Recurrent episodes of anaphylaxis in a patient with haemophilia B: a case report

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Introduction

Haemophilia B is an X-linked disorder resulting in coagulation factor IX (FIX) deficiency that is treated with the administration of exogenous FIX obtained from plasma of healthy donors or by a DNA recombinant technique[1]. The development of an inhibitor antibody against exogenous FIX is a serious complication and occurs in 1-3% of patients with haemophilia B and in 25-30% of patients with haemophilia A. Interestingly, in patients with haemophilia B, inhibitor development is associated with the risk of anaphylactic reaction to FIX administration. This reaction can occur concurrently with inhibitor detection or weeks or months apart regardless of which source of FIX replacement is used, plasma or recombinant. For this reason, the guidelines recommend that the first 20 administrations of FIX concentrate should be performed in hospital[1,2].

Common features of patients who develop a factor IX inhibitor are occurrence of an allergic/anaphylactic reaction early in life, a high inhibitor titre (>5 Bethesda units [BU]), exposure to various types of factor IX products, and the presence of abnormalities of the factor IX gene (*F9*)[3]. Patients with complete gene deletions or rearrangements of *F9* have an approximately 50% risk of inhibitor development, while those with nonsense or frame shift mutations have a risk of approximately 20%[4-5]. This suggests that the greater the impairment of FIX synthesis, the higher the risk of anaphylaxis, although this phenomenon may occur in patients with nonsense mutations[4-6].

The precise mechanism of this adverse reaction remains unclear and the various hypotheses that had been considered include extracellular distribution of the small FIX protein with potential mast cell activation[7,8], complement activation by IgG1 antibody formation[9], an IgE-mediated hypersensitivity response[10], higher amounts of exogenous protein (the concentration of FIX is much higher than that of factor VIII)[11] and the absence of tolerance to FIX in patients with mutations resulting in a complete absence of FIX production[12]. Moreover, in contrast to antibodies against FVIII, antibodies against FIX may form circulating immune complexes that can initiate anaphylaxis when the individual is re-exposed to FIX concentrate[6].

We describe a case of three anaphylactic reactions in a patient with haemophilia B after exposure to FIX of different origins.

Case report

A 9-month old boy was diagnosed with severe haemophilia B after investigations for the occurrence of spontaneous subcutaneous haematomas. His factor IX clotting activity was <1% and *F9* analysis on chromosome X revealed a point mutation at exon H (nucleotide 30863, cytosine to thymine) inducing the stop codon TGA (g 30863 C>T; Arg 248 stop).

At 10 months of age, the boy underwent a T9-L2 laminectomy because of a spontaneous spinal epidural haematoma and he was treated for the first time with recombinant FIX (rFIX; BeneFIX®, Wyeth Europa Ltd, Taplow, United Kingdom). After administering the 31st dose of recombinant FIX, an anaphylactic reaction occurred, characterised by severe cough, respiratory distress, and peripheral cyanosis. The infusion was stopped and the patient was treated with hydrocortisone and intravenous fluids. His inhibitor titre was 0.8 BU and peaked at 1.6 BU 7 days later. Over the subsequent 6 years the boy was treated on demand with recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk, Bagsværd, Denmark) (90 μg/kg every 4-6 hours or 270 μg/kg/die), to avoid the risk of anaphylactic reactions. An activated prothrombin complex concentrate (APCC, e.g. FEIBA® [Baxalta Innovations, GmbH, Wien, Austria]) was added in the case of hospitalisation for right elbow haemarthrosis, which was the target joint. Throughout these 6 years, the inhibitor titre was always negative. Given the recurrent elbow haemarthroses with a persistently negative inhibitor titre, a re-challenge with recombinant FIX was performed (30 IU/kg/dose).

The initial two infusions, administered under strict medical control in the emergency room, were uneventful, but the third triggered an anaphylactic reaction characterised by abdominal pain, respiratory arrest, and severe hypotension. Concurrently, the inhibitor titre increased to 0.6 BU. Hydrocortisone, epinephrine and intravenous fluids were administered with resolution of the symptoms. Subsequently, rFVIIa (90 μg/kg every

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4-6 hours or 270 μg/kg/die) was used on demand for recurrent haemarthroses and, in the few instances of non-response, FEIBA was added (80 IU/kg/dose).

