Anaphylactic reaction to low-molecular-weight porcine factor VIII concentrates

The management of bleeding in patients with inhibitors to factor VIIIC remains an unsolved clinical problem despite considerable advances in understanding of the molecular biology of factor VIII. Porcine and bovine factor VIII concentrates have been used in the past, especially with severe bleeding problems associated with high antibody levels.[1] Anaphylactic and allergic reactions and thrombocytopenia, however, have greatly limited their usefulness.[2]

A new highly purified preparation of porcine factor VIIIC, the low-molecular-weight component,[3] has recently become available (Hyate:C, Speywood Laboratories). Mayne *et al*[4] proposed that this product might be valuable in treating patients with haemophilia who had developed antibodies to factor VIIIC. We report a severe anaphylactic reaction after the use of Hyate:C in a non-haemophiliac with an acquired inhibitor to factor VIIIC, which suggests that some caution should be shown in its use.

Case report

A 71-year-old man suddenly developed spontaneous bruising and a massive ileopsoas haematoma with femoral nerve palsy. This haemostatic defect was due to an acquired inhibitor to factor VIIIC, present at a concentration of 13 U/ml,[5] resulting in a plasma factor VIIIC concentration of only 0·01 U/ml. Initial treatment with human factor VIII concentrates was unsuccessful. With the inhibitor titre rising to over 50 U/ml and no evidence of clinical improvement, treatment with porcine Hyate:C was started. He was given 2000 IU Hyate:C after an intramuscular injection of 10 mg chlorpheniramine maleate. Though there were no immediate ill effects, after 75 minutes he developed a severe anaphylactic reaction, with distinct bronchospasm, widespread pulmonary crepitations, peripheral vasoconstriction, and rapid atrial fibrillation. Immediate administration of adrenaline, hydrocortisone, and further chlorpheniramine maleate produced a slow improvement, and over the next 24 hours these symptoms gradually subsided.

Further treatment with porcine concentrates was totally unjustifiable; this was regrettable, particularly in view of the excellent laboratory response obtained with the plasma concentration of factor VIIIC rising to 0·4 U/ml one hour after the infusion. Furthermore, the platelet count did not fall despite the severity of the reaction and no antibodies to porcine factor VIIIC were detectable after treatment.

Comment

Use of porcine factor VIII concentrates has previously been severely restricted because of allergic reactions and thrombocytopenia.[2] Hyate:C is a highly purified preparation of porcine factor VIII that contains only trace amounts of non-factor VIII protein, thus reducing side effects.[3] Unfortunately, the severe reaction after its use in our patient suggests that, as with other porcine products, allergic reactions that might limit its usefulness may occur. A small test dose should therefore be administered before infusion of therapeutic doses to identify more clearly patients who might be at risk of developing such problems.

We thank Dr P A M Bailey, consultant haematologist, and Dr J A Cameron, consultant physician, of Dumfries and Galloway Royal Infirmary, who referred this patient to our department.

[1] Conard J. Inhibitors of blood coagulation. In: Thomson JM ed. *Blood coagulation in haemostasis*. Edinburgh: Churchill Livingstone, 1980:212.
[2] Austen D. Factor VIII. In: Biggs R, ed. *The treatment of haemophilia A and B and von Willebrand's disease*. Oxford: Blackwell, 1978:38.
[3] Johnson AJ, MacDonald VE, Semar M, *et al*. Preparation of the maior plasma fractions by solid-phase polyelectrolytes. *J Lab Clin Med* 1978; 92:194-210.
[4] Mayne EE, Madden M, Crothers IS, Ingles T. Highly purified porcine factor VIII in haemophilia A with inhibitors to factor VIII. *Br Med J* 1981:282:318.
[5] Tse D, Fekete L, Shanbrom E. A simple procedure for accurate quantitation of factor VIII inhibitors. *Thrombosis et Diathesis Haemorrhagica* 1970;23:19-25.

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Department of Haematology, Glasgow Royal Infirmary, Glasgow G4 OSF
J G ERSKINE, MRCP, MRCPATH, senior registrar in haematology (present appointment: consultant haematologist, Ballochmyle Hospital, Mauchline, Ayrshire)
J F DAVIDSON, FRCP(ED), MRCPATH, consultant haematologist

Reactions to low-molecular-weight porcine factor VIII concentrates

SIR,—We should like to comment on Drs J G Erskine and J F Davidson's report (20 June, p 2011) on the use of porcine factor VIII in the light of our own experience with this product.

