A PROSPECTIVE STUDY OF THE INCIDENCE OF ACUTE AND CHRONIC HEPATITIS IN HAEMOPHILIACS AS A RESULT OF FIRST EXPOSURE TO FACTOR VIII AND IX CONCENTRATE OR CRYOPRECIPITATE.

INTRODUCTION

The hepatitis surveillance programme at Oxford has shown that the group of haemophiliacs with the highest incidence of acute hepatitis are those patients exposed to freeze dried concentrate for the first time(1). Most of these are patients with mild coagulation defects who require few transfusions, usually of cryoprecipitate only. Since the risk of chronic hepatitis following an acute attack of non-A, non-B hepatitis after a transfusion of factor VIII concentrate is between 20 and 40%, it is important that an accurate estimate should be made of the incidence of transfusion hepatitis in this group.

A preliminary study carried out at the Oxford Haemophilia Centre showed that 9 out of 9 patients treated with factor VIII or IX concentrate for the first time contracted non-A, non-B hepatitis. Seven of these patients were given NHS factor VIII with a pool size of between 1426 and 2504 plasma donations per batch.(2)

It is proposed to extend these observations by undertaking similar studies in other Haemophilia Centres to compare the incidence of acute hepatitis after first exposure to factor VIII and IX concentrate of different brands and to obtain accurate information about the risk of chronic sequelae. There are also several commercial products under development where attempts have been made to inactivate viruses present in the concentrate using heat, UV light and β-propio-lactone or other method. The only way of determining whether any of these methods is effective in inactivating hepatitis viruses in these products is by chimpanzee inoculation or a prospective study in haemophiliacs who have had no previous exposure to concentrate. Chimpanzees are in short supply, so in the absence of laboratory tests for non-A, non-B, hepatitis trials in patients likely to be susceptible to non-A, non-B, hepatitis present the only possible way of evaluating this risk.

OBJECT

To assess the risk of contracting non-A, non-B, hepatitis and hepatitis B after first exposure to factor VIII or IX concentrate, both NHS and commercial and to compare this with the risk after treatment with cryoprecipitate or any other product which may have a reduced risk of transfusion hepatitis.

To assess the risk of chronic sequelae after both hepatitis B and non-A, non-B, hepatitis.

METHOD

i) Patients at each of the collaborating Haemophilia Centres who have received less than 2 transfusions of factor VIII or IX concentrate in the past year will be considered for this study.

Categories of patient who will be considered are;-

(a) Haemophiliacs, carriers of the haemophilia gene, Christmas Disease or Von Willebrand's Disease patients who are about to undergo an elective treatment requiring cover with concentrate or cryoprecipitate.

(b) Patients in the above categories who are seen in the Haemophilia Centre as an emergency and require immediate treatment with concentrate etc.

ii) Procedure. Patients who attend one of the collaborating Haemophilia Centres during the course of the study who forfill the criteria given in (i) will be admitted to the project. The objects of the study will be explained to them, and their consent, or that of their parents obtained if they are under 18 years of age.

Prior to the start of treatment with any product, each patient will undergo a full clinical examination with special reference to liver disease, and blood will be taken for hepatitis A and B serology, full blood count before treatment is started. If the patient is seen as an emergency, then as many tests will be performed as is compatible with the clinical situation.

With each episode, an effort will be made to ensure that only one batch of one brand of factor VIII or IX is used for each treatment episode where concentrates are used. If more than one batch is used, then these should be from the same brand of concentrate.

Patients will be followed up for 12 months following their treatment episode, in the absence of any transfusion hepatitis. Liver function tests and hepatitis A and B serology will be carried out at appropiate intervals. Blood will be collected 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 three months after the onset and then monthly for six months. Follow up after this will be six monthly for the next two and a half 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 appendix I, 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 appropiate laboratory tests. It is hoped to make a collection of sera from suitable cases of non-A, non-B, hepatitis for use in the development of tests for the serological diagnosis of this disease.

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, which will last for 3 years.

HOUSEHOLD CONTACTS

These will be investigated prospectively. Serum specimens for hepatitis A and B serology and liver function tests will be obtained from adult household contacts of haemophiliacs, subject to informed consent on the entry of each patient to the project. These will be repeated six months after the index patient receives his first transfusion. If the patient contracts hepatitis then serum specimens will again be taken from the household contacts and repeated six months later. If a household contact develops hepatitis, then this will be investigated so as to obtain an accurate diagnosis. If possible faecal samples will be colleeted from teh index case and household contacts if the patient develops hepatitis while at home.

SAMPLE SIZE

The preliminary study at Oxford has shown that about 20-30 patients will be needed for each brand of product studied apart from new products for which fewer patients will be required.

RESULTS

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

1) The type of product transfuaed.

2)The transfusion history of each patiemt

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.

9)The type of procedure for which each transfusion was given.

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REFERENCES

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