HEPATOTOXIC PROFILE OF FLUCONAZOLE

Thesis Submitted for the Partial Fulfillment of the Master Degree in Clinical Toxicology

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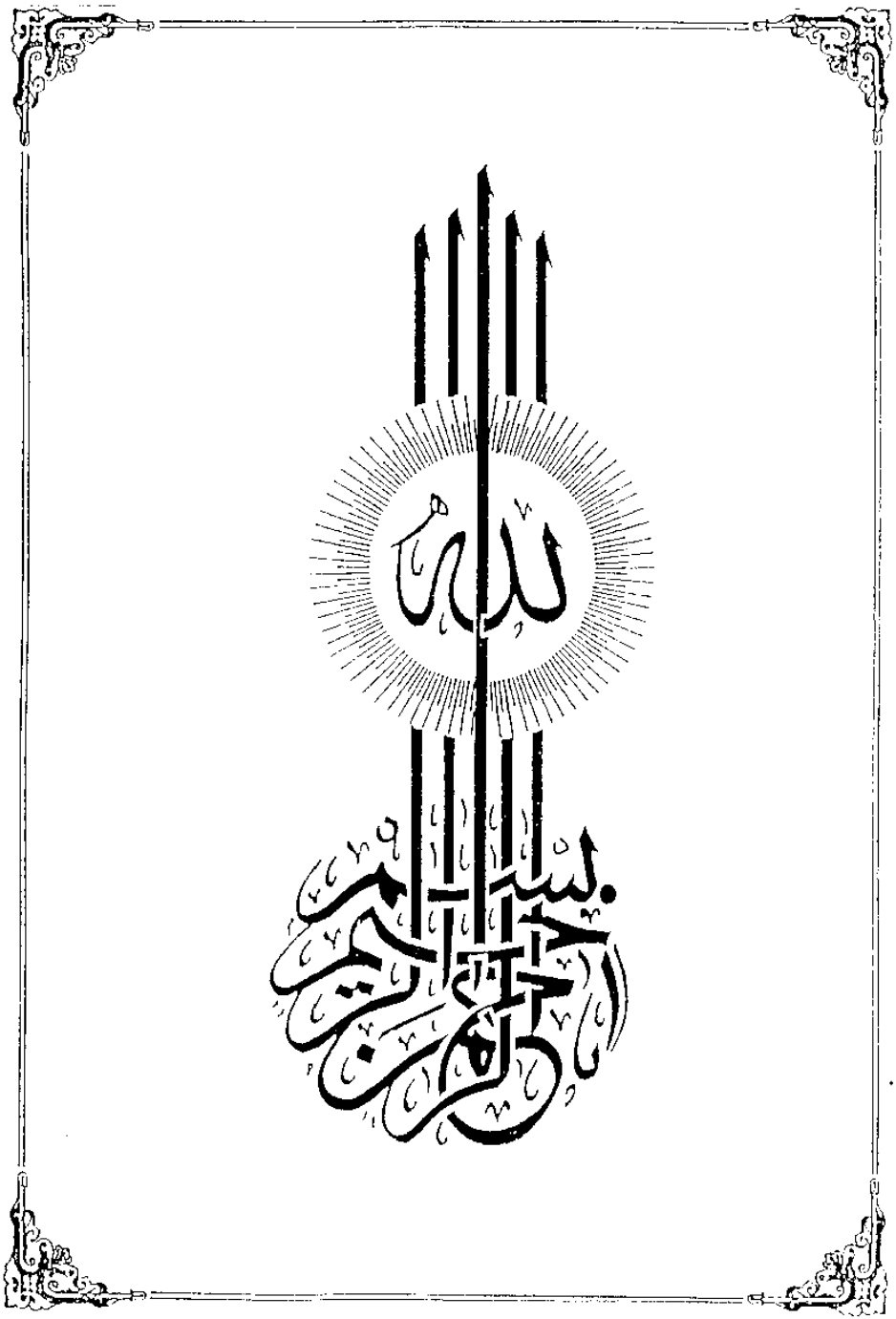

