MEASUREMENT OF UNCONJUGATED HYPERBILIRUBINEMIA IN GILBERT'S SYNDROME DURING COMPULSORY FASTING

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ABSTRACT

Objective: We investigated the effect of compulsory fasting on unconjugated hyperbilirubinemia in ten adult patients with Gilbert's syndrome during Ramadan (a fasting period of 30 days).

Methods: At 4 a.m. and 8 p.m. they were given meals which contained a total of approximately 2500 cal. After the 4 a.m. baseline measurement was taken, the patients did not eat or drink anything for 16 hr for religious reasons. The serum total and indirect bilirubin concentrations were measured every week during this 4 week period of compulsory fasting.

Results: Prefasting basal mean serum bilirubin concentrations were: total bilirubin 1.4±0.06 mg/dl, conjugated bilirubin 0.4±0.03 mg/dl, unconjugated bilirubin 1.0±0.05 mg/dl. On the first day after a 16 h fasting the values were: total bilirubin 2.6±0.06 mg/dl, conjugated bilirubin 0.4±0.03 mg/dl and unconjugated bilirubin 2.1±0.12 mg/dl. In this period, conjugated bilirubin remained unchanged while total and unconjugated bilirubin significantly increased compared to the basal value ($p<0.013$). On the 7th, 14th, and 30th day of fasting the serum total and unconjugated bilirubin decreased to basal value. The mean total bilirubin level was 1.4±0.04 mg/dl, 1.4±0.11 mg/dl and 1.3±0.06 mg/dl on the 7th, 14th and 30th day respectively. The mean unconjugated bilirubin level was 0.9±0.04 mg/dl, 0.9±0.09 mg/dl and 0.8±0.09 mg/dl respectively.

Conclusion: Compulsory fasting during Ramadan (a period of 30 days) resulted in an increase in plasma unconjugated bilirubin concentrations on the first day of fasting. Then it decreased to basal value on the 7th, 14th and 30th day in patients with Gilbert's syndrome. It is assumed that these results may be important in diagnosing Gilbert's syndrome and its clinical features in the Muslim population.

Key Words: Unconjugated hyperbilirubinemia, Gilbert's syndrome, Compulsory fasting

INTRODUCTION

Gilbert's syndrome has been generally defined as mild, chronic, or intermittent unconjugated hyperbilirubinemia that occurs in the absence of overt hemolysis and intrinsic liver disease(1). Although this apparent syndrome may be caused by more than one factor, it seems that, in addition to mild unconjugated hyperbilirubinemia, the most consistent biochemical abnormality is persistent partial reduction of hepatic bilirubin uridine diphosphate glucuroyltransferase (UDPG-T) activity (2,3). Although the diagnosis of Gilbert's syndrome is most often made by exclusion of structural liver abnormalities and hemolysis and by the repeated finding of unconjugated hyperbilirubinemia, it is well known that Gilbert's syndrome also can be diagnosed by more specific tests (4). The measurement of bilirubin kinetics after an intravenous injection of cold crystalline pigment (5,6) or radiolabelled bilirubin (7) or computation by mathematical methods from survival of ^{51}Cr-labelled erythrocytes (8) permits the most reliable documentation of impaired bilirubin clearance. Latent Gilbert's syndrome may be unmasked by hemolytic stress (9) and the measurement of bilirubin clearance may be insufficiently sensitive in such instances. In the absence of structural liver disease, a reduced hepatic bilirubin activity UDPG-T is the most reliable marker for identifying people who carry the genetic predisposition for this disorder (10,11). In most cases, however, needle biopsy of the liver is not ethically justified in the absence of clinical and biochemical signs of liver disease. The most popular noninvasive tests used in the diagnosis of Gilbert's syndrome are the caloric restriction (12-14) and the nicotinic acid tests (15,16). In both instances these provocative tests produce a significant increase (more than 100% of basal values)

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of serum unconjugated bilirubin in the vast majority of Gilbert's patients.

The Muslim community forms about one third of the world's population. Unconjugated bilirubin may be increased in patients with Gilbert's syndrome during compulsory fasting. Therefore, we investigated the effect of compulsory fasting on unconjugated hyperbilirubinemia in patients with Gilbert's syndrome.

MATERIALS AND METHODS

The subjects of this study were ten adults with mild, chronic or recurrent, unconjugated hyperbilirubinemia in whom hemolysis was not evident and the usual tests of liver function were within normal limits. Overt hemolysis was excluded by the absence of anemia and reticulocytosis. The serum bilirubin concentration was estimated by the Mallory-Evelyn modification of the Van den Berg reaction (17). Serial determination of fractional serum bilirubin were obtained throughout the Ramadan (a period of 30 days). At 4 a.m. and 8 p.m. they were given meals which contained a total of approximately 2500 cal (approximately 30 gr of carbonhydrate, 20 g protein and 10 gr of fat). After the 4 a.m. baseline measurement was taken, the patients did not eat or drink anything for 16 h for religious reasons.

The serum total and indirect reacting bilirubin concentrations were measured every week during this month of compulsory fasting. Student's t-test was used for statistical analysis (18).

RESULTS

The results are summarized in fig. 1. The prefasting basal mean serum bilirubin concentration was: total bilirubin 1.4±0.06 mg/dl, conjugated bilirubin 0.4±0.03 mg/dl, unconjugated bilirubin 1.0±0.05 mg/dl. On the first day after a 16 h fasting the values were: total bilirubin 2.6±0.06 mg/dl, conjugated bilirubin 0.4±0.03 mg/dl and unconjugated bilirubin 2.1±0.12 mg/dl. In this period conjugated bilirubin remained unchanged while total and unconjugated bilirubin significantly increased compared to the basal value ($p<0.013$). On the 7th, 14th and 30th day of fasting the serum total and unconjugated bilirubin decreased to basal value. The mean total bilirubin levels were 1.4±0.04 mg/dl, 1.4±0.11 mg/dl and 1.3±0.06 mg/dl on the 7th, 14th and 30th day respectively. The mean unconjugated bilirubin levels were 0.9±0.04 mg/dl, 0.9±0.09 mg/dl and 0.8±0.09 mg/dl respectively.

DISCUSSION

This study indicates a reciprocal relationship between compulsory fasting and the degree of hyperbilirubinemia in Gilbert's syndrome. The serum bilirubin concentration increases after a brief fasting in all patients with Gilbert's syndrome. In contrast, the mean serum bilirubin concentration did not change during the second and third and fourth week of compulsory fasting. It is important to recognize that the rate of elevation in Gilbert's syndrome is very rapid, maximum values reached within 24 to 48 hours (19). This immediate effect of fasting on serum

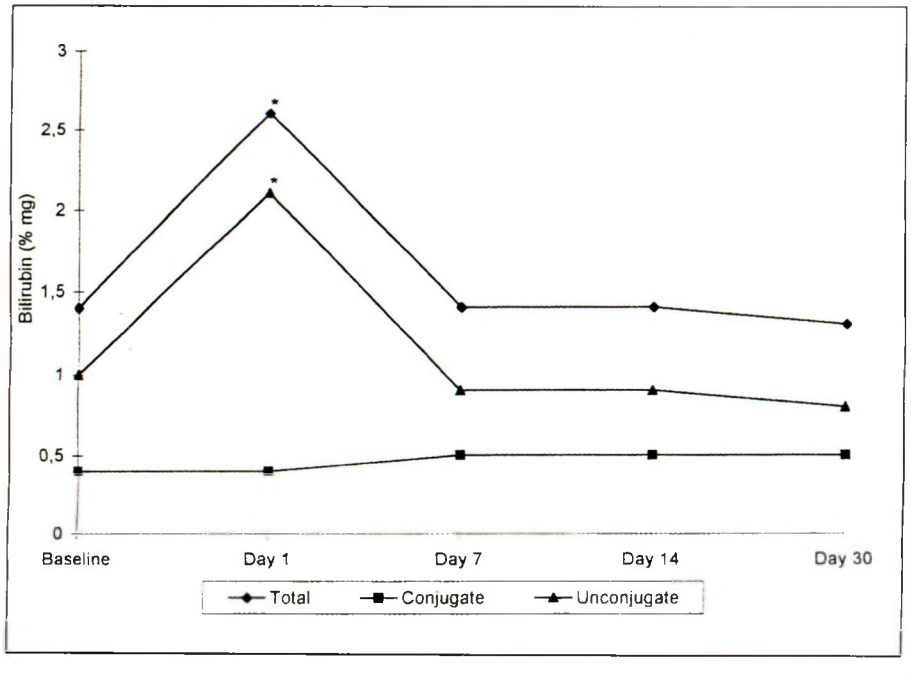

Fig.1: Level of serum bilirubin value in patients with Gilbert's syndrome during compulsory fasting (X±SEM) (*$p<0.05$ difference from basal level)

unconjugated bilirubin concentration in patients with Gilbert's syndrome contrasts sharply with the apparently prolonged period of fasting required to induce a significant increase in plasma bromsulfalein retention reported for obese subjects (19). It is well know that reduction of caloric intake causes a much greater absolute rise in serum bilirubin concentration in patients with Gilbert's syndrome compared to normal people (12). Almost 70 years ago, Gilbert and Herscher (20) reported that the serum bilirubin concentration in 3 normal adults was maximal after an overnight fasting. More substantial studies showed that the serum bilirubin level increased slightly, but remained within the normal range in healthy individuals after a brief fasting (20,21).

Fluctuation in the level of serum bilirubin has been considered characteristic in patients with Gilbert's syndrome (21). Various factors have been implicated to explain these fluctuations, although usually without quantitive evidence. The factors most commonly mentioned are physical exertion, emotional upset, infection and alcohol. In the light of current observations, caloric deprivations may well account for some of the naturally occurring fluctuations of serum bilirubin in patients with this disorder. It is not excluded that additional factors, independent of caloric intake, may also affect the level of serum bilirubin in this disorder. The mechanism of the reciprocal relation between caloric intake and the degree of hyperbilirubinemia in Gilbert's syndrome is unknown. It is known that starvation of rats leads to a significant decrease in hepatic uridine diphosphate glucuronyl transferase activity which is not due to generalized catabolism of liver protein. The stress of starvation of course was much more severe for the rat than reduced caloric intake for man. It remains a possibility that the fasting does in fact reduce the conjugating enzyme, though it is unlikely to be the entire explanation. The study found that decreased clearance of ^{3}H-bilirubin on fasting was associated with a decreased rate of transfer of bilirubin into the liver cell. This is presumably independent of subsequent conjugation. In only one patient did investigators find evidence for decreased conjugation (22).

In conclusion, compulsory fasting during Ramadan resulted in an increase in plasma unconjugated bilirubin concentration on the first day of fasting. Then it decreased to basal values on the 7th, 14th and 30th day in patients with Gilbert's syndrome. It is assumed that these results may be important in diagnosing Gilbert's syndrome and its clinical features in the Muslim population.

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