HISTOLOGICAL AND HISTOCHEMICAL STUDIES ON THE EFFECT OF RIFAMPICIN AND ISONIAZID ON THE LIVER AND KIDNEY OF ALBINO RAT

THESIS

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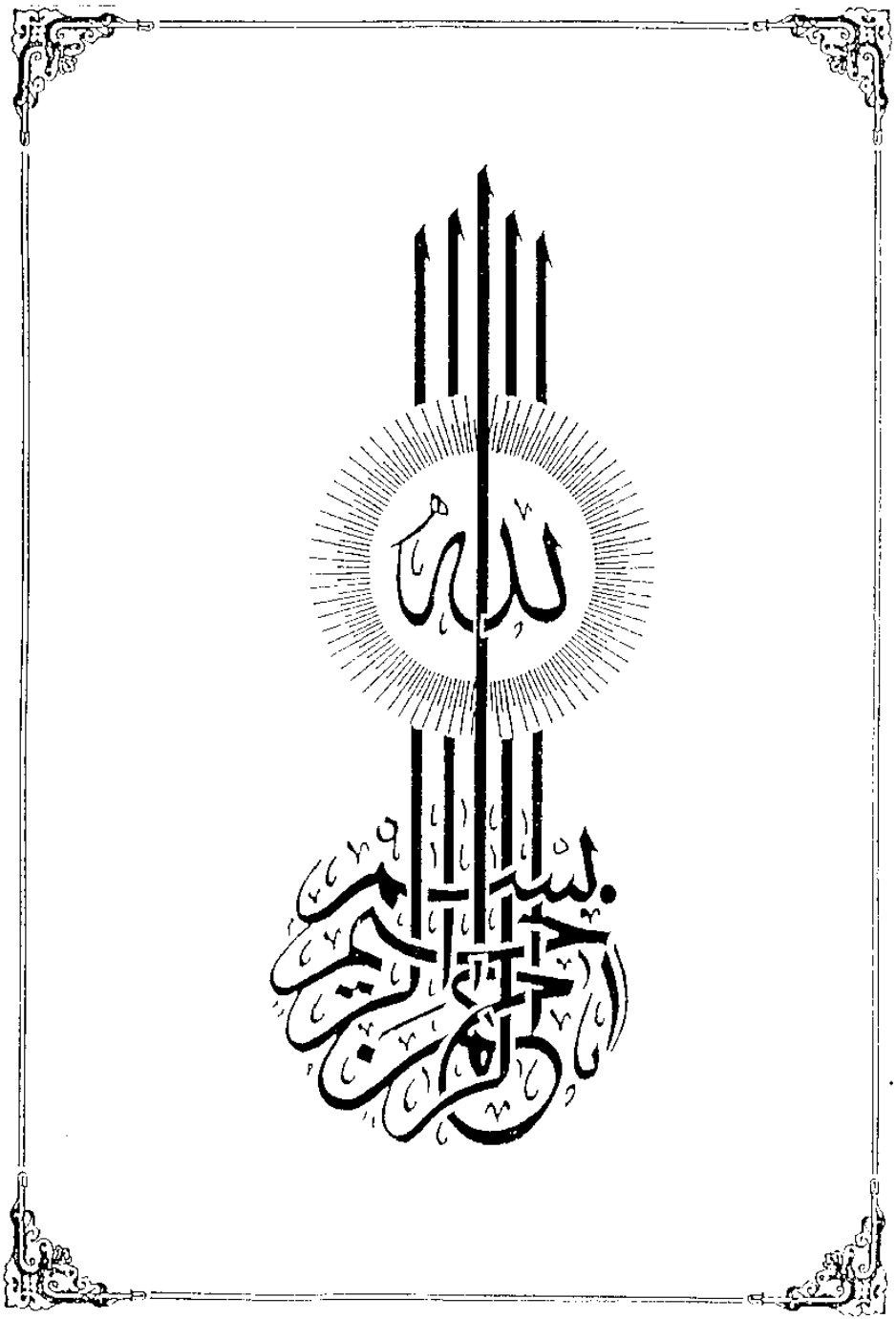

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INTRODUCTION
AND
AIM OF WORK

