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GALACTOSE BLOOD CLEARANCE AS A MEASURE OF HEPATIC BLOOD FLOW

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PREVIOUS experiments (7) have shown that after a single intravenous injection of galactose the hepatic removal of galactose is independent of its arterial concentration (Fig. 1) and at low concentrations the hepatic clearance is almost complete. This has suggested that hepatic blood flow could be determined by the Fick method without hepatic catheterisation, by the measurement of galactose clearance during an infusion of galactose which maintained a constant arterial concentration that was

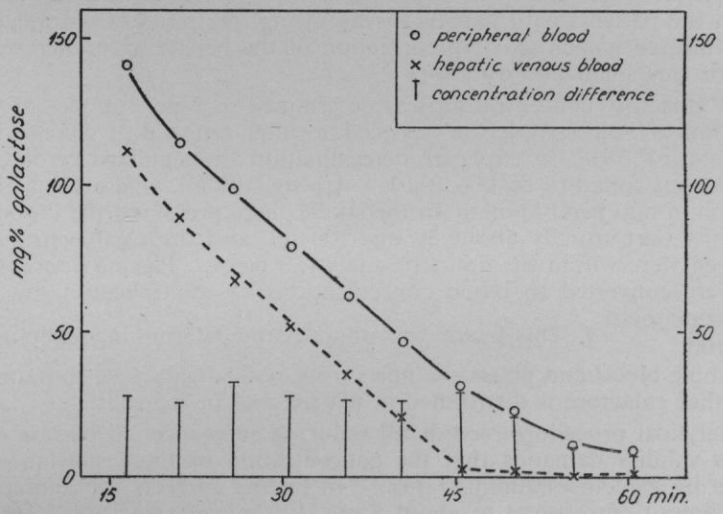

Fig. 1. Galactose concentrations in an artery and hepatic vein after a single injection of galactose (0·5 g./Kg. body weight) in a patient with normal galactose elimination. Reproduced from Acta physiol. scand., 1954, **32**, 355.

low enough to allow the assumption that the hepatic venous concentration would be near to zero. The blood clearance of para-amino hippurate is accepted as a measure of renal blood flow in a similar manner.

In the present study measurements of hepatic blood flow made by galactose clearance are compared with measurements made by the widely accepted bromsulfalein clearance and extraction method (2). In a number of subjects the galactose content of hepatic venous blood has been measured and the per cent galactose extraction by the liver has been determined.

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Because clearance of para-amino hippurate is considered an unreliable method of measuring renal plasma flow when renal function is impaired (1) an investigation of the reliability of the galactose method in patients with hepatic disease and in a patient who had consumed ethyl alcohol has been made.

Methods

All subjects were studied in the morning at rest in bed some hours after a meal. No premedication was given. An infusion of an analysed solution of galactose (Merck) was given by a calibrated pump. In some cases a priming dose of 5 gm. of galactose was given. About thirty minutes after the infusion was started 3 to 10 (mean 6) samples of arterial blood were drawn at 5 minute intervals. In some normal subjects and all patients with hepatic disease, a preliminary estimate of the galactose eliminating capacity of the liver was made from the slope of the arterial concentration curve after a single intravenous injection of galactose (7). In the normal subjects in whom this was not done, care was taken that galactose infusion was not greater than 300 mg./min.. It has been shown that in normal subjects the galactose elimination capacity of the liver is greater than 350 mg./min. (8). In all cases a constant arterial concentration of galactose was assumed to indicate that the infusion was smaller than the elimination capacity of the liver. Urine was collected by catheter every 15 minutes during the experiment and urinary galactose was determined as reducing substance removed by galactose fermenting yeast. In the normal subjects the mean urinary excretion of galactose was 9 mg. per min., or about 3 per cent of the infused amount; in the patients with hepatic disease 4 mg. per min. was excreted or 2 per cent of the infused galactose. No correction of the hepatic clearance was deemed necessary for this small urinary loss.

Plasma galactose concentration was determined in 2 ml. samples of plasma by a modification of Somogyi-Nelson's procedure after removal of glucose by glucose oxidase (Notatin)* (9). In triplicate determination the standard error of a single measurement was found to be $1 + (0{\cdot}01 \times C)$ mg./100 ml. where C. is the plasma concentration in mg. per 100 ml.. In the studies here presented the blood galactose concentrations were usually about 30 mg./100 ml. and the small variations which were observed were within the limits of analytical error. Plasma concentrations of galactose were converted to blood concentrations by multiplication by the factor $(1-\frac{0{\cdot}4 \times \text{hæmatocrit}}{100})$. This factor was obtained by determining galactose concentration in whole blood and plasma samples from pooled galactose containing blood. It suggests that galactose is distributed in plasma and in red cells.

