Package leaflet

ANTIHEMOPHILIC FACTOR (HUMAN)
Method Four, Dried
HEMOFIL®

Antihemophilic Factor (Human), Method Four,* Dried, HEMOFIL® is a stable, dried preparation of human antihemophilic factor (Factor VIII, AHF, AHG) in concentrated form with minimal quantities of other proteins and is intended for use in therapy of classical hemophilia (hemophilia A).

Classical hemophilia is a bleeding disease characterized by a life-long tendency to prolonged hemorrhage. The biochemical lesion appears to be a deficiency of a specific plasma protein, antihemophilic factor.

Sahli[1] and his co-workers first demonstrated that freshly drawn whole blood from a non-hemophilic donor would accelerate the clotting of hemophilic blood. Alexander and Landwehr[2] and other investigators mentioned in their bibliography have confirmed this observation and have shown that plasma and certain blood fractions also cause a reduction in the clotting time of hemophilic blood.

For many years the only treatment for bleeding in hemophilia was the use of fresh blood or plasma, or fresh-frozen plasma. The inconvenience of using these materials was largely overcome when Hyland Antihemophilic Plasma, dried, became available. However, the use of plasma is limited by the large volumes needed to raise the hemophiliac's circulating AHF to hemostatic levels. The circulation becomes hypervolemic and overloaded with protein, there may be evidence of cerebral edema,[3] and cardiac embarrassment may occur.[4] This is particularly dangerous if bleeding is rapid or prolonged, or if surgery is required.

To obviate this problem, there has been a great deal of effort to prepare concentrates of antihemophilic factor adequate for therapeutic use. Concentrates prepared from bovine and porcine blood contain great amounts of AHF, but their use has been limited because of their species antigenicity. Hyland Antihemophilic Factor (Human) preparations, being of human origin, carry no risk of foreign substance reaction. HEMOFIL is prepared very rapidly and gently from fresh normal human plasma by the method of Fekete and Shanbrom.[5] Because of its high concentration and relatively low protein content, HEMOFIL may be administered either by intravenous drip infusion or by direct intravenous syringe injection.

Antihemophilic Factor (Human), Method Four, Dried, HEMOFIL offers many advantages, the most significant of which are:

(1) It is of homologous origin.

(2) It supplies higher potency AHF[5] than glycine or cryoprecipitate preparations[6-8] with relatively smaller amounts of fibrinogen and other protein, furnishing adequate AHF without excessively overloading the circulatory system.

*Patents pending

(3) Each lot is assayed and labeled for its AHF [redacted] making possible estimation of dose needed and prediction of effect expected. (Dosage with plasma is less exact, since the AHF level in the plasma of normal individuals varies from about 50% to about 200% of normal [9-12])

(4) Because of predictable effect, therapy may be managed without repeated determination of AHF level when the patient is very young, when veins are poor, or when laboratory service is not immediately available.

(5) Blood group isoagglutinins are present in amounts which are not clinically significant in the dosage needed to control hemarthroses and other relatively slight bleeding episodes in the absence of inhibitors. When larger or frequently repeated doses are needed, as when inhibitors are present or when pre- and post-surgical care is involved, see discussion under "Cautions."

(6) In dry form, AHF appears very stable, in contrast to its erratic decay in fresh or frozen plasma.

(7) This AHF preparation can be given rapidly, either by intravenous drip infusion or direct syringe injection, with no significant reactions.

(8) In the experience thus far, urticaria has not been seen, and in hemophiliacs known to be allergic to plasma, no "plasma reactions" have been encountered.

(9) Sufficient amounts may be administered to overcome inhibitors, thus eliminating the need for bovine or porcine preparations.

(10) It reconstitutes rapidly and easily without formation of bubbles or foam which can inactivate AHF.

DOSAGE

Each bottle of Antihemophilic Factor (Human), Method Four, Dried, HEMOFIL is labeled with the number of AHF units which it contains, one AHF unit being defined as the activity present in 1 ml of average normal pooled human plasma less than one hour old (100% AHF level).

The amount of AHF which a hemophiliac requires for normal hemostasis varies with circumstances and with the patient. The amount of factor to be supplied will depend on the degree of deficiency and on the AHF level desired. It has been suggested by McMillan *et al.*[13] that the AHF level be raised to 30 to 60% of "normal" for at least 10 days postoperatively. However, to control hemarthrosis in classical hemophilia, it may be necessary to raise the AHF level to only 5 to 10% of the "normal" concentration.