Tuberculosis is still frequently met with clinically. Administration of rifampicin in combination with isoniazid may represent the optimal therapy for all forms of disease caused by sensitive strains of Mycobacterium Tuberculosis. The large majority of patients can be treated successfully with rifampicin which was newly introduced in the 1960s. On the other hand, isoniazid is still considered to be the primary weapon for the therapy of tuberculosis *[Goodman, L.S. and Gilman A. 1980]* Hence, rifampicin and isoniazid were chosen for the present study to be used singly and in combination. Both rifampicin and isoniazid produced undesirable side effects most notably toxic hepatitis *[Black et al., 1975; Mitchell et al., 1975; Dutt et al., 1983 and Parthasarathy et al., 1986]* and nephritis *[Gabow et al., 1976; Barnes et al., 1984 and Cohn et al., 1985]*.

The present work was an attempt to study the effects of rifampicin and isoniazid alone and in combination on the liver and kidney of albino rats.

REVIEW OF LITERATURE

Randolph and Joseph (1953) observed jaundice in a patient treated with 150 mg isoniazid daily for one and a half months. A liver biopsy was performed 5 days after the appearance of jaundice. It showed increase in the connective tissue in the periportal zone, reduplication of small bile ducts and vacuolation of the liver cells.

Merritt and Fetter (1959) reported a case of hepatic cirrhosis in a patient treated daily with 300 mg of isoniazid for 50 days.

Cohen et al., (1961) reported a case of isoniazid induced jaundice, resulting in a fulminating submassive necrotic hepatitis with hepatic coma and death. They observed that jaundice, with laboratory and histologic findings of hepatocellular necrosis, occurred after starting isoniazid therapy. Continued isoniazid therapy was associated with fatal hepatitis.

Scharer and Smith (1969) demonstrated an elevation of the serum transaminases, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT), in 10% of asymptomatic patients during the first two months of isoniazid administration. Interruption of the drug

showed a return of the enzyme levels to normal. In addition, they demonstrated scattered small foci of mononuclear inflammatory cells, vacuolation of the liver cells and an increase in the number of kupffer cells in liver biopsy.

Smith and Scharer (1970) stated that in approximately 10 percent of healthy patients receiving isoniazid alone for chemoprophylaxis, asymptomatic increase of serum transaminase concentrations occurred within the first two months of therapy. They also added that the serum enzyme concentrations returned to normal while the drug was continued.

Brummer et al., (1971) mentioned that the risks of developing liver disease in patients receiving isoniazid were very small.

Pool, Stradling and Worrlledge (1971) tried daily rifampicin in a single dose of 600 mg, combined with other drugs, usually streptomyc in and isoniazid for three months. In 16% of the patients treated, a pyrexial syndrome occurred. In one of these patients they observed temporary renal failure and in another precipitous thrombocytopenia. In 33% of the patients, antibodies to rifampicin were detected in the blood.

Byrd and Elliott (1972) evaluated the toxicity of isoniazid used as a secondary chemoprophylactic agent in 160 adults. They reported frequent evaluation of the serum glutamic oxaloacetic transaminase (SGOT) level. They found that no patient developed jaundice.

Garibaldi R.A. et al., (1972) stated that isoniazid has been widely recognized as a safe and effective chemotherapeutic agent against tuberculosis since 1952. Numerous studies of isoniazid in combination with other antituberculous drugs have demonstrated its therapeutic efficacy . In the two decades since its introduction, isoniazid was implicated as a possible hepatotoxic in a small number of case reports. Few serious side effects of isoniazid used alone for chemoprophylaxis have been reported. However, the early chemoprophylaxis trials attempted to identify only overt toxic side effects of isoniazid and would have failed to detect cases of subclinical hepatitis.

Maddrey and Boitnott (1973) made a study on hepatitis secondary to isoniazid given as a chemoprophylactic drug for tuberculosis in a dose of 300 mg daily with an avarage duration of 12 weeks in 14 patients. The hepatic lesions ranged from a mild, relatively patchy hepatitis to massive hepatic necrosis. They observed that the histological

findings were in general quiet similar to those of viral hepatitis.

