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Annotation

CLOTTING FACTOR CONCENTRATES FOR RESISTANT HAEMOPHILIA

The introduction of cryoprecipitate and freeze-dried concentrates of factor VIII has revolutionized the clinical management of haemophilia and allowed the development of home and other forms of treatment. Although several complications of these materials have been described the most important immediate problem is the development of antibodies to factor VIII that render the patient resistant to conventional treatment. The results of immunosuppressive therapy in this situation have been disappointing. Limited success has been described in patients who were poor immunological responders and when treatment was commenced early during the immunization process (Dormandy & Sultan, 1975; Hultin *et al*, 1976) but it may be more effective in patients with autoimmune antibodies to factor VIII (Green, 1971). Recently, new and confusing methods have been advocated for managing these resistant patients using blood products including potentially dangerous preparations of activated clotting factors. This annotation reviews these newer methods. Emphasis will be given to the problems of patients with haemophilia but, where appropriate, reference will also be made to non-haemophilic patients who develop antibodies of similar specificity.

Factor VIII Concentrates

Large doses of factor VIII concentrates can sometimes secure a haemostatic effect, for instance in closed bleeds, even in the presence of such a potent antibody that the level of factor VIII does not rise (Rizza & Biggs, 1973). Presumably in such cases the factor VIII is instantaneously effective before it is neutralized. Factor VIII concentrates alone, however, are more likely to be effective in patients with a lower titre of antibodies in whom it may be possible to obtain a haemostatic level of circulating factor VIII. Attempts to determine the amount of factor VIII needed to overcome an inhibitor have not usually been successful and Blatt *et al* (1977) used an arbitrary loading dose of 10 000 units of high-potency concentrate followed by 300–1000 units per hour by continuous infusion in an average adult. The author, also arbitrarily, has used bolus doses equivalent to the patient's approximate plasma volume, e.g. 3000 u, once to three times a day when the level of factor VIII antibody has been less than 5–10 u (Biggs & Bidwell, 1959) per ml (*vide infra*). Disadvantages of using large doses of freeze dried factor VIII concentrates include the development of an anamnestic response, the cost, the risk of haemolysis from blood group isoantibodies, high fibrinogen levels and haemolysis with less pure preparations and the transmission risk of hepatitis. If the antibody shows appropriate specificity *in vitro*, it may be possible to obtain haemostatic levels of factor VIII for a while with a porcine concentrate (Speywood Laboratories). This material, however, causes thrombocytopenia, is also expensive and may increase the immunological response. It is rarely if ever needed.

The antibody level after treatment can be followed by an inhibitor assay. There are, unfortunately, several different assays, most of which express the activity in terms of arbitrary

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units per ml of plasma (Biggs & Bidwell, 1959; Rizza & Biggs, 1973; Kasper *et al*, 1975). The reaction kinetics of different factor VIII antibodies are variable. Some follow a second order type of reaction but others are more complex so that it is difficult to relate accurately one assay method to another when different reaction times and antigen–antibody concentrations are used. The autoantibodies in patients with acquired haemophilia are also likely to be heterogeneous and to give complex reaction kinetics. Sometimes the inhibitor coexists with measurable endogenous factor VIII although the latter does not seem to be effective *in vivo* (Bloom *et al*, 1966). It certainly cannot be assumed that one unit of antibody measured by any standard method neutralizes one unit of factor VIII activity either *in vitro* or *in vivo*. In general, one unit of activity measured by the Biggs & Bidwell (1959) method is approximately equivalent to two Bethesda units (Kasper *et al*, 1975) and to three or four units measured by the Rizza & Biggs (1973) technique, but this relationship is not necessarily always valid. Clearly there is need for international standardization of the assay method. Nevertheless the measurement of the antibody level after treatment with factor VIII concentrates is important. Some patients have a brisk anamnestic response. Others are 'poor' immunological responders and these patients react more favourably both to factor VIII concentrates and to immunosuppressive therapy. Patients with mild haemophilia who have developed antibodies have usually been of this type. An anamnestic response of autoantibodies to transfused factor VIII is theoretically less likely than in the case of alloantibodies and is correspondingly less well documented. The immunological response of individual patients is clearly relevant to treatment but can only be determined by therapeutic trial.

