Treatment of Hemophilia A and B

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INTRODUCTION

Treatment for patients with hemophilia and other bleeding disorders has evolved over the past several decades. Replacement of the specific missing plasma protein is necessary for hemostasis to occur. Lyophilized factor concentrate products contain these proteins. This chapter will address purity and viral safety issues for most of the coagulation products currently available. Dosing and nursing implications relative to documentation will also be discussed.

Therapeutic management of bleeding disorders requires prompt treatment of bleeding episodes to minimize complications arising from blood accumulating in joint spaces and/or other tissues and organs. Various treatment regimens for non-complicated and complicated bleeding episodes are currently available. Primary and secondary prophylactic treatment is discussed in Chapter 7 of this Nursing Handbook.

FACTOR REPLACEMENT CONCENTRATES AND VIRAL INACTIVATION

Factor concentrates are either prepared by recombinant DNA technology or derived from pools of human plasma. Currently there are several recombinant factor VIII (FVIII) products and two recombinant factor IX (FIX) products available with high specific activities (the amount of desired clotting factor per mg of total protein). Plasma-derived clotting factor products are also available.

RECOMBINANT CLOTTING FACTORS

Technological advances in the manufacture of coagulation proteins have resulted in the development of recombinant concentrates. These ultra-pure products are derived from Chinese hamster ovary (CHO) or baby hamster kidney (BHK) cells that have been transvected with the human factor VII, FVIII, or FIX gene. Although the cell lines used in fermentation are considered to be free of viruses, these concentrates are still subjected to a combination of viral clearance and inactivation steps to ensure safety and purity. The first generation recombinant FVIII product that is still available is Recombinate (Baxter), and it is stabilized with added human albumin. Second generation products, KogenateFS (Bayer) and HelixateFS (CSL Bering), are formulated with sucrose at the end of the manufacturing process. BeneFIX recombinant FIX (Pfizer), Rixubis recombinant FIX (Baxter), and NovoSeven recombinant FVIIa (NovoNordisk) are totally recombinant without the addition of animal or human plasma proteins during manufacture or formulation. The two third-generation factor VIII products that are now available are Advate (Baxter) and Xyntha

(Pfizer). Both of these concentrates are free from plasma in both manufacture and formulation.

PLASMA-DERIVED FACTOR CONCENTRATES

FVIII and FIX plasma-derived products that are produced utilizing human plasma are still available but are used less frequently, particularly in the United States. The plasma-derived FVIII products are MonoclateP (CSL Behring) and Hemofil-M (Baxter). Plasma-derived products containing FIX are AlphaNineSD (Grifols) and Mononine (CSL Behring). Three plasma-derived products containing both FVIII and VWF are Alphanate (Grifols), HumateP (CSLBehring), and Wilate (Octapharma).

Before the plasma manufacturing process begins, donors are rigorously screened and their plasma donations tested for a variety of contaminants such as HIV, Hepatitis A, hepatitis B, hepatitis C, Parvovirus B19, and West Nile virus.

During the manufacturing process of plasma-derived blood products, the plasma is subjected to viral inactivation methods as well as elimination steps to kill viruses and remove foreign proteins. Plasma viral inactivation is achieved by heat treatment, pasteurization, solvent/detergent treatment, monoclonal antibody separation, and/or ultra-filtration.

From 1997 through 2012, the Centers for Disease Control and Prevention (CDC) maintained surveillance of recipients of factor concentrates for viral transmission. The last transmission of HIV by an American produced, plasma-derived factor concentrate occurred in 1987. Transmission was attributed to infusion of an outdated product that was dry heated and made from plasma that was not screened for HIV. No viral-inactivated concentrate made from HIV-antibody-screened plasma has been known to transmit HIV. The transmission of Hepatitis A, B, and C is also tracked by the CDC and has disappeared in the factor concentrates manufactured in the United States since the advent of serologic and NAT testing and viral inactivation methods.

PRODUCT SELECTION

Product selection can be a complex issue. Many considerations including efficacy, cost, safety, vial size, and ease of administration are important to patients and families. Staying current relative to technology and safety is the responsibility we all share. By seeking up-to-date information and having frank and open discussions with patients and families about factor products and treatment, we can help ease some of the stress associated with these decisions.

INFORMATION SOURCES FOR LICENSED FACTOR PRODUCTS

All dosing information contained in this chapter should be considered as general guidelines; doses should be tailored to the individual patient. The reader is advised to consult the product information inserts supplied by the manufacturers for the most current information about all products discussed in this chapter. In addition, Hemophilia Treatment Centers (HTCs) and The National Hemophilia Foundation (NHF) carry the latest information about all products available. The Medical and Scientific Advisory Council (MASAC) of NHF reviews therapeutic products and offers treatment guidelines and recommendations. [1] The NHF web site www.hemophilia.org lists all of the current MASAC recommendations. Bleeding disorders care providers are strongly encouraged to notify and provide information to patients and families when new factor products are licensed.

HEMOPHILIA TREATMENT

The amount of factor concentrate replacement therapy required to achieve hemostasis varies with each patient's weight, factor deficiency, severity, and bleeding circumstance. The normal factor activity level in persons without hemophilia ranges from approximately 50% to 150%. Persons with severe hemophilia have less than 1% of the normal level of either FVIII or FIX in their blood. Individuals with moderate hemophilia have baseline factor levels of approximately 1% to 5%, and those with levels that are 6 to 49% are considered to have mild hemophilia.

Not all injuries or bleeding episodes may require the same dose of factor concentrate. Depending on the severity of the bleeding episode, the desired initial factor activity level may range from 30% or 40% to approximately 100%. Emergency situations require different treatment strategies, as do inhibitor patients; these will be discussed in Chapters 8 and 12 of this Nursing Handbook.

Hemorrhages or bleeding episodes are classified as minor, major, or severe. Minor hemorrhages (e.g., early joint bleeds and soft tissue bleeds) generally require 30% to 50% activity level for both FVIII and FIX replacement. A single dose of factor concentrate may be sufficient to achieve hemostasis and resolve a minor bleeding episode. Major hemorrhages, such as advanced joint and muscle bleeds, require individualized dosing. These hemorrhages, indicated by swelling, warmth, limited motion, and tenderness in joints and soft tissue, require higher levels of circulating factor levels to stop the bleeding. Additionally, subsequent infusions of factor concentrates may be necessary to maintain hemostasis and prevent re-bleeding. Life-threatening or severe hemorrhages (e.g., CNS involvement, eye, neck or throat, gastrointestinal tract, surgery) require sustained factor activity levels of 50% to 100% for several days or weeks for both FVIII and FIX-deficient patients.

Two important factors that affect hemophilia management are joint disease and the development and treatment of inhibitors. Recent clinical trials have evaluated joint disease prevention as well as the role of von Willebrand factor-containing factor VIII concentrates in inhibitor development and treatment in hemophilia A. In 2007, the Joint Outcomes Study showed that prophylaxis with recombinant factor VIII can prevent joint damage and decrease the frequency of joint and other hemorrhages in young boys with severe hemophilia A. [2] As of 2010, the currently available data from laboratory and clinical studies have been mixed but do not reveal definitive evidence supporting a role for von Willebrand factor-containing factor VIII concentrates in the prevention of inhibitor development and inhibitor eradication in hemophilia A. [3] New global clinical trials are currently underway to address these issues. [4]

ADMINISTRATION OF FACTOR CONCENTRATES

Factor concentrates should be infused as soon as possible following the start of a bleeding episode. Delays in treatment may result in prolonged recovery and the need for more factor infusions to control bleeding, as well as permanent damage to joints, muscles, and other organs.

According to manufacturing prescribing information, factor concentrates are administered intravenously via IV bolus. Rate of infusion is dependent on the particular product used.

Each vial of FVIII and FIX concentrate is labeled with the total number of units expressed as International Units (IU). Vials of factor concentrate range from 200 to 3,000 units per bottle. Dose calculations can rarely be exact due to the variability in lot yields. It is not essential to administer exact doses; doses within 10% above the ordered number of units are acceptable. Never waste factor concentrate by using a portion of a vial and discarding the rest. Infuse the full vial, as overdosing is not an issue. Always choose a vial size that is as close as possible to the desired dose, but always round up to the nearest whole vial size, never down.

Although the activity level is expressed as a percentage, it is used in calculation as a whole number. The following formula may be used as a general guide in determining the number of units to be administered.

DOSING FOR FACTOR VIII PRODUCTS

1 unit of factor VIII/kg will increase circulating factor VIII level by 2%
Pt weight in Kg x 50 units/kg = 100% correction.
Example: a 30-kg patient requiring 100% of factor VIII
30 kg x 50 units/kg = 1500 units of factor VIII to be infused to reach 100%

DOSING FOR FACTOR IX PRODUCTS

1 unit of factor IX/kg will increase circulating factor IX level by 1%
Pt weight in Kg x 100 units/kg = 100% correction
Example: a 30 kg patient requiring 100% of factor IX
30 kg x 100 units/kg = 3000 units of factor IX to be infused to reach 100%
N.B. BeneFIX (Pfizer) may require 120-130 units/kg to reach 100% circulating FIX level.

ADDITIONAL CONSIDERATIONS

PK or recovery studies maybe needed to determine adequate dosing. Factor recovery and half-life studies also provide important information for development of patient-specific dosing guidelines. Some HTCs perform such studies before beginning prophylactic or episodic treatment plans or before elective surgery. When given preoperatively, factor concentrate should be administered as close to the time of surgery or the procedure as possible, because peak plasma concentration levels of FVIII and FIX occur within 15 minutes of administration.

ADVERSE REACTIONS

The administration of factor concentrate products will occasionally cause reactions including hives, itching, stuffy nose, chest pain, dizziness, shortness of breath, temperature elevation, headache, palpitation, mild chills, nausea, or stinging at the infusion site. Reactions can occur during an infusion or one to two hours following an infusion. In addition, reports of anaphylactic reactions have occurred in patients with inhibitors to factor IX. Because of these potential severe reactions, most HTCs administer to hemophilia B patients a test dose of FIX in a controlled clinical setting, and many recommend that the first 10-20 doses of factor IX be given at the HTC or a clinical infusion center where resuscitation equipment is readily available.

Note that most patients with anaphylaxis to FIX products have large or total deletions of their FIX gene. Thus early genotyping may identify patients at greatest risk of this complication so that appropriate precautions can be taken when administering FIX concentrates to these patients.

HOME THERAPY

When appropriate, patients, families and payers greatly benefit from home therapy, that is, the infusion of factor concentrates in the home by the patient or a trained family member. Home therapy is usually encouraged, can be complicated and will be discussed in detail in Chapter 7.

Patients with known allergic reactions to factor concentrates may require pre-medication with an antihistamine such as Benadryl. Since allergic reactions can occur at any time, Benadryl should be kept on hand at home even for patients who have not shown an allergic reaction. Some HTCs encourage families and patients to keep an Epi-pen in the home as well.

NURSING CONSIDERATIONS

The nurse should document the following:
1. Date and time of infusion
2. Manufacturer/brand, lot number and expiration date of factor
3. Rate of infusion
4. Total dose infused
5. Site of infusion
6. Infusion reactions or complications
7. Pretreatment medications
8. Response or reaction to treatment; response may not be immediately evident
9. Follow-up instructions and recommendations

TREATMENT OF MILD HEMOPHILIA A

Some individuals with mild hemophilia A respond to a non-factor product called desmopressin acetate.

Desmopressin acetate (DDAVP) is a synthetic analog of the natural antidiuretic hormone, arginine vasopressin. DDAVP causes von Willebrand factor (VWF) to be released from the stores in the endothelial cells that line the blood vessels. VWF then binds to FVIII as it is released from the liver, protecting it from degradation. Following the administration of DDAVP, circulating FVIII and VWF levels may rise approximately three-fold in responsive patients. Transient rises in plasma levels of FVIII in mild to moderate Hemophilia A patients and some von Willebrand Disease patients may be sufficient to achieve hemostasis in certain clinical situations. (See DDAVP package insert) Spontaneous or mild injuries such as oral/mucosal bleeding and epistaxis are generally well controlled with the use of DDAVP.

Desmopressin is available as an intravenous form called DDAVP Injectable and a nasal spray form called Stimate Nasal Spray for Bleeding. Stimate has been shown to be efficacious in the treatment of mild Hemophilia A and von Willebrand Disease. It is important to determine an individual's response to DDAVP or Stimate prior to using either for treatment. A test dose should be administered (see dosage guidelines below) to the patient while in a non-bleeding state. Following a test dose of either DDAVP or Stimate, FVIII and VWF levels are measured at predetermined time points to

assess if these factor levels rise adequately.

DOSAGES AND ADMINISTRATION GUIDELINES

DDAVP Injectable is administered intravenously at a dose of 0.3 mcg/kg of body weight. It is diluted in 30 ml normal saline and infused slowly over 30 min. (See DDAVP package insert for dilution guidelines). DDAVP injection is available in single dose ampoules or multidose vials.

Stimate Nasal Spray for Bleeding is a convenient way to administer a high concentration of desmopressin acetate in a nasal spray. This formulation contains 150 mcg/0.l ml (one spray), enabling a 300-mcg dose to be easily administered with 2 nasal sprays to an adult or adolescent patient weighing over 50 kg. (See Stimate package insert) Pediatric patients weighing less than 50kg generally receive one spray for a dose of 150 mcg. Each vial contains approximately 24 sprays; exceeding this number of sprays in the vial will result in inadequate delivery of Stimate. The patient or a family member should be taught to keep track of total number of doses administered per vial.

IMPORTANT WARNINGS

ADVERSE REACTIONS

A low concentration formulation of desmopressin acetate (DDAVP nasal spray) at a concentration of 0.1 mg/ml is available for the treatment of diabetes insipidis and primary nocturnal enuresis. This formulation is not effective for the treatment of Hemophilia A or VWD and should never be used for treatment of bleeding episodes. Clinicians should write prescriptions explicitly stating Stimate Nasal Spray for Bleeding and not generic DDAVP to avoid dispensing errors.

Facial flushing, transient headaches, nausea, and abdominal cramps have been noted with the administration of DDAVP. These symptoms usually disappear by slowing the infusion rate. Transient hypertension or hypotension may also be a side effect. DDAVP should be used with caution in patients with a history of venous thrombosis or cardiac disease, as reports of thrombotic events exist.

DDAVP and Stimate cause water retention and can lead to hyponatremia and seizures unless water intake is limited for several hours after administration. DDAVP and Stimate should only be given once every 24 hours. If a hospitalized patient has an IV running, it should be with Normal Saline or Lactated Ringer's solution only. DDAVP and Stimate should be also used with caution in children under 2 years of age and in the elderly. Both of these age groups are at greater risk for water intoxication, hyponatremia, and seizures.

Tachyphylaxis (diminishing response) can occur when DDAVP is given on a daily basis. This phenomenon appears most frequently in patients with mild Hemophilia A. Thus DDAVP and Stimate should not be given for more than 3-5 days in a row. For post-operative management of patients with mild hemophilia A, administration of DDAVP can be alternated with factor VIII concentrate.

NURSING CONSIDERATIONS

Blood pressure and pulse should be monitored during infusions. If used preoperatively, DDAVP should be administered 30 minutes prior to the scheduled procedure. DDAVP is a potent anti-diuretic agent. The HTC staff should alert all operating room personnel that the administration of unrestricted intravenous fluids may result in an SIADH-like syndrome of hyponatremia due to excessive water resorption from the kidneys (water intoxication). Only Normal Saline or Lactated Ringer's Solution should be administered in the Operating Room after administration of IV DDAVP.

The rise in FVIII plasma levels after DDAVP is rapid. Peak values are reached within 30 to 45 minutes, but it may require as much as an hour to achieve them. A second dose may be given 24 hours after the initial dose. However, the increase in FVIIl activity may be less than the initial peak due to the relatively slow synthesis and release from the endothelial cells. Repeat administration after 48 hours generally reproduces the original response.

DOCUMENTATION

The nurse should document the following:

1. Date and time of infusion or administration
2. Rate of infusion
3. Blood pressure
4. Dose infused or administered
5. Site of infusion
6. Infusion reactions and complications. Reactions can occur during an infusion or one to two hours following an infusion.
7. Fluid restriction education
8. Stimate education for home use should include: steps for administration, indications for use, frequency of administration, home documentation, fluid restriction and adverse events
9. Patient response to treatment (may not be immediately evident). May require phone follow up.

ANTIFIBRINOLYTIC AGENTS

Antifibrinolytics are particularly effective in areas where fibrinolysis appears to contribute to prolongation of bleeding, as in mucous membranes (nose, mouth, and throat) and with dental procedures. These agents can be given alone or as an adjunct therapy with DDAVP or factor VIII concentrates. Currently there are two antifibrinolytic agents available in the United States in an oral form. They are Aminocaproic acid (Amicar) and Tranexamic acid (Lysteda). Both of these agents will be discussed in another chapter.

CONCLUSION

The nurse and HTC staff can help the patient and family by providing them with thoughtful clinical care and detailed educational materials and assistance. Clinicians and consumers are encouraged to contact their local comprehensive HTC or the National Hemophilia Foundation for teaching tools and resources. In addition, most factor replacement manufacturers offer a wide variety of patient educational materials regarding their products and the treatment of bleeding disorders.

Patients and their families are encouraged to discuss treatment options, strategies and recommendations with HTC staff and to read all available materials to have their questions addressed and answered. This will enable them to make informed decisions regarding their care and treatment choices.

REFERENCES

1. Medical and Scientific Advisory Council. MASAC recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised April 2013). New York, National Hemophilia Foundation 2013; MASAC Document 217.
2. Manco-Johnson MJ, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med 2007; 357:535-44.
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4. Batorova A, et al. Special lectures in haemophilia management. Haemophilia 2010; 16 (Suppl. 5), 22-8.