CLONIDINE

Newborn use only

2021

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	An α2-agonist used to produce reduction in blood pressure and 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]
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] **ORAL OR IV intermittent dosing:** 1 microgram/kg/dose 8 hourly and titrate it up to a maximum 2 micrograms/kg/dose 6 hourly. [2, 3] [Group consensus] **Acute severe hypertension:** 10 microgram/kg infused over 4 hours. Additional dose of 5 microgram/kg may be given over 2 hours. [4] Consider continuous intra-arterial monitoring. **Chronic hypertension:** Oral: 0.5 to 2.5 microgram/kg/dose 6 to 8 hourly. [5, 6] **Neonatal abstinence syndrome:** Initial therapy: 5 microgram/kg/day divided in 6 to 8 doses (oral recommended). Increase dose by 25% every 24 hours to a maximum 12 microgram/kg/day according to neonatal abstinence syndrome scores. [7] **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.

	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. Renal: commence on a low dose in infants with renal impairment and adjust according to response. Hepatic: not applicable.
Maximum dose	Neonatal abstinence syndrome: 12 microgram/kg/day. [7] 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. [2]
Total cumulative dose	
Route	IV Oral
Preparation	**IV continuous infusion (for sedation):** Infusion strength: 1 mL/hour = 1 microgram/kg/hour Prescribed amount: 50 microgram/kg clonidine make up to 50 mL 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.** **IV intermittent dose for sedation and acute severe hypertension:** 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. **Oral:** 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).
Administration	**Continuous IV infusion** Use a dedicated infusion line to avoid boluses **IV intermittent** Sedation: Infuse over 10 minutes. Acute severe hypertension: Infuse over 4 hours.
Monitoring	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.
Contraindications	Hypersensitivity to the drug. Heart block or severe ventricular dysfunction.
Precautions	Rebound hypertension may occur after cessation. Rebound neonatal abstinence syndrome may occur after cessation. May need to reduce dose in infants with renal impairment.
Drug interactions	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.
Adverse reactions	Hypotension, bradycardia, rebound hypertension, somnolence and xerostomia. [5]
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** A single RCT [2] enrolling 112 term newborn infants on mechanical ventilation on fentanyl and midazolam administered clonidine 1 µg/kg/hour or placebo on day 4 after intubation. 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. [8] [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. [9] **Perioperative sedation** There are no trials in neonates of clonidine as an adjunct to perioperative care. 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. [10, 11] **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. [12]

Three RCTs of clonidine in infants with NAS have used differing strategies. [7, 13, 14] Bada et al [7] 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). 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 [14] 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. 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 [13], in 80 infants with NAS treated with oral diluted tincture of opium, compared oral clonidine 1 µg/kg every 4 hours versus placebo. 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 as a result of myocarditis, sudden infant death syndrome, and homicide, all after hospital discharge and before 6 months of age.

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. [15]

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 [5, 16]. The ESCAPE Trial [17] 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. [LOE II GOR B]

There are few case reports of clonidine use for neonatal hypertension [4, 18, 19]. 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. [4]

Doses of oral clonidine for treatment of chronic hypertension in neonates [5] and paediatric patients [6] in expert reviews vary from 2–10 µg/kg/day in 3 or 4 divided doses, maximal 25 µg/kg/day.

Safety

Clonidine may cause hypotension, bradycardia, rebound hypertension, somnolence and xerostomia. [5]

