewer BP excursions beyond these BP limits compared with NIC. Clevidipine is a safe and effective treatment for acute hypertension in patients undergoing cardiac surgery.

Article 3: Devlin J, et al, Fenoldopam Versus Nitroprusside for the Treatment of Hypertensive Emergency, *The Annals of Pharmacology*, May 2004, Volume 38, p. 755-759.

The objective of this study was to compare the efficacy, safety, and cost of sodium nitroprusside versus fenoldopam for the treatment of hypertensive emergency.

This study was a retrospective analysis of consecutive patients with hypertensive emergency admitted to a university-affiliated, level 1 trauma center from 1999 to 2001 and treated with either nitroprusside ( $n = 21$ ) or fenoldopam ( $n = 22$ ) for  $>30$  minutes. Time to reach mean arterial pressure (MAP) goal, change in MAP over time, time to initiation of oral antihypertensive therapy, change in renal function, incidence of cyanide toxicity, and cost of therapy were compared between groups.

Demographic parameters were similar between groups, except renal failure, which was more prevalent in the fenoldopam group (10% vs 46%;  $p = 0.009$ ). Neither the mean  $\pm$  SD pretreatment MAP (nitroprusside  $168 \pm 19$ ; fenoldopam  $163 \pm 19$ ;  $p = 0.45$ ), time to reach MAP goal (3.6 [0.4–30] vs 4 [1–22] h;  $p = 0.51$ ), nor infusion duration (18 [0.7–113] vs 18 [3–74] h;  $p = 0.45$ ) differed between the patient groups. Time to initiation of oral antihypertensive therapy was similar between nitroprusside- (4.5 h [0.5–22]) and fenoldopam- (6.5 h [1–100]) treated patients;  $p = 0.65$ ). Additional intravenous antihypertensives were administered to 16 patients in each group ( $p = 0.80$ ). Change in creatinine clearance and incidence of tachycardia did not differ between groups. No symptoms of cyanide toxicity were detected. Cost of drug therapy was greater with fenoldopam (\$597.60, \$199.20–6675.20); than nitroprusside (\$2.66, \$1.68–3.48;  $p < 0.001$ ).

Treatment of hypertensive emergency with fenoldopam appears to result in patient outcomes equivalent to those with nitroprusside but at a substantially higher cost.

**Summarizing Comments:**

- Clevidipine is not yet available in the Dayton area but should be available shortly.
- Clevidipine appears to be highly effective at maintaining BP in a tight range. Whether this improves patient outcome has not yet been proven.
- Attractive features of clevidipine include a modest side effect profile, safety across a wide array of hypertensive emergencies, simple non-weight based dosing, rapid “on/off”, metabolized by RBC esterases so no adjustments required in renal or hepatic failure patients, and BP can be monitored non-invasively.
- Nipride, while not ideal in head injury patients or patients with renal failure did compare favorably (particularly in the fenoldopam study). While it is an old drug, it is effective, and when used in the correct settings, side effects can be minimal and/or easily managed.
- The VELOCITY study was lacking any type of comparison drug or other appropriate control group. There was no power analysis completed, nor was any statistical analysis completed.