Ind. J. Physiol. Pharmac., Volume 33, Number 1, 1989

# HEPATIC DRUG METABOLIZING CAPACITY OF PATIENTS OF CIRHOSIS BEFORE AND AFTER CLINICOBIOCHEMICAL RECOVERY

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( Received on September, 1988 )

**Summary :** The present study was undertaken to determine whether, along with clinicobiochemical recovery there was associated restoration of hepatic drug metabolizing capacity in patients of cirrhosis after treatment of their cirrhosis, using serum antipyrine half life, the ideal index. Estimation of serum antipyrine half life before (26.34±2.4 hr) and after (18.83±2 hr) clinicobiochemical recovery showed significant ($P<0.01$) improvement in drug metabolizing capacity of liver. Biochemical parameters of liver function tests except serum total proteins and prothrombin time showed simultaneous improvement.

**Key words :** antipyrine half life drug metabolism cirrhosis liver

## INTRODUCTION

Chronic hepatocellular disease is known to be associated with decrease capacity of liver to metabolize drugs (1, 2, 3). Antipyrine is principally metabolized by the mixed function oxidase system of liver and its serum half life has been widely used as a model index for quantitative assesement of hepatic microsomal drug metabolising enzyme function (4, 5, 6) in man. Though prolongation of antipyrine half life has been correlated with severity of disease in patients of cirrhosis (7), the restoration of antipyrine half life associated with clinicobiochemical recovery phase has not yet been ascertained. The present study was aimed to investigate this aspect.

## MATERIALS AND METHODS

14 Male patients of cirrhosis (age range, 35-60 years; one patient, 19 years) included in this study were routine admissions to department of Medicine, LTMG Hospital. Patients were non smokers and were instructed not to take alcohol at least one week before and during the study period. Patients were evaluated clinically and with laboratory indices of routine liver function tests for assessing severity of liver disease. A full drug history was taken. Care was taken not to administer any drug which is known to affect liver microsomal enzyme levels. Serum antipyrine half life and liver function tests were measured in each patient within 3 days of admission to hospital (8) and repeated after 10-12 weeks of routine therapy (vitamin $B_{12}$, 2 tablets twice a day; oral furosemide, 40 mg once a day and high protein diet, 70 gm per day). By using the patients as their own controls, inter-individual variation in antipyrine metabolism was eliminated for assessing the change in antipyrine half life during phase of recovery from the disease process.

*Antipyrine test :* After an overnight fast, antipyrine was given PO 18 mgm/kg, as aqueous solution).

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Serial venous blood collections (6 ml) were made at 0, 2, 4, 8 and 24 hr after administration of antipyrine. Antipyrine was measured in serum by zinc precipitation spectrophotometric method of Brodie *et al.* (9). Elimination half life was calculated from the extrapolation of linear part of time-serum concentration curve of antipyrine on a semilog graph. Changes in antipyrine half life were compared by Students 't' test. 6 Normal drug free age, matched healthy subjects were studied for laboratory control values of antipyrine half life.

## RESULTS AND DISCUSSION

Mean (± S.E.M.) antipyrine half life in 6 normal subjects who served as laboratory control was 12.1±0.66 hr. In patients with active cirrhosis, mean antipyrine half life was 26.36±2.40 hr showing a significant ($P<0.01$) prolongation. The individual values of antipyrine half life in 14 patients before treatment are illustrated in Table I. A large variation between subjects was evident with values ranging from 1?.6 hours to 35.6 hr. Only one patient (No. 7) in the study group had antipyrine half life within normal range. The very young age of this patient (19 years) with greater reserve capacity of liver for metabolizing drugs, might be a factor, as otherwise this patient had marked cirrhosis and impairment of liver function tests. Patients with serum albumin below 3 gm% had longer antipyrine half life. Out of these 14 patients, follow up study could be done on 6 patients. At the end of 10-12 weeks of the therapy, mean antipyrine half life was significantly shortened to 18.83±2.00 hr (Table II). There was simultaneous trend for recovery in biochemical liver function tests, particularly serum albumin, total and direct bilirubin, SGOT and serum alkaline

TABLE I : Individual values of antipyrine half life in patients of cirrhosis during active disease phase.

