Haemophilia (1998), 4, 574–576

Management of haemophilia B patients with inhibitors and anaphylaxis

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Summary. The development of inhibitor antibodies is a serious complicaiton of haemophilia in young children. Occurrence of anaphylaxis at the time of inhibitor development is a recently described complication unique to haemophilia B. Management of these inhibitor patients with allergy is complicated due to the absence of any readily available products for treatment of acute bleeding episodes. Clinical experience suggests that recombinant activated factor VII is the most appropriate and logical treatment for acute bleeding episodes in these patients. From the limited information available regarding immune tolerance induction (ITI) in these patients, it appears that ITI regimens have been only minimally successful and are associated with a high rate of complication (nephrotic syndrome).

Keywords: Hemophilia B, FIX inhibitor, anaphylaxis, rFVIIa.

Occurrence of anaphylaxis simultaneously or following the development of inhibitors in haemophilia B patients is a recently described serious complication of replacement therapy [1, 2]. Patients with this unique complication pose critical treatment related problems, since the only readily available treatment for haemophilia B inhibitor patients in the United States are Factor IX (FIX) containing prothrombin complex concentrates (PCCs) or activated PCCs, the very same products that induced anaphylaxis to start with. Recombinant factor VIIa (rFVIIa) is not licensed for use in the USA, thus limiting the choice of treatment for a bleeding episode in these patients, although it is licensed in Europe and some other countries and is the drug of choice there.

Clinical experience

Over 30 haemophilia B patients world-wide have been reported to have inhibitors and anaphylaxis (17 in the US, nine in Europe, one in Canada and five in Japan). Two of the patients are from our treatment center and are included in the 18 patients reported in 1997 [1].

Anaphylaxis has been temporally associated with inhibitor development in the majority of these patients [1, 2]. Both events have generally occurred early in life (median age 16 months) after relatively few exposure days (median number of exposure days, 11). These patients are from various ethnic and racial groups (Caucasian, African-American, Hispanic, Asian) and have high responding inhibitors (median titer 48 BU). They had received various types of FIX products; ultrapure products were used in 11 of 18 patients at the time of anaphylaxis. Alternate factor IX concentrates were tried in several of these patients and all those who received alternate FIX products had severe allergic reactions to those products also. Genotype data available revealed that total gene deletions and major derangements such as missing exons and stop codon abnormalities constituted the majority of patients with inhibitors and anaphylaxis [17, 18].

Discussion

Management of haemophilia B inhibitor patients with anaphylaxis is complicated and stressful due to the unavailability of factor concentrates that do not induce anaphylaxis. Treatment in these patients has two major goals: (1) to control severe acute bleeding episodes and (2) to eradicate the inhibitor by immune tolerance induction.

Management of acute bleeding episodes by inhibitor bypassing agents

FIX products. Inhibitor development severely compromises the management of acute bleeding episodes since one cannot achieve therapeutic FIX levels even with the use of large quantities of FIX concentrates. Anaphylaxis with the development of FIX inhibitor makes it impossible for these patients to receive any FIX containing products unless the patient is desensitized thoroughly. Desensitization to FIX has been attempted in several of

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Received 14 December 1997; accepted 9 January 1998

these patients with no consistent response. Even though some of these patients were able to tolerate FIX after desensitization, the majority required premedication with antihistamines and steroids. Thus, FIX containing PCCs and APCCs do not appear to be the treatment of choice for controlling acute bleeding episodes in these patients. However, in cases of life-threatening bleeding episodes, one may decide to use these products after premedication while arrangements are being made to obtain rFVIIa on a compassionate protocol. Risks and benefits of a readily available treatment must be discussed with the patient and his family in the context of the severity of the bleeding episode prior to administering PCC or APCC.

