Galactose elimination capacity as a prognostic index in patients with fulminant liver failure

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SUMMARY   In 25 patients with fulminant hepatic failure the prognostic value of a quantitative liver function test, the galactose elimination capacity, was assessed and compared with routine liver function tests and clinical features. The galactose elimination capacity was significantly higher ($p < 0.05$) in the five patients who survived than in the 20 patients who died. None of the other liver function tests was significantly different. The values of the galactose elimination capacity overlapped considerably between survivors and non-survivors, but all patients with a galactose elimination capacity below 12·8 µmol galactose/min and kg body weight died. The disease among most patients who died having a galactose elimination capacity greater than 13 µmol ran a subacute course. It is suggested that quantitative liver function tests be included when new treatments of fulminant hepatic failure are investigated.

The high mortality in acute liver failure (Saunders and Terblanche, 1975), and the complete recovery of patients who survive (Karvountzis *et al.*, 1974) has been a strong impulse to apply drastic, expensive, and perhaps also hazardous therapeutic measures (Eiseman *et al.*, 1965; Trey *et al.*, 1966; Burnell *et al.*, 1973; Gazzard *et al.*, 1974). However, none of these treatments is of proven value, and it cannot be excluded that recovery, when it occurs, is spontaneous. This makes it highly desirable to identify patients with a high chance of recovery. Clinical features and laboratory tests have been found to contain little, if any, prognostic information.

The present study aims at elucidation of the prognostic value of a quantitative liver test, the galactose elimination capacity, in patients with acute liver failure.

Methods

All patients were admitted to this department because of impending or manifest acute liver failure with hepatic encephalopathy. One patient (no. 15) had uncomplicated hepatitis beginning 115 days before the actual admission. She was treated in another hospital and discharged after two months but readmitted 43 days later because her condition

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had relapsed. Eight days later she developed hepatic coma. Otherwise no previous liver disease was suspected in any of the patients. Only patients reaching coma grade III (Trey *et al.*, 1966) were included in the study. The sex, age, and aetiology of the liver disease are shown in Table 1. Sixteen of the patients were females, and nine were males. The assumed aetiology of the liver disease (Table 1) was virus hepatitis in 19 patients. Twelve of these were classified as type A hepatitis. HB_sAg was not investigated in two of these (nos. 7 and 15) and was negative in the others. With a classification based on epidemiological data seven of the patients were classified as type B hepatitis. HB_sAg was positive in three (nos. 16, 17, 19), negative in three (nos. 3, 4, 20), and not performed in one (no. 18). Drug hepatitis was suspected in six patients, five of whom had recently been exposed to halothane and one who had been treated with ryfamycin (Rifampicine) and isoniazid (Isoniazide).

All patients were treated in the intensive care liver unit by trained personnel and received standard anti-coma treatment, consisting of 20% glucose *via* a gastric tube as the only supply of calories, sterilisation of the gut with Neomycin, 4 g daily, and purgation with magnesium sulphate. Additional treatment (Table 1) consisted of infusion of fresh frozen plasma, corticosteroids, from 30 to 80 g prednisone daily, exchange blood transfusions (5000 ml), or extracorporeal pig liver perfusions (Ranek *et al.*, 1971). Assisted respiration through a nasotracheal

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Table 1 *Sex, age, and aetiology of hepatic failure in 25 patients: duration of disease and coma, and final outcome, and galactose elimination capacity*

Case no.	Sex	Age (yr)	Aetiology	Duration (days)			Galactose elimination capacity ($\mu mol \cdot min^{-1} \cdot kg^{-1}$)	Outcome
				Disease before adm.	Coma before adm.	Coma during adm.		
1	F	22	VH/A	4	1	3	21·7	Survived
2	M	44	VH/A	10	1	3	14·4	—
3	M	25	VH/B	30	4	1	16·2	—
4	M	25	VH/B	5	2	13	12·8	—
5	M	45	DH (hal)	7	1	3	22·8	—
6	F	17	VH/A	37	1	16	19·5	Died
7	F	24	VH/A	26	1	6	11·1	—
8	F	25	VH/A	9	1	3	9·5	—
9	F	32	VH/A	15	1	4	11·8	—
10	F	37	VH/A	30	4	3	9·3	—
11	F	42	VH/A	60	9	4	21·2	—
12	F	63	VH/A	30	2	11	15·6	—
13	F	63	VH/A	30	8	24	14·2	—
14	M	63	VH/A	10	3	4	5·8	—
15	F	69	VH/A	115	2	12	14·3	—
16	F	24	VH/B	7	1	2	6·8	—
17	F	28	VH/B	28	1	3	11·8	—
18	M	44	VH/B	18	1	16	10·3	—
19	M	57	VH/B	13	2	1	14·9	—
20	M	62	VH/B	14	2	4	6·8	—
21	F	47	DH (hal)	4	0	10	16·9	—
22	F	51	DH (hal)	11	0	22	12·1	—
23	F	54	DH (hal)	34	0	42	13·9	—
24	F	56	DH (hal)	4	1	6	5·6	—
25	M	62	DH (Rifamp. + INH)	5	1	5	13·0	—

hal: halothane.

tube was initiated before hypoxia or hypercapnia developed. Peritoneal dialysis was performed if renal failure developed. Blood was analysed regularly for the following components: haemoglobin, sodium, potassium, creatinine, urea, pCO_2, O_2 saturation, standard bicarbonate, base excess, prothrombin, bilirubin, alanine aminotransferase, and alkaline phosphatases. Blood glucose was examined four times daily. Serum ammonia was examined at various intervals, usually every second or third day.

Electroencephalography (EEG) was performed regularly during the encephalopathic period until the patient either died or recovered. If the EEG revealed no activity, a cervical arteriography was performed. If intracerebral circulation could not be demonstrated, the patient was considered brain dead.

The galactose elimination capacity was determined either shortly after admission or at the time when the patient developed encephalopathy in the department. The original procedure was modified as follows: a fixed dose of 25 g galactose was injected intravenously in the course of five minutes. Capillary blood samples were drawn from the ear lobe at intervals of five minutes from 25 to 60 minutes after start of the injection, and a urine sample was collected after four hours (except in anuric patients). Galactose concentrations were determined enzymatically (Kurz and Wallanfalz, 1970), and the galactose elimination capacity was computed (Hewlett-Packard 9810) with a programme providing corrections for urinary excretion and uneven distribution of galactose (Tygstrup, 1961). In anuric patients the galactose elimination was not performed during peritoneal dialysis. For the statistical evaluation Fisher's exact test and the Mann-Whitney test were used.

Results

Twenty per cent of the patients survived (95% confidence limits: 6·8-40·7%).

There was no significant difference (Table 2) between those who survived and those who died as far as the following variables were concerned: sex, age, duration of disease before admission, duration of coma before or during admission, coma grade on admission, dominant frequency of the electroencephalogram, and liver dullness. No difference was found among surviving and non-surviving patients regarding treatment schedules, as outlined in Table 2. A low blood glucose level (< 2·0 mmol/l) was recorded once in six of the patients who died. Persistent hypoglycaemia was not seen. In none of the survivors was hypoglycaemia recorded. In five of the patients who died cessation of cerebral blood flow was demonstrated. In none of these patients was hypoglycaemia recorded.

The results of the liver tests that were performed

Table 2 *Coma grade on admission, dominant frequency of EEG, liver size, different treatments, and possible concomitant causes of death*

Case no.	Grade of coma (0-IV) on admission	First EEG dominant frequency (Hz)	Liver dullness*	Treatment						Possible concomitant cause of death
				S	PI	ET	PLP	AV	PD	
1	III	NP	D	0	0	×	0	0	0	—
2	III	2-3	N	0	0	×	0	0	0	—
3	III	2-3	N	×	0	0	0	0	0	—
4	III	1·5-3	D	×	0	×	×	×	0	—
5	IV	1·5-3	D	0	0	×	0	×	0	—
6	I	1·5-3	N	×	0	×	0	0	0	Hypoglycaemia
7	II	3-4	D	0	×	×	×	×	0	Hyaline membranes in lungs
8	II	3	D	0	0	×	0	×	0	Cardiac arrest
9	III	1-3	N	0	×	×	0	×	0	
10	IV	2-4	N	0	0	0	0	×	0	
11	IV	1·5-3	D	×	×	×	0	×	0	Hypoglycaemia, generalised candidiasis infection
12	IV	1·5-2	D	×	×	×	×	×	×	
13	II	2-3	A	0	0	0	0	×	×	Hypoglycaemia
14	III	2-4	D	0	×	×	0	×	0	Hypoglycaemia
15	III	2-4	N	0	×	×	0	0	×	
16	III	1·5-3	D	0	0	×	0	×	0	
17	III	0	A	0	0	×	0	×	0	
18	I	NP	N	×	×	×	×	0	0	Miliary tuberculosis
19	III	2-3	D	0	×	0	0	×	0	Cardiac arrest
20	III	NP	D	0	×	×	0	×	0	Hypoglycaemia
21	0	2	D	0	0	×	0	×	0	
22	0	NP	N	0	×	×	0	0	×	Subphrenic absces
23	0	4-6	D	×	×	0	0	0	0	
24	III	2-3	D	0	×	×	0	×	0	Subarachnoidal haemorrhage
25	III	2-4	N	0	0	0	0	×	0	Hypoglycaemia

*N: normal. D: diminished. A: absent. NP: not performed. S: corticosteroids. PI: fresh frozen plasma. ET: exchange transfusion. PLP: pig liver perfusion. AV: assisted ventilation. PD: peritoneal dialysis.
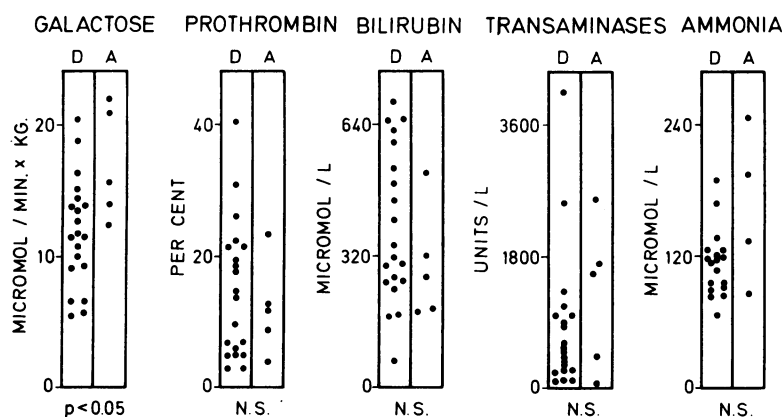
Fig. 1 *Values of the galactose elimination capacity, prothrombin, bilirubin, transaminases, and ammonia in patients who died (D), and those still alive (A).*

initially are shown in Fig. 1. The galactose elimination capacity was significantly lower ($p < 0.05$) in patients who died. The mean galactose elimination capacity was 17.6 ± 4.5 (SD) and 12.2 ± 4.3 $\mu mol \cdot min^{-1} kg^{-1}$, respectively. The results of repeated determination of the galactose elimination capacity are shown in Fig. 2. In patients who survived the galactose elimination capacity increased significantly. This was not the case in patients who died.

The other liver tests showed no significant difference between the two groups.
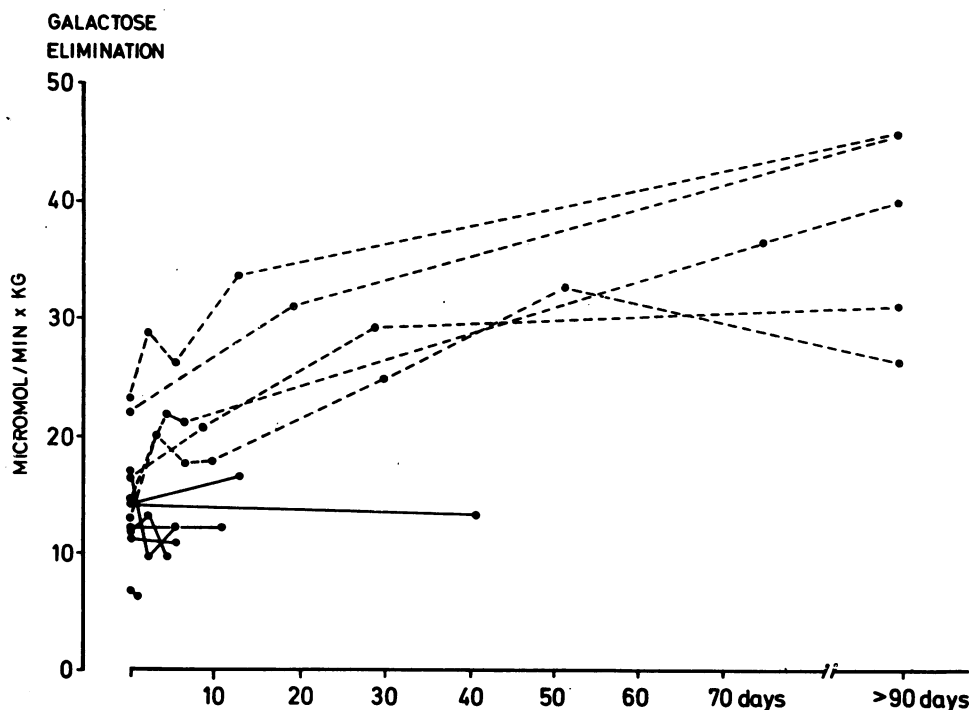
Fig. 2 *Values of the galactose elimination capacity obtained at various intervals in the same patient. Broken lines: survivors; solid lines: fatal cases. The interval between the last galactose elimination capacity test performed and death varied from 0 to nine days.*

In patients who survived the liver histology was normal three to 12 months after the coma episode. In the other patients liver histology at necropsy revealed subtotal or total liver cell necrosis.

Discussion

In our 25 patients with fulminant hepatic failure, none of the usual liver tests was of any value as prognostic markers. Neither the prothrombin value nor blood ammonia differed between those who survived and those who died. This is in accordance with works by Reynolds (1969), and by Saunders *et al.* (1972), but not with that of Demedts *et al.* (1974), who found blood ammonia to be significantly higher in nine patients who died, compared with five patients who survived. Furthermore, the initial prothrombin values were not significantly different but before a third exchange transfusion was performed the prothrombin value (percentage of normal) was significantly higher in the survivors.

Coagulation factor VII is probably a better prognostic marker than the prothrombin time, as shown by Dymock (1975). In 18 patients he found that all 10 patients with a factor VII concentration above 9% survived, while eight patients with concentrations below 9% died.

Other proteins synthesised by the liver that are used as prognostic markers are α_1 antitrypsin and α_1 foetoprotein. Rueff *et al.* (1975) measured plasma concentrations of α_1 antitrypsin in 24 patients with fulminant hepatitis and coma. In nine of 16 patients who died plasma concentrations were below 1·70 mg/ml, while only one of eight survivors had a concentration of α_1 antitrypsin below that level ($p < 0.001$).

Murray-Lyon *et al.* (1975) measured α_1 foetoprotein in serum from 48 patients with fulminant hepatic failure. In seven of 17 survivors α_1 foetoprotein was positive ($> 50 \mu g/ml$) compared with two of the 31 fatal cases. Although not all patients who recovered were foetoprotein positive the demonstration of this protein may indicate liver cell regeneration.

An evaluation of liver histology and prognosis has been performed in 38 patients by Opolon *et al.* (1975). Hepatocyte volume in liver biopsies from patients with fulminant hepatic failure was significantly smaller in patients who died, but approximately half of the cases had hepatocyte volumes

corresponding with the survivors. The major draw-back of the histological evaluation is, however, that most centres hesitate to perform liver biopsies in these patients because of the risk of bleeding, although this complication was not seen in Opolon's series.

Few quantitative liver function tests are available for the assessment of the liver function in fulminant hepatic failure. The conjugation of cholic acid was measured in 14 patients by Horak and Waldram (1975). The conjugation measured three hours after injection of labelled cholic acid was significantly ($P < 0.001$) reduced in the six patients who died.

The metabolism of certain drugs may also be considered as a quantitative liver function test. In patients with paracetamol liver damage, the plasma half life of unchanged paracetamol was the most reliable early guide to prognosis (Prescott *et al.*, 1971), but the material contained only one patient who developed hepatic coma. The clearance of phenazone was found to distinguish between patients with and without hepatic encephalopathy (Andreasen and Ranek, 1975), but its prognostic use in fulmin-ant hepatic failure remains to be shown.

In the present material, no patient with fulminant hepatic failure having a galactose elimination capacity below 12·8 μmol/min and kg body weight survived. Analysis of the eight patients who died having a galactose elimination greater than 13 μmol/min and kg body weight revealed that six (nos. 6, 11, 12, 13, 15, and 23) ran a clinically subacute course, while the disease lasted longer than 30 days. One patient died from cardiac arrest (no. 19). The time interval from the beginning of the liver disease and the duration of coma before the patient enters the hospital varies considerably. In a patient who is admitted early in the course of the disease the liver function may further deteriorate after hospitalisation. Thus a relatively high galactose elimination capacity may be found on admission, although the patient subsequently dies from hepatic failure. This was seen in one patient (no. 21), who had a galactose elimination capacity of 16·9 μmol/min and kg body weight on admission and 9·6 μmol the following day. Repeated determinations of the galactose elimination capacity (Fig. 2) therefore make prognostication more reliable, which is, of course, also the case for most other tests.

The advantage of the galactose elimination capa-city is that it is relatively simple to perform, especi-ally if capillary blood is used instead of arterial blood, and it lasts only one hour, whereas most other metabolic investigations last several hours. It is not influenced by changes in hepatic blood flow or supportive treatments performed the same day, as, for example, exchange transfusion or infusion of fresh frozen plasma, which influence, for instance, prothrombin and bilirubin concentrations.

Although galactose elimination is not a vital function, it is probably a measure of the functioning liver cell mass (Tygstrup, 1966). A quantitative liver function test reflecting the metabolic capacity of the liver also contains prognostic information. If the metabolic capacity is low, it is reasonable to assume that the prognosis is bad.

It is of considerable practical value that quan-titative liver function tests are further investigated and evaluated. They may make the evaluation of different treatments in acute liver failure more com-parable by ensuring that patients with a similar degree of impaired liver function have been examined. The frequently optimistic preliminary reports on new treatments may be due to accidental selection of patients with a relatively good liver function. Another point of practical value is to determine whether a quantitative liver function test can define a critical level, indicating the minimum of liver function which permits the survival of the patient (a 'survival limit'). Similarly a 'regeneration limit' may exist, and from a possible difference between the 'survival limit' and the 'regeneration limit' it may be possible to estimate the amount of 'liver assist' that is needed. Finally, treatment of patients with liver function below the 'regeneration limit' can be omitted, unless a liver transplantation is performed.

In the present series a 'survival limit' correspond-ing to about 12 μmol galactose metabolised/min and kg body weight is suggested, Whether this limit is influenced by the various types of supportive treatment given to some of the patients is unknown, but none of these treatments is of proven value. In patients with fulminant hepatic failure and a total duration of the disease less than five weeks this survival limit seems to be of prognostic significance. However, further investigation are needed. For instance the effect of age upon this 'survival limit' cannot be estimated in the present series.

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