Chapter III

Material and Methods

Materials

1. Reagents

    1.1 Lithium slope standard solution cat no. 473606

    1.2 Lithium electrode fill solution cat no. 473614

    1.3 Reference electrode fill solution cat no. 478882

    1.4 Calibrants and reagents pack and Deproteinizer / Conditioner pack cat no. 473605

2. Apparatus

    2.1 654 Na+/K+/Li+ Analyzer (Ciba Corning Diagnostic,Ltd.)

Methods

1. Subjects

The subjects studied were Thai inpatients with various kinds of psychiatric disorders at Srithunya Hospital. All patients in this study were not in critically ill. Patients were pleased to involve in this study. All patients were treated with lithium with or without other psychotropic drugs to control their present illness according to the traditional physician prescribing practices.

All of the available patient data related to the study were recorded; including age , sex , weight , height , medical history, psychiatric

diagnosis, drug administered, dosage regimens, serum creatinine and other clinical and laboratory data.

2. Dosage Regimen and Administration

Patients were treated with lithium as lithium carbonate along with other psychotropic drugs such as antipsychotics , antidepressant drugs , anti-anxiety agents. The drug was prescribed by physician at the usual dosage regimen as those in general practice at Srithunya Hospital and was recorded for individual patients. Dosage regimen of lithium carbonate is commonly divided into two or more doses a day by oral administration and the pharmacological responses were carefully monitored before any blood sample were collected.

3. Sample Collection

The serum lithium concentration was considered to achieve steady state after the given fixed dosage regimens of the drug were given to the patients for at least seven days. The blood sample was drawn from patients at the appropriate time in the morning before the first lithium dose in the morning and twelve hours ($\pm$30 mins) after the evening dose. If the patients developed signs and symptom of intoxication, concentration was urgently checked.

All the blood samples were analyzed as undiluted whole blood immediately and definitely within two hours of collection. Whole blood was kept at room temperature only.

4. Analytical Method

Lithium concentration was measured by ion selective electrode (ISE) technique using the 654 Na+/K+/Li+ Analyzer of Ciba Corning Diagnostic Ltd.This analyzer measures the lithium ion concentration similar to the way a pH electrode measures hydrogen ions.

5. Monitoring

5.1 Lithium Concentration Evaluation

Therapeutic range of lithium concentration from population data in this study is 0.5 - 1.2 mEq/L.

5.2 Evaluate the clinical response of the patients both in term of efficacy and adverse effects of lithium. The disappearance of target symptoms such as hyperactivity (sleep disturbance, agitation, destructiveness, anxiety) is a sensitive and highly reliable indicator of effectiveness.

If adverse effects tend to generate to intoxication or one or more signs of intoxication (coarse hand tremor, vomiting, diarrhea, dysarthria, hyperreflexia, oliguria, impaired consciousness, seizures and coma) occurred , the lithium concentration had to be checked urgently.

5.3 Adjusting Lithium Dosage Regimen by Pharmacokinetic Method.

If lithium concentrations were not within therapeutic range and the clinical responses were not satisfactory, the new lithium dosage regimen was calculated by the pharmacokinetic equations (Equation 7 in Appendix A) and the dosing interval was rounded up and adjusted to a figures convenient for dosage administration. (Equation 8 in Appendix A).

After the new dosage regimen was calculated, the physician was then informed.

5.4 New Dosage Administration

The new dosage regimen was then administered to the patients whose lithium level were not within therapeutic range along with unsatisfactory clinical response. After the patients were on a new fixed dosage regimen (as described in 5.3) of lithium for at least seven days, blood sample was again drawn at 12 hours after the last dose and the lithium concentration was analyzed by Ion Selective Electrode Technique (654 Na+ /K+ /Li+ Analyzer).

5.5 If lithium concentration in 5.4 was not within therapeutic range, the process in 5.3 and 5.4 were repeated until the desired therapeutic range and good clinical responses were achieved.

6. Data Analysis

6.1 General Evaluation

General characteristics of the patients included in this study were evaluated according to their age, sex, weight and height.

Percentage of patients taking various dosage regimens of lithium carbonate were determined.

6.2 Evaluation the measured lithium concentrations of the patients.

Lithium concentration was evaluated whether it was within therapeutic range,subtherapeutic range or overtherapeutic range.

Percentage of patients whose lithium concentration was within each range were determined.

6.3 Observation for any relationship between the lithium levels and the clinical response (efficacy and adverse effects or toxicities).

6.4 Blood lithium level of the patient taking different dosage regimens of lithium carbonate was observed and compared the effects of age and weight within the same dosage regimens.