Recombinant FVIIa (rFVIIa): Two haemophilia B patients with inhibitors and anaphylaxis from our treatment center have received rFVIIa on a compassionate protocol for treatment of various types of bleeding problems with excellent results [3]. Two of them have received rFVIIa on 3 and 10 occasions over the past 18 months. All bleeding episodes resolved over a period of 1–4 days. rFVIIa was given in the recommended dosage of 90 μg/kg body weight, repeated every 2–3 h as necessary. The maximum number of doses used per 24 h was six. No serious adverse effects were observed. Several of the haemophilia B inhibitor patients with anaphylaxis reported from Europe also have tolerated rFVIIa without any adverse effects [4, 5]. rFVIIa thus appears to be the most logical treatment for this subgroup of haemophilia B inhibitor patients who also have severe allergy to FIX. However, rFVIIa is not licensed in the USA and is not readily available at the treatment centers. Hence, one has to have a plan of action in effect to treat a haemophilia B inhibitor patient with anaphylaxis when he comes in to an emergency room with a life-threatening bleeding episode.

Eradication of the inhibitor by immune tolerance induction (ITI)

Unlike haemophilia A, experience with immune tolerance induction in haemophilia B inhibitor patients is very limited. Thrombogenicity of PCCs, unavailability of high purity FIX products until recently, and low prevalence of FIX inhibitors in general are some of the reasons for this limited experience. In addition, there is no standard methodology for ITI. Most regimens included frequent and large doses of factor concentrates over an extended period of time. In the absence of any licensed, readily available effective treatment, a subset of 12 patients with inhibitors and anaphylaxis from a group of 18 has undergone ITI (Table 1). Only two of the 12 patients had favorable responses with decreases in inhibitor titers and were able to receive high purity FIX products for treatment of bleeding episodes.

Table 1. Immune tolerance in FIX inhibitor patients with anaphylaxis.

Methods	No. of patients	Success	Failure	Complications
FIX alone	7	1	6	2 NS
FIX+IVIG	1	1 partial	0	
FIX+IVIG+CTX	2	0	2	
FIX+ plasmapheresis	1	0	1	
FIX+IVIG+CTX +1A	1	0	1	
Total	12	2 (17%)	10 (83%)	2 (17%)

CTX, cyclophosphamide. IA, immune affinity column. NS, nephrotic syndrome.

The complications related to ITI in haemophilia B inhibitor patients with anaphylaxis appear to be extremely high. Two of the 12 in a group of 18 who tried ITI developed nephrotic syndrome while undergoing ITI [6]. Other recent reports of nephrotic syndrome during ITI from Germany (two cases) [7, 8] and Sweden (two cases) (L. Tengborn, E. Berntorp, pers. comm.) in haemophilia B inhibitor patients with anaphylaxis suggest a direct relationship between ITI and nephrotic syndrome. In each case reported, nephrotic syndrome developed 8–9 months after starting ITI. Nephrotic syndrome in relation to ITI is resistant to steroids and cyclophosphamide. Rental biopsy results available in one patient showed membranous glomerulo-nephritis suggesting immune complex mediated glomerular disease. Immunohistochemical staining by monoclonal antibody to FIX was negative. One patient who received no treatment for nephrotic syndrome had slow, spontaneous resolution of his nephrotic syndrome 7 months post-FIX infusions.

Conclusions and recommendations

In view of the life-threatening nature of anaphylaxis in haemophilia B inhibitor patients the following recommendations and clinical practice suggestions may be considered when treating young children with haemophilia B.

1. At the time of diagnosis and initial discussion, consider discussing these unique complications regarding treatment with the family.

2. Since these events have occurred early in life with relatively few exposures, consider giving the first 10–20 infusions of FIX at a medical facility equipped to handle life-threatening emergencies.

3. Consider identifying the children at greatest risk by obtaining molecular diagnosis (genotype) of severe haemophilia B at the time of initial presentation. Those with large deletions and frame shift mutations can then be monitored closely during the first 10–20 exposure days.

4. Since the success rate with immune tolerance is poor with an extremely high complication rate of nephrotic syndrome, reassessment of the risks and benefits associated with ITI is warranted in those inhibitor patients with allergy to FIX.

5. When rFVIIa is not readily available and if one decides to start a patient on ITI, routine urinalysis must also be included among other tests during ITI.

Currently, there is no treatment available for those inhibitor patients who fail rFVIIa and ITI. We have to be optimistic that in the near future, transplantation technology (organ and bone marrow) will be advanced enough to offer that modality as a definitive treatment for these inhibitor patients with severe allergy to FIX.

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