pressure appear, the infusion rate should be decreased. In such instances it is advisable, initially, to stop the infusion until the symptoms disappear, then resume the infusion at a slower rate.

Administration: Use Aseptic Technique

When reconstitution of Factor IX Complex, Proplex T, is complete, its infusion should commence within three hours. However, it is recommended that the infusion begin as promptly as is practical.

The reconstituted material should be at room temperature during infusion.

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

A. Intravenous Drip Infusion

When a Hyland Immuno administration set is used, follow directions for use printed on the administration set container. When an administration set from another source is used, follow directions accompanying that set where necessary. The use of a Hyland Immuno administration set is recommended as it contains a suitable filter.

B. Intravenous Syringe Injection

1. Attach filter needle to syringe and draw back plunger to admit air into the syringe.
2. Insert needle into the reconstituted Factor IX Complex.
3. Inject air into bottle and then withdraw the reconstituted material into the syringe.
4. Remove and discard the filter needle from the syringe; attach a suitable needle and inject intravenously at a rate **not exceeding 3 mL per minute**.
5. If patient is to receive more than one bottle of concentrate, the contents of two bottles may be drawn into the same syringe, by drawing up each bottle through a separate unused filter needle. This practice lessens the loss of concentrate. Please note, filter needles are intended to filter single bottles of Factor IX Complex only.

How Supplied

Factor IX Complex, Proplex T, is furnished with a suitable volume of Sterile Water for Injection, USP; a double-ended needle; and a filter needle.

Storage

Factor IX Complex, Proplex T, should be stored under ordinary refrigeration (2 to 8˚C, 36 to 46˚F). Avoid freezing to prevent damage to the diluent bottle.

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Factor IX Complex Heat Treated Proplex T

Warning: This is a potent drug with potential hazards. For maximal safety and efficacy, carefully read and follow directions below.

Description

Factor IX Complex, Heat Treated, Proplex T*, is a sterile product prepared from pooled normal human plasma. It contains, in concentrated form, clotting Factors II (prothrombin), VII (proconvertin), IX (PTC, antihemophilic factor B), and X (Stuart-Prower factor). Other proteins are also present in minimal amounts. The product also contains a small amount of heparin, 1.5 units or less per mL of reconstituted material, as a stabilizing agent. This amount does not affect the clinical usefulness of the complex in moderate dosage.

Factor IX Complex **must** be administered intravenously.

During the manufacturing process, this product was heated for 144 hours at 60˚C. This heating step was designed to reduce the risk of transmission of hepatitis and other viral infections. No procedure has been shown to be totally effective in removing viral infectivity from Factor IX Complex.

Clinical Pharmacology

Factor IX Complex is a combination of vitamin K-dependent clotting factors found in normal plasma. The administration of Factor IX Complex, Proplex T, provides an increase in plasma levels of Factor VII and Factor IX and can temporarily correct the coagulation defect of patients with deficiencies in these factors. Plasma levels of Factors II and X will also be increased.

The half-life of Factor VII in non-treated Factor IX Complex administered to Factor VII deficient patients has been found to range from 3 to 6 hours.[1,2]

The half-life of Factor IX in non-treated Factor IX Complex administered to Factor IX deficient patients has been found to range from 24 to 32 hours.[3,4]

The effectiveness of the heating step in reducing viral infectivity was assessed by *in vitro* viral inactivation studies using, as markers, viruses not commonly found in plasma. When known quantities of these viruses were added to the product, the heat treatment employed inactivated the following quantities of virus:

Sindbis	10.5 Log_{10}
Vesicular Stomatitis	5.6 Log_{10}
Pseudorabies	1.4 Log_{10}

In addition, it has been shown that Cytomegalovirus does not survive the manufacturing process. As these data indicate, all viruses are not equally affected by the heat treatment. Work by Colombo, *et al* with first-exposure hemophiliacs who received heat treated Antihemophilic Factor (Human) shows that while some reduction of hepatitis infectivity may have been achieved by heat treatment, a substantial portion of the patients who had not previously received blood products developed signs and/or symptoms of hepatitis.[5] (See **Warnings**).

*Manufactured under U.S. Patent No. 4,495,278.