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List of Abbreviations

* Acquired Immunodeficiency Syndrome	AIDS
* Alkaline phosphatase	ALP
* Area under the plasma concentration-time curve	AUC
* Direct Bilirubin	D.B.
* Glomerular filtration rate	GFR
* Indirect Bilirubin	I.B.
* Minimal inhibitory concentration	MIC
* Peak plasma concentration	C max
* Renal clearance	CLR
* Serum Glutamic Oxaloacetic Transaminase	SGOT "AST"
* Serum Glutamic Pyruvic Transaminase	SGPT "ALT"
* Total Bilirubin	T.B.

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Introduction and Aim of the Work

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INTRODUCTION

Most fungi are completely resistant to the action of antibacterial drugs. Only a few chemicals have been discovered that inhibit fungi pathogenic for humans, and many of these are relatively hazardous. The need for better antifungal drugs has been made more pressing by the greatly increased incidence of local and disseminated fungal infections in immunodeficient patients. Among the antifungal drugs currently available, some are difficult to administer, some are used only topically and some others can be used orally for systemic infection but resistance often develops ***(Jawetz, 1992).***

The development of a new systemically acting oral antifungal was considered a major breakthrough ***(Van Cautern et al., 1989).***

Fluconazole is a new triazole antifungal agent with novel pharmacokinetic properties, which contribute to its therapeutic activity ***(Grant and Clissold, 1990).***

The most serious adverse effect which may be caused by azole derivatives is the hepatic affection ***(Stern et al., 1988).*** Hence further studies are needed to evaluate fluconazole hepatotoxic potential ***(Saag and Dismukes, 1988).***

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AIM OF THE WORK

I. The theoretical part of the work is to review the pharmacokinetics, pharmacodynamics, therapeutic uses and adverse effects of the antifungal fluconazole with special reference to its hepatic brunt.

II. The experimental part of the work is to prove or to exclude its hepatotoxic effect, its dose relation, and whether it is reversible.

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Review of Literature

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TOXIC RESPONSES OF THE LIVER

Because the aim of this thesis is to study the possible hepatotoxic effect of one of the antifungal agents, it is important to throw light on the different mechanisms by which various drugs possibly cause liver toxicity.

Introduction:

Liver injury induced by chemicals has been recognized as a toxicologic problem for over 100 years ***(Zimmerman, 1978).*** Around 1880, scientists were concerned about hepatic disposition of lipids following exposure to yellow phosphorus. Hepatic lesions produced by carbon tetrachloride and chloroform were also studied in laboratory animals over 50 years ago. During the same period, the association between excessive ethanol consumption and hepatic cirrhosis was established ***(Plaa, 1992).***

It was recognized early that "liver injury" is not a single entity; the lesion observed depends not only on the chemical agent involved but also on the duration of exposure. After acute exposure, there is usually hepatocellular lipid accumulation (steatosis), hepatocellular necrosis, or hepatobiliary dysfunction, whereas cirrhotic or neoplastic changes are usually considered to be the result of chronic exposure. Some forms of liver injury are reversible, while others result in permanent damage of the organ ***(Plaa, 1992).***

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Structural organization of the liver:

The relationship between the hepatic cell, its vascular supply, and the biliary system has been represented by the hexagonal lobule, as introduced by ***Kiernon in 1833.*** In the center of this lobule, there is the terminal hepatic venule (central vein) and at the periphery, the portal space, containing a branch of the portal vein, a hepatic arteriole and a bile duct. Based on this configuration, zonal pathologic lesions of the hepatic parenchyma are classified as centrilobular (pericentral), midzonal, or peripheral.

