Failure of factor VIII inhibitor bypassing activity (Feiba) to secure haemostasis in haemophilic patients with antibodies

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SUMMARY Factor IX concentrates have been widely advocated in the treatment of haemophilic patients with factor VIII inhibitors. Five such patients were given the 'activated' factor IX concentrate—factor VIII inhibitor bypassing activity (Feiba)—for 14 separate bleeding episodes. In six of the episodes, including two with external blood loss, bleeding progressed in spite of treatment. In none of the other eight episodes was there a prompt response, and it was not possible to ascribe a definite therapeutic effect.

A major complication of modern haemophilia therapy is the development of antibodies to factor VIII. This occurs in about 10% of treated patients, who become resistant to further treatment. Large doses of factor VIII may be effective in patients with low-titre inhibitors (Rizza and Biggs, 1973; Blatt *et al.*, 1977), and plasmapheresis using a continuous-flow cell separator has been employed to lower the inhibitor titre sufficiently to allow factor VIII replacement to be effective in others (Edson *et al.*, 1973; Pintado *et al.*, 1975). Another and controversial approach has been the use of 'factor IX' concentrates. These contain the vitamin K dependent factors II, VII, IX, and X as well as factor XI, but some lack factor VII, and all types may become 'activated' during preparation. Such 'active' concentrates fail their thrombogenicity tests and are not used for the treatment of Christmas disease. It has been claimed that these accidentally activated factor IX concentrates, for example, Autoproplex, Hyland (Fekete *et al.*, 1972; Kurczynski and Penner, 1974), may contain a clotting factor intermediate which bypasses the site of action of factor VIII, and hence factor VIII antibodies, in the coagulation sequence and thus exerts a therapeutic effect in resistant haemophilic patients. Preparations purposely made to contain 'activated' factors have also been produced, for example, factor VIII inhibitor bypassing activity (Feiba, Immuno, Austria), and it has been claimed that these also exert a therapeutic effect even in the case of external bleeding (Preston

et al., 1977). Recently, it has been claimed that non-activated or 'routine' factor IX preparations (eg, Konyne, Cutter; Proplex, Hyland) may also be effective (Abildgaard *et al.*, 1976; Kelly and Penner, 1976; Lowe *et al.*, 1976). In contrast to these reports, Pollock and Lewis (1976) found no benefit from using these products in one patient.

In this paper we report the unsuccessful use of the activated 'factor IX' preparation Feiba in a series of episodes of bleeding in haemophilic patients with factor VIII antibodies.

Patients and methods

All five patients were severe haemophiliacs (procoagulant factor VIII 0%) who had developed factor VIII antibodies previously. Routine coagulation tests were performed using standard techniques (Biggs, 1976). Factor VIII inhibitor (antibody) assays were performed as described by Biggs and Bidwell (1959). Immunoradiometric assay (IRMA) of factor VIII related antigen was carried out as described by Peake and Bloom (1977).

Results

Fraction Feiba from seven different batches was used to treat 14 separate bleeding episodes. The clinical details are summarised in Table 1. On six occasions therapy with Feiba was combined with factor VIII concentrate, as recommended by Schimpf *et al.* (1977), at a dosage of 32-114 units/kg. In six of the 14 episodes, including two with external blood

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Table 1 Use of fraction Feiba—summary of clinical results