Beaudry et al., (1974) reported that in 6.8% of children receiving isoniazid for tuberculosis chemoprophylaxis, serum glutamic oxaloacetic transaminase (SGOT) increased two months after start of medication. They recommended a lower dose of isoniazid in order to decrease the incidence of hepatotoxicity in programs using isoniazid for the prophylaxis of tuberculosis.

Scheuer et al., (1974) studied eleven patients with clinical or biochemical evidence of liver damage during antituberculous therapy. All patients had received isoniazid and rifampicin and some had given para-aminosalicylic acid, streptomycin and ethambutol or prednisolone. They observed that hepatitis occurred within a month of treatment in six patients. They attributed hepatitis to be due to rifampicin alone or in combination with isoniazid.

Black et al., (1975) made an analysis of the overt hepatic disease that developed in 114 patients while taking isoniazid for chemoprophylaxis in a dose of 300 mg daily. They observed jaundice in 10% and hepatomegaly in 30% of the cases. They also reported an elevated serum levels of bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transminase (SGOT) and serum glutamic pyruvic transaminase

(SGPT). The onset of the mild subclinical liver injury or the overt hepatic-like disease was found to occur from one week to many months after initiation of isoniazid therapy. There was a decrease in the serum levels of transaminases and bilirubin within one week after cessation of the treatment in some patients. Sections of hepatic tissue from 33 of the patients showed periportal fibrosis and occasional likage of the partal areas by fibrous tissue together with cellular infiltration in the portal areas. There was also focal areas of hepatocellular necrosis.

Cochran, Moorhead and Platts (1975) stated that acute renal failure had been associated with intermittent rifampicin therapy. They reported a case that received para-amino-salicylic acid, isoniazid and rifampicin 3 days per week for abdominal tuberculosis. After 9 months the drugs were stopped and were given again one month later. The patient became anuric after 5 days. They found that the liver biopsy was normal, but the renal biopsy showed acute tubular necrosis.

Comstock and Edwards (1975) mentioned that there was growing enthusiasm for preventing tuberculosis by treating tuberculin reactors with isoniazid. They added that hepatitis could be a significant side effect of isoniazid. The probability of developing definite or probable hepatitis

during a year's treatment with isoniazid ranged from 2.4 to 19.2 per 1,000 depending on the age.

Van Daele et al., (1975) reported a case treated with isoniazid 12 mg/kg/day, ethambutol 20 mg/kg/day and rifampicin 11mg/kg/day. Liver biopsy was performed on the eighteenth day. Histopathologically the changes resembled a hepatitis-like lesion.

Gabow et al., (1976) stated that rifampicin was the first line drug inthe treatment of tuberculosis and its use was associated with heptotoxicity and acute renal failure. They reported a case of a 49 year old man that was treated with isoniazid, rifampicin and ethambutol for active pulmonary tuberculosis. The rifampicin therapy was discontinued for five weeks after 35 days of the treatment. They performed a renal biopsy one week later. The biopsy showed active interstitial nephritis and a mild proliferative glomerulonephritis.

Kumar et al., (1976) noticed that rifampicin therapy induced acute renal failure which was reversible. They reported a case of a 56 years old tuberculous woman who developed proteinuria seven days after starting rifampicin therapy.

Litt et . al., (1976) reported that isoniazid had been shown to cause transient elevations in serum enzymes of hepatic origin in adults and in children. Isoniazid-associated liver disease had generally been considered mild, although significant hepatitis resulting in coma and death had been noted on occasion.

Ellard et . al., (1978) stated that, isoniazid is acetylated in humans and certain laboratory animals to acetylisoniazid. This is then hydrolysed to isonicotinic acid and monoacetylhydrazine. This monoacetylhydrazine converted by the hepatic microsomal enzymes to a potent acetylating agent capable of causing hepatic necrosis. So rapid acetylators would be at greater risk of hepatic toxicity than slow acetylators.

Kopanoff et . al., (1978) suggested that age appeared to be a predominant factor influencing the risk of developing isoniazid related hepaitis. Also, drinking alcohol, especially on a daily basis, seemed to enhance the risk of hepatitis.

Rapp et . al., (1978) made a study on one hundred sixteen children received isoniazid therapy for tuberculous infection. Children were treated with 10 to 15 mg of isoniazid per kg of body weight per day. This high-dose isoniazid had been suggested as a cause of hepatotoxicity.