THE METABOLISM OF DIGITOXIN IN HEPATIC CIRRHOSIS OF HUMAN SUBJECTS

H. Hamamoto, H. Takeda, T. Katoh, T. Tokuoka, K. Kitamura, T. Takanashi and M. Bamba*

Digitoxin, 1 mg, was orally administered to 12 cirrhotic patients (the 6 in a clinically compensated and the 6 in a decompensated state) and their serum concentrations were measured at 6 hours and everyday through 7 days by radioimmunoassay. The serum half-life of digitoxin in these groups and normal subjects, determined from the serum concentrations, was as follows: 4.7 ± 0.55 days for controls, 4.9 ± 0.45 days for the compensated group and 5.3 ± 0.35 days for the decompensated group. No statistically significant difference could be found in half-life among these groups. (P > 0.2).

The same dose of digitoxin was orally administered to 6 cirrhotic patients and 6 control subjects and their left ventricular systolic time intervals, LVET and QS3, were determined at 6 hours and every morning for 7 days. Cardiac responses, exhibited by decrease in the systolic time intervals, in both control subjects and cirrhotic patients dissipated in fair parallel during the ensuing 4 days and returned to base line level by 5 days. From these both biological half-life and physiological effect, it may be concluded that overall metabolism of digitoxin in cirrhotic patients is not disturbed.

HEPATIC cirrhosis is not an infrequent complication of chronic congestive heart failure.

Although there is ample evidence1–3 that the liver is the metabolic site of a cardiac glycoside, its metabolism in hepatic disorder is not well known. F. Marcus and associates4 reported that there was no disturbance in the metabolism of digoxin in cirrhotic patients. As for digitoxin, there are a few studies about its metabolism in experimentally induced hepatic damage in animals5,6 however, very little information is available to human subjects7.

It is generally accepted that while digoxin, which is water soluble, is removed from the body in an unaltered state by the kidney, digitoxin is almost totally degraded in the liver and excreted as metabolites in urine. Therefore it might be anticipated that metabolism of digitoxin in hepatic derangement is disturbed. The purpose of this study is to investigate whether digitoxin metabolism is altered under the condition of terminal disorder of liver dysfunction, i. e. hepatic cirrhosis in human subjects.

Key Words:
Drug metabolism
Digitoxin metabolism
Hepatic cirrhosis
Systolic time intervals
Digitoxin radioimmunoassay

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The Metabolism of Digitoxin in Hepatic Cirrhosis of Human Subjects

METHODS

Subjects

Serum digitoxin levels were determined in 6 normal subjects and 12 patients with liver cirrhosis. According to the clinical severity, the cirrhotic patients were classified into compensated and decompensated group. The compensated group included 6 patients who were in a relatively stable state, while the decompensated group of 6 patients exhibited severer clinical symptoms such as ascites and remarkable jaundice. Mean age for normal subjects was 44.2 years (±14.3, SD) and for cirrhotic patients 53.4 years (±12.6, SD). None of the patients exhibited sings of cardiac decompensation or renal insufficiency as indicated by normal or a slightly elevated blood urea nitrogen and creatinine levels. Normal serum levels of Na, K and Cl were maintained at the time of this investigation. The diagnosis of liver cirrhosis was made on the ground of clinical and laboratory findings and in 6 cases of them it was confirmed by the histological examination as indicated in Table I. But the etiology of cirrhosis was not elucidated. Systolic time intervals were measured in 6 normal subjects and 6 cirrhotic patients (3 compensated and 3 decompensated).

Measurement of serum digitoxin

Digitoxin, 1 mg, was orally administered early in the morning after overnight fasting. The subjects were allowed to take their usual meals thereafter. Digitoxin tablets of the same brand were employed. Blood samples were drawn in the fasted state at 6 hours, 1 day, 3, 5 and 7 days after the administration of digitoxin and their serum levels were determined by radioimmunoassay method as described in our previous paper.

Determination of systolic time intervals

The recording of systolic time intervals was carried out in the fasting state before blood sampling at 9:00 a.m. one through 7 days after the administartion of digitoxin. Between these determinations the subjects were allowed to ambulate freely and they were instructed to rest in the supine position 30 minutes prior to each measurement. Those who smoke were asked to refrain from smoking at least one hour before the examination.

