Public Health Laboratory Service

Public Health Laboratory
Withington Hospital
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22nd March, 1983

Our ref JC/PH Your ref

DRAFT LETTER

Dear Director,

TRIALS OF 'HEPATITIS REDUCED' FACTOR VIII

The Hepatitis Working Party has drawn up the enclosed protocol, as a result of discussions at the Haemophilia Reference Centre Directors meeting, for use in trials of this product to assess the efficacy of the different methods used for the removal of hepatitis viruses. You will see that the class of patients to be given these products are those who have had no previous treatment with factor VIII concentrate.

It is likely that there are only a limited number of these patients in the U.K. who will require factor VIII therapy in any one year. We will be grateful if you would notify Dr. J. Craske of any approaches from commercial firms with a proposal to evaluate their product.

From our calculations, it is possible that all products likely to come onto the market within the next year can be catered for if the trials are arranged on a collaborative multi-Centre basis. There is a danger that the firm whose product is first on the market will use up all suitable patients if a number of Centres evaluate the product without exchanging information. This would mean that a year or so may elapse without adequate trials being arranged for other products. It is also important to ensure that the firm concerned agrees to adhere to the protocol as outlined in the enclosed documents.

We hope that this will encourage you to identify suitable patients for inclusion in the trial so that these can be located before any products become available. Discussions can then proceed when the number of patients available and the number of products for evaluation is known.

Thank you for your co-operation.

Yours sincerely,

J.Craske
Charles Rizza
Arthur Bloom

U.K. HAEMOPHILIA HEPATITIS WORKING PARTY

# TRIALS OF 'HEPATITIS REDUCED' FACTOR VIII CONCENTRATE IN THE N.H.S. - ASSESSMENT OF RESIDUAL INFECTIVITY

## INTRODUCTION

The recent development of 'hepatitis reduced' factor VIII, where attempts have been made to reduce the infectivity of concentrates due to hepatitis viruses by pasteurisation, β-propiolactone, UV light and chemical treatment, has made it important to obtain objective evidence as to the safety of these products with regard to (1) the risk of transfusion of hepatitis, (2) the survival of factor VIII in vivo and (3) tests to exclude the presence of immune complexes and other factors which might cause allergic reactions. This is to exclude the possibility that the methods used to inactivate hepatitis viruses in factor VIII concentrate might alter or denature other plasma proteins present.

Trials for (2) and (3) can be carried out by evaluating the use of 'hepatitis free' concentrate in severe haemophiliacs on regular factor VIII therapy. The assessment of residual infectivity of concentrate for non-A, non-B hepatitis and hepatitis B can only be carried out on patients known to be susceptible to non-A, non-B hepatitis. A prospective study (a) of 30 patients each given one or two batches of factor VIII to cover an operative procedure or other treatment requiring concentrate showed that all 9 patients who had not received blood concentrates before, contracted non-B hepatitis after receiving their first transfusion of either U.S. commercial factor VIII or NHS factor VIII.

It is proposed to assess the residual infectivity of brands of 'hepatitis reduced' factor VIII by means of a clinical trial in patients who have not previously been treated with factor VIII or IX concentrate.

## METHODS

The decision to include any patient in these trials will be made by the Director of the local Haemophilia Centre responsible for the care of any patient, based on the following criteria:-

Subjects will be selected from infrequently treated patient groups who have not previously been treated with factor VIII concentrate. They should not have received any blood products in the 6 months prior to entry into the trial, and preferably have received less than 50 donor units of cryoprecipitate ( or 3500 factor VIII units) in the past. They should also be $HB_sAg$, Anti-$HB_s$ and Anti-$HB_c$ negative. The actual criteria used will depend on the number of patients available; the group with the least previous exposure to blood products will be chosen. They should also have had no previous hepatitis. A record of their transfusion history and past hepatitis should be included in the case notes for the trial.

For each new product it is intended to prospectively follow the occurrence of hepatitis in a series of 10 patients. Five batches will be studied; each batch will be given to 2 patients, so that 10 patients will be treated with each product under evaluation.

## PROCEDURE

Patients attending any of the collaborating Haemophilia Centres during the course of the project who fulfill the criteria given will be admitted to the study. The object of the study will be explained to them, and their consent or that of their parents obtained, if under 16 years of age.

