Clinical Evaluation of Galactose Tolerance Test as an Index of Liver Dysfunction with Special Reference to the Glucoseoxidase-O-Toluidine Boric Acid Method for Determination of Galactose in Blood

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Since practically all galactose absorbed by the intestines is converted into glucose by the liver, the state of liver function can be ascertained by administering a given amount of galactose to the subject and determining the volume of galactose excreted in urine or found in the circulating blood after a prescribed period of time. This is the Galactose Tolerance Test.

The history of this test is surprisingly old as it was first reported by R. Bauer[1] of Vienna in 1906. The procedure of determination employed at the time was chiefly the Benedict reaction of reduced substances in urine following oral administration of galactose. In 1928, Raymond et al.[2] reported a method using yeast to destroy glucose at the time of galactose determination, and Shay et al.[3] applied this method for the elimination of glucose in urine making it possible to use this tolerance test on diabetis mellitus patientts. They pointed out that this methods was also particularly useful in the differentiation of the diseases which caused jaundice.[4] The procedure of intravenous administration was introduced by King et al.[5] in 1940 and the galactose was determined by copper reducing reaction after destroying glucose with yeast, after with the blood galactose tolerance curve was plotted. In 1962, De Verdier and Hjelm[6] determined galactose specifically using galactose oxidase, and in 1967 $ZnSO_4$ was added the reaction solution to eliminate uric acid which interferes with color development.[7] In 1963, Watson[8] reported the method of using o-toluidine for color production of galactose after destroying glucose with glucose oxidase. In 1966, Tengström et al.[9] stated the "T 1/2 method" should be used to express the galactose value obtained by intravenous administration and the galactose oxidase method of Hjelm et al, and a few reports supporting this view were presented.[10]-[12]

In Japan this tolerance test is not used as a routine procedure, and there have

been no recent reports on this method.

Hjelm's galactose oxidase method[7] and Watson's glucose oxidase method are new approaches to galactose determination, but both require step of deproteinization. Although the former is a reactin specific for galactose, because the coloration of ascorbic acid in the blood cannot be removed, it always requires the additional troublesome step on determining a sample blank and then substracting its reading from the galactose value.

For the purpose of using the galactose tolerance test as a routine liver function test, the authors introduced the Glucose Oxidase O-Toluidine Boric Acid Method[13] as a practical, simple and quick method of determination. The special advantages of this method are that the step of deproteinization is not required and the determination can be made with an ultramicro sample. This method of quantitation was developed by administering 40 g of galactose orally to 60 patients the majority of whom suffering of liver diseases. The results of this investigation are presented hereunder.

METHD OF EXPERIMENT

1) Administration of galactose

The method of administration was in accordance with that of Shay et al.[4] **Forty grams of galactose (Katayama, first class*) is dissolved in about 200 ml of warm water** and administered orally to all recipients in the fasting state early in the morning. The same amount of galactose was given regardless of sex, age and weight. As a control, 1 ml of blood is drawn from the antecubital vein prior to galactose administration, and after administration 1 ml is drawn on 6 occasions at 30 minute intervals, making a total of 7 collections. In patients in whom it is difficult to drawn blood by Syringe, the finger tip is punctured and peripheral blood is collected. After collection of blood, the serum is separated within 30 minutes and stored at 4°C until all 7 collections are completed, after which both the galactose and glucose values are determined.

2) Method of determination

Quantitative determination of galactose is performed by the Glucose Oxidase O-Toluidine Boric Acid Method reported earlier.[13] That is, 0.2 ml of glucose oxidase solution is added to 20 λ of serum and after 60 minutes at 37°C glucose will become decomposed. To this is added 2.0 ml of o-toluidine boric acid (O-TB) reagent, and determination is made at a wave length of 635 mμ after color production by heating.

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* The drawback in the use of galactose is that it is expensive. The first class type produced by Katayama Kagaku Co., does not contain glucose.

Quantitative determination of glucose was performed by the O-TB method.[15] However, as the degree of coloration between glucose and galactose differ after reaction with O-TB reagent, the substance which reacts with the O-TB reagent in serum is measured by the use of the glucose calibration curve in accordance with the O-TB method, and the value thus obtained is considered the total glucose value (GT). The true glucose value (GL) is sought by subtracting from the total glucose value the product of the forementioned galactose value (GA) and coefficient 1.49.* That is, $GL = GT - GA \times 1.49$.