Abildgaard *et al.*[8] reported that infusion of 1 unit of AHF per kg body weight consistently produces an increase of 2% (of "normal"), while Smedsrom and Tiselin[14] found that 3.8 to 4.0 units per kg produce an increase of 10% (of "normal" AHF level. (The former authors worked with boys 6 months to 14 years of age, while the latter worked primarily with adults.) The following formulas can therefore be used to calculate approximately the expected response from a given dose or the dose required for a given effect:

I. Units required =
body weight (in kg) x 0.4 x
desired AHF increase (in % of "normal")

or

II. Expected AHF increase (in % of "normal") =
$$\frac{\text{units administered}}{\text{body weight (in kg)} \times 0.4}$$

The data of Abildgaard *et al.* would call for a factor of 0.5 instead of 0.4 in the above formulas.

The validity of these formulas can be verified by the knowledge that circulating plasma makes up some 4 to 5% of body weight. Thus, a boy weighing 20 kg. has some 800 to 1000 ml of circulating plasma. If he had zero AHF initially, 200 units of AHF would be expected to make his plasma level of AHF about 20 to 25%. By formula II,

$$\text{Expected increase} = \frac{200}{20 \times 0.4} \qquad 25\%$$

If the same 20 kg boy had an initial level of 10% and it was desired to raise his level to 60% (an increase of 50%), formula I will show

$$\text{Units required} = 20 \times 0.4 \times 50 = 400 \text{ units.}$$

There is some evidence that in a hemophiliac with severe bleeding, particularly if he has not been recently treated, up to double the calculated initial dose may be needed to produce the desired AHF level, after which the formulas apply.

The half-life of AHF administered to hemophiliacs has been variously estimated at 8 to 24 hours.[15-19] In the severe hemophiliac, the half-life of the first dose of AHF in any [illegible] appears to be at the lower end of the range, but for subsequent doses it may be safely estimated as at least 12 to 15 hours in the absence of inhibitors and "active bleeding." Assuming a half-life of 12 hours, in the second example above (initial level 10%), the boy may be expected, 12 hours after the dose was administered, to have an AHF level of about 30% if no more were given in the meantime.

Although dosage can be estimated by these calculations, it is strongly recommended that whenever possible appropriate laboratory tests be performed on the patient's plasma at suitable intervals to assure that adequate AHF levels have been reached and are maintained. A complete set of reagents, including a reference plasma, is available from Hyland for determination of AHF level by the partial thromboplastin time correction method.

If the AHF level fails to reach expected levels or if bleeding is not controlled after apparently adequate dosage, the presence of AHF inhibitors should be suspected. By appropriate laboratory procedures, the presence of AHF inhibitors can be demonstrated and quantitated in terms of AHF units neutralized by each ml of plasma or by the total estimated plasma volume. After sufficient dosage to neutralize inhibitors, additional dosage produces predicted clinical response. It should be noted that when inhibitors are present, measurement of Lee White clotting time may be a better index of adequacy of dosage than measurement of circulating AHF.

In a classical hemophiliac, 30 years of age, with pre-existing AHF inhibitors, marked improvement was obtained by direct syringe infusion of HEMOFIL. During a 7-minute period, administration of 2,700 units overcame AHF inhibitors. Over a 43-day period, this patient received 44,000 units of AHF in six infusions with no ill effects.

OTHER USES

This concentrate is not known to contain clotting factors other than AHF in sufficient quantity to be useful therapeutically. The concentrate can be of significant value in patients (not true hemophiliacs) with acquired factor VIII inhibitors. For example, prompt clinical response was obtained with a similar preparation in a 54-year-old female with renal hemorrhage.[20] Prior to infusion, 1 ml of her plasma neutralized 15 units of AHF. After intravenous drip infusion of 35,000 units of AHF in 90 minutes, circulating inhibitors were overcome and hemostasis was obtained. A month later, her inhibitor level dropped from 15 units to 4 units, and her partial thromboplastin time shortened from 140 seconds to 88 seconds.

In such other uses, the dosage of the concentrate should be controlled by frequent laboratory determinations of circulating AHF. With constant monitoring of the patient's physical condition, the Method Four product can be administered as rapidly as possible. If the AHF inhibitor level is low (5,000 units or less in the total plasma volume), direct intravenous syringe injection may be used. With high inhibitor levels (over 5,000 units), rapid intravenous drip infusion is preferable.

CAUTIONS

Identification of the deficiency as one of Factor VIII is imperative before administration of this highly purified Antihemophilic Factor. No benefit may be expected from this product in treating other deficiencies.

This concentrate is prepared from large pools of fresh human plasma. Such plasma may contain the causative agents of viral hepatitis. There is no known laboratory test to demonstrate either the presence or the absence of such agents, and the concentrate has not been subjected to any treatment known to diminish the risk of transmission of hepatitis since such treatments greatly increase the loss of AHF activity during preparation. The concentrate should, therefore, be used when its expected effect is needed in spite of the unkn[redacted] hepatitis risk associated with its use. Special considerat[redacted] should be given to the use of this concentrate in newborns and infants where a higher morbidity and mortality may be associated with hepatitis.

No reactions have been reported similar to those described in individuals receiving multiple transfusions of plasma.[21-24] However the physician should be prepared to treat such a reaction if it should occur.

This preparation contains blood group isoagglutinins in amounts which are not clinically significant in the dosage needed to control hemarthroses and other relatively slight bleeding episodes in the absence of inhibitors. However, when larger or frequently repeated doses are needed, as when inhibitors are present or when pre- and post surgical care is involved, patients of blood groups A, B, and AB should be monitored for signs of intravascular hemolysis and falling hematocrit values. The only reported case[25] showing this phenomenon is that of a young 140-pound adult surgical patient of blood group A who received 43,000 AHF units over 40 days without ill effects, then in the following 9 days received 57,000 AHF units. During the latter 9 days, he exhibited progressive hemolysis, falling hematocrit, positive direct Coombs test, and circulating anti-A agglutinin. His anemia was corrected by the administration of compatible group O cells. The reported anti-A content of one lot of Antihemophilic Factor (Human) which he received is not typical of current production.

Since all solutions containing fibrinogen, as does HEMO[redacted] tend to cause the ground surfaces of glass syringes to stick, plastic (disposable) syringes are recommended whenever administration by syringe is desired.

The administration set and any concentrate not immediately injected should be discarded.

CONTRAINDICATIONS

There are no known contraindications to the use of this concentrate.

The free amino acid (glycine) content of the concentrate has been reduced to less than 0.02 gm per ml of reconstituted product. It is theoretically possible that very intensive therapy with this concentrate in a patient with severe liver or kidney damage could overload the "detoxification" mechanism, but no clinical or laboratory evidence of this has been seen.

RECONSTITUTION

When reconstituted as directed below, the solution appears stable, without potency loss, for at least twenty-four hours at room temperature (22° to 25°C). However, it is recommended that the solution be administered within three hours after reconstitution because of the possibility of bacterial contamination during reconstitution. The reconstituted material should not be refrigerated as irreversible precipitation of active material may occur.

1. Warm diluent (water) and concentrate in unopened bottles to between 30° and 37°C; keep at 30° to 37°C during reconstitution.
2. Remove metal seals and caps from concentrate and diluent bottles to expose central portions of rubber stoppers.
3. Cleanse stoppers with germicidal solution.

When furnished with administration set:

4. Remove protective covering from one end of double-ended needle, using care not to touch exposed end. Insert exposed needle through diluent stopper.

   NOTE: To transfer total volume of diluent, position lumen of needle in diluent bottle flush with inside of diluent stopper.
5. Remove protective covering from other end of double-ended needle, using aseptic precautions as above. Invert diluent bottle over upright concentrate bottle and insert free end of double ended needle through concentrate bottle stopper at point marked "IN." Vacuum in concentrate bottle will draw in diluent.
6. Disconnect the two bottles by removing needle from concentrate bottle stopper. Then agitate or rotate concentrate bottle until all concentrate is dissolved. Reconstitution usually requires less than 5 minutes, but may require longer. AHF activity is not diminished by holding the material at 30° to 37°C for as long as one hour. **Be sure that concentrate is completely dissolved; otherwise, active material will be removed by the filter.** The material is now ready for administration (see "A" below).

