The Antiepileptic Drug Diphenylhydantoin Affects the Structure of the Human Erythrocyte Membrane

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Phenytoin (diphenylhydantoin) is an antiepileptic agent effective against all types of partial and tonic-clonic seizures. Phenytoin limits the repetitive firing of action potentials evoked by a sustained depolarization of mouse spinal cord neurons maintained *in vitro*. This effect is mediated by a slowing of the rate of recovery of voltage activated Na^+ channels from inactivation. For this reasons it was thought of interest to study the binding affinities of phenytoin with cell membranes and their perturbing effects upon membrane structures. The effects of phenytoin on the human erythrocyte membrane and molecular models have been investigated in the present work. This report presents the following evidence that phenytoin interacts with cell membranes: a) X-ray diffraction and fluorescence spectroscopy of phospholipid bilayers showed that phenytoin perturbed a class of lipids found in the outer moiety of cell membranes; b) in isolated unsealed human erythrocyte membranes (IUM) the drug induced a disordering effect on the polar head groups and acyl chains of the erythrocyte membrane lipid bilayer; c) in scanning electron microscopy (SEM) studies on human erythrocytes the formation of echinocytes was observed, due to the insertion of phenytoin in the outer monolayer of the red cell membrane. This is the first time that an effect of phenytoin on the red cell shape is described. However, the effects of the drug were observed at concentrations higher than those currently found in plasma when phenytoin is therapeutically administered.

Key words: Phenytoin, Antiepileptic Drug, Erythrocyte Membrane