The recording and measurement of systolic time intervals were carried out and the same abbreviations of systolic time intervals such as LVET and QS2 were employed as described by Weissler which are shown in Fig. 1. As all the subjects in this study revealed sinus rhythm, five consecutive cardiac cycles were analyzed to find the average. Because of the daily variation in systolic time intervals, the initial baseline values for each subject were obtained on three successive days at 9:00 a.m. before drawing blood samples and they were averaged to give mean values. The baseline and observed values of LVET and QS2 were corrected for heart rate according to the regression equation reported by Weissler and referred to as ET index and QS2 index. The deviation of the observed ET index and QS2 index at an indicated time from each own mean baseline values of ET index and QS2 index represent ΔET and ΔQS2 respectively. Statistical analysis was carried out by Student paired “t” test.

RESULTS

The time course of serum digitoxin levels

Six normal subjects received 1 mg of digitoxin orally and their serum concentrations of digitoxin were determined serially from 1 to 6 hours after administration as shown in Fig. 2. A peak of serum digitoxin level was attained in one hour and gradually declined over 4 to 6 hours during
serum-tissue equilibration of the drug.

With the knowledge that 6 hours is enough for the serum digitoxin level to equilibrate with that of tissue, the next study was carried out to measure serum concentration of digitoxin starting from 6 hours and during the ensuing 7 days in 6 normal subjects and 12 cirrhotic patients (the 6 in a compensated state and the rest in a decompensated state). The time course of serum digitoxin level of normal subjects was compared with that of cirrhotic patients in decompensated state as depicted in Fig. 3a and compensated state as shown in Fig. 3b. Both groups of cirrhotic patients exhibited no statistically significant difference (P > 0.2) in the serum concentration from normal subjects at each indicated time.

The serum concentration of digitoxin declined in a linear fashion when plotted on a semilogarithmic scale, from which the serum half-life of digitoxin of these groups was calculated and summarized in Fig. 4. The compensated group revealed no apparent difference in serum half-life from control subjects. On the other hand the half-life of the decompensated group was prolonged to some extent, however, it was not statistically significant (P > 0.2).

*Time course of systolic time intervals*

Our previous study indicated that metabolites of digitoxin exhibit a nearly identical affinity with digitoxin antibody and they were simultaneously assayed with digitoxin in radio-immunoassay, which raises a possibility that the values obtained by this assay method may not precisely reflect the true serum concentration of the unchanged form of digitoxin. It is for this reason that the inotropic effect of digitoxin using the noninvasive method of left ventricular

Fig.2. Changes in serum digitoxin level in 6 volunteers during the first 6 hours after administration of 1 mg of digitoxin.

Fig.3. Changes in serum digitoxin concentration in control subjects and cirrhotic patients during 7 days following a single oral doses of 1 mg of digitoxin. The cirrhotic patients of 3a are in a decompensated state and 3b are in a compensated state of hepatic cirrhosis. P values represent statistical significance of the difference in serum concentration of digitoxin between the two groups at each indicated time.
Fig. 4. Serum half-life of digitoxin in 6 control subjects, 6 patients of decompensated and 6 of compensated liver cirrhosis.

Fig. 5. Changes in LVET and QS2 in three volunteers during the first 6 hours following 1 mg of digitoxin.

ΔET and ΔQS2 are expressed as deviation in milliseconds, from the base line level.

P values represent the possibility that mean base line levels may occur by chance at the indicated times.

Fig. 6. Changes in LVET in 6 control subjects and 6 cirrhotic patients at 6 hours and during ensuing 7 days after the administration of digitoxin.

Fig. 7. Changes in QS2 in 6 control subjects and 6 cirrhotic patients at 6 hours and during ensuing 7 days after the administration of digitoxin.

systolic time intervals was compared between the cirrhotic patients and the control subjects.

Three normal volunteers were subjected to observation of systolic time intervals, LVET and QS2 from 1 to 6 hours after the administration of digitoxin as shown in Fig. 5. A significant decrease in systolic time intervals was present at 2
hours and reached maximum effect at 4 to 6 hours.

Changes in systolic time intervals were observed in 6 normal subjects and 6 cirrhotic patients from 6 hours through the ensuing 7 days after the administration of digitoxin. Fig. 6 illustrates changes in LVET as expressed in ΔET. During the ensuing 7 days the cardiac response to digitoxin in both control subjects and cirrhotic patients dissipated in fair parallel and returned to base line level by 5 days (P > 0.2). Nearly the same result was observed with changes in ΔQS₂, as shown in Fig. 7.

DISCUSSION

It is generally recognized² that over 90% of digitoxin absorbed is catabolized in the liver. A previous study using guinea pigs⁵ stated that LD₃₀ was markedly decreased in the liver damage by CCl₄. Contrary to our initial expectation, the results of this study demonstrate that the overall metabolism of digitoxin in liver cirrhosis of human subjects is not disturbed. Not only serum half-life but also the serum level of digitoxin in hepatic cirrhosis 7 days after its administration show no significant differences from those of normal subjects (P > 0.2).

