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ANTIHEMOPHILIC FACTOR (HUMAN) HEAT-TREATED
KOATE®-HT

DESCRIPTION

Antihemophilic Factor (Human), heat-treated, Koāte®-HT, 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-HT 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-HT contains highly purified and concentrated Factor VIII. The Factor VIII is 50-200 times purified over whole plasma. When reconstituted as directed, Koāte-HT contains approximately 25-40 times as much Factor VIII as an equal volume of fresh plasma. Koāte-HT has been heat-treated for 72-77 hours at 68°C.

Each bottle of Koāte-HT contains the labeled amount of antihemophilic factor activity in AHF/International Units (AHF/IU). One AHF unit is equivalent to one International Unit. 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. Koāte-HT must be administered by the intravenous route.

CLINICAL PHARMACOLOGY

Hemophilia A is an 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. Surgery on such individuals is not feasible without first correcting the clotting abnormality. The administration of Koāte-HT 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 usually 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.[2,3,4] 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.[3] Studies with Koāte-HT in hemophilic patients have demonstrated a biologic half-life of approximately 9-15 hours.[2]

This product has been heated and there is no evidence of adverse effect upon the product. Final evaluation of the effect upon potential infectivity will be determined in prospective studies and from the results of studies in chimpanzees.

INDICATIONS AND USAGE

Koāte-HT 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-HT 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.

Koāte-HT is not indicated in the treatment of von Willebrand's disease.

CONTRAINDICATIONS

None known.

WARNINGS

Kōate-HT concentrate is a purified dried fraction taken from large pools of fresh human 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[5] have concluded that those who have had little exposure to blood products have a higher risk of developing hepatitis after introduction of clotting factor concentrates. For such patients, especially those with mild hemophilia, they recommend single donor products. 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-HT is intended for treatment of bleeding disorders arising from a deficiency in Factor VIII. This deficiency should be proven prior to administering Koāte-HT, since no benefit may be expected from its use in treating hemorrhages due to other causes.

2. Administer promptly (within 3 hours) after reconstitution. Do not refrigerate after reconstitution. NOTE: Although Koāte-HT 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-HT 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.[6-8] If hemolytic anemia develops, administration of type O packed red blood cells should be considered.[6]

6. Administration equipment and any reconstituted Koāte-HT not used should be appropriately discarded.

Pregnancy Category C

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

ADVERSE REACTIONS

Allergic reactions may result from the administration of AHF preparations.[9,10]

DOSAGE AND ADMINISTRATION

Each bottle of Koāte-HT 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[11] 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-HT has demonstrated an essentially identical dose-response relationship.[2] Therefore, the following formulae provide a guide for dosage calculations:

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

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

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.[12-14] Mild superficial or early hemorrhages may respond to a single dose of 10 AHF/IU per kg,[4],[15] 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.[15-17]

Mild Hemorrhage

In cases of mild 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 hemostasis.[15],[18] 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.[15,18-20] 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[18] 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, the dosage of Koāte-HT 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, and the Factor VIII level desired. All efforts should be made to follow the course of therapy with Factor VIII level assays.

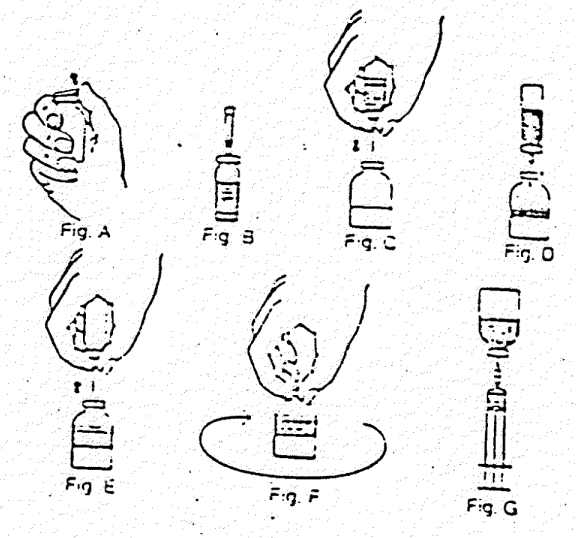
The clinical effect of Factor VIII is the most important element in evaluating the effectiveness of treatment. It may be necessary to administer more Koāte-HT than would be estimated in order to attain satisfactory clinical results. If the calculated dose fails to attain the expected Factor VIII levels, or if bleeding is not controlled after adequate calculated dosage, the presence of a Factor VIII inhibitor should be suspected. Its presence should be substantiated and the inhibitor level quantitated by appropriate laboratory procedure. When an inhibitor is present, the dosage requirement for AHF is extremely variable and the dosage can be determined only by the clinical response.

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

Reconstitution

Vacuum Transfer

1. Warm the unopened diluent and concentrate to room temperature (not to exceed 37°C, 99°F.)
2. Remove the plastic flip-top caps (Fig. A) and aseptically cleanse the rubber stoppers of both bottles.
3. Remove one end of the protective cover from the plastic transfer-needle cartridge and penetrate the stopper of the diluent bottle (Fig. B) with the needle.
4. Remove the remaining protective cover of the plastic transfer-needle cartridge. Invert the diluent bottle and penetrate the center of the rubber stopper on the concentrate bottle (Fig. C) with the needle.
5. The vacuum will draw the diluent into the concentrate bottle. If the vacuum is not present the diluent will not flow and that bottle should not be used (Fig. D).
6. After removing the diluent bottle and transfer needle (Fig. E), shake vigorously for 15-30 seconds, then swirl continuously until completely dissolved (Fig. F).
7. Withdraw the completely dissolved Koāte-HT solution into the syringe through the filter needle which is supplied in the package (Fig. G). Replace the filter needle with an appropriate sterile injection needle, e.g., 21 gauge X 1 inch, and inject intravenously.
8. If the same patient is to receive more than one bottle of Koāte-HT, the contents of two bottles may be drawn into the same syringe through a filter needle 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

Koāte-HT 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-HT 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, and 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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