Specialised Medication – Phenytoin (Injectable) for Adult Patients Guideline

1. Guiding Principles

This document provides guidance for the prescription and administration of phenytoin via the intravenous route for adult patients.

2. Guideline

- For Paediatric Patients, refer to the Perth Children's Hospital – Phenytoin - Paediatric accessible via HealthPoint.

2.1 Presentation[1]

- 100mg in 2mL ampoules
- 250mg in 5mL ampoules

2.2 General Indication(s) for Phenytoin[1]

- Epilepsy, including simple and complex partial (focal) seizures, and generalised tonic-clonic seizures.
- Status epilepticus (intravenous).

2.3 Contraindications

- Porphyria[1]
- History of the following cardiac conditions (due to the effect of phenytoin on ventricular automaticity)[1, 3]:
  - Sinus bradycardia.
  - Sinoatrial (SA) block.
  - Second- and third-degree atrioventricular [2] block.
  - Stokes-Adams syndrome.
- Known hypersensitivity to phenytoin or other hydantoins[3].

2.4 Precautions

- Pregnancy – Australian category D (human placental transfer has been demonstrated).[1, 4] Use with extreme caution with the decision made upon an individual basis by considering the risks and benefits to both mother and foetus. Exposure during pregnancy is associated with malformations such as cleft lip/palate, heart defects, craniofacial anomalies and hypoplasia; hypotension, respiratory depression, hypothermia and withdrawal symptoms in the newborn have been reported.[4] Seek Specialist Advice. Further information available from King Edward Memorial Hospital Drug Information Centre (Ph: 08 6458 2723).
- Lactation – May be used.[1] Monitor infant for sedation and decreased sucking action.[4]

- Hypersensitivity syndrome with phenytoin, carbamazepine or phenobarbitone (avoid use) .[1]
- Asian ancestry – increased likelihood of genetic predisposition (HLA-B*1502 allele) to severe skin reactions (10-fold higher incidence of Stevens-Johnson Syndrome) .[1, 5]
- Absence and myoclonic seizures – lack of efficacy.[1]
- Use with caution in patients with known hypotension and/or severe myocardial insufficiency. In patients with cardiovascular disease, parenteral administration may result in atrial/ventricular conduction depression, ventricular fibrillation or reduced cardiac output.[3]
- Diabetes – Risk of hyperglycaemia through inhibition of insulin secretion.[1, 3]

2.5 Drug interactions

Drug interactions with phenytoin are extensive therefore, a comprehensive list is beyond the scope of this document. Multiple references are to be consulted including the Approved Product Information (available via MIMs), AMH, and specialised drug interaction texts; Specialist and/or Clinical Pharmacist advice is to be considered.

2.6 Dosage

Status epilepticus (adult)[1]: 15-20mg/kg. The British National Formulary(BNF) recommends this loading dose is capped at a maximum of 2g.[6] An additional dose of 5mg/kg may be given after 12 hours if necessary.

2.7 Administration

PHENYTOIN solution is very alkaline. Injection via the INTRAMUSCULAR (IM) or SUBCUTANEOUS (SUBCUT) route is NOT recommended.
Soft tissue irritation and inflammation (ranging from slight tenderness to extensive necrosis and sloughing) may occur both with AND without the extravasation.[7]

Historically, most cardiac adverse effects were associated with rapid IV administration or erratic, manual bolus/infusion. Therefore, an infusion control device is to ALWAYS be used.[2]

Maximum rate is generally 50mg/minute[3], although elderly patients (or those with cardiovascular disease, or cardiopulmonary compromise)[2] are most at risk of adverse reactions and in general should have their administration rate reduced to a maximum of 25mg/minute (or preferably further to 5-10mg/minute) .[2, 7]

DO NOT MIX WITH OTHER DRUGS

Method of Administration[3, 5, 7]