When intended for administration by syringe:

4. Without touching exposed needle, attach filter needle to syringe (use plastic syringe), withdraw entire contents of the diluent (water) bottle into syringe, then inject diluent into bottle of dry concentrate.
5. Withdraw needle from the concentrate bottle stopper, leaving needle on syringe, and protect needle from contamination. Agitate or rotate concentrate bottle until all concentrate is dissolved. Reconstitution usually requires less than 5 minutes, but may require longer. AHF activity is not diminished by holding the material at 30° to 37°C for as long as one hour. **Be sure that concentrate is completely dissolved; otherwise, active material will be removed by the filter.** Proceed with administration (see "B" below).

ADMINISTRATION

NOTE: To avoid precipitation of cold-insoluble globulin containing AHF activity, the solution should not be below room temperature during infusion.

A. Intravenous Drip Infusion

1. After reconstituting the concentrate as directed above, remove administration set from container.
2. Close control clamp tightly.
3. Fill the administration set with sterile saline; this will lessen the possibility of producing an extravascular clot during venipuncture.

4. Remove airway needle from tube covering stopper-puncture needle of set. With bottle in upright position, puncture stopper at "OUTLET" indentation with airway needle to relieve any pressure or vacuum in bottle; then insert airway needle through "AIR" indentation of stopper.

5. Remove and discard tube protecting stopper-puncture needle of set (near drip chamber) and insert needle through "OUTLET" indentation of stopper. Push needle into stopper only far enough for lumen to clear the stopper in order to administer all of contents. Suspend bottle in inverted position.

6. Gently squeeze and release drip chamber to allow it to partially fill with liquid if not already filled with saline.

7. Hold needle adapter at opposite end of tubing in upright position, remove plastic cover without disturbing needle, then remove and attach vein needle, taking care not to touch exposed end.

8. Open control clamp to displace any air bubbl[redacted] tubing and fill needle with liquid. Close clamp and insert vein needle into vein.

9. Open clamp and allow liquid to flow into vein as rapidly as is tolerated by the patient. Reduce flow rate (10 drops approximate 1 ml) if pulse rate rises significantly.

10. If cotton pledget in airway becomes moistened with solution, the pledget may be removed and the administration continued.

11. If the same patient is to receive more than one bottle of concentrate, the administration set may be removed from one bottle and inserted in the next, providing care is taken to avoid entrapment of air in the set. This practice avoids loss of concentrate in the set and makes additional venipunctures unnecessary. When administration of the concentrate is finished, it is desirable to again connect the administration set to a saline bottle and flush into the vein any concentrate remaining in the set. Avoid introduction of air into the tubing.

12. Discard administration set after use. Also discard any concentrate not used at one time.

CAUTION: Do not puncture drip chamber or tubing. Puncturing can cause an intake of air which may l[redacted] embolism. It is recommended that administration be made with administration set furnished since it contains a suitable filter.

Intravenous Syringe Injection

As a precautionary measure, the physican should determine the pulse rate before and during administration of the AHF concentrate. Should a significant increase of pulse rate occur, reduce the rate of administration or discontinue. Usually 10 to 20 ml may be injected over a 3-minute period.

1. After reconstituting the concentrate as described above, re-insert filter needle (on syringe) through the bottle stopper.

2. Inject air and aspirate the reconstituted AHF into the syringe.

3. Remove and discard the filter needle from the syringe; attach the 21x1 (vein) needle, and inject intravenously.

4. If the same patient is to receive more than one bottle of concentrate, the contents of two bottles may be drawn into the same syringe through filter needles before attaching the vein needle. For additional bottles, the same syringe may be refilled through filter needles; this practice lessens the loss of concentrate.

STORAGE

Hyland Antihemophilic Factor (Human), Method Four, Dried, HEMOFIL should be stored under ordinary refrigeration (2° to 8°C, 35° to 46°F). Freezing should be avoided as breakage of the diluent bottle might occur.

HOW SUPPLIED

Hyland Antihemophilic Factor (Human), Method Four, Dried, HEMOFIL® is furnished with a suitable volume of Sterile Water for Injection.

The number of units of AHF activity, as determined for each [illegible]s stated on the label of each bottle.

HEMOFIL Antihemophilic Factor (Human) has been processed and tested in accordance with requirements of the U.S. Public Health Service and is distributed under U.S. Government License No. 140.

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