3) **Subjects**

a) **Normal subjects.** The tolerance test was performed on 15 members of the clinical laboratory (6 males and 9 females) who were in good health and had normal "blood spectra**"[16] as well as normal clinical laboratory test results. Their ages ranged from 20 to 40. During the performance of the tolerance test, they did not take any special rest, but carried out their respective routine assignments.

b) **Hepatitis cases.** Twenty-three in-patients of Kawasaki Hospital who had been diagnosed as hepatitis on the basis of clinical symptoms, physical findings and laboratory tests (chiefly GPT, bilirubin anb LDH isozyme) were selected. This number includes some whose diagnosis had been confirmed by liver biopsy.

c) **Liver cirrhosis cases.** The tolerance test was performed on a total of 7 in-patients who had been carefully selected, 4 based on liver biopsy, 1 on laparotomy and 2 on physical and clinical laboratory findings.

d) **Diabetes mellitus cases.** Selected were 7 cases whose fasting blood sugar was in excess of 120 mg/dl and whose 2-hour glucose tolerance test results after administration of 50 g of glusose were in excess of 200 mg/dl.

e) **Others.** Selected slso as subjects were 1 case who had been diagnosed as having hepatoma, 1 with metastasis of the gastric cancer to the liver, 1 with congestive liver, 1 with systemic lupus erythematodes, 2 with duodenal ulcers and 2 with hypertension on the basis of physical examination and various laboratory tests. The diagnoses of cases with liver and gastric cancers were confirmed subsequently by autopsy.

4) **Other liver function tests**

For the purpose of making careful selection of cases, all serum collected as galactose control material was subjected to determination of "blood spectrum,"[16] electrophoresis[17] and isozyme analysis[18] etc. on the same day but prior to the galactose tolerance test. The "blood spect um" value used was that obtained by ultramicro quantitation.[19] The BSP value used was only that determind within 10 days after the day of the galactose tolerance test.

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* The glucose-galactose color ratio under the O-TB method is 1 : 1.49 ($n=10$, $CV=1.1$ %)

** Laboratory diagnosis based on determinations of 16 chemical constituents of blood which enable the appraisal of genaral condition and functional state of the liver and kidney.

EXPERIMETNT RESULTS

1) Blood galactose value prior to galactose administration

The blood galactose values obtained at early morning during fasting state are presented by disease for comparison (Table 1). The values for those with liver disorders and diabetes mellitus are slightly higher than the values for normal persons.

Table 1. Early Morning Fasting State Blood Galactose Values (mg/dl)

Disease	No. of Cases	Mean Value	Maximum Value	Minimum Value
Normal Persons	15	2.3	4.1	1.0
Hepatitis	23	5.8	12.9	3.0
Liver Cirrhosis	7	5.4	8.4	3.3
Hepatoma	1	6.1	—	—
Metastasis to Liver (Gastric Cancer)	1	5.3	—	—
Congestive Liver	1	6.2	—	—
Diabetes Mellitus	7	5.0	10.5	3.2
Others (SLE, Duodenal Ulcer, Hypertension)	5	3.3	5.1	1.9

2) Changes in galactose value after galactose administration

When galactose was administered orally, the changes of galactose value in blood produced a curve with a peak between 30 to 90 minutes and gradually decreasing thereafter. This is shown by disease in Figure 1, while the mean, maximum and minimum values are presented in Table 2.

Table 2. Mean, Maximum and Minumum Values of Galactose toleraucе Curve in Various Diseases

Normal Persons (15 cases)

Minutes after administration	30	60	90	120	150	180
Mean	21.3	33.4	17.0	5.5	3.7	3.1
Maximum	44.1	81.9	14.2	11.6	5.3	4.7
Minimum	4.2	9.4	5.3	3.2	2.5	2.1

Hepatitis (23 cases)

Minutes after administration	30	60	90	120	150	180
Mean	86.9	129.3	112.7	71.0	37.1	17.2
Maximum	168.3	190.9	172.6	154.4	138.3	68.2
Minimum	30.3	88.1	72.2	27.4	8.5	4.3

Liver cirrhosis (7 cases)

Minutes after administration	30	60	90	120	150	180
Mean	73.6	124.4	153.1	129.0	97.3	68.0
Maximum	160.2	170.5	209.7	180.2	152.3	134.2
Minimum	25.1	81.3	105.6	85.1	52.9	22.4

Diabetes Mellitus (7 cases)

Minutes after administration	30	60	90	120	150	180
Mean	75.9	102.9	71.9	38.3	16.3	8.4
Maximum	131.2	170.2	134.5	74.6	31.1	18.3
Minimum	36.3	58.2	37.5	20.0	7.3	3.2

