Renal Excretion of Galactose in Man, with Determination of the Maximal Tubular Reabsorption for Galactose

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Abstract: TENGSTRÖM, B. Renal Excretion of Galactose in Man, with Determination of the Maximal Tubular Reabsorption for Galactose. *Scand. J. clin. Lab. Invest.* **21**, 321-326, 1968.
The urinary excretion of galactose and glucose was determined in ten patients during periods of constant arterial plasma concentration of galactose, obtained by continuous intravenous infusion. The relationship between excretion rate and plasma concentration of galactose indicated that no renal threshold for galactose exists. The tubular reabsorption of galactose was studied as a function of the plasma concentration and the glomerular filtration rate, assuming galactose to be freely filtered in the glomeruli, and not excreted in the tubuli, but reabsorbed in a rate-limited system. The maximum reabsorption of galactose was calculated to be 1.22 mg per ml of filtrate (95% confidence interval: 0.88-2.00 mg/ml). The 'affinity' constant of the reabsorption process was estimated to be 1.37 mg/ml (95% confidence interval: 0.99-2.00 mg/ml). Indications were found of competition between galactose and glucose for a common tubular reabsorption mechanism.

Key-words: Biological transport; galactose; kidney tubules

Second to metabolism in the liver, renal excretion of galactose is probably the most important way by which galactose is eliminated from the body.

The urinary excretion of galactose is one of the parameters measured on evaluation of the liver function by peroral galactose tolerance tests (1, 14). In intravenous tests (16, 17) the galactosuria constitutes a source of error in the determinations. It is therefore important to know how galactose is treated in the human kidney, a matter that does not appear to have been systematically investigated previously.

Dominguez & Pomerene (4) and Eiler, Althausen & Stockholm (5) presented data from dogs, showing a fairly constant clearance of galactose within a wide range of plasma concentrations. These two investigations may be misleading, however. In the former the values were obtained at rapidly falling plasma concentrations and furthermore, it was supposed that all the reducing substance appearing in the urine was galactose, although part of it will probably have been glucose. In the latter investigation the clearance values refer only to plasma concentrations above 1 mg/ml.

Increasing clearance of galactose with increasing plasma concentrations has been demonstrated in the cat by Gammeltoft & Kjerulf-Jensen (6), and in man by the same authors and also by Tygstrup (17). For man the same is also indicated by the results of Waldstein, Greenburg, Biggs & Corn (19), although the figures were interpreted by the authors as showing a constant clearance.

The observations of Gammeltoft & Kjerulf-Jensen (6) and Waldstein et al. (19) were made during periods of constant plasma galactose concentration, but the values obtained were either too few or too widely dispersed to allow definite

conclusions. The clearance values of Waldstein et al. average 60 ml/min at concentrations below 0.4 mg/ml, and 110 ml/min at higher concentrations.

Tygstrup (17) obtained values about half as high. In his experiments, however, a constant plasma galactose level was maintained only at concentrations below 0.5 mg/ml.

The aim of this investigation was to study the urinary excretion of galactose at different renal loads at a steady state, obtained by continuous infusion of galactose at a constant rate.

A particular aim was to throw further light on the question of whether or not a renal threshold for galactose exists, and also, under certain assumptions, to determine the maximal tubular reabsorption rate for galactose. As far as is known to the author, it has not been determined before.

BASIC ASSUMPTIONS

The following assumptions concerning the renal treatment of galactose were made:

a) Galactose is freely filtered in the glomeruli, which means that its concentration, P, in the glomerular filtrate is the same as in the plasma (or in reality plasma water).

b) Galactose is actively reabsorbed in the tubules, but not excreted. This is analogous to what is known about glucose (see 13).

There are reasons to believe that galactose and glucose are treated in a similar way by the tubules, as it has been shown that glucose can inhibit the reabsorption of galactose in the cat, and that the reabsorption of galactose is inhibited by phlorizin poisoning in rabbits, cats, and dogs (6). In addition, it has been found that slices of rabbit renal cortex can accumulate galactose against a concentration gradient in vitro (11).

c) As for glucose, the tubular reabsorption of galactose, T, is positively correlated to the glomerular filtration rate, GFR (18).

d) The tubular reabsorption of galactose is also dependent on the concentration in the glomerular filtrate. The transport of the galactose molecules is supposed to follow a reaction system involving a catalyst or some carrier, which is regenerated in a final and practically irreversible step. In such a situation it can be shown (8) that the overall reaction rate, in this case the reabsorption rate normalized with respect to GFR, will depend on the concentration in the following manner:

$$T/GFR = \frac{k_1}{1+\frac{k_2}{P}} \qquad (1)$$

It is easy to see that k_1 equals $(T/GFR)_{max}$. k_2 is formally identical to the Michaelis constant, but obviously has no simple interpretation in this case. The equation can be written:

$$T/GFR = \frac{(T/GFR)_{max}}{1+\frac{K}{P}} \qquad (2)$$

MATERIAL AND METHODS

Continuous intravenous infusions of galactose were given in eighteen voluntary patients in order to obtain a constant plasma galactose concentration for a period of time long enough to study the urinary excretion of galactose and glucose. In eight patients no such steady state was obtained, and they were therefore excluded from the material.

