CLONIDINE

Newborn use only

2024

Alert	Hypertension may recur after cessation. Neonatal abstinence syndrome may recur after cessation. Evidence is insufficient to assess the efficacy and safety of clonidine for sedation and analgesia in term and preterm newborn infants receiving mechanical ventilation.
Indication	Sedation Hypertension Neonatal abstinence syndrome
Action	A central α2- adrenergic agonist with inhibitory effects on the release of noradrenaline in the locus coeruleus. This produces reduced sympathetic nervous activity with analgesia, and a decrease in arousability, blood pressure and heart rate.[1,2] Compared with dexmedetomidine, clonidine has a lower selectivity for α2-receptors (α1: α2ratio of 1:1620 for dexmedetomidine versus 1:220 for clonidine). As central α2 effects are sedative, clonidine is less sedating than dexmedetomidine.
Drug type	Sedative, hypnotic. Centrally acting α2-agonist.
Trade name	Catapres Ampoules MZ Clonidine HCl Injection APO-Clonidine Tablets Catapres 100 Tablets Catapres 150 Tablets Oral solution or suspension: Compounded by pharmacy in-house (check which strength is stocked with Pharmacy Department).
Presentation	**IV preparations:** 150 microgram/mL ampoule **Oral preparations:** 100 microgram/tablet, 150 microgram/tablet Solution or suspension: Compounded by pharmacy in-house (check which strength is stocked with Pharmacy Department). IV clonidine (ampoule) may be given orally either neat or diluted with water prior to administration to give a suitable dose volume.
Dose	**Sedation**: **IV continuous infusion:** Loading dose of 0.5 to 1 microgram/kg over 15 minutes followed by a continuous infusion of 0.2 microgram/kg/hour and titrate up to a maximum of 1 microgram/kg/hour in hemodynamically stable neonates.[2,3,4] **ORAL OR IV intermittent dosing:** 1 microgram/kg/dose 8 hourly and titrate it up to a maximum 2 micrograms/kg/dose 6 hourly.[1,5-8] (Group consensus) **Chronic hypertension:** Oral: 0.5 to 2.5 microgram/kg/dose 6 to 8 hourly.[9,10] **Neonatal abstinence syndrome (ANMF consensus):**[1,5,6,16,,28,29] Oral starting dose: 0.5 – 1 microgram/kg/dose 4 to 6 hourly and titrate the dose as per the need. Increase dose by 25% every 24 hours to a maximum 12 microgram/kg/day according to neonatal abstinence syndrome scores.[1,6] **Weaning/ceasing clonidine:** If a neonate has received regular clonidine for >5 days, the dose should be weaned by about 50% each day for 2 to 3 days (reflecting an average half-life of 17 hours in neonates) before ceasing the drug. Watch for tachycardia, hypertension, sweating, agitation, but remember these may also be opioid withdrawal symptoms.[6] Intravenous clonidine can be converted to oral/nasogastric route when requirements are less than 0.75 microgram/kg/hour. The same daily dose is divided into 3 doses for 8 hourly administration (i.e. 4 to 6 microgram/kg orally every 8 hours). [Group consensus]
Dose adjustment	Therapeutic hypothermia: no information. ECMO: no information.

<table>
<tr><td></td><td>Renal: commence on a low dose in infants with renal impairment and adjust according to response.
Hepatic: not applicable.</td></tr>
<tr><td>Maximum dose</td><td>IV infusion for sedation: 2 microgram/kg/hour has been reported.[4,11]
Neonatal abstinence syndrome: 12 microgram/kg/day.[1,6]
Hypertension: 25 microgram/kg/day has been reported. However, it is recommended to use in combination with other antihypertensive agents rather than at higher dose as a single agent.[10]</td></tr>
<tr><td>Total cumulative dose</td><td></td></tr>
<tr><td>Route</td><td>IV
Oral</td></tr>
<tr><td>Preparation</td><td><u>IV continuous infusion</u>

<table><tr><th>Infusion strength</th><th>Prescribed amount</th></tr><tr><td>1 mL/hour = 1 microgram/kg/hour</td><td>50 microgram/kg clonidine make up to 50 mL</td></tr></table>Draw up 1 mL (150 microgram) of Clonidine and add to 4 mL of sodium chloride 0.9% to make a final volume of 5 mL with a concentration of 30 microgram/mL.
FURTHER DILUTE
Draw up 1.7 mL/kg (50 microgram/kg clonidine) and add to sodium chloride 0.9% to make a final volume of 50 mL with a concentration of 1 mL/hour = 1 microgram/kg/hour.

