A. Phenytoin

I. Introduction

The synthesis of 5,5-diphenylhydantoin was reported by BILTZ in 1908. In 1937 PUTNAM and MERRITT reported that it elevated the threshold to electrically induced seizures in cats. In 1938 MERRITT and PUTNAM reported that it provided effective treatment for chronic seizures, without sedation, in patients with convulsive disorders. Since then phenytoin has been one of the mainstays of seizure therapy. In 1968 WALLIS et al. reported success in the treatment of status epilepticus with high doses of phenytoin given intravenously. A water-soluble prodrug was developed in the 1980s to simplify the parenteral administration of phenytoin (see Sect. B on fosphenytoin, below).

In the early 1950s, WOODBURY recognized the importance of Na⁺ gradients in the mechanism of action of phenytoin (WOODBURY 1955, 1980). Stereoselective arene oxidation was reported by BUTLER et al. in 1976 to be the initial step in phenytoin metabolism and this was elaborated on by McLANAHAN and MAGUIRE (1986). Of the cytochrome P450 isoenzymes, CYP2C9 has been identified as the major (VERONESE et al. 1991) and CYP2C19 as the minor (LEVY and BAJPAI 1995) one involved in phenytoin metabolism. SPIELBERG et al. (1981) and KIM and WELLS (1995) have shown that toxic effects with tissue damage may be produced by the arene oxide and free radical intermediates that occur during phenytoin metabolism.

II. Chemistry and Use

1. Chemistry

Phenytoin, 5,5-diphenylhydantoin, is a white crystalline material with a molecular weight of 252.3. A poorly water-soluble weak acid, it has a pKₐ value of 8.3. Its sodium salt has a molecular weight of 274.3, so that 100 mg of it is equivalent to 91.8 mg acid phenytoin on a molar basis. For parenteral use, the salt is dissolved in a mixture of propylene glycol, ethanol and water, and the pH is adjusted to 12.0 with sodium hydroxide. The conversion factor from mg/l to μmol/l is 3.96.
2. Indications and Use
Phenytoin is available for oral administration in the form of capsules (usually 100 or 30 mg of the sodium salt), tablets (usually 50 mg acid phenytoin) and suspension (6 or 25 mg/ml acid phenytoin). There are various absorption characteristics of the products from different manufacturers. The strength of the parenteral preparation is usually 50 mg of the sodium salt (46 mg acid phenytoin) per millilitre. Phenytoin is used to prevent generalized tonic-clonic seizures and partial seizures with or without generalization and is also beneficial in the treatment of tic douloureux. The recommended starting dose is 300 mg daily for adults and 5 mg/kg daily for children. The usually effective daily dosages are 300–500 mg in adults and 5–7 mg/kg in children. Increases of dose in the higher dosage range should be made in small instalments because of a non-linear response of plasma phenytoin levels to dose increases. Monitoring of plasma phenytoin levels is helpful in dosage regulation. In the treatment of status epilepticus 1000 mg (18 mg/kg) or more is given intravenously at a rate up to 50 mg/min, while monitoring the blood pressure, ECG, pulse and respiration. The administration rate may be reduced, if indicated. If a rapid effect is desired from oral phenytoin administration, 300 mg may be given every 4 h to a total of 1000–1200 mg.

III. Pharmacodynamics
Phenytoin has been classified as a type I anticonvulsant which modifies maximal electroshock seizures, blocks sustained repetitive firing and prevents tonic-clonic and some partial seizures but is ineffective against pentylenetetrazole-induced convulsions and does not modify GABAergic synaptic transmission or the T-type calcium currents in thalamic relay (pacemaker) nuclei (Macdonald 1989).

Of the numerous clinical effects of phenytoin, the most useful is its ability to attenuate or control chronic seizures at non-sedative drug concentrations, and to stop ongoing seizures at the high drug concentrations achieved by giving large doses of the drug rapidly. It has this effect mainly by preventing or reducing the propagation of seizure activity from its area of origin rather than by abolishing it in situ. Thus in a patient having partial clonic seizures, phenytoin given intravenously in 250 mg instalments up to a total of 1250 mg gradually decreased and then stopped the clonic movements of the arm while spike activity in the EEG continued unchanged (Wallis et al. 1968). In the laboratory, in cats rendered epileptic with intracortical penicillin deposits, repeated instalsments of phenytoin reduced and finally abolished clonic limb movements, but even very large amounts of phenytoin had little effect on cortical spike activity (Louis et al. 1964).

The best understood mechanism in the prevention of seizure spread by phenytoin is the drug’s ability to reduce post-tetanic potentiation (Esplin 1955; Raines and Standaert 1966). Post-tetanic potentiation is a physiologi-