Phenobarbital (Phenobarbitone) 2024

Newborn use only

<table>
<tr><td>Alert</td><td>High risk medicine.
Phenobarbital is reported in mg/L. To convert to micromol/L, multiply by 4.306.</td></tr>
<tr><td>Indication</td><td>1. Treatment of neonatal seizures.[1-7]
2. Initial treatment of non-opioid neonatal abstinence syndrome (NAS).[8-10]
3. Add-on treatment of opioid NAS uncontrolled by morphine at maximum dose (if 3 consecutive NAS scores average ≥ 8 or 2 consecutive NAS scores average ≥12).
4. Treatment of hyperbilirubinaemia (unclear role). [11]
5. Treatment of cholestasis (unclear role).[12]
6. Preparation for liver scintigraphy (unclear role).[11]</td></tr>
<tr><td>Action</td><td>Enhances inhibitory neurotransmission via activation of GABA receptor.</td></tr>
<tr><td>Drug type</td><td>Anticonvulsant.
Sedative.</td></tr>
<tr><td>Trade name</td><td>Phenobarbitone (Aspen) Solution for injection; Phenobarbital (Arrow) Tablets; Phenobarbital (Orion) Elixir</td></tr>
<tr><td>Presentation</td><td>IV: 200 mg/mL ampoule (contains 10% ethanol and 67.8% propylene glycol)
Oral: 15 mg/5 mL oral liquid (contains 9.6% alcohol); 10 mg/mL and 9mg/mL alcohol free liquid can be manufactured by local pharmacy; 30 mg tablets.</td></tr>
<tr><td>Dose</td><td>Anticonvulsant
IV Loading dose 20 mg/kg/dose infusing with a maximum infusion rate of 1 mg/kg/minute.
Additional IV loading doses 10 mg/kg may be administered at 30-minute intervals, if necessary, with a maximum cumulative loading dose of 40 mg/kg.
IV or Oral Maintenance dose: 4 mg/kg/dose DAILY (3−5 mg/kg/dose), to commence 24 hours after the loading dose. Titrate the dose as per seizure control and therapeutic concentrations.

Other indications
<table>
<tr><td>Indication</td><td>Loading dose</td><td>Maintenance dose 24 hours after loading dose</td></tr>
<tr><td>Neonatal Abstinence Syndrome</td><td>Optional - 15 mg/kg ORAL</td><td>5 mg/kg/day in 1−2 divided doses ORAL and titrate to NAS score.</td></tr>
<tr><td>Jaundice</td><td>-</td><td>5 mg/kg every 24 hours ORAL</td></tr>
<tr><td>Liver scintigraphy</td><td>-</td><td>5 mg/kg/day in 2 divided doses ORAL for 5 days prior to scan</td></tr>
</table></td></tr>
<tr><td>Dose adjustment</td><td>Therapeutic hypothermia – No dose adjustment.[13,14]
ECMO: Dose remains the same and guided by the therapeutic drug monitoring.[14]
Renal impairment: In severe renal impairment dose should be reduced by 50%[27]
Hepatic impairment: use with caution, dose reduction is recommended.</td></tr>
<tr><td>Maximum dose</td><td></td></tr>
<tr><td>Total cumulative dose</td><td></td></tr>
<tr><td>Route</td><td>IV and oral</td></tr>
<tr><td>Preparation</td><td>IV: Draw up 1 mL (200 mg of Phenobarbital) and add 9 mL water for injection to make final volume of 10 mL with a final concentration of 20 mg/mL.
Oral elixir or liquid: Draw up prescribed dose.
Oral tablet: Pregnant staff are not to crush or disperse tablets. Crush and dissolve a 30 mg tablet in 3.75 ml of water for injection to make a final concentration of 8 mg/mL solution. Give prescribed amount, discard unused portion.</td></tr>
<tr><td>Administration</td><td>IV:
Loading dose: Infuse over 20 minutes with a maximum infusion rate 1 mg/kg/minute using a light safe extension set.
Maintenance dose: Bolus over 5 minutes.
Oral:
Give immediately before or with feeds to minimise GI irritation.</td></tr>
<tr><td>Monitoring</td><td>Serum concentrations for seizure control and therapeutic hypothermia:
24 hours after starting phenobarbital. Serum target: 15−40 mg/L (65-172 micromol/L). Consider repeating concentrations 1 week after the commencement and subsequent concentrations as per clinical need.
Consider liver function tests.</td></tr>
</table>