The analytical procedure records all reducing substances in plasma other than glucose; its validity demands that the concentration of these substances remains constant during galactose administration. In fasting subjects the amount of these substances present correspond to about 3 mg./100 ml. of galactose. To determine the validity of the Notatin method of estimation of blood galactose some samples of blood were analysed by determination of the amount of reducing substance removed by a galactose fermenting strain of yeast.† The results which were satisfactory are shown in Table I.

In those subjects in whom hepatic venous catheterisation was performed, hepatic venous blood samples were drawn at the same time as arterial samples for galactose analysis to determine the per cent galactose extraction of the liver. In some of these subjects the hepatic blood flow was determined by the bromsulfalein clearance and extraction method of Bradley, Ingelfinger, Bradley and Curry (2). Bromsulfalein concentration was measured by Gaebler's method (5).

* Kindly given by Leo Pharmaceutical Products, Copenhagen.
† Kindly supplied by the Carlsberg Laboratory, Copenhagen.

TABLE I

Galactose concentrations (mg./100 ml.) determined as increase of non-glucose reducing substance during galactose infusion (Notatin method), and as non-glucose reducing substance removed from the same blood by galactose-fermenting yeast (Yeast method, " true " galactose).

		Notatin method	Yeast method
Case No. 20 (" normal ")	artery	16·7	16·0
	hepatic vein	1·4	1·8
Case No. 32 (cirrhosis)	artery	26·9	26·4
	hepatic vein	11·5	11·8

Twenty five hospital patients with no clinical or laboratory signs of hepatic dysfunction were studied. Most of them had been admitted to hospital on account of minor cardio-pulmonary or abdominal complaints. In 8 of them, galactose clearance measurements were made without hepatic catheterisation (Table II); in 17, hepatic catheterisation was performed. Galactose clearance and extraction was measured in all and hepatic blood flow by the bromsulfalein method in 15 of these patients (Table III).

Three patients were studied at the beginning of recovery from acute viral hepatitis of moderate severity. Four patients with cirrhosis of the liver were studied; two were mild cases and two were advanced, one having ascites and œdema and the

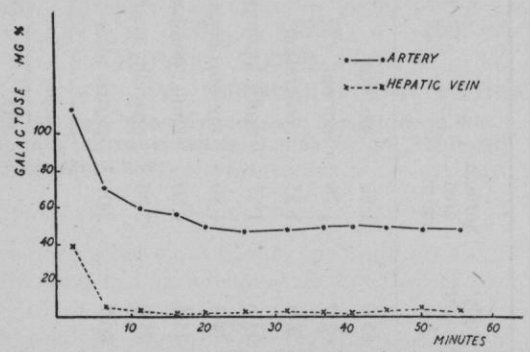

Fig. 2. Galactose concentrations in an artery and hepatic vein during galactose infusion in a subject with normal galactose elimination (Case 11, Table III). At zero time 5 g. of galactose was injected intravenously.

other jaundice. This last patient was studied twice at an interval of five months, her clinical state being the same on each occasion. One patient who had normal hepatic function (No. 19) was restudied after consuming 20 gm. of ethyl alcohol (Fig. 4 Table III and IV). The blood alcohol concentrations thus obtained do not interfere with determination of blood galactose.

Results

Galactose blood clearance. This was determined in 25 patients with normal hepatic function (Table II and III). The mean clearance was 1,420 ml./min. (S.D.= 370). This gives a measurement of hepatic blood flow which is similar to that obtained by other workers with the bromsulfalein method (2).

TABLE II

Galactose blood clearance in subjects with assumed normal galactose elimination capacity.

Exper. No.	Initials	Sex	Age years	Body weight Kg.	Surface area sq. m.	Diagnosis	Galactose blood clearance ml./min.	Infusion rate mg./min.	Arterial blood galactose mg./100 ml.
1	K.S.	M	20	65·0	1·88	gastritis	1010	267	26·5
2	M.J.	M	23	62·0	1·76	normal	1020	309	30·2
3	S.D.	M	45	52·6	1·55	coarctation	1390	273	19·6
4	A.F.	M	48	64·6	1·77	aortic incompetence	1460	314	21·5
5	B.A.	F	19	70·3	1·80	thyrotoxicosis (mild)	1310	242	18·4
6	B.K.	F	40	75·5	1·80	famil., non-hæmolyt. jaundice	1460	370	25·4
7	N.N.	M	50	75·0	2·06	anacidity (same case as 22)	1680	334	19·9
8	L.J.	M	54	80·7	2·01	gastric ulcer	1470	310	21·2
						Mean	1350	302	22·8
						S.D.	231	41	4·1

The mean galactose blood clearance per Kg. body weight and per sq. metre surface area was 22·2 ml./Kg./min. (S.D.=5·61) and 806 ml./sq. m./min. (S.D.=184) respectively.

