سامية محمد مصطفى

شبكة المعلومات الجامعية

بسم الله الرحمن الرحيم

سامية محمد مصطفى

شبكة المعلومات الجامعية

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

شبكة المعلومات الجامعية

سامية محمد مصطفى

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

سامية محمد مصطفى

شبكة المعلومات الجامعية

بعض الوثائق الأصلية تالفة

سامية محمد مصطفى

شبكة المعلومات الجامعية

بالرسالة صفحات لم ترد بالأصل

Liver and Drugs

An assay for partial fullfilment of

Master Degree of general Medicine

By

Khaled Ahmed Mazen
MBB. Ch Cairo University

Supervisors

Prof. Dr.

Sherief Medhat Nageuib

Prof. Of internal Medicine
Faculty of medicine
Cairo University

Prof. Dr.

Kamel Saad El-Dein Hishmat

Prof. Of internal Medicine
Faculty of medicine
Cairo University

Cairo University
Faculty of medicine
2003

* * * * * * * *

Acknowledgment

- First we thank **ALLAH** for every thing forever.

- Then I would like to thank Prof. Dr. Sherief Medhat Nageuib for his great help.

- I would like also to thank Prof. Dr. Kamel Saad El-Dien Hishmat for his great help.

- Without their help this research could not be done.

- Then I would like to thank Directors of laboratory of Military medical a academy. Where I find many sources and up dated Medical Journals of Hepatology which gives me great help.

Contents

Liver and Drugs

Introduction

Drugs can cause toxic effects which can mimic almost every naturally occuring liver disease in man. About 2% of all cases of jaundice in hospitalised patients are drug induced. About one – quarter of cases of fulminant hepatic failure in the USA are thought to be medicament – related (Sherlock and Dooley 2002) .

Acute hepatites is by far the most common drug induced liver lesion . The gold standard for classification of drug-induced hepatitis is the liver histology. In all cases of acute hepatitis there is at least some degree of inflammation without fibrosis. This inflammation may be associated with necrosis of the hepatocytes " cytolytic hepatitis " with cholestasis " cholestatic hepatitis: or with both necrosis and cholestasis " Mixed hepatitis" Mechanisms of hepatotoxicity could be related to the therapeutic effect of the drug itself or to the formation of hepatotoxic metabolites through cytochrome P450 (Pessayre et al 1999)

Formation of reactive matabolites by cytochrome P-450. May lead to direct toxicity while the combination of cytochrome P450 and the immune system may lead to the immune destruction of hepatocytes (Pessayre et al 1995)

Prolonged damage to the hepatocytes whatever the initial mechanism may lead to chronic hepatitis and cirrhosis. (Zimmerman 1978) Drugs and chemicals can cause lesions at all levels of the vascular systems of the liver perhaps through toxicity to endothelial cells.

the molecular and cellular mechanisms remain unknown Tumour development after exposure to chemicals is a long stepwise process (Pessayre et al., 1999).

Aim of work

In this review we aim to clarify the relation between the commonly used drugs in Egypt and the liver.

We hope to answer the question? Which drug should be avoided particularly for diseased liver and which drug can be safely given.

Chapter 1

IMPORTANCE, TYPES AND DIAGNOSIS

Of Drug-Induced Liver Diseases

Importance of Drug-Induced Liver Diseases

Drug-induced liver injury is a major challenge, both for the pharmaceutical industry, because hepatic injury is a frequent cause of drug recall, and for the physician, who can cure his patient by establishing the diagnosis and withdrawing the durg, whereas failure to recognize the liver disease and/or its drug aetiology may lead either to the worsening of the acute liver lesions or the progressive development of chronic liver lesions. Drug-induced liver injury is not uncommon, and may indeed be the main cause of hepatitis in elderly subjects receiving many drugs. **[Benhamou et al. 1986]**

Acquiring some knowledge of drug-induced liver lesions may seem a formidable task, however. Indeed, a thousand drugs may be hepatotoxic. **[Stricker et al. 1992]**

Marketing of hepatotoxic durgs: The main reason, however, for the steady release of hepatotoxic drugs is that clinical trials are extremely expensive and are therefore restricted to several hundred or a few thousand patients. If the frequency of clinical hepatitis is low (1/1000 or less) it will go undetected in these clinical trials. Additional factors may further contribute to the inefficientcy of clinical trials in the detection of hepatotoxicity. Some drugs may be intended for short use (e.g. antibiotics) and clinical trials are accordingly devised. When, however, the drug is released on the market, some patients may start taking it for longer periods. This will leave more time for immunization to

occur, for example, and cases of immunoallergic hepatitis may then appear.

Frequency of adverse drug reactions among recipients The frequency of clinical hepatotoxicity often remains undermined.

Therefore, one should be able to estimate this frequency from the number of prescriptions. Although this reporting is supposed to be mandatory in several countries, there are many reasons why it tends to be neglected. It is clear that frequencies estimated from the spontaneous reporting of adverse events by physicians probably represent gross underestimates of the real frequencies. **[pessayre et al. 1999]**

Prevalence of adverse drug reactions among various causes of liver disease

One would like also to know what is the proportion of patients with drug-induced hepatic injury among all patients affected with liver disease at a given time. Surveys conducted among patients admitted to liver units have given proportions ranging from 2 to 5 per cent of cases of jaundice and about 10 per cent of cases of hepatitis. **[Esterbauer et al. 1991]**

An estimate is possible, however, in cases that are necessarily sent to the hospital, such as cases of fulminant hepatits. In a large survey of causes for fulminant hepatitis, 10 to 15 per cent of cases were probably drug induced. **[Bernuau et al. 1987]**

Hepatic Drug Metabolism

Phase 1. The main drug-metabolizing system resides in the microsomal fraction of the liver cell (smooth endoplasmic fraction of ther liver cell (smooth endoplasmic reticulum). The enzymes concerned are mixed function mono-oxygenases, cytochrome c-reductase and cythochrome P450. Reduced NADPH in the cytosol is a co-factor. The drug is rendered more ploar by hydroxylation or oxidation. Alternative phase 1 drug-metabolozing reactions include the conversion of alcohol to acetaldehyde by alcohol dehyrogenases found mainly in the cytosolic fraction.

Enzyme inducers include barbiturates, alcohol, anaesthetics, hypolgycaemic and anticonvulsant agents, griseofupvin, rifampicin, glutethimide, phenylbutazone and mepropamate. Enlargement of the liver following the intdouction of drug can be related to enzyme induction.

Phase 2. These biotransformations involve conjugation of the drug or drug metabolite with a small endogenous molecule. The enzymes concerned are usually not confined to the liver, but are present there at high concentration.

Active transport. This system is located at the biliary pole of the hepatocyte. The mechanism is energy dependant and can be saturated.

Bilary and urinary excretion. Factors determining whether the metabolized drug will be excreted ultimately in bile or urine

are multiple and many are unclear. Highly polar substances excreted unaltered in the bile and also those which become more polar after conjugation. Those with a molecular weight exceeding 200 tend to be exccreted in the bile. As the molecular weight falls, the urinary route becomes more important. **[Sherlock et al, 2002]**