Plasmapheresis has been used to reduce the circulating level of factor VIII antibody either in an attempt to secure a haemostatic response to factor VIII concentrates or, in one report, to reduce the antibody level prior to dental surgery (Cobcroft *et al*, 1971). Exchange transfusion is cumbersome and is not usually used for this purpose. Plasmapheresis is best performed with a continuous flow cell separator (Edson *et al*, 1973; Pintado *et al*, 1975; Mibashan, 1977) and has become a relatively routine, if time consuming procedure, in many centres. It is possible to exchange 5 litres or more using fresh frozen plasma and to reduce the antibody level by 80%. This may allow effective replacement therapy with large doses of freeze-dried factor VIII concentrates (Mibashan, 1977). The antibody tends rapidly to reappear in the circulation albeit at reduced level, possibly from the extravascular space, but repeated plasmapheresis may be effective. When used prior to elective surgery (Cobcroft *et al*, 1971) plasmapheresis was performed with saline once or twice a week for 6 weeks to avoid an anamnestic response and it was considered important to first establish that the antibody level was not rising. The use of cell separators is not advised when patients are positive for hepatitis associated antigen because they may form a spray, and the procedure is usually impracticable in children because of the size of the cannulae needed and the necessity of avoiding traumatic or femoral venepunctures. In these patients plastic plasmapheresis packs can be used.

Factor IX Concentrates

The use of concentrates containing the vitamin K dependent clotting factors constitutes the most recent and controversial aspect of current therapy. Breen & Tullis (1969) were the first to report this use of 'factor IX' concentrate for the treatment of factor VIII deficiency. Fekete *et al* (1972) briefly described the use of an 'activated' preparation, Auto-Factor IX, Hyland, for the

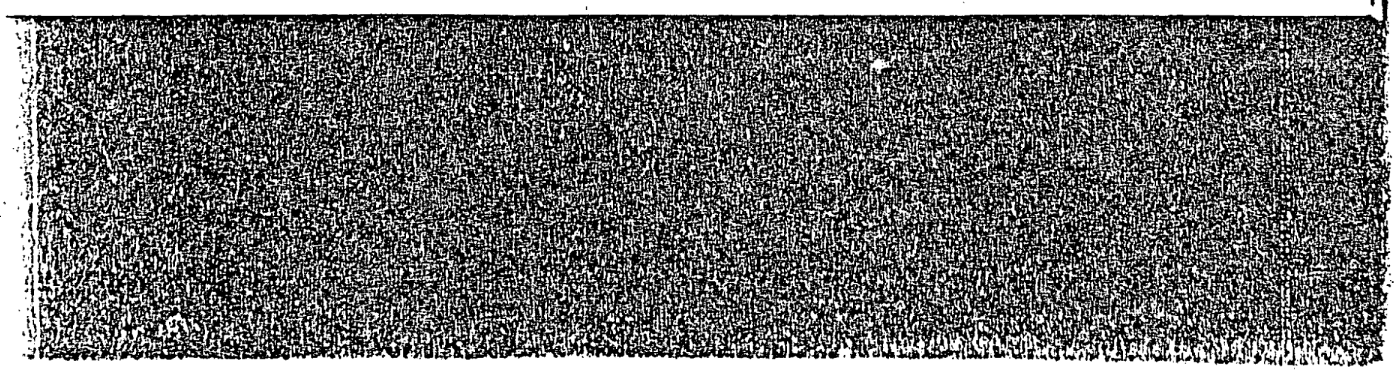
control of bleeding in patients with factor VIII antibodies, but the first substantial account was that of Kurczynski & Penner (1974) who claimed that Auto-Factor IX (Autoproplex, Hyland) successfully arrested bleeding on 60 occasions in six haemophiliacs and two non-haemophiliacs with factor VIII antibodies without causing complications. Since then a number of case reports and more extensive series of patients have been described and the therapeutic trials have been extended to include 'non-activated' factor IX concentrate (Abildgaard *et al*, 1976; Kelly & Penner, 1976).

