Phenytoin
Newborn use only

2020

<table>
<tr><td>Alert</td><td>Rapid IV infusion can cause cardiovascular collapse. As part of the Australian national harmonisation program, as of May 2016, all therapeutic drugs except lithium are now reported in mass units: microgram/L, mg /L etc. Phenytoin is now reported in mg/L. To convert from mg/L (microgram/mL) to micromol/L, multiply by 3.964.</td></tr>
<tr><td>Indication</td><td>Treatment of neonatal seizures.[1-4]</td></tr>
<tr><td>Action</td><td>Phenytoin exerts its activity by inhibition of neuronal sodium influx, suppression of sodium action-potentials, inhibition of neuronal calcium influx, enhancement of GABA neurotransmission, and blockade of inotropic receptors for glutamic acid.</td></tr>
<tr><td>Drug type</td><td>Hydantoin derivative anticonvulsant</td></tr>
<tr><td>Trade name</td><td>Dilantin, DBL Phenytoin Injection, Phenytoin Sandoz Injection
Dilantin Paediatric Suspension</td></tr>
<tr><td>Presentation</td><td>100 mg/2 mL ampoule
30 mg/5 mL oral suspension</td></tr>
<tr><td>Dose</td><td>
<table>
<tr><th>Route</th><th>Dose [1-6]</th></tr>
<tr><td>IV</td><td>Loading dose: 20 mg/kg

Maintenance dose: Start 12 hours after loading dose.
First 7 days of life:
Term infants: 2.5 mg/kg/dose every 12 hours (range 4–8 mg/kg/day)
Preterm infants: 2.5 mg/kg/dose every 24 hours. Titrate as per serum concentrations.

8–30 days:
Term infants: 2.5 mg/kg/dose every 8 hours (range 4–8 mg/kg/day)
Preterm infants: 2.5 mg/kg/dose every 12 hours. Titrate as per serum concentrations.

Beyond 30 days:
Term infants: 2.5 mg/kg/dose every 6 hours
Preterm infants: 2.5 mg/kg/dose every 8 hours. Titrate as per serum concentrations.</td></tr>
<tr><td>Oral</td><td>Maintenance: start same as for IV. Average oral bioavailability 75%. Monitor concentrations and adjust dose accordingly.</td></tr>
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</td></tr>
<tr><td>Dose adjustment</td><td>Therapeutic hypothermia: Check serum concentration at 24 hours after loading and on day 4 and 7 if therapy continued.[7]
ECMO: Larger doses may be needed to achieve comparable serum concentration.[8]
Renal impairment: Insufficient information to recommend any specific dose adjustment.
Hepatic impairment: Dosage escalation should be gradual.</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 & Oral</td></tr>
<tr><td>Preparation</td><td>IV: Draw up 1 mL (50 mg) and add 9 mL sodium chloride 0.9% to make final volume of 10 mL with a concentration of 5 mg/mL. Maximum dilution is 5 mg/mL. Administer through filter immediately after dilution. Do NOT use if solution becomes cloudy or hazy.

Oral: Shake bottle well prior to measuring dose.</td></tr>
<tr><td>Administration</td><td>IV Infusion: Infuse over 30 minutes (maximum 1 mg/kg/minute) with a syringe pump preferably via a central line or large vein (rare risk of purple glove syndrome with peripheral administration). Flush the line with sodium chloride 0.9% before the infusion and after completion of the infusion. IV Maintenance dose can be infused over 5 minutes (maximum 1 mg/kg/minute).</td></tr>
</table>

