

Monitoring phenytoin serum concentrations

Phenytoin is a commonly used anticonvulsant but is one of the most difficult drugs to dose appropriately. It has a narrow therapeutic range and, because of saturable metabolism, small dose increases can result in disproportionately large increases in serum concentrations. It is therefore difficult to predict the best dose for a patient without monitoring serum concentrations.

Phenytoin pharmacokinetics

Phenytoin has an oral availability of >90% but is slowly absorbed, reaching peak concentrations 2-4 hours or longer after an oral dose. It is highly protein bound (~90%) and extensively metabolised by hepatic CYP2C9 and CYP2C19. Only about 5% of the dose is excreted unchanged in the urine.

The defining feature of phenytoin pharmacokinetics is saturable metabolism at therapeutic doses. This means that, strictly speaking, phenytoin does not have a half-life but an 'apparent half-life' which varies in relation to serum concentration. This is usually quoted as an 'average half-life' of 22 hours but can range from 6 hours, at very low concentrations, to 60 hours or more in overdose.

The therapeutic range

Serum phenytoin concentrations of 40-80 µmol/L are adequate to control the majority of seizures with a low risk of toxicity. Note that some patients achieve adequate seizure control with serum concentrations as low as 20 µmol/L while others tolerate concentrations as high as 100 µmol/L.

Indications for phenytoin concentration monitoring:

- To confirm toxicity.
- To assess compliance and therapeutic failure.
- To confirm appropriate dose adjustment.
- To confirm effects of drug interactions.

Dosage and serum concentration monitoring

Adult loading dose: 15-20mg/kg (total body weight).

Route	Rate	Monitoring	When to start the maintenance dose
IV	Max: 50mg/min (25mg/min in elderly or cardiac patients)	ECG, pulse, respiratory rate, BP	6-8 hours after the loading dose
Oral	Divide into three increments and give every 2 - 3 hours		24 hours after the loading dose

Serum concentrations can be measured 2 - 4 hours after an IV load or 24 hours after an oral load. Further monitoring will still be required after initiating a maintenance dose.

Adult maintenance dose: usually 4-6mg/kg.

Trough concentrations should be measured at least 5 days after initiating or adjusting a phenytoin dose. Note that steady state may take substantially longer (10 days or more in some cases).

Low concentrations

Re-loading:

When serum concentrations are low, and rapid seizure control is required, a "loading dose" can be given. The dose required to achieve therapeutic concentrations can be estimated using a proportion of the full loading dose (15mg/kg). For example, a dose of 10 mg/kg is expected to raise serum concentrations by ~ 40 µmol/L.

Maintenance dose adjustment:

Before increasing the maintenance dose consider non-compliance, drug interactions and whether the concentration was measured at steady state. Dose increases in patients not at steady-state can result in high concentrations that may not manifest for several weeks. Phenytoin doses should be increased cautiously in 30-100mg increments (30mg increments at the top end of therapeutic range).

Toxicity

Phenytoin toxicity is a clinical diagnosis supported by elevated serum concentrations. Note that toxicity can also manifest within the therapeutic range in some patients.

Symptoms of toxicity	Usual concentration
nystagmus	>80 µmol/L
slurred speech, ataxia, nausea, vomiting	>120 µmol/L
mental status changes, confusion, lethargy	>160 µmol/L
seizures	>200 µmol/L

Management of toxic concentrations:

- Withhold phenytoin.
- Measure phenytoin concentrations regularly (eg daily). Toxic concentrations often fall slowly initially and can take several days to reach the therapeutic range. Once in the therapeutic range concentrations can decline rapidly. Do not allow concentrations to fall precipitously as this can provoke seizures.
- Reinitiate phenytoin at an adjusted dose once the concentration approaches the top of the therapeutic range.

Free phenytoin concentrations and protein binding

About 90% of circulating phenytoin is bound to serum albumin. The remaining free (unbound) fraction is responsible for drug action and is directly available to the liver for metabolism. Standard serum assays measure total phenytoin, which includes both bound and free drug.

A common misconception is that when protein binding is reduced (eg from low albumin) free phenytoin concentrations will increase. This is not so. Free phenytoin concentrations remain relatively stable because excess free drug is metabolised by the liver. The net effect is a reduction of total phenytoin concentrations. Caution is therefore required in patients who have reduced albumin and low total phenytoin concentrations, as the free phenytoin concentration may actually be in the therapeutic range.

When to measure free phenytoin concentrations

- Patients with albumin less than 30g/L.
- Patients with impaired renal function.
- Patients on valproate.
- Elderly patients with albumin at the low end of normal.

Pharmacokinetic drug interactions with phenytoin

Phenytoin is a strong inducer of hepatic drug metabolising enzymes and may reduce serum concentrations of many hepatically cleared drugs (eg oral contraceptives, carbamazepine, dexamethasone).

In turn, other drugs can alter phenytoin serum concentrations by:

- induction of CYP2C9 or 2C19, resulting in ↓ phenytoin concentrations (eg rifampicin, phenobarbital)
- inhibition of CYP2C9 or 2C19, resulting in ↑ phenytoin concentrations (eg amiodarone, fluconazole)
- reduced intestinal absorption, resulting in ↓ phenytoin concentrations (eg antacids, calcium)
- displacement from protein binding sites along with inhibition of CYP2C9 or 2C19 (eg valproate). The net result is that total phenytoin concentrations may be reduced but free phenytoin concentrations may increase.