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The Galactose Elimination Capacity in Control Subjects and in Patients with Cirrhosis of the Liver

By

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The elimination rate of galactose from the body is, theoretically, a valuable indicator of the liver function, particularly if the hepatic elimination capacity can be measured. The galactose elimination capacity may be determined with good approximation by an intravenous, single-injection galactose test (12). In order to study the clinical value of this test, it was applied to a group of control subjects and to patients with impaired liver function due to cirrhosis.

Methods

The patients were examined while they were still lying in their beds, 15 hours after a meal. Galactose was given intravenously, on the average 483 (S.D. 41) mg/kg body weight, dissolved in 100 ml of water and injected within 6 minutes. In the control subjects arterial samples were drawn at intervals of 3 min. during the period from 20 to 35 min. after the start of the injection, and then at intervals of 5 min. to 45 or 60 min. after the start. In patients with cirrhosis blood samples were drawn at intervals of 5 min. during the period from 20 to 60 or 75 min. after the start. The analytical procedure of Tygstrup et al. (11) was employed.

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The rectilinear part of the plasma galactose concentration-time curve was delimited graphically, and the slope was calculated by regression. The galactose elimination capacity (GE) was calculated as

$$GE = (M - U) / (t_{c=o} + 7) \quad (1)$$

where M is the amount injected, U the amount of galactose excreted in the urine, $t_{c=o}$ the extrapolated time when the concentration is zero, and 7 a correction for uneven distribution of galactose during the test (13).

Material

The control material consists of 96 inpatients in whom liver disease was not suspected. They suffered from a variety of disorders such as chronic bronchitis, asthma, constipation, heart disease without congestive failure, and (as the most frequent diagnosis) neurosis.

The material of patients with cirrhosis comprises 35 cases. In 32 of the patients the diagnosis was confirmed histologically (biopsy or autopsy). The etiology was probably alcoholism in 6 patients (1 female and 5 males), and viral hepatitis in 7 patients (4 females and 3 males); it was unknown in 22 patients (15 females and 7 males).

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Table I. Mean values and SD of data from intravenous galactose tests in control subjects and patients with both the results of the initial test in each patient, and the results of all the tests, including repeated tests in

	Age (yrs)	Body weight (kg)	BSA (sqm)	Galactose elimination capacity		Slope of elimination curve
				mg/min	mg/min/sqm	(mg/l/min)
Control subjects						
	Total	♀	♂	♀ ♂	♀ ♂	Total ♀ ♂
No.	96	32	64	32 64	32 64	96 32 64
Mean	35.7	60.3	67.5	1.63 1.81	438 482	267 47.6 42.3
SD	13.4	15.4	9.7	0.20 0.14	92 87	43 8.5 7.6
Var. coeff. (%)	37.5	25.5	14.1	12.5 7.9	21.0 18.1	16.0 17.9 18.0
Patients with cirrhosis						
	Initial test / Total	Initial test / Total	Initial test / Total	Initial test / Total	Initial test / Total	Initial test / Total
No.	35 101	35 101	35 101	35 101	35 101	35 101
Mean	50.6 55.0	63.0 61.4	1.64 1.65	235 244	142 149	17.9 20.7
SD	13.7 10.7	13.6 10.9	0.16 0.14	69 74	58 48	8.3 10.1
Var. coeff. (%)	27.1 19.4	21.6 17.8	9.8 8.5	29.4 30.2	40.8 31.9	46.4 48.6

In 15 of the patients with cirrhosis the intravenous galactose test was repeated at different stages of the disease. Repeated tests were included only if the interval between them was at least 3 months, or if a significant change in the clinical state of the patient had occurred. In 5 patients more than 5 tests were performed (one patient 6 tests, two patients 8 tests, one patient 11 tests, and one patient 14 tests). Altogether 101 tests in patients with cirrhosis were included.

Results

Control subjects

In table I the mean values and the variation of the observations are given. It appears that in some observations there is a significant difference between females and males. Thus the galactose elimination capacity is smaller in females. This difference disappears, however, if the elimination capacity is given in relation to body weight or to body surface area. By regression the following equations were found, assuming linear relationships:

$$GE = 171 + 4.54 \times kg; \quad r = +0.607; \quad s = 72.6; \qquad (2)$$

and

$$GE = -45 + 293 \times sqm; \quad r = +0.594; \quad s = 73.5; \qquad (3)$$

where GE is the galactose elimination capacity, r is the correlation coefficient, s is the standard deviation of GE from the regression line (residual standard deviation). In equation (2) the intercept is different from zero ($P < 0.001$), in equation (3) it is not significantly different. The partial correlation between galactose elimination and body weight for constant body surface is $+0.170$, and between galactose elimination and body surface for constant body weight $+0.074$. This indicates that body weight is the determining factor.