The results of the investigation are therefore based on ten patients (six men and four women), aged 35-73 years. Their normal renal function was demonstrated by the absence of proteinuria, and by serum creatinine values of 0.7-1.2 mg/100 ml before the investigation, and by endogenous creatinine clearance values of 72-143 ml/min per 1.73 m^2 body surface area, determined at the experiments. In two of the patients there was mild arterial hypertension. Otherwise the patients had diseases which presumably did not influence the renal function.

The patients were fasted, but were given 500 ml of water by mouth before the beginning of the experiments, during which 0.9% sodium chloride was administered by intra-arterial infusion at a rate of about 500-1000 ml per hour. Care was taken continuously to supply fluid at a rate well above the diuresis.

30% (w/v) galactose solution (AB Kabi, Stockholm, Sweden) was infused intravenously at a constant rate by means of motor-driven syringes. Infusion rates of 0.27-2.83 ml/min were used. In some patients two different infusion rates were maintained during the same experiment. As a rule, a primary dose of 3-36 g of galactose was injected rapidly before the infusion was started, in order to raise the plasma concentration quickly.

Blood samples were taken in heparinized tubes at 5- or 10-minute intervals via a polythene catheter inserted into the brachial artery. The samples were centrifuged without delay, and the plasma collected.

The urine was collected by an indwelling catheter in the bladder. The collection was made during one or more periods of about 30 minutes, beginning after an infusion time of 60-90 minutes. The bladder was washed out with 20-30 ml of 0.9% sodium chloride at the end of each collection period, the length of which was carefully noted.

The plasma samples were always analysed immediately after the end of the experiment. The urinary samples were generally kept at −20°C for one or two days before analysis. Only those urinary samples were used for calculations which corresponded to periods of a constant plasma galactose level. Accordingly, in one patient three samples were obtained, in six patients two samples, and in three patients one sample.

Galactose in plasma (3, 9) and in urine (15) was determined by galactose oxidase. The galactose oxidase reagent was obtained from AB Kabi, Stockholm, Sweden, as a kit ready for use.

Glucose in plasma (10) and in urine (15) was determined by glucose oxidase. The reagent was prepared in the laboratory.

Creatinine in plasma and urine was determined in a Technicon Auto-Analyzer® (Method file N-11 a). In this method most unspecific chromogens are eliminated through dialysis. At normal plasma creatinine levels, calculated values of endogenous creatinine clearance therefore correspond to the glomerular filtration rate (7).

All determinations were made in duplicate or triplicate, and the mean values used in the calculations.

RESULTS

The results from a typical experiment are shown in Fig. 1. Results from all the experiments are given in Table I.

Galactose was excreted in the urine even at very low plasma concentrations of galactose, a urinary excretion of 1.90 mg/min being found at a plasma galactose level of 0.09 mg/ml, which was the lowest concentration used in the experiments.

T/GFR was plotted against P (Fig. 2). According to equation (2) the curve obtained may be regarded as part of a rectangular hyperbola, the

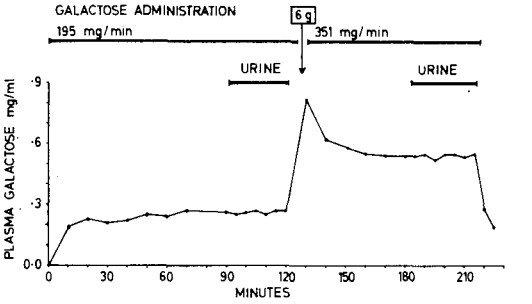

Fig. 1. Plasma concentration during intravenous infusion of galactose (patient No. 2). After 128 min a rapid injection of 6 g of galactose was given, and the infusion rate was increased from 195 to 351 mg/min. Urine was collected during two periods of constant plasma galactose level.

