0002-9270/96/9105-0991$03.00/0
THE AMERICAN JOURNAL OF GASTROENTEROLOGY

Vol. 91, No. 5, 1996
Printed in U.S.A.

The Galactose Elimination Capacity Test: A Study of the Technique Based on the Analysis of 868 Measurements

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Objectives: **Our objective in this study was to analyze the correspondence of galactose concentration-on-time-decay curve to theoretical assumptions and the confidence limits of the determination of galactose elimination capacity.** ***Methods:*** **We analyzed a retrospective series of 868 galactose elimination tests, performed on subjects with and without liver disease. Zero-order kinetics of galactose elimination was tested by comparison of the residual variance of linear regression with that obtained after quadratic transformation. The uncertainty in determination of galactose elimination capacity was calculated on the regression line by computing the 95% confidence limits of the estimate.** ***Results:*** **The time-course of galactose concentration suggested an initial uneven distribution, and the first (20-min) data point deviated significantly from the regression. The galactose decay curve in plasma rejected linearity in 13% of tests; after exclusion of the first data-point, linearity was rejected in only 3% of cases. The 95% confidence interval of galactose elimination capacity was on average ± 16%, but in individual tests it was as large as ± 60–80%. The uncertainty of the test was not affected by linearity. It was larger, with poor fitting of the experimental data on the regression of galactose concentration on time, low number of data points, and low galactose elimination. It was maintained within ± 20% only when residual variance was ≤ 2% of total variance (nearly 50% of tests).** ***Conclusion:*** **The methodology for the determination of galactose elimination capacity leads to considerable uncertainty as to the final result, which must be considered whenever the test is used for clinical purposes in the decision-making process. It tends to be larger in patients with advanced disease and can be accurately calculated so as to contribute to a proper evaluation of the test result.**

INTRODUCTION

Considerable interest has centered on the study of dynamic liver function tests in patients with liver disease (1), to derive data useful for prognostic purposes and in medical decision making. Based on the assumption that the elimination rate of a substance from the blood represents the capacity for uptake and elimination from the liver, some kinetic parameters can be derived that measure the functional liver mass; *i.e.*, the functional evaluation of the liver can be described in terms of the velocity of a metabolic process (2).

This velocity depends on substrate concentrations, and the relation between substrate levels and metabolic reactions in the intact organism follows the simple kinetics of enzymatic reactions (Michaelis-Menten kinetics). The metabolic process may be saturated, and at very high substrate concentrations, the velocity of the process equals V_{max} (3).

Galactose is one of the most widely used test substances. It can be infused at rates able to saturate its metabolism to glucose (4). Under these experimental conditions, the elimination rate of galactose from blood follows zero-order kinetics (4) and is a measure of the capacity of the system (*i.e.*, the intact organism and, indirectly, the liver) in this metabolic reaction (3).

The galactose elimination capacity (GEC) test has been extensively studied in animals and in man for at least 30 yr. Commonly, the test is performed after intravenous bolus injection of galactose, and the elimination rate during the period between 20 and 60 min is used to calculate the hepatic removal of galactose. However, after the initial assessment performed by Tygstrup (3), no study has ever reported in detail the fitting of experimental data with theoretical assumptions in large series of patients with and without liver disease.

Data derived from a large series of tests performed during the last 15 yr in our department have been used to validate the test and to determine the limits of Tygstrup's technique (3), widely used in the clinical setting as a quantitative measure of liver function.

MATERIALS AND METHODS

Subjects

Since 1978, we have been using the galactose elimination test in a variety of patients with and without liver disease. The present retrospective study is based on the data obtained

Received June 14, 1995; accepted Jan. 10, 1996.

in 1015 tests. The analysis was limited to 868 cases in which at least five determinations of blood galactose after intravenous galactose bolus injection were available and/or suitable for analysis (see below). One hundred and four tests had been performed in 95 subjects free of hepatic disease; they had been studied for several years, mainly for evaluation of the effects of aging on liver function in humans. Therefore, their age range was extremely wide (17–90 yr); in any case, they had no evidence of previous or actual liver disease, and routine liver function tests were always within the normal range.