Contraindications	Hypersensitivity to phenobarbital or any ingredients. Any forms of acute porphyria.
Precautions	Use with caution in renal or hepatic impairment. Dependence may develop with prolonged use – consider weaning instead of abrupt withdrawal (Refer to special comments section). Therapeutic hypothermia may increase the serum concentrations of phenobarbital
Drug interactions	Morphine, fentanyl, midazolam, and other CNS depressants may have an additive effect with phenobarbital in causing respiratory depression. Consider starting phenobarbital at the lower end of the dose range in these patients. Blood concentrations of amiodarone, amlodipine, carbamazepine, clindamycin, clonazepam, colecalciferol (cholecalciferol; Vitamin D), dexamethasone, diazepam, digoxin, hydrocortisone, itraconazole, levetiracetam, metronidazole, midazolam, nifedipine, prednisolone, propranolol, sotalol, sildenafil, sirolimus, tadalafil, and voriconazole may be reduced if administered concurrently with phenobarbital. Concurrent administration of phenytoin with phenobarbital has variable effects on serum concentrations of either drug. Serum concentrations should be monitored for both drugs.
Adverse reactions	Drowsiness, lethargy - sucking reflex may be impaired and feeding may be poor. Respiratory depression, apnoea. Hypotension, laryngospasm, bronchospasm, apnoea - if IV administration is too rapid. Phlebitis, tissue necrosis if extravasation occurs.GI intolerance. Physical dependence and tolerance. May occur with prolonged use: Folate deficiency, hepatitis, hypocalcaemia.
Compatibility	Fluids [15]: Sodium chloride 0.45%, sodium chloride 0.9%, glucose 5%, glucose 10%. Y-site [15]: Aciclovir, alfentanil, amikacin, Amino acid solutions, aminophylline, amphotericin B lipid complex, amphotericin B liposome, anidulafungin, argipressin (vasopressin), ascorbic acid, atropine, azathioprine, azithromycin, aztreonam, bivalirudin, bumetanide, calcium chloride, calcium gluconate, cefazolin, ceftazidime, ceftriaxone, clindamycin, colistimethate sodium, dexamethasone sodium phosphate, dexmedetomidine, digoxin, dopamine, epoietin alfa, fentanyl, fluconazole, fluorouracil, furosemide, ganciclovir, gentamicin, heparin sodium, hydrocortisone sodium succinate, ibuprofen lysine, indomethacin, insulin regular, labetalol, linezolid, lorazepam, magnesium sulfate, mannitol, meropenem, metaraminol, methylprednisolone sodium succinate, metoprolol, metronidazole, milrinone, morphine sulfate, naloxone, glyceryl trintirate, nitroprusside sodium, octreotide, palonosetron hydrochloride, pamidronate, pancuronium, pentoxifylline, piperacillin/tazobactam, potassium chloride, propofol, propranolol, ranitidine, rocuronium, sodium acetate, sodium bicarbonate, tigecycline, tirofiban, tobramycin, urokinase, vancomycin, vecuronium, voriconazole, zoledronic acid. **Variable compatibility:** ampicillin, benzylpenicillin, erythromycin lactobionate, hydralazine, imipenem-cilastatin, lidocaine, pantoprazole, penicillin G potassium, penicillin G sodium, suxamethonium (succinylcholine).
Incompatibility	Fluids: Lipid emulsions. Y-site[15]: Adrenaline (epinephrine), alemtuzumab, amiodarone, atracurium, caspofungin, cefotaxime, cefoxitin, cefuroxime, diazepam, dobutamine, doxycycline, esmolol, midazolam, noradrenaline (norepinephrine), paracetamol, phenytoin, protamine, pyridoxine, sulfamethoxazole-trimethoprim, suxamethonium, tacrolimus, thiamine, verapamil.
Stability	Use diluted/opened solution as soon as possible.
Storage	Protect from light. Store below 25°C. Schedule 4 Appendix D (S4D) medication.
Excipients	Phenobarbitone (Aspen) Solution for injection: Ethanol, propylene glycol and water for injections.
Special comments	**Elimination half-life:** In infants 28-41 weeks gestation: Half-life of the drug was estimated (mean+SD) to be 114-2 ± 43.0 h, 73.19 ± 24.17 h and 41.23 ± 13.95 h in patients 1 - 10, 11 - 30 and 31 - 70 days old, respectively; neonates with perinatal asphyxia undergoing hypothermia 173.9±62.5 hours. Converting from mass units to SI units: 1 mg/L = 4.306 micromol/L. The general taper recommended for phenobarbital is 10-25% of the original dose every month. A faster taper is recommended for patients on therapy for less than 1 month.[16]
Evidence	**Background** Seizures are prevalent in the neonatal period, occurring in about 1 to 3/1000 newborns and majority are secondary to acute brain injury from various etiologies.[3] High neonatal seizure burden is associated with worse neurodevelopmental outcomes. Phenobarbital is effective against seizures of a range of etiologies but has serious cardio-respiratory and long term neurodevelopmental adverse effects**.**

