CHAPTER I

INTRODUCTION

Background and Rationale

Although Withering (1785) reported effects of his digitalis preparation on such clinically important body functions as disappearance of dropsy, character and frequency of the pulse, nausea, vomiting, and diarrhea, few studies on pharmacokinetics (pharmaco-drugs, kinetics-movement) became available until the last half of the 20th century. Garrett (1970) defined pharmacokinetics as the study of the time courses of absorption, distribution, metabolism, and excretion of drugs in the intact total organism. This means that the drug should be measured in available compartments of the body, such as blood, tissues, and excreta, to gain an idea of these as functions of time and dosage.

Digitalis pharmacokinetic has become the key to clinical use of the drugs during the past three decades. Drug movement and disposition is the answer to a better understanding of the clinical effect on the patient. (Doherty et al., 1978)

Digoxin is by far the most commonly prescribed cardiac glycoside. Other glycosides have little or no advantage over digoxin, and such advantage as they may have is offset by the benefit of general familiarity with the one drug. Such benefit is of extreme importance in drugs (such as the cardiac glycosides) which have a high potential for toxic effects, and a relatively low therapeutic ratio. In recent years a beneficial impact on mortality in congestive heart failure has been demonstrated to result from the addition of various types of vasodilating agents to digoxin therapy. (Cohn et al., 1986; CONSENSUS Trial, 1987) Angiotensin converting enzyme inhibitors (ACEIs) would be expected to have all the advantageous properties of conventional vasodilators in severe heart failure and also to have substantial additional benefits, including the correction of hypokalemia, which might ameliorate the toxic effects of digoxin excess. Logically, digoxin decreases heart size and rate, whereas ACEIs decrease the load, so that the combination should be better than either agent alone. (Opie et al., 1991; Packer et al., 1993)

Angiotensin Converting enzyme inhibitors are now being prescribed frequently in patients with heart failure. While ACEI increases renal blood flow in patients with congestive heart failure by preventing angiotensin II mediated renal artery constriction, it reduces glomerular filtration rate (Cleland, Dargie, Hodsman, Ball et al., 1984; Mujais et al., 1984)

Since digoxin is largely excreted by the kidney unchanged, glomerular filtration rate is important in regulating the serum level of digoxin. Several studies investigated pharmacokinetic interactions between different ACEIs and digoxin.(Cleland et al.,1986; Douste-Blazy et al.,1986; Johnson et al.,1991; Miyakawa, Kobayashi, and Shionoiri,1987; Morris et al.,1985) However, none of the pharmacokinetic parameters data of Thai patients has been established.

This study was designed to establish some pharmacokinetic parameters for Thai patients with heart failure, to evaluate some pharmacokinetic equations and parameters from literature used to calculate drug levels (predicted values), to compare the calculated drug levels with the measured drug levels in blood (measured values), and to assess the effect of oral doses of FDA approved ACEIs "captopril" and "enalapril" on steady state digoxin kinetics.

Objectives

1. To generate some pharmacokinetic parameters of digoxin for Thai patients with heart failure who received digoxin with or without captopril or enalapril.

2. To compare the digoxin pharmacokinetic parameters among the groups of patients who received digoxin with and without captopril or enalapril.

3. To compare the serum digoxin concentrations obtained from the patients (measured values) with the calculated concentrations (predicted values).

4. To create an appropriate equation for calculating digoxin clearance from the patients' creatinine clearance.

The Significance of the study

1. This study will provide some pharmacokinetic parameters for Thai patients which may be used to create equation for proper estimation of the appropriate digoxin dosage regimens for each individual patients either manually or when computer program is applied.

2. This study will provide some information about the effect of oral doses of captopril and enalapril on steady-state digoxin kinetics in Thai patients.

3. This study will enable to determine whether the pharmacokinetic parameters and equations that are widely used in foreign countries can be used to predict digoxin levels accurately. If so, this method shall be recommended for calculating dosage regimens of digoxin for Thai patients.

4. This study will provide an equation which may be used to estimate digoxin clearance from the patient's creatinine clearance.

5. This study should be provide some information about an initiation of the possible method for therapeutic digoxin level monitoring in Thai patients.