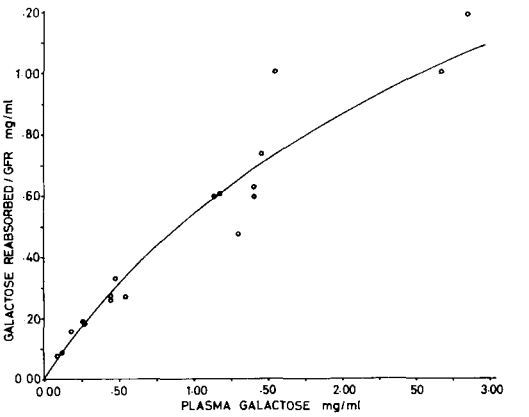

Fig. 2. Reabsorption of galactose normalized with respect to glomerular filtration rate, in relation to plasma concentration of galactose.

Table I. *Values obtained at infusion experiments with galactose in ten subjects. GFR=endogenous creatinine clearance for the actual body surface area of the individual. T=tubular reabsorption of galactose. Gal.=galactose. Glu.= glucose*

Patient, No., sex, and age	Body surface area m^2	GFR ml/min	Gal. infus. mg/min	Urinary and wash volume ml/min	Gal. in plasma mg/ml	Gal. in urine mg/ml	T/GFR mg/ml	Glu. in plasma mg/ml	Glu. in urine mg/ml	Glu. excretion mg/min
1. F 71	1.73	140	144	1.47	0.18	1.70	0.16	1.25	0.08	0.12
			270	1.90	0.47	10.20	0.33	1.30	0.26	0.49
2. F. 73	1.74	72	195	1.33	0.26	4.00	0.19	1.90	0.00	0.00
			351	1.45	0.54	13.50	0.27	1.90	0.30	0.44
3. M 35	2.31	163	144	1.88	0.09	1.01	0.08	0.97	0.06	0.11
			351	3.17	0.26	3.70	0.19	1.11		
4. F 73	1.68	77	81	1.43	0.12	1.50	0.09	0.94	0.21	0.30
			468	3.13	1.17	13.80	0.61	0.93	0.33	1.03
5. M 55	2.05	135	465	3.66	0.44	6.10	0.27	1.14	0.30	1.10
			468	4.52	0.44	5.50	0.26	1.14	0.28	1.27
6. F 59	1.63	93	465	3.00	1.54	16.40	1.01	0.95	0.89	2.67
7. M 45	1.78	139	630	8.67	1.30	13.20	0.48	1.16	0.98	8.50
8. M 47	1.97	85	351	5.00	1.13	9.00	0.60	1.10	0.47	2.35
9. M 49	2.14	129	630	7.33	1.45	12.50	0.74	1.20	0.83	6.08
			630	4.50	1.40	22.00	0.63	1.20	1.24	5.58
			630	5.17	1.40	20.00	0.60	1.15	1.15	5.95
10. M 39	1.82	151	849	15.33	2.66	16.25	1.01	1.05	0.49	7.51
			831	18.33	2.84	13.50	1.20	1.10	0.35	6.42

asymptotes of which give the values of $(T/GFR)_{max}$ and $-K$. In order to determine these values a graph was made of $\frac{1}{T/GFR}$ in relation to $\frac{1}{P}$ (Fig. 3), which yielded a straight line in the interval of the observed values with the regression equation:

$$y=1.12x+0.82 \qquad (r=0.94)$$

The line was extrapolated to the intercepts on the ordinate and the abscissa. The former intercept resulted in a value of 1.22 mg/ml for $(T/GFR)_{max}$, with a 95% confidence interval of 0.88-2.00 mg/ml. $\frac{1}{K}$, which is equal to $\frac{b_0}{b_1}$ in the regression equation:

$$y=b_1x+b_0$$

was calculated to be 0.37 ml/mg, resulting in a value of 1.37 mg/ml for K. The variance for $\frac{1}{K}$ was calculated as

$$\frac{s^2_1}{K}=\frac{s^2_{b_0}+b^2_0}{s^2_{b_1}+b^2_1}-\frac{b^2_0}{b^2_1}$$

This gave a 95% confidence interval for K of 0.99-2.22 mg/ml.

The urinary excretion of glucose increased with increasing galactose load; this is shown in Fig. 4. Fifteen of the excretion figures were obtained in nine individuals at plasma glucose concentrations within the rather narrow range of 0.93-1.30

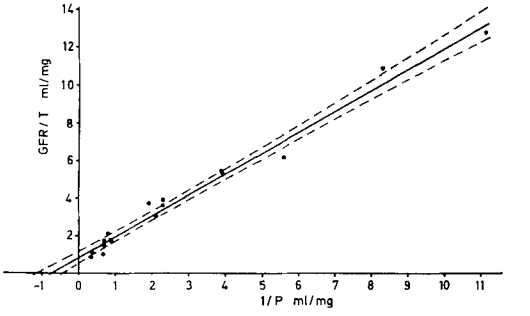

Fig. 3. Plot of reciprocal values of plasma galactose concentration and normalized galactose reabsorption. The regression line and a 95% confidence interval are shown.