Efficacy

Treatment of neonatal seizures: Phenobarbital (PHB) has been recommended as first-line treatment for neonatal seizures.[1-4] In RCTs, PHB (target plasma concentration 25 mg/L) was reported to be similarly as effective as phenytoin (target plasma concentration 3 mg/L) for control of electrical seizures (43% versus 45%); and PHB 20 mg/kg was reported to be more effective than phenytoin 20 mg/kg at controlling clinical seizures (72% versus 15%) (LOE II, GOR C).[5-7]

A single high-quality trial has shown that PHB is more effective than LEV for treatment of neonatal seizures but had more adverse events.[17] Of the three meta-analysis, one suggested that there was no evidence to replace PHB as first-line agent for neonatal seizures while the other two showed non-superiority of LEV over PHB.[2,3,4] Levetiracetam may be associated with a lower risk of adverse events such as hypotension and respiratory depression. However, these studies were relatively small, heterogeneous, and equivocal about subsequent need for inotropic support and mechanical ventilation.[3,17,18] There was no difference in the mortality or long-term neurodevelopmental outcomes between the phenobarbital and levetiracetam group.[3,17,18]

Summary: PHB is at least as efficacious and safe as other drugs like phenytoin and levetiracetam. PHB is the preferred first-line drug for neonatal seizures. The existing evidence is insufficient to recommend other drugs over phenobarbital.[2]

Prevention of seizures in infants with perinatal asphyxia: In term or near-term infants with perinatal asphyxia, prophylactic PHB (20−40 mg/kg loading dose) prevents seizures. There was no reduction in mortality and there are few data addressing long-term outcomes (LOE I, GOR C).

Treatment of neonatal abstinence syndrome (NAS): PHB is recommended as add on treatment of NAS secondary to opioid withdrawal not controlled by an opioid (LOE I, GOR C).[8]

PHB is recommended as initial treatment of NAS secondary to sedative withdrawal (LOE I, GOR C).[8]

PHB should be commenced at a dose of 5 mg/kg/day split into two divided doses. The dose should be titrated to achieve control of NAS according to the NAS score. It is unclear whether a loading dose of PHB should be used. If used as initial therapy (rather than in addition to an opioid), then a loading dose is likely to achieve more rapid control of symptoms.[9,10]

In one retrospective study, if sufficient to control symptoms, treatment with opioids only, resulted in shorter duration of hospital stay in newborns exposed to opioids, or multiple substances including opioids during pregnancy.[19]

Treatment of hyperbilirubinaemia: A meta-analysis (3 RCTs, 497 infants) found PHB (loading dose 10−30 mg/kg; maintenance 5 mg/kg/day) reduced peak serum bilirubin, duration of and need for phototherapy and need for exchange transfusion in preterm very low birth weight neonates. There are not enough data to evaluate adverse effects and neurodevelopmental outcome (LOE I, GOR C).

Preparation for hepatobiliary scintigraphy and treatment of neonatal cholestasis: The role of PHB in preparation for hepatobiliary scintigraphy is unclear (LOE I, GOR C).[11] Ursodeoxycholic acid is the preferred agent for this purpose (refer to ursodeoxycholic acid formulary). PHB may have a role in treatment of pruritis caused by intrahepatic cholestasis.[12]

Pharmacokinetics

In infants with seizures, PHB 15−20 mg/kg loading dose with additional 5−10 mg/kg doses to maximal plasma concentration of 40 mg/L (172 micromol/L) resulted in a plateau of the response rate. Plasma concentrations >50 mg/L (215 micromol/L) were associated with sedation and feeding difficulty.[20]

The clearance of PHB increases with birth weight and postnatal age but is reduced at a concentration >50 mg/L (215 micromol/L).[21] Bioavailability is 50% after oral administration. Simulations recommend a loading dose 20 mg/kg and maintenance 2.5 − 5 mg/kg/day for intravenous administration and loading dose 40 mg/kg and maintenance 5 − 11 mg/kg/day for oral administration to meet a target PHB concentration between 15 and 30 mg/L (64.5 and 129.1 micromol/L) (LOE IV GOR C).[22]

The clearance may also be reduced in infants with perinatal asphyxia undergoing therapeutic hypothermia.[23-25] In term infants treated with hypothermia, an initial PHB loading dose of 20 mg/kg with an additional 10−20 mg/kg if needed is recommended (LOE IV GOR C).[25-26]