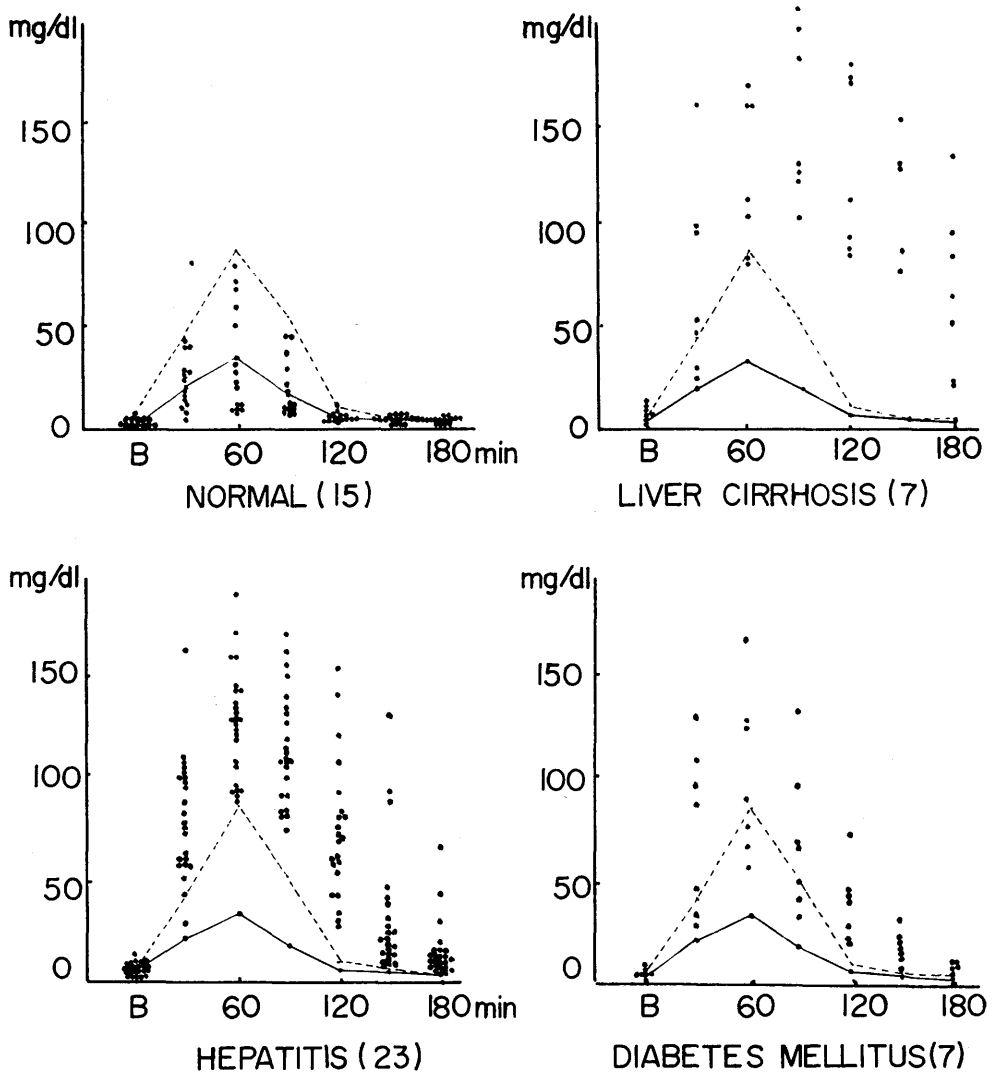


Fig. 1. Changes with Time After Administration of Galactose by diseases

B: Before administration of galactose.
( ): No. of cases.
——: The mean of the normal.
……: The mean + 2S.D. of the normal.

Normal subjects (15 cases). The blood galactose value gradually increased after administration and reached its peak at about 60 minutes, and after 120 minutes the value dropped below 12 mg/dl in all cases.

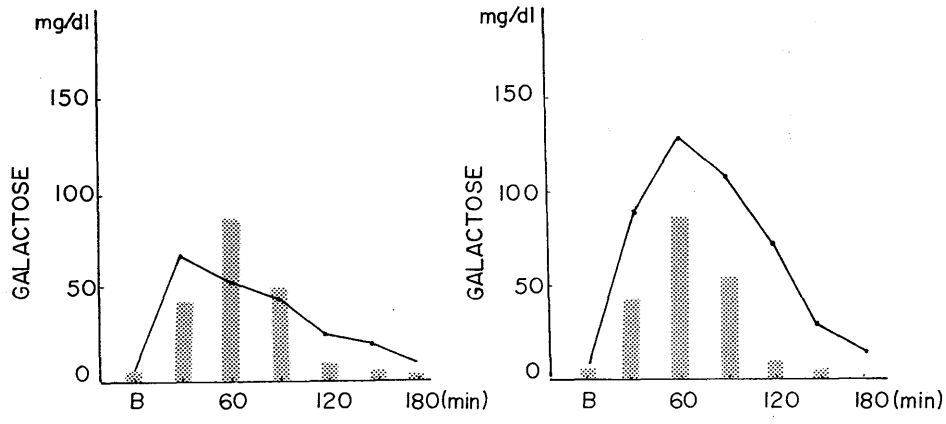
Hepatitis (23 cases). The galactose value was consistently higher than normal subjects at all times and galactose was found to be retained in the blood for a longer period. However, the maximum concentration was found to be at 60 minutes.