Extraction of galactose by the liver. The mean hepatic extraction of galactose in 17 patients with normal liver function was 88 per cent (S.D.=6), Table III, which is significantly lower than 100 per cent ($P<0{\cdot}001$).

Simultaneous measurements of blood galactose clearance and hepatic blood flow. In 15 patients with normal hepatic function (Table II) simultaneous determinations of blood galactose clearance and of hepatic blood flow by the bromsulfalein method were made. The correlation between the measurements is shown in Fig. 3. The coefficient of linear correlation is +0·75. The ratio of blood galactose clearance to hepatic blood flow did not differ significantly from unity (mean 0·98 : S.D.=0·24).

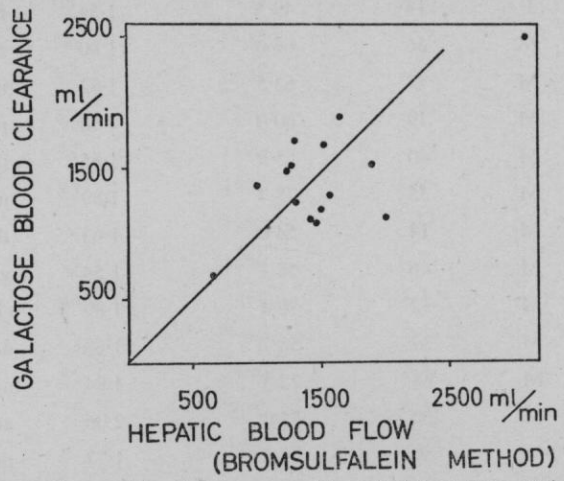

Fig. 3. Correlation of galactose blood clearance and hepatic blood flow, as determined by bromsulfalein, in subjects with normal galactose elimination (cf. Table III). The line represents the average ratio between the values.

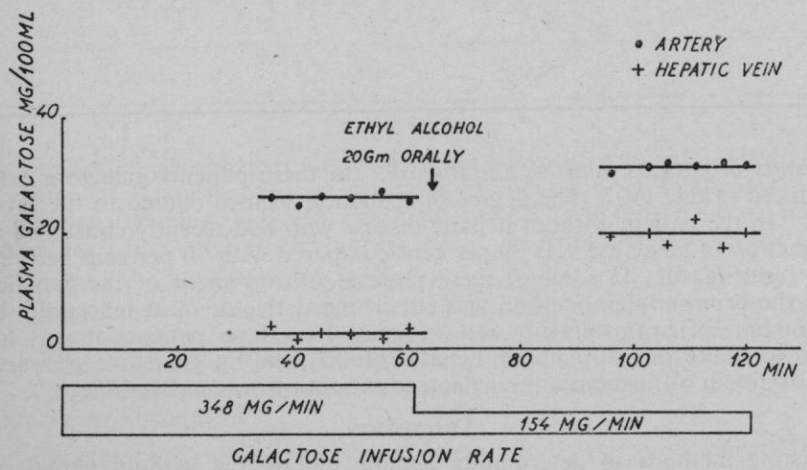

Fig. 4. Galactose concentrations in an artery and hepatic vein during galactose infusion in a normal subject before and after ingestion of ethyl alcohol (Case 19, Table III and Table IV respectively).

TABLE

Galactose blood clearance and hepatic blood flow
subjects with assumed

Exper. No.	Initials	Sex	Age years	Body weight kg.	Surface area sq. m.	Diagnosis
9	F.R.	M	35	60·3	1·69	duodenal ulcer
10	L.C.	M	57	56·5	1·69	" dumping syndrome "
11	K.J.	F	14	49·5	1·54	normal
12	K.M.	M	36	66·0	1·80	neurosis
13	G.C.	M	47	63·5	1·82	bronchitis
14	C.H.	M	19	60·0	1·68	pulmon. stenosis (operated)
15	O.M.	M	40	55·9	1·65	thrombophlebitis
16	A.N.	M	35	77·7	1·89	neurosis
17	T.H.	M	14	54·0	1·63	thyrotoxicosis (moderate)
18	B.H.	M	46	50·1	1·54	gastric ulcer
19	A.J.	M	32	70·4	1·89	chronic indigestion
20	J.T.	M	29	58·7	1·68	aortic incompetence
21	H.J.	M	38	72·3	1·84	arterial hypertension
22	N.N.	M	50	75·0	2·06	anacidity (same case as 7)
23	H.W.	M	50	73·5	1·77	pulmonary fibrosis
24	R.R.	M	39	56·5	1·66	chronic indigestion
25	K.M.	M	30	75·1	1·71	chronic indigestion

Results in patients with hepatic disease. In these patients galactose extraction was reduced (Table IV). The degree of reduction seemed related to the severity of disease. In the patient without hepatic disease who had recently consumed alcohol the extraction of galactose was 39 per cent compared with 90 per cent before taking alcohol (*see* Fig. 4). In some of these patients measurement of the hepatic blood flow by the bromsulfalein method was either impossible or most inaccurate because the extraction of bromsulfalein was so small. In these patients it was however possible to make an estimate of hepatic blood flow by galactose clearance and extraction for in all instances the galactose extraction was measurable.