1. Ensure appropriate intravenous access to a **large proximal vein or central line** is available (injection via a large gauge needle or intravenous catheter). Note, phenytoin sodium is highly alkaline and irritant, and may result in "purple glove syndrome" (progressive distal limb oedema, discolouration, pain which in severe cases may involve extensive skin necrosis and limb ischaemia) if administered via peripheral line.
2. Ensure adequate facilities are available to institute recommended monitoring (see 2.10 to 2.12).
3. Dilute the prescribed dose in **sodium chloride 0.9%** to a final concentration of between 3mg/mL and 10mg/mL.
4. Flush with sodium chloride 0.9% prior to administration.
5. Ensure an appropriate in-line filter (0.2micron to 0.5micron) is *in situ*
6. Prior to administration, visually inspect the prepared solution for particulate matter – do not use if the solution is not clear, and free from haze or precipitation.
7. Infuse at the rate prescribed (see above - 2.7 Administration).
8. Flush with sodium chloride 0.9% after administration is complete.

2.8 Expiry

Prepared infusion: Must be prepared immediately and infused within two hours[7].

2.9 Adverse effects

The following adverse effects relate specifically to **acute** intravenous administration of the phenytoin, and the specific monitoring required.

Phenytoin has range of dose-related and idiosyncratic adverse effects.[5] This section is not intended to be exhaustive (other adverse effects are possible) and the reader is to refer to appropriate texts such as the AMH and/or Approved Product Information (available via eMIMs).

Common (>1%) adverse effects include hypotension, thrombophlebitis, local skin reactions such as necrosis, and "purple glove" syndrome (progressive distal limb oedema, discolouration and pain, which may progress to soft tissue necrosis and limb ischaemia)[1].

Rare (<0.1%) adverse effects include CNS depression, ventricular dysrhythmias.[1]

2.10 Monitoring requirements

Intravenous phenytoin has the potential to cause hypotension, cardiac arrhythmias, impaired cardiac conduction, cardiovascular collapse or central nervous system (CNS) depression.[6]

2.11 Clinical Monitoring – Maintenance Dosing

The monitoring practices for doses below 500mg vary significantly between institutions, and in many cases is opinion-based. In non-urgent situations where it is necessary to administer maintenance doses via the intravenous route (i.e. where a patient cannot take phenytoin orally), the dose is to be given at a rate **not exceeding 10mg/minute**. In these circumstances, **continuous** cardiac monitoring and blood pressure monitoring is not considered necessary.
The following monitoring is recommended:

- 12-lead ECG before the initial intravenous dose
- Blood pressure readings every 15 minutes
- Pulse readings every 15 minutes
- Observation for respiratory depression every 15 minutes.

These monitoring parameters are to be completed during administration and for one (1) hour after completion of the infusion.[8]

The Medical Officer is to be informed of any anomaly to enable further evaluation if necessary.

Patients with diabetes or clinically deemed to be at risk of hyperglycaemia are to receive monitoring of their blood glucose levels.

2.12 Clinical Monitoring – Loading Dosing

Administration of loading doses is to be only given in a setting with suitably qualified staff with the ability to implement **continuous cardiac monitoring and blood pressure monitoring**, along with **observation for respiratory depression** during administration.[3]

Blood pressure and pulse are to be monitored every 15 minutes for 1 hour after administration.[8]

Patients with diabetes or clinically deemed to be at risk of hyperglycaemia are to receive monitoring of their blood glucose levels.

2.13 Therapeutic Drug Monitoring

Phenytoin has complex pharmacokinetics which the prescriber is to be aware of. Key points include:

- Saturable hepatic metabolism, therefore a small change in dosage may result in a disproportionately large change in phenytoin concentration.[1]
- A high degree of protein binding (approximately 90 percent) may result in altered free phenytoin levels in patients whose protein-binding characteristics differ from normal (patients with hypoalbuminaemia, uraemia, acute trauma, and pregnancy) – this may necessitate the use of free-phenytoin assays (see 2.10 Monitoring Requirements below).[3]
- There is considerable inter-patient and intra-patient variability in phenytoin pharmacokinetics.[3]

Therapeutic serum concentrations are required to derive a suitable dosage regimen.