Liver cirrhosis (7 cases). As in the case of hepatitis, retention of galactose was markedly longer than the normal subjects and the value was higher than in hepatitis case. The peak of concentration was noted at 90 minutes.

Diabetes mellitus (7 cases). Probably due to delay in conversion into glucose within the liver as in the case of hepatic diseases, a high galactose value was observed. The peak was observed at 60 minutes.

Other diseases. In hepatoma (1 case), a pattern similar to that of normal subjects was observed up to 90 minutes, but at 120 minutes the value became higher (Fig. 2-a).

In gastric cancer with metastasis to the liver (1 case), a curve indicating retention of galactose was noted as in the other liver diseases, and there were findings suggestive of hepatic insufficiency (Fig. 2b). The 1 case with congestive liver caused by cardiac insufficiency had a blood galactose retection pattern similar to hepatitis and liver cirrhosis. Excluding the cases with liver disorders and diabetes mellitus, the galactose tolerance curve for all other diseases was similar to that of normal subjects.



a. HEPATOMA

b. LIVER METASTASIS (GASTRIC CANCER)

Fig. 2. Galactose Tolerance Curve in Hepatoma and Liver Metastasis
▒ indicates normal range.

The differences between the upper limits of normal values and the lower limits of values in various liver diseases and diabetes mellitus were compared by time, and it was noted that the maximum differences were presemt at 120 minutes. The 120 minute values by the various diseases are as shown in Figure 3.

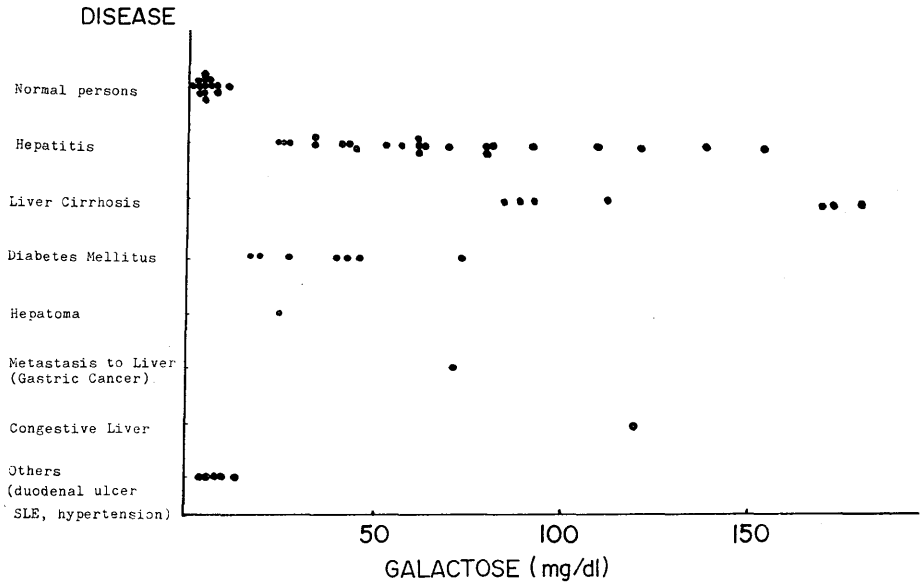


Fig. 3. Comparison of 120 Minute Values by Disease

3) Changes in the galactose tolerance curve by stage of disease

The cases admitted with hepatitis received galactose tolerance tests at the time of hospitalization and at a certain period thereafter to make comparisons of changes in the curve following treatment. Typical cases are shown in Figure 4.

Case A had a GPT value of 28 Mizobe units[20] (normal value is 0–10 units) at time of hospitalization and gamma globulin was 30.5 %. At the end of 60 days, both returned to normal, the former dropping to 3 units and the latter to about 25 %. The 120 minute value of the galactose tolerance curve in this case at time of hospitalization was high at 59 mg/dl, but 60 days later it had decreased to 8 mg/dl.

Case B had been hospitalized for jaundice. The 120 minute tolerance test value at time of admission was an extremely high 122 mg/dl, and on reexamination at the 80th day it had dropped to 62 mg/dl, but was still higher than that of a normal person. The GPT value at time of hospitalization was 146 units with the gamma globulin being 41.6 % which led us to assume the patient had rather severe liver disorder. After 80 days, the former was down to 12 units and the latter 29.2 %, but these values were still higher than normal, which suggests the disease state in this case had become chronic.