<u>IV intermittent dose</u>
Draw up 1 mL (150 microgram) of Clonidine and add to 4 mL of sodium chloride 0.9% to make a final volume of 5 mL with a concentration of 30 microgram/mL.
FURTHER DILUTE
Draw up 1.7 mL (50 microgram) and add to sodium chloride 0.9% to make a final volume of 50 mL with a concentration of 1 mL = 1 microgram.

<u>Oral</u>
Tablet: Disperse 100 microgram tablet in 20 mL sterile water. Tablet will disperse within 2 minutes. Shake or stir until an even dispersion is formed and then measure the required dose immediately.
IV clonidine (ampoule) may be given orally as either neat or diluted with water prior to administration to give a suitable dose volume.
Solution or suspension: Compounded by pharmacy in-house (check which strength is stocked with Pharmacy Department).</td></tr>
<tr><td>Administration</td><td>Continuous IV infusion
Use a dedicated infusion line to avoid boluses.
IV intermittent
Sedation: Infuse over 10 minutes.</td></tr>
<tr><td>Monitoring</td><td>Neonatal abstinence syndrome: monitor Neonatal Abstinence Syndrome scores, cardiorespiratory observations and intermittent blood pressure.
Sedation of infants on mechanical ventilation: continuous electrocardiogram (ECG) and/or oxygen saturation and continuous or intermittent blood pressure, pain and comfort scores.
Hypertension: For initial treatment, continuous ECG and/or oxygen saturation, and continuous or intermittent blood pressure monitoring.</td></tr>
<tr><td>Contraindications</td><td>Hypersensitivity to the drug.
Heart block or severe ventricular dysfunction.</td></tr>
<tr><td>Precautions</td><td>Rebound hypertension may occur after cessation.
Rebound neonatal abstinence syndrome may occur after cessation.
May need to reduce dose in infants with renal impairment.</td></tr>
<tr><td>Drug interactions</td><td>Clonidine will enhance the effects of anaesthetics, sedatives, hypnotics and opioids.
Clonidine will interact with other hypertensives; NSAIDs; α2-adrenergic blockers eg phentolamine; β-blockers; digitalis glycosides; tricyclic antidepressants; and α-blocking neuroleptics.</td></tr>
<tr><td>Adverse reactions</td><td>Hypotension, bradycardia, rebound hypertension, somnolence, and xerostomia.</td></tr>
</table>

