Liver Function and Blood Flow in Normal Man during Infusion of Vasopressin

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In five patients without liver disease the splanchnic blood flow, galactose uptake, and oxygen consumption were followed after infusion of vasopressin. The galactose uptake, as well as the oxygen consumption, appeared to be practically independent of the marked reduction in blood flow after vasopressin. 'Liver mass' determination by galactose is therefore not influenced by changes in hepatic blood flow.

Key-words: Galactose elimination; hepatic blood flow; liver function; vasopressin

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The elimination rate of galactose under suitable conditions (8) is assumed to represent the capacity of the liver for galactose uptake, and has been used as a measure of 'liver mass' (9). To accept this one must require that hepatic galactose uptake is little influenced by extraneous factors. So far only ingestion of ethanol is known to produce a major effect on galactose elimination (7). The present work was undertaken to assess the effect of severe reduction of splanchnic blood flow by vasopressin on the galactose uptake.

MATERIAL AND METHODS

The material comprises 5 patients in whom extensive examinations were carried out to elucidate the cause of recurrent, uncharacteristic abdominal pain. All pertinent routine examinations, including the studies presented here, failed to clarify this question. The sex, age, body weight and height of the patients are given in Table I.

The examinations were performed with the patient fasting and resting, 2 hours after administration of 200 mg of phenobarbitone. In local anaesthesia percutaneous catheterization of the femoral artery and vein was done ad modum Seldinger, and the tip of the venous catheter was placed in the hepatic veins under fluoroscopic control. A continuous intravenous infusion of 2.9 mmoles per minute of galactose (d-galactose, Kabi) and of 460 μg/min of indocyanine green (Hynson, Westcott & Dunning) was given after priming doses (40 mmoles and 8.2 mg, respectively). Thirty minutes were allowed for equilibration, then samples of arterial and hepatic venous blood

were drawn simultaneously every 7 minutes during 150 minutes.

The first 3 samples were used as control, then 14 units of vasopressin (lysin-8-vasopressin, Sandoz) were infused intravenously in the course of 14 minutes. During the infusion a rise in systolic blood pressure ranging from 0 to 45 mm of Hg (mean 26 mm) was noted. The ECG did not change. During the infusion and for a short time afterwards, the patients had abdominal sensations of varying degree; in one patient (No. 3) they were similar to his usual complaints. No other side-effects were noted.

Galactose in blood was determined enzymatically (2), indocyanine green (ICG) was measured spectrophotometrically (11), and oxygen saturation reflectometrically (12) with calculation of the oxygen content from the oxygen capacity.

The splanchnic blood flow (SBF) was calculated for each sampling interval by

$$SBF = \frac{I - \triangle A \cdot V}{\bar{A} - hv} \cdot \frac{1}{1 - Hct}$$

where I is the infusion rate of ICG, $\triangle A$ is the change in arterial concentration of ICG during the interval, V is the volume of distribution of ICG (assumed to be 5 per cent of the body weight), $\bar{A}$ and hv are the mean concentrations of ICG of arterial and hepatic venous blood, respectively, during the sampling interval, and Hct is the red cell volume ratio of the blood.

The splanchnic uptake of galactose and oxygen were calculated from the mean arteriohepatic venous blood concentration differences of the substances during the sampling interval, multiplied with the SBF.

Table I. Splanchnic blood flow and metabolism before and following infusion of vasopressin

No.	1	2	3	4	5	Mean
Sex	M	M	M	F	F	
Age	54	32	47	42	36	
Body weight (kg)	69	63	51	55	60	
Height (cm)	182	179	167	159	169	
	Splanchnic blood flow (litres per min.)					
Control period	1.28	1.09	1.06	0.84	1.48	1.15
Period I	0.65	0.48	0.57	0.43	0.76	0.58
Period II	0.88	0.70	0.80	0.69	1.14	0.84
Period III	1.10	1.11	0.97	0.78	1.25	1.04
	Splanchnic galactose uptake (mmoles per min.)					
Control period	2.07	2.22	1.22	1.45	1.73	1.74
Period I	2.12	1.77	1.30	1.51	1.82	1.70
Period II	2.06	2.57	1.16	1.68	1.89	1.87
Period III	1.91	2.52	0.87	1.73	1.66	1.75
	Splanchnic oxygen consumption (mmoles per min.)					
Control period	3.51	2.06	2.41	2.47	2.60	2.61
Period I	2.65	2.16	2.06	2.08	2.37	2.27
Period II	3.40	2.34	2.21	2.32	2.85	2.62
Period III	4.06	2.47	2.35	2.38	2.96	2.84

Period I is from 5 to 25 minutes, period II from 25 to 60 minutes, and period III from 60 to 80 minutes, after start of infusion of vasopressin.

RESULTS

Table I gives the average splanchnic blood flow, galactose uptake, and oxygen consumption, before and during three periods after infusion of vasopressin in all the patients, and the individual determinations in one patient (No. 1) are shown in Fig. 1. Fig. 2 shows the average changes in relation to the control values for all patients.

