Annotation

INTRAVASCULAR COAGULATION AND THE LIVER

The relationship between liver disease, abnormal bleeding and haemostatic defects is well established and has been the subject of several recent comprehensive reviews (e.g. Walls & Losowski, 1971; Roberts & Cederbaum, 1972). One of the most important concepts, however, concerns the possible role of intravascular coagulation in the pathogenesis of liver disease and of the associated haemostatic failure. Despite rapid accumulation of knowledge, the interpretation of laboratory data is often controversial and this fact together with the wider availability of potentially dangerous therapeutic materials warrants a brief review of selected recent developments in this important field.

Evidence for Intravascular Coagulation in Liver Disease

Reduced levels of plasma fibrinogen occur in both acute and chronic liver disease. In acute hepatic necrosis this is characteristically a late event and has usually been regarded as being due to impaired hepatic synthesis. In chronic liver disease, such as cirrhosis, the occurrence of increased fibrinolysis has been recognized for over half a century and has been attributed both to impaired hepatic clearance of plasminogen activator and to deficient synthesis of fibrinolytic inhibitors. In 1960, Bergström, Blombäck & Kleen noted that plasma therapy aggravated fibrinogen deficiency in a patient with cirrhosis. They suggested that the increased fibrinolysis which they detected was secondary to intravascular coagulation. Zetterqvist & von Francken (1963) and Johansson (1964) extended this observation into practical therapeutics by treating cirrhotic patients with heparin but the beneficial effects were not clear-cut. The concept of intravascular coagulation in liver disease was placed on a more rational basis by the work of Tytgat et al (1968a, 1971) who found that the biological half-life of labelled fibrinogen was reduced in patients with cirrhosis and that the fractional and total catabolic rate was increased. These abnormalities tended to be reversed by treatment with heparin and similar observations were made for prothrombin and plasminogen (Collen et al, 1972). Hörder (1969) also found that in patients with cirrhosis laboratory findings consistent with disseminated intravascular coagulation (DIC), i.e. low platelet count, low fibrinogen and factor V, were reversed by heparin treatment, and platelet changes thought to be due to DIC have been observed (Thomas, 1972).

Although these observations were mainly concerned with chronic liver disease, similar and more profound coagulation changes were simultaneously observed in terminal liver failure and acute hepatic necrosis (Ménaché et al, 1968). Tytgat et al (1968b) noted that the coagulation changes in patients with hepatic coma could not be completely reversed by exchange transfusion and they suggested that this was due to intravascular coagulation. In an initial study on six patients with acute hepatic necrosis mainly due to viral hepatitis, Rake et al (1970) detected increased rate of disappearance of radioactive fibrinogen and the clinical and laboratory changes improved on heparin therapy. In these patients and in seven others, additional indirect evidence suggested intravascular coagulation. This included the presence

Correspondence: Dr A. L. Bloom, Department of Haematology, University Hospital of Wales, Heath Park, Cardiff CF4 4XW.
of fragmented red cells, prolongation of the thrombin clotting times, slight reduction of fibrinogen levels, thrombocytopenia, reduced plasminogen and increased levels of fibrinogen-related antigen (FDP) in the absence of increased circulating plasminogen activator. In a later study by this group (Clark et al., 1973a), 36 patients with paracetamol-induced liver damage were comprehensively investigated. In all but the most severely affected patients fibrinogen synthesis was increased but it was catabolized rapidly. Many of the secondary changes described above were observed together with positive protamine sulphate tests. The authors considered that the evidence was consistent with intravascular coagulation. In experimental studies in rats similar conclusions were reached after liver necrosis had been induced with carbon tetrachloride (Rake et al., 1973). Inhibition of fibrinolysis exerted a deleterious effect, possibly by removing a protective mechanism, a consideration which may contra-indicate this form of treatment in clinical practice.

Possible pathogenetic mechanisms for the occurrence of intravascular coagulation in liver disease were considered by Liehr et al. (1972) and by Verstraete et al. (1974). They suggested that in cirrhosis vascular and haemodynamic changes could contribute by exposing blood to expanded collaterals and distorted splanchnic circulation in the presence of impaired hepatic clearing mechanisms. In more acute liver failure exposure of blood to necrotic hepatocytes could trigger local intravascular coagulation. Local intravascular coagulation may also be triggered by antigen-antibody reactions and this may be particularly relevant in the case of liver transplant (Flute et al., 1969). In all cases it is conceivable that deposition of fibrin in local vasculature may in itself further impair hepatic integrity and hence haemostatic function. In order to prevent this and encouraged by their initial results Rake and his colleagues (1971) intensively treated four patients in severe acute hepatic failure with fresh frozen plasma to replace coagulation factors and with heparin to prevent their consumption. All four patients survived. In a larger series of 40 patients the same group (Clark et al., 1973b) compared the effect of this intensive treatment with the results obtained in patients managed without particular emphasis on improving coagulation. All the latter patients died but four of the heparinized patients survived and in this group as a whole coagulation studies improved. The heparin-treated group, however, included more patients suffering from paracetamol poisoning and in these patients the prognosis may be better than in other forms of hepatic necrosis (Gazzard et al., 1974).