Patients with hepatic dysfunction (764 tests in 508 patients) had liver disease ranging from chronic persistent or active hepatitis (116 tests) to liver cirrhosis. In this last group, the test was performed in 318 cases belonging to the Child-Pugh (5) class A, 222 class B, and 108 class C. In a few subjects with chronic hepatitis, the test was also performed in the absence of any alteration in routine liver function tests. In cirrhosis, the test was never performed in the presence of ascites, but only after resolution of clinically detectable ascites, under diuretic treatment. No tests had been performed in patients with acute hepatitis.

In all cases, renal function was normal or only minimally compromised, the upper limit of serum creatinine being 1.6 mg/dl.

METHODS

The test was always performed in the morning, after an overnight fast. Galactose concentrations were determined in capillary blood at 5- to 10-min intervals, between 20 and 70 min after intravenous injection of 500 mg/kg body weight of galactose in 30% water solution (w/v). Zero time was set at the start of the infusion, which lasted between 2 and 3 min. Sampling time was chosen according to routine liver function tests, to obtain galactose concentrations at the end of the test above 40 mg/dl. In the absence of liver disease, or in subjects with chronic hepatitis without cirrhosis, the sampling schedule consisted of six determinations at 5-min intervals between 20 and 45 min after injection. To compensate for the delayed elimination of galactose and to improve the reliability of the estimate of the regression of galactose concentration on time, since 1986 the sampling time was delayed up to 70 min in cirrhosis with overt liver cell failure, and capillary blood was sampled at 10-min intervals. Any determination <40 mg/dl was not used in the assessment of the elimination rate, because previous studies have shown that at blood galactose concentrations lower than 40 mg/dl, a significant, systematic deviation of the experimental data from linearity may be present (6). Blood galactose was determined enzymatically (Test Combination Galactose, Boehringer, Mannheim, Germany). In our laboratory, the intra-assay coefficient of variation of galactose measurement is within ± 3%.

The calculation of GEC was performed according to Tygstrup's method (3). Briefly, galactose elimination was presumed to follow a zero-order kinetics, and the linear regression of galactose concentration on time was extrapolated to the time $t_{c=0}$. To allow for time displacement between extra- and intravascular galactose concentration (7 min), time $t_{c=0} + 7$ was considered as the time of galactose elimination from the body.

Galactose elimination capacity (Q in mg/min) was calculated as $(D - U)/(t_{c=0} + 7)$, where D is the dose infused, and U is the urinary excretion, assumed to be equal to 10% of the injected dose.

To test zero-order kinetics of the blood galactose concentration-on-time-elimination curve, the data were analyzed, as suggested by Snedecor and Cochran (7), by computing the variance of the quadratic regression $Y = a + b_1X + b_2X^2$, where Y is galactose concentration, and X is time. This equation assumes first-order kinetics of galactose elimination rate. Zero-order kinetics of the elimination curve is rejected if the coefficient b_2 is statistically significant, *i.e.*, the quadratic transformation significantly increases the variance explained by the regression.

The confidence limits of any GEC determination depend on the 95% confidence interval of $t_{c=0} + 7$, which is calculated on the regression line $Y = a + bX$, where for $Y = 0$, $X = -a/b$. Coefficient a corresponds to the theoretical galactose concentration at time $t = 0$ ($C_{t=0}$ in μmol/L), b is the slope of linear regression (in mg/dl per min). The 95% confidence interval (95% CI) of the ratio $-a/b$ was also calculated according to Snedecor and Cochran (6), using the so-called linear calibration analysis, and hence the 95% CI of GEC, after correction for time displacement.

Differences between mean values were tested for significance by paired and unpaired t test, as appropriate. To determine the factors involved in the uncertainty of GEC measurements, a series of data potentially correlated with 95% CI of GEC were first tested in linear regression analysis. Following this, all parameters significantly correlated with 95% CI were entered in a stepwise multiple regression analysis.

All statistical analyses were carried out by means of StatView II™ program (Abacus Concepts, Fullerton, CA) implemented on a personal computer. Data in the text and in Table 1 are reported as means [SD].

