Chapter I

Introduction

Background and Rationale

Lithium was discovered in 1817 and first used medically to treat gout in 1858. (Ward, Musa and Bailey, 1994) It was first reported beneficial in psychiatric patients in 1949 (Carson, 1992 ; Ward , Musa and Bailey, 1994) . Although lithium has been used in a variety of psychiatric and medical illness , for example, schizophrenia, depression, aggression, prophylaxis of unipolar disorder, prophylaxis of schizo-affective disorder, the drug of choice of lithium is the treatment of acute manic episodes and prophylaxis of bipolar disorder (Carson, 1992 ; Peet and Pratt, 1993 ; Ward et al., 1994 ; Vertrees and Ereshefsky , 1995) .

Lithium is one of the mood stabilizers (Fast and Preskorn, 1993 ; Laraia and Stuart, 1995). Pharmacological effects of lithium can not be explained by precise mechanism. Some hypotheses were explained by simple theories of partial substitution of various cations (Na+,K+,Mg+,Ca++) and this inhibits the second-messenger systems of cAMP, cGMP and phosphatidylinositol , as well as increase the turn over rate of neurotransmitters , for example, norepinephrine and serotonin (Carson, 1992; Ward et al., 1994; Vertrees and Ereshefsky, 1995) .

Dosage forms of lithium available in the present are rapid release tablet / capsule , liquid and sustained release tablet / capsule in mostly lithium carbonate salt. Pharmacological effects of lithium fundamentally

depend on the lithium itself , so the effects of the different salts are similar (Carson, 1992). After absorption , lithium is widely distributed throughout the body. Tissues in which lithium is found include brain, liver, spleen, kidney, thyroid gland, saliva, blood, muscle, bone, and RBC (Amdisen, 1986 ; Ward et al., 1994 ; Vertrees and Ereshefsky, 1995). Therefore adverse effects of lithium could occur in various organs of the patients . Adverse effects of lithium are related with the blood lithium concentrations (Amdisen, 1986 ; Vertrees and Ereshefsky, 1995) , however many adverse effects of lithium occur even at therapeutic levels (Salem, 1983). In clinical practice , lithium level monitoring is primarily based on serum or plasma concentrations , due to the convenient and the sufficient correlation between lithium concentration and clinical responses (Carson, 1992; Ward et al., 1994; Vertrees and Ereshefsky, 1995) .

The dosage required to achieve therapeutic serum concentration shows wide interindividual variation . Additionally, lithium has quite a narrow therapeutic index . The dose which achieves therapeutic benefit is almost the same as that causing the toxic effect. Signs and symptoms of lithium toxicity are vomiting, diarrhea, coarse hand tremor, slurred speech, unconscious, epileptiform seizures, polyuria, and coma (Peet and Pratt ,1993). The toxic effects can be severe or lethal. So the prescribing of lithium should be seriously concentrated. The blood lithium concentrations must be within the optimum therapeutic range and the adverse effects should be reduced or supposed to be none.

There are significant differences in pharmacokinetic properties between species and significant variations between individuals of the same species (Amdisen and Carson, 1986). In humans, both the interindividual and intraindividual variation in serum concentrations are broad compared to the narrow therapeutic index. Consequently, the daily dose needed by one patient may not be the same for another patient, or for the same patient at another time. The best known and probably most important causes of these variations are the wide ranges in the normal renal excretion rate and apparent distribution volume. Furthermore, during the lithium treatment there may be some factor affecting lithium's pharmacokinetic properties that cause changes in lithium excretion. Circumstances which affect to lithium excretion include disease status, diets, and drug interactions (Peet and Pratt ,1993). Monitoring lithium therapy is therefore important especially in those patients with several interacting factors.

The most common reasons for monitoring lithium concentration are to ensure that concentration are initially within the currently accepted therapeutic range and then to monitor ongoing therapy, assessment of toxicity, efficacy, and compliance. Since plasma concentration determinations are essential owing to lithium's narrow therapeutic index, empirical dosing is not recommended (Vertrees and Ereshefsky ,1995).

Since lithium therapeutic monitoring was reported to be advantage for the patients, but there were very few studies in Thai patients. This study is therefore designed to gain some information about the pharmacokinetic parameters of lithium in Thai patients. Lithium blood concentrations will be

measured in patients with various psychiatric disorders at Srithunya Hospital along with close monitoring on their good clinical responses throughout the treatment with lithium. Observation on the efficacy, the possibility of undertreatment, overdosage and lithium toxicity are concomitantly detected. When the lithium levels are not within the therapeutic range and the desired clinical responses are not achieved, calculation to adjust for a more appropriate dosage regimen will be initiated and the physicians will be informed and consulted. The monitoring of the results of the treatment along with the clinical status of the patients are aimed to achieve the excellent point, i.e. efficacy and safety for each individual patients.

General objective

1. To use pharmacokinetic theories to adjust for a more appropriate dosage regimens of lithium for individual patients whose blood lithium concentrations are not in the therapeutic range accompany with ineffective clinical responses and/or adverse effects or toxicities.

2. To evaluate whether or not the present dosage regimen of lithium which the physicians usually prescribe for the patients will result in blood lithium concentration which is within the therapeutic range.

Specific objective

1. To compare the measured blood lithium concentrations with the calculated levels obtained from predicted pharmacokinetic parameters of the patients through his/her serum creatinine.

2. To study the relationship between the blood lithium concentration and the clinical responses (efficacy and adverse effects or toxicities) of the patients during the treatment of psychiatric disorders with lithium.

The Significance of the Study

1. This study will make the treatment of psychiatric disorders with lithium more efficiency and less toxic/adverse effects by close monitoring and adjusting dosage regimens of lithium using pharmacokinetic parameters.

2. This study will give the information about the relationship between the lithium concentration and the clinical responses both in efficacy and adverse effects or toxicities in Thai patients.

3. This study will provide the information about the appropriate dosage of lithium in the treatment of psychiatric disorders in Thai patients.

4. This study will give the information about the different of blood lithium concentrations obtained from measured values and calculated values (predicted values) using patients' pharmacokinetic parameters.

5. This study should initiate the method of lithium therapeutic level monitoring in hospital in the future.