

RGH Pharmacy E-Bulletin

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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

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Therapeutic drug monitoring for phenytoin

The antiepileptic phenytoin requires therapeutic drug monitoring during its use to ensure adequate seizure control and to avoid toxicity. Phenytoin inhibits voltage and use dependent sodium channels and can be used for the management of partial and generalized epileptic seizures.

Phenytoin is metabolised by hepatic enzymes, but this metabolism is saturable. In fact, not only is the metabolism saturable, but there is large inter-patient variability as to when the saturation occurs. As such, small changes in phenytoin dose can result in disproportional changes in serum concentration. The half life of phenytoin can vary from 7-42 hours due to its variable metabolism, and steady state can take seven to twenty-eight days to achieve.

As well as being metabolised by hepatic enzymes, phenytoin also induces hepatic enzymes and many drug interactions occur with phenytoin due to this. This type of interaction occurs because the serum concentrations of other drugs are decreased during concurrent treatment with phenytoin: examples include decreased anticoagulant effect with warfarin, and possible failure of oral contraception. Phenytoin is also a highly protein bound drug, and competition for binding sites with other medications is another source of interaction.

The saturable metabolism of phenytoin, the effect of interacting drugs and inter-patient variability of phenytoin metabolism are all reasons why therapeutic drug monitoring of phenytoin is essential in order to achieve adequate seizure control and to limit toxicity.

The therapeutic range for total serum phenytoin concentration is usually quoted as 10 - 20mg/L (40 - 80µmol/L). However if the serum concentration of albumin is low, in the presence of chronic renal failure, or in situations where there is competition for protein binding sites from other medications; the free (unbound) serum phenytoin concentration better reflects therapeutic effects, and has a cited reference range of 1 - 2mg/L.

The dose of phenytoin in adults should be initiated at 4 – 5 mg/kg daily and the dose adjusted after approximately two weeks (according to response and the serum concentration). Due to the non-linear pharmacokinetics of phenytoin, dose adjustments should be made in a fashion that accommodates the serum concentration: if the concentration is less than 5 mg/L, the dose can be increased by 100 mg/day. If the concentration is above 5 mg/L the dose should only be increased by 30 mg/day. Re-measurement of the serum concentration will be needed to assess the effects of the dosage adjustment.

Preparations of phenytoin contain either phenytoin or phenytoin sodium (where 100mg phenytoin sodium is equivalent to 92mg phenytoin). Changing between preparations may warrant closer monitoring.

It is important to remember that clinical signs of toxicity may occur even if the serum concentration is below the upper limit of the quoted therapeutic range. Conversely, some patients may tolerate and require doses that result in serum concentrations higher than the upper end of the therapeutic range.

Common signs of phenytoin toxicity include nystagmus, ataxia and changes in mental state. Other side effects include decreased concentration, sedation, lethargy, visual disturbances, gingival hypertrophy and osteomalacia.

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FOR FURTHER INFORMATION – CONTACT THE PHARMACY DEPARTMENT ON 82751763 or email: chris.alderman@rgh.sa.gov.au
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