It has been reported that HIV is heat labile and that it is inactivated by treatment with 19-20% alcohol.[6,7,8] Lengthy exposure to 20% ethanol occurs in the Cohn cold ethanol fractionation procedure from which this product is derived. In a retrospective study conducted with patients receiving Anti-Inhibitor Coagulant Complex, Autoplex, which is also derived from the Cohn process, none of the patients who received Anti-Inhibitor Coagulant Complex, Autoplex, exclusively seroconverted for HIV antibodies, while 56% of those patients who received other treatment modalities seroconverted during the three year study.[9] Heat treatment has also been shown to be an effective means of inactivating HIV.[10] In a study comparing heat treated Antihemophilic Factor (Human), Hemofil T, to untreated Antihemophilic Factor (Human) products, none of the patients receiving the heat treated product developed antibodies to HIV, while 17% of the patients receiving untreated products did seroconvert by the end of the study.[11]

Indications and Usage

Factor IX Complex, Proplex T, is indicated for:

1. Factor IX deficiency (Hemophilia B, Christmas disease). The intravenous administration of Factor IX Complex, Proplex T, is intended to prevent or control bleeding episodes in patients with this deficiency. Factor IX Complex should not be used in patients with mild Factor IX deficiency for whom fresh frozen plasma is effective.
2. Bleeding episodes in patients with inhibitors to Factor VIII. Lusher, *et al*,[12] have described the use of Factor IX Complex in hemarthroses occurring in hemophiliacs with inhibitors to Factor VIII.
3. Factor VII deficiency. The Factor VII content present in Factor IX Complex, Proplex T, has been shown to be effective in prevention or control of bleeding episodes in patients with Factor VII deficiency.[13]

Contraindications

None known.

Warnings

The use of Factor IX Complex is potentially hazardous in patients with signs of fibrinolysis and in patients with disseminated intravascular coagulation (DIC).

This product is prepared from pooled human plasma which may contain the causative agents of hepatitis and other viral diseases. Prescribed manufacturing procedures utilized at the plasma collection centers, plasma testing laboratories, and the fractionation facilities are designed to reduce the risk of transmitting viral infection. However, the risk of viral infectivity from this product cannot be totally eliminated.

Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly non A, non B hepatitis.

Precautions

General

Identification of the deficiency as one of either Factor IX, Factor VII or Factor VIII with inhibitors is essential before administration of the Factor IX Complex, Proplex T, is initiated.

With the exception of its use in treating hemarthroses occurring in Factor VIII-inhibitor patients, no benefits may be expected from this product in treating deficiencies other than those of Factor IX or Factor VII.

Caution: It is important that the dosage regimen chosen is carefully evaluated with respect to the entire spectrum of factors present in this product. Levels of Factors II, IX and X should be monitored during therapy to prevent unnecessarily high levels of these factors, which may increase the risk of intravascular coagulation. Factor IX Complex, Proplex T, is prepared by calcium phosphate absorption of cold ethanol precipitated material and therefore, contains higher ratios of Factor VII and Factor X to Factor IX than products prepared by Sephadex exchange.[14]

The use of high doses of prothrombin complex concentrates has been reported to be associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism.[1, 12, 15, 16]

If signs of intravascular coagulation, thrombosis, or emboli occur, which include changes in blood pressure and pulse rate, respiratory distress, chest pain and cough, the infusion should be stopped promptly. In general, the risk of enhancing DIC may be reduced by raising the patient's Factor VII or Factor IX level to not more than about 50% of normal. If the need exists to raise the patient's Factor IX or Factor VII level higher than 50% of normal, the physician should monitor infusion of material to detect signs and symptoms of DIC.

Special caution should be taken in the use of this concentrate in newborns, where a higher morbidity and mortality may be associated with hepatitis, and in individuals with pre-existing liver disease.

Laboratory Tests

Since the dosage of Factor IX Complex, Proplex T is calculated on the basis of its potency, frequent laboratory tests to monitor the effectiveness of treatment usually are unnecessary. This is particularly true for single dose treatment of an uncomplicated hemarthrosis. However, if a major bleeding episode is being treated in the hospital, or if adequate hemostatic levels of Factor VII or Factor IX are needed to permit performance of surgery, Factor VII or Factor IX assays should be performed at least once a day, prior to infusion, to ensure that the daily dose of Factor IX Complex is sufficient to maintain adequate levels of the desired clotting factor.

Pregnancy

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

Adverse Reactions

As with other plasma preparations, reactions manifested by chills and fever may occasionally be seen,[17,18] particularly when large doses of Factor IX Complex, Proplex T, are administered.

A rate of infusion that is too rapid may cause headache, flushing, and changes in pulse rate and blood pressure. In such instances, stopping the infusion allows the symptoms to disappear promptly. With all but the most reactive individuals, the infusion may be resumed at a slower rate. (See **Rate of Administration**.)