Several reasons may account for the conflicting results between the experimental animals and human subjects of this study. The experimental animals may have been in a terminal state of liver cirrhosis with extremely poor liver function and it is conceivable that other organs may also have been seriously affected, while the cirrhotic patients in the present study even those in the uncompensated state were in relatively good general condition. They did not exhibit severe jaundice and also their nutritional status, which affect the rate of detoxication in the liver, was not so disturbed. It is also important to note that species differences¹³,¹⁴ of hepatic metabolism and enterohepatic recirculation of digitoxin are considerable. Thus, estimations of drug toxicity derived from laboratory experiments on animals should be applied to humans with considerable caution.

Factors which may be concerned in the plasma half-life of digitoxin involve hepatic circulation, hepatic metabolism, hepatic excretion, biliary excretion, enterohepatic recirculation, and renal function.

In the subjects for this study renal function was not so disturbed as shown by normal or slightly elevated values of blood urea nitrogen and creatinine.

The lack of symptoms of profound biliary obstruction in our cases should exclude the influence of biliary excretion & enterohepatic recirculation on the alteration of plasma half-life.

Therefore, in the present study a change in plasma half-life, if there were, is a direct reflection of hepatic drug removal and could be the result of decreased hepatic circulation, impaired hepatic metabolism or excretion.

With regard to hepatic circulation, intrahepatic small vessels are restricted in liver cirrhosis by surrounding fibrotic connective tissues and there are arterio-venous or veno-venous anastomoses through which a drug entering the hepatic circulation might by-pass hepatic cells¹⁵ thus resulting in the reduction of its hepatic uptake and contributing to prolongation of its serum half-life.

Drugs are generally converted to water soluble substances by drug metabolizing enzymes located in the liver microsome, thus enhancing their urinary excretion. Digitoxin which is lipid soluble is likewise converted into water soluble compounds in the liver through two pathways². The one is conversion to digoxin by 12β-hydroxylation and the other is sugar cleavage by hydrolysis, followed by consequent conjugation reactions with glucuronic acid & sulfuric acid. Although there are some investigations concerning the activity of drug metabolizing enzymes in hepatic cirrhosis in animals¹⁶,¹⁷ little is known about human subjects. Schoene et al.¹⁸ demonstrated a reduction in the activity of various drug metabolizing enzymes in hepatic cirrhosis with human liver biopsy samples. From our present investigation it is unclear whether these enzyme reactions involved in the metabolic pathways of digitoxin are affected, however, it is conceivable that minimum enzyme activity is enough to metabolize such a small quantity of 1 mg digitoxin administered to the subjects in this study or in the usual clinical practice.

The high percentage of serum retention of indocyanine green in all the cases of the present study as shown in Table I would suggest the dysfunction of hepatic excretion which might well result in a prolongation of serum half-life.

It is widely acknowledged that over 90% of digitoxin is bound to serum albumin¹⁹. As is usually true with hepatic cirrhosis, remarkable hypoproteinemia is seen in all our cases. Klotz et al.²⁰ suggested that only the unbound drug present in blood delivered to the liver is extrac-
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table by that organ, from which it might be anticipated that the decreased serum binding of digitoxin in cirrhosis would increase its blood clearance, thus compensating the decreased hepatic circulation and excretion, resulting in an essentially unaltered serum half-life.

Looking at the overall metabolism of other drugs in cirrhotic human subjects, previous investigations are almost contradictory. Some workers failed to show delayed detoxication of such drugs as tolbutamide21 barbiturates22 or phenylbutazone23 and others have shown a prolonged serum half-life of chloramphenicol24 and clindamycin25 Comparatively large dose from 50 to 500 mg of those drugs were administered in their studies. By contrast 1 mg of digitoxin was given in our study, from which it is reasonable to assume that hepatic metabolism of digitoxin is not disturbed as stated above.

It has been suggested that phenobarbital, phenylbutazone26 and spironolactone27 enhance the metabolic breakdown of digitoxin by microsomal enzymes.

Levi et al.28 reported that some previous investigators might have failed to demonstrate that liver disease impairs drug metabolism in man because the importance of other drug pretreatment and its influence on micosomal enzymes was not appreciated. In this present study it was confirmed that treatment of such drugs known to influence digitoxin metabolism was discontinued.

The above results that the overall metabolism of digitoxin is not disturbed, should be applied to clinical practice with considerable caution. Renal insufficiency and hypokalemia in particular, which are not infrequent complications of hepatic cirrhosis should be taken into account.

REFERENCES
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