SESLHDMG/104

Medicine Guideline

Clevidipine

Areas where Protocol/Guideline applicable	Critical Care Services (i.e., Intensive Care, Emergency Medicine, Coronary Care) where close monitoring of arterial and venous pressure can be performed.
Authorised Prescribers:	Critical Care Staff Specialist, Cardiology Staff Specialist, Emergency Medicine Staff Specialist, Medical officers under supervision of specialists in areas specified above
Indication for use	• Short term (<12 hours) control of severe hypertension where oral therapy is not feasible, appropriate or ineffective[1] **AND** • tight blood pressure (BP control) is critical[1] **AND** • where first- or second-line IV therapy have failed (e.g. IV glyceryl trinitrate (GTN), labetalol, hydralazine, sodium nitroprusside (SNP), clonidine, alpha-adrenergic antagonists (phentolamine)[6]
Clinical condition Patient selection: Inclusion criteria	Severe hypertension includes any of the following features[9]: • Systolic BP >180 mmHg • Diastolic BP >120 mmHg • New or progressive end organ damage or dysfunction resulting from hypertension including acute coronary syndromes, aortic dissection, hypertensive encephalopathy, subarachnoid haemorrhage, malignant hypertension with acute kidney injury, acute retinopathy or acute pulmonary oedema.
Proposed Place in Therapy	**When first- or second line anti-hypertensive therapy failed in**: • Hypertensive crisis[5] • Perioperative BP control where short term, strict BP control is required to prevent further clinical deterioation[5,6,8], e.g. aortic dissection[11], vascular surgery, subarachnoid haemorrhage, arteriovenous malformations and interventional neuroradiology procedures • Rapid controlled and titratable BP is required, e.g. autonomic dysreflexia[10] • Limited experience in mild-to-moderate essential hypertension and acute severe hypertension
Adjunctive Therapy	Labetalol, Esmolol, IV GTN, hydralazine, SNP, clonidine, alpha-adrenergic antagonists[6,8,9]
Contra-indications	• Known allergy to Clevidipine, soybeans soy products, eggs or egg products or to any of the excipients[1,2,3] • Defective lipid metabolism such as pathologic hyperlipidaemia, lipoid nephrosis or acute pancreatitis accompanied by hyperlipidaemia[1,2,3] • Severe aortic stenosis: excessive afterload reduction can reduce myocardial oxygenation and systemic hypotension[1,2,3] • Cardiogenic shock[2]

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Precautions	• Co-administration of propofol infusion and intralipid TPN due to caloric and lipid load (1 mL of Clevidipine = 200 mg of lipid or 2 kcal)[1] • Hypotension and reflex tachycardia may occur after rapid reduction in BP. If occurs, reduce dose[1]. • Heart failure – due to possible negative inotropy. Monitor heart failure patients[1,2,3]. • Prolonged Clevidipine infusions may cause rebound hypertension. Monitor for at least 8 hours after the infusion is stopped[1]. • Hepatic or renal impairment: No dose adjustment is required[1,2,3] • Elderly patients: start at a lower dose[1,2,3] • Pregnancy and lactation: No data. Short terminal half-life and high protein binding suggest very little active drug will cross the placenta or excreted in breast milk. Risk-benefit assessment required in dividual patient cases[1,2,3,7]. • Pheochromocytoma: No information to guide use of Clevidipine in treating hypertension associated with pheochromocytoma[1].
Important Drug Interactions	Unlikely pharmacokinetic drug interactions with Clevidipine as Clevidipine is rapidly metabolised by hydrolysis in vivo. Appear to have limited potential for inhibiting or inducing any CYP enzyme. However, Clevidipine may alter the effects of other medications as below[5:] • **Clopidogrel** – may result in a reduction of the antiplatelet effect • **Lacosamide** – in combination with any calcium channel blocker may prolong PR interval on ECG • **Digoxin** – in combination with any calcium channel blocker may result in complete heart block • **Dantrolene** – in combination with any calcium channel blocker may result in severe hyperkalaemia • **Epirubicin** – in combination with any calcium channel blocker may increase the risk of heart failure.
Dosage	Administer **UNDILUTED** (concentration 0.5 mg/mL) via continuous IV infusion. <u>Initial Dose:</u> • Start at **2 – 4 mL/hr** (1 – 2 mg/hr) (start at a lower dose in elderly)[1,2,3,4] • Double the dose at 90 second intervals until approaching the target BP range. An increase of 2 – 4 mL/hr produces a 2 – 4 mmHg reduction in systolic BP. • Once within range, adjust dose every 5 to 10 minutes as needed <u>Maintenance Dose</u>: • Generally, **8 – 12 mL/hr** (4 – 6 mg/hr)[1,2,3,4] Maximum infusion rate of 64 mL/hr (32 mg/hr) (in severe hypertension)[1,2,3] • No more than 1000 mL or an average of 42 mL/hr (21 mg/hr) of Clevidipine infusion is recommended per 24-hour period due to its lipid load[1,3] • Little experience with infusions beyond 72 hours at any dose[1,2,3]