Compatibility	Fluids: Sodium chloride 0.9%. Y-site: aminophylline, dobutamine, dopamine, epinephrine, fentanyl, heparin, ketamine, labetalol, lignocaine, lorazepam, magnesium sulphate, methadone, morphine HCl, glyceryl trinitrate, norepinephrine, potassium chloride.
Incompatibility	Y-site: midazolam, verapamil
Stability	Tablet dispersed in water: make a fresh solution for each dose and use immediately. Check with Pharmacy Department for compounded oral suspension or solution.
Storage	Ampoule: Store below 25°C. Protect from light. Tablet: Store below 25°C. Check with Pharmacy Department for compounded oral suspension or solution.
Excipients	Ampoule: Sodium chloride, hydrochloric acid and water for injections. Catapres Tablet: Maize starch, lactose monohydrate, calcium hydrogen phosphate, colloidal anhydrous silica, povidone and stearic acid. APO-Clonidine Tablet: Allura Red AC, hyprolose, microcrystalline cellulose, magnesium stearate, maize starch, lactose monohydrate, calcium hydrogen phosphate, colloidal anhydrous silica. Check with Pharmacy Department for compounded oral suspension or solution.
Special comments	
Evidence	Clonidine is an α2-agonist used to produce reductions in blood pressure and sedation that has been used for treatment of hypertension, sedation of ventilated infants and perioperative sedation. Compared with dexmedetomidine, clonidine has a lower selectivity for α2-receptors (α1: α2ratio of 1: 1620 for dexmedetomidine versus 1: 220 for clonidine). As central α2 effects are sedative, clonidine is less sedating than dexmedetomidine.[1] **Efficacy** **Neonates receiving mechanical ventilation:** In a single RCT, clonidine infusion 1 µg/kg/hour or placebo was administered to 112 mechanically ventilated term newborn infants who were on IV fentanyl and midazolam.[2] The median duration of clonidine infusion was 7 days starting from the fourth day of mechanical ventilation. In this study, no differences in mortality [RR 0.69, 95% CI 0.12 to 3.98], duration of mechanical ventilation (7.1 days versus 5.8 days, P = 0.07) or duration of stay in the intensive care unit were reported. Sedation scale values (COMFORT) and analgesia scores (Hartwig) during the first 72 hours of infusion were lower in the clonidine than the placebo group. Clonidine 1 µg/kg/hour in ventilated newborns reduced fentanyl and midazolam demand with deeper levels of analgesia and sedation without substantial side effects. This was not demonstrated in older infants, possibly due to lower clonidine serum levels. Evidence is insufficient to show the efficacy and safety of clonidine for sedation and analgesia in term and preterm newborn infants receiving mechanical ventilation.[12] (LOE II GOR D) There are no trials comparing clonidine versus dexmedetomidine in paediatric patients. A systematic review of dexmedetomidine use in paediatric patients found dexmedetomidine was associated with similar sedation scores to midazolam, a reduction in opioid use with use of a higher dose dexmedetomidine 0.5 µg/kg/hour but not 0.25 µg/kg/hour infusion, and reduced duration of mechanical ventilation compared to paediatric patients treated with midazolam and fentanyl.[13] **Perioperative sedation** In addition to the RCT mentioned above, a retrospective study reported use of clonidine for sedation in 32 term born neonates who received a cardiac surgery at a median postnatal age of 22 days. Post operatively, IV clonidine bolus doses of 0.5–1 µg/kg/dose were given initially up to a cumulative dose of 2 µg/kg, after which an infusion was started at 0.5 µg/kg/hr and increased to a maximum of 2 µg/kg/hr to ensure infant's COMFORT B score between 10-20. Thereafter, clonidine infusion was continued for up to 72 hours. Authors reported a favourable hemodynamic profile and shorter stay in the intensive care in infants who received clonidine in addition to morphine for sedation compared to midazolam and morphine.[3] A systematic review in paediatric patients almost all over 1 year of age, found clonidine premedication 4 µg/kg may reduce postoperative pain in children. Side effects were minimal, but some of the studies used atropine prophylactically with the intention of preventing bradycardia and hypotension. (LOE I GOR C children) Infants enrolled in the trials were ≥1 year age.[14,15] **Neonatal abstinence syndrome (NAS)**

Network meta-analysis of pharmacological treatments for NAS included buprenorphine, clonidine, diluted tincture of opium and clonidine, diluted tincture of opium, morphine, methadone, and phenobarbital. In network meta-analysis, clonidine had non-significant change in length of treatment (mean difference versus morphine –10.52 days [–24.05 to 2.92]), median rank 2 (6 to 1) and length of stay (days: mean difference versus morphine, –6.09 (–12.93 to 0.79), median rank 2 (7 to 1). Rate of treatment failure was not reported.[16]

