**Phenobarbital, Primidone and Other Barbiturates**

**Comment**

Adjunctive or first-line therapy for partial and generalized seizures (including myoclonus). Ineffective in absences. Phenobarbital is also used for status epilepticus and neonatal seizures. Highly effective antiepileptic drug, used as first-line therapy in many parts of the world because of broad-spectrum efficacy against many seizure types, feasibility of once-daily dosing and low cost. Because of its inferior tolerability to other drugs, particularly in children, it is rarely used as first line when cost is not the primary consideration. Potent enzyme inducers.

**FDA indications**

Phenobarbital: Epilepsy (adult and peds)

Primidone: Epilepsy, adjunct or monotherapy (adult and peds)

**Mechanism**

At high concentrations – as in status epilepticus – PB limits high-frequency repetitive firing of action potentials, possibly by interacting with Na and K transmembrane transport and conductance, and reduces cellular metabolism at the level of mitochondria or membrane ion gradients PB. PB decreases the Ca2+ influx in presynaptic nerve endings, which could decrease release of excitatory neurotransmitters - these effects on ion transport appear to be more related to its sedative and/or anaesthetic properties than to its anticonvulsant action.

At ‘therapeutic’ concentrations, PB produces modest changes in membrane conductance, but exerts its anticonvulsant action mainly by increasing postsynaptic GABAergic inhibition. GABA-A-R are composed of different subunits, that may be responsive to PB, or BDZ, or both. Phenobarbital increases the open gating duration of the Cl- channel, without affecting the opening frequency. In contrast, BDZ increase opening frequency without affecting open or burst duration.

Interestingly, BDZ do not directly activate channels but only modify the GABA binding affinity (so affecting receptors involved in active firing); PB can directly promote channel opening even in the absence of GABA (so affecting all receptors).

Pb worsens spike--wave discharges in animal models of absence seizures - and is clinically ineffective for absence epilepsy.

Although primidone itself has anticonvulsant activity, much of its effect can be ascribed to metabolically derived phenobarbital. The other metabolite, phenylethylmalonamide (PEMA) may or may not be anticonvulsant.

**Phenobarbital**

**Usual dose**

*Oral.* Initial: 30 or 50 mg/day in adults and 3 mg/kg in children. The dose can be titrated by 30- to 50-mg every 1 or 2 weeks, as tolerated. The usual maintenance dose is 90-120 mg/day; 3–8 mg/kg/day (children); 0.4 mg/kg/day (neonates).

*Intravenous (status epilepticus).* Adults: 10 mg/kg infused over 10 min or more (50-75 mg/min). Children and neonates 1520 mg/kg at a rate of 100 mg/min. These doses may be followed by a maintenance daily dose of 14 mg/kg (adults) or 3-4 mg/kg (children and neonates).

**Dose frequency**

1–2 times/day

**Serum levels**

10–40 mg/L. Although phenobarbital therapy can be adjusted solely on the basis of clinical response, measurement of serum drug concentrations may be useful.

Elimination of phenobarbital by all routes is slow and the average elimination half-life after single doses is between 70 and 130 h, the longest of the frequently used AEDs

**Primidone**

**Usual dose**

*Adults and children > 9 years.* Initial: 62.5 mg at bedtime, to be increased gradually. Maintenance: 500–1000 mg/day.

*Children < 9 years.* Initial: 50 mg at bedtime, to be increased gradually. Maintenance: 10–25 mg/kg/day

**Dose frequency**

2–3 times/day

**Serum levels, labs**

- 3-12 mg/L

- The target range for unchanged primidone has a merely indicative value. In most cases it is sufficient to monitor the serum concentration of metabolically derived phenobarbital

- CBC, C-12 every 6 months
Important interactions

Phenobarbital is an enzyme inducer and stimulates the metabolism of many other antiepileptic drugs and other drugs. Serum phenobarbital levels are increased by co-administration of valproic acid and some other drugs. Primidone is converted to phenobarbital and therefore interactions described with phenobarbital also apply to primidone. Enzyme-inducing drugs increase the phenobarbital–primidone ratio in serum.

Important side effects

Sedation, ataxia, dizziness, insomnia, hyperkinesis (children), mood changes (especially depression), aggressiveness, cognitive dysfunction, impotence, reduced libido, folate deficiency, vitamin K and vitamin D deficiency, osteomalacia, Dupuytren's contracture, frozen shoulder, rash.

Contraindications

- porphyria