

## INTRODUCTION

Clevidipine is a third generation intravenous dihydropyridine calcium channel antagonist approved for treatment of acute hypertension when oral therapy is not feasible or desirable. It is an arterial vasodilator that is metabolized by plasma esterases; therefore, it is eliminated independently of the liver and kidney.<sup>1</sup> Clevidipine has been studied for the control of perioperative hypertension<sup>2,5</sup> as well as for the management of hypertensive crises<sup>6</sup> when immediate blood pressure control is clinically necessary. Benefits include its tolerability, rapid onset and offset, and easy titration with predictable response. Other continuously infused intravenous antihypertensives used in the neurocritical care patient population include nicardipine, labetalol, and esmolol; however these medications are limited by contraindications, adverse reactions, titration ability, and duration of action.<sup>7</sup> In addition, the formulation of clevidipine is beneficial in fluid-restricted patients when compared to other agents which deliver significantly more volume.

### Guideline Recommendations for use of Antihypertensives in Neurological Hypertensive Emergencies

Condition	Recommendations/Comments	Suggested Agents
Acute ischemic stroke <sup>7,8</sup>	Reduce blood pressure by no more than 10-15% in the first 24 hours; treat only for the following indications: • Planned thrombolysis and BP >185/110 mmHg. Target BP < 180/105 mmHg • Evidence of concomitant noncerebral acute end organ damage • BP >220/120 mmHg	If SBP >220 or DBP 121-140 mmHg: labetalol or nicardipine If DBP >140 mmHg: nitroprusside Other agents (hydralazine, enalaprilat, etc) may be considered when appropriate
Intracerebral hemorrhage <sup>7,9</sup>	Treat only when SBP >200 and DBP >110 or MAP >130 • SBP >200 or MAP >150: o aggressive treatment with IV infusion • SBP >180 or MAP >130 with possibility of elevated ICP: o intermittent or continuous IV medications while maintaining CPP ≥60 mmHg • SBP >180 or MAP >130 without evidence of elevated ICP: o consider modest BP reduction (e.g. MAP 110 or BP 160/90) using intermittent or continuous IV medications	Nicardipine Labetalol
Aneurysmal subarachnoid hemorrhage <sup>10</sup>	SBP >160 increases the risk of re-bleeding	Nicardipine or clevidipine may be better than labetalol and nitroprusside

Clevidipine was added to the formulary at our institution in December 2010 with restriction to cardiac and neurological intensive care units. Because of its cost, it was recommended by the Pharmacy and Therapeutics (P&T) Committee to evaluate its appropriateness of use as well as safety and efficacy.

## METHODS

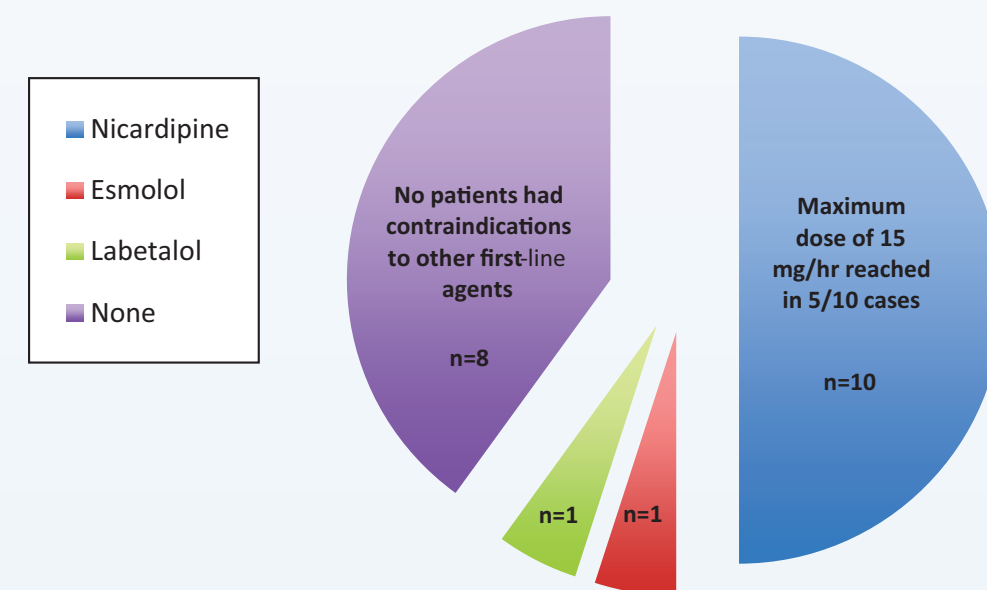
Twenty patients receiving clevidipine in the Jefferson neurological intensive care units (NICUs) between September 2011 and December 2012 were retrospectively identified. Patient information including age, gender, allergies, height, weight, admitting diagnosis, and past medical history was collected. Indication for use, dose, duration of therapy, concomitant antihypertensive administration, blood pressure measurements, time to achieve blood pressure goal, and adverse events were also assessed. Published guidelines were reviewed to determine whether clevidipine was an appropriate choice for the indication. Cost of therapy was calculated for each patient.

## RESULTS

### Demographics & Baseline Characteristics

Parameter	Results
Male, n (%)	9 (45)
Female, n (%)	11 (55)
Mean age in years (range)	45.7 (24-77)
Past medical history, n (%)	
• Hypertension	17 (85)
• Heart failure/cardiomyopathy	3 (15)
• Coronary artery disease	2 (10)
• Diabetes	5 (25)
• Intracerebral hemorrhage	1 (5)
• Acute ischemic stroke	5 (25)
• Atrial fibrillation	2 (10)
• Asthma	4 (20)
• Acute kidney injury	4 (20)
• Chronic kidney disease	5 (25)
Admitting diagnosis, n (%)	
• Intracerebral hemorrhage	5 (25) (1 with dissection)
• Acute ischemic stroke	4 (20)
• Subarachnoid hemorrhage/aneurysm	4 (20)
• Anoxic brain injury	2 (10)
• Cryptococcal meningitis	2 (10)
• Brain tumor	1 (5)
• Arteriovenous malformation	1 (5)
• Seizure	1 (5)
Central line access, n (%)	12 (60)

### Antihypertensive Continuous Infusions Tried Before Clevidipine



- Of the patients who did not receive continuous antihypertensive infusions prior to clevidipine:
  - Two patients received intermittent parenteral antihypertensives prior to clevidipine
  - One patient had an acute myocardial infarction during admission. Cardiology recommended intermittent IV metoprolol, which was not ordered
  - Two patients had nicardipine ordered first but it was not administered
- The patient who received esmolol reached the maximum dose; then nicardipine was added and titrated to the maximum dose.
- Eight patients received intermittent parenteral antihypertensives prior to clevidipine initiation:
  - Labetalol: 5 patients
  - Hydralazine: 2 patients
  - Metoprolol: 1 patient

### Clevidipine Use

Parameter	Results
Mean time on clevidipine infusion	50.6 hours (range 6-140 hours)
Mean dose	7.5 mg/hr
Mean time to blood pressure goal*	62.6 minutes

\*in patients who were not already at goal (n =11)

### Clevidipine Safety

Parameter	Results, n (%)	Comments
Hypotension requiring fluid bolus or use of vasopressors	3 (15)	1 patient on both clevidipine (21 mg/hr) and labetalol
Decreased oxygen saturation*	7 (78)**	Several attributed to other causes (i.e. aspiration, sepsis)
Increased triglycerides (TG)	5 (25)	All on concurrent propofol; TG increases ranged from 50-215%

\*defined as increasing oxygen requirements after clevidipine started in non-intubated patients  
 \*\*among non-intubated patients (n=9)

### Triglyceride (TG) Increases Associated with Clevidipine Initiation

Patient	Initial TG (mg/dL)	TG (mg/dL) after clevidipine initiation
1	643	1294
2	103	325
3	85	166
4	131	256
5	153	230

### Cost and Volume Comparison of IV Antihypertensives for Continuous Infusion in the Neurological ICU

Agent	Price Range per Day	Volume per Day
Clevidipine	1-21 mg/hr \$61-\$1311	48 mL – 1 L
Nicardipine (pharmacy prepared)	5-15 mg/hr \$54-\$162	1.2 L – 3.6 L (0.1 mg/mL) 600 mL – 1.8 L (0.2 mg/mL) 120 mL – 360 mL (1 mg/mL)
Nicardipine* (0.1 mg/mL premixed bags)	\$493-\$1478	1.2 L – 3.6 L (0.1 mg/mL)
Labetalol	1-2 mg/min \$21-\$41	288 mL – 576 mL
Esmolol**	0.3-3 mcg/kg/min \$26-\$265	252 mL – 1 L

\* Prior to the nicardipine shortage, premixed bags were typically used only when rates were less than 5 mg/hr

\*\*Esmolol dose and volume based on 70-kg patient

### Clevidipine Cost

- The mean cost per patient was \$831.53
- This does not account for drug waste attributed to discarding the drug every 12 hours

## DISCUSSION

- Clevidipine use was deemed appropriate in 7 of 20 patients (35%) based on contraindications and adequate trials of other agents.
- A cost analysis showed a projected cost savings of \$3940 if the other 65% of patients had received another recommended agent instead of clevidipine. This estimation was determined by comparing the actual cost of clevidipine based on patients' doses and duration to the cost of another first-line agent assuming it was given at the maximum rate for the same duration that clevidipine was used.
- Although elevated triglycerides were seen in 5 patients, there were no cases of acute pancreatitis.
- Limitations to this medication use evaluation include the retrospective data collection using electronic nursing charting, small sample size, and cost analysis assumptions.
- The findings were presented to the Neuroscience Subcommittee of the P&T Committee as well as the P&T Committee, resulting in the creation of institutional guidelines in August 2013. These were approved by the Medical Executive Committee in September 2013. The guidelines allow clevidipine to be used as the first-line agent only for patients with intracerebral hemorrhage and unsecured intracranial aneurysm. Clevidipine may be used for 24 hours, after which time its use must be reevaluated and the feasibility of switching to another agent be addressed.

## CONCLUSION

- Clevidipine is the most expensive continuous intravenous anti-hypertensive.
- Clevidipine remains an appropriate choice for acute blood pressure management.
- However, due to its high cost, the duration of therapy can be targeted as a cost-reduction initiative.
- Triglyceride monitoring is essential, particularly in patients who are receiving concomitant propofol.
- Comparative studies are needed to help determine clevidipine's place in therapy.

## REFERENCES

- The Medicines Company. Cleviprex® (Clevidipine) Injectable Emulsion, for intravenous use Prescribing Information. Parsippany, NJ; 2011.
- Powrozynk AVV, Vuylsteke A, Naughton C, et al. Comparison of clevidipine with sodium nitroprusside in the control of blood pressure after coronary artery surgery. *Eur J Anesth* 2003;20:697-703.
- Levy JH, Mancao MY, Gitter R, et al. Clevidipine effectively and rapidly controls elevated blood pressure preoperatively in cardiac surgery patients: the results of the randomized, placebo-controlled efficacy study of clevidipine assessing its preoperative hypertensive effect in cardiac surgery-1. *Anesth Analg* 2007;105:918-25.
- Singla N, Warltier DC, Gandhi SD, et al. Treatment of acute postoperative hypertension in cardiac surgery patients: an efficacy study of clevidipine assessing its postoperative antihypertensive effect in cardiac surgery-2 (ESCAPE-2), a randomized, double-blind, placebo-controlled trial. *Anesth Analg* 2008;107:59-67.
- Aronson S, Dyke CM, Stierer KA, et al. The ECLIPSE trials: comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients. *Anesth Analg* 2008;107:1110-21.
- Pollack CV, Varon J, Garrison NA, et al. Clevidipine, an intravenous dihydropyridine calcium channel blocker, is safe and effective for the treatment of patients with acute severe hypertension. *Ann Emerg Med* 2009;53:329-38.
- Marik PE and Varon PE. Hypertensive crises: challenges and management. *Chest* 2007;131:1949-62.
- Jauch EC, Saver JL, Adams HP, et al. Early management of acute ischemic stroke. *Stroke* 2013.
- Morgenstern LB, Hemphill JC, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2010;41:2108-29.
- Connolly ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage. *Stroke* 2012;43:1711-37

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