Significance of intravascular coagulation and fibrinolysis in acute hepatic failure

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SUMMARY Twenty-two patients with acute hepatic failure were studied to determine the incidence and magnitude of intravascular coagulation and fibrinolysis and their relation to the severity of bleeding and prognosis. The mean platelet count, Thrombotest, plasminogen activator, and plasminogen were reduced; the reduction in fibrinogen was not statistically significant. Fibrin/fibrinogen degradation products were only moderately increased. Hepatic fibrin deposition was not extensive, being present in 11 of 22 hepatic sections, more in areas of confluent necrosis than in the sinusoids. The combination of increased fibrin/fibrinogen degradation products with decreased plasminogen activator, plasminogen, and thrombocytopenia is consistent with a diagnosis of intravascular coagulation and secondary local fibrinolysis. However, neither of these processes was severe. Severity of bleeding was related only to plasminogen levels and prognosis only to Thrombotest levels. There was no relation between hepatic histological and haematological findings. Heparin therapy is not indicated in the routine management of acute hepatic failure, as intravascular coagulation is not severe and heparin may itself cause massive bleeding.

Bleeding in patients with acute hepatic failure is mainly due to impaired synthesis of coagulation factors but increased consumption of platelets and these factors may contribute. In addition fibrinolysis, secondary to intravascular coagulation, could worsen the bleeding diathesis if it resulted in a high level of fibrin/fibrinogen degradation products. Recently, heparin therapy has been advocated by Rake, Flute, Shilkin, Lewis, Winch, and Williams (1971), as it has been shown to prolong 125I fibrinogen survival and raise plasma fibrinogen levels in patients with hepatocellular failure. These workers have suggested that intravascular coagulation may contribute significantly to liver damage and that early and intensive therapy with heparin and plasma may improve the prognosis.

The aim of our study was to determine the incidence and magnitude of intravascular coagulation and fibrinolysis. The contribution of these disturbances to the bleeding diathesis and their relationship to the prognosis was assessed.

Patients and Controls

Twenty patients in fulminant acute hepatic failure (Trey and Davidson, 1970) and two patients with mild acute hepatic failure were studied (table I). There were eight male and 14 female patients, aged from 8 to 78 years, with a mean age of 43.2 years. They were usually studied within two days of admission when they had not received blood or plasma transfusions, although parenteral vitamin K1 had been given. The control group (12 males and nine females, aged 21-61 years) consisted of healthy medical and laboratory personnel.

Methods

Haemoglobin and platelet count were measured on the Coulter counter and the Thrombotest (Owren, 1959) was performed. Plasminogen activator activity was measured by the euglobulin lysis time (Januszko and Dubieńka, 1965); the results were expressed as units of activity per millilitre of plasma from the

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transfusions usually and bleeding sites ecchymoses, O-III: to grade II, encephalopathy: by severity was

Patient Diagnosis Encephalopathy Bleeding Thrombotest Platelet Plasminogen Plasminogen Fibrinogen FDP
No. (Grade) (Grade) (%) Count (per mm³) Activator (units/ml) (units/ml) (mg/100ml)(µg/ml)
1 Carbon tetrachloride poisoning I 0 18 182 000 3.6 2.8 530 13.3
2 Acute fatty liver of pregnancy I I 38 125 000 3.0 — — 15
3 Halothane I II 10 140 000 1.2 <0.5 440 10
4 Acute fatty liver of pregnancy I I 6 144 000 3.8 <0.5 330 107
5 Halothane I 0 100 318 000 3.9 3.3 349 —
6 Viral hepatitis II II 16 275 000 11.3 0.8 182 5
7 Viral hepatitis II I 11 61 000 4.3 1.3 230 5
8 Viral hepatitis II I 15 94 000 9.0 <0.5 163 20
9 Viral hepatitis III I 8 13 000 12.6 1.2 — 20
10 Acute fatty liver of pregnancy III III 25 115 000 4.0 1.5 324 20
11 Halothane III II 5 132 000 — 1.0 120 —
12 Acute fatty liver of pregnancy III II 25 96 000 3.5 <0.5 290 40
13 Viral hepatitis IV I 12 95 000 27.0 0.9 111 10
14 Paracetamol IV I 18 256 000 3.6 <0.5 118 10
15 Paracetamol IV I 15 183 000 4.0 1.0 235 10
16 Viral hepatitis IV I 10 101 000 2.2 <0.5 337 10
17 Viral hepatitis IV II 8 242 000 3.5 0.6 130 10
18 Paracetamol IV II 19 115 000 <1.0 0.8 560 20
19 Halothane IV II 18 55 000 3.3 — — 20
20 Viral hepatitis V II 15 225 000 11.6 0.7 211 —
21 Halothane V I 5 5 37 3.0 350 40
22 Halothane V II < 5 180 000 <1.0 <0.5 155 20

Table I Clinical and haematological findings
FDP = Fibrin/fibrinogen degradation products.

formula \( \frac{1300}{t} \) of Januszko and Dubinska (1965), where \( t \) is the lysis time in minutes. Plasminogen was measured by a caseinolytic assay (Allkaersig, Fletcher, and Sherry, 1959) and fibrinogen by a thrombin clotting method (Quick, 1959). Fibrin/fibrinogen degradation products were assayed on microtitre plates, using Burroughs Wellcome reagents, by a modification of the tanned red cell haemagglutination inhibition assay described by Das, Allan, Woodfield, and Cash (1967). Needle specimens of liver were obtained in all patients, either during recovery, when coagulation studies were satisfactory, or within 15 minutes of death (table II). The liver sections were stained with Martius-Scarlet-Blue (Lendrum, Fraser, and Slidders, 1962) in order to detect the sites of fibrin deposition.

The severity of hepatic failure at the time of the study was assessed by the grade of encephalopathy, by severity of bleeding, and by the Thrombotest level (table I). Patients fell into the following grades of encephalopathy: grade I, confusion; grade II, drowsiness; grade III, stupor; grade IV, coma with response to painful stimuli; grade V, coma with no response to pain. Severity of bleeding was graded from 0-III: grade 0, no bleeding; grade I, petechial haemorrhages, ecchymoses, and slight oozing from venepuncture sites (transfusions not required); grade II, drainage of altered blood from the stomach and bleeding from the aforementioned sites (plasma transfusions usually required); grade III, drainage of fresh blood from the stomach, with extensive bleeding from other sites (blood and plasma transfusions required). Linear regression analysis and the Wilcoxon rank sum test were used to determine the statistical significance of the results (Wilcoxon and Wilcox, 1964). The results were expressed as mean and range, as the distribution was non-Gaussian.

Results

SEVERITY OF HEPATIC FAILURE

More than half the patients were in grade III-V encephalopathy at the time of the study. Grade I encephalopathy was seen in five patients, grade II in three, grade III in four, grade IV in seven, and grade V in three patients (table I). Of the five patients with grade I encephalopathy, one subsequently progressed to grade II and four to grade III. Bleeding was present in all save two patients. Grade I bleeding occurred in 10 patients and grade II in nine; only one patient had massive (grade III) bleeding.

Thrombotest levels at the time of the study were below 20% in all but four patients. One of these had a level of 100%, associated with transient grade I encephalopathy and rapid clinical recovery. Eight patients had levels of 10% or less despite vitamin K₁ therapy.

Linear regression analysis showed an inverse relationship between Thrombotest levels and both the grade of encephalopathy and severity of bleeding (fig 1). However, this relationship was not statistically significant, though in the case of encephalopathy it only just failed to attain statistical significance (\( r = -0.4047; 0.05 < p < 0.1 \)). All
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PLATELET COUNT AND FIBRINOlyTIC STUDIES

The mean platelet count (111,000 per mm³, range 13,000-318,000 per mm³) was reduced. Eight patients had a normal platelet count and in the remainder the platelet count was but moderately reduced. Only one patient had less than 50,000 platelets per mm³.

The results of fibrinolytic studies are shown in figure 3. The shaded area represents the range (mean ± 2 standard deviations) in 21 normal controls. Mean plasminogen activator activity was decreased (5.72 units/ml, range < 1.0-27 units/ml, p < 0.02). Only four of the 22 patients had normal and one increased plasminogen activator activity (figure 3). The highest levels occurred in patients whose liver failure ran a more prolonged course.

The mean level of fibrin/fibrinogen degradation products was increased (21.3 µg/ml, range 5.107 µg/ml, p < 0.01), but this increase was moderate (fig 3). Six patients had levels at the upper limit of the normal range and only one had levels exceeding 100 µg/ml. Two of the highest levels occurred in patients with acute fatty liver of pregnancy complicated by preeclampsia and intrauterine death of the foetus.

The mean plasminogen level was significantly decreased (1.0 units/ml, range < 0.5-3.3 units/ml, p < 0.01) but the decrease in fibrinogen (272 mg/100 ml, range 111-560 mg/100 ml, p < 0.1) did not reach statistical significance. Fibrinogen values were widely scattered; some patients, particularly those with hepatic failure due to drugs or toxins, had high normal or increased levels.

RELATIONSHIP OF HAEMATOLOGICAL FINDINGS TO BLEEDING AND PROGNOSIS

Severity of bleeding was related only to plasminogen levels (fig 4); there was an inverse linear relationship between plasminogen levels and severity of bleeding (r = -0.53, p < 0.025), y = 1.97 - (0.61)x.

Prognosis was related only to Thrombotest levels (fig 2).

HEPATIC HISTOLOGY

Hepatic specimens were obtained from all patients (table II) either during convalescence (nine patients) or immediately after death (13 patients). The mean interval between the haematological and histological studies was 8.4 days (range 0-44 days). Some intrasinusoidal fibrin was present in eight of the 22 specimens; most of the fibrin was present in areas of confluent necrosis (fig 5). In five specimens fibrin was also seen in portal or hepatic vein radicles. Two of these specimens were from patients with acute fatty liver of pregnancy and neither biopsy showed hepatic necrosis.

There was no relation between histological findings...
PLASMINOGEN ACTIVATOR (units/ml)  F.D.P. (pg/ml) PLASMINOGEN (units/ml) FIBRINOGEN (mg/100ml)

Fig 3  Fibrinolytic studies.

and the indices of coagulation or fibrinolysis. The amount of fibrin deposition was related neither to the severity of bleeding nor to the prognosis.

Discussion

The haematological findings in most patients were consistent with intravascular coagulation and secondary local fibrinolysis. However, neither of these processes appeared to be severe, as evidenced by the levels of platelets, fibrinogen, and fibrin/fibrinogen degradation products. Liver histology indicated that fibrin deposition was not extensive. The incidence and severity of bleeding at the time of the study were not significantly related to any of the indices of coagulation or fibrinolysis apart from plasminogen levels. Prognosis was related only to the Thrombotest level; this is in keeping with the experience of Cook and Sherlock (1965), who found that the prothrombin ratio was the best prognostic index.

The platelet count was normal or moderately decreased in most patients, which suggests that consumption of platelets was not severe.

Plasminogen activator activity was decreased in most patients and was unrelated to bleeding. Four patients had normal and one increased levels of plasminogen activator. All these patients had a more prolonged illness and in three of them liver histology
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Table II  Histological findings

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Interval (Days)</th>
<th>Encephalopathy Grade at time of Haematological Study</th>
<th>Site of Fibrin Deposition</th>
<th>Degree of Liver Necrosis (g)</th>
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<td>Portal/Central Vein</td>
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Fig 5 Liver histology (MSB stain × 40). The red stain in the portal vein indicates coagulated plasma and that in the sinusoids, fibrin. Deposits of fibrin are also seen in areas of necrosis.

showed nodular regeneration. These patients may have been developing cirrhosis, which is often associated with increased plasminogen activator activity.

Fibrin/fibrinogen degradation products may impair haemostasis by interfering with fibrin polymerization, platelet function, and the thrombin-fibrinogen reaction (Larrieu, Marder, and Inceman, 1966). The level of fibrin/fibrinogen degradation products at which this occurs is uncertain, but moderate increases do not appear to cause bleeding. The levels in this study were only moderately increased and were unrelated to the severity of bleeding.

The highest levels occurred in patients with acute fatty liver of pregnancy complicated by preeclampsia and intrauterine death of the foetus. The two latter conditions are associated with increased levels of fibrin/fibrinogen degradation products, which are attributed to increased local fibrinolysis following intravascular coagulation (Bonnar, Davidson, Pidgeon, McNicol, and Douglas, 1969).

Plasminogen levels were decreased, probably owing to consumption of plasminogen both by increased fibrin deposition and by local fibrinolysis. The low plasminogen levels may have been caused by uptake of plasminogen in areas of hepatic fibrin deposition and might thus have been unrelated to intravascular coagulation. Decreased plasminogen synthesis could be a contributory factor but there is no definite evidence that plasminogen is synthesized by the liver. Barnhart and Riddle (1963) found high concentrations of plasminogen in the eosinophil leukocytes.

Our findings of decreased plasminogen activator activity and plasminogen with increased levels of fibrin/fibrinogen products are similar to those of Rake et al (1970). However, the mechanism underlying the apparently conflicting findings of decreased plasminogen activator activity with decreased plasminogen and increased fibrin/fibrinogen degradation products is uncertain. Johnson and Merskey (1966) have postulated that such findings could result from the formation of local fibrin deposits, with adsorption of plasminogen...
activator, plasminogen, and plasmin on the fibrin clot, followed by lysis of the clot.

The mean fibrinogen level was not significantly decreased, which suggests that consumption of fibrinogen was not severe. Alternatively, a rapid rate of consumption could have been balanced by increased synthesis or release of fibrinogen.

Popper and Franklin (1948) found intrasinusoidal thrombi in toxic hepatic necrosis. In the present study, there were fibrin deposits in 11 of 22 liver biopsy specimens. The relationship between hepatic intravascular coagulation and necrosis is unclear. While most of the fibrin occurred in areas of confluent necrosis it was difficult to establish the exact site of fibrin deposition. Intrahepatic fibrin deposition is seen in cases of disseminated intravascular coagulation without evidence of hepatic necrosis (Whitehead, 1972). In this connexion, it is noteworthy that some of the most prominent intravascular fibrin deposition occurred in two patients with acute fatty liver of pregnancy, neither of whom had hepatic necrosis. The absence of fibrin from the remaining 11 specimens could be due to sampling error. Alternatively, removal of fibrin may have been more complete in these patients than in the others. Lysis of fibrin deposits may occur very rapidly, as shown by the results of thrombin infusions in rats (Margaretten, Csavossy, and McKay, 1967). There was no relation between the histological findings and the indices of coagulation or fibrinolysis; this may be due in part to the variable interval between haematological and histological studies.

Although correction of the coagulation disturbance may be facilitated by combining heparin therapy with plasma infusions (Rake et al, 1971), there is no firm evidence that this regime improves the prognosis. What is clear is that heparin therapy has its dangers. Guilin, Rueff, and Ménaché (1972) treated seven patients with heparin and plasma under strict laboratory control and found that thrombocytopenia was corrected in three patients. However, three patients died of massive gastrointestinal haemorrhage. Clark, Rake, Flute, Borirakchanyavat, and Williams (1972) treated 16 patients, in acute hepatic failure due to paracetamol overdose, with carefully monitored heparin and plasma. Coma developed in 12 patients, nine died and bleeding was a major cause of death in three of these. In the present study, in which heparin was not used, only one of 22 patients died from massive haemorrhage. We therefore feel that heparin therapy may be dangerous and is not indicated in the routine management of acute hepatic failure.

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Requests for reprints should be sent to Professor Sheila Sherlock.

References