Concentrates containing factor IX were first introduced for the treatment of haemophilia B (Christmas disease). Original preparations contained factors II, VII, IX and X (and also factor XI), but later ones lack factor VII. For convenience they will all be called 'factor IX concentrates'.

It was soon realized that some of these factors may be 'activated' during the fractionation process and thereby become thrombogenic. Manufacturers have therefore used heparin at certain stages during the fractionation procedures and have applied *in vitro* or animal 'thrombogenicity' tests in attempts to exclude the thrombogenic effect. In clinical practice these precautions have been remarkably effective although thrombotic complications have been reported in U.S.A. and Continental Europe after use of factor IX concentrates for surgery in Christmas disease (Kasper, 1975) and in other conditions. Batches of factor IX concentrate which 'failed' a manufacturers thrombogenicity tests were discarded for use in patients with Christmas disease and were considered to be 'activated'. Unfortunately there is no uniform test for thrombogenicity and three or more have been described (Bidwell & Dike, 1966; Pepper *et al*, 1977). Material which has passed the tests of one manufacturer may fail miserably that of another and yet be used quite safely for the treatment of patients with Christmas disease.

The initial reports on the use of activated factor IX preparations in haemophilia seem to have referred to material which had been produced during a normal manufacturing process for factor IX concentrate but which had failed that particular manufacturer's thrombogenicity tests. Because such materials accelerated clotting tests of haemophilic plasma it was reasoned that they may contain an activated factor or intermediate which would bypass the site of action of factor VIII and the antibody in the coagulation sequence but that generalized systemic intravascular coagulation would be prevented by natural inhibitors. The results of Kurczynski & Penner (1974) seemed to support this view. Attempts were now made deliberately to produce an activated product which would be effective in haemophilia. Ekert & McVeagh (1975) treated one patient with thrombin-activated factor IX concentrate and claimed success but the material which has received most attention is that produced by the Austrian firm Immuno (Elsinger, 1977).

This material, originally called Fraction R, appears to represent an attempt to produce factor IX concentrate purposely activated under controlled conditions to produce a factor VIII inhibitor bypassing activity (Feiba). This activity is detected by the shortening of the partial thromboplastin time of a standard inhibitor plasma. An arbitrary Feiba unit thus has been defined but it is not necessarily related to that of any other clotting factor. The term Feiba thus really applies to this particular material although it has been applied by some authors to the active agent, if any, present in other factor IX concentrates and effective in securing haemostasis in patients with factor VIII antibodies. Recently there has been a decline in the availability of 'accidentally' activated factor IX concentrates as manufacturers have tightened their



product control for the treatment of Christmas disease. For this reason and because of the vagaries of thrombogenicity testing some clinicians have turned to 'non-activated' or routine factor IX concentrates for the treatment of haemophilic patients.

The substance in these products which is supposed to control bleeding in haemophilia A is unknown and may be different in various products. It does not seem to be simply one of the activated coagulation factors such as IXa or Xa but chromatographic studies have suggested that it is a derivative or combination of two factors, e.g. factor X and thrombin or a dimer of a factor X activation product (Tishkoff, 1975; Pepper *et al*, 1977). When administered to patients the *in vitro* changes are usually slight and it is unusual to see evidence of disseminated intravascular coagulation. The kaolin-cephalin clotting time and prothrombin time may be moderately shortened and the non-activated PTT to a greater extent (Lowe *et al*, 1976). However, the most consistently observed effect is shortening of the whole blood clotting time (WBCT) although not usually to within the normal range. According to Vermylen *et al* (1978) this effect on the WBCT is because Feiba enhances a factor X activator activity of platelets.