In the control subjects no relation was found between the galactose elimination

cirrhosis. The control material is divided into females and males. In the patients with cirrhosis there are given some patients

Extrapolated time at c = 0 (min)	Residual concentration at		Excreted in urine (g)		Vol. of distribution			
	45′ (mg/l)	60′ (mg/l)			(l)		% of body weight	
Control subjects								
Total	Total	Total	♀	♂	♀	♂	♀	♂
96	96	96	32	64	32	64	32	64
60.6	456	200	3.03	3.69	10.5	13.0	17.8	19.5
9.0	228	130	1.44	1.05	2.1	1.9	3.2	3.0
14.9	50.0	65.0	47.6	28.4	19.9	14.8	17.7	15.6
Patients with cirrhosis								
Initial test / Total	Initial test / Total	Initial test / Total	Initial test / Total		Initial test / Total		Initial test / Total	
35 / 101	35 / 101	35 / 101	35 / 101		35 / 101		35 / 101	
115.9 / 115.9	1,047 / 1,044	849 / 797	2.74 / 2.93		15.8 / 14.5		25.2 / 23.6	
34.9 / 40.2	259 / 257	310 / 305	1.66 / 1.47		4.1 / 3.7		4.7 / 4.7	
30.1 / 34.7	24.7 / 24.6	36.5 / 38.3	60.6 / 50.2		25.9 / 25.6		18.7 / 19.7	

capacity and the clinical diagnosis, but the values tended to be lower in patients with peptic ulcer. In the latter group, consisting of 12 males, the galactose elimination capacity was on the average 440 mg/min. (S.D. 75), and when this is compared with the reamining male controls (mean 489 mg/min., S.D. 89), the P-value of the difference is between 0.1 and 0.05.

The galactose elimination capacity tended to decrease with increasing age, the decrease amounting to about 1 mg/min. per year. The P-value of the correlation coefficient between elimination capacity per sq·m. and age is between 0.1 and 0.05.

The volume of distribution was smaller in the females than in the males, and this difference is not eliminated by relating the volume to body weight. In the female controls the relation, determined by regression, was

$$V = 4.31 + 0.102 \times kg; \quad r = +0.732; \tag{4}$$

and in the male controls

$$V = 7.67 + 0.079 \times kg; \quad r = +0.397; \tag{5}$$

where V is the volume of distribution, r the correlation coefficient. The regression coefficients of equation (4) and (5) are not significantly different ($0.4 > P > 0.2$), but the difference between the adjusted means, amounting to 1.88 l, is highly significant ($P < 0.001$). The galactose elimination capacity was positively correlated to the volume of distribution ($r = +0.518$, $P < 0.001$).

Patients with cirrhosis

Table I also shows the observations made in the patients with cirrhosis. The mean values and standard deviations are given. There was no demonstrable difference between female and male patients as to galactose elimination capacity

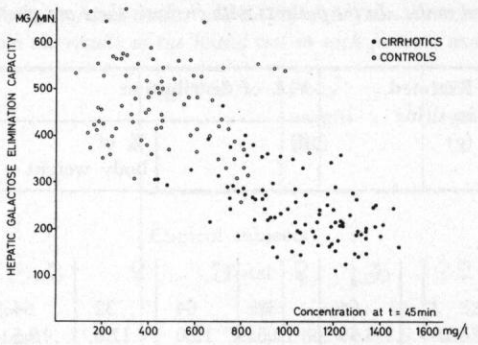

Fig. 1. Correlation between galactose elimination capacity and the residual concentration of galactose 45 min. after the start of the injection.

