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The use of fresh frozen plasma or a concentrate of factor IX as replacement therapy before liver biopsy

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SUMMARY Thirty patients with various types of chronic liver disease and a prothrombin time prolonged for four or more seconds who required needle liver biopsy for diagnostic purposes were given either fresh frozen plasma or a concentrate of clotting factors as a prophylactic measure.

The prothrombin time returned to within normal limits in seven of the 15 patients given the concentrate and in three of those receiving fresh frozen plasma. Levels of factors II, IX, and X showed increases of about 30% following concentrate administration; corresponding rises in the group given fresh frozen plasma were less. This was because of the smaller quantity of clotting factors administered with fresh frozen plasma and the increase in factor II and IX activity/kg body weight/unit of clotting factor injected was greater when fresh frozen plasma was used. In neither group was there clinical evidence of bleeding, but it was of interest that most of the clotting factor levels, except in factor II, before biopsy were above those normally required for haemostasis.

No evidence of disseminated intravascular coagulation was found with the concentrate injection, and the most worrying finding was the appearance of HBAg some months later in three patients, two from the concentrate group and one from those given fresh frozen plasma. However, the conversion of these patients to HBAg positive may be unrelated to the clotting factor replacement therapy.

The risk of bleeding with a liver biopsy is considered to increase if the prothrombin time is prolonged more than three seconds (Sherlock, 1968). There are, however, some patients with prolonged prothrombin times in whom this investigation is needed for diagnostic purposes. Prophylactic administration of clotting factors would be expected to reduce the risks of bleeding in these patients, and for some years it has been our practice to infuse fresh frozen plasma immediately before liver biopsy. With the development of a concentrate of clotting factors which can be given as a single intravenous injection, the necessity for an indwelling intravenous catheter and the administration of the water and sodium load present in fresh frozen plasma could be avoided. Such concentrates contain a high concentration of clotting factors II, IX and X, the levels of which are all reduced in liver disease (Roberts and Cederbaum, 1972), and in this paper we describe a comparison with fresh frozen plasma in the correction of the coagulation defect in patients with a prolonged prothrombin time requiring a liver biopsy. Particular attention was paid to the possible development of intravascular coagulation following the infusion of the concentrate, as we had previously observed this in patients with fulminant hepatic failure given another concentrate preparation (Gazzard, Lewis, Pannell, Bidwell, Rizza, and Williams, 1974).

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Patients and Methods

The series comprised 30 patients admitted to hospital between September 1973 and June 1974, who required liver biopsy and in whom the prothrombin time was prolonged four or more seconds. The relevant clinical data are given in table I, including the platelet count which was above 50 × 10^9/l in all instances. The first 15 patients were given 600 ml of fresh frozen plasma intravenously over a period of half an hour, followed by a further 300 ml six hours later. The second 15 patients were given, by slow intravenous injection, 20 ml of a concentrate of clotting factors. This contained 2 000 units of

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Patient	Age (yr)	Diagnosis	Plasma Bilirubin (μmol/l)	Aspartate Aminotransferase (iu/l)	Platelet Count (/l × 10⁹)
Given Fresh Frozen Plasma					
1	38	Active chronic hepatitis	85	240	128
2	50	Active chronic hepatitis	50	141	97
3	56	Active chronic hepatitis	11	54	95
4	51	Active chronic hepatitis	10	241	128
5	63	Active chronic hepatitis	35	> 250	134
6	32	Subacute hepatic necrosis	400	650	121
7	46	Subacute hepatic necrosis	190	130	140
8	53	Alcoholic cirrhosis	90	185	138
9	53	Alcoholic cirrhosis	155	139	200
10	42	Alcoholic cirrhosis	87	89	128
11	53	Alcoholic cirrhosis	51	140	115
12	58	Alcoholic cirrhosis	40	85	98
13	44	Alcoholic cirrhosis	90	54	113
14	48	Sarcoidosis	11	25	80
15	52	Congenital erythrocytic protoporphyria	80	52	167
Given a Concentrate of Factor IX					
16	53	Active chronic hepatitis	22	240	67
17	63	Active chronic hepatitis	400	2050	109
18	65	Active chronic hepatitis	88	216	113
19	48	Active chronic hepatitis	24	80	102
20	59	Alcoholic cirrhosis	108	122	190
21	37	Alcoholic cirrhosis	27	75	112
22	36	Alcoholic cirrhosis	34	47	71
23	54	Alcoholic cirrhosis	60	113	76
24	53	Alcoholic cirrhosis	20	71	69
25	62	Extrahepatic biliary obstruction	105	750	155
26	50	Haemochromatosis	22	96	109
27	35	Halothane-associated hepatitis	21	61	195
28	53	Chronic persistent hepatitis	94	66	127
29	45	Partial nodular transformation	60	82	102
30	37	Cardiac fibrosis	112	50	150

Table I *Clinical and biochemical data on the 30 patients studied at the time of biopsy*

factors II, IX, and X, and less than 80 units of factor VII (Prothromplex, Serological Products Ltd).

Percutaneous needle liver biopsy was performed with a Trucut needle 30 min after injection of the concentrate or after the initial infusion of fresh frozen plasma. After the biopsy the patients were observed carefully for clinical evidence of bleeding. The occurrence of severe pain or tenderness was recorded, the blood pressure and pulse rate being monitored hourly for the first six hours and then four hourly for the next 18 hours. The packed cell volume was estimated before biopsy and again 24 hours later. Prothrombin time (using the Manchester thromboplastin reagent) and thrombin clotting times were performed by routine methods (Denson, 1972) and expressed as a ratio with the normal control. Platelets were counted visually. Fibrinogen was estimated by a gravimetric technique (Denson, 1972) and the level of fibrin degradation products was measured using the tanned red cell haemagglutination inhibition assay (Merskey, Lalezari, and Johnson, 1969). The levels of clotting factors II and IX were determined by a two-stage assay, and those of factors V, VII (using a patient-deficient plasma) and factor X by a one-stage assay (Denson, 1972). Plasma for clotting factor assays was stored at −20°C for two to three weeks and assayed in batches.

Blood samples before infusion of concentrates and between six and eight weeks afterwards were examined for hepatitis B antigen (by immunodiffusion, immunoelectrophoresis and radioimmunoassay), except in four patients who were HBAg positive before biopsy.

Results

There was no clinical evidence of bleeding in any of the patients in the two groups. No patient required a blood transfusion, although the packed cell volume dropped by 11% in one patient 24 hours after biopsy. Two patients developed superficial thrombophlebitis following extravascular injection of a small quantity of the concentrate. In 27 of the 30 patients the prothrombin time had improved when retested 30 min following the end of infusion of fresh frozen plasma or concentrate (fig 1). However, in only three patients receiving fresh frozen plasma and seven receiving the concentrate had the prothrombin time returned to within normal limits (three sec or less prolonged). Overall, the prothrombin time prolongations appeared slightly greater in the patients given fresh frozen plasma, although in all other

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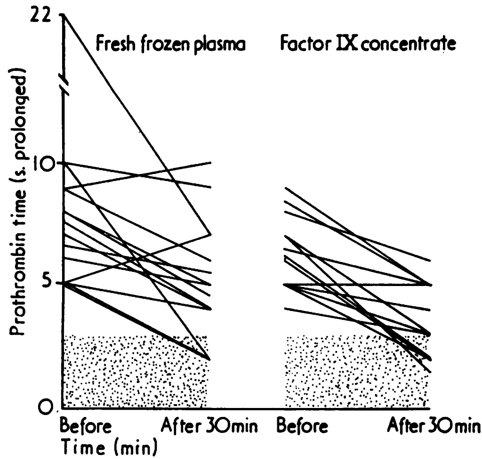

Fig 1 *The prothrombin time in seconds prolonged over control immediately before biopsy and 30 min after the completion of an infusion of fresh frozen plasma or a factor IX concentrate.*

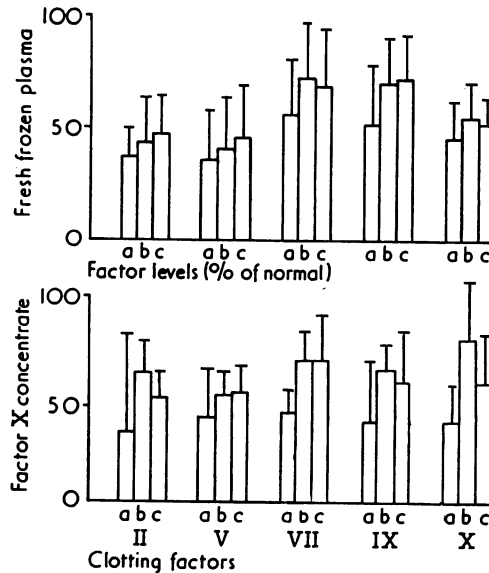

Fig 3 *Mean values (and standard deviation) of clotting factor levels for the two groups of patients taken at 30 minutes (b) and 20 hours (c) following either a factor IX concentrate or fresh frozen plasma infusion compared with those found before liver biopsy (a).*

respects the two groups appeared comparable.

No laboratory evidence of intravascular coagulation was detected at three min, 30 min, six or 24 hr following infusion of the concentrate. The thrombin clotting time was abnormally prolonged in six patients before biopsy, but these values did not rise further following the infusions. The platelet count fell by more than 20% of the initial count in only two patients, and in no case were raised levels of fibrin degradation products detected. No fall was seen in the plasma fibrinogen levels, which were always 2·0 g/l or more.

CLOTTING FACTOR ASSAYS

Initial levels were reduced to a similar degree in both groups of patients and were always above 10% of the normal value (fig 2). The samples taken 30 min following the administration of fresh frozen plasma showed a rise in the levels of factors II, V, VII, IX, and X, which was most pronounced for factors VII and IX (fig 3). The levels were still increased 24 hr later, although there was some fall in the levels of factor VII compared with those recorded 30 min after infusion. The patients given the concentrate showed a considerably greater rise in levels of factors II, VII, and X. This was because more clotting factors were administered using the concentrate than with fresh frozen plasma, eg, 2000 and 600 units

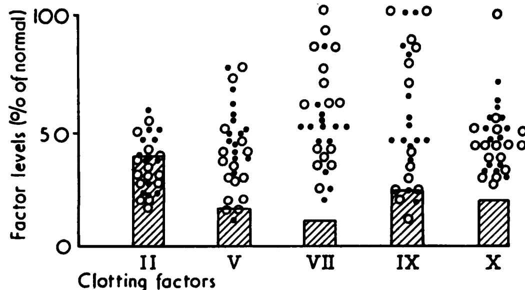

Fig 2 *Levels of individual clotting factors immediately before biopsy in the 30 patients included in this study. The squares represent those patients receiving fresh frozen plasma.*

Factor	Increase in Clotting Factor Activity/kg/unit of Factor Administered (%/kg)	
	Fresh Frozen Plasma	Concentrate
II	1·0 (0·75)	0·8 (0·67)
V	1·1 (0·97)	—
VII	2·0 (1·6)	—
IX	1·9 (1·5)	0·84 (0·62)
X	1·0 (0·97)	1·4 (0·65)

Table II *Mean increase in clotting factor activity /kg body weight/unit of the factor administered produced in the two groups of patients*[1]

[1]The standard deviation is also shown.

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of factor II respectively. However, when the observed increase in activity of factors II and IX was expressed per kg body weight per unit of clotting factor infused, this was greater with fresh frozen plasma than with the concentrate (table II). Neither the initial prothrombin time nor the change in this following replacement therapy could be correlated with the levels of any of the individual clotting factors.

Of eight patients given concentrate who were initially HBAg negative and in whom follow-up samples were available, one became positive by immunodiffusion eight weeks later. There was no change in clinical signs or biochemical tests at this time, but in another cirrhotic patient who became positive at four months having been negative when tested at six weeks, this was accompanied by an acute hepatitic illness. Both these patients were in the ward for about four weeks after the time of the liver biopsy, but neither of them was given additional blood or blood products. Similarly, one patient in the group given fresh frozen plasma in whom HBAg was detected by radioimmunoassay four months later developed clinical and biochemical evidence of acute hepatitis.

Discussion

Partial correction of the coagulation defect was achieved in both groups of patients and in neither were there any immediate side effects attributable to the use of these prophylactic measures. The advantage of a concentrate over fresh frozen plasma in replacement therapy is that much larger quantities of clotting factors can be administered in a small volume of fluid. One potential hazard of concentration infusion already referred to, namely, disseminated intravascular coagulation, was not observed. This may be because intravascular coagulation is already present in the patients with fulminant hepatic failure, whereas in the cirrhotics it is less constant or severe. Another possibility is that in the present cases sufficient liver function remained to clear from the circulation small amounts of activated clotting factor infused with the concentrate. Since pooled plasma is used in the preparation of the concentrate, an important potential complication is the transmission of viral hepatitis, although each donor is screened by radioimmunoassay at regular intervals and the concentrate is also tested by the same technique. Three of our patients became HBAg positive, two following infusion of concentrate and one after being given fresh frozen plasma. The plasma from which the fresh frozen plasma was prepared had also been screened for HBAg. Another possibility is that these patients acquired the virus from other patients in the ward, although in previous detailed studies of the ward we could find no convincing evidence of such cross infection (Bentley, Haynes, Sharpstone, Taylor, Zuckerman, and Williams, 1972).

The yield of factors II and IX in the circulation of our patients from the concentrate was lower than after fresh frozen plasma. This may relate to rapid clearance of clotting factors altered during the concentration process. The concentrate does not contain factor V, but small increases were observed in the levels of this clotting factor following infusion. As the factor V-deficient plasma used in the assay may also have reduced factor II levels, increases in this following administration of the concentrate could account for the apparent rises in factor V recorded. Other workers have noted that concentrates of factor IX only produce partial correction of the prothrombin time in patients with cirrhosis and have attributed this to the lack of factor V in the preparation (Sandler, Rath, and Ruder, 1973). The rises in factor VII were of interest, as the concentrate only contains small amounts of this clotting factor, but other workers have also noted this effect (Dr Eibl, personal communication).

In our patients, the levels of all the clotting factors, except factor II, were above those required for haemostasis as quoted by Rizza (1972). Although the influence of multiple clotting factor deficiencies on the development of the bleeding tendency is not known, it is likely that only replacement of factor II was important in these cases. Thus, a better routine screening test for patients before liver biopsy may be the Normotest or Thrombotest which are said to be more sensitive to a reduction in factor II levels than the one-stage prothrombin time (Hadchouel, Toubouli, and Caroli, 1973). Many other factors, including platelet numbers and function and vascular fragility, may be equally important in determining the likelihood of bleeding, and whether replacing clotting factor is really worthwhile in the type of patient we studied is uncertain. Nevertheless, the risks of bleeding after biopsy in such cases, if it did occur, would be high, and so it would seem reasonable to continue to use some form of clotting factor replacement such as fresh frozen plasma, even though its value prophylactically may be difficult to prove.

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