ACETAMINOPHEN AND ALCOHOL INDUCED HEPATOTOXICITY

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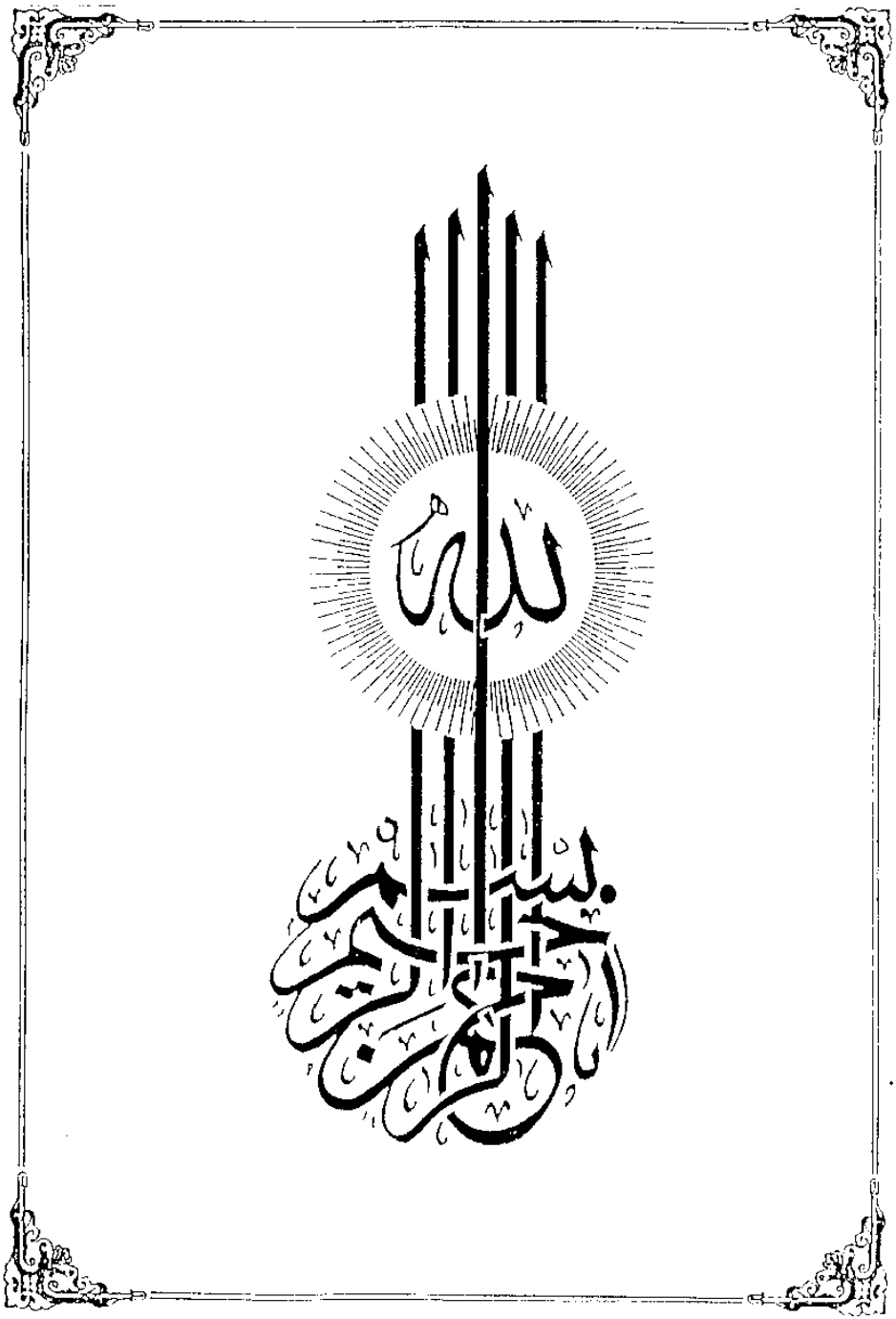

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INTRODUCTION

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Liver injury induced by chemicals has been recognized as a toxicologic problem for about 100 years (Sollmann, 1957 and Zimmerman, 1974). Before 1950, investigators were primarily interested in the injury produced by exposure to nontherapeutic agents likely to occur in an occupational environment. Since 1974, the primary concern is about drug-induced injury (Plaa, 1980). Hepatic injury due to medicinal agents is the facet of hepatotoxicity of most interest to clinicians (Zimmerman, 1982).