Discussion

Existing methods of determining hepatic blood flow without hepatic venous catheterisation depend on the removal of colloidal substances after a single intravenous injection has been given (3, 4, 10, 11). Dobson and Jones found the extraction of

III

during hepatic venous catheterisation in normal galactose elimination.

	Galactose blood clearance ml./min.	Galactose extraction percentage	Hepatic blood flow (bromsulfalein) ml./min.	Blood clearance/ hepatic blood flow	Galactose infusion rate mg./min.	Arterial blood galactose mg./100 ml.
	1840	93			217	11·8
	1710	86			294	17·2
	660	95	670	0·98	270	41·2
	1670	91	1500	1·12	284	17·0
	1890	92	1630	1·16	378	20·0
	1700	88	1280	1·34	381	22·4
	1180	73	1490	0·79	370	31·4
	1230	82	1300	0·95	308	25·0
	1500	90	1240	1·21	341	22·7
	1300	86	1550	0·84	303	23·3
	1510	90	1260	1·20	348	22·7
	1120	91	1990	0·56	164	14·7
	1530	85	1890	0·81	324	21·2
	2500	77	3100	0·81	299	11·9
	1370	92	1000	1·38	323	23·5
	1080	94	1450	0·75	310	28·6
	1100	86	1420	0·77	311	28·2
Mean	1460	88	1520	0·98	307	22·5
S.D.	421	6	543	0·24	55	7·3

colloidal chromium phosphate in dogs was never below 85 per cent. This has never been investigated in man but the extraction of colloidal gold in 3 patients studied by Vetter, Falkner and Neumayr (10) was 77, 81 and 87 per cent. Krook in a later study (6) of six patients found the highest extraction to be only 55 per cent.

Vetter and his colleagues (11) found the hepatic blood flow measured by colloidal gold was greater than that determined by the bromsulfalein method. The coefficient of linear correlation was +0·66. The mean ratio of the two methods was 0·84 and from their data it can be calculated that this differed significantly from unity ($P < 0·025$). The difference between the two methods was attributed to the extra hepatic extraction of bromsulfalein.

Because in normal subjects the hepatic extraction of galactose is only of the order of 90 per cent it would be expected that this would give a measure of hepatic blood flow that was 10 per cent too low. The fact that the galactose blood clearance and

TABLE IV

Galactose blood clearance and hepatic blood flow measured by bromsulfalein and by galactose during hepatic venous catheterisation in subjects with reduced galactose elimination capacity. Queries stand for unmeasureable values.

Exper. No.	Initials	Sex	Age years	Diagnosis	Galactose blood clearance ml./min.	Galactose extraction percentage	Hepatic blood flow (bromsulf-alein) ml./min.	Hepatic blood flow (galactose) ml./min.	Galactose infusion rate mg./min.	Arterial blood galactose mg./100 ml.
26	H.J.	M	33	acute epidemic hepatitis	1840	72	?	2557	256	13·9
27	G.M.	F	28	acute epidemic hepatitis	1460	76	?	1920	349	23·9
28	H.J.	M	38	acute epidemic hepatitis	1550	78	?	1990	204	13·1
29	H.C.	M	43	cirrhosis of the liver (mild)	1610	76	1650	2120	219	13·6
30	A.A.	M	66	cirrhosis of the liver (mild)	1050	63	1740	1660	206	19·7
31	P.A.	M	67	cirrhosis of the liver (mode-rate)	670	68	960	990	296	44·0
32	A.L.	F	57	cirrhosis of the liver (severe)	860	57	?	1510	204	23·7
33	A.L.	F	57	cirrhosis of the liver (severe)	730	63	580	1160	209	28·7
19	A.J.	M	32	alcohol ingestion 20 g. (Table III)	540	39	1070	1350	147	27·3

the hepatic blood flow measured by bromsulfalein agree so well suggests that the bromsulfalein method gives a value for hepatic flow that is also too low, but the data here presented is insufficient to establish this.

Summary

Galactose blood clearance can be measured in normal subjects without hepatic vein catheterisation. In a group of 25 patients with no apparent hepatic disease, the mean clearance was 1,460 ml./min. (S.D.=370). In a group of 15 of these patients the hepatic blood flow was determined simultaneously by the bromsulfalein method and there was a close correlation between the two measurements.

In patients with impaired liver function the hepatic galactose extraction was reduced. It is possible using hepatic venous catheterisation to measure hepatic blood flow by the Fick method with galactose in patients whom the bromsulfalein method cannot give accurate results.

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