A Study On Serum Digoxin Level : Analytical Evaluation And Clinical Implications In A Sample Of Egyptian Patients On Digoxin Therapy

Thesis Submitted For Partial Fulfilment

Of The Degree Of Doctor Of Medicine

By

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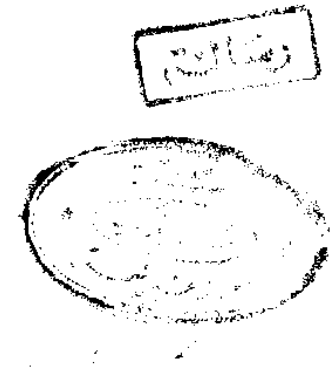

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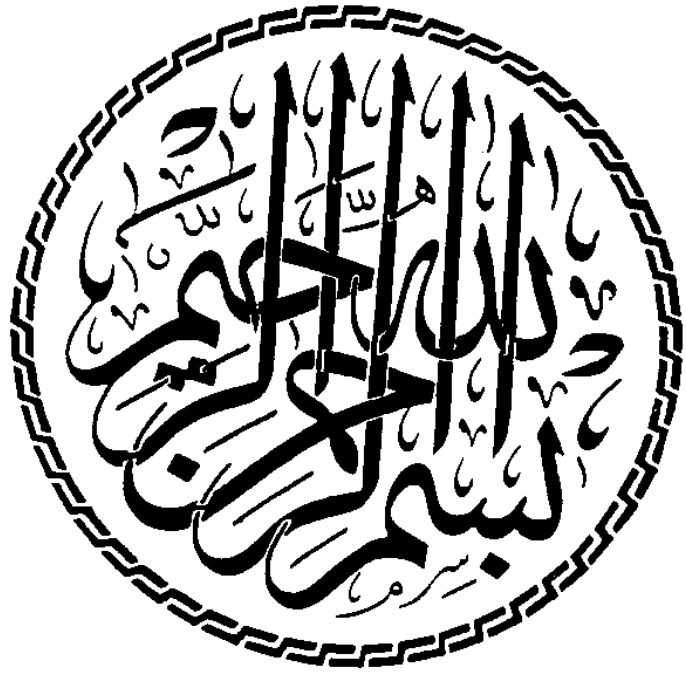