There is no doubt that polyelectrolyte-fractionated porcine factor VIII (PE porcine VIII, Hyate: C, Speywood Laboratories) should be used with caution, but transfusion reactions severe enough to necessitate stopping therapy are unusual. Over the last year we have given 34 courses of PE porcine VIII therapy to eight patients with circulating antibodies to factor VIII (anti-VIII). Of a total 246 infusions, only one was followed by a reaction judged sufficiently severe to justify stopping treatment. Although reactions of lesser degrees of severity are relatively common—27 infusions were followed by some significant reaction and 21 courses of therapy were complicated by at least one—reactions were generally short lived, well tolerated by patients, and did not give rise to serious clinical concern.

Reactions which follow PE porcine VIII are usually "pyrogenic" in type, and rarely have features suggestive of immediate-type hypersensitivity. The onset is typically delayed 30-60 minutes after the start of the infusion. There is often a transient pyrexia, and the patient complains of nausea, headache, and coldness. There may be vomiting and shivering. Symptoms usually start subsiding within 5-15 minutes. We have never seen shock, and only once observed breathlessness—the symptom which caused us to stop treatment. Reactions are most often seen early in a course of treatment, tending to lessen in severity with repeated infusions. We use 100 mg intravenous hydrocortisone and 10 mg intravenous chlorpheniramine as prophylaxis before the first infusion of a course, decreasing the dosage if treatment continues without problems; but we have no strong evidence that these measures are effective. We also give a small intravenous test dose of PE porcine VIII before the first infusion of a course but have not found this particularly reliable as an indicator of risk of reactions. Multiple courses of therapy may be given without an increasing tendency to reactions—the patient whose treatment was terminated has since had a further seven courses (35 infusions) with only six mild reactions.

Bleeding in patients with anti-VIII is often severe and difficult to control, and risks of therapy must be weighed against likely benefits. We have found PE porcine VIII to be highly effective in stopping major bleeding which has failed to respond to human factor VIII. It has also been used successfully to cover elective surgery. The material lacks several of the disadvantages of earlier or alternative preparations,[1] and we believe its introduction to be a real therapeutic advance. Porcine heparin and insulin given intravenously are rarely complicated by transfusion reactions and one is optimistic that the problems with PE porcine VIII can be similarly resolved. Meanwhile, we suggest that the material should be used only in major haemophilia centres, where adequate facilities and expertise are available for stringent monitoring. In particular, we would urge that no surgical procedure should be undertaken without a full preoperative assessment of the characteristics of the patient's anti-VIII.

P B A KERNOFF
E G D TUDDENHAM

Haemophilia Centre,
Royal Free Hospital,
London NW3 2QG

[1] Bloom AL. *Br J Haematol* 1978;40:21-7.

HIGHLY PURIFIED PORCINE FACTOR VIII IN HAEMOPHILIA A

SIR,—The management of patients with haemophilia A who have an inhibitor to factor VIII:C, especially those who have previously had a classical anamnestic antibody response after infusion of human factor VIII, remains problematical.[1] Excellent clinical responses have been reported with polyelectrolyte-fractionated highly purified porcine factor VIII concentrate ('Hyate C'; Speywood).[2,3] Most important has been the low incidence of any appreciable rise in anti-human or anti-porcine inhibitor levels, despite prolonged therapy. We wish to report the use of this material in an inhibitor patient who responded at first but subsequently had a marked increase in an anti-human inhibitor and acquired a significant anti-porcine inhibitor with severe clinical bleeding unresponsive to highly purified porcine factor VIII.

A 7-year-old boy, weighing 18·6 kg, was admitted for elective dental extraction of fourteen primary milk teeth with root abscess and recurrent bleeding. Haemophilia A (factor VIII:C level 2%) had been diagnosed when he was 1 year old, and an inhibitor had been detected 2 years later. Bleeding episodes since then had been controlled with human factor VIII concentrate and an activated prothrombin complex concentrate ('FEIBA'; Immuno Ltd). However, he had received no specific therapy for 13 months before this admission. On admission his anti-human inhibitor level was 112 U/ml (New Oxford) and his anti-porcine level 2·05 U/ml. He was given an infusion of 3120 units hyate C and the factor VIII:C level rose from <0·01 to 1·13 IU/ml. Dental clearance was performed, with normal haemostasis during the operation. Over the next 4 days he received a total of 14 820 units of hyate C, maintaining his factor VIII:C level continuously above 0·22 IU/ml. During this period, healing proceeded normally with no bleeding from the tooth sockets. However, on the fourth postoperative day, his anti-human inhibitor level had risen to 2243 U/ml, but his anti-porcine level was only 6·8 U/ml. On the fifth day, infusions of hyate C were stopped and oral tranexamic acid was given. By the seventh day, his anti-human inhibitor level was 2163 U/ml but his anti-porcine level was now 786 U/ml. As the tooth sockets were dry and healing well, he was discharged home.

