Population Pharmacokinetics of Phenytoin in Thai Epileptic Patients

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ABSTRACT

The study determined the population estimates for K_m and V_{max} of phenytoin in Thai patients. The serum phenytoin concentrations collected prospectively from outpatients who received phenytoin were analyzed to estimate population pharmacokinetic parameters. There were 197 steady-state concentrations and associated dosage rates (mg/day) from 167 outpatients. The data were analyzed using NONMEM, a computer program designed for population pharmacokinetic analysis that allows pooling of data from many individuals. The maximum elimination rate (V_{max}) was estimated to be 690 mg/d, based on the assumption that the bioavailability of orally-administered phenytoin was 100%. The Michaelis-Menten constant (K_m) value was 16.10 mg/L. The volume of distribution (Vd) was estimated to be 81.90 L. The interindividual variability of V_{max}, K_m, and Vd was estimated to be 87.46%, 0.15% and 23.96% respectively. The intraindividual (residual) random variability of serum phenytoin concentration was 27.55%. It appears as a linear function of weight on K_m (0.265*Wt). Vmax was significantly reduced in patients who consumed alcohol ($p<0.01$). Vmax of patients who did not consume alcohol was 649 mg/d (SD=135) while V_{max} of patients who consumed alcohol was 260 mg/d (SD=63.8). Km was significantly increased in patients who consumed alcohol ($p<0.01$). K_m of patients who did not consume alcohol was 16.1 mg/L (SD=3.49) whereas K_m of patients who consumed alcohol was 23.6 mg/L (SD=5.89). The population pharmacokinetic parameters of phenytoin for Thai epileptic patients were different and higher than the parameters obtained in previous studies. The population pharmacokinetic parameters of phenytoin will be useful for designing dosage regimens in Thai epileptic patients. The dosage regimens for patients who consume alcohol should be initiated at lower dose than the standard dose and gradually increased to the maintenance dose.

Key words: Population pharmacokinetics, Phenytoin, Michaelis-Menten, Thai, K_m, V_{max}

INTRODUCTION

Approximately 1% of the general Thai population has epilepsy. Thus it is estimated that there are more than 600,000 epileptic patients in Thailand (Chulalongkorn Comprehensive Epilepsy Program, 2001). Phenytoin is an anticonvulsant drug, frequently prescribed in adults and children. Present approved uses of phenytoin include: primary or secondary generalized tonic-clonic seizures, simple and complex partial seizures, mixed seizure types which include partial or generalized tonic-clonic seizures and tonic-clonic status epilepticus.

Dosage adjustment of phenytoin is complicated because of the nonlinear (Michaelis-Menten) pharmacokinetics exhibited by this drug (Thomson and Whiting, 1992). A small increase in dose can result in a disproportionate increase in serum phenytoin concentration