File FVIII.
0025

HUMAN ANTIHAEMOPHILIC FRACTION
INTERMEDIATE PURITY FACTOR VIII

This fraction is a concentrate of human blood coagulation factor VIII prepared from the plasma of voluntary blood donors by methods based on those of Newman et al (1971) and James and Wickerhauser (1972). It is prepared on behalf of the Department of Health and Social Security in laboratories at Elstree and Oxford (headquarters, Blood Products Laboratory, Lister Institute of Preventive Medicine, Elstree, Herts. WD6 3AX). The name of the manufacturing laboratory is stated on label.

The fraction is usually available only through Haemophilia Centres as these have the assay facilities needed to monitor its use. The treatment of patients with deficiencies of coagulation factors requires clinical expertise and, whether undertaken at hospital or at home, should always be directed by a doctor, experienced in the management of haemorrhagic disorders.

Storage:

Factor VIII is a labile protein. The material may be stored in a deep-freeze at -40°C for more than a year without detectable loss of potency. As this is not always possible, the label carries the instruction: "Store in the dark at below +6°C" and a statement of the activity at the time of preparation. During a year at 4° to 6°C some activity may be lost and in the latter part of the storage period allowance for a 10% loss should be made when calculating the dose (see below).

Reconstitution:

The container of concentrate and the water for solution should be brought to 30° to 37°C. The volume of sterile pyrogen-free distilled

water indicated on the label is then added to the freeze-dried material, and the container is agitated gently until solution is complete. A clear or slightly opalescent solution is usually obtained in about fifteen minutes or less. If a gel or clot forms discard the solution and inform the laboratory (address on the bottle). Should more than one container be required to make up the dose, the contents of the required number of containers are pooled.

Administration:

Transfusion should be started as soon as solution is complete. Although the material rarely causes side effects, the dose, especially the first dose, should be given slowly (approximately 3 ml per minute). The solution must not be stored and it is recommended that infusion should be completed within three hours of reconstitution. The material must not be given by "continuous infusion" over many hours, and it should not be added to any other fluid given, including whole blood.

A No. 21 "butterfly" needle is convenient for giving the solution, using either a syringe or transfusion set according to the size of the dose. Plastic disposable syringes should be used, as ground glass syringes tend to stick with this solution .

Dose:

The number of units needed and duration of treatment depend on the lesion being treated. If the rise in the concentration of factor VIII in the plasma following administration of concentrate is expressed in international units per 100 ml plasma and the total dose given in international units of factor VIII per kg body weight is calculated, "the response" is defined by the ratio:

$$\text{Response} = \frac{\text{Rise in plasma factor VIII (in international units per 100 ml)}}{\text{Dose in international units/kg body weight}}$$

The 'theoretical value' for this ratio (2·4) is rarely reached. It is variable even in the same patient; a range of 1·6 - 2·2 is usual but values outside this range may be found. A low value may indicate that the plasma contains an antibody to factor VIII and appropriate tests should be done.

The following table indicates the approximate levels of factor VIII required for haemostasis in various circumstances.

| Lesion | Concentration of factor VIII desired in patient's blood immediately after transfusion (iu per 100 ml) | Initial dose of factor VIII (iu/kg body weight) |
|---|---|---|
| Minor spontaneous haemarthrosis, and muscle haematoma. | 15 - 20 | 7 - 13 |
| Severe haemarthrosis and muscle haematoma, haematoma in potentially dangerous situations; haematuria | 20 - 40 | 9 - 25 |
| Major surgery | See below | |

A dose of 1 iu/kg will give, on average, a rise of about 2 iu/100 ml plasma. If the desired concentration or clinical response is not achieved, another dose should be given the same day. If an abnormally low response persists, carry out a test for specific antibody to factor VIII. The doses mentioned are only rough guides since there is considerable variation in response from patient to patient. It is usual to give the contents of the number of whole containers nearest to the calculated dose. Doses may be repeated at intervals of 8, 12 or 24 hours as needed to maintain the desired concentration of factor VIII.

Major surgery:

Major surgery should be undertaken only where there are facilities for assaying factor VIII so that the patient's response can be assessed. The patient's plasma should be tested for antibody to factor VIII before operation. If antibody is not present, a pre-operative dose of 35-50 iu per kg is given to raise the plasma factor VIII concentration to 80% or more of average normal. During the first few days after operation the plasma factor VIII concentration is monitored and the dose repeated 6-hourly or 8-hourly as needed, so that the concentration does not fall below 30-50% of average normal. After the first few days the frequency of the dose may be reduced. The course of treatment must usually be continued for ten days or longer.

If the plasma factor VIII concentration does not reach the expected level, or falls off with a reduced half-life (less than twelve hours), the presence of an antibody to factor VIII should be suspected and the appropriate laboratory tests done. The treatment of patients with antibodies to factor VIII is outside the scope of these notes.

Warning:

(1) Intermediate purity factor VIII concentrate contains blood group antibodies derived from the starting plasma in amounts which are insignificant in the normal treatment of haemarthrosis and muscle haemorrhage. If very large doses have to be given to a patient belonging to blood group A, B or AB, watch should be kept for signs of intravascular haemolysis.

(2) All donations of blood from which plasma is derived for the preparation of this fraction are screened for the presence of $HB_sAg$ by

radioimmunoassay or reversed passive haemagglutination and each batch of concentrate is tested by radioimmunoassay. Nevertheless the most sensitive tests cannot eliminate the possibility that the fraction may be icterogenic. Therefore the risk of transmitting hepatitis cannot be disregarded.

(3) Patients congenitally deficient in factor VIII may develop antibodies to factor VIII following treatment. This risk does not appear to be increased by the use of concentrate (Biggs, 1974) but patients should be monitored from time to time, especially if there is any doubt about the clinical effectiveness of a dose of factor VIII.

References:

Biggs, R. (1974) Jaundice and antibodies directed against factor VIII and IX in patients treated for haemophilia or Christmas disease in the United Kingdom. British Journal of Haematology, 26, 313-329.

Newman, J., Johnson, A.J., Karpatkin, M.H. & Puszkin, S. (1971) Methods for the preparation of clinically effective intermediate- and high-purity factor VIII concentrates. British Journal of Haematology, 21, 1-20.

James, H.L. & Wickerhauser, M. (1972) Development of large-scale fractionation methods III Preparation of a factor VIII concentrate of intermediate-purity. Vox Sanguinis, 23, 402-412.

Johnson, A.J., Karpatkin, M.H. & Newman, J. (1971) Clinical investigation of intermediate--and high purity antihaemophilic factor (factor VIII) concentrates. British Journal of Haematology, 21, 21-41.

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