Serum level determinations are to be obtained at least seven to ten days after treatment initiation (unless a loading dose has been used), dosage change or addition/cessation of other potentially interacting drugs – this allows for steady state concentrations to be attained.[3]

Free phenytoin levels should be used in patients with hypoalbuminaemia or chronic renal failure (seek Specialist or Clinical Pharmacist advice if free phenytoin assay is unavailable; AMH and the Approved Product Information may also be reviewed) .[1, 3]

Trough levels provide information about the clinically effective serum level range and confirm patient compliance.[3]

Peak levels indicate an individual's threshold for emergence of dose-related side effects.[3]

Target (therapeutic) trough concentrations are[1]:

- Total phenytoin 10-20mg/L (40-80 micromol/L)
- Free phenytoin 1-2mg/L (4-8 micromol/L).

3. Roles and Responsibilities

Medical Officer

- Completing orders for the medication on the appropriate chart.
- Ensuring the appropriate venous access is inserted.
- Ensuring that the appropriate monitoring facilities are available in the ward/hospital in which intravenous phenytoin is being administered.
- Document any modification to observation parameters on the Adult Observation Response Chart (MR140A).
- Reviewing recorded observations regularly and alter treatment where required.
- Completing all treatment and duties within scope of practice.

Registered Nurse

- Recording observations as directed and notify the medical officer of any abnormal reading, as per the Adult Observation Response Chart (MR140A) and any charted modifications.
- All ECGs performed by the Registered Nurse must be sighted by the Medical Officer for interpretation. The Registered Nurse is to have advanced life support competency.
- Preparing the medication in readiness for treatment checking with another registered nurse, enrolled nurse or medical officer.
- Completing all nursing duties for the patient within scope of practice.

4. Records Management

Clinical: Health Record Management Policy

5. Evaluation

Clinical incidents relating to the dosing and administration of intravenous phenytoin are to be zero (0).

6. Standards

National Safety and Quality Health Service Standards (Second edition 2017) – 4.1, 4.15

7. References

1. AMH [database on the Internet]. Australian Medicines Handbook Pty. Ltd. 2017 [cited 9/2/2017]. Available from: http://www.amh.net.au.
2. W.J. Siebert, A.D. McGavigan. Requirement for cardiac telemetry during intravenous phenytoin infusion: guideline fact or guideline fiction? Internal Medicine Journal. 2013;43:7-17.
3. DBL Phenytoin Injection BP (Approved Product Information) [database on the Internet]. MIMS Australia. [cited 9/2/2017].
4. Y.C. Loke, editor. Pregnancy and Breastfeeding Medicines Guide. Parkville, Victoria, Australia: Royal Women's Hospital; 2010.
5. eTG [database on the Internet]. Therapeutic Guidelines Ltd. 2011 [cited 9/2/2017]. Available from: http://www.tg.org.au.
6. British National Formulary (BNF) [database on the Internet]. Medicines Complete. 2017 [cited 1/3/2017]. Available from: www.medicinescomplete.com [subscription required].
7. Phenytoin Sodium [monograph]. In: N. B, N. C, K. S, editors. Australian Injectable Drugs Handbook. 6th ed. Collingwood, Victoria, Australia: The Society of Hospital Pharmacists of Australia; 2014. p. 328-9.
8. Phenytoin: Drug Information [database on the Internet]. Lexicomp Inc. 2017 [cited 9/2/2017].

8. Related Forms

MR140A Adult Observation and Response Chart (A-ORC)

9. Related Policy Documents

WACHS High Risk Medications Procedure

10. Policy Framework

Clinical Governance, Safety and Quality Policy Framework

This document can be made available in alternative formats on request for a person with a disability

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Directorate:	Medical Services	**EDRMS Record #**	ED-CO-14-5171
Version:	3.00	**Date Published:**	24 January 2019