RESULTS

Linearity of galactose concentration-on-time curve

Blood galactose concentrations 20 min after galactose injection were extremely variable, ranging from 77 to 270 mg/dl (mean 129 [24]) (Table 1). They were slightly higher in patients with liver disease, irrespective of the degree of hepatocellular failure. At the end of the observation period, galactose concentrations were reduced on average by 54 [21] mg/dl, with a remarkable difference between subjects with/without liver disease.

The R^2 values of linear regression analysis of galactose concentration on time were always statistically significant,

TABLE 1
Kinetic Parameters of Galactose Elimination in Healthy Subjects and in Patients with Liver Disease

Parameter	Healthy Subjects (n = 104)	Liver Disease (n = 764)
$C_{t=20}$ (mg/dl)	124 [24] (82–171)	131 [23] (77–270)
Δ galactose (mg/dl)	69 [20] (34–125)	52 [20] (11–181)
Slope (mg/dl per min)	−2.98 [0.98] (−6.48–−1.50)	−1.81 [0.68] (−5.12–−0.29)
$C_{t=0}$ (mg/dl)	182 [40] (117–307)	166 [31] (101–360)
VD (liters)	17.1 [4.0] (7.1–26.2)	19.4 [4.5] (6.6–41.0)
$t_{c=0}$ + 7 (min)	70.8 [11.3] (52.9–111.8)	107.3 [30.8] (57.0–445.7)
GEC (mg/min)	432 [86] (230–702)	310 [86] (83–608)

Results are expressed as means [SD] and (range). $C_{t=20}$ is the actual blood galactose concentration at time t = 20 min; Δ galactose is the difference in blood galactose concentration between the 20-min sample and the last sample during the test; $C_{t=0}$ is the estimated blood galactose concentration at time t = 0 min; VD is the theoretical volume of distribution of injected galactose, and $t_{c=0}$ + 7 is the theoretical time of galactose elimination from the body, both after correction for uneven distribution. All of the differences between normal subjects and patients with liver disease are statistically significant.

the fitting being slightly better in normal subjects (R^2 = 0.97 [0.03]) than in patients with liver disease (0.96 [0.04]; $p < 0.01$). However, when the time courses of galactose concentration were tested for linearity by means of the significance of coefficient b_2 of the quadratic regression, zero-order kinetics was rejected in 113 tests [13 in controls and 100 in subjects with liver disease (chronic hepatitis, 14 cases; Child A cirrhosis, 49 cases; Child B, 27 cases; Child C, 10)], *i.e.*, in more than 13% of cases.

The blood concentration of galactose at time t = 20 min, estimated by linear regression, was lower than the measured value on average by 0.9 [3.9] mg/dl. This difference, although quantitatively small, was statistically highly significant (paired t 7.0; $p < 0.0001$) in both groups. In 583/868 tests, the estimated concentration at time t = 20 min was lower than the measured value, which is significantly different from random distribution (X^2 = 52.0; $p < 0.001$).

Twenty-minute blood galactose concentrations were slightly higher in tests in which linearity was rejected (133 [23] mg/dl), compared with values measured in tests in which linearity was accepted (129 [24]; p = 0.08). After exclusion of the 20-min data, linearity was still rejected in only 25/868 tests (one test in healthy subjects and 24 tests in patients with liver diseases). In patients with liver disease, nonlinearity was not associated with the Child-Pugh class. On the contrary, the exclusion of the last data point in the 740 tests in which six determinations were available failed to improve significantly the linearity of the curve.

Confidence limits of galactose elimination capacity

The theoretical time of galactose elimination, after correction for uneven distribution ($t_{c=0}$ + 7), was on average increased by 50% in patients with liver disease ($p <$ 0.0001); it varied by a factor of 2 in normal subjects and by a factor of 8 in patients with liver disease. Consequently, the estimated GEC was variable in both groups, possibly reflecting the age-related decline of liver function in normal subjects (mean 6.50 [0.93]; range 4.01–8.51 mg/kg/min), and the largely variable degree of hepatocellular failure in patients with liver disease (mean 4.48 [1.11]; range 1.01–7.89), in whom GEC progressively declined in relation to hepatocellular failure (chronic hepatitis, 6.0 [0.9]; Child A cirrhosis, 4.8 [0.7]; Child B, 3.9 [0.5]; Child C, 3.1 [0.6]).