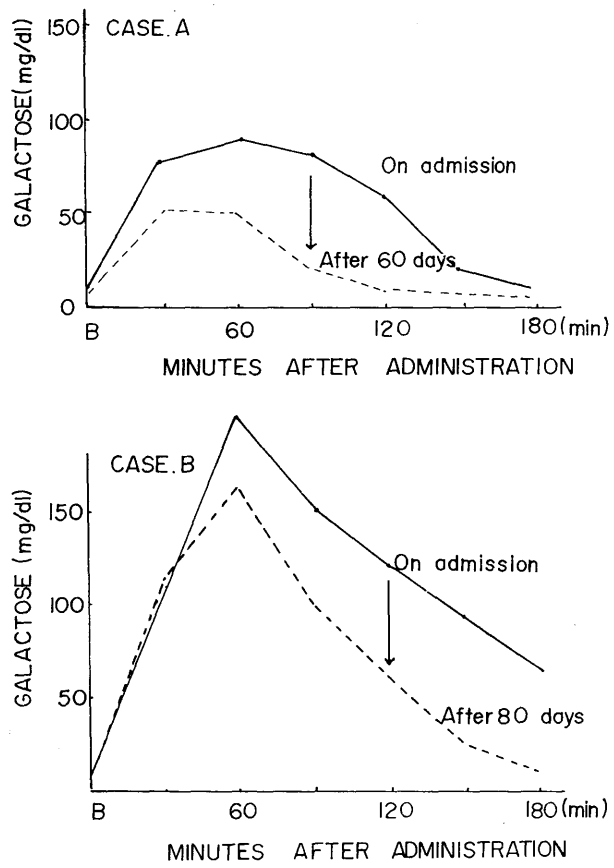


Fig. 4. Changes in Galactose Tolerance Curve by Disease State
B: Before administraiton.

4) **Correlation with other liver function tests**

Study of the correlation between the 120 minute galactose value and so-called routine liver function tests of albumin, cholinesterase, BSP, icteric index, alkaline phosphatasse and GPT was made. As shown in Figure 5, the respective correlation co-efficients were unexpectedly low.

5) **Changes in blood glucose value following galactose administration**

In order to learn how the galactose absorbed by the intestines is converted into glucose by the liver, the serum left over from the galactose determination was used for measurement of glucose. From this was subtracted the pre-administration glucose value, and the difference was considered the value of converted glucose (Fig. 6).