It appears that the splanchnic blood flow during the first period after vasopressin is reduced to about half of the control value, and is nearly restored during the third period. The average galactose uptake remains unchanged, and the splanchnic oxygen consumption is slightly reduced during the first period ($p = 0.05$), and tends to rise a little above the control value during the third period.

The arterial concentration of ICG in all cases rose steeply immediately after the infusion of vasopressin was started, reaching a peak about 16 minutes after start of the infusion, followed by a more gradual decline. This is assumed to reflect changes in the hepatic uptake of ICG, and enters the calculation of the splanchnic blood flow. The calculated hepatic uptake of ICG is depicted in Fig. 3, together with the uptake in relation to the mean arterial concentration of the same interval ('ICG blood clearance'). The uptake is decreased for a short period, followed by a slight increase. The blood clearance is initially reduced to the same extent and returns slowly towards the control value.

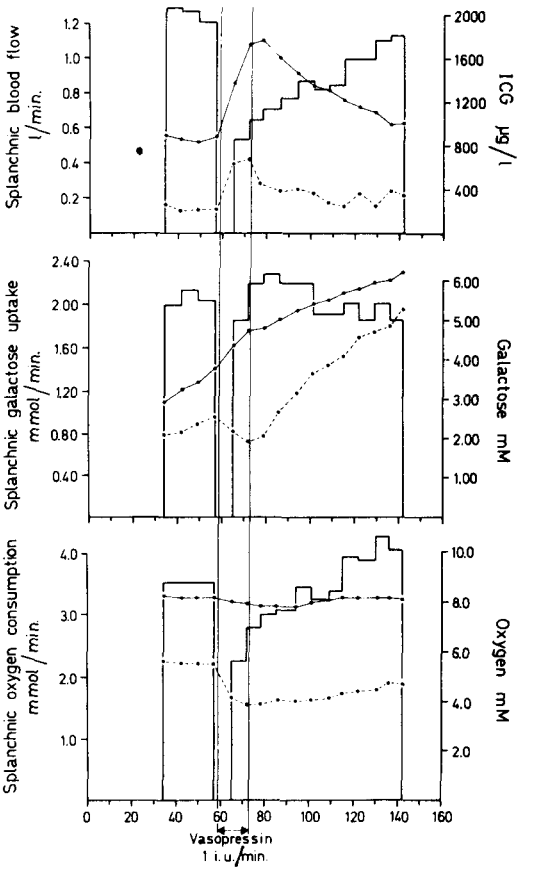

Fig. 1. Data from patient No. 1. The left ordinate refers to the columns, the right to the arterial (●—●—●—●) and hepatic venous (● - - ● - - ●) concentrations. The abscissa indicates minutes after start of the infusion of ICG and of galactose.

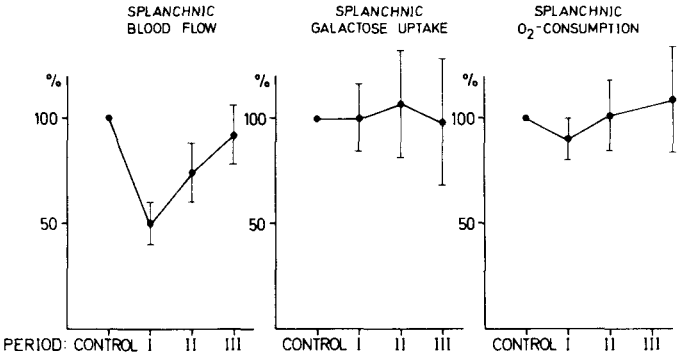

Fig. 2. Changes in splanchnic blood flow and metabolism during vasopressin as per cent of control values (mean ± 2 × SEM). Period I is from 5 to 25 minutes, period II is from 25 to 60 minutes, and period III from 60-80 minutes, after the start of the vasopressin infusion.

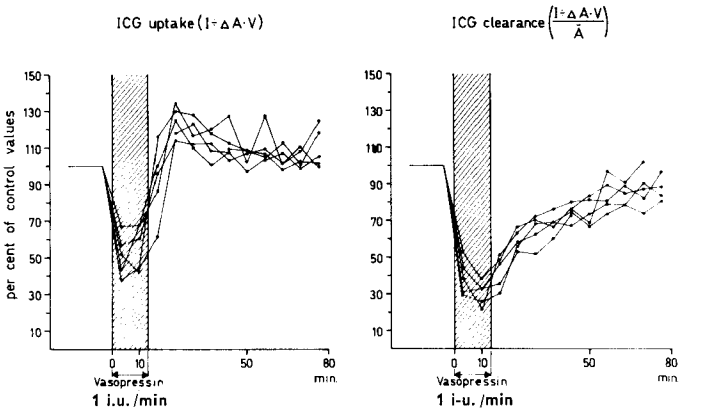

Fig. 3. ICG uptake and clearance as per cent of control value during and following infusion of vasopressin. The abbreviations are explained in the text.

DISCUSSION

The results presented indicate that the functional capacity of the liver, as measured by the galactose removal rate, is unaffected by a reduction to 50 per cent of the hepatic blood flow. This interpretation depends to a large extent on the blood flow determination, which is also used for calculation of the galactose uptake.