Reports on the clinical use of factor IX concentrates have been controversial. Following the initial reports with Autoproplex, Abildgaard *et al* (1976) claimed success with the use of 'non activated' Konyne for 64 episodes in five patients whilst Kelly & Penner (1976) treated 90 episodes in 13 patients using 'non activated' Proplex and noted subjective and objective improvement in 38 instances. Success has also been claimed for the use of Feiba (Mannucci *et al*, 1976; Preston *et al*, 1977) and Anderle (1976) has reviewed its use in 104 episodes at several centres. Treatment of closed bleeding was difficult to assess but in eight cases of minor surgery bleeding only occurred in one case. Unsuccessful use of these preparations is less likely to be reported but has been noted by Pollock & Lewis (1976) and by the present author in 14 episodes including two with external bleeding for which large doses were used (Parry & Bloom, 1978). On the other hand, control of external bleeding after surgery or dental extractions has been claimed by Lowe *et al* (1976) for Proplex and by Preston *et al* (1977) for Feiba and by several other authors.

Reported side effects of using these preparations are uncommon but potentially serious. Laboratory signs of intravascular coagulation were reported by Stenbjerg & Jorgensen (1977a) in one patient treated by Feiba, and transient amaurosis has also occurred (Rasche *et al*, 1977). Stenbjerg & Jorgensen (1977b) have reported resistance to Feiba in one case possibly due to stimulation of natural inhibitors. Disappointingly, a few preparations or batches of factor IX concentrates and Feiba have been contaminated with factor VIII and an anamnestic rise of factor VIII antibody has occasionally been observed (Allain & Kreiger, 1975; Mannucci *et al*, 1976).

The reasons for the conflicting reports on the effect of factor IX concentrates and their disadvantages have been reviewed by Blatt *et al* (1977). Assessment of results with closed bleeds is subjective. Bleeding often stops just with rest and immobilization and other forms of treatment often also have been used. No controlled clinical trials have been reported and the variable nature of the lesions, different levels and type of antibodies and the small number of patients at each centre make these trials difficult to conduct. The doses and method of administration of the factor IX concentrates have been variable. Doses have often been expressed as units of factor IX but these are not necessarily related to the active agent or the Feiba unit, and the factor IX assay itself may be affected by an activated intermediate. The

methods of manufacture of most products including Feiba have not been released or may periodically change. The preparations thus vary from manufacturer to manufacturer or even from batch to batch. Dosage schedules have therefore been empirical. There is no reliable *in vitro* method to determine a therapeutic effect but most schedules for which success has been claimed have recommended doses of 20–80 'units'/kg at 6- or 8-hourly intervals. There are anecdotal recent reports that the newer and less thrombogenic factor IX preparations are also less effective in factor VIII antibody patients (Penner & Kelly, 1977) and it should be noted that some of them may contain heparin. On the credit side the factor IX preparations are less expensive than massive doses of factor VIII concentrate. The effect, if any, is not influenced by the antibody level, and there is less risk of an anamnestic response.

