Cardiotoxic Effects of Tricyclic Antidepressant Drugs versus Digitalis preparation

Thesis
Submitted for partial fulfillment of Master Degree in
Clinical Toxicology

By

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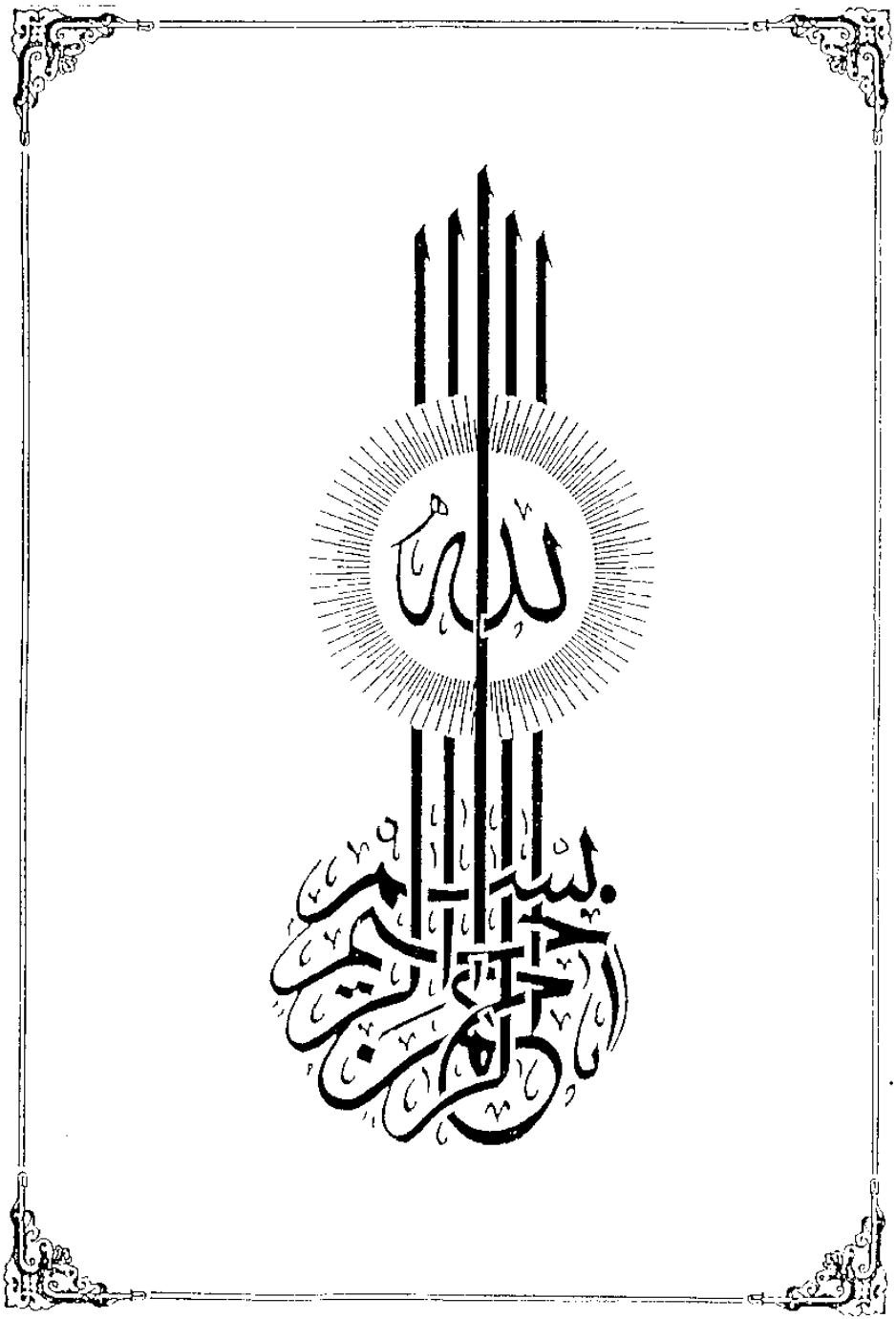

الآثار السمية على القلب بالأدوية ثلاثية الحلقة المضادة للاكتئاب بالمقارنة بمركبات الريجوكسين

رسالة مقدمة من

الطبيب / فايز عبد السلام أبو بكر

توطئة للحصول على درجة الماجستير فى السموم الاكلينيكية

تحت اشراف

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INTRODUCTION

Every medication is potentially hazardous. Drug therapy can create serious problems including permanent injury death (ranging from morbidity up to mortality). Moreover, physician does not fully evaluate the possibility of "abuse" before prescribing medication. This is of particular importance in tricyclic antidepressant group of drugs because of their wide availability and generous use in prescription in our community.