He had to be readmitted 7 days later with persistent continuous bleeding from the tooth sockets for the previous 24 hours with a resulting fall in haemoglobin from 11·2 to 8·5 g/dl. His anti-human inhibitor level was now 1986 U/ml and his anti-porcine level 708 U/ml. He received an infusion of 3900 units of hyate C but there was no increase in his factor VIII:C level of <0·01 IU/ml, and bleeding from the tooth sockets continued unabated. On the following day, his bleeding was controlled by an infusion of 2000 units of FEIBA which shortened the activated partial thromboplastin time from 115 to 82 s (control 30–36).

Although haemostasis was at first well controlled the infusions of porcine factor VIII stimulated a brisk rise in an anti-human inhibitor followed by the rapid appearance of a discrete anti-porcine inhibitor. A subsequent infusion of porcine factor VIII failed to control bleeding and there was no rise in the factor VIII:C level. Individual haemophiliac patients with inhibitors vary considerably in their clinical and immunological responses to the various therapeutic materials available. In particular, any new material should be carefully assessed in each inhibitor patient. In contrast to the previous reports we observed a marked anamnestic response when purified porcine factor VIII was infused alone. This prohibited further effective therapy with this material when secondary haemorrhage occurred.

Department of Haematology,
Middlesex Hospital Medical School,
London W1

P. HEWITT
I. J. MACKIE
S. J. MACHIN

1. Bloom AL. Factor VIII inhibitors revisited. *Br J Haematol* 1981; 49: 319–24.
2. Mayne EE, Madden M, Crothers IS, Ingles T. Highly purified porcine factor VIII in haemophilia A with inhibitors to factor VIII. *Br Med J* 1981; 282: 318.
3. Kernoff PBA, Thomas ND, Lilley PA, Tuddenham EGD. Clinical experience with polyelectrolyte-fractionated porcine factor VIII concentrate. *Br J Haematol* 1981; 49: 131 (abstr).

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Immune Response Induced by Porcine Factor VIII in Severe Hemophiliacs with Antibody to F VIII

Dear Sir,

The treatment of patients with severe haemophilia A who have developed an antibody to F VIII : C remains an unsolved problem when they are of the high responder type. Single infusion of activated or non-activated prothrombin complex concentrates is efficient in only 50–64% of the cases (1, 2). In our query for a better treatment, a highly purified porcine factor VIII (Hyate C – Speywood laboratories) was used. Some evidence has been given that this product provided satisfactory clinical response and did not affect the inhibitor titre (3).

We want to report our data concerning 3 single doses of Hyate C infused in 2 patients with severe haemophilia A. Both patients are high responders and the antibody to F VIII : C was detected in November 1977 with a maximum level at 20 u. Oxford units 15 days post-infusion for patient 1 and April 1973 with a maximum level at 4 Oxford units measured 2 months after factor VIII infusion in patient 2 due to the family indocility. Since then, they did not receive any human factor VIII. The inhibitor titres were low at the time of the first infusion of porcine factor VIII (Table 1). None of them had received any porcine material prior to the reported episodes.

Porcine factor VIII concentrate was used for the treatment of acute haemarthroses (right elbow and right ankle for patient 1, left ankle for patient 2). 1200 units were slowly infused (flow rate: 1ml/mn). The overall clinical response, evaluated on pain, swelling and joint mobility was excellent for infusion 1 and good for infusions 2 and 3. Pain relief, decreased swelling and rapid recovery of joint mobility were observed in all instances. Minimal adverse reactions were observed after each infusion (fever, headache, shiver, skin rash) but none of them required either steroids or adrenaline.

Sixty min post-infusion, maximal VIII : C plasma level was observed corresponding to 32–56% of the expected recovery (Table 1). In our experience of factor VIII recovery, the maximal activity is observed 30 to 60 min after infusion (4).

In patient 1, the platelet count dropped from 266,000 to 181,000 mm^3 and from 323,000 to 235,000, 30 min after the first and second infusion respectively. Platelet counts were back to preinfusion level within 4 hr. No change occurred in patient 2.