The risk of thrombosis is present with the administration of Factor IX Complex.

Dosage and Administration

Each bottle of Factor IX Complex, Proplex T, is labeled with both the Factor IX and Factor VII content. The Factor IX content is expressed in International Units per bottle and is traceable to the World Health Organization International Standard through a secondary concentrate standard. The Factor VII content is expressed in units per bottle and is traceable to pooled normal plasma through a secondary standard.

The amount of Factor IX Complex, Proplex T, required to restore normal hemostasis varies with the circumstances and with the patient. Dosage depends on the degree of deficiency and the desired hemostatic level of the deficient factor. As a guide to calculation of dosage, experience[4,19] indicates that the following formulas may be used:

Factor IX Deficiency

Units required to raise blood level percentages:

1.0 unit/kg x body weight (in kg) x desired increase (% of normal)

If a 70 kg (154 lb) patient with a Factor IX level of 0% needs to be elevated to 25%, give 1.0 unit/kg x 70 kg x 25 = 1750 units

In preparation for an following surgery, levels above 25%, maintained for at least a week after surgery, are suggested. Laboratory control to assure such levels is recommended. To maintain levels above 25% for a reasonable time, each dose should be calculated to raise the level to 40% to 60% of normal. (See **Precautions**.)

The preceding dosage formula for Factor IX deficiency is presented as a reference and a guideline. Exact dosage determinations should be made based on the medical judgment of the physician regarding circumstances, condition of patient, degree of deficiency, and the desired level of Factor IX to be achieved. If inhibitors to Factor IX appear to be present, sufficient additional dosage to overcome the inhibitor would be needed.

For maintenance of an elevated level of the deficient factor, dosage may be repeated as often as needed. Clinical studies suggest that relatively high levels may be maintained by daily or twice-daily doses, while the lower effective levels may require injections only once every two or three days. A single dose may be sufficient to stop a minor bleeding episode.[20,21]

Factor VIII Inhibitor

In using Factor IX Complex in the treatment of hemarthroses occurring in hemophiliacs with inhibitors to Factor VIII, dosage levels approximating 75 Factor IX units per kg of body weight have been employed.[12]

Anti-Inhibitor Coagulant Complex, Autoplex T, is recommended when hemarthroses occurring in hemophiliacs with inhibitors to Factor VIII cannot be resolved by administration of Factor IX complex, and in other types of bleeding episodes in Factor VIII-inhibitor patients.

Factor VII Deficiency

Units required to raise blood level percentages:

0.5 unit/kg x body weight (in kg) x desired increase (% of normal)

Repeat dose every 4 to 6 hours as needed.

If a 70 kg (154 lb) patient with a Factor VII level of 0% needs to be elevated to 25%, give 0.5 unit/kg x 70 kg x 25 = 875 units.

In preparation for and following surgery, levels above 25%, maintained for at least a week after surgery, are suggested. Laboratory control to assure such levels is recommended. To maintain levels above 25% for a reasonable time, each dose should be calculated to raise the level to 40 to 60% of normal. (See **Precautions**).

The preceding dosage formula for Factor VII deficiency is presented as a reference and a guideline. Exact dosage determinations should be made based on the medical judgment of the physician regarding circumstances, condition of patient, degree of deficiency, and the desired level of Factor VII to be achieved. If inhibitors to Factor VII appear to be present, sufficient additional dosage to overcome the inhibitor would be needed.[22,23]

Reconstitution: Use Aseptic Technique

1. Bring Factor IX Complex, Proplex T, (dry concentrate) and Sterile Water for Injection, USP, (diluent) to room temperature.
2. Remove caps from concentrate and diluent bottles to expose central portions of rubber stoppers.
3. Cleanse stoppers with germicidal solution.
4. Remove protective covering from one end of double-ended needle and insert exposed needle through diluent stopper.
5. Remove protective covering from other end of double-ended needle. Invert diluent bottle over the upright concentrate bottle, then rapidly insert free end of the needle through the concentrate bottle stopper at its center. The vacuum in the concentrate bottle will draw in the diluent.
6. Disconnect the two bottles by removing needle from diluent bottle stopper, then remove needle from concentrate bottle. Swirl or rotate bottle until all material is dissolved. Be sure that the material is completely dissolved, otherwise active material will be removed by the filter.

Note: do not refrigerate after reconstitution.

Rate of Administration

Factor IX complex should be infused slowly, at a rate of approximately two to three mL per minute. If headache, flushing, changes in pulse rate or blood