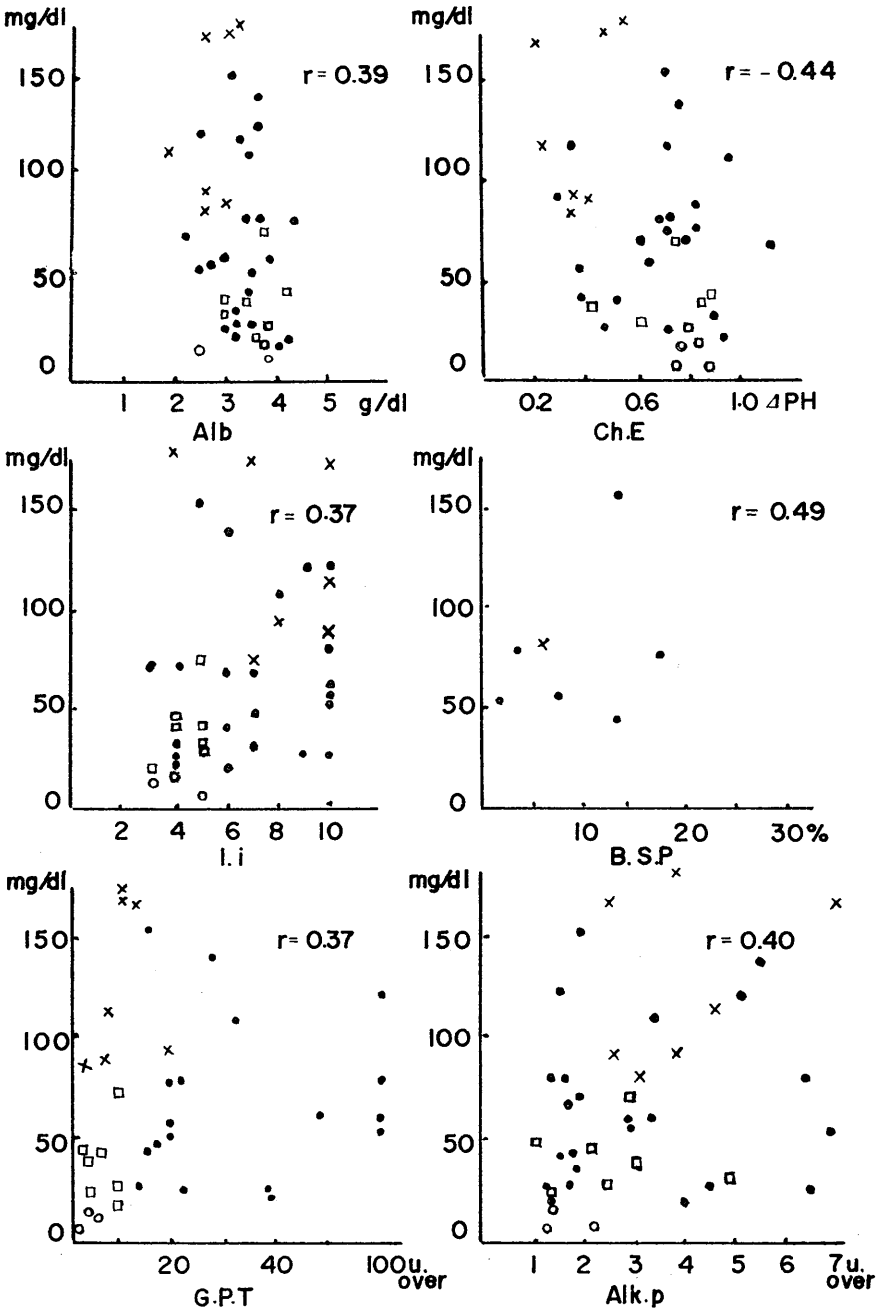


Fig. 5. Correlation Between Post-Administration 120 Minutes Value and Other Liver Function Tests

× ····· Liver Cirrhosis ● ····· Hepatitis and Liver Disorder

□ ····· Diabetes Mellitus ○ ····· Others

GPT is given in Mizobe units. Alk. Phosphatase is given in Bodansky units.

In normal persons, a peak was noted in all cases at 30 minutes after which the value gradually decreased, and by 60 minutes it dropped below the pre-administration value. This phenomenon was considered to be due to the fact that the amount of sugar metabolized is greater than the amount of converted glucose produced.