Prior to the start of treatment each patient will undergo a full clinical examination, with special reference to liver disease, and blood will be taken for hepatitis A and B antibody and a full blood count and liver function tests before treatment is started. A record should be made of their detailed transfusion history and past attacks of hepatitis. If the patient is seen as an emergency, then as many tests will be performed as is compatible with the situation.

Patients will be followed up for 52 weeks following their treatment episode in the absence of any transfusion hepatitis. Liver function tests and tests for hepatitis A and B markers, CMV and EBV will be carried out at appropriate intervals. Blood will be collected before treatment and at weeks, 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 40 and 52 post-transfusion. If a patient develops evidence of acute hepatitis, his liver function tests and hepatitis B serology will be followed fortnightly until his condition resolves, or for 3 months after the onset, and if his condition has not resolved, then monthly for six months. Follow-up after this will be 3 monthly for the next 2 years.

## DEFINITION OF HEPATITIS

A patient will be considered to be suffering from acute hepatitis if he develops clinical symptoms and signs as described in form C1, or shows an increase of at least two and a half times the upper limit of normal serum aminotransferase levels, having had normal values previously.

Hepatitis will be classified as acute icteric (raised serum bilirubin)
.. anicteric
.. symptomless

This may be of two varieties; - hepatitis B or non-A, non-B. Hepatitis A, cytomegalovirus infection, glandular fever and toxoplasmosis will be excluded by appropriate laboratory tests.

## LABORATORY TESTING

It is hoped that the sera obtained from patients in this project will be made available to the Hepatitis Working Party for use when tests for non-A, non-B hepatitis become available. A collection of sera from 40 patients treated with factor VIII and IX both NHS and commercial currently used in the U.K. in a prospective study at the Oxford Haemophilia Centre have been established at the Public Health Laboratory, Withington Hospital, Manchester by Dr. Craske.

While the basic laboratory tests may be carried out at the Microbiology Laboratory serving the local Haemophilia Centre, stored aliquots of each specimen (2.0ml serum) obtained from all patients during the period of follow-up should be sent to Dr. J. Craske, Public Health Laboratory, Withington Hospital, Manchester M20 8LR. Any tests not available locally can be arranged by request to Dr. Craske. This will provide a more stringent test of the inactivation procedure used in the preparation of 'hepatitis reduced' factor VIII. Advantage must therefore be taken of this unique opportunity to make a collection of specimen obtained in this study.

## FOLLOW-UP

Patients whose liver function tests remain elevated for one year after the acute attack of non-A, non-B hepatitis or become carriers of hepatitis B virus will be referred to the local liver clinic for investigation of chronic liver disease. Liver biopsy will not be carried out unless clinically indicated.

TRANSFUSION RECORDS

Detailed transfusion records will be kept for all patients followed in the project. Copies of the completed follow-up form T1 will be sent to Dr. Craske at the end of the study.

RESULTS

At appropriate intervals in the project, the incidence of acute hepatitis, both B and non-A, non-B, will be assessed in relation to:-

1) The type of produce transfused

2) The transfusion history of each patient

3) The disease category and severity of coagulation defect of each patient.

4) The ratio of symptomatic to symptomless cases of hepatitis for hepatitis B and non-A, non-B hepatitis.

5) The age of the patients

6) The amount of factor VIII or IX transfused to each patient

7) The attack rate for each brand of product

8) The incidence of chronic sequelae for each product and type of hepatitis

The record form of each patient will be reviewed by Dr. Craske and the Director of the Haemophilia Centre caring for the patient. The results of the trial and the conclusions of the Hepatitis Working Party on the implications of the results will be reported to the Committee of the Haemophilia Centre Reference Directors. The manufacturers of the product under trial will be sent a report of the trial, with copies to the Medicines Division, D.H.S.S., and Dr. Walford, D.H.S.S.

REFERENCE

a) Craske, J., Fletcher, Mary, Paver, K.W., Rizza, C.R., Spooner, R.J.D., and Trowell, Joan. Factor VIII and IX related non-A, non-B hepatitis:- preliminary results of a prospective study of patients treated with NHS concentrate - In Preparation.

J. Craske 22.3.83.
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