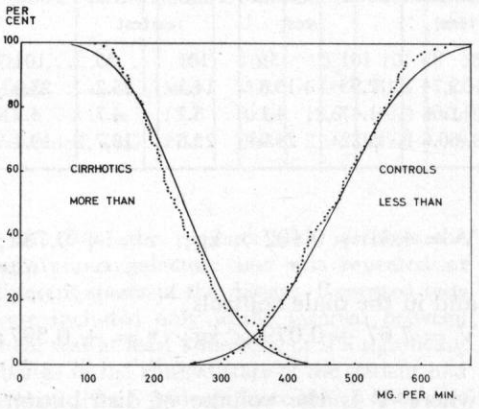

Fig. 2. Distribution and overlapping of determinations of the galactose elimination capacity in control subjects and patients with cirrhosis. The lines show a normal distribution.

in the initial tests. In both the initial and the total number of tests the galactose elimination capacity was not correlated to age, body weight or body surface area. The galactose elimination capacity was significantly higher ($P < 0.05$) in 39 tests made during prednisone treatment than in untreated patients (mean 263 mg/min., S.D. 73.7, and 232 mg/min., S.D. 71.8). In 40 observations made in patients with ascites or edema it was significantly lower ($P < 0.001$) than in patients wihtout these signs (mean 210 mg/min., S.D. 60, and 267 mg/min., S.D. 64).

The volume of distribution was significantly greater ($P < 0.001$) in patients with ascites or edema than in those without (mean 17.1 l, S.D. 3.6, and 12.8 l, S.D. 2.7). The volume of distribution was smaller ($P < 0.02$) in the patients treated with prednisone than in the untreated group (mean 13.3 l, S.D. 3.4, and 15.2 l, S.D. 3.7). The volume of distribution was correlated to body weight as in the control material. The regression equation was

$$V = 1.22 + 0.216 \times kg; \quad r = +0.638; \tag{6}$$

The intercept is not significantly different from zero, and there was no significant difference between female and male patients. The galactose elimination capacity was negatively correlated to the volume of distribution ($r = -0.362$, $P < 0.001$).

The galactose elimination capacity and the residual concentrations 45 and 60 minutes after the injection are, as expected, highly correlated (-0.773 and -0.805, respectively, including both controls and cirrhotics), but still these concentrations are of limited value as a measure of the galactose elimination capacity, particularly when the latter is high (fig. 1). The standard deviation of the galactose elimination capacity from the regression line, with the residual concentration at 45 minutes as independent variable, is 88 mg/min., and with the concentration at 60 minutes as independent variable 82 mg/min.

It appears from table I that the urinary excretion of galactose is slightly but insignificantly smaller in the cirrhotics than in the controls. This is also the case when the excretion is expressed as a percentage

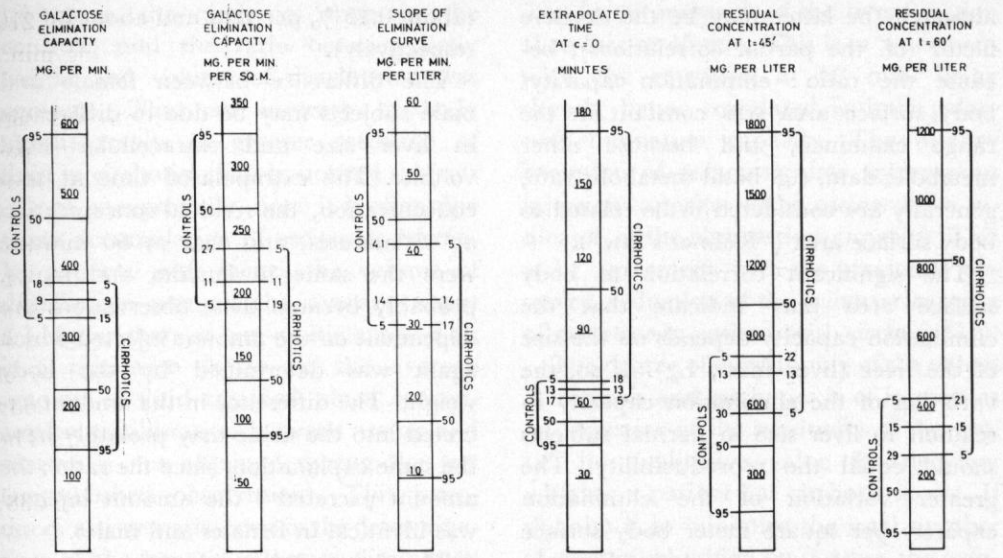

Fig. 3. Diagrammatic presentation of the distribution and overlapping of values in control subjects and patients with cirrhosis. Per cent of obervations less then (upper part) or more than (lower part) the values indicated. The 5, 50, and 95 % limits are indicated together with the percentages at the overlap point.

of the amount injected (11.0 and 10.0%, respectively). In agreement with this the correlation between galactose elimination capacity and amount excreted in the urine is positive in the total material ($r = + 0.196$, $P < 0.01$).