	Oral: May be given with or without feeds but administration with respect to feeds should be consistent. If possible, give apart from other medications.
Monitoring	Monitor blood pressure and continuous ECG during stabilisation. Infusion-related reactions: Monitor for hypotension, bradycardia and arrhythmias during infusion. Other monitoring during stabilisation on phenytoin therapy: Continuous cardiorespiratory monitoring, blood pressure, renal function, liver function, blood glucose, full blood count. Long-term therapy: Consider thyroid function tests, calcium, phosphate, 25(OH)D and alkaline phosphatase. Therapeutic Drug Concentration Monitoring: Note phenytoin elimination half-life is variable and steady-state may not yet be reached (can take up to 5–10 days) in the initial serum samples. Take initial concentration 24 hours after loading dose and then weekly if continued on phenytoin therapy. Concentrations need to be monitored more closely in very preterm or extreme low birth weight infants. Adjust the dose as per serum concentration and seizure control. In preterm infants, monitoring needs to be individualised because of long and variable half-life. Dosage/dose form changes: Serum concentrations should also be checked after dose adjustments or dose form change (e.g. switching from IV to oral) during stabilisation therapy with similar timing as above. Target Range: Note reference ranges are in total phenytoin concentration; reference ranges are different for free phenytoin concentrations. Serum therapeutic range infants ≤ 28 days: 6–15 mg/L (24–60 micromol/L); infants > 28 days: 10--20 mg/L (40–80 micromol/L). In severely ill infants and those with hypoalbuminaemia, uremia or concomitant valproic acid, consider measuring free phenytoin concentrations. For free phenytoin, target range is 0.5 to 1.4 mg/L (2 to 5.6 micromol/L). Typical free phenytoin is one-tenth of total phenytoin as phenytoin is 90% protein bound. If total concentration is above upper range but below 30 mg/L (120 micromol/L), withhold dose. Concentrations above 30 mg/L (120 micromol/L) are considered toxic and infant may display signs of overdose and should be monitored especially for cardiovascular symptoms/signs. Adjustment of dose according to serum concentration: Phenytoin does not follow linear kinetics so an increase in dose may cause a disproportionate increase in serum concentration. If a dose increase is required, do so gradually (no more than 10% of the daily dose at any one time) and consult pharmacy/neurologist.
Contraindications	Known hypersensitivity to phenytoin, severe sinus bradycardia, and sinoatrial block, second and third degree AV block or Stokes - Adams syndrome.
Precautions	If patient is hypotensive prior to starting phenytoin, consult the treating neonatologist. If impaired hepatic or renal function, may require decreased dosage. Phenytoin is highly protein bound. Concentration of free phenytoin is higher in infants with hypoalbuminaemia and may cause toxicity even if the total phenytoin serum concentration is within therapeutic range. Increased free fraction of phenytoin can also occur in infants with hyperbilirubinemia, renal impairment, or uraemia. Consider weaning instead of abrupt cessation of the drug (see special comments section).
Drug interactions	Monitor phenytoin concentrations closely if given concurrently with the following medications: Erythromycin, trimethoprim/sulfamethoxazole, amphotericin, fluconazole, miconazole, amiodarone, omeprazole and ranitidine which may increase phenytoin concentrations. Fluoroquinolones (e.g. ciprofloxacin, moxifloxacin), rifampicin, folic acid and calcium may decrease phenytoin concentrations. In the case of calcium, administration should be separated by at least 1 hour to reduce the interaction. Concurrent administration of phenytoin with phenobarbital (phenobarbitone) has variable effects on serum concentrations of either drug. Serum concentrations should be monitored for both drugs. Some medications are affected by phenytoin (monitor the concentration of the medication if possible): folic acid, thyroxine, vitamin D, calcium, corticosteroids (e.g. dexamethasone), caffeine, frusemide, digoxin and vecuronium may have their concentrations reduced. Phenytoin may also lower the blood concentrations of methadone, possibly manifesting withdrawal earlier in neonatal abstinence syndrome. Other interactions: Diazoxide may reduce the serum concentration of phenytoin and phenytoin may increase the hyperglycaemic effects of diazoxide. Dopamine used concurrently with phenytoin may cause profound hypotension. Beta-blockers (e.g. propranolol, sotalol) used concurrently with phenytoin may cause hypotension and may produce additive cardiac depressant effects.