Classification of chemical induced liver injury:

Morphologically, chemical-induced liver injury can manifest itself in different ways. The acute effects can consist of an accumulation of lipids (steatosis, fatty liver) and the appearance of degenerative processes leading to cell death (necrosis). The necrotic process can affect small groups of isolated parenchymal cells (focal necrosis), group of cells located in zones (centrilobular, midzonal, or periportal necrosis), or virtually all the cells within a hepatic lobule (massive necrosis). Steatosis can also be zonal or more widespread ***(Lewis and Zimmerman, 1989).***

In addition to acute hepatic necrosis and steatosis, there is cholestasis. This lesion results in diminution or cessation of bile flow, leading to retention of bile salts and bilirubin. The retention of bilirubin leads to presence of jaundice. Another hepatic lesion, a type of chemical-induced hepatitis resembling that produced by viral infections, can occur with certain drugs ***(Zimmerman, 1978).***

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In 1979, a classification scheme for drug and chemical-induced liver injury was formulated and the hepatic lesions were divided into two categories. Type I lesions are those that are "predictable, dose-and time-dependent, occurring in most, if not all, subjects exposed to appropriate doses of the causative substance; the lesions are usually reproducible in animals". Type II lesions are those that are "non-predictable, dose- and time-independent, occurring sporadically and often becoming apparent only after monitoring a large number of exposed individuals. The lesions are usually not reproducible in animals". The distinction between type I and type II is not based on the morphologic characteristics of the liver injury ***(Davidson et al., 1979).***

For a morphologic classification, five categories of liver reactions are present. *The first* is called "zonal hepatocellular alterations without inflammatory reaction". The substances included in this group all produce zonal changes, either necrosis or steatosis. The group includes, acetaminophen, carbon tetrachloride, ethanol, tetracycline and many other drugs. This type of injury is the best understood type of hepatic injury because of its great reproducibility in several animal species, its dose dependence, and its predictable character (a type I lesion).

The second category is called "intrahepatic cholestasis". This group contains chemicals that are capable of producing in a small percentage of the population, a jaundice resembling that produced by extrahepatic biliary obstruction. Examples are, Amitriptyline, Diazepam, Azathioprine and

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Chlorpromazine. The important histologic features of this responses are presence of bile stasis, dilatation of the canaliculi with subsequent loss of the microvilli, and occurrence of focal necrosis. This response is considered a type II lesion.

The third category is called "hepatic necrosis with inflammatory reaction". The progression to a massive necrosis characteristic of viral hepatitis is a prominent feature. Examples are, Colchicine, Halothane, Phenylbutazone and Isoniazide. This response is considered a type II lesion and its incidence is extremely low.

The fourth category is called "unclassified group". This group contains a variety of hepatic injuries that do not fit into any type of scheme. The lesions can be associated with manifestations of pathology in several other organs.

The fifth category consists of those agents producing "hepatic cancer" ***(Popper and Schaffner, 1959).***

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Mechanisms of liver injury:

[I] Accumulation of lipids:

A number of agents that produce liver injury also cause the accumulation of abnormal amounts of fat, predominantly triglyceride, in the parenchymal cells causing fatty liver e.g. Acetaminophen, Aflatoxin, Carbon tetrachloride and Chloroform. Triglyceride accumulation is the result of an imbalance between the rate of synthesis and the rate of release of triglyceride by the parenchymal cells into the systemic circulation ***(Lombardi, 1966).*** Tetracycline induces steatosis and interferes with triglyceride secretion ***(Deboyser et al., 1989).***

When hepatic triglyceride is released into the plasma, it is not released as such but is combined with a lipoprotein. Drugs as carbon tetrachloride and ethionine can lower the level of circulating lipoprotein ***(Recknagel, 1983).***

Steatosis does not necessarily lead to death of the hepatocytes. Ethionine and cycloheximide cause fat accumulation without producing necrosis. Promethazine protects rats against the necrogenic effects of carbon tetrachloride ***(Rees et al., 1981).***

[II] Protein synthesis:

With many hepatotoxicants known to produce necrosis, certain morphologic changes occur rapidly after the administration of the agent. Loss of cytoplasmic basophilic material occurs before the appearance of

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