It is now well established that subjects exposed to several chemical agents simultaneously can exhibit altered pharmacologic or toxicologic responses. The effect of a second drug can have a marked influence on the response elicited by a previously administered drug and vice versa. In the field of therapeutics such drug interactions have been well described. With hepatotoxicity, interactions have been observed. Many of these have led to the discovery that biotransformation to a more active metabolite is involved in the hepatotoxic

reponse. In addition to these, other instances of potentiation of hepatotoxicity have been described (Plaa, 1980).

The chief means of exposure to a known hepatotoxicant is through the intake of excessive amounts of ethanol. the enormous morbidity and mortality associated with alcohol abuse make it a major contemporary public health problem (Avery, 1980).

Persons who regularly use alcohol frequently take acetaminophen instead of aspirin because of the well known gastrointestinal side effects of alcohol and aspirin combination (McClain et al., 1980). Acetaminophen is now among the most commonly used analgesics. It is well tolerated at therapeutic doses, and does not cause gastrointestinal haemorrhage. (Lancaster, 1980).

This work is aimed to discuss the hepatotoxic effect of acetaminophen, alcohol, combination of the two drugs, and whether or not the hepatotoxicity of acetaminophen is increased by ethanol concomitant use.

REVIEW OF LITERATURE

ACETAMINOPHEN

(Paracetamol)

History:

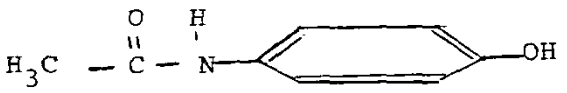
Acetaminophen was first synthesized at Johns Hopkins University in 1877 and was first used in clinical medicine in 1893 by Von Mehring (Spooner and Harvey, 1976). In 1950 it was marketed in United States of America as a substitute for phenacetin in analgesic mixture. (Ameer and Greenblatt, 1977).

Acetaminophen is proved to be safer than phenacetin which is toxic to the kidney (Varley et al., 1980).

Because it is well tolerated without many of the side effects of aspirin, and is available over the counter it has gained a place as a common house hold analgesic. (Linden and Rumack, 1984).

Chemistry:

Acetaminophen is N-acetyl para-amino phenol (Ameer and Greenblatt, 1977). It is the active metabolite of phenacetin resulting from its de-ethylation (Bleehen, 1983). It has the following chemical structure:-



After (Windholz et al., 1983).

The antipyretic activity of the compound resides in the aminobenzene structure (Flower et al., 1985).

Physical properties:

Acetaminophen is a white odourless crystals or crystalline powder with a bitter taste, its melting point is from 168°C to 172°C. It is soluble in 1 in 70 of water, 1 in 20 of boiling water, 1 in 7 to 10 alcohol but it is insoluble in ether. A saturated solution has a pH of 5.1 to 6.5 (Reynolds and Prosad, 1982). The stability of acetaminophen is high in aqueous solution, the half-life in a solution buffered at pH 6 had been estimated to be 21.8 years. Degradation was catalysed by acids and bases and the half life was 0.73 years at pH 2 and 2.28 years at pH 9. It must be stored in air tight containers, and it must be protected from light. (Reynolds and Prosad, 1982).

Popularity:

Acetaminophen was available in the United States of America without prescription since 1955 (Spooner

and Harvey, 1976).

