BRIEF ADMINISTRATION GUIDE

(For more detailed guideline information please see the following pages)

Indications: Treatment of neonatal seizures[1-3]

Route:
- Intravenous (loading and maintenance dosing)[2-5]
- Oral (maintenance dosing only)[2,4,6,7]

Dose:

Loading Dose

15 to 20 mg/kg by IV Infusion over 30 to 60 minutes[1-5,8]

Maintenance Dose
- Initially 2.5 mg/kg twice daily by IV infusion or orally, commencing 12 hours after the loading dose[1,2,4,5,8]
- Dose should be individualised according to clinical response and plasma phenytoin concentration (usual range 4 to 8 mg/kg daily)[4,5,8]

Supplied as:
- Phenytoin sodium 100 mg/2 ml ampoule[4]
- Phenytoin 30 mg/5 ml oral suspension[4]

Preparation and administration:

Intravenous
- Use undiluted or dilute in sodium chloride 0.9% at a concentration of 5 mg/ml or greater[1-3,9].
- Draw up prescribed dose.
- Prepare diluted phenytoin immediately before use and infuse through a 0.22 micron in-line filter. Inspect the solution carefully and do not use if precipitation or haziness occur[1,4,8-11].
- Infuse loading dose over 30 to 60 minutes[2,3,11].
- Infuse maintenance dose at a maximum rate of 1 mg/kg/minute[1,4,5,8-10].
- Administer into a large vein through a large gauge needle or IV catheter. Flush the needle and line with sodium chloride 0.9% after administration at the same rate of infusion[1,4,5,8-11].
- Discard any remaining solution.

Oral (maintenance dosing only)
- Shake the bottle well prior to use and draw up the prescribed dose[4,5].
- May be administered with or without feeds, but should remain consistent[7].

Monitoring:

- Monitor blood pressure, pulse, respiratory rate, and ECG continuously during infusion and every 15 minutes for 1 hour after administration[1,5,8,9,11].
- Monitor for injection site reactions and extravasation[1,5,11].
- Observe for signs and symptoms of rapid administration and hypersensitivity[7,9,11].
- Monitor CBC, liver function, renal function and blood glucose levels[2,5,7].
- Phenytoin serum trough levels should be taken 48 hours after IV loading dose, then at least weekly if therapy continued[1,3].
- Therapeutic total phenytoin level (trough): 40 – 80 micromol/L[2,3,6,10].
- Therapeutic free phenytoin level (trough): 3 – 8 micromol/L[10].

1. Purpose and scope

To facilitate the safe and effective use of phenytoin in the Neonatal Intensive Care Unit (NICU).

2. Drug

Drug	Phenytoin, phenytoin sodium
Drug action	Phenytoin is an anticonvulsant that stabilises neuronal membranes by increasing efflux or decreasing influx of sodium ions across cell membranes in the cells of the motor cortex during generation of nerve impulses[3,5,6,10]. Other mechanisms which may contribute to its activity include inhibition of neuronal calcium influx, enhancement of GABA neurotransmission, and blockage of inotropic receptors for glutamate[7,10]. Pharmacokinetics are dose-dependent and unpredictable in the neonate, with relatively small margins between full therapeutic effect and a minimally toxic dose of phenytoin. Phenytoin is highly protein bound (85% to 90%). Bilirubin displaces phenytoin from protein-binding sites, resulting in increased serum free phenytoin concentration. Elimination is via urinary excretion of phenytoin and its metabolites and the rate is increased during first few weeks of life[1,2].
Indications	• Treatment of neonatal seizures[1-3]
Presentation	• Phenytoin sodium 100 mg/2 ml ampoule[4]. Clear colourless to faint yellow solution. Excipients include propylene glycol, ethanol, sodium hydroxide/hydrochloride acid, water for injection[11]. • Phenytoin 30 mg/5 ml oral suspension[4]. Reddish-pink solution[6].
Route	• Intravenous (loading and maintenance dosing)[2-5] • Oral (maintenance dosing only)[4,6] <u>Note:</u> Oral absorption can be reduced or erratic in neonates[2,3,5]. Intramuscular administration is not recommended as it can crystallise in muscle[1,5,9,10].
Dose	**Loading Dose** 15 to 20 mg/kg by IV Infusion over 30 to 60 minutes[1-5,8]. **Maintenance Dose** • Initially 2.5 mg/kg twice daily by IV infusion or orally, commencing 12 hours after the loading dose[1,2,4,5,8]. • Dose should be individualised according to clinical response and plasma phenytoin concentration (usual range 4 to 8 mg/kg daily)[4,5,8]. <u>Note:</u> • Phenytoin does not follow linear kinetics so an increase in dose may be disproportionate to the 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[7]. • Phenytoin sodium (injection) 100 mg is approximately equivalent in therapeutic effect to phenytoin base (oral suspension) 92 mg. Care is needed when switching between formulations and additional therapeutic drug monitoring and dose adjustment may be required[4,5].