Dye extraction methods, using e.g. ICG or bromsulphthalein, are primarily designed for steady state measurements, and a number of uncertainties arise when the conditions are changing, as they are in the examinations presented. The correction for changing arterial concentrations is an approximation, since the change is assumed to be linear, and the distribution of the dye is assumed to be complete. Errors in these assumptions may become important when the correction to be made is large, but the magnitude and the direction of the error cannot be predicted.

Changes in the concentration level of the dye will also affect the determination of the arterio-hepatic venous difference unless correction is made for the mean transit time of the blood through the splanchnic system. Simultaneous determinations of the arterial and hepatic venous concentrations will lead to underestimation of the blood flow when the concentration rises, and to overestimation when it falls. The error will increase when the splanchnic flow falls and when the splanchnic blood volume rises. It is likely that the splanchnic volume falls after infusion of vasopressin, thus reducing the error, but as the splanchnic volume was not measured, the magnitude of the error is unknown.

Finally, the representativity of the hepatic venous blood samples may be doubted when great changes occur. The mean hepatic venous concentration of a substance during a sampling period is determined as the average of the two samples limiting the period, i.e. the concentration course between two observations is assumed to be a straight line. This is definitely not the case in the period during which the infusion of vasopressin was started, and this period therefore is omitted from the calculations. As to the remaining periods, this assumption is considered to be a satisfactory approximation.

Even if the combined effect of these errors cannot be quantitated, it is likely that it cannot modify the main conclusion drawn from the examinations, viz that the splanchnic flow falls and that the galactose removal is practically unchanged following vasopressin. The fall in the blood flow is comparable with previous observations with similar (5, 6), and different methods (1). The constancy of the galactose elimination is confirmed by inspection of the arterial galactose concentration curves, which have practically the same slope during the control period and the periods after vasopressin. An exception from this is the peri-

od during which the infusion of vasopressin was started (see Fig. 1). It appears that the galactose removal during part of this period is reduced, possibly because the hepatic blood flow has been so severely reduced that the amount of galactose carried to the liver is smaller than the elimination capacity. The methods employed for determination of the hepatic galactose uptake could not detect such acute effects.

The relative constancy of the hepatic galactose uptake and oxygen consumption during vasopressin-induced reduction of the blood flow indicates that the function of the liver cells is not affected. From intravital microscopy of the liver circulation (3), it has been concluded that changes in the blood flow through the liver results in changes in the number of sinusoids perfused, the velocity of the blood being relatively constant. If this was the case, at least half of the sinusoids should have been closed during the first period after vasopressin in the present experiments, and the parenchymal cells, adjoining these sinusoids, would not have received any galactose which they could remove. There is no reason to assume that the remaining liver cells can compensate in such a way that a constant total galactose removal can be maintained. A more plausible explanation is that under the conditions studied an even reduction of the flow in all sinusoids takes place.

The change in ICG uptake, which is also considered to be a function of the parenchymal cells, is more difficult to evaluate because of the large changes in concentration. If the elimination rate is directly proportional to the concentration, as is generally assumed (4), the 'blood clearance' is a more appropriate measure of this function. It appears that the clearance varies in parallel with the splanchnic blood flow. A constant relation between clearance and blood flow means that the extraction ratio is also constant. This is considered to be in accordance with the concept of an even distribution of the reduced flow through all sinusoids.

The influence of augmented liver blood flow was not investigated, because an effect of reduced flow was considered much more likely. In view of the results obtained with reduced flow, it seems justified to conclude that the hepatic galactose removal capacity is independent of the blood flow.

The main purpose of the present work was to see if changes in the hepatic blood flow would influence the galactose elimination capacity, as determined by the clinical intravenous galactose test (10). Direct measurement of the hepatic galactose uptake during hepatic venous catheterization and infusion of galactose was preferred to the usual single injection technique with determination of the arterial concentration course, because the former method is better suited to detection of rapid changes. The arterial concentrations, however, were kept within the interval used in the clinical test. At these concentrations the hepatic-galactose-eliminating enzyme system is assumed to be saturated, and the reported results therefore also apply to the clinical test.

The principal difference between the technique used in the present study and the clinical intravenous galactose test is that the latter will include any extrasplanchnic galactose removal. Little exact information is available about the galactose elimination outside the liver and kidneys. Unfortunately, no figures for the galactose elimination capacity determined by the clinical test were available in the patients of the present study for comparison of both methods. It must be noted that in patient No. 3 the hepatic galactose uptake was clearly below the normal lower limit for galactose elimination capacity. The patient had no clinical signs of liver disease, the routine liver tests were normal, but liver biopsy was not made. The possibility that the normal lower limit for galactose elimination capacity is higher than that of the hepatic galactose uptake on account of extrahepatic galactose elimination cannot at the moment be excluded. This cannot, however, affect the conclusion that the galactose elimination capacity is independent of the hepatic blood flow, since it is very unlikely that a presumed extrahepatic galactose elimination is dependent on this flow.

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