Because no reaction was observed with FEIBA, which also contains human FIX, 7 months later, at age of 8 years, it was decided to start a desensitisation protocol with gradual dose increments of plasma-derived FIX (Aimafix®, Kedrion SpA, Castelvecchio Pascoli, Italy) up to 50 IU/kg for 5 days. After 1 month of treatment, the inhibitor titre remained 0 BU. The patient continued with prophylactic administration of plasma-derived FIX twice a week (50 IU/kg/dose) without any bleeding or allergic complications. This resulted in a better quality of life due to the reduction of episodes of haemarthrosis.

Two years after the second anaphylactic reaction, at 11 years of age, the patient developed an important muscle haematoma in the proximity of the right long radial extensor of the wrist, which needed five infusions of plasma-derived FIX at high dosage (56 IU/kg/die for 3 days and then, because of absence of clinical improvement, 94 IU/kg/die for a further 2 days). After 184 administrations of plasma-derived FIX, a third anaphylactic reaction occurred with abdominal pain, dyspnoea, cyanosis, and hypotension. The infusion was stopped and the patient was treated with hydrocortisone, epinephrine and intravenous fluids with gradual improvement of the symptoms. The inhibitor titre was 3.5 BU and peaked at 7.6 BU 2 weeks later. Subsequently, the patient returned to an on-demand regimen with rFVIIa (90 μg/kg every 4-6 hours or 270 μg/kg/day) to treat episodes of right elbow haemarthrosis, muscular haematomas and ankle haemarthrosis; the FIX inhibitor was no longer detectable.

Discussion

Eradication of the inhibitor by immune tolerance induction (ITI) and the treatment of acute bleeding episodes are the major problems in these patients. In fact, ITI is less effective in haemophilia B than in haemophilia A, the success rate in the former being 40% or less[1,13]; this is in part because a severe allergic or anaphylactic reaction is an obstacle to successful and safe ITI[2].

A further complication of ITI in patients with haemophilia B is the development of nephrotic syndrome, which usually occurs 8 to 9 months after the commencement of the ITI[1]. The high antigen exposure together with rapid extravascular dissemination of FIX molecules have been implicated in the pathogenesis of this complication[2,3].

Therapeutic options include desensitisation protocols by gradual increments of FIX dosages under coverage with systemic corticosteroids and antihistamines. Bon *et al*. recently reported a case of successful desensitisation with a low-dose regimen of 40 U/kg/day of FIX concentrate while a previous regimen with high dose of 150 U/kg/day was withdrawn because of an anaphylactic reaction[14]. Alternative strategies are based on damping the immune response through a combination of various immunosuppressive drugs (cyclophosphamide, intravenous immunoglobulins and/or prednisone) with or without plasmapheresis[1,15]. A promising approach is the use of rituximab, a monoclonal antibody directed against the CD20 antigen present on mature B lymphocytes, to reduce or downregulate the production of anti-FIX inhibitor. Various reports describe eradication of inhibitors in children with allergic manifestations to FIX concentrates using rituximab[2,16]. Although this treatment is appealing, larger studies are needed to clarify the potential side effects on long-lasting B lymphocyte depletion.

The management of acute bleeding in patients with inhibitors and anaphylaxis is complicated because these patients cannot be given any product containing FIX (FIX concentrates, FIX-containing prothrombin complex concentrates [PCC] and APCC-FEIBA) unless they have been desensitised before. For those patients who have not been adequately desensitised, and/or who still have a high-titre FIX inhibitor, rFVIIa can be used until bleeding stops[3]. The use of rVIIa for prophylactic therapy may be limited by the agent's short half-life, a lack of experience with its use in this manner and prohibitive cost[17].

We report a case of recurrent anaphylactic reactions to FIX, which occurred not only after exposure to the first doses of FIX but also after several years and a high number of doses. The reaction was triggered by both recombinant and plasma-derived FIX. This suggests that a haemophilia B patient with an inhibitor remains at life-long risk of developing anaphylactic reactions irrespective of desensitisation protocol. In terms of patient safety, re-exposure to FIX, in a patient with a history of inhibitor production, especially if it is given as replacement therapy for bleeding, requires strict medical control at every infusion.

Authorship contributions

MM, EB and SC wrote the manuscript; MM and EB collected the data; GP performed the tests for inhibitors; SC, EB and RB took care of the patients. All Authors approved the manuscript.

Keywords: anaphylaxis, haemophilia B, immune tolerance, FIX inhibitor

The Authors declare no conflicts of interest.

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