Contraindications	• Known hypersensitivity to phenytoin or any component of the injection[5,8] • IV injection: sinus bradycardia, sino-atrial block, second- and third degree heart block, Stokes-Adams syndrome[4,5,8] • Hypoglycaemic or absence seizures[5,6,10]
Precautions	• Hypotension, heart failure[2,8] • HLA-B*15:02 allele in individuals of Han Chinese or Thai origin, avoid unless essential (increased risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis)[1,4,8,10] • Diabetes (risk of hyperglycaemia)[1,4,5,10] • Porphyria[1,4,5,10] • Hepatic impairment, hyperbilirubinemia[1,5,8,10] • Hypoalbuminaemia[4,5,10] • Renal impairment[1,5,8,10] • Hypothyroidism, may alter thyroid hormone serum concentrations with chronic administration[5] • Previous history of adverse hematologic reaction to any drug may be at increased risk of blood dyscarsias[5]
Incompatibilities	• Compatible with sodium chloride 0.9% for dilution[8,11] • Phenytoin is highly unstable in any IV solution and should not be mixed with any other drugs or administered via the same Y-site due to its low solubility and increased the risk of precipitation or crystallisation[10,11] • Phenytoin has numerous drug interactions including[2-4,6,10]: ▪ Phenytoin may increase the levels of phenobarbitone ▪ Phenytoin may decrease the level of caffeine, corticosteroids, digoxin, furosemide, levothyroxine. nimodipine, paracetamol, pancuronium, vecuronium ▪ Phenytoin level may be increased by erythromycin, sulphonamides, amphotericin B, azole antifungals, diazepam, amiodarone, nifedipine, omeprazole, ranitidine ▪ Phenytoin level may be decreased by carbamazepine, vigabatrin, fluoroquinolones, folic acid, rifampicin, calcium
Adverse effects	• Nausea, vomiting, constipation[2,4,10] • Injection site reactions including purple glove syndrome, venous irritation, phlebitis[2,5,8] • Extravasation can cause inflammation and tissue necrosis due to high pH and osmolality[1,3,5] • Rapid administration is associated with bradycardia, hypotension, cardiac arrhythmias[1,2,5,8,9] • Signs of toxicity may include nystagmus, dyskinesias, cardiovascular collapse, CNS depression, respiratory depression. High serum concentrations associated with seizures[1,2,4,5,10] • Hyperglycaemia, hypoinsulinaemia[1,4,5] • DRESS, Stevens-Johnson syndrome, Toxic Epidermal Necrolysis[4,5,6,10] • Blood dyscrasias including megaloblastic anaemia, leucopenia, thrombocytopenia, and aplastic anaemia[4,5,6,10] • Long term effects include gingival hyperplasia, coarsening of the facial features, hirsutism, osteomalacia[1,4,5,6,10] • Rare: hepatotoxicity, peripheral neuropathy, dyskinesia, interstitial nephritis, anticonvulsant hypersensitivity syndrome[4,5,6,8,10]