Patient	Lesion	Dose	Additional factor VIII	Clinical response to Feiba	Inhibitor titre (u/ml)	
					Pre	2 weeks post
A	1 Haemarthrosis elbow	96 u/kg × 2 20 u/kg 6-hrly 2 days	No	Slow	32	24
	2 Haemarthrosis elbow	113 u/kg × 1 20 u/kg 6-hrly 2 days	Yes	Nil	24	—
	3 Traumatic haematomata face, trunk*	60 u/kg × 2	Yes	Nil	45	30 000
	4 Haematoma of calf	40-180 u/kg 6-hrly 2 days	Yes†	Nil	1150	425
	5 Haemarthrosis elbow	70 u/kg 12-hrly 7 days	Yes†	Slow	390	—
	6 Haemarthrosis wrist	52-70 u/kg 12-8-hrly 6 days	Yes†	Nil	400	—
B	1 Ilio-psoas haematoma	15 u/kg 8-hrly 4 days	Yes	Slow	8	11
	2 Haemarthrosis elbow	86 u/kg × 1 15 u/kg 6-hrly 4 days	No	Slow	1.1	0.4
		100 u/kg × 1 44 u/kg 6-hrly 5 days	No	Slow	11	60
D	1 Haemarthrosis knee	100 u/kg × 1 30 u/kg 6-hrly 2 days	No	Slow	7	8
	2 Haemarthrosis knee	30 u/kg 6-hrly 2 days	Yes†	Slow	3.8	2.9
	3 Haemarthrosis knee	30-60 u/kg 8-hrly 4 days	Yes	Nil	2	10
E	1 Laceration ear lobe*	128 u/kg 8-hrly × 2	Yes†	Nil	42	22
	2 Haematoma forearm	110 u/kg × 1	Yes†	Slow	23	60

*External bleeding

†Given concurrently with Feiba (15)

loss, the bleeding progressed in spite of therapy with Feiba, and additional treatment was necessary. In patient A, episode 3, this consisted of plasmapheresis using an Aminco continuous-flow cell separator, which lowered the inhibitor titre from 45 to 7 units/ml and enabled factor VIII concentrate to be used successfully in large doses: 374 units/kg initially, then 189 units/kg every 12 hours for four days. In the other eight episodes none showed a prompt response to Feiba, and subsequent improvement was slow, often not beginning until a few days after the start of treatment. In these episodes it was not possible to be certain of a definite therapeutic effect of Feiba because slow resolution may have been due to bed rest alone.

The whole blood clotting time (WBCT), prothrombin time (PT), kaolin cephalin clotting time (KCCT), thrombin clotting time (TCT), and platelet count were performed before and after each infusion of Feiba. Factors II, V, VIII, and IX and fibrinogen assays were also performed. The results are summarised in Table 2. Only a minimal shortening of the PT and KCCT was seen on each occasion. The greatest effect was observed on the WBCT, as previously reported by Elsinger (1977). No evidence of disseminated intravascular coagulation was observed, and platelet counts, fibrinogen, and factor V levels remained unchanged.

For four of the bleeding episodes, no additional factor VIII was given, yet in one patient (C) there

Table 2 Feiba: Laboratory data—maximum change

Patient		PT (s)		KCCT (s)		WBCT (min)		TCT (s)	
		from	to	from	to	from	to	from	to
A	1	14	12	102	97	55	20	12	13
	2	15	12	112	99	—	—	11	10
	3	12	11	120	86	50	23	12	11
	4	12	10	104	80	49	20	10	14
	5	13	9	138	120	30	19	12.5	10
	6	12	9	112	93	35	22	14	13
B	1	15	14	118	114	—	—	14	13
	2	14	11	132	128	55	35	15	13
C		14	12	132	118	—	—	15	13
D	1	10	12	123	96	45	36	12	14
	2	11	11	138	128	45	30	15	14
	3	14	12	130	116	40	24	15	14
E	1	15	11	94	82	63	25	16	15
	2	15	11	149	139	37	29	19	20

No evidence of disseminated intravascular coagulation was observed in any treatment episode.

was an associated secondary rise in the factor VIII inhibitor titre. This phenomenon has been previously reported (Allain and Krieger, 1975; Mannucci *et al.*, 1976) and is probably due to small quantities of factor VIII present in the prothrombin complex concentrates. The batch of Feiba used for our patient was examined using a sensitive immunoradiometric assay for factor VIII related antigen (FVIII_RAg), and 0.2-0.3 u/dl was detected. In addition, greater or lesser amounts were found in several other factor IX concentrates (Table 3). Although FVIII_RAg is not the same antigen as that of pro-coagulant factor VIII the finding probably indicates contamination with the latter. In patients who received factor VIII concentrate, an anamnestic response was detected after three of the seven episodes (Table 1).

