

PROTOCOL FOR STUDY OF BPL FACTOR VIII CONCENTRATE, 8Y :

2nd PROSPECTIVE STUDY

1. TITLE OF PROJECT

AN EVALUATION OF THE INCIDENCE OF NON-A NON-B HEPATITIS AND TRANSMISSION OF OTHER VIRUSES AFTER A FIRST EXPOSURE TO BPL FACTOR VIII CONCENTRATE, 8Y.

2. BACKGROUND

Some 15-25% of multi-transfused haemophiliacs have liver biopsy evidence of chronic active hepatitis or cirrhosis, and recent studies suggest that liver disease is an increasingly common cause of death.<sup>1,2</sup>

A major cause of liver disease is thought to be the transmission of the agent(s) responsible for non-A, non-B hepatitis (NANBH) by therapeutic clotting factor concentrates. In patients receiving conventional unheated concentrates for the first time, acute post-infusion NANBH is a virtual certainty,<sup>(3,4)</sup> implying invariable contamination of these products. Because there are no reliable serological tests for NANBH, attempts to eliminate this contamination have largely focussed on the possibility of sterilizing concentrates by chemical or physical means.

Although heating in the freeze-dried state at 60°C is probably effective against human immunodeficiency virus (HIV),<sup>(5,6,7,8)</sup> clinical studies in 'first exposure' recipients have shown that the incidence of NANBH still remains close to 100%.<sup>(9,10,)</sup> Heating in solution appears to be more effective in neutralizing NANBH,<sup>(11, 12)</sup> but there is a penalty in decreased yield of factor VIII.

The Blood Products Laboratory (BPL) has recently developed fractionation

methods which allow factor VIII to be heated to 80°C for 72 hours with minimal loss of factor VIII activity. This material is issued under the code name 8Y.

A pilot clinical study using 18 batches of 8Y and similarly heat treated factor IX (9A) in 16 patients who had never been exposed to large donor pool concentrates suggested that the heating process was effective in neutralizing NANBH agent(s). However, some aspects of the protocol used in this pilot study were not sufficiently stringent. In particular, several of the patients had previously been treated with substantial quantities of cryoprecipitate. In several instances evidence was collected from patients who could not comply with the follow-up protocol including one patient who had an unexplained short-term rise in transaminase levels.

Having established that the incidence of NANBH after 8Y factor VIII seems to have been reduced, the purpose of this second study is to re-assess the product under the more stringent clinical trial conditions which are now internationally accepted to be required for this type of study.

### 3. OBJECTIVES

The purpose of this study is to assess the incidence of NANBH and transmission of other viruses in patients receiving a BPