Revista Médica del IMSS

Volumen *Volume* **43** **Suplemento** *Supplemento* **2005**

Artículo:

Hemophiliacs with inhibitors: How to manage them?

Primera versión: 11 de agosto de 2005
Versión definitiva: 12 de agosto de 2005
Aceptado: 18 de agosto de 2005

Sandra Vallin-Antunes

Serviço de Hemofilia
Disciplina
de Hematologia
e Hemoterapia.
Universidade Federal
de São Paulo
Brasil

Comunicación con:
Sandra Vallin-Antunes
Tel. y fax:
(55 11) 5539 6829
Dirección electrónica:
sandra@hemato.epm.br

Hemophiliacs with inhibitors: How to manage them?

Introduction

Inhibitors are antibodies that neutralize factor VIII or IX. It is considered as one of the most severe and important complication of hemophilia treatment. Although many clinical and laboratory efforts are being done on this field, still generates higher morbidity and mortality, due to the poor control of bleeding with standard treatment.

The inhibitor incidence in hemophilia A is 20-30 %, most of them occurring in severely affected patients, and in hemophilia B is 4 %.[1]

Basic concepts, diagnosis and Investigation of inhibitor to factor VIII and IX

Inhibitors are neutralizing antibodies, with a polyclonal high affinity immunoglobulin G (IgG). Anti-factor VIII antibodies are directed against active sites of factor VIII molecule. A_2 domain (Factor IX binding site), A3 domain (von Willebrand factor binding site), furthermore C_1 and C_2 domains (phospholipid binding site) are involved with major immunogenicity. According to Moreau et al, 2000, these antibodies against these sites interfere with FVIII protein function through mechanisms such as steric hindrance and immune complex formulation and clearance.[2]

The inhibitor screening is performed using the activated partial thromboplastin time (APTT). A plasma patient and a pooled plasma mixture should be measured immediately after mixing and after incubation.[3]

Factor VIII inhibitor quantification has been performed by Bethesda assay which may give false positive results due to a pH shift and reduced protein concentration unrelated to the presence of inhibitor. The Nijmegen modification of the assay avoids this pH shift.[3]

Factor IX inhibitors should be quantified using the Bethesda method.[3]

Titers are expressed in Bethesda units (BU) and one BU is defined as the amount of inhibitor which inactivates 50 % of FVIII content in a mixture of the patients' plasma and pooled plasma under specific conditions. They are classified as low titer (< 5 BU) and as high titer (> 5 BU). Most of the high titer patients are "high responding" or presents anamnestic response, with titers that rises to greater than 5 BU after exposure to exogenous FVIII. Low responding inhibitors, generally, are not anamnestic and more frequently transient.[4]

Inhibitors in hemophilia B presents with several distinguished features, such as: anaphylaxis or anaphylactoid reactions to FIX-containing products, most of them in patients with large deletions; the relative lack of success of immunotolerance induction (ITI) and development of nephrotic syndrome as a result of ITI.[5,6]

Although inhibitor formation in both types of hemophilia follow the similar mutation types, the incidence of inhibitors in hemophilia B is quite low compared at hemophilia A. Perhaps the high homology of FIX to the other vitamin K-dependent clotting factors could explain this difference.[6]

Palabras clave
✓ hemofilia
✓ anticuerpos
✓ inhibidores
✓ título

Key words
✓ haemophilia
✓ antibodies
✓ inhibitors
✓ titer

Issues affecting incidence

A variety of factors, genetics or environmental, are involved in the development of inhibitors. In the first group are: kind and severity of hemophilia, ethnics, hemophilia genotype and imunnophenotype. It is widely described that major gene defects such as intron 22 inversion, large deletions and stop codons, are involved with inhibitor development.[2]

Many studies related the inhibitor formation with MHC classes, particularly MHC Class II genes DQ, DR, DP due to their function which is to present extra cellular antigen – such as substituted FVIII – to the patient's immune system.[6]

Among the environmental risk factors, there are: the product type, the most controversial; the site of hemorrhage; the coexistence of inflammation; the intensity of replacement therapy; and breastfeeding.[2]

In 2000, Yee & Lee proposed breastfeeding as a way to induce oral immune tolerance to FVIII, based on the similarity between a glycoprotein in human milk, human milk fat globule, and plasma FVIII and FV. [7] However, Knobe et al., in a 2002 study of a Swedish population, reported no protective effect of breastfeeding on the development of inhibitors.[8]

Recently, studies are showing higher incidence of inhibitors in patients who received the first factor concentrate infusion before 6 months of age.[9,10] So, there is a tendency to postpone the first treatment as much as possible.

Clinical management of inhibitor patients

Inhibitors should be screened prior to any surgical procedure or whenever intensive replacement therapy is being performed. As part of clinical and laboratory comprehensive care, children should be screened every 3-12 months or every 10-20 exposure days, whichever occurs first, and adults each 12 month or whenever clinically indicated.[11]

There are two different ways to face inhibitors: in actively bleeding episodes and in patients without bleeding in order to eradicate the antibody. The control of bleeding is obtained with the so called "bypassing" agents. On the other hand, the eradication can be achieved with ITI. This last approach attempts to achieve antigen acceptance and restore normal pharmacokinetics of FVIII concentrate.

Although there are a variety of protocols, using different amounts of FVIII concentrates, associating or not immunosuppressive agents, there is no consensus of which is the most useful.[12]

Thereafter all of them are very expensive, the effectiveness of this approach is life-long.

Some therapies are able to reduce the inhibitor titer, such as plasmapheresis and high doses of immunoglobulin, and can be useful in some clinical states.[1]

Products available for the treatment of bleeding in patients with inhibitors to factor VIII and IX

Low titer patients usually can continue to treat bleeding episodes with FVIII or IX concentrate in a sufficiently high dose.[1]

High titer patients cannot received FVIII concentrate in enough amounts to overcome the antibody and also there is the need of choosing another product, which can "bypass" the need of FVIII in clot formation. These are the "bypassing agents", represented by the prothrombin complex concentrate (PCCs), the activated prothrombin complex concentrate (aPCCs) and recombinant activated factor VII (rFVIIa).[4]

PCCs contain factors II, VII, IX and X and are plasma derived products.[4]

APCCs contain more active components than PCCs and were developed specifically for use in inhibitor patients. The main content is factor VII activated and factors II, IX and X in inactivated form.[4]

APCCs mechanisms of action seem to be multifactorial, involving "bypass" simultaneously in the three coagulation pathways. The mixture of two proteins of prothrombinase complex (prothrombin and activated factor X - FXa) mimetizes aPCC action. In addition, prothrombin facilitates FXI binding to platelets and acts as an antagonist to the inhibitory effect of kininogen in FXI activation, depending on the platelet by thrombin. Finally, FXa induces the activation of FVII endogenous, enhancing the extrinsic pathway activity.[13]

APCCs are administered in doses of 50-100 IU/Kg weight, up to twice daily, depending on the severity of clinical not exceeding 200 IU/kg daily, because of the thrombogenicity risk. Small amounts of FVIII are present at aPCCs and this can lead to boost antibody titers. Thrombotic adverse events associated with aPCCs are higher when there is additional thrombotic risk factors and failure in the adherence to dosing guidelines.[13]

rFVIIa is recognized as useful in the treatment of inhibitors in hemophilia A and B, independently of the titers. It is being used in the dose of 90-12 0μg/kg body weight in intervals of 2-3 hours, due to the short half-life. Studies on safety, efficacy, mechanism of action and pharmacokinetics are extensively published.[14-16]

PCCs, aPCCs and rFVIIa have unpredictable hemostatic effect and there is no laboratory assay to monitor efficacy or optimal dosing.[4]

