

APPENDIX C(i)

U.K. HAEMOPHILIA CENTRE DIRECTORS HEPATITIS WORKING PARTYFactors to be considered in the Selection of Hepatitis Reduced Products for Clinical Trial - Evaluation of residual infectivity for Hepatitis Viruses

Several manufacturers will shortly be in a position to offer trial batches for evaluation of their residual infectivity according to the trial protocols recently considered by the Reference Centre Directors and circulated to all Directors.

These products seem to be of 3 types:-

- 1) The freeze dried product is heated in the presence of compounds (e.g., sucrose) which stabilise the factor VIII activity, but reduce the quantity of infective virus in the product by pasteurisation. Heat inactivation is applied to the point where there is no significant loss of factor VIII coagulant activity. The temperature is usually 60°C, the exact conditions are a commercial secret, but the heat is known to be applied after the freeze drying process.

Two such products are:-

(i) Hemofil T (Exception from Clinical Trial Certificate obtained) - trial now underway

(ii) Factorate HT - available in 3 months

- 2) The plasma is treated with chemicals (e.g., β -propiolactone + U.V. light in the presence of detergent) or (Tween 80) which render the viruses uninfected while preserving the coagulant activity. The products involved are:-

Factor VIII manufactured by BIOTEST in West Germany - no plans are likely to involve trials of this product in the U.K. There is about a 25% loss of factor VIII activity.

Kryobulin (Immuno) - still under development; available later this year?

- 3) The product is pasteurised by heating at 60°C in the presence of stabilisers for factor VIII, but this is done under conditions where hepatitis B virus may be inactivated. The strains of non-A, non-B hepatitis virus which are used experimentally in chimpanzees have been found to be more heat labile than hepatitis B and are assumed to be destroyed by this process. Unfortunately this reduces the factor VIII activity by 50% and this means that the product price would be high (? 40p per factor VIII unit).

Bchringwerke A.G., manufacturers of Germany have developed such a product which has undergone clinical trial in Germany. It is unlikely that they would consider applying for a British product licence unless an approach was made to them. Since their unheated product is not marketed here this may take some time.

Factorate HT will be available within 3 months, and presumably exception for a Clinical Trial Certificate will be obtained in due course.

Opinion i) The degree of heat treatment received by both American products may lessen the infection risk for non-A, non-B hepatitis viruses, but by what degree can only be ascertained by clinical trial in human subjects.

It is unlikely that the hepatitis B virus infection will be significantly affected by the heat treatments used in the above products. Hepatitis B vaccine will have to be used to eliminate this risk.

- ii) Both the German products from Behringwerke and Biotest seem to be likely to have a significant reduction of their contamination rates with hepatitis B and non-A, non-B viruses, but the significant loss of factor VIII activity will increase the price of this product and might produce shortages of supply if the demand was high. Thirty-one batches have been used in a clinical trial with, so far, no cases of hepatitis. However, details of the precise classes of patient studied are not yet available.
- iii) The Acquired Immune Deficiency Syndrome (AIDS) and transfusions of factor VIII. So far 16 cases of this syndrome which fit the criteria used by the Centre for Disease Control (CDC) Atlanta, Georgia, have been reported in the U.S.A. Five cases have been reported from Europe. This includes the suspect case notified to me recently in the U.K. Though the incidence in U.S. haemophiliacs is low (1 case per 1,500 persons at risk) and there is, as yet, no hard evidence relating specific products or batches to particular cases, the infective theory for the causation of this disease is still the one that fits all the known facts about AIDS.

Consideration must, therefore, be given to the possibility that factor VIII concentrate prepared from plasma donations obtained in the U.S.A. might be contaminated with a putative infectious agent associated with the cause of AIDS.

Since there is no information as to the physical characteristics of such an agent, the materials used to reduce the risk of transfusion hepatitis, such as heat treatment, cannot be relied upon to render factor VIII concentrate manufactured from the same plasma free from such an agent. The only product which may be free from the risk, and is made from U.S. commercial plasma, is the Merck, Sharp and Dohme hepatitis B vaccine and this is treated with formalin, pepsin at pH2 and 8 molar urea. All the commercial heat treated products and the Biotest brand of factor VIII are made in part from plasma obtained from commercial sources in the U.S.A. There is, as yet, no product which is not made from sources likely to carry a risk of a putative virus associated with AIDS being present in the plasma pool from which the factor VIII is fractionated and which is heat treated.

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This will cause a problem when the criteria for clinical trials of these products in the U.K. have to be considered. Since the only way of ensuring the susceptibility to non-A, non-B viruses is by using patients who have not previously received factor VIII or IX concentrate, a choice will have to be made between using heat treated products from commercial sources, which might carry a small risk of AIDS transmission, or using NHS concentrate which appears to carry a 100% chance of transmitting non-A, non-B hepatitis.

There is, therefore, a considerable ethical problem when considering the evaluation of the new heat treated products for their residual infectivity in clinical trials in patients infrequently treated with factor VIII who have no prior exposure to freeze dried concentrate.

It is to be hoped that a hepatitis reduced product will be available from NHS sources before long.

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