Pharmacokinetics

Clonidine displays age-related changes in pharmacokinetics attributable to the maturation of clearance during infancy. [20] It has a long elimination half-life (16.9 hours in neonates, 11.4 hours in infants and 7.4 hours in children). [2, 21] Long half-lives necessitate the use of loading doses in order 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.[3] A target plasma concentration of above 2 µg/L has been proposed. [2] 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]
Practice points	**Neonatal abstinence syndrome:** The optimal regimen to manage symptomatic NAS is unclear. [15] In infants with NAS secondary to opioid withdrawal, clonidine 5 microgram/kg/day up to a maximum 12 microgram/kg/day in 6-8 divided doses may reduce need for morphine treatment and duration of treatment. [7] [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. [8] [LOE II GOR D] **Chronic hypertension:** Recommend to use 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, Garlitz K, Caldwell R, Capilouto G, Li Y, Leggas M, Breheny P. Morphine versus clonidine for neonatal abstinence syndrome. Pediatrics. 2015;135:e383-91. 2. Hunseler C, Balling G, Rohlig C, Blickheuser R, Trieschmann U, Lieser U, Dohna-Schwake C, Gebauer C, Moller O, Hering F, Hoehn T, Schubert S, Hentschel R, Huth RG, Muller A, Muller C, Wassmer G, Hahn M, Harnischmacher U, Behr J, Roth B, Clonidine Study G. Continuous infusion of clonidine in ventilated newborns and infants: a randomized controlled trial. Pediatr Crit Care Med. 2014;15:511-22. 3. Binda Ki Muaka P, Proesmans W. Intravenous clonidine in severe childhood hypertension. Acta Paediatrica Belgica. 1980;32:247-51. 4. Batisky DL. Neonatal Hypertension. Clinics in Perinatology. 2014;41:529-42. 5. Dionne JM, Abitbol CL, Flynn JT. Hypertension in infancy: Diagnosis, management and outcome. Pediatric Nephrology. 2012;27:17-32. 6. Verlhac C, Lannoy D, Bourdon F, Titecat M, Frealle E, Nassar C, Berneron C, Odou P. Physicochemical and Microbiological Stability of a New Oral Clonidine Solution for Paediatric Use. Pharmaceutical Technology in Hospital Pharmacy. 2018;3:79-90. 7. Romantsik O, Calevo MG, Norman E, Bruschettini M. Clonidine for sedation and analgesia for neonates receiving mechanical ventilation. Cochrane Database of Systematic Reviews. 2017. 8. Hayden JC, Breatnach C, Doherty DR, Healy M, Howlett MM, Gallagher PJ, Cousins G. Efficacy of alpha2-Agonists for Sedation in Pediatric Critical Care: A Systematic Review. Pediatr Crit Care Med. 2016;17:e66-75. 9. Lambert P, Cyna AM, Knight N, Middleton P. Clonidine premedication for postoperative analgesia in children. Cochrane Database of Systematic Reviews. 2014. 10. 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. 11. Disher T, Gullickson C, Singh B, Cameron C, Boulos L, Beaubien L, Campbell-Yeo M. Pharmacological Treatments for Neonatal Abstinence Syndrome: A Systematic Review and Network Meta-analysis. JAMA Pediatr. 2019;173:234-43. 12. Agthe AG, Kim GR, Mathias KB, Hendrix CW, Chavez-Valdez R, Jansson L, Lewis TR, Yaster M, Gauda EB. Clonidine as an adjunct therapy to opioids for neonatal abstinence syndrome: a randomized, controlled trial. Pediatrics. 2009;123:e849-56. 13. Surran B, Visintainer P, Chamberlain S, Kopcza K, Shah B, Singh R. 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. 14. Ghazanfarpour M, Najafi MN, Roozbeh N, Mashhadi ME, Keramat-Roudi A, Megarbane B, Tsatsakis A, Moghaddam MMM, Rezaee R. Therapeutic approaches for neonatal abstinence syndrome: a systematic review of randomized clinical trials. Daru. 2019;27:423-31. 15. Dhull RS, Baracco R, Jain A, Mattoo TK. Pharmacologic Treatment of Pediatric Hypertension. Current Hypertension Reports. 2016;18 (4) (no pagination). 16. Wuhl E, Trivelli A, Picca S, Litwin M, Peco-Antic A, Zurowska A, Testa S, Jankauskiene A, Emre S, Caldas-Afonso A, Anarat A, Niaudet P, Mir S, Bakkaloglu A, Enke B, Montini G, Wingen AM, Sallay P,

Jeck N, Berg U, Caliskan S, Wygoda S, Hohbach-Hohenfellner K, Dusek J, Urasinski T, Arbeiter K, Neuhaus T, Gellermann J, Drozdz D, Fischbach M, Moller K, Wigger M, Peruzzi L, Mehls O, Schaefer F. Strict blood-pressure control and progression of renal failure in children. New England Journal of Medicine. 2009;361:1639-50.
17. 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.
18. Veenhoven RH, Vande Walle JG, Donckerwolcke RA, Wit JM, Griffiven AW, Derkx FH, Schalekamp MA. A neonate with idiopathic hyperaldosteronism. Pediatr Nephrol. 1991;5:680-4.
19. 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.
20. 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.
21. Larsson P, Nordlinder A, Bergendahl HT, Lonnqvist PA, Eksborg S, Almenrader N, Anderson BJ. Oral bioavailability of clonidine in children. Paediatr Anaesth. 2011;21:335-40.
22. https://www.micromedexsolutions.com.acs.hcn.com.au/micromedex2/ accessed 14/02/2020
23. https://www.mimsonline.com.au.acs.hcn.com.au/ accessed 14/02/2020
24. https://amhonline.amh.net.au.acs.hcn.com.au/search?q=clonidine accessed 14/02/2020

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