6.5 Comparison between the predicted and measured blood lithium levels.

The predicted lithium concentrations were calculated from the available patients data such as age, sex, body weight, height, serum creatinine , using equation 1 - 9 in Appendix A. The predicted values were compared with the measured values using student paired t-test. After lithium concentration was evaluated, the pharmacokinetic parameters such as lithium clearance and half-life could be obtained from this measured lithium concentration. The pharmacokinetic parameters obtained from measured lithium concentration and those calculated from patients' general data including their serum creatinine were compared using student paired t-test.

6.6 Comparison between lithium clearances calculated from serum creatinine and those calculated from the measured lithium concentrations using student paired t-test.

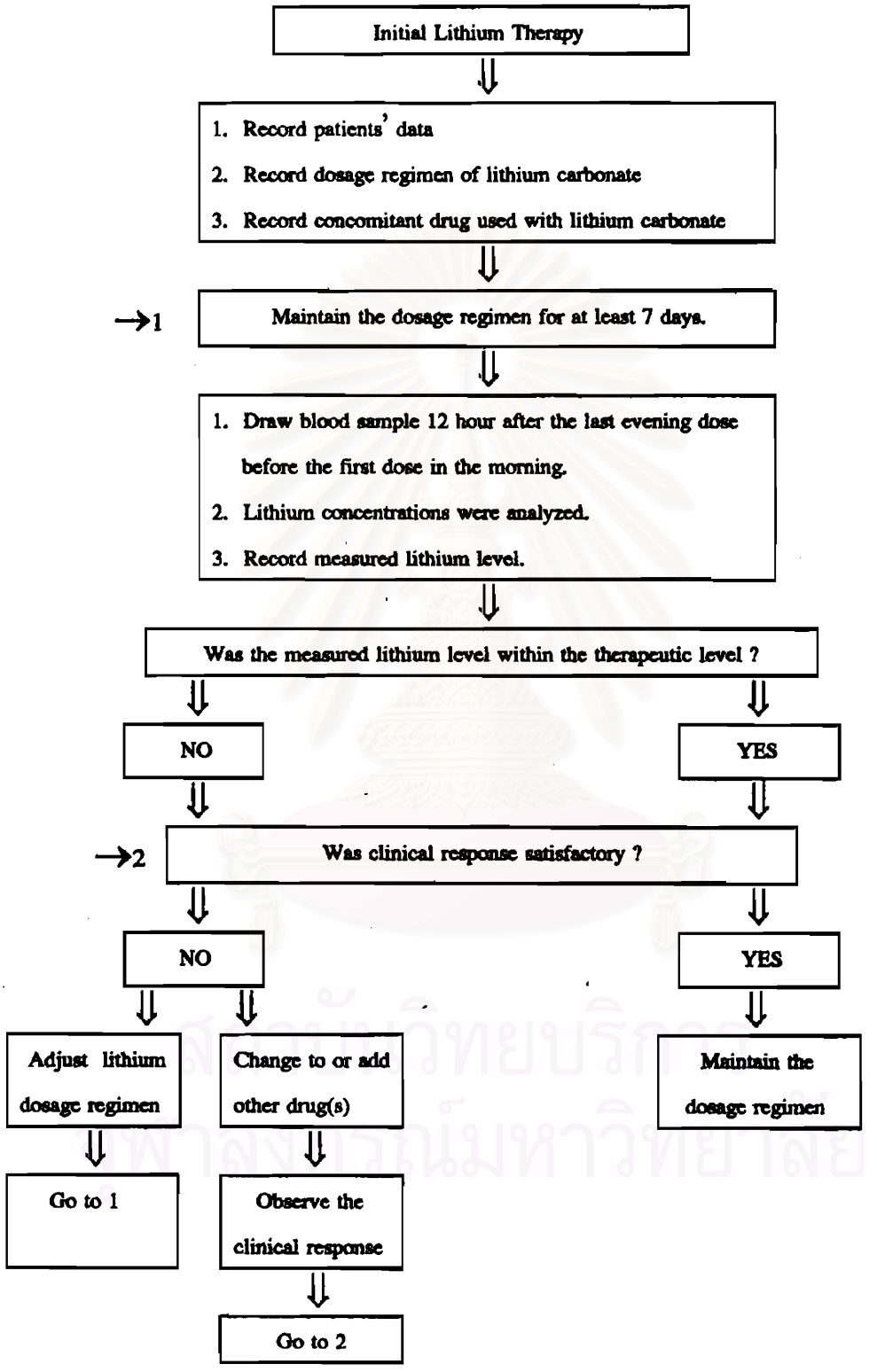

FIGURE II THE FLOW PROCESS OF THE STUDY.