Three RCTs of clonidine in infants with NAS have used differing strategies.[1,5,6] Bada et al in infants ≥35 weeks' gestation with NAS compared morphine 0.4 mg/kg/day versus clonidine 5 µg/kg/day divided into 8 doses as initial treatment of NAS. A 25% dose escalation every 24 hours was possible per protocol (maximum of 1 mg/kg per day for morphine and 12 µg/kg per day for clonidine).[1] After control of symptoms, the dose was tapered by 10% every other day. Infants treated with clonidine (n = 16) versus morphine (n = 15) had decreased duration of treatment (median 39 days versus 28 days; P = .02), improved NNNS scores and lower height of arousal and excitability (P < .05). One-year motor, cognitive, and language scores did not differ between groups. Surran et al in 64 infants compared morphine 0.32 to 0.8 mg/kg/day divided 3 hourly and clonidine 6 to 12 µg/kg/day divided 6 hourly according to NAS Score versus morphine sulfate 0.32 to 0.8 mg/kg/day divided 3 hourly and phenobarbital 6 to 12 mg/kg/day divided 8 hourly.[6] Clonidine dose was weaned by halving daily dose every 24 hours for 2 steps then ceasing. Phenobarbital reduced duration of treatment 4.6 days, (95% CI: 0.3, 8.9; P=0.03). Two clonidine treated infants failed NMS-weaning attempts and were switched to phenobarbital whereas there were no failures occurred in the phenobarbital group. However, 3 (8.8%) infants in the phenobarbital group, manifested over sedation signs (poor feeds and mild respiratory depression) and serum phenobarbital measures were supratherapeutic (>40 mg/dL) and required dosage adjustment. There were no arrhythmias or abnormal BPs observed (hypo- or hypertension) in the clonidine group, no inpatient mortality and no infant was re-admitted to the hospital within 1 week post discharge. Agthe et al in 80 infants with NAS treated with oral diluted tincture of opium, compared oral clonidine 1 µg/kg every 4 hours versus placebo.[5] Median length of therapy was reduced in the clonidine group (11 versus 15 days), although 7 infants in the clonidine group required restarting opium after initial discontinuation. Clonidine reduced opioid use and rate of treatment failures (0% versus 12.5%). Hypertension, hypotension, bradycardia, or desaturations did not occur in either group. Three infants in the clonidine group died because of myocarditis, sudden infant death syndrome, and homicide, all after hospital discharge and before 6 months of age. Leikin et al studied 14 neonates.[28] The mean gestational age was 30.1 weeks (range 24.4–40.7 weeks); three patients were full-term. Eleven had been on intravenous fentanyl for sedation; three were born to opioid-dependent mothers. All neonates were treated with clonidine, administered in doses of 0.5–1 microgram/kg orally every 6 hours. No neonate received opioids. Mean duration of treatment was 6.8 days (range 4–15). Mean abstinence scores were 6.4 pretreatment (range 0–20) and 1.9 post-treatment (range 0–5). No neonates suffered an adverse event (hypotension, bradycardia, excessive sedation, and oxygen desaturation) from clonidine administration, and no seizures were identified.[28]

Conclusion: The optimal regimen to manage symptomatic NAS is unclear due to the low quality, small size and short-term outcomes considered in the published studies.[17]

Hypertension

For chronic hypertension, expert opinion suggested that drug therapy should be initiated mainly because sustained BP elevation may have renal, cardiac, and central nervous system effects.[10,18,19] The ESCAPE Trial of 385 children 3 to 18 years with chronic kidney disease (GFR 15-80 mL/minute/1.73 m^2), hypertension was treated with ramipril 6 mg/ m^2/day and patients were randomly assigned to intensified blood-pressure control (target 24-hour mean arterial pressure below the 50th percentile) or conventional blood-pressure control (mean arterial pressure 50-95th percentile) achieved by the addition of antihypertensive therapy that does not target the renin–angiotensin system. Intensified blood-pressure control, with target 24-hour blood-pressure levels in the low range of normal, confers a substantial benefit with respect to renal function among children with chronic kidney disease.[18] (LOE II GOR B)

There are few case reports of clonidine use for neonatal hypertension.[9,20,21] One study of 11 infants and children with severe arterial hypertension associated with renal failure reported a single dose of clonidine 10 µg/kg infused over 4 hours, or an additional dose of 5 µg/kg resulted in a satisfactory response in 9 patients.[22]