The 95% CI of slope varied on average within ± 18%, whereas the 95% CI of $C_{t=0}$ varied within ± 7%. The apparent volume of distribution of injected galactose was on average 17.1 [4.0] liters in normal subjects and was significantly larger in patients advanced with liver disease (chronic hepatitis, 17.0 [4.6]; Child A cirrhosis, 18.9 [4.3]; Child B, 20.5 [4.4]; Child C, 21.3 [4.1]; ANOVA: p = 0.0001). When expressed per kilogram body weight, the distribution volume of galactose increased 0.26 [0.05] L/kg in healthy subjects to a maximum of 0.31 [0.05] in patients with Child C cirrhosis (ANOVA: p = 0.0001). The 95% CI of apparent volume of distribution varied on average within ± 10% in normal subjects and ± 8% in liver patients.

In the whole series, the average 95% CI of GEC measurement was 32% (between −18% and +14% of the calculated value), but in individual tests it was as large as 140% (from −89% and +51%). Uncertainty was slightly lower in normal subjects (25 [16]%) than in patients with liver disease. In the latter, it was progressively larger according to the degree of hepatocellular failure and reduced GEC (chronic hepatitis, 26 [20]; Child A cirrhosis, 31 [20]; Child B, 36 [22]; Child C, 42 [26]; ANOVA: p = 0.0001). The exclusion of the 113 tests in which linearity was rejected did not produce any remarkable improvement in the CI of GEC, which now ranged from 25 [17]% in healthy subjects to 42 [26]% in Child C cirrhosis.

The CI of GEC significantly correlated with GEC, number of samples available for GEC calculation, coefficient a and b slope, first (20-min) and last galactose concentration, differences in galactose concentration in the course of the test, and, most of all, with the residual variance expressed as percent of total variance (r = 0.952).

Stepwise multiple regression identified in sequence, residual variance, followed by number of samples, b slope (Fig. 1), and first galactose concentration (Fig. 2), as determinants in the uncertainty of GEC measurement. These four parameters accounted for nearly 95% of the uncertainty of GEC, the most important being residual variance in individual tests, which accounted for approximately 90% of uncertainty. Accordingly, the uncertainty of GEC measurement increased dramatically with small changes in the re-

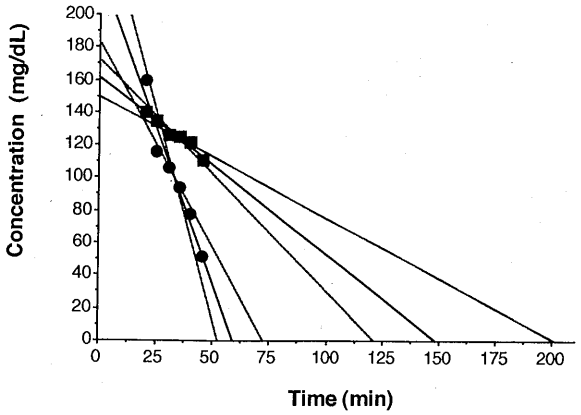

FIG. 1. Effects of galactose elimination rate (slope of the regression of galactose concentration on time) on the 95% confidence interval of $t_{c=0}$, and hence, 95% CI of GEC. Test no. 46 *(closed circles)* and test no. 378 *(closed squares)* have a similar initial galactose concentration and coefficient of determination, but different elimination rates, which results in different galactose concentrations at the end of the experimental period (test 46, 51 ·mg/dl; test 378, 110 mg/dl) at 45 min. The 95% CI of the intercept on X axis varies from −6 to +12 min in test no. 46 and from −30 to +53 in test no. 378.