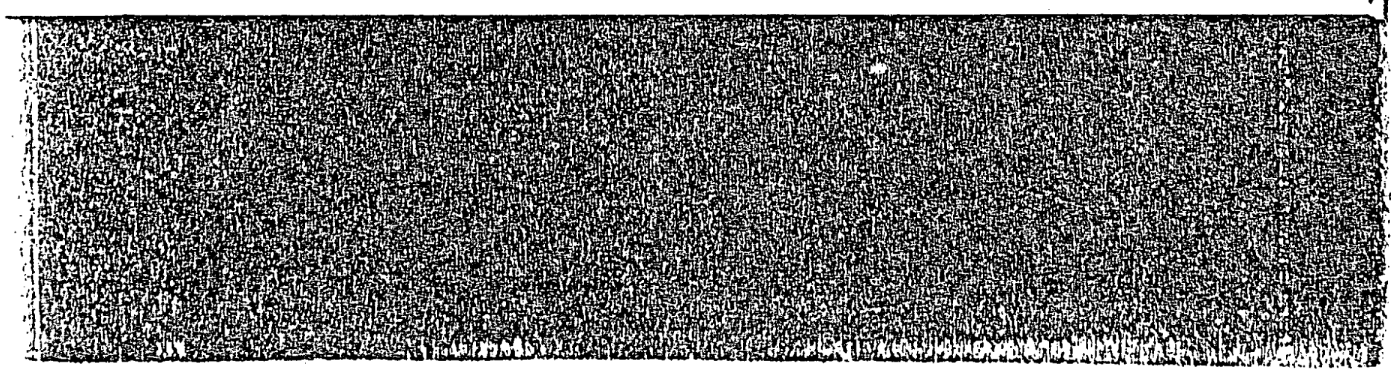
Combined Use of Factor VIII and Factor IX Concentrates

Recently Schimpf *et al* (1977) and Brackmann *et al* (1977) have claimed that combined use of factor VIII and Feiba were not only as effective in controlling bleeding as larger doses of Feiba used alone but when used regularly could actually lead to disappearance of the antibody in some patients. Doses of factor VIII ranged from 30 to 150 u/kg and of Feiba 30–120 u/kg administered three to seven times each week. It is not clear if a permanent state of immune tolerance was achieved or if continued treatment is needed but huge amounts of concentrates were required. In one patient described by Brackmann & Gormsen (1977) over 1 188 000 units of factor VIII concentrate, 300 000 units of factor IX concentrate and 250 000 units of Feiba were administered over a period of 5 months and it was not clear if this was an ongoing commitment. Not only would the cost of this treatment, £1000 daily per patient in the U.K., be prohibitive for most centres but if widely prescribed would raise important questions regarding the distribution and redistribution of blood products.

Other Methods of Treatment

The presence of an antibody increases the importance of immobilization and supportive treatment. Local application of topical thrombin or Russel's viper venom is sometimes effective for surface bleeding and fibrinolytic inhibitors such as epsilon amino caproic or tranexamic acid may be helpful particularly for bleeding from the mucus membranes and nose. Although they have been used in combination with Feiba (Preston *et al*, 1977) their use with these factor IX preparations should be circumspect because of the thrombogenic risk. Bloom & Hutton (1975) have described the use of platelet concentrates in these patients based on the possibility that platelets may adsorb coagulation factors, protect them from the antibody and convey them to the injured site. In the light of the findings of Vermylen *et al* (1978) this form of treatment may be more rational than at first envisaged but platelets are themselves antigenic and can only be recommended as a last resort.

Although the development of factor VIII antibodies in patients with haemophilia has not been as serious to life as at first feared, treatment clearly is not yet satisfactory. The most reliable results are obtained with high potency factor VIII concentrates, particularly in patients with modest antibody levels. It is certainly unreasonable to allow such patients to become incapacitated for fear of inducing an anamnestic response. To allow for this treatment national estimates for freeze-dried factor VIII concentrates will need to be continually revised. It is reasonable to try factor IX preparations for patients with more potent antibodies, for those



who are brisk immunological responders, and combined with factor VIII concentrate, for serious bleeding. Even so there is little doubt that they are much less effective than are factor VIII concentrates in normally responsive haemophiliacs. There is urgent need for co-ordinated clinical assessment of reasonably characterized products and for identification of the active agent, if any, which they contain. Hopefully some of these answers will be provided by multicentre assessments at present under way in several countries. Meanwile use of these materials should be restricted to centres fully equipped to assess their clinical and haematological effects.

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