TRIAL OF SNBTS 'HEPATITIS REDUCED' FACTOR VIII CONCENTRATE - 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, -propriolactone, 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, South of the border, 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 US commercial factor VIII or NHS factor VIII.

It is proposed to assess the residual infectivity of SNBTS 'hepatitis reduced' factor VIII by means of a clinical trial in patients who have not previously been treated with large pool factor VIII concentrates.

METHODS

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 in the past. They should also be HBsAg, anti-HBs and anti-HBc 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.

PROCEDURE

Patients attending any of the collaborating Haemophilia Centres during the course of the project who fulfil 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 12 months 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 (see below). Blood will be collected before treatment and at weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 40 and 52 weeks post-transfusion. Follow-up after the 52 week study will be 3 monthly for the next 2 years. 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.

DEFINITION OF HEPATITIS

A patient will be considered to be suffering from acute hepatitis if he develops relevant clinical symptoms and signs, or shows an increase of at least two and 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 held for use when tests for non-A, non-B hepatitis become available.

While the basic laboratory tests may be carried out at the Microbiology Laboratory serving the local Haemophilia Centre, stored aliquots of each specimen (2.0 ml serum) obtained from all patients during the period of follow-up should be sent to Dr R J Crawford at the Glasgow & West of Scotland Blood Transfusion Centre, Law Hospital, Carluke, Lanarkshire. Any tests not available locally can be arranged by request to Dr Crawford. 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 opportunit to make a collection of specimens 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 may be referred to the local liver clinic for investigation of chronic liver disease. Liver biopsy will not be carried out unless indicated in the clinical management of individual patients.

TRANSFUSION RECORDS

Detailed transfusion records will be kept for all patients followed in the project. Copies of the completed follow-up form should be sent to Dr R J Crawford 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 transfusion history of each patient

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

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

(4) The age of the patients

(5) The amount of factor VIII transfused to each patient

(6) The attack rate

(7) The incidence of chronic sequelae and the type of hepatitis.

It is the intention of the SNBTS to make the data from the studies available to the UK Haemophilia Centre Hepatitis Working Party.

REFERENCE

Fletcher, M L, Trowell, J M, Craske, J, Pavier, K and Rizza, C R. Non-A, non-B hepatitis after transfusion of factor VIII in infrequently treated patients. BMJ, 287, 1754

ASSESSMENT OF RESIDUAL INFECTIVITY OF SNBTS "HEPATITIS REDUCED" FACTOR VIII CONCENTRATES FOR NON-A, NON-B OR HEPATITIS B VIRUSES

VIRAL HEPATITIS FOLLOW-UP*

ıtient	SURNAME:	PRODUCT UNDER TRIAL
	FORENAME(S):	HAEMOPHILIA CENTRE
	D.O.B.	FACTOR VIII LEVEL
	DIAGNOSIS:	

revious history of hepatitis

ıte of last treatment:

ɜasoɯ for current treatment — Batch No. of concentrate:

ıte of current treatment — Amount (Factor VIII Units)

ST ENQUIRY		PRE-TREATMENT SAMPLE DATE	FOLLOW-UP DATES				
ilirubin (µmol/l)							
lanine amino-ransferase (iu/l)							
spartate amino-ransferase (iu/l)							
lkaline phosphatase							
BsAg**	R I A						
ıti-HBc	RIA						
ati-HBs							
ati-HAV							
ati-HAV IgM							
ati-CMV							
ati-EBV							
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istory of transfusion ince last seen enter Yes/No f Yes Product and Date)							

'atient	SURNAME:	PRODUCT UNDER TRIAL
	FORENAME(S):	HAEMOPHILIA CENTRE

EST ENQUIRY		PRE-TREATMENT SAMPLE	FOLLOW-UP DATES				
ilirubin (µmol/l)							
lanine amino-ransferase (iu/l)							
spartate amino-ransferase (iu/l)							
lkaline phosphatase							
Bs. *	RIA						
nti-HBc	RIA						
nti-HBs							
nti-HAV							
nti-HAV IgM							
nti-CMV							
nti-EBV							
linical illness uggestive of hepatitis in[illegible] last seen en[illegible] Yes/No)							
istory of transfusion ince last seen enter Yes/No f Yes Product and Date)							