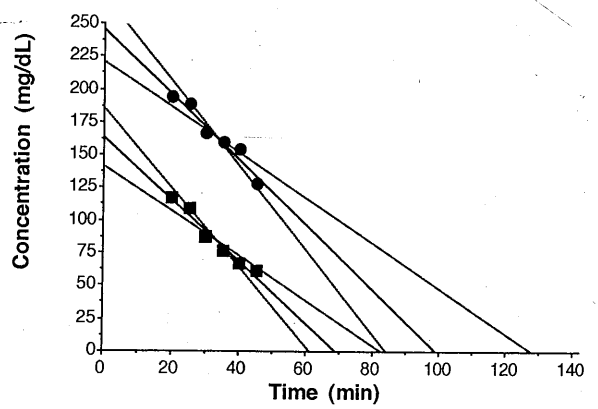

FIG. 2. Effects of galactose concentrations on the 95% confidence interval of $t_{c=0}$, and hence 95% CI of GEC. Test no. 368 *(closed circles)* and test no. 432 *(closed squares)* have similar slope and coefficient of determination, but galactose concentrations are nearly halved in the second case. The 95% CI of the intercept on X axis varies from −15 to +30 min in test no. 368 and from −8 to +14 in test no. 432.

sidual variance and remained within ± 18% only when it did not exceed 2% of total variance. The same was true when only tests that did not reject linearity were considered.

Separate analysis of GEC uncertainty, performed in normal subjects and in patients with liver disease, both as a whole and subgrouped according to severity of liver disease, did not reveal any remarkable differences.

DISCUSSION

The aim of this study was to demonstrate whether the assumptions making GEC a quantitative liver function tests are fulfilled in a large series of experiments performed during the last 15 yr in a university department with a specific interest in liver disease. The test was simplified to make it feasible for routine use, and in the course of the years it was performed for the most part by trained nurses. The results were sometimes used for decision making in patients with liver disease, and a careful evaluation of the limits of the technique is mandatory for this purpose.

The study shows that, in the range of concentrations usually obtained after the standard intravenous bolus injection of 500 mg/kg body weight of galactose, and in the time period suggested by Tygstrup (3), the assumptions that make GEC a quantitative test of liver function are not always satisfied. In 13% of tests, linearity was rejected, and therefore the maximum velocity (capacity) of the system does not seem to be attained. Deviation from linear fitting probably depends on several factors: *a)* uneven distribution of injected galactose in the first part of the elimination curve, which may still be operating at time t = 20 min; *b)* first-order urinary excretion of galactose, which was not corrected for in our tests, where a standard excretion of 10% of injected dose was considered; *c)* the well-known change of elimination kinetics (from zero- to first-order kinetics) at low galactose concentrations, *i.e.*, the passage from a saturation, substrate-independent condition to flow-dependent elimination (8–10). Problem *a)* can be avoided, in most cases, by considering only samples drawn 25 min or more from the start of infusion, because only a negligible proportion of tests (3%) still reject linearity after exclusion of the 20-min galactose concentration.

The possibility that nonlinearity derives from oversimplification that results from assuming that urinary galactose elimination is a fixed amount of injected dose, is less likely. In advanced cirrhosis, the urinary excretion of galactose might be reduced, due to reduced filtration, but nonlinearity in our series was not significantly associated with Child C cirrhosis. Tydstrup (3) reported that the renal clearance of galactose produces a deviation from the straight line that falls within the analytical error, suggesting that the renal loss of galactose can be regarded as constant during the test period. Renal excretion accounts for 5–20% of the injected dose. The use of a fixed factor (10%) in patients with normal liver function and in cirrhosis has been suggested in an attempt to make the test feasible for clinical studies (3) without reducing its validity. Alternatively, it would be necessary to obtain timed urine samples to correct concentration-independent hepatic elimination for concentration-dependent urinary excretion, but the determination of urinary galactose contrasts with the need for simple, bedside-feasible tests to measure liver function. At present, much work is being performed in search of rapid, easy-to-repeat tests of liver function (11, 12), but no test has, so far, gained widespread use. Whereas oversimplification may deduct from validity, the need for timed urine collection may prevent the use of the test in clinical hepatology. Indeed, most of the clinical studies in which GEC has been used as a quantitative liver test assumed the fixed 10% correction for urinary elimination.