In the United States of America and Great Britain 5000 patients with acetaminophen poisoning are admitted anually to hospitals and 50-100 died (Dreisbach, 1983).

Factors related to the increase use of acetaminophen.

1- Substitution of acetaminophen for aspirin because of concern about salicylate induced gastritis and bleeding.

2- Replacement of phenacetin by acetaminophen.

3- Increase availability of Distalgesic (acetaminophen and dextropropoxyphene) the most commonly used analgesic in Britain since 1979. (Proudfoot, 1982).

Preparations:

Acetaminophen is available in tablet, capsule and suppository form, also it is available as a syrup (Linden an Rumack, 1984).

combinations:

Acetaminophen is found in hundreds of combined preparations as narcotics, antihistamines, sympathomimetics, anticholinergics, phenothiazines and muscle

relaxants (Linden and rumack, 1984). Also with other potent analgesics including phenylbutazone, dihydrocodeine and aspirine. These combinations result in acute poisoning with them which is difficult to assess, and lead to important changes in the absorption and metabolism of acetaminophen. (Proudfoot, 1982).

Therapeutic dose:

The adult dose is 0.5 to 1 gm every 4 hours, but not to exceed 4 gm/day (Rogers et al., 1980). For children, 3 months up to 1 year → 60 - 120 mg/dose, from 1 up to 6 years → 120-250 mg/dose, from 7 up to 12 years up to 500 mg/dose. These doses may be given 3-4 times daily as required (Reynolds and Prosad, 1982). The toxic dose is 140 mg/kg (Dreisbach, 1983).

Pharmacokinetics:

Acetaminophen is absorbed rapidly and almost completely from the G.I.T. (Shearn, 1982). The dissociation constant (PKa) of acetaminophen is 9.5 (Laurence and Bennett, 1982).

It is mostly non ionized at gastric pH, however, acetaminophen like most other drugs is predominantly

absorbed from the upper small intestine (Climents et al., 1978). The absorption of acetaminophen is greatly inhibited by food especially carbohydrates and by drugs which decrease gastric motility (Hanson, 1984).

On the other hand, the absorption rate and relative bioavailability are increased by concomitant administration of metoclopramide and also by exercise (Rogers et al., 1981). Acetaminophen is minimally metabolized to inactive metabolites during absorption (Rawlins et al., 1972).

Protein binding of acetaminophen is negligible (5 to 20 percent) at therapeutic doses, but may be higher during acute intoxication (20 to 50%) (Flower et al., 1985).

Therapeutic acetaminophen levels are in the range of 7 to 20 ug/ml, but the relationship between serum acetaminophen concentration and intensity of therapeutic effect is not linear in all cases (Koch-Weser, 1976). Acetaminophen is distributed unevenly to various tissues. With therapeutic dose, its apparent volume of distribution is about 9 L/kg (Levy, 1981).

Acetaminophen can cross the placenta (Louis, 1986). The metabolism of acetaminophen occurs predominantly in the liver, 20-30% by sulfation and 45-55% by glucoronidation which are excreted in the urine, small amounts (0-2%) of unchanged drug. (Czajka, 1982). In addition, some of the drug (4%) is metabolised by the cytochrome P-450 mixed function oxidase system in the liver to a toxic metabolite which is normally detoxified by preferential conjugation with hepatic glutathione and excreted in the urine as conjugates of cysteine and mercapturic acid (Louis, 1986).

The metabolites are excreted in the urine (Linden and Rumack, 1984). The average elimination half-life is 1 to 4 hours, half-life is slightly prolonged in neonates (2.2 to 5 hours) and in patients with cirrhotic livers (Louis, 1986). Accumulation in the body is thus unlikely with the usual therapeutic doses (Varley et al., 1980).

However, administration of acetaminophen to patients with impaired renal function results in increased accumulation of conjugated acetaminophen in plasma, but only minor changes in the plasma concentrations of free acetaminophen (Flower et al., 1985).