	Doses of oral clonidine for treatment of chronic hypertension in neonates and paediatric patients in expert reviews vary from 2–10 µg/kg/day in 3 or 4 divided doses, maximal 25 µg/kg/day.[9,10] **Safety** Clonidine may cause hypotension, bradycardia, rebound hypertension, somnolence, and xerostomia.[3-8] **Pharmacokinetics** Clonidine displays age-related changes in pharmacokinetics attributable to the maturation of clearance during infancy.[23, 24] It has a long elimination half-life (16.9 hours in neonates, 11.4 hours in infants and 7.4 hours in children). Clearance in neonates is approximately one-third of that in adults.[23] Long half-lives necessitate the use of loading doses to reach therapeutic concentrations within a reasonable time. Without a loading dose, steady state would only have been achieved toward the end of the 72-hour study period for neonates.[21] Bioavailability of orally administered clonidine formulations has been estimated to be approximately 55% in children.[26] A target plasma concentration of above 2 µg/L has been proposed. Clonidine titrated infusions with a loading dose of 2 µg/kg followed by a continuous infusion of up to 2 µg/kg/hour are recommended in hemodynamically stable PICU patients to achieve adequate sedation. Clonidine titrated infusions with a loading dose of 1 µg/kg followed by a continuous infusion of up to 1 µg/kg/hour are recommended in hemodynamically stable neonates.[2,4]
Practice points	**Neonatal abstinence syndrome:** The optimal regimen to manage symptomatic NAS is unclear.[17] In infants with NAS secondary to opioid withdrawal, clonidine may reduce need for morphine treatment and duration of treatment.[1,5,16] (LOE II, GOR C) **Sedation:** Evidence is insufficient to show the efficacy and safety of clonidine for sedation and analgesia in term and preterm newborn infants receiving mechanical ventilation.[12] (LOE II GOR D) **Chronic hypertension:** Recommend using at lower doses (2–10 µg/kg/day) in 3 or 4 divided doses in combination with other antihypertensive agents rather than at higher dose as a single agent.
References	1. Bada HS, Sithisarn T, Gibson J, et al. Morphine versus clonidine for neonatal abstinence syndrome. Pediatrics. 2015;135: e383-91. 2. Hunseler C, Balling G, Rohlig C, et al. Continuous infusion of clonidine in ventilated newborns and infants: a randomized controlled trial. Pediatr Crit Care Med. 2014; 15:511-22. 3. Kleiber N, de Wildt SN, Cortina G, et al. Clonidine as a First-Line Sedative Agent After Neonatal Cardiac Surgery: Retrospective Cohort Study. Pediatr Crit Care Med. 2016 Apr;17(4):332-41. 4. Hayden JC, Bardol M, Doherty DR, et al. Optimizing clonidine dosage for sedation in mechanically ventilated children: A pharmacokinetic simulation study. Paediatr Anaesth. 2019 Oct;29:1002-1010. 5. Agthe AG, Kim GR, et al. Clonidine as an adjunct therapy to opioids for neonatal abstinence syndrome: a randomized, controlled trial. Pediatrics. 2009;123: e849-56. 6. Surran B, Visintainer P, Chamberlain S, et al. Efficacy of clonidine versus phenobarbital in reducing neonatal morphine sulfate therapy days for neonatal abstinence syndrome. A prospective randomized clinical trial. J Perinatol. 2013; 33:954-9. 7. Gauda EB, Chavez-Valdez R, Northington FJ, et al. Clonidine for sedation in infants during therapeutic hypothermia with neonatal encephalopathy: pilot study. J Perinatol. 2022;42:319-327. 8. Arenas-López S, Riphagen S, Tibby SM, et al. Use of oral clonidine for sedation in ventilated paediatric intensive care patients. Intensive Care Med. 2004 Aug;30(8):1625-9. 9. Batisky DL. Neonatal Hypertension. Clinics in Perinatology. 2014; 41:529-42. 10. Dionne JM, Abitbol CL, Flynn JT. Hypertension in infancy: Diagnosis, management, and outcome. Pediatric Nephrology. 2012; 27:17-32. 11. Neubert A, Baarslag MA, Dijk MV, et al. The CLOSED trial: CLOnidine compared with midazolam for SEDation of paediatric patients in the intensive care unit: study protocol for a multicentre randomised controlled trial. BMJ Open. 2017 Jun 21;7(6): e016031. 12. Romantsik O, Calevo MG, Norman E, Bruschettini M. Clonidine for sedation and analgesia for neonates receiving mechanical ventilation. Cochrane Database of Systematic Reviews. 2017 13. Hayden JC, Breatnach C, Doherty DR, et al. Efficacy of alpha2-Agonists for Sedation in Pediatric Critical Care: A Systematic Review. Pediatr Crit Care Med. 2016;17: e66-75 14. Lambert P, Cyna AM, Knight N, Middleton P. Clonidine premedication for postoperative analgesia in children. Cochrane Database of Systematic Reviews. 2014. 15. Zhu A, Benzon HA, Anderson TA. Evidence for the Efficacy of Systemic Opioid-Sparing Analgesics in Pediatric Surgical Populations: A Systematic Review. Anesth Analg. 2017; 125:1569-87