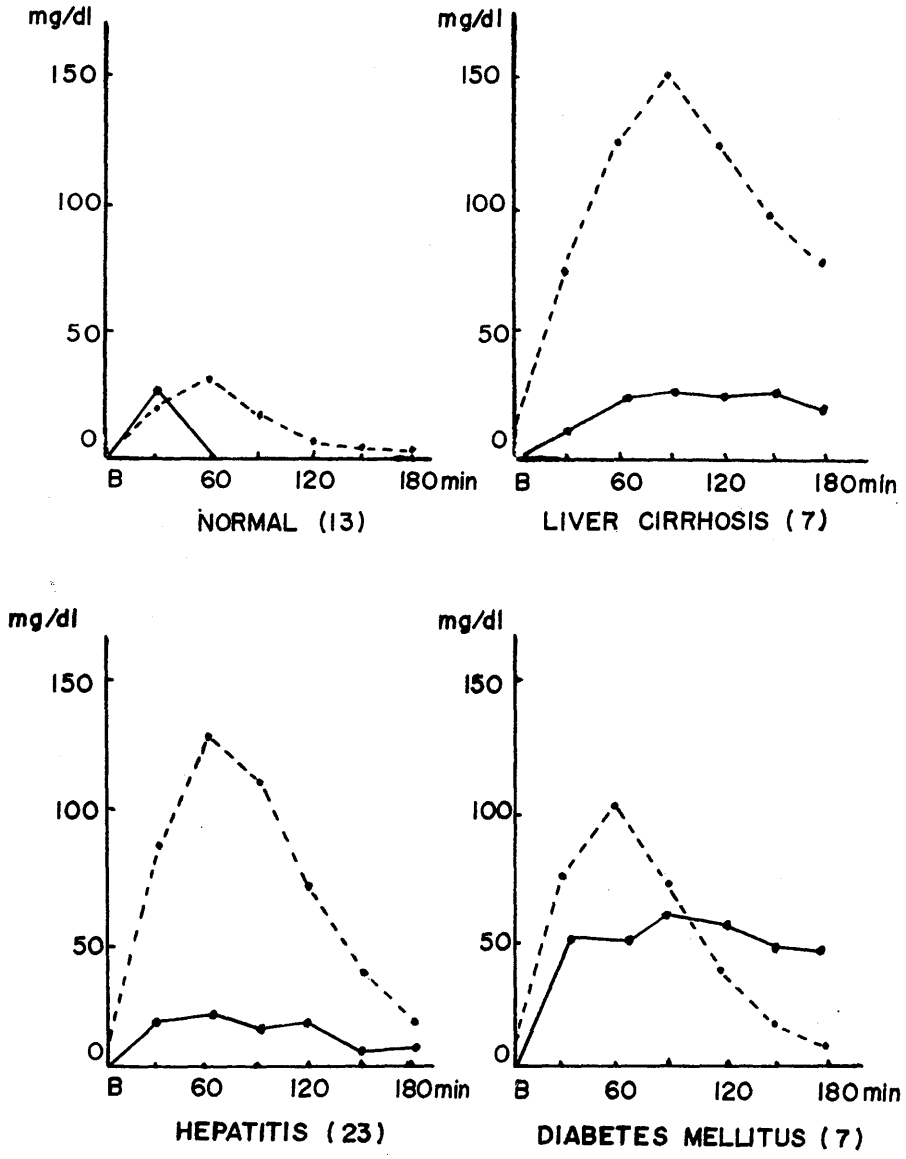


Fig. 6. Changes in Blood Glucose After Administration of Galactose

•——• : Converted glucose value ·····• : Galactose value

( ) : No. of cases

Figures are mean values of all cases.

In hepatitis and liver cirrhosis the peak for converted glucose was apparent at about 60 minutes, after which the values in both diseases decrease, although the drop was more gradual in liver cirrhosis.

In diabetes mellitus the peak of the converted glucose curve was even further delayed and appeared at 90 minutes, and a high value persisted even as long as 180 minutes.

The ratio of glucose and galactose values plotted against time is shown in Figure 7. In normal persons, the ratio rose rapidly and reached its peak in 30 minutes, and thereafter it decreased. The ratio of glucose and galactose values in the hepatitis and liver cirrhosis cases was approximately 1 : 5 and the 30 to 180 minute values were unchanged. On the other hand, in diabetes mellitus, the ratio at 30 minutes after administration was about the same as that of normal person, but subsequently with the lapse of time it increased, and at 180 minutes was as high as 5.1.

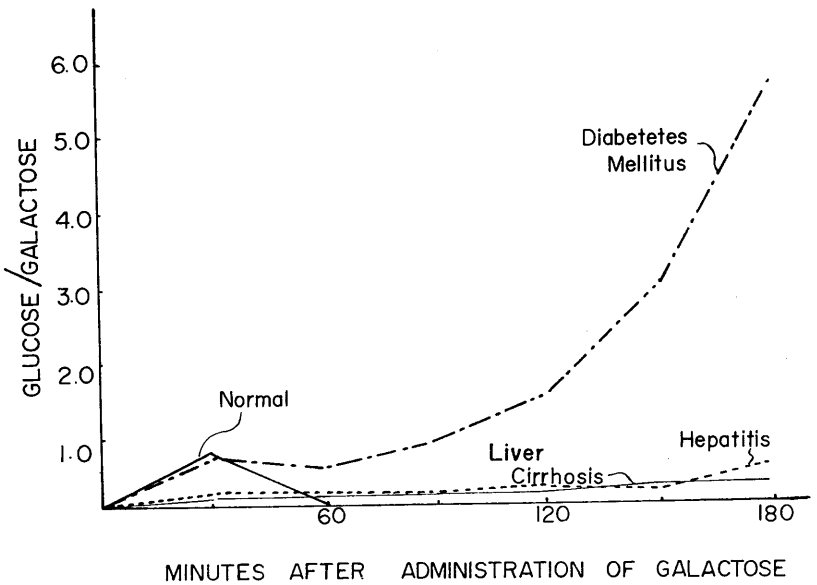


Fig. 7. Changes with Time of Converted Glucose Value/Galactose Value

CONSIDERATIONS

As explained above, in all diseases with liver disturbances there was definite retention of galactose in blood, and our results proved to be more reliable than those reported in the past. Particularly, in cases with liver cirrhosis galactose retention was greater than those with other types of liver disturbances. Further, the peak of the blood galactose curve which reflects intestinal absorption, was

attained at 90 minutes in the former and at 60 minutes in the latter, which suggested marked glucose metabolism disturbance in liver cirrhosis. Also, as the blood galactose value was high, it indicates that there was adequate intestinal absorption. Therefore, as the peak in the blood galactose curve was present at 90 minutes in liver cirrhosis alone, it is felt this can be used as a differential diagnostic procedure from the other diseases.

In all diseases the galactose value prior to administration (fasting state) was slightly higher than in normal subjects, but as the concentration is low the error in determination value is great, therefore, it is dangerous to conclude that a subject has liver disease on the basis of the fasting state value alone.

Rommel[21] et al. state that when the oral administration procedure is used, it is best to make the diagnosis of liver disturbance on the basis of the galactose value determined 90 minutes after administration, but in the present study it was found that the 120 minute value was better (Fig. 3). Further, the effects of intestinal absorption were smaller in our procedure. Therefore, in routine tests, it is felt that two determinations, that is, prior to administration and at 120 minutes after administration, are sufficient enough to serve the purpose of the test, and that repeated blood collections made to plot the tolerance curve are not necessary.

