Plasma exchange and human factor VIII concentrate in managing haemophilia A with factor VIII inhibitors

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Summary and conclusions

Plasma exchanges were combined with human factor VIII concentrate therapy in the treatment of major bleeding episodes in five patients with haemophilia A and factor VIII inhibitors. All patients had a good clinical response to combined treatment. Inhibitor levels showed satisfactory falls before rapid secondary increases of inhibitor levels took place. A sixth patient with von Willebrand's disease and a factor VIII clotting activity inhibitor was successfully prepared for operation using plasma exchange. Postoperative haemostasis and healing were normal. In two patients the plasma exchanges were relatively more effective than the administered human factor VIII in reducing the levels of factor VIII inhibitor. Combined plasma exchange and human factor VIII treatment may offer a rapidly effective means of reducing factor VIII inhibitor levels in this group of patients, together with significant saving of costs.

Introduction

Patients with haemophilia A and inhibitors of factor VIII may present major problems of management.¹ There is no shortage of treatments for use in bleeding episodes, and the choice includes human factor VIII,² human factor IX (non-activated),³ prothrombin complex concentrates,^{4,5} animal factor VIII,⁶ immune suppressives,^{7,8} and plasma exchange.⁹ The existence of such a list indicates that no single treatment is consistently successful.

combined with plasma exchange in an attempt to reduce inhibitor levels rapidly and secure early haemostasis. We also sought information about the relative efficacy of the two modes of treatment.

Patients and methods

Patients with haemophilia A were selected for treatment with combined human factor VIII concentrate and plasma exchange if they showed potentially life-threatening or crippling bleeding and were known to have previously had a factor VIII inhibitor level above 10 Biggs-Bidwell¹⁵ units/ml of plasma or they had potentially life-threatening bleeding with an inhibitor, although it had not previously been measured (case 3). Of the six patients treated five presented with serious bleeding episodes, while the sixth had von Willebrand's disease with a factor VIII clotting activity inhibitor and needed surgery.

Case 1 had a massive thigh haematoma. Nerve or vascular compression was imminent. Case 2 had a large forearm bleed with total ulnar and median nerve pareses. Case 3 had sustained trauma to the jaw with a submandibular haematoma causing trismus and dysphagia. Any extension of his haematoma could have caused airways obstruction. Case 4 had been struck by a car and had sustained hip and forearm fractures. Case 5 had tense bilateral elbow haemarthroses and was at risk of fixed flexion deformities. Case 6 was having repeated dental abscesses, and total dental clearance was indicated.

Human factor VIII concentrate was started immediately at a dose of 40 IU/kg body weight/8 hourly and continued until an anamnestic response occurred and the patient became refractory to further factor VIII.

Plasma exchange was started as soon as possible. A Haemonetics Corporation Model 30 cell separator was used. Plasma exchanges were repeated daily until the inhibitor level fell below 1 unit/ml of

TABLE 1—Inhibitor responses to treatment

Case No	No of exchanges	Total volume (l)	Inhibitor level (Biggs-Bidwell ¹⁵ units)				Maximum factor VIII level (% of average normal)
			Previous high	Pre-exchange	Postexchange	Postexchange peak	
1	4	13	14	6.5	0	2500	—
2	1	3.5	15	1.7	<1.0	37	49
3	2	6	—	6.0	1.0	945	30
4	3	7.5	234	5.6	0	975	71
5	3	8	55	24.0	1.0	170	16
6	2	6	22	1.8	≤1.0	220	156

A commonly used approach to treatment includes giving high-dose human factor VIII concentrate to neutralise the inhibitor after which haemostatic levels of free circulating factor VIII are obtained. This form of treatment is, however, very expensive and may be relatively ineffective in treating patients with high titre inhibitors.¹⁰

There have been scattered reports of the use of plasma exchange as an adjunct to factor VIII treatment.¹¹⁻¹³ Use of the cell separator has facilitated the procedure of plasma exchange.¹⁴

We describe a small series of patients with haemophilia A and factor VIII inhibitors in whom human factor VIII treatment was

plasma. The replacement solution for cases 1-5 was plasma protein fraction or cryoprecipitate supernatant plasma and for case 6 modified fluid gelatin; material derived from blood plasma being contra-indicated before operation to avoid stimulation of his factor VIII inhibitor. Factor VIII assays¹⁶ were performed using citrated blood samples drawn immediately before giving a dose of factor VIII concentrate. Plasma inhibitor levels were measured daily in cases 1-3 and also before and after plasma exchange in cases 4-6.

