Treatment of Single Factor Deficiencies: A Case Study Approach

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von Willebrand disease and hemophilia A are the two most common inherited bleeding disorders.[1] The diagnosis, treatment, and monitoring of patients with these conditions requires frequent interaction between the patient's physician and the clinical laboratory. In many institutions, coagulation factor concentrates are dispensed from the blood bank along with other blood-derived products, while the special coagulation laboratory offers assays to monitor response to treatment. It is important in these instances that there is open communication among the staff of those laboratories and an understanding of the important issues in the management of patients with von Willebrand disease or hemophilia A with or without inhibitor.[2] In this discussion, such issues are highlighted using a case study-based approach.

CASE 1: von WILLEBRAND DISEASE

A 40-year old white female was hospitalized to have left total knee arthroplasty on the next day. Her past medical history was significant for severe von Willebrand disease and multiple episodes of hemarthrosis in the affected joint. The orthopedic surgeon called the coagulation consultant to decide on von Willebrand factor replacement for surgery.

Although von Willebrand disease is classically associated with manifestations of abnormal primary hemostasis such as mucosal bleeding, in the severe form of this disease, patients also have a deficiency of factor VIII and suffer from joint bleeds. The deficiency of factor VIII is a consequence of increased proteolysis of this factor in the absence of normal levels of von Willebrand factor to protect it in the circulation. Until a few years ago, cryoprecipitate was the product of choice to treat patients with severe von Willebrand disease. However, plasma-derived concentrates of von Willebrand factor are now available and have become the first choice for treatment of this condition. Since von Willebrand factor and factor VIII circulate together, these replacement products contain both factors. The only Food and Drug Administration (FDA) approved product is Humate-P® which contains approximately 2.5 times more von Willebrand factor than factor VIII. In order to calculate the appropriate dose of factor to prepare the patient for surgery, several patient-specific pieces of information are necessary (Table 1). The data for this patient were:

- Baseline von Willebrand factor level: <1% or <0.01 units/mL of plasma
- Baseline factor VIII level: 1% or 0.01 units/mL of plasma
- Target von Willebrand factor level: 90% to 100% or 0.9 to 1 unit/mL of plasma (for major surgery)
- Weight: 107 lb or 48.5 Kg (1 lb = 0.453 Kg)
- Hematocrit (HCT): 25%
- Blood volume (BV): weight (48.5 Kg) x 70 mL/Kg (for patients with body mass index (BMI) < 25; multiply by 60 mL/Kg if BMI between 25 and 30; and by 50 mL/Kg if BMI > 30) = 3,395 mL
- Plasma volume (PV): BV x (1 – HCT) or 3,395 x 0.75 = 2,546 mL
- Dose in units: (desired activity [0.9 to 1 unit/mL] - baseline activity [zero]) x PV = 2,291 to 2,546 units

Thus, in order to increase the von Willebrand factor level from zero to close to 100%, she should receive the appropriate number of vials of Humate-P that more closely add to the calculated dose of 2546 units. Since each lot of coagulation factor concentrates contain different amounts of each factor, the person dispensing the dose should calculate how

many vials are necessary to fulfill the order. To be certain that the calculated dose is correct, a factor level can be measured 1 hour after the infusion is complete. In this patient, the von Willebrand factor (ristocetin cofactor activity) and factor VIII levels were 90% and 73%, respectively. Since the half-life of von Willebrand factor is approximately 12 hours, the following doses for maintenance of factor levels for surgery and the post-operative period should be half of the loading dose (approximately 1,250 units) repeated every 12 hours. Even when the patient is stable and not bleeding, it is necessary to follow von Willebrand factor levels once a day while in the hospital. It is also important to remember that if subsequent factor VIII levels are measured in these patients, they will be higher than expected based on the amount of factor VIII given. The reason for this discrepancy is that once von Willebrand factor is provided, the factor VIII level will reflect the added effect of what was infused through Humate-P plus the endogenous production of factor VIII which now resists proteolysis in plasma. Finally, factor replacement needs to be continued at home for seven to ten days post-operatively and the patient needs to seek immediate medical attention if abnormal bleeding ensues.

CASE 2: HEMOPHILIA A

A 35-year old white male with mild hemophilia A was admitted for persistent bleeding from a skin cut incurred by a car fender several hours earlier. His past medical history was significant for appendectomy, which resulted in prolonged bleeding. The hematologist ordered replacement therapy after seeing the patient and reviewing the history and laboratory data.

In treating patients with hemophilia A, the degree of factor VIII deficiency (mild, moderate, or severe) will affect treatment.[3] Many patients with mild hemophilia A can avoid factor replacement by relying on DDAVP (1-deamino-8-D-arginine-vasopressin), which induces the release of factor VIII/von Willebrand factor from endothelial cells and platelets. If factor concentrates are indicated by the physician, the two main sources of factor VIII are plasma or recombinant technology. The factors purified from plasma undergo viral inactivation steps to decrease the risk of transmitting infection by lipid-enveloped viruses such as hepatitis B and C and human immunodeficiency virus (HIV). These high-purity factor VIII products (Table 2) are the first line therapy for patients who have received plasma products before or are already infected with one or more of these viruses. Newly diagnosed patients, those never treated with plasma-derived factor previously or those whose previous treatment is unknown, should receive factor VIII produced by recombinant technology in tissue culture (Table 2). Unfortunately, these factors are sometimes in short supply and not readily available. For those instances, one needs to realize that the plasma-derived products have never been shown to transmit hepatitis or HIV, thus constituting a very safe alternative.[4]

The data for the calculation of the factor VIII dose for this patient were as follows:

- Baseline factor VIII level: 19% or 0.19 units/mL of plasma (mild hemophiliac)
- Factor VIII inhibitor assay - negative
- Serology for hepatitis C - positive

Table 1. Important patient data to calculate coagulation factor replacement

Deficient factor, i.e., von Willebrand factor, Factor VIII, Factor IX
Presence or absence of factor inhibitor
Baseline factor level
Reason for replacement to establish target level
Weight in Kg
Hematocrit
Calculated blood and plasma volumes
Half-life of factor to decide on dosage interval

Table 2: Coagulation factor products to treat Hemophilia A

High-purity plasma-derived factor VIII products
Hemophil-M
Koate-HP
Monarch-M
Monoclate-P

Factor VIII prepared by recombinant technology
Bioclate
Helixate
Kogenate
Recombinate

Alternatives for patients with factor VIII inhibitors
Activated prothrombin complex concentrates:
Autoplex T
FEIBA
Recombinant factor VIIa (NovoSeven)
Porcine factor VIII (Hyate C)

- Target factor VIII level: 75% or 0.75 units/mL of plasma
- Weight: 160 lb or 72.5 Kg (1 lb = 0.453 Kg)
- Hematocrit (HCT): 35%
- Blood volume (BV): weight (72.5 Kg) x 70 mL/Kg = 5,100 mL
- Plasma volume (PV): BV x (1 – HCT) or 5,100 x 0.65 = 3,315 mL
- Dose in units: (desired activity [0.75 units/mL] - baseline activity [0.19 units/mL]) x PV = 1,856 units of plasma-derived factor VIII (loading dose).

Since the factor VIII circulating half-life is between eight to 12 hours, the patient should receive approximately 900 units of factor VIII two or three times daily depending on the severity of the bleeding, the clinical response and the factor VIII levels measured throughout treatment.[5]

CASE 3: HEMOPHILIA A WITH INHIBITOR

A 47-year old male with hemophilia A presented to the emergency department complaining of left knee swelling. The patient reported that he has a factor VIII inhibitor and cannot receive factor VIII concentrates to stop the hemorrhage. The coagulation service was consulted. Review of the laboratory records confirmed that the patient suffers from severe hemophilia A and developed a factor VIII inhibitor since the first time he was tested at our hospital six years previously.

Approximately one third of patients with severe hemophilia A, those with <1% factor VIII activity, develop an IgG alloantibody directed to the factor after exposure to plasma-derived or recombinant factor VIII. The amount of inhibitor is quantitated by the Bethesda assay and the inhibitor is expressed in terms of Bethesda units (BU). One Bethesda unit is defined as the reciprocal of the patient's plasma dilution that inactivates 50% of the amount of factor VIII in normal human plasma. When the patient has less than five to ten 10 BU of inhibitor, he may be treated with enough factor VIII to overcome the presence of the inhibitor in the plasma and supply a hemostatic level. However, after further exposure to factor VIII, the level of inhibitor can increase significantly. In the case of this patient, for instance, his inhibitor was at 2 BU when he received factor VIII injections in the past. When he returned to the outpatient clinic two months later, his inhibitor level had increased to 225 BU. Since then, he has required an alternative treatment to stop bleeding or prepare him for a surgical procedure. Options for patients with inhibitors are described in Table 2. Since porcine factor VIII is not being produced, only the first two types of products are currently available in the United States. In our hospital we have used FEIBA as the first choice for many years. The dose of FEIBA is calculated by multiplying the patient's weight in Kg by 50 or 100 units and the dose interval varies from every six to every 12 hours with a maximum daily dose of 200 units/Kg per day. The total daily dose and the interval between injections depend on the severity of the bleed and the response to treatment.[6] The doses are independent of the patient's inhibitor level and there is no laboratory test to monitor therapy. Clinical response is the only parameter to be followed. The last statement also applies to NovoSeven, recombinant activated factor VII, which is the newest product to treat patients with factor VIII inhibitors. The dose of NovoSeven is 90-120 mg/Kg repeated every two to three hours until the bleeding has stopped.

CONCLUSION

The treatment of patients with single coagulation factor deficiencies has improved considerably in the last decade. Patients and physicians now count on a number of safe alternatives to control or prevent hemorrhage for the various disease states. It is imperative, however, that the proper diagnosis be available in order to choose the right product. Coordination between the laboratory and the physicians taking care of the patient will ensure the most efficient and cost-effective sequence of tests, factor injections, and therapy monitoring. In order to have clinical and laboratory expertise available, patients with von Willebrand disease and hemophilia are often referred to tertiary care centers instead of being managed in smaller facilities with fewer resources. A recent review of our records demonstrated that the average cost of treatment of these patients is a major portion of the Transfusion Medicine budget.

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