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Antihemophilic Factor (Human) Koāte®

SEE SECTIONS ENTITLED "DESCRIPTION" AND "WARNINGS" FOR DISCUSSION OF HEPATITIS RISK

DESCRIPTION

Antihemophilic Factor (Human), Koāte,* is a sterile, stable, purified, dried concentrate of human Antihemophilic Factor (Factor VIII, AHF, AHG) intended for use in therapy of classical hemophilia (hemophilia A).

Koāte is purified from the cold insoluble fraction of pooled fresh-frozen plasma by modification and refinements of the methods first described by Hershgold, Pool, and Pappenhagen.[1] Koāte contains highly purified and concentrated Factor VIII. The Factor VIII is 50-200 times purified over whole plasma, and when reconstituted as directed, Koāte contains approximately 25-40 times as much Factor VIII as an equal volume of fresh plasma.

Each bottle of Koāte contains the labeled amount of antihemophilic activity in AHF/International Units (AHF/IU). One IU, as defined by the World Health Organization Standard for Blood Coagulation Factor VIII, human, is approximately equal to the level of AHF found in 1.0 ml of fresh pooled human plasma. One AHF unit is equivalent to one International Unit. Koāte must be administered by the intravenous route.

CLINICAL PHARMACOLOGY

Hemophilia A is a hereditary bleeding disorder characterized by deficient coagulant activity of the specific plasma protein clotting factor, Factor VIII. In afflicted individuals, hemorrhages may occur spontaneously or after only minor trauma, and surgery on such individuals is not feasible without first correcting the clotting abnormality. The administration of Koāte provides an increase in plasma levels of Factor VIII and can temporarily correct the coagulation defect in these patients.

After infusion of AHF, there is an instantaneous rise in the coagulant level, followed by an initial rapid decrease in activity, and then a subsequent much slower rate of decrease in activity.[2,3] The early rapid phase may represent the time of equilibration with the extravascular compartment, and the second or slow phase of the survival curve presumably is the result of degradation and reflects the true biologic half-life of the infused AHF.[4] Studies with Koāte in hemophilic patients have demonstrated an initial 50% disappearance time of five hours, and a biologic half-life of approximately 13 hours.[5] There were no significant differences in half-life between bleeding and nonbleeding patients.[6]

INDICATIONS AND USAGE

Koāte is indicated for the treatment of classical hemophilia (hemophilia A) in which there is a demonstrated deficiency of activity of the plasma clotting factor, Factor VIII. Koāte provides a means of temporarily replacing the missing clotting factor in order to correct or prevent bleeding episodes, or in order to perform emergency and elective surgery on hemophiliacs.

Antihemophilic Factor (Human) is not effective in the treatment of von Willebrand's disease.

CONTRAINDICATIONS

None known.

WARNINGS

Antihemophilic Factor (Human), Koāte* concentrate is a purified dried fraction of pooled plasma obtained from many paid donors. Although each unit of plasma has been found nonreactive for hepatitis B surface antigen (HBsAg) using a U.S. federally approved test with third-generation sensitivity, the presence of hepatitis viruses in such pools must be assumed.

Kasper and Kipnis* have concluded that those who have had little exposure to blood products have a high risk of developing hepatitis after introduction of clotting factor concentrates, such as this product. For those patients, especially those with mild hemophilia, they recommend single donor products. However, for patients with moderate or severe hemophilia who have received numerous infusions of blood or blood products, they feel that the risk of hepatitis is small. They believe that the clotting factor concentrates have so greatly improved the management of severe hemophilia that these products should not be denied to appropriate patients.

Isolated cases of Acquired Immune Deficiency Syndrome (AIDS) have been reported in hemophilics who have received blood and/or coagulation factor concentrates, including Factor VIII concentrates. It is not known if the disease is due to a transmitted specific agent, secondary to multiple antigenic exposures, or to some other mechanisms. The physician and patient should consider that Factor VIII concentrates may be associated with the transmission of AIDS and weigh the benefits of therapy accordingly.

PRECAUTIONS

General

1. Koāte is intended for treatment of bleeding disorders arising from a deficiency in Factor VIII. This deficiency should be proven prior to administering Koāte, since no benefit may be expected from its use in treating other causes of hemorrhage.
2. Administer promptly (within 3 hours) after reconstitution. Do not refrigerate after reconstitution. NOTE: Although Koāte is fully stable, without potency loss, for at least 24 hours at room temperature after reconstitution, the recommendation to administer promptly after reconstitution is intended to avoid the ill effect of any possible bacterial contamination occurring during reconstitution.
3. Administer only by the intravenous route.
4. A filter needle should be used prior to administering.
5. Koāte contains levels of blood group isoagglutinins which are not clinically significant when controlling relatively minor bleeding episodes. When large or frequently repeated doses are required in patients of blood groups A, B, or AB, there is a possibility of intravascular hemolysis.[7,8] If hemolytic anemia develops, administration of type O packed red blood cells should be considered.[7]
6. Administration equipment and any reconstituted Koāte not used should be discarded.

Pregnancy Category C

Animal reproduction studies have not been conducted with Koāte. It is also not known whether Koāte can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Koāte should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Allergic reactions may result from the administration of AHF preparations; these include chills, fever, and hypersensitivity reactions.[7,8]

DOSAGE AND ADMINISTRATION

Each bottle of Antihemophilic Factor (Human), Koāte* has the AHF activity in AHF/IU stated on the label of the bottle. One AHF unit is equivalent to one International Unit. The Factor VIII potency in the reconstituted product allows intravenous infusion by direct syringe injection or drip infusion.

Abildgaard, *et al*[9] have reported from studies in hemophilic children a linear dose response relation with an approximate yield of 2% rise in Factor VIII activity for each unit of Factor VIII per kg of body weight transfused. Clinical experience with Koāte has demonstrated an essentially identical dose-response relationship.[10] Therefore, the following formulae provide a guide for dosage calculations:

$$\text{Expected Factor VIII increase (in \% of normal)} = \frac{\text{AHF/IU administered} \times 2.0}{\text{body weight (in kg)}}$$

$$\text{AHF/IU required} = \text{body weight (kg)} \times \text{desired Factor VIII (\% normal)} \times 0.5$$

All efforts should be made to follow the course of therapy with Factor VIII level assays. It may be dangerous to assume any certain level has been reached unless direct evidence is obtained.

Prophylaxis of spontaneous hemorrhage

The level of Factor VIII required to prevent spontaneous hemorrhage is approximately 5% of normal while a level of 30% of normal is the minimum required for hemostasis following trauma and surgery.[11,12] Mild superficial or early hemorrhages may respond to a single dose of 10 AHF/IU per kg of AHF,[11,12] leading to an *in vivo* rise of approximately 20% Factor VIII level. In patients with early hemarthrosis (mild pain, minimal or no swelling, erythema, warmth, and minimal or no joint limitation), if treated promptly, even smaller doses may be adequate.[11,12]

Mild hemorrhage

In cases of minimal hemorrhage, therapy need not be repeated unless there is evidence of further bleeding.

Moderate hemorrhage and minor surgery

For more serious hemorrhages and for minor surgical procedures, the patient's plasma Factor VIII level should be raised to 30-50% of normal for optimum clot formation.[11,12] This usually requires an initial dose of 15-25 AHF/IU per kg, and if further therapy is required, a maintenance dose of 10-15 AHF/IU per kg every 8-12 hours.

Severe hemorrhage

In patients with life-threatening bleeding, or hemorrhage involving vital structures (central nervous system, retropharyngeal and retroperitoneal spaces, iliopsoas sheath), it may be desirable to raise the Factor VIII level to 80-100% of normal in order to achieve hemostasis.[11,12,13] This may be achieved with an initial AHF dose of 40-50 AHF/IU per kg and a maintenance dose of 20-25 AHF/IU per kg every 8-12 hours.

Major surgery

For major surgical procedures, Kasper[11] recommends that a dose of AHF sufficient to achieve a level of 80-100% of normal be given an hour before the procedure. It is recommended that the Factor VIII level be checked prior to going to surgery to assure the expected level is achieved. A second dose half the size of the priming dose should be given about five hours after the first dose. The Factor VIII level should be maintained at a daily minimum of at least 30% for a healing period of 10-14 days, depending on the nature of the operative procedure.

The above discussion is presented as a reference and a guideline. It should be emphasized that the dosage of Koāte required for normalizing hemostasis must be individualized according to the needs of the patient. Factors to be considered include the weight of the patient, the severity of the deficiency, the severity of the hemorrhage, the presence of inhibitors,

ınd the Factor VIII level desired. All efforts should be made to follow the ourse of therapy with Factor VIII level assays.

The clinical effect of Factor VIII on the patient is the most important ele- nent in evaluating the effectiveness of treatment. It may be necessary to dminister more Koāte than would be estimated in order to attain satisfac- ory clinical results. If the Factor VIII level fails to attain that expected losage, or if bleeding is not controlled after adequate calculated dosage, he presence of Factor VIII inhibitor should be suspected. Its presence hould be substantiated and the inhibitor level quantitated by appropriate aboratory procedure. When an inhibitor is present, the dosage require- nent for AHF is extremely variable and the dosage can be determined on- y by the clinical response.

Parenteral drug products should be inspected visually for particulate natter and discoloration prior to administration, whenever solution and ontainer permit.

IECONSTITUTION

Vacuum Transfer

Warm the unopened diluent and concentrate to room temperature (not o exceed 37°C, 99°F).

Remove the plastic flip-top caps (Fig. A), and aseptically cleanse the ubber stoppers of both bottles.

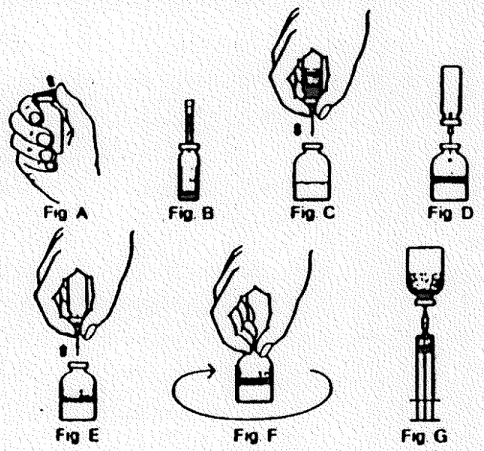
Remove one end of the protective cover from the plastic transfer needle artridge and penetrate the stopper of the diluent bottle (Fig. B) with the eedle.

Remove the remaining protective cover of the plastic transfer-needle artridge. Invert the diluent bottle and penetrate the rubber seal on the oncentrate bottle (Fig. C) with the needle.

The vacuum will draw the diluent into the concentrate bottle. If the acuum is not present the diluent will not flow and that bottle should not e used (Fig. D).

After removing the diluent bottle and needle (Fig. E), shake vigorously or 15-30 seconds, then swirl continuously until completely dissolved ig. F).

Withdraw the completely dissolved Antihemophilic Factor (Human), oāte® solution into the syringe through the filter needle which is supplied the package (Fig. G). Replace the filter needle with an appropriate terile injection needle, e.g., 21 gauge × 1 inch, and inject intravenously.



8. If the same patient is to receive more than one bottle of Koate, the contents of two bottles may be drawn into the same syringe through filter needles before attaching the vein needle.

Rate of Administration

The rate of administration should be adapted to the response of the individual patient, but administration of the entire dose in five to ten minutes is generally well tolerated.

HOW SUPPLIED

Antihemophilic Factor (Human), Koāte® is supplied in single dose bottles with the total units of Factor VIII activity stated on the label of each bottle. A suitable volume of Sterile Water for Injection, USP, a sterile double-ended transfer needle and a sterile filter needle are provided.

STORAGE

Koāte should be stored under refrigeration (2-8°C, 35-46°F). Storage of lyophilized powder at room temperature (up to 25°C or 77°F) for three months, such as in home treatment situations, may be done without loss of Factor VIII activity. Freezing should be avoided as breakage of the diluent bottle might occur.

CAUTION

U.S. Federal law prohibits dispensing without a prescription.

LIMITED WARRANTY

A number of factors beyond our control could reduce the efficacy of this product or even result in an ill effect following its use. These include improper storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration, and biological differences in individual patients. Because of these factors, it is important that this product be stored properly, that the directions be followed carefully during use, and that the risk of transmitting hepatitis be carefully weighed before the product is prescribed.

No warranty, express or implied, including any warranty of merchantability or fitness, is made. Representatives of the Company are not authorized to vary the terms or the contents of the printed labeling, including the package insert, for this product except by printed notice from the Company's Berkeley office. Prescriber and user of this product must accept the terms hereof.

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