(mean 1.11) mg/ml. Two determinations in one individual were made at a plasma glucose concentration of 1.90 mg/ml.

The extrarenal elimination of the galactose administered, i.e. essentially the elimination by the liver, was calculated as the difference between the amount infused and the amount excreted per minute. It was found to increase at a rising infusion rate (Fig. 5). It did not reach a maximum within the range of infusion rates used in these experiments. The maximal hepatic elimination of galactose thus appeared to be above 600 mg/min.

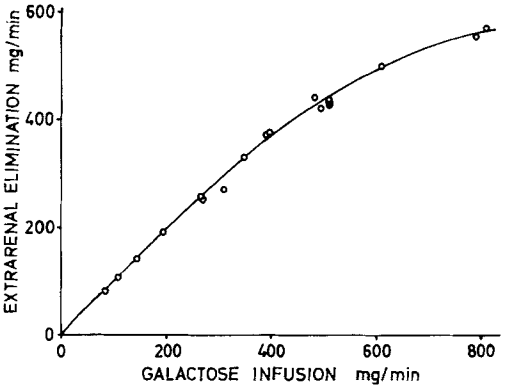

Fig. 5. Extrarenal elimination of galactose in relation to infusion rate. Values calculated per 1.73 m^2 body surface area.

DISCUSSION

Although the occurrence in man of a dependence of galactose excretion on plasma concentration has been indicated by earlier experiments (6, 17, 19), the relevant relationship has not been clearly demonstrated before. The finding of a constant galactose clearance at different plasma concentrations in the dog (4, 5) is probably the result of unsuitable experimental conditions rather than of a difference between species.

The present data give strong support to the opinion that a renal threshold for galactose does not exist in the same sense as for glucose, where practically no excretion occurs at plasma concentrations below 1.8 mg/ml. But it is evident that a threshold zone for galactose may be spoken of, covering plasma concentrations from zero to the point where the reabsorption maximum is reached. Fig. 2 indicates that this will occur well above the highest concentration in these experiments.

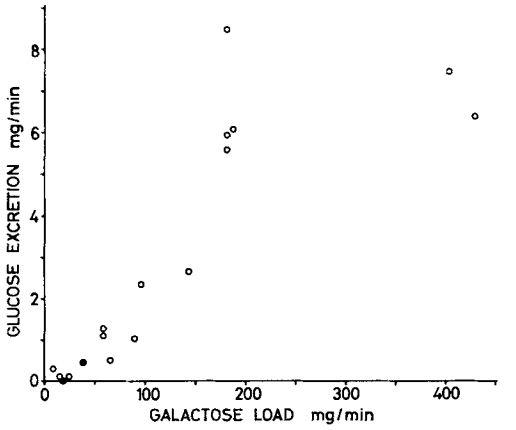

Fig. 4. Excretion of glucose in relation to tubular load of galactose. Open circles refer to patients with plasma glucose of 0.93-1.30 mg/ml, filled circles to a patient with plasma glucose of 1.90 mg/ml.

The different efficiency of the renal thresholds for glucose and galactose is expressed by different values of the 'affinity' constant in the transport equation (2). For galactose it was found here to be 1.37 mg/ml. Burgen (2), making essentially the same assumptions about the tubular transport system as in the present investigation, calculated the constant for glucose to be less than 0.05 mg/ml.

The values for $(T/GFR)_{max}$ and K for galactose could not be determined here with very high precision. Apart from the uncertainty indicated by the confidence intervals of the values determined, the precision is also affected to an unknown extent by the risk that lies in the extrapolation of the line in Fig. 3 from $\frac{1}{P}$ values of 0.35 to zero. In order to diminish the uncertainty due to the extrapolation, determinations would be necessary at plasma concentrations considerably higher than 3 mg/ml. Attempts to obtain such concentration levels were not regarded as justifiable owing to the risk of causing thrombophlebitis by the large and protracted infusions then required. The highest infusion rate in the present experiments,

849 mg/min, is of the same magnitude as the maximal infusion rates used by Waldstein et al. (19) and Tygstrup (17).

It has been shown that the tubular reabsorption of fructose and galactose in cats (6), and xylose in dogs (12) is inhibited by elevated concentrations of glucose in the plasma. It therefore appears that these monosaccharides compete for the same reabsorption mechanism. A competition between galactose and glucose for tubular reabsorption in man, too, was suggested here by the increasing glycosuria at rising tubular loads of galactose in the patients with a plasma glucose level of about 1 mg/ml.

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