3. Administration

Competency for administration	This procedure is carried out by, or under, the direct supervision of a registered nurse/registered midwife who holds current Waikato DHB Generic Medicine Management and IV certification as well as Neonatal specific competency NCV/NAC.
Preparation & Administration	**Intravenous** • Use undiluted or dilute in sodium chloride 0.9% at a concentration of 5 mg/ml or greater. Note undiluted phenytoin may cause venous irritation due to the high pH[1-3,9]. • Draw up prescribed dose. • Diluted phenytoin may precipitate so prepare immediately before use and infuse through a 0.22 micron in-line filter. Inspect the solution carefully and do not use if precipitation or haziness occur[1,4,8-11]. • Infuse loading dose over 30 to 60 minutes[2,3,11]. • Infuse maintenance dose at a maximum rate of 1 mg/kg/minute[1,4,5,8-10]. Note rates of up to 3 mg/kg/minute have been used but rapid administration is associated with cardiovascular adverse effects[1,5,8-10]. • Administer into a large vein through a large gauge needle or IV catheter. Flush the needle and line with sodium chloride 0.9% after administration at the same rate of infusion to avoid local irritation of the vein[1,4,5,8-11]. • Discard any remaining solution. **Oral (maintenance dosing only)** • Shake the bottle well prior to use[5]. • Draw up the prescribed dose using a calibrated oral dosing syringe[5]. • May be administered with or without feeds, but should remain consistent[7].
Observations and management	**Monitor the following:** • Blood pressure, pulse, respiratory rate, and ECG continuously during infusion and every 15 minutes for 1 hour after administration. More frequent monitoring for a longer duration may be required for emergency use[1,5,8,9,11]. • Injection site reactions and extravasation[1,5,11]. • Symptoms of rapid administration including cardiovascular collapse, and signs and symptoms of hypersensitivity to phenytoin particularly skin rash[7,9,11]. • CBC, liver function, renal function and blood glucose levels[2,5,7]. • For long term therapy consider monitoring thyroid function tests, calcium, phosphate, and vitamin D levels[5,7]. **Phenytoin Therapeutic Drug Monitoring:** • Initial serum phenytoin trough levels should be taken 48 hours after IV loading dose[1,3]. If rapid therapeutic levels are needed, a level may be drawn 2 hours after IV loading dose[11]. • If therapy is continued, phenytoin trough levels should be taken weekly, and after any dose adjustment or drug formulation change e.g. switching IV to oral therapy[7]. • More frequent monitoring may be required in very pre-term or extremely low birth weight infants[7]. • Free phenytoin levels must be taken in infants with hypo- or hyper-bilirubinaemia, renal impairment, uraemia, or concomitant use of sodium valproate as the free phenytoin level may be higher, causing

	toxicity, even if the total phenytoin concentration is within therapeutic range[5,7,8,10]. • Therapeutic total phenytoin level (trough): 40 – 80 micromol/L[2,3,6,10]. • Therapeutic free phenytoin level (trough): 3 – 8 micromol/L[10]. • Concentrations greater than 120 micromol/L are considered toxic. The infant may display signs of overdose and must be closely monitored[7]. • Phenytoin does not follow linear kinetics so an increase in dose may be disproportionate to the 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[7].
Special considerations (audit, funding, storage)	• Prepare intravenous infusion immediately before use; diluted solutions must be infused within 4 hours[9,11]. • Store at room temperature (below 25) and protect from light[5,6,9,10,11]. • Sodium content: 0.2 mmol sodium per 50 mg phenytoin sodium ampoule[11] • The pH of phenytoin is 12[9,11]
Rescue medication	Discontinue phenytoin immediately and seek urgent medical assistance if signs of overdose or toxicity, severe adverse reactions or anaphylaxis occur. Supportive therapy may include ventilation, volume expansion, inotropes and/or antiarrhythmic agents[2]. If extravasation occurs, stop infusion immediately and disconnect (leave needle/cannula in place), gently aspirate extravasated solution (do NOT flush the line), remove needle/cannula, and elevate extremity[5].

4. Associated documents

- Waikato DHB. Phenobarbitone sodium in NICU Drug Guideline. Document # 2952.
- Waikato DHB. Midazolam for NICU Drug Guideline. Document # 2939.

5. References

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