It was found that the incidence of poisoning by tricyclic antidepressant is increasing, probably because of their wide spread use in the treatment of depression in adults and enuresis in children (Dawling, et al., 1989).

By the early 1960s, central nervous system and cardiovascular toxicity were recognized as major complications of tricyclic overdose and fatalities were recorded in both children and adults (Lee, 1961 , Silverman, 1993).

Tricyclic antidepressants are among the most common agent involved in drug overdose and drug-related death in the United States. One -fourth of overdose-related hospitalization involve a tricyclic agents (Silverman, 1993).

Digitalis preparations are also widely spread drugs among physicians prescribed for treatment of heart failure as well as other medical conditions. Digitalis has been described as

having the smallest therapeutic/toxic range of any commonly used drugs as there is a very small margin between therapeutic and toxic doses (Eagle and Harber, 1989).

A report from National Center for health in the United States 1977 showed that, up to 15 per cent of all medical admission were taking digitalis, and 20 to 30 per cent of these patients showed signs of toxicity varied from 3 to 25 per cent and was especially common in the elderly . But, the development of an exciting antidote to this poisoning and good supporting care has meaningfully improved the prognosis of the digitalis - toxic patients (Silverman, 1993).

The toxic effects of these drugs (TCAs-digitalis) continue to cause the main concern in the poisoned patients and also in therapeutic doses (Blackwell et al, 1978 , Vicellio, 1993).

Aim of the work

The present work includes review of tricyclic antidepressant and digitalis compound with special emphasis on cardiotoxicity of these representative drugs.

PART I

TRICYCLIC ANTIDEPRESSANTS

Historical Review

The tricyclic antidepressant compounds are group of three ringed drugs that structurally and pharmacologically resemble phenothiazines. Psychotropic compounds were synthesized in Europe in the late nineteenth century as a part of the development of aniline dyes such as methylene blue. Ehrlich, 1890 even suggested that methylene blue might be used to treat psychoses.

In 1948, imipramine was the first tricyclic compound synthesized and was originally intended as a hypnotic effect because of its sedative properties. Kuhn suggested the use of imipramine for endogenous depression in 1958 (Kuhn, 1959). Imipramine became a popular substitute for electroshock therapy in severe-depression. Amitriptyline, introduced subsequently, was equally efficacious but more sedating.

By the early 1960s, central nervous system and cardiovascular toxicity were recognized as major complications of tricyclic overdose and fatalities were recorded in both children and adults (Noack, 1960 ; Lee, 1961).

Early reviews of hospitalized overdose cases revealed mortality rate of 15%. (Steel , et al 1967). Improvement in supportive and intensive care have reduced the overall mortality since 1977 (Callaham, and Kassel, 1991).

Since, 1980, "second generation" antidepressant or newer anti depressive agent were introduced into clinical practice. They include amoxapine , maprotiline, trazodone and fluoxetine with similar therapeutic efficacy to the standard TCAs (Silverman,1993).

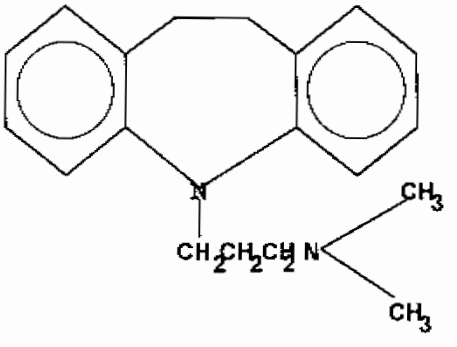
CHEMISTRY
and
STRUCTURE-ACTIVITY RELATIONSHIP
of
Tricyclic Antidepressants

This group includes :

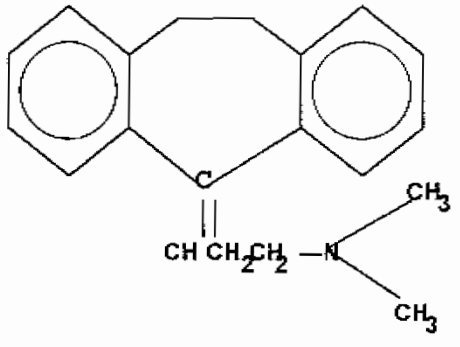
(a) Tertiary amine drugs as : Imipramine (Tofranil) and Amitriptyline (Tryptizol).