Although the results of heparin therapy were therefore inconclusive they raised the possibility of improved management of acute hepatic failure. At the same time the development of coagulation factor concentrates promised an answer to the haemodynamic limitations of plasma treatment. Both coagulation concentrates and heparin are potentially dangerous and it is therefore appropriate to review the considerations which, in the present context, may limit or contra-indicate their use. These constraints may be discussed under three headings. (1) Doubt of the importance of intravascular coagulation in liver disease. (2) Incomplete knowledge concerning the efficacy of heparin therapy. (3) The potential hazards of coagulation factor replacement.

Evidence against the Importance of Intravascular Coagulation in Liver Disease

The evidence cited above suggests a role for intravascular coagulation in liver disease but this concept has not received universal support. Much of the difficulty derives from the fact
that the coagulation changes which occur are complex and possibly due to several causes. In addition some of the changes which may be expected from failure of synthesis such as deficiency of prothrombin and factor V also occur in intravascular coagulation. Corrigan *et al* (1973) compared the coagulation changes in hypofibrinogenaemic patients suffering from severe liver disease with those observed in patients with other causes of DIC. Although the changes were similar the elevated levels of factor VIII in liver disease contrasted sharply with the decreased levels found in the other cases, a phenomenon which has been noted by other workers. The role of factor VIII in liver disease in fact deserves further consideration. Hepatic synthesis of factor VIII was suggested by animal transplantation (Webster *et al*, 1971) and immunological (Bloom & Giddings, 1972) studies but evidence for extra-hepatic sites was also obtained. Recent work on the nature of factor VIII suggests that it is associated with a high molecular weight protein—factor VIII related protein (FVIIIIRP)—which is reduced or abnormal in von Willebrand's disease and is present on vascular endothelium (Bloom *et al*, 1973). Levels of FVIIIIRP are raised in hepatocellular disease (Green & Ratnoff, 1974; Holmberg & Nilsson, 1974) and may even be disproportionately high when compared to those of procoagulant factor VIII. The raised levels of procoagulant factor VIII and FVIIIIRP may represent impaired catabolism or excess release from the damaged liver but are more likely reactive phenomena. These findings support the evidence of Neill & Straub (1970) that the elevated levels of procoagulant factor VIII detected in patients with acute hepatic necrosis are not assay artefacts or activation effects. Herold & Straub (1973) have summarized the alternative explanations to DIC which could account for these coagulation changes in liver necrosis due to hepatitis and mushroom poisoning. In their patients platelet counts were inconsistently depressed and FDP levels inconsistently raised. The fall of fibrinogen was related to the fall of other plasma proteins and this suggested extravascular loss. It was suggested that this could occur into the gastrointestinal tract, into exudates or, in more chronic disease, into ascitic fluid. The prolongation of the thrombin clotting time frequently observed in acute hepatic necrosis has also not been satisfactorily explained. The levels of FDP are rarely raised sufficiently to account for it. One possibility is that abnormal fibrinogen is synthesized (Soria *et al*, 1970; von Felten *et al*, 1969) or that a precursor fibrinogen is released from necrotic parenchymal cells. This could be catabolized more rapidly than normal and polymerize more slowly. The possibility of abnormal fibrinogen was also considered by Brodsky *et al* (1970) who noted a lack of correlation between impaired platelet and fibrinogen survival in patients with hepatocellular disease who were investigated using an *in-vivo* radioactive label. The observations of Charm & Wong (1970) may also be relevant. They subjected normal plasma to *in vitro* shearing forces and noted that fibrinogen was degraded. They correlated the shearing degradation of fibrinogen with its normal *in vivo* survival. It is conceivable that haemodynamic changes in liver disease could alter these forces and reduce fibrinogen survival. In addition, raised levels of FDP may be derived from extravascular fibrinous exudates, from extravascular blood or because of delayed reticulo-endothelial clearance in the affected liver. Finally, although hyperplasminaemia is not usually detected in acute liver disease, fibrinogenolysis could also contribute to increased fibrinogen turn-over in some cases. The changes in other coagulation factors are also amenable to alternative explanations such as diminished synthesis and extravascular loss, whilst platelet production may be impaired or they may be pooled in the spleen. Perhaps the most reliable
evidence of intravascular coagulation during life is the response to heparin, but in individual patients this is mainly valid in chronic disease (e.g. Tytgat et al, 1971). It is possible that newer methods such as radioimmunoassay of specific FDP or fibrinopeptides may help to resolve these problems but this is difficult to foresee. Meanwhile the concept of DIC in patients with liver disease is often open to debate. Whilst it is reasonable and likely that local intravascular fibrin deposition will occur in an acutely inflamed liver and has been detected histologically (Hillenbrand et al, 1974) there is yet no incontrovertible evidence for DIC in these disorders.

The Efficacy of Heparin Therapy

In keeping with the above constraints the efficacy or desirability of heparin therapy has not yet been proved by controlled prospective trials. Gazzard et al (1974) treated 22 patients suffering from paracetamol-induced hepatic necrosis. Eleven received fresh-frozen plasma and 11 received heparin as well. The severity of the coagulation changes correlated with the clinical severity, but in contrast with previous results from these workers (Clark et al, 1973b) there was no difference in the outcome between the patient groups. Hillenbrand et al (1974) also studied 22 patients with acute hepatitis. Although changes which could be attributed to DIC were observed these were not severe and the authors concluded that the potential benefit of heparin treatment would not outweigh the risks.

The Use of Coagulation Factor Concentrates

Whilst the value of heparin therapy in acute and chronic liver disease remains to be determined the use of coagulation factor concentrates must also be reviewed. The preparation of concentrates which contain the vitamin-K dependent factors II, VII, IX and X has been described by Bidwell et al (1972). Four-factor concentrates are prepared by elution from calcium phosphate (e.g. ‘PPSB’) or DEAE sephadex (e.g. ‘Konyne’). Recently concentrates have been prepared by elution from DEAE cellulose. These contain factors II, IX and X but are deficient in factor VII. These concentrates are highly potent, have low total protein content and can be administered in small volume. They therefore solve the haemodynamic problems of fresh frozen plasma. They would therefore seem to be ideal in liver disease for a trial of replacement therapy in conjunction with heparin, or for preparation for biopsy or surgery. It is possible, however, that some of these preparations contain activated coagulation factors, administration of which would be undesirable in the presence of possible intravascular coagulation. The possibility that the four-factor concentrates may be activated has been recognized in the past and heparin was added during preparation to prevent this. The effective use of these concentrates in liver disease has been described (Ménaché et al, 1959; Soulier et al, 1969) but there is clear evidence that early crude preparations induced defibrination (Ménaché et al, 1959; Tullis et al, 1965). Sandler et al (1973a) treated several cirrhotic patients with ‘Konyne’ and noted that the expected clinical and laboratory response did not occur. In addition there are recent reports of thromboembolic complications following the use of four-factor concentrates in patients with Christmas disease after operation (Kasper, 1973) and of coagulation changes consistent with DIC in patients with viral hepatitis (Guillin et al, 1971). In one of the latter patients the undesirable coagulation changes were not entirely prevented by heparin therapy.

Although these reports are disturbing they must be considered in perspective. Concen-
trates containing these coagulation factors have been used extensively in the United Kingdom for many years including cover of major surgery in patients with Christmas disease (Bidwell et al, 1972) but similar complications have not been reported. It is probable that different preparations vary in their thrombogenic effect. The nature of the active agent apparently present in some preparations has not been established with certainty but the concentrates often contain low levels of antithrombin III, the protective effect of which is also reduced in liver disease. Several methods have been devised in attempts to detect a thrombogenic effect. Tests for thrombin activity have been described (Bidwell & Dike, 1966) and intravascular coagulation has been produced experimentally in animals (Triantaphyllopoulos, 1972). Aronson (1974) has outlined an animal model using venous stasis. With the concentrate tested thrombosis was prevented by the addition of heparin but not by soybean trypsin inhibitor, which inhibits factor Xa, or by di-isopropylfluorophosphate which inhibits thrombin, factor VII and factor Xla. Aronson therefore attributed the effect to factor IXa but it is not known if any of these methods are relevant to human therapy.

In addition to the possible thrombogenic effects of liver factor concentrates Sandler et al (1973b) have reported a high incidence of serum hepatitis in patients, including those with pre-existing liver disease, who were treated with 'Konyne' for the maintenance of surgical haemostasis. Screening of the concentrate for hepatitis-associated antigen by radioimmunoassay or by electron microscopy failed to detect icterogenic batches. It is of course uncertain if all concentrates are similarly contaminated but it is doubtful even if screening of individual donors will entirely eliminate this risk. The danger of hepatitis seems to be lower in patients with Christmas disease, presumably as a result of repeated exposure, but the possibility poses a further undesirable hazard in patients with liver disease or vitamin K deficiency which has not yet been fully assessed.

Although the presence of significant intravascular coagulation in patients with hepatocellular disease has not been unequivocally established the use of coagulation factor concentrates should be approached with caution. In vitamin K deficiency or anticoagulant overdose their use is more rational and probably safer in this respect but should still be carefully controlled. The concentrates do not contain factor V and some lack factor VII, both of which may be important in maintaining normal haemostasis and both of which are often deficient in liver disease. In these circumstances use of fresh frozen plasma, although limited by volume restriction, may be more appropriate. The dilemma of heparin therapy is also unresolved, but this is not peculiar to liver disease. The possibility of local or disseminated intravascular coagulation has been suggested in an ever widening variety of disorders. If the diagnosis is not sometimes fallacious it would appear to be a frequent paraphenomenon or perhaps a fundamental pathological response. In any event the wisdom of heparin treatment, particularly in the presence of bleeding, should always be carefully reviewed. In the end the efficacy and safety of these forms of treatment can only be decided by carefully controlled trials at units experienced in the management of liver disease and blood coagulation disorders.

A. L. Bloom

Department of Haematology,
University Hospital of Wales,
Heath Park, Cardiff
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