Recently, aPCCs are being administered as prophylactic treatment to patients with inhibitors instead of being used just as "on demand" treatment. This approach of giving aPCC doses of 50-100IU/Kg 3 times weekly seems to be reasonable in preventing joint bleeds and subsequently, joint damage in hemophiliacs with inhibitors.[4]

Final Remarks

During the last decades hemophilia treatment has greatly improved, giving to the patients the perspective of living with good quality of life and having a productive existence. However, this is not yet possible to inhibitor patients, due to the cost of treatment regimens, not affordable world widely. Until recently, surgery in inhibitor patients were performed just in emergences, because of the possibility of uncontrolled bleeding. Nowadays, considering the good products marketed, surgical elective procedures are a reality and morbidity is becoming less frequent in these patients.

References

1. Kasper CK. Diagnosis and management of inhibitors to Factor VIII and IX. An introductory Discussion for Physicians. Treatment of Hemophilia Monograph Series, N0 34. World Federation of Hemophilia; September 2004. Available at: http://www.wfh.org/Content_Documents/TOH-Monographs/TOH-34_English_Inhibitors.pdf. Accessed August 1st, 2005.
2. Dimichele D. Inhibitors: resolving diagnostic and therapeutic dilemmas. Haemophilia 2002; 8: 280-287.
3. UKHCDO. Guideline. The diagnosis and management of Factor VIII and IX inhibitors: a guideline from the UK Haemophilia Centre Doctors' Organization. Br J Haematol 2001;111:78-90.
4. Leissinger CA. Prevention of bleeds in hemophilia patients with inhibitors: emerging data and clinical direction. Am J Hematol 2004;77:187-193.
5. Key NS. Inhibitors in congenital coagulation disorders. Br J Haematol 2004;127:379-391.
6. Oldenburg J, Tuddenham E. Genetic basis of inhibitor development in severe haemophilia A and B., En: Rodríguez-Merchan EC, Lee CA, editors. Inhibitors in patients with haemophilia. 1st edition. Oxford: Blackwell Publishing; 2002.
7. Yee TT, Lee CA. Oral immune tolerance induction to factor VIII via breast milk, a possibility? Haemophilia 2000; 6: 591.
8. Knobe, KE, Tengborn LI, Petrini P, Ljung RCR. Breastfeeding does not influence the development of inhibitors in hemophilia. Haemophilia 2002;8: 657-659.
9. Lorenzo JI, Lopez A, Altisent C, Aznar JA. Incidence of factor VIII inhibitors in severe haemophilia: the importance of patient age. Br J Haematol 2001;113: 600-603.
10. van der Bom JG, Mauser-Bunschoten EP, Fischer K, van den Berg HM. Age at first treatment and immune tolerance to factor VIII in severe hemophilia. Thromb Haemost 2003; 89: 475-479.
11. Srivastava A. WFH treatment guidelines work group. Guidelines for the management of Hemophilia. World Federation of Hemophilia; 2005. Available at: http://www.wfh.org/Content_ Documents/Other_Publications/Guidelines_Mng_Hemophilia.pdf. Accessed August 1st, 2005.
12. Dimichele D, Rivard G, Hay C, Antunes S. Inhibitors in haemophilia: clinical aspects. Haemophilia 2004;10(Suppl.4):140-145.
13. Luu H and Ewenstein B. FEIBA saqfety profile in multiples modes of clinical and home-therapy application. Haemophilia 2004; 10(suppl.2): 10-16.
14. RodrÍguez-Merchan EC, Rossino A. Literature review of surgerie management in inhibitor patients. Haemophilia 2004;10(suppl. 2):22-29.
15. Levi M, Peters M, Buller HR. Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: a systematic review. Crit Care Med 2005; 33: 883-890.
16. Siddiqui MA and Scott LJ. Recombinant factor VIIa (Eptacog Alfa): a review of its use in congenital and acquired haemophilia and other congenital bleeding disorders. Drugs 2005; 65: 1161-1177. rm