16. Disher T, Gullickson C, Singh B, et al. Pharmacological Treatments for Neonatal Abstinence Syndrome: A Systematic Review and Network Meta-analysis. JAMA Pediatr. 2019; 173:234-43.
17. Ghazanfarpour M, Najafi MN, Roozbeh N, et al. Therapeutic approaches for neonatal abstinence syndrome: a systematic review of randomized clinical trials. Daru. 2019; 27:423-31.
18. Wuhl E, Trivelli A, Picca S, et al. Strict blood-pressure control, and progression of renal failure in children. New England Journal of Medicine. 2009; 361:1639-50.
19. Dhull RS, Baracco R, Jain A, Mattoo TK. Pharmacologic Treatment of Pediatric Hypertension. Curr Hypertens Rep. 2016 Apr;18(4):32.
20. Deitrick J, Stevenson K, Nguyen D, Sessions W, Linga V, Vasylyeva T. Hypertension secondary to renal hypoplasia presenting as acute heart failure in a newborn. Clin. 2019; 25:10.
21. Veenhoven RH, Vande Walle JG, Donckerwolcke RA, et al. A neonate with idiopathic hyperaldosteronism. Pediatr Nephrol. 1991; 5:680-4.
22. Binda Ki Muaka P, Proesmans W. Intravenous clonidine in severe childhood hypertension. Acta Paediatrica Belgica. 1980; 32:247-51
23. Potts AL, Larsson P, Eksborg S, Warman G, Lonnqvist PA, Anderson BJ. Clonidine disposition in children; a population analysis. Paediatr Anaesth. 2007; 17:924-33.
24. Sheng Y, Standing JF. Pharmacokinetic reason for negative results of clonidine sedation in long-term-ventilated neonates and infants. Pediatr Crit Care Med. 2015; 16:92-3
25. Verlhac C, Lannoy D, Bourdon F, et al. Physicochemical and Microbiological Stability of a New Oral Clonidine Solution for Paediatric Use. Pharmaceutical Tech in Hosp Pharmacy. 2018; 3:79-90.
26. Larsson P, Nordlinder A, Bergendahl HT, et al. Oral bioavailability of clonidine in children. Paediatr Anaesth. 2011; 21:335-40.
27. MerativeTM Micromedex® Complete IV Compatibility (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com/ (cited: Aug/15/2024).
28. Leikin JB, Mackendrick WP, Maloney GE, Rhee JW, Farrell E, Wahl M, Kelly K. Use of clonidine in the prevention and management of neonatal abstinence syndrome. Clinical Toxicology. 2009 Jul 1;47(6):551-5.
29. Hudak ML, Tan RC, Committee on Drugs, Committee on Fetus and Newborn, Frattarelli DA, Galinkin JL, Green TP, Neville KA, Paul IM, Van Den Anker JN, Papile LA. Neonatal drug withdrawal. Pediatrics. 2012 Feb 1;129(2):e540-60.

VERSION/NUMBER	DATE
Original 1.0	28/05/2020
Version 2.0	15/12/2020
Version 3.0	29/07/2021
Version 4.0	9/09/2021
Version 5.0	23/08/2024
Current 5.0 (minor errata)	17/10/2024
REVIEW	23/08/2029

Authors Contribution of the current version

Original author/s	Nilkant Phad, Srinivas Bolisetty
Evidence Review	Nilkant Phad, Srinivas Bolisetty
Expert review	
Nursing Review	Benjamin Emerson-Parker
Pharmacy Review	Cindy Chen, Mohammad Irfan Azeem, Thao Tran
ANMF Group contributors	Bhavesh Mehta, Rebecca Barzegar, Kerryn Houghton, Martin Kluckow, Mohammad Irfan Azeem, Rebecca O'Grady, Susanah Brew, Thao Tran, Michelle Jenkins, Stephanie Halena, Natalia Srnic, Renae Gengaroli, Bryony Malloy, Benjamin Emerson-Parker, Samantha Hassall
Final editing	Srinivas Bolisetty, Thao Tran, Nilkant Phad
Electronic version	Thao Tran, Natalia Srnic, Cindy Chen, Ian Callander
Facilitator	Dr Srinivas Bolisetty