Results

The clinical results were satisfactory. Each patient showed haemostasis of sufficient duration to permit the resolution of haematomas and healing to start. Case 2 showed a rapid resolution of his haematoma, and nerve function has gradually returned. Case 6 showed normal haemostasis at operation, and subsequent healing was normal.

Table I shows the effects of treatment on inhibitor levels. In this table the number of exchanges is also equivalent to the number of days that elapsed before the inhibitor level was reduced below 1 unit/ml of plasma. Each patient showed a rise in inhibitor level starting on

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the fifth day of treatment. Five patients were of "high response" type as shown by the high postexchange peak inhibitor levels. Case 2 showed an "intermediate" pattern of response.

Factor VIII recovery values, performed on cases 2, 3, 4, and 6 showed factor VIII levels sufficient to permit normal haemostasis. Pre- and postplasma exchange inhibitor levels were measured in cases 4-6. Case 5 (table II) showed good falls in inhibitor levels during plasma exchange and further smaller falls in levels between the end of one exchange and start of the next. Case 4 (table III) showed a similar response pattern, although his presentation level of inhibitor was lower than that of case 5. Case 6 (table IV), who was

TABLE II—Case 5: Response to combined treatment

Days		Inhibitor level (u/ml)
0-0		24.2
1-0	Pre-exchange ①	18.0
1-3	Postexchange	8.4
2-0	Pre-exchange ②	8.4
2-4	Postexchange	3.8
3-0	Pre-exchange ③	2.8
3-4	Postexchange	1.4
4-0		1.0
5-0		5.0

TABLE III—Case 4: Response to combined treatment

Days		Inhibitor level (u/ml)
0-5	Pre-exchange ①	5.6
1-2	Postexchange	2.8
1-8	Pre-exchange ②	1.8
2-2	Postexchange	≤ 1.0
2-8	Pre-exchange ③	≤ 1.0
3-2	Postexchange	0.0
6-0		0.0
7-0		24.0

TABLE IV—Case 6: Response to plasma exchange

Days		Inhibitor level (u/ml)
-3-0	Pre-exchange ①	1.8
-2-6	Postexchange	< 1.0
-2-0	Pre-exchange ②	≈ 1.0
-1-6	Postexchange	≤ 1.0
	Surgery	
+6-0		≤ 1.0
+7-0		2.7
+8-0		47

being prepared for surgery, received non-plasma derived replacement fluid. Reduction of his inhibitor-levels reflects the effects of plasma exchange separate from the neutralisation effect of administered factor VIII. Although he showed falls of inhibitor levels during exchanges, there was a slight rise in level between exchanges.

Discussion

The decision of whether or not to treat a particular episode of bleeding in a patient with haemophilia A who is known previously to have had a factor VIII inhibitor may be difficult. If the haemorrhage is likely to produce serious permanent damage or threaten life there is little alternative but to treat. If the inhibitor is currently at a low level five or more days of factor VIII treatment alone will suffice to permit most lesions to heal normally.

If the patient has a high level inhibitor at presentation, however, the situation is complex. A haemophilia centre with large amounts of human factor VIII at its disposal may choose to give

this material in high dosage to effect neutralisation of the inhibitor.¹⁰ That such an approach might fail is shown by the results in case 5. We may conjecture that if this patient had received factor VIII only, it is unlikely that the inhibitor would have fallen to a level low enough to allow free factor VIII to appear for prolonged periods in his plasma before the secondary rise in inhibitor rendered him refractory to further administered factor VIII. He would then have been in a worse condition, showing not only a lack of improvement of his lesions, but the subsequent high rise in inhibitor could have made him more difficult to manage during future episodes of bleeding.

The effects of combined treatment in lowering inhibitor levels in cases 4 and 5 show that the falls occurring during plasma exchange are greater than those between exchanges. During this latter period, however, some diffusion of extra vascular inhibitor into the vascular space can be presumed to occur, and the probable function of the administered factor VIII is to bind the inhibitor so that the bound inhibitor/factor VIII complex may be removed at the next plasma exchange.

The results for case 6, where plasma exchange was used alone without concurrently administered factor VIII, show a small rise in inhibitor level between plasma exchanges and are compatible with diffusion of extravascular inhibitor into the circulation.

Taken as a whole, our results suggest that combining human factor VIII treatment with plasma exchange can produce better results in inhibitor patients than either treatment used alone. With combined treatment, significant quantities of factor VIII, which otherwise would have been necessary to neutralise the inhibitor before achieving therapeutic plasma levels may be saved. Such an approach should allow haemostasis to be produced at an earlier stage and ensure maximum duration of haemostasis before the secondary rise in inhibitor level starts.

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(Accepted 13 October 1980)