| *Subject No.* | *Age (Year)* | *Body weight (kg.)* | *Antipyrine half life (hr)* |
|---|---|---|---|
| 1 | 45 | 48 | 19.1 |
| 2 | 40 | 71 | 26.0 |
| 3 | 45 | 50 | 25.6 |
| 4 | 40 | 47 | 35.2 |
| 5 | 52 | 48 | 22.4 |
| 6 | 60 | 68 | 30.2 |
| 7 | 19 | 45 | 12.5 |
| 8 | 30 | 40 | 26.2 |
| 9 | 42 | 52 | 22.2 |
| 10 | 56 | 56 | 33.8 |
| 11 | 38 | 50 | 35.2 |
| 12 | 35 | 45 | 34.4 |
| 13 | 60 | 45 | 18.6 |
| 14 | 45 | 55 | 28.5 |
| Mean | 46.8 | 54.9 | 26.36±2.40 |

TABLE II : Serum antipyrine half-life before and after clinicobiochemical recovery.

| *Subject Number* | *Serum antipyrine half life (hr)* | | |
|---|---|---|---|
| | *Before* | *After* | *% Change* |
| 1 | 19.1 | 12.2 | 35% |
| 2 | 26.0 | 21.2 | 16% |
| 3 | 35.2 | 26.4 | 31.1% |
| 4 | 33.0 | 16 4 | 61 |
| 5 | 23 5 | 20.2 | 29% |
| 6 | 34.4 | 16.6 | 52.9% |
| Mean±S.E.M. | 29.36±2.52 | 18.83±2.00* | 37.5 |

*$P<0.01$ with respect to before treatment value.

TABLE III : Biochemical characteristics of study patients.

| *Laboratory test* | *Normal Range* | *Before treatment Mean±S.E.M.* | *After treatment Mean±S.E.M.* | *P Value (before Vs after treatment)* |
|---|---|---|---|---|
| Total serum protein gm% | 6-7.5 | 6.8 ±0.3 | 7.8 ±0.2 | NS |
| Serum albumin gm% | 4-5 | 2.5 ±0.52 | 3.8 ±0.46 | P<0.05 |
| Total bilirubin mgm% | 0-1 | 6.56±0.71 | 3.76±0.47 | P<0.01 |
| Direct bilirubin mgm% | 0-3 | 3.9 ±1.42 | 0.95±0.72 | P<0.01 |
| Icteric index units | 3.5 | 3.9 ±1.05 | 0.8 ±0.31 | P<0.01 |
| SGOT units | 4-40 | 59.6 ±7.02 | 37.0 ±6.08 | P<0.05 |
| Prothrombin time seconds | | 21.69±1.15 | 20.00±2.0 | NS |
| Alkaline Phosphatase B.U. | 1.1 to 4.0 | 6.0 ±1.2 | 4.8 ±1.0 | P<0.05 |

phosphatase (Table III). Table II also depicts % change in antipyrine half life in individual patients. Significant change in antipyrine half life is defined as an alteration of more than 10% from the subject's control value, because in a basal state a subject's antipyrine half life is generally reproducible to less than 10% of intial basal value (10). In all the 6 patients change in antipyrine half life is more than 10% (range, 11% to 51%) of the pretreatment values. The results of this study indicate a correlation between clinicobiochemical recovery and reduction of antipyrine half life which was prolonged in patients of cirrhosis. Thus hepatic microsomal drug metabolizing capacity which is known to be impaired in cirrhosis, tends to recover simultaneously along clinicobiochemical recovery after patients are treated for their cirrhosis. Possible explanations for improved elimination of antipyrine during clinicobiochemical recovery phase could be (a) altered drug distribution due to changes in electrolyte and water distribution (b) changes in liver blood flow and (c) increased rate of metabolism due to increased protein synthesis. Earlier workers (7) have shown that assuming complete rapid absorption of antipyrine given by oral route, there was no correlation of the half life of antipyrine with the presence of gross fluid retention. Antipyrine is a model drug for drugs which are eliminated independantly of liver blood flow; hence better blood flow too, could not be the possible reason for improved elimination of antipyrine The latter could be due to increased rate of metabolism due to increased protein synthesis. High protein diet administered to these patients, could be one of the factors, since dietary protein is known to have a clear inducing effect on the rates of oxidative metabolism of antipyrine (11). Biochemical parameters of recovery also show a increase in serum albumin level indicating improved protein synthesis though the increase in total proteins was not significant. The results of the study could

be important therapeutically in view of the fact that antipyrine test is widely used as a model index of hepatic drug metabolizing capacity (1, 2, 3) and as an indicator of liver dysfunction (3). Whichever may be the explanation, better understanding of hepatic drug metabolizing capacity during active disease phase as well as during recovery phase would allow designing of more rational drug regimens and should be taken into account while considering dosage and choice of drugs.

## ACKNOWLEDGEMENTS

The authors are grateful to Prof. H. L. Dhar, Head, Department of Pharmacology, for his keen interest in this study and to Dean LTMG Hospital for providing facilities for this work.

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