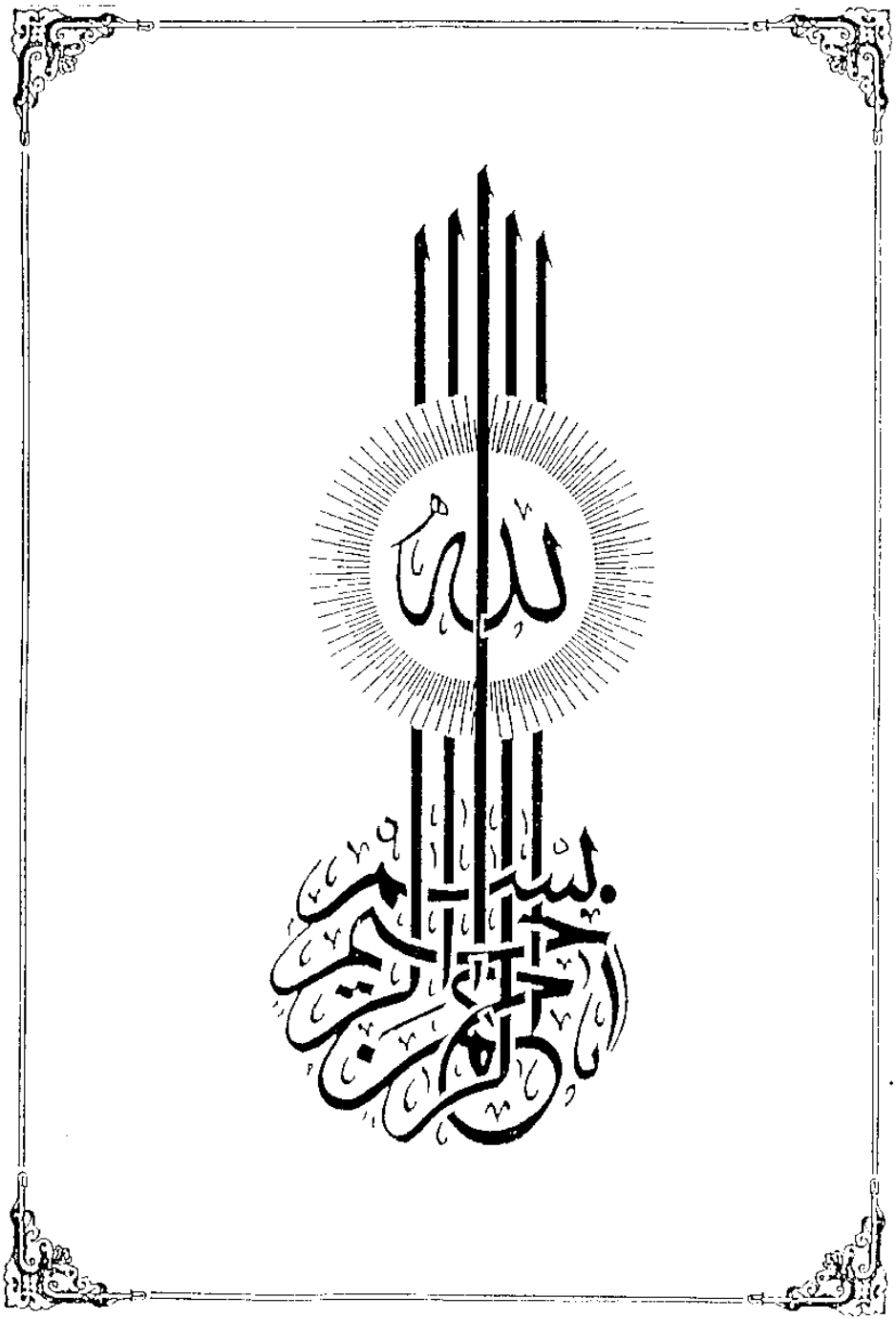

Dedicated to :

My Parents

Husband

& Children

For Their

Endurance , Sacrifice , Support

&

Love.

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Figures in the Review of Literature are adopted from Applied Therapeutic Drug Monitoring. Volume I : Fundamentals [Eds.] Moyer T.P. and Boeckxrl. The American Association for Clinical Chemistry. Library of Congress. Washington D.C. [1982].

INTRODUCTION
AND
AIM OF WORK

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INTRODUCTION

Digoxin, a cardiac glycoside, is one of the most widely used drugs all over the world. Due to its low toxic/therapeutic ratio, digoxin intoxication persists as one of the most prevalent adverse drug reactions encountered in clinical practice. It has in fact plagued the medical profession for over 200 years. The estimated prevalence of digitalis toxicity among hospitalized patients in the 1970's ranged from 15-30% with significant morbidity and mortality [George, 1983].. At present, the incidence has dropped to lower values but is still alarming [Smith et al., 1988].

The dilemma of the diagnosis of digoxin toxicity and judging the proper therapeutic dosage is faced by many clinicians. It can only be resolved through the increased understanding of the basic clinical pharmacology of cardiac glycosides, and the continuing advances in the field of analytical techniques, both of which form the basis for ***digoxin therapeutic drug monitoring.***

AIM OF THE WORK

The aim of this work included :

1- The analytical evaluation of 3 methods for digoxin assay namely radioimmunoassay [RIA], enzyme-linked immunosorbent assay [ELISA], and enzyme multiplied immunoassay technique [EMIT].

2- A study of digoxin-like immunoreactive substances [DLIS] in uremic patients.

3- Determination of the therapeutic range of serum digoxin for each kit both in patients with normal renal function and in patients with renal impairment.

4- Evaluation of the diagnostic value of serum digoxin concentration measurements in suspected digoxin toxicity.

5- Estimation of the pharmacokinetic parameters of digoxin in a sample of Egyptian cardiac patients on digoxin therapy with normal hepatic and renal functions.

6- Designation of the recommended dosage regimen in cardiac patients with normal hepatic and renal functions.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

CHAPTER I

THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring [TDM] is the timely measurement of drug concentration in blood and other body fluids and the subsequent evaluation and interpretation of these results. This provides the basis for rational adjustment of drug dosage and scheduling for the benefit of patient management [Marks, 1985].

A. *HISTORICAL BACKGROUND*

For hundreds of years, appropriate dosage regimen had been established in individual patients by *trial* and *error*. This trial and error therapy placed both the patient and his physician at the mercy of unknown factor - the kinetics of the drug in that

patient - which resulted in great variations in the therapeutic response [Pippenger, 1982].

The therapeutic regimen depending on the administration of the *"usual dose"* is also hazardous. The usual dose of most potent drugs may have little effect in some persons, causes serious toxicity in others, and is fully satisfactory in few. Many patients require drug doses higher than the standard dosage schedules to obtain a sufficiently intense pharmacologic effect. On the other hand, other patients develop adverse reactions to drug therapy because the dose is too high for them. The habitual administration of the conventional dose can be satisfactory only when a drug's therapeutic margin is very large, and when its full therapeutic potential is not required [Koch-Weser et al., 1969].

Therapy with potent drugs, becomes safer and more effective when dosage is adjusted to the need and tolerance of each patient [Koch-Weser, 1972]. Consequently, attempts were made to tailor the dosage of drugs to suit individual patients by monitoring their *"pharmacologic effects"* and increasing or decreasing the dose accordingly. For example, digoxin was "individualized" by counting the pulse rate and / or inquiring about the presence and severity of undesirable side effects. The dose of salicylates was increased in treatment of rheumatic fever until dose dependent side effects ; notably tinnitus ; appeared and then slightly decreased in order to produce maximum therapeutic benefit with minimum or zero toxicity. However, it was appreciated that this method of adjusting dosage was not applicable to all or even to