The separation between the observations in patients with cirrhosis and those obtained in the control subjects cannot be calculated from the mean values and standard deviations given, because both groups are heterogenous and the values are not evenly distributed. The distribution and the overlapping of the values for the galactose elimination capacity of the controls and the cirrhotics may be seen from fig. 2. The curve of normal distributions with the mean values and standard deviations given in table I are shown. The theoretical curves show slightly better separation between controls and cirrhotics than the actual observations do. In fig. 3 the overlapping of the values of the galactose elimination capacity and of some of the other data from the galactose test is depicted. The overlapping is smallest in the case of the galactose elimination capacity, but it is of the same order of magnitude in all of them.

Discussion

Repeated determinations of the galactose elimination capacity in the same subject show that the reproducibility of the method is about 10 per cent (13). In the present control material the variation is about 20 per cent, and when related to body surface area, as estimated by the Du Bois height-weight chart, about 16 per cent. It seems more reasonable to correlate the elimination capacity with body surface area than with body weight,

although the latter may be the decisive factor (cf. the partial correlations), because the ratio : elimination capacity/ body surface area was constant in the range examined, and because other metabolic data, e.g. basal metabolic rate, generally are considered to be related to body surface area ("Rubner's law").

The significant correlation to body surface area may indicate that the elimination capacity depends on the size of the liver (liver mass, L_m). If so, the variation of the elimination capacity in relation to liver size in normal subjects should equal the reproducibility. The greater variation of the elimination capacity per square meter body surface shows that either the correlation between body surface and liver size or the correlation between liver size and elimination capacity is incomplete. The former correlation probably exists at least *inter species* (6), but it is not well defined in man, probably owing to the considerable error involved in the determination of both parameters in relation to their absolute variation. The latter correlation requires normal liver function, and with the normality criteria used in the present work this may not be so in all the subjects. For instance the tendency to lower values in the patients with peptic ulcer may reflect a slightly impaired liver function in this condition (1).

The influence of the age of the subjects on the elimination capacity has no practical significance, but reduced liver-function in old people has also been observed with other tests (7). It may be related to a diminution of liver size with age (10) or to a generally decreased metabolic activity. The decrease in the galactose elimination capacity is of the same order of magnitude as the reduction in the basal metabolic rate (3) (about 0.25 % per year and about 0.4 %, respectively).

The difference between female and male subjects may be due to differences in liver size and extracellular fluid volume. The extrapolated time at zero concentration, the residual concentration at 45 minutes, and that at 60 minutes were the same in females and males, probably because these observations are dependent on the amount injected which again was determined by the body weight. The difference in the amount excreted into the urine may probably have the same explanation, since the ratio : the amount excreted / the amount injected was identical in females and males.

The slope of the elimination curve in the blood approximately equals the ratio: elimination capacity / volume of distribution. It was higher in females than in males, showing that in the females the volume was relatively more reduced than the elimination capacity. The volume of distribution was about 18 % of body weight in females and 20 % in males, i.e. close to the values frequently given for the extracellular volume (2). The volume of distribution is not, however, a constant fraction of the body weight; the fraction decreases with increasing body weight (see equation (3) and (4)). In the extensive study of Moore et al. (4) a similar relationship between the body weight and several parameters of body composition was found. With regard to the extracellular volume, their regression equations are very similar to equation (3) and (4), their regression coefficients for females and males are the same, and the difference between the adjusted means is statistically significant, as with the present method.

The volume of distribution expressed as a percentage of body weight was

higher in the cirrhotics than in the controls, and the ratio between body weight and volume of distribution was constant. Thus an increase in body weight results in greater retention of fluid in cirrhotics than in normal subjects — not unexpectedly, since it is often due to an accumulation of ascites or edema. In patients with ascites the volume of distribution was on the average about 4 l higher than in non-ascitic cases. This is a minimum figure for the average amount of fluid retained, since concentration equilibration between ascites and plasma is not obtained during the test (unpublished observation). This introduces a systematic error in the determination of the hepatic galactose elimination capacity, causing it to be over-estimated (13). The elimination capacity was significantly less in cases with ascites, however, and the error is thus too small to hide the fact that the liver function usually is more reduced in patients with ascites. The same appears from the negative correlation between the elimination capacity and the volume of distribution in cirrhotics. In the control subjects the correlation was positive, probably because both the galactose elimination capacity and the volume of distribution were positively correlated with body weight.