Finally, problem *c)* can be avoided by excluding any data

point below 40 mg/dl, as suggested by Tygstrup (3), and as we always did in our tests.

A final source of deviation from linearity, considering the low number of data points in our tests, may be analytical imprecision (see below). In any case, the error introduced by curvilinearity, which leads to overestimation of GEC, is probably negligible in the clinical setting, as demonstrated by the very small difference in GEC after exclusion of the 20-min galactose concentration (324 [95] mg/min *vs.* 317 [95]).

More intriguing is the evidence of a large 95% CI band in the calculation of GEC on the basis of linear regression analysis. Indeed, the final value of GEC is not an exact figure, but derives from the best fitting of the experimental data, subject to confidence limits. Mathematically, the regression line computed by the least-squares method to calculate $t_{c=0} + 7$ is the line that minimizes the residuals in a sheaf of straight lines centered in mean y and mean x, which crosses the X axis at $-a/b$. The 95% CI of GEC, calculated from the 95% CI of $-a/b$, was extremely large, in part because of the need to extrapolate the regression line outside the range of experimental data (7).

As expected, the main factor determining the 95% CI of GEC was the fitting of the experimental data, expressed by residual variance. In our series, a residual variance $\leq 2\%$ of total variance corresponded to a 95% CI of GEC within $\pm$ 12% in healthy subjects and $\pm$ 15% in subjects with liver disease, where it increased with progressive hepatocellular failure. Such good fitting of experimental data was achieved in 422 of 868 GEC determinations (nearly 50% of tests), but the uncertainty of GEC increased dramatically with increasing residual variance, to become as large as $\pm$ 60–80% in a minority of cases, primarily in patients with advanced liver failure due to the additive effect of reduced slope.

The large confidence interval of any GEC measurement may be one reason for the failure to document linearity in the decline of hepatic function with time (13), and must be considered whenever GEC is used in the decision-making process. In patients with end-stage liver disease, GEC rarely falls below 150 mg/min, and values around 100 are nearly incompatible with life (14). Also a 20% uncertainty in GEC measurement at values around 150 mg/min may reduce the validity of the test for prognostic purposes and may affect decision-making (*e.g.*, in the selection of patients for liver transplantation).

The uncertainty in GEC measurement must also be considered whenever the test is used to assess the effects of drugs or surgical procedures on liver function. According to the present data, an average 10% variability is expected on repeated GEC determinations on the sole basis of the CI of the regression, independent of analytical precision and of any specific effect of the tested procedure on liver function. An old study reported a 10% variability of GEC on repeated measurements in the same subjects (15), but in a subsequent study, variability increased to 20% (16). In two control subjects, Bianchi *et al.* (17) reported a variability of 4% and 15% in GEC measured at 2-month intervals. Accordingly, a 10% decrease of GEC in patients with cirrhosis at risk of bleeding and treated with propranolol was not statistically significant (18). Only effects potentially larger than the intrinsic variability of the test are likely to be demonstrated by the technique.

It might be argued that part of the uncertainty demonstrated in the present study might be avoided by better precision in blood galactose determination. The precision in our laboratory ($\pm$ 3% for intra-assay variation) falls within values currently accepted for analyte determination, but errors may also be introduced by sampling itself (incorrect filling of capillary tubes). "Out-liers" might be disregarded during calculation of GEC. This procedure, however, presumes critical evaluation of the time-course of extinction coefficients. Moreover, when only a few (five or six) samples are available, the improvement of fitting obtained by removal of an out-lier may be offset by the enlargement of CI due to a reduced number of data points, so that the final result is not improved.

In conclusion, the present study stresses the limits of the GEC test and the importance of careful evaluation of data derived from the time-curve of galactose elimination, for proper evaluation of any GEC determination in the decision-making process. However, the test probably compares favorably with basal tests of liver function or oversimplified dynamic tests, based on a single determination of substrates or products (19, 20), because the reliability of the results can be mathematically calculated and, hence, its validity can be precisely assessed in individual patients.

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