Adverse reactions	Administration-related reactions: Extravasation causes tissue inflammation and necrosis due to high pH and osmolality. Monitor IV insertion site. May cause bradycardia, arrhythmias, hypotension during infusion (more common if administration is too rapid). Pharmacological adverse reactions: Cardiac arrhythmias, hypotension, hyperglycaemia, constipation, interstitial nephritis, hepatitis, macrocytosis, megaloblastic anaemia (usually responds to folic acid supplementation) and blood dyscrasias. More likely with long-term use: Gingival hyperplasia, hirsutism, coarsening of facial features, folic acid deficiency, vitamin D deficiency, osteomalacia and hypothyroidism (only a few case reports in patients taking thyroxine, not in euthyroid patients). Rare but potentially fatal skin reaction: Phenytoin is associated with the anticonvulsant hypersensitivity syndrome a variant of Drug Reaction with Eosinophilia and Skin manifestations (DRESS). If DRESS is suspected , stop phenytoin immediately. Symptoms include: skin eruptions including Stevens Johnson syndrome or toxic epidermal necrolysis, eosinophilia, acute hepatotoxicity; fever; and abnormal lymph nodes; facial and/or tongue swelling; hives. There is marked cross-reactivity with other aromatic anti-epileptics.. The human leukocyte antigen (HLA) allele responsible for this reaction is almost exclusively expressed in patients of Asian ancestry including Chinese, Filipino, Malaysian, South Asian Indian, Korean, Japanese and Thai. Signs of phenytoin overdose: Nystagmus, cardiovascular collapse and/or CNS depression and dyskinesias. High serum concentrations are associated with seizures.
Compatibility	Fluids: Sodium chloride 0.9% Y-site: Do not mix with other drugs.
Incompatibility	Fluids: Glucose 5%, glucose 10%, Y-site: Amino acid and lipid solutions. Do not mix with other drugs.
Stability	Diluted IV solution should be used as soon as possible. Discard unused portion.
Storage	Store below 25°C. Protect from light.
Excipients	
Special comments	Elimination half-life 7–42 hours depending on concentration. Half-life is longer in first 7 days of life. Tapered dosing may be required in infants with epilepsy.
Evidence	**Efficacy** Initial treatment of neonatal seizures: Phenytoin (free concentration target level 3 mg/L) compared to phenobarbital (phenobarbitone) (free concentration target level 25 mg/L) has been reported to have similar efficacy in control of electrical seizures (one RCT: LOE II).[1] Phenytoin 20 mg/kg compared to phenobarbital (phenobarbitone) 20 mg/kg was reported to be less effective in controlling clinical seizures (one RCT, LOE II).[2] Phenytoin was shown to only provide about a 10% to 15% increase in seizure control when given following phenobarbital (phenobarbitone) failure.[1] Consider phenytoin for treatment of neonatal seizures refractory to a first-line anticonvulsant. (GOR C) Maintenance treatment of neonatal seizures: Evidence is insufficient to guide maintenance treatment for prevention of seizure recurrence after neonatal seizures. Current recommendations include to wean to one maintenance seizure medication prior to discharge; and consider weaning all seizure medication prior to discharge if single or rare seizures and if seizure-free for at least 48--72 hours and risk of recurrence not felt to be unusually high.[3] Recommended dosing is phenytoin 15--20 mg/kg IV, followed by 4--10 mg/kg IV, daily in 2 to 3 divided doses with close monitoring of plasma phenytoin concentrations. Inject slowly at a rate not exceeding 1 mg/kg/min. Continuous monitoring of the electrocardiogram and blood pressure is essential.[4] (GOR B) Side effects: The incidence of side effects is unclear. Reported side effects (12.5%) from a loading dose included respiratory depression, bradycardia, oxygen desaturation, drowsiness, vomiting, pyrexia, twitching and hypotension.[5] Reported side effects from maintenance treatment (all age groups) include gastrointestinal side effects (abdominal pain, nausea and vomiting); drowsiness/tiredness/fatigue/sedation; rash; decreased libido or impotence; motor disturbance (including ataxia, incoordination, nystagmus, tremor); dysmorphic and idiosyncratic side effects (gum hypertrophy, hirsutism, acne, other skin problems) and cognitive side effects and impairments, including slowing of mental function, inattention, psychomotor retardation, depression and memory problems.[6]

	Pharmacokinetics: In children, phenytoin loading dose 20 mg/kg may result in supratherapeutic concentrations.[5] (LOE IV) During the first week after birth, plasma half-life is so variable that no fixed dosage regimen can be derived. Beyond the second week, 8 mg/kg/24 hours is probably inadequate for most infants.[9] (LOE IV) In preterm infants the t½ was much longer (75.4 ± 64.5 h) and more variable.[9] (LOE IV) Postnatal age independently influenced clearance. Switching from enteral to intravenous routes may require a dosage adjustment (enteral bioavailability 0.76, 95% CI 0.44 to 1.07), although similar serum concentrations have been reported in preterm infants irrespective of route.[10,11] (LOE IV, GOR C) In a small case series of term neonates on phenytoin as single drug or in combination with phenobarbitone, the mean daily dose of phenytoin was significantly higher in neonates on ECMO compared to non-ECMO neonates (20 vs 11mg/kg/day; p=0.04) with comparable drug levels (8.4 vs 7.4 mg/L; p=0.56).[8] Monitoring: Therapeutic target for total phenytoin is 10 to 20 mg/L (40 to 80 micromol/L) and for free phenytoin 0.5 to 1.4 mg/L (2 to 5.6 micromol/L).[12] (LOE IV, GOR C). Total phenytoin concentrations are unreliable for directing therapy in critically ill children. Free phenytoin concentrations should be routinely measured in critically ill children to prevent possible intoxications and ensure therapeutic dosing.[13] When free phenytoin concentrations cannot be routinely measured, use total phenytoin concentration with a derivative of the Sheiner-Tozer equation: Ctotaladjusted = [Ctotalmeasured x 10.2 – 0.24 x (ALB – 42) + 0.067 x (UREA – 7)+ 2.53 x VALP] ÷ 10.2.[13-14] Note, however, that the Sheiner-Tozer equation and all its derivatives are regarded, in general, as biased and imprecise.[14] In children with hypoalbuminaemia, uraemia or concomitant valproic acid use, ensure close treatment monitoring and consider a dose reduction of phenytoin a priori.[13] (LOE IV, GOR C) To convert from mg/L (microgram/mL) the factor is 3.964. Simply multiply the mg/L value to obtain the value in micromol/L. Hypothermia can significantly reduce clearance of phenytoin compared with normothermic patients and during and after rewarming phase. There is limited data about saturable metabolism and modelled using Michaelis-Menten Kinetics in neonates. It is advisable to closely monitor the concentration of phenytoin in neonates during therapeutic cooling and rewarming phase.[7]
Practice points	
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