10 days post-infusion a definite rise in antibody titre against human factor VIII was observed in all cases. Since no other blood derivative was given to these patients, this indicates that Hyate C is indeed immunogenic and able to trigger an anamnestic rise of the antibody titre. These data differ from what is claimed by the manufacturer (3).

In our experience, as already mentioned by Kernoff and Tuddenham (5), porcine factor VIII has been clinically effective and minimal adverse reactions were observed. However we have consistently observed a significant rise of the antibody titre which does not allow to use Hyate C for trivial haemorrhages but confines its use to life threatening bleeding episodes.

Table 1

	Infusions 1	2	3
Dose of porcine FVIII u/kg	27,9	27,9	45,3
VIII : C plasma level (time post-infusion)			
15 min	13,5	ND	15,5
30 min	16,5	12,5	35,5
60 min	24	18	51
4 hr	20	ND	32,5
12 hr	9,5	ND	20,5
VIII : C recovery (%)	43	32	56
Antibody titre: before	0,5	1,7	0,45
10 d. post-infusion	1,7	3,6	2,2

VIII : C recovery is calculated as $\frac{\text{observed VIII : C level} \times 100}{\text{expected VIII : C level}}$

Expected VIII : C level = $\frac{\text{FVIII : C infused (u)}}{\text{Plasma volume (ml)}} \times 100.$

F. Verroust
Centre pour enfants hémophiles
Croix Rouge Française
78940 – La Queue-les-Yvelines, France
J. P. Allain
C. N. T. S. Orsay, France

References

1 Lüscher J M, Shapiro S S, Palascak J, Rao V, Levine P H, Blat P M. Efficacy of prothrombin complex-concentrates in hemophiliacs with antibodies to Factor VIII. N Engl J Med 1980; 303: 421–425.
2 Sjamsoedin L J M, Heijnen L, Mauser-Bunschoten E P, Van Geijlswijk J C, Van Houwelinger H, Austen P, Sixma J. The effect of activated prothrombin-complex concentrate (Feiba) on joint and muscle bleeding in patients with hemophilia A and antibodies to Factor VIII. N Engl J Med 1981; 305: 717–721.
3 Heath D. Highly purified porcine factor VIII in haemophilia A with inhibitors to Factor VIII. Br Med J 1981; 282: 654–655.
4 Allain J P, Verroust F, Soulier J P. In vitro and in vivo characterization of Factor VIII preparations. Vox Sang 1980; 38: 68–80.
5 Kernoff P B A, Tuddenham E G D. Reactions to low-molecular-weight porcine factor VIII concentrates. Br Med. J 1981; 283: 381–382.

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Experience with highly purified porcine factor VIII in a patient with haemophilia A and a factor VIII inhibitor

B.T. COLVIN, MA, MRCP, MRCPath, MARY AINSWORTH, FIMLS & CAROLE BUCKLEY, BSc, MB, BS
Department of Haematology, The London Hospital Medical College, Whitechapel, London E1 2AD

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Summary Highly purified porcine factor VIII has been advocated for the treatment of bleeding episodes in patients with haemophilia who have inhibitors to factor VIII. This approach has been successful in a patient with an intermediate potency inhibitor showing little cross-reactivity to porcine material. As in some other reported cases, a severe allergic reaction occurred on one occasion but did not preclude the subsequent use of the porcine concentrate in carefully controlled conditions.

Keywords: porcine factor VIII, haemophilia A with inhibitors

The use of highly purified porcine factor VIII, Hyate:C, Speywood (Heath 1981) in the treatment of patients with inhibitors to factor VIII was first described by Mayne *et al.* (1981). Since then a number of publications have described the uses and dangers of this product in a variety of patients with congenital or acquired deficiencies of the factor VIII molecule (Erskine & Davidson 1981, Kernoff & Tuddenham 1981). Despite initial hopes of low antigenicity, the development of antibodies to porcine factor VIII has now been reported (Hewitt, Mackie & Machin 1982).

Our own observations on the use of Hyate:C in a patient with haemophilia A and an inhibitor to factor VIII illustrate the indications for this form of treatment and the precautions which need to be taken in its use.

Methods

Two stage factor VIII assays were performed using a commercial kit (Diagnostic Reagents Limited, Thame, Oxon). Inhibitory activity was measured by the new Oxford method described by Austen & Rhymes (1975). Human factor VIII from commercial sources and Hyate:C, Speywood were used in the assays of anti-human and anti-porcine activity respectively.

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