The fact that there was poor correlation with the various liver function tests is probably due to the inclusion of cases with such diseases as diabetes mellitus which do not bring about much change in liver function, but do present high galactose values. However, there were several cases of hepatitis in the cured stage in whom all test findings were normal with the exception of high galactose values. Therefore, this indicated that the 120 minute value of the galactose tolerance test is more sensitive than the other liver function tests, and as a matter of fact, the authors would like to stress that it is an independent test. However, in the comparison of this test against BSP, it was found that the latter was slightly more sensitive as had been poined out by Tengström.[9] However, as the two tests are different in nature, they do not necessary correlate well with one another. Therefore, it is felt that in the determination of whether or not there is parenchymal disorder of the liver, the patient should always be subjected to both tests. From this point of view, the experiment of Zieve et al.[22] where galactose, BSP and benzoic acid were mixed together and then administered simultaneously by intravenous injection after which determintion for all were made at the same time is quite noteworthy.

Owen et al.[23] reported that in the cured stage of hepatitis, excretion of galactose into the urine ceases prior to disappearance of clinical symptoms. Boller[24] performed galactose tolefance tests both during the night and day, and reported that the prognosis was poor among those with a high nocturnal value. In our investigations, it was noted that there was change in the galactose tolerance curve in accordance with changes in symptoms, but we were unable to determine the prognosis.

Shay et al.[3] reported that, based on the fact galactose metabolism is not directly affected by insulin and other hormones, it was possible to differentiate the type of liver disorder even in cases with complicating diabetes mellitus by measuring urine galactose. In other reports on the results of oral administration, there is little review of the effects of diabetes mellitus. In the experiments of Tengström et al.[10] using the intravenous administration method, it was reported that no effects of diabetes mellitus were noted. The results obtained by the present authors after administration of galactose showed a higher blood concentration than normal, and at the same time the value of converted glucose was also high. As the quantitative determintion used in this study is capable of adequately decomposing glucose even in high concentrations in excess of 400 mg/dl,[13] the above cannot be considered due to error in the quantitative determintion of galactose. Thus, it is felt such a phenomenon is not due to liver dysfunction caused by diabetes mellitus, but due to retention of converted glucose in blood resulting from insulin deficiency, and this high blood glucose secondarily inhibits the conversion of galactose to glucose by the liver, resulting in both galactose and glucose being retained in the blood. Therefore, when the patient has diabetes mellitus, it is dangerous to attempt to determine the degree of liver function by galactose tolerance test alone. However, when the ratio of converted glucose value to galactose exceeds 1.0 (Fig. 7) for the post administration 120 minute value, it may be useful as a method for determining the degree of insulin deficiency as well as the state of pancreatic function.

Owen[23] and Tengström et al.[9] have reported that there is retention of galactose in blood in thyroid diseases, but we have not performed tolerance tests in cases with such diseases.

Colcher et al[25] administered galactose intravenously, and after the galactose value was plotted against time on semi-logarithm paper, it was noted taht a linear relationship was obtained with lapse of time. Further, Tengström et al.[9] using a similar procedure, presented the blood concentration of galactose in T 1/2 values. However, in their reports it is merely stated that the galactose value is higher than the normal value by 89 % in liver cirrhosis, 45 % in acute hepatitis, and 64 % in liver cancer, and the results are not as constant as those obtained in the present investigation.

Theoretically, the intravenous method is ideal, but as a large volume of galactose must be administered within a short period of time and there have been cases of shok reported by this method,[26] it is difficult to decide which is better. On the basis of our experience, we believe that with the exception of patients with diarrhea and difficulty in swallowing, the oral method is as simple and practical as the glucose tolerance test, and also the results obtained are good enough to permit an assessment of the state of the liver function.

SUMMARY

The authors have made a review of the merits and disadvantages of the oral galactose tolerance test by administration of 40 g of galactose in 60 cases using a simple quantitative determination of serum galactose reported earlier.

The oral galactose tolerance curve in all cases with hepatic insufficiency was higher than the values of normal persons. Specifically, the blood galactose value in cases with liver cirrhosis was elevated, showing a peak at 90 minutes compared to 60 minutes in all other disease states and in normal persons.

It was found that the use of the post administration 120 minute value was satisfactory for the determination of presence or absence of hepatic insufficiency. Therefore, it was found that for routine tests it was not necessary to plot the tolerance curve based on several repeated blood samples, but that 2 samples, one collected prior to administration and the other at 120 minutes after administration were sufficient. When the latter value was more than 20 mg/dl, indication retention in the blood, this could be interpreted as confirming the presence of a liver disorder. However, consideration should be given to the fact that the blood galctose value is also high in diabetes mellitus.

It was noted that correlation between the 120 minute value and other liver function tests was poor and that the galactose tolerance test was an independent liver function test which gave results that changed according to the disease stage and degree of severity and thus was useful in determining the state of recovery of hepatic function.

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