Phenytoin, introduced in 1938, is the oldest anti-seizure drug on the market. It works primarily on the motor cortex where it increases the activity of sodium-potassium pumps in order to increase hyperpolarization and reduce excitability of neurons by slowing the recovery of voltage-gated sodium channels from the inactive state. It also reduces the conductance of calcium. Phenytoin is a weak acid with a $pK_a$ of 8.3 and is a member of the hydantoin family of antiseizure drugs; it is similar to barbiturates in structure. It is effective in tonic-clonic (grand mal) and partial seizures.

Phenytoin is available in numerous dosage forms. Oral forms include an immediate release capsule, a sustained-release capsule (Kapseal), a chewable tablet (Infatab), and an oral suspension. The Infatab and the oral suspension are available in the free-acid forms of the drug, whereas the capsule is only available in the salt form. The free acid contains about 8% more free drug, so care should be taken when switching between the chewable tablets and the capsules. Parenteral forms of phenytoin used to be available, but are now only available as generics, since fosphenytoin was introduced in 1996. Fosphenytoin is the phosphate ester prodrug of phenytoin. Fosphenytoin is converted to phenytoin in the plasma and has no activity prior to this conversion.

Dosages vary according to various methods of administration. For instance, extended release capsules are given as a 30mg or 100mg capsule three times a day not to exceed 300mg/d, whereas Infatabs are given as a 50mg tablet. The suspension form is given 5ml three times a day. IV Phenytoin is dosed at 15-20 mg/kg at a maximum of 50
mg/min. The fosphenytoin is dosed the same, but at a maximum infusion rate of 150 PE/min (Phenytoin Equivalents). On occasion, IM injections are given at 100-200 mg every 4 hours, however this for neural prophylaxis during neuromuscular surgery. The rectal mode of administration is a new, experimental method. It is given at 7 mg/kg rectally with IV solution and the patient must remain supine for at least 30 minutes.

Phenytoin forms precipitates very easily in vivo because of its low aqueous solubility. Consequently, IM administration is not recommended with phenytoin because the precipitates lead to erratic absorption. The phosphate ester of phenytoin (fosphenytoin) is more than 4400 times more soluble because of its increased polarity from hydrophilic interactions with the phosphate group. Fosphenytoin has a maximum solubility of 142mg/ml. Because part of fosphenytoin is cleaved, 75mg of fosphenytoin is bioequivalent to 50mg of phenytoin.

Peak level times vary according to the methods of administration. Infatabs and suspensions reach peak concentrations in approximately the same time: 1.5 to 3 hours. These two forms are approximately equal because Infatabs are chewable and are absorbed readily. Kapseals reach a peak concentration in 4-12 hours. In IV uses, peak concentrations occur at the end of infusion and vary according to the form, either phenytoin or fosphenytoin. Fosphenytoin has a delayed, lower peak concentration due to the time necessary to complete conversion to the active form. Conversion of fosphenytoin to phenytoin is rapid and complete; fosphenytoin has a half-life of approximately 15 minutes where it is converted to phenytoin by phosphatases.

Absorption of phenytoin via the oral route is slow, variable, and sometimes incomplete. This is due to its low aqueous solubility, even in the intestines where the pH
is basic and more ideal for weak acid absorption. Particle size and pharmaceutical additives affect both the rate and extent of absorption. The absorption rate is also dose dependant: a 200mg oral dose may reach a peak systemic concentration in 1-2 hours, whereas an 800mg dose may require up to 18 hours. Because of this dose-dependant relationship, oral-loading doses for treatment of status epilepticus should be administered in divided doses. Naturally, absorption is not an issue for fosphenytoin since all routes of administration are parenteral.

Bioavailability will be decreased in the presence of enteral nutritional products, but is usually about 90-100% bioavailable. Once absorbed, phenytoin is 88-93% protein bound, mostly to albumin. Fosphenytoin is about 95-99% protein bound. When given parenterally, similar concentration profiles for phenytoin and fosphenytoin can be achieved with a higher infusion rate for the fosphenytoin is employed. Maximum systemic concentrations for fosphenytoin will be slightly lower than for the phenytoin sodium when comparing equivalent doses.

Phenytoin is widely distributed throughout the body, including the CSF, saliva, semen, GI fluids, and bile. Concentration in the CSF is proportional to the blood serum concentrations: varying from approximately 90% to 120%. The peak volume of distribution is about 0.6L/kg. Fosphenytoin cannot access the CNS until its conversion to phenytoin. Phenytoin binds to the endoplasmic reticulum of the brain, liver, muscles and fat.

Degradation of phenytoin occurs in the endoplasmic reticulum of the liver, where it is parahydroxylated to an inactive metabolite conjugated with glucuronic acid to form a glucuronide. It is mostly secreted in the urine and less then 5% is excreted in the active
form. Mostly the metabolite enters the urine by active tubular secretion and not as a glomerular filtrate. Below the saturation concentration, first-order metabolism is followed. However, above the saturation concentration, metabolic degradation follows a slower, zero-order process, contributing to toxicity.

Half-lives also vary according to the dosage form. The half-life of the chewable Infatabs is approximately 14 hours with a range of 7 to 29 hours (because absorption and metabolism are both dose dependant). Sustained-release preparations have a half-life that averages 22 hours with a range of 7 to 42 hours. Steady state therapeutic concentrations are achieved at least 7 to 10 days after initiation of therapy with the recommended dose of 300mg/d (5-7 half-lives).

Because of the saturatable metabolic enzyme system in the liver, there is a non-linear relationship between dose and plasma serum level concentration. At therapeutic concentrations, this enzyme system is almost at saturation, thus in the therapeutic dosing range, small increases in dose lead to larger than anticipated changes in blood serum concentrations. A common clinical error is to increase dosage from the 300mg/d to 400mg/d. Toxicity quickly develops. Some of the most notable toxicities associated with phenytoin and fosphenytoin treatment are cardiac arrhythmias with or without hypotension and CNS depression. Furthermore, people with hepatic or renal disease and those displaying hypoalbuminemia or uremia are at risk to develop toxicities.
BIBLIOGRAPHY