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Duration of therapy	• Less than 12 hours (no experience for use for greater than 72 hours[1,2,3]) • Should not cease abruptly due to risk of rebound effect. • Down titrate infusion by halving the rate every 10 minutes. • When re-introducing longer-acting oral anti-hypertensives and/or vasodilators, consider the lag time of onset of the oral agent's effect. Continue BP and heart rate (HR) monitoring until desired effect is achieved[1.] • Monitor BP and HR for 8 hours post infusion cessation and until desired effect is achieved.
Prescribing instructions	• To be ordered on eMR and eRIC, with no diluent built-in
Presentation & Storage	• Each vial contains 25mg/50mL • Store at 2 to 8˚C in refrigerator • Protect from light • Once removed from fridge, store unopened vials at room temperature for up to 2 months (do not return to fridge)[4].
Administration Instructions	• Gently invert vial before use to ensure uniformity of the emulsion prior to administration. • Once spiked, begin infusion immediately and use within 12 hours[1,4]. • ***CAUTION*** **Clevidipine is formulated in lipid, a milky-white emulsion looks exactly like propofol in a syringe. Label drawn up syringe immediately.** • Infuse **UNDILUTED continuously,** via a central line or peripheral line via an IV infusion • Does not require protection from light during administration[1]. • Y-site compatible: sodium chloride 0.9%, glucose 5%, Hartmann's[4] • NOT in the same line or injection site as other medications[4].
Monitoring requirements	• Continues cardiac monitoring (ECG, HR, BP). BP must be measured at least hourly for the duration of the infusion and for 8 hours post infusion[1,2,3,4]. • Antihypertensive effect is reduced within 5 to 15 minutes of stopping the infusion[1]. • Prolonged infusions and not transitioned to another antihypertensive should be monitored for rebound hypertension for at least 8 hours after infusion is stopped[1,2,3,4]. Post infusion BP and HR can be monitored every 2 to 3 hours on a general ward, which preferably has a cardiac monitor. If this is not feasible, then continue monitoring in ICU/HDU/CCU.
Adverse effects	• Atrial fibrillation • Reflex tachycardia • Nausea • Vasodilatory effects including headache, flushing, dizziness, hypotension • Peripheral oedema (due to redistribution of extracellular fluid rather than fluid retention)

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Management of Complications	• Hypotension: 1. Stop infusion[10] 2. Give IV vasoconstrictors e.g. metaraminol or noradrenaline to restore BP • Tachycardia: Stop the infusion • Headache: Simple analgesia should suffice or reduce dose
Basis of Protocol/Guideline:	1. Cleviprex® (Clevidipine) Australian Product Information, version 3.0, revised 26th May 2021. Chiesi Australia Pty Ltd 2. Australian Medicines Handbook, January 2024 revision. Online via CIAP [Accessed 4th March 2024] 3. Clevidipine monograph in Micromedex® Solutions via CIAP. Version updated on 21st February 2024 [Accessed 22nd March 2024] 4. Australian Injectable Drugs Handbook 9th edition via CIAP [Accessed 25th March 2024] 5. Clevidipine monograph in http://litfl.com/clevidipine (Life in the Fast Lane). Version updated on 22nd March 2023. [Accessed 3rd April 2024]. 6. Perioperative management of hypertension. UpToDate version 34.0 via CIAP [Accessed 25th March 2024] 7. Briggs Drugs in Pregnancy and Lactation: A reference Guide to Fetal and Neonatal Risk 12th edition via CIAP [Accessed 25th March 2024] 8. Rivera A, Montova E, Varon J. Intravenous clevidipine for management of hypertension. Integr Blood Press Control 2010; 3: 105-111. 9. Management of Hypertension in the SESLHD Ward Settings. (SESLHDGL/068). SESLHD Hypertension policy development working party. Published September 2018. 10. Drug Prescribing Guideline HNELHD DPG 23_08 ICU - Clevidipine, Hunter New England Local Health District. Published 19th October 2023. 11. Overview of acute aorta dissection and other acute aortic syndromes. UpToDate version 27.0 (last updated on 18th September 2023) via CIAP [Accessed 25th March 2024] 12. Aronson S, Dyke C, Stierer K 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.
Groups consulted in development of this guideline	SGH and POWH Critical Care Medical and Pharmacy

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