CHAPTER I
INTRODUCTION

Seizures and epilepsy are often seen in patients of all ages. Epidemiological studies indicated that they may affect children and adolescent more than any other age groups.(1,2,3) The goal of epilepsy therapy with antiepileptic drug is to achieve complete seizure control without adverse effects. The rational management is important to select an effective antiepileptic drug with minimal adverse reactions and cost. Determinative the optimal dosage or concentration; precise titration of dosage and ability to maintain effective concentrations under varying patient circumstance is a key principle of drug therapy. Knowledge of pharmacokinetics of each antiepileptic drug will lead to better antiepileptic drug concentration monitoring and will improve this outcome.

Valproic acid is an important drug for treatment of childhood epilepsy because of its broad therapeutic spectrum. It is effective for both generalized seizures and partial seizures, particular generalized tonic-clonic seizures, absence seizures, myoclonic seizures and generalized seizures more than one type.(4,5,6) Additional, It has the relative low incidence of adverse hyperactive behavior problems. The reported target concentration range of valproic acid is 50-100 mg/L for treatment of seizures.(7) The therapeutic range for valproic acid remains in completely defined. Optimal seizure control occurs when serum valproic acid concentration exceeds 40 to 50 mg/L.(5) However, the use of valproic acid in children is complicated by marked intra- and interpatient variations.(8,9) It's also different from that in adult. Clearance of valproic acid in children is approximate 50% greater than that in adult.(4,7) It is known that the alteration of hepatic function by age, body weight and other concomitant antiepileptic drugs affect clearance and volume of distribution of valproic acid. Valproic acid is a high protein binding drug. Elimination of valproic acid occurs primarily by hepatic metabolism and is classified as restrictive(5), which makes total clearance dependence on both free fraction

and intrinsic clearance. For drugs such as valproic acid, intrinsic clearance represents the maximum capacity of the liver to clear unbound drug; hence, either intrinsic clearance or valproate free fraction can alter steady state serum concentration-dose ratio. The estimation of either serum or plasma of non-protein-bound component of this drug, which is pharmacologically active and is the form that is cleared from the general circulation can be the useful information for the treatment of patients with epilepsy. Generally, only unbound drug is free to cross the blood brain barrier and correlates best with brain and spinal fluid concentrations. The previous study(10) found that the correlation between free plasma valproic acid and total CSF concentration was higher than that between total plasma valproic acid and total CSF concentration. Therapeutic drug monitoring service usually determines the total serum concentrations of antiepileptic drugs despite the fact that both therapeutic and toxic effects are related to their free drug concentrations. Some attempts have been made to measure the free serum concentration of an antiepileptic drug in patients receiving monotherapy, but the routine assaying of free concentration in patients would not be practicable due to both technical and financial reasons. To overcome the apparent shortcoming, methods for calculating free concentration from measure of the total concentration and albumin concentration in serum have been devised and have been shown to provide accurate prediction of the free level in patients receiving monotherapy. Although the serum albumin concentration in children reaches that of adult levels in first year of life, however, several studies have indicated that there are variations of these in children.(8) Therefore these variations may affect pharmacokinetic parameters and correlation between dose and total concentration. Estimating pharmacokinetic parameters from unbound concentration may be more accurate than from total concentration. The ability to measure the serum concentrations of antiepileptic drugs, and the widespread use of this procedure has markedly improved the treatment given to patients with epilepsy during the past decade.

The number of samples necessary to adequately describe a patient's pharmacokinetic parameters to guide therapy varies. The number of samples can be range from as few as two to a "panel" of drug concentration measurements. Use of the panel (ie, three or more drug concentration measurements (DCMs) reduces the effect of assay and collection errors on pharmacokinetic parameters estimation. Conversely, the price of monitoring increases with each additional DCMs. In this study we tried to predict valproic acid pharmacokinetic parameter from two DCMs since they were reasonable for monitoring in clinical setting including their usefulness and economic point of view. (7,11)

Previous studies have reported pharmacokinetic parameters in adults, which were calculated from total drug concentration. In children, pharmacokinetic studies mostly involved only small numbers of patients and measured only total serum concentrations. The objectives of this study are as follow: 1) to determine the pharmacokinetic parameters of valproic acid from total and unbound concentrations and 2) compare pharmacokinetic parameters and define the relative of patient characteristics on pharmacokinetic parameters.