Determination of the galactose elimination capacity is rather time-consuming. If it could be assessed with reasonable accuracy from the concentration in a single blood sample, this would be a great practical advantage. It appears from fig. 1 that the correlation between elimination capacity and residual concentration is satsifactory only when the elimination capacity is low; the retention test therefore is relatively insensitive. Zieve et al. (14) claim that the retention at 60 min. is a better measure of the liver function than that at 45 min. This is in agreement with the retention at 60 min. being slightly better correlated with the galactose elimination capacity. The urinary excretion of galactose after intravenous injection appears to be useless as an indicator of the elimination capacity. This is in agreement with the previously observed reduction of the urinary clearance of galactose in patients with cirrhosis (12).

The degree of overlapping of the values in controls and cirrhotics is of interest as an indicator of the sensitivity of the test, i.e. its qualitative value for deciding whether a patient has cirrhosis or not. If the aim is to minimize the total number of cases misclassified by the test, the overlap point must be used as the limit between normal and abnormal galactose elimination capacity, provided that the material consists of the same number of cirrhotic and non-cirrhotic patients. If non-cirrhotic patients dominate, the limit should be fixed at a lower value, and *vice versa*. The purpose of the test may be, however, to exclude cirrhosis, in which case a higher limit should be used, e.g. a limit exceeded by only 5 % or 1 % of the patients with known cirrhosis. This is how the bromsulphalein-retention test is generally used, 5 % retention being considered the highest normal limit. According to Zieve & Hill (15, 16) 10 % of normal subjects and 9.8 % of cirrhotic patients are misclassified if 8.2 % retention is regarded as the dividing point, but if 5 % retention is used, less than 5 % of cirrhotic patients and about 30 % of normals will be on the wrong side. Thus the test does not distinguish between cirrhotic and non-cirrhotic patients, but between patients who should be further tested and those who need not. From the data presented it seems unlikely that the

galactose elimination capacity will be any better than the bromsulphalein-retention test for this kind of screening.

When the present material is used to define the limit between cirrhotic and non-cirrhotic patients, it should be borne in mind that the latter group does not consist of normal subjects in the physiological sense. Had this been the case, the separation would probably have been better, but it would be less useful for the clinical purpose of the test. Yet it may be necessary to revise the normal range of the test if, for example, old patients, or patients with peptic ulcers are more frequent. One should also consider whether the material of cirrhotic patients is comparable with the present one. It is known that cirrhosis may vary clinically in different areas (9); moreover, the number of mild cases may depend very much on the other diagnostic procedures used, especially on the indications for liver biopsy. In the present material there are rather too many mild cases, owing to the inclusion of repeated tests on some of the patients (only those surviving some time could undergo several tests).

The overlapping of the values found in controls and cirrhotics, shown in fig. 3, would probably have been smaller if the materials had been more homogenous. There has to be some overlapping, however, since in a liver biopsy cirrhotic changes do not preclude the presence of a normal amount of normally functioning liver cells. Furthermore the wide range of the normal values means that in many subjects the elimination capacity may be reduced 20 % or more without falling below the normal limit. With a physiological variation of 20 % (standard deviation) the minimum probable error of diagnosis in patients with e.g. 50 % loss of function will be 10 % (8). A narrowing of the normal range (for instance, by relating it to the body surface area) is desirable, but as shown in fig. 3, this serves to increase the overlapping, presumably because the cirrhosis influences the determination of the body surface area. A patient with marked wasting will have an elimination capacity per square meter that is disproportionately high, and when large amounts of ascites are present, determination of the body surface area loses its physiological meaning. The separation could be improved only by relating the elimination capacity to the pre-morbid body surface area, but this can rarely be done with accuracy.

The conclusion is that the galactose elimination capacity, just like the other known biochemical liver tests, is not diagnostic for cirrhosis (5). The sensitivity of the test is utilized fully only if the subject can be made his own control, as in the evaluation of different kinds of treatment, or if groups of observations can be compared by statistical analysis.

Summary

The galactose elimination capacity was determined with the single injection technique in 96 control subjects. It was significantly smaller in females than in males, unless it was expressed in relation to body surface area.

In 35 patients with cirrhosis of the liver, 101 determinations were performed. Nine per cent of the values in control subjects and patients with cirrhosis were overlapping, and the separation could not be improved by relating the elimination capacity to body surface area. The physiological variation implies that it may be impossible to decide if the liver function is normal or not from a single determination of the galactose elimina-

tion capacity, but if a reference value is obtainable, either in the same subject or in a comparable group, small variations in the liver function may be detectable.

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