(b) Secondary amine drugs as: Desipramine (Norpramin) and Nortriptyline (Aventyl).

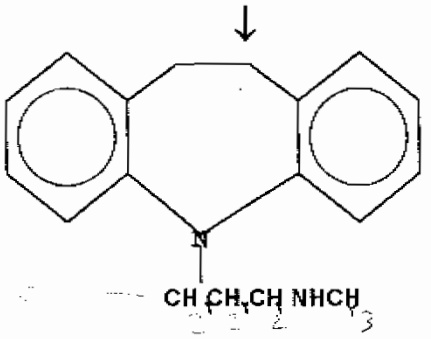
They have a 6-7-6 ring structure of the molecule imipramine. The prototype of all tricyclic is dibenzebine derivative. The next drug with the same general properties and antidepressant activity to be introduced was amitriptyline, dibenzocycloheptane which is chemically related to the thioxanthine neuroleptics. Amitriptyline can be produced by replacing the ring nitrogen with carbon atom (Usdin, 1978).



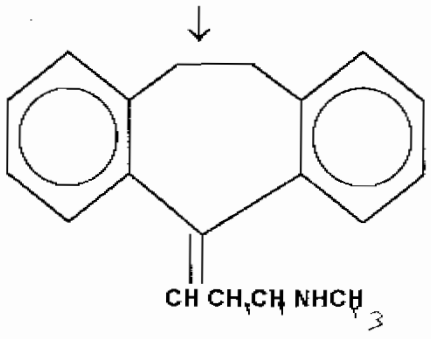
Imipramine



Amitriptyline



Desipramine



Nortriptyline

Fig (1) (Usdin, 1978)

Elimination of one of the N-methyl groups on the terminal group of imipramine has produced desipramine. It was found that secondary amine has similar activity to that of imipramine as an antidepressant, although there are some pharmacological dissimilarities. It is now certain that desipramine is no more effective or rapidly acting than imipramine. The same generalization can be made from the comparison between amitriptyline and nortriptyline (Usdin, 1978).

Most of the tricyclic antidepressants have a 2-carbon chain and still retain significant antidepressant properties. The potency of the drug increases with the degree of angular arrangement of the phenyl ring in its molecule . The degree of substitution on the terminal amino group affect the activity of the compound on the re-uptake systems, so the secondary amines tend to the more potent inhibitors than the tertiary amines (Petracek et al., 1978).

PHARMACOKINETICS
of
Tricyclic Antidepressants

Absorption :

Tricyclic antidepressant agents are well absorbed after oral administration. High doses of these strongly anticholinergic agents can slow gastero-intestinal activity and gastric emptying time, resulting in slower or erratic absorption of these and other drugs taken concomitantly (Bowman & Rand, 1980).

Distribution :

Once TCA drugs are absorbed, they are widely distributed because of their lipophilic properties. TCA drugs have a high apparent volume of distribution implying that they are concentrated in some tissues and indeed they have been found to be concentrated in the myocardium (Laurence & Bennett, 1980). They are strongly bound to plasma proteins and to the constitute of the tissues. Plasma half life of tricyclic antidepressant drugs varies from 10-200 hours, with imipramine at lower end (10-20) hours and protriptyline at upper limit (50-200) hours (Laurence & Bennett, 1980). Amitriptyline has been estimated to have half life ranging from 9-25 hours which may be longer in overdosage (Reynold, 1993).

Toxic effects of these drugs can be expected when their concentrations in plasma rise above 1 ug/ml and can occur at even half of this value (Baldessarini, 1990). plasma → concentrations are associated with therapeutic effect in a range