Table 3 Factor IX concentrates: FVIII_RAg by immunoradiometric assay

Concentrate	FVIII _R Ag (u/ml × 10 ³)	Concentrate	FVIII _R Ag (u/ml × 10 ³)
1	0.36	5	0.01
	0.42		0.026
	1.47		0.056
	0.16	6	0.23
	0.39		
	0.27	7	0.35
	0.24		0.34
	0.11		0.27
2	14	8	0.19
	6	('Activated')	0.20
	3.2		0.25
	3.6		
3	2.7		
4	0.27		

Discussion

There are at least 18 reports claiming that factor IX concentrates of various types have secured haemostasis in haemophilic patients with inhibitors. In the present study, using the activated factor IX concentrate Feiba (Immuno), we have been impressed by the apparent lack of success of this form of treatment not only in closed bleeds, which are difficult to assess, but also in two patients with external bleeding even when used in high dosage and in combination with factor VIII concentrate (Schimpf *et al.*, 1977; Brackmann *et al.*, 1977). The reasons for the conflicting results are difficult to determine. As discussed by Blatt *et al.* (1977), assessment of closed bleeds is subjective, and bleeding may stop with rest and immobilisation. 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. Doses have often

been expressed as units of factor IX, but these are not necessarily related to the active agent or to the Feiba unit, and the factor IX assay itself could be affected by an activated clotting intermediate. The Feiba unit has been arbitrarily defined by the manufacturers (Elsinger, 1977) and, because it is related to the shortening of the clotting time of an antibody plasma, would be expected to be related more than the factor IX unit to a clinical effect. The methods of manufacture of most products, including Feiba, have not been released or may periodically change. The preparations may thus vary from product to product or even from batch to batch. Dosage schedules are therefore almost meaningless and entirely empirical. There is no reliable *in-vitro* method against which to assess a therapeutic effect although, as confirmed in the present study, there is usually moderate but incomplete correction of the whole blood clotting time (Elsinger, 1977). There is a recent report that the newer and possibly less thrombogenic factor IX preparations may be correspondingly less effective in factor VIII antibody patients (Kelly and Penner, 1976).

On the credit side, and as confirmed in the present study, untoward side-effects are few although there has been a report of disseminated intravascular coagulation (Stenbjerg and Jørgensen, 1977a), resistance to Feiba (Stenbjerg and Jørgensen, 1977b), and one disturbing case of transient amaurosis (Rasche *et al.*, 1977). Anamnestic response of factor VIII antibody is less likely to occur than with factor VIII concentrate, and the treatment is certainly much less expensive. Recently, Brackmann *et al.* (1977) and Schimpf *et al.* (1977) have claimed that a combination of high doses of factor VIII and factor IX concentrates may be effective and that sustained use may even lead to the disappearance of the factor VIII antibodies, but this claim has yet to be substantiated. The high cost, for example £1000 a day for many months in one patient (Brackmann and Gormsen, 1977), and the redistribution of blood products involved are undesirable aspects of this treatment programme.

The initial enthusiastic reports of the use of these activated factor IX preparations for the treatment of haemophilic patients with antibodies have led to their widespread uncontrolled use and the publication of several confirmatory reports. Our experience suggests that this impression may have been over optimistic, and there is no doubt that Feiba is not as effective as are factor VIII concentrates in normally responsive haemophiliacs. There is an urgent need for more controlled investigations of the manufacture and clinical effects of the materials, which will probably need to be assessed on a multicentre basis. If one of them is really effective then characterisa-

tion and isolation of the active principle could help to solve this important clinical problem.

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