Practice points	

References	1. Pressler RM, Abend NS, Auvin S, et al. Treatment of seizures in the neonate: Guidelines and consensus-based recommendations-Special report from the ILAE Task Force on Neonatal Seizures. Epilepsia. 2023 Oct;64(10):2550-2570. 2. Kumar J, Meena J, Yadav J, Saini L. Efficacy and Safety of Phenobarbitone as First-Line Treatment for Neonatal Seizure: A Systematic Review and Meta-Analysis. J Trop Pediatr. 2021 Jan 29;67(1):fmab008. 3. Hooper RG, Ramaswamy VV, Wahid RM, Satodia P, Bhulani A. Levetiracetam as the first-line treatment for neonatal seizures: a systematic review and meta-analysis. Dev Med Child Neurol. 2021 Nov;63(11):1283-1293. 4. Qiao MY, Cui HT, Zhao LZ, Miao JK, Chen QX. Efficacy and Safety of Levetiracetam vs. Phenobarbital for Neonatal Seizures: A Systematic Review and Meta-Analysis. Front Neurol. 2021 Nov 18;12:747745. 5. Slaughter LA, Patel AD, Slaughter JL. Pharmacological treatment of neonatal seizures: a systematic review. Journal of child neurology. 2013;28:351-64. 6. Painter MJ, Scher MS, Stein AD, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. The New England journal of medicine. 1999;341:485-9. 7. Pathak G, Upadhyay A, Pathak U, Chawla D, Goel SP. Phenobarbitone versus phenytoin for treatment of neonatal seizures: an open-label randomized controlled trial. Indian pediatrics. 2013;50:753-7. 8. Osborn DA, Jeffery HE, Cole MJ. Sedatives for opiate withdrawal in newborn infants. Cochrane database of systematic reviews. 2010:CD002053. 9. National clinical guidelines for the management of drug use during pregnancy, birth and the early development years of the newborn. Ministerial Council on Drug Strategy; 2006. 10. Guidelines for the management of substance use during pregnancy birth and the postnatal period. NSW Ministry of Health; 2014. 11. Malik D, Khan SH, Ali SW, et al.. Comparison of phenobarbitone and ursodeoxycholic acid in drug-augmented hepatobiliary scintigraphy for excluding the diagnosis of obstructive cholestasis in neonatal cholestasis syndrome. Nuclear medicine communications. 2015;36:827-32. 12. Cies JJ, Giamalis JN. Treatment of cholestatic pruritus in children. Am J Health-Syst Pharm. 2007;64:1157-62. 13. Lutz IC, Allegaert K, de Hoon JN, Marynissen H. Pharmacokinetics during therapeutic hypothermia for neonatal hypoxic ischaemic encephalopathy: a literature review. BMJ paediatrics open. 2020;4(1). 14. Šíma M, Michaličková D, Slanař O. What is the Best Predictor of Phenobarbital Pharmacokinetics to Use for Initial Dosing in Neonates? Pharmaceutics. 2021 Feb 25;13(3):301. 15. MerativeTM Micromedex® Complete IV Compatibility (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com/ (cited: Aug/14/2024). 16. St. Louis EK, Gidal BE, Henry TR, Kaydanova Y,Krumholz A, McCabe PH, et al. Conversions between monotherapies in epilepsy: Expert consensus. Epilepsy and Behaviour 2007;11:222-234. 17. Sharpe C, Reiner GE, Davis SL, eta al. NEOLEV2 INVESTIGATORS. Levetiracetam Versus Phenobarbital for Neonatal Seizures: A Randomized Controlled Trial. Pediatrics. 2020 Jun;145(6):e20193182 18. Gowda VK, Romana A, Shivanna NH, Benakappa N, Benakappa A. Levetiracetam versus Phenobarbitone in Neonatal Seizures - A Randomized Controlled Trial. Indian Pediatr. 2019 Aug 15;56(8):643-646. 19. Kushnir A, Garretson C, Mariappan M, Stahl G. Use of Phenobarbital to Treat Neonatal Abstinence Syndrome From Exposure to Single vs. Multiple Substances. Front Pediatr. 2022 Jan 31;9:752854. 20. Gilman JT, Gal P, Duchowny MS, Weaver RL, Ransom JL. Rapid sequential phenobarbital treatment of neonatal seizures. Pediatrics. 1989;83:674-8. 21. Yukawa M, Yukawa E, Suematsu F, et al. Population pharmacokinetics of phenobarbital by mixed effect modelling using routine clinical pharmacokinetic data in Japanese neonates and infants: an update. J Clin Pharm Ther. 2011;36:704-10. 22. Marsot A, Brevaut-Malaty V, Vialet R, et al. Pharmacokinetics and absolute bioavailability of phenobarbital in neonates and young infants, a population pharmacokinetic modelling approach. Fundam Clin Pharmacol. 2014;28:465-71.

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