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Clevipidine for Hypertensive Urgency and Emergency

By: **Gretchen D'Arcangelo, Pharm.D.**

Introduction: Hypertensive emergencies are defined by potentially life-threatening elevations in blood pressure (BP) greater than 180/120 mmHg and are also paired with organ dysfunction.¹ Hypertensive urgencies, on the other hand, do not have the characteristic organ dysfunction present. These hypertensive crises are said to account for up to 3% of emergency department admissions, with about three-fourths of those admissions due to hypertensive emergencies.² In patients with either hypertensive urgency or emergency, immediate BP reduction should be attempted either with oral or intravenous (IV) antihypertensives as appropriate.¹ Intravenous agents utilized for these clinical scenarios could include nifedipine, sodium nitroprusside, or clevipidine, with the agent selected based on appropriate patient-specific factors. Clevipidine (Cleviprex®), a dihydropyridine calcium channel blocker, is approved by the Food and Drug Administration

(FDA) for the reduction of BP when oral therapy is not feasible or desirable.³

Pharmacokinetics: Following IV administration, clevipidine is rapidly metabolized by blood and tissue esterases giving it a very quick onset of action and short half-life.³ Its pharmacologic effect starts within 2 to 4 minutes with a duration of action of up to 15 minutes.

Efficacy and Safety: Patients undergoing cardiac surgery diagnosed with hypertension in the past 6 months were included in a randomized, double-blind, placebo-controlled evaluation of clevipidine.⁴ Treatment failure, defined as failure to decrease systolic BP (SBP) by $\geq 15\%$ from baseline or inability to complete the study, occurred in 82.7% of the placebo group compared to only 7.5% of the clevipidine-treated group with a time to target SBP ($\leq 15\%$ base-

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Tramadol: No Longer the Codeine Alternative

By: **Maria Sellas, Pharm.D.**

Introduction: Tramadol (Ultram®) is a centrally-acting, synthetic opioid analgesic used for moderate to severe pain.¹ Although this schedule IV controlled substance is not approved by the Food and Drug Administration (FDA) for use in children under 16 years old, it is used off-label in pediatrics at a recommended dosage range of 1-2 mg/kg/dose every 4 to 6 hours.² On September 21, 2015, the FDA issued a Drug Safety Communication regarding a serious risk of slowed or difficult breathing in children under the age of 17, who re-

ceived tramadol.³ Those who were given tramadol for pain control following a tonsillectomy and/or adenoidectomy were thought to be at a greater risk for this adverse effect.

Pharmacogenomics of Tramadol: Tramadol is extensively metabolized by the Cytochrome P450(CYP)2D6 and CYP3A4 isoenzymes. Through the CYP2D6 enzyme system, tramadol is metabolized to an active metabolite, O-desmethyltramadol, which has a 200-

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line SBP) of 6 minutes in the treatment arm.⁴ A similarly designed trial evaluated patients undergoing cardiac surgery who were randomized to either clevidipine or placebo in the postoperative setting; this investigation found that treatment failure occurred in 79.6% of placebo-treated patients compared to 8.2% of clevidipine-treated patients with a median time to target SBP of 5.3 minutes for clevidipine.⁵ Another study involving cardiac surgery patients found no significant difference in 30-day safety endpoints including death, myocardial infarction, stroke, and renal dysfunction in those treated with clevidipine compared with sodium nitroprusside, nitroglycerin, or nicardipine.⁶ Finally, in an open-label, single-arm trial evaluating the use of clevidipine in patients with severe persistent hypertension defined as SBP >180 mmHg and/or diastolic BP >115 mmHg, clevidipine use was associated with a reduction in BP within the individualized patient-specific target BP range in 88.9% of patients with a median time to achievement of 10.9 minutes.⁷

Dosing and Administration: The recommended starting dose of clevidipine is 1-2 mg/hr which is then titrated based on BP response.³ For titration, the dose can be doubled in short (90 second) intervals initially; however once the BP is nearing goal, smaller dosage increases should be employed at longer time intervals (every 5 to 10 minutes). It is estimated that a 1-2 mg/hr increase will produce an additional 2-4 mmHg decrease in SBP. The standard maintenance dose that achieves appropriate therapeutic response in a majority of patients is between 4-6 mg/hr; however higher doses may be required for severe hypertension. Clevidipine is formulated as an oil-in-water, lipid emulsion. Due to lipid load restrictions, it is recommended not to exceed 1000 mL/day (2000 kcal/day) of this medication. Patients receiving clevidipine and being transitioned to oral antihypertensive agents should be monitored for at least 8 hours after discontinuation due to the risk of rebound hypertension.

Clevidipine Clinical Pearls:

- Once the clevidipine vial is punctured, any product remaining after 12 hours should be discarded and all IV lines used for administration and delivery should be changed.
- Clevidipine contains 2 kcal/mL of lipids, compared to propofol which contains 1.1 kcal/mL.^{3,8} If given together, attention should be paid to the cumulative amount of kilocalories being administered from both products.
- Like propofol, clevidipine should not be sent through the pneumatic tube system.

Availability and Cost: Clevidipine is available as a 0.5 mg/mL, 50 mL vial with a suggested wholesale price (SWP) of \$108.⁹ Nicardipine, which is available as a 20 mg/200 mL IV piggyback, has a SWP of \$114. Sodium nitroprusside is available as a 25 mg/mL, 2 mL vial and has a SWP of \$1057.

Formulary Status: Clevidipine, which was FDA-approved in 2008, was added to the Cleveland Clinic Health System (CCHS) Formulary in 2015 in response to a significant cost increase to sodium nitroprusside. Its use in adults throughout CCHS is unrestricted at this time. It remains non-formulary for pediatric patients.

References:

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003 Dec;42(6):1206-52.
2. Zampaglione B, Pascale C, Marchisio M, Cavallo-Perin P. Hypertensive urgencies and emergencies: prevalence and clinical presentation. *Hypertension*. 1996;27(1):144-7.
3. Cleviprex® (clevidipine butyrate) injectable emulsion for intravenous use [package insert]. Parsippany, NJ: The Medicines Company; Dec 2014.
4. Levy JH, Mancao MY, Gitter R, Kereiakes DJ, Grigore AM, Aronson S, et al. Clevidipine effectively and rapidly controls blood pressure preoperatively in cardiac surgery patients: the results of the randomized, placebo-controlled efficacy study of clevidipine assessing its preoperative antihypertensive effect in cardiac surgery-1. *Anesth Analg*. 2007 Oct;105(4):918-25.
5. Singla N, Warltier DC, Gandhi SD, Lumb PD, Sladen RN, Aronson S, 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 Jul;107(1):59-67.
6. Aronson S, Dyke CM, Stierer KA, Levy JH, Cheung AT, Lumb PD, 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 Oct;107(4):1110-21.
7. Pollack CV, Varon J, Garrison NA, Ebrahimi R, Dunbar L, Peacock WF. Clevidipine, an intravenous dihydropyridine calcium channel blocker, is safe and effective for the treatment of patients with acute severe hypertension. *Ann Emerg Med*. 2009 Mar;53(3):329-38.
8. Diprivan® (propofol) [prescribing information]. Lake Zurich: Fresenius Kabi USA, LLC; February 2014.
9. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp Inc; 2016 : January 4, 2016.

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fold greater affinity for the mu-opioid receptor than the parent drug.^{2,4} Genetic variability in the CYP2D6 isoenzyme can cause differences in the drug's metabolic rate and consequent serum concentration levels. Patients with increased CYP2D6 activity, classified as ultra-rapid metabolizers, produce more of the active metabolite and may experience toxicity even after receiving a typical daily dosage.³ Mutations in CYP2D6 causing ultra-rapid metabolism of substrates occur in approximately 1-7% of the population. However, in some ethnic groups, the prevalence is as high as 29%.⁵

Case Report: The FDA Drug Safety Communication involving tramadol was prompted by a published case report of a five year old boy who experienced severe respiratory depression following ambulatory adenotonsillectomy for obstructive sleep apnea syndrome.⁶ There were no reported complications with the patient's surgical procedure or recovery in the hospital. Six hours after the procedure, the patient was discharged home with tramadol to be dosed approximately 1 mg/kg for pain. The patient received a single dose of tramadol at 11:00 pm the night of his procedure. The following morning, the patient's parents found him lethargic and brought him back to the hospital. Upon arrival in the emergency department, the patient was comatose, with pin-point pupils, minimal respiratory effort, and frequent desaturations. Following noninvasive ventilation and the administration of three 0.5 mg doses of naloxone in the pediatric intensive care unit, the patient quickly improved. He was weaned 2 hours later and discharged home the following day. Genotyping of the child revealed the presence of duplicate alleles corresponding to CYP2D6*2x2/CYP2D6*2 genotype, which denotes an ultra-rapid metabolizer.

Repeat of Past Events: Codeine, which is converted to morphine (its active metabolite) by the CYP2D6 enzyme system, can also cause toxicity in ultra-rapid CYP2D6 metabolizers. In 2012, the FDA issued a warning against the use of codeine in children undergoing tonsillectomy and/or adenoidectomy.⁵ This warning was in response to reports involving three patients who died following doses of codeine within the typical dosage range and another case in which a patient suffered life-threatening respiratory depression. These patients were later determined to be CYP2D6 ultra-rapid metabolizers. Although all four of these children had underlying obstructive sleep apnea, as part of a safety review update, the FDA issued a black box warning indicating that codeine is contraindicated for all children undergoing tonsillectomy and/or adenoidectomy.⁷

What's in Store for Tramadol? The FDA is currently investigating the pharmacogenomic impact of tramadol in the pediatric population. It is encouraging medical professionals to report any adverse events related to tramadol to the FDA's MedWatch Safety Information and Adverse Event Reporting Program. Alternatives to tramadol should be utilized for pediatric patients post-tonsillectomy and/or adenoidectomy until a final determination can be made by the FDA.^{3,7}

References:

1. Tramadol Hydrochloride [package insert]. Memphis, TN: Northstar Rx LLC; May 2015.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp Inc.; October 13, 2015.
3. FDA Drug Safety Communication: FDA evaluating the risks of using the pain medicine tramadol in children aged 17 and younger. U.S. Food and Drug Administration. September 21, 2015.
4. Crews KR, Gaedigk A, Dunnenberger HM, Leeder JS, Klein TE, Caudle KE, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update. *Clin Pharmacol Ther.* 2014 Apr;95(4):376-82.
5. FDA Drug Safety Communication: Codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death. U.S. Food and Drug Administration. August 8, 2013.
6. Orliaguet G, Hamza J, Couloigner V, Denoyelle F, Lariot MA, Broly F, et al. A Case of Respiratory Depression in a Child with Ultrarapid CYP2D6 Metabolism after Tramadol. *Pediatrics.* 2015 Mar;135(3):e753-5.
7. Safety review update of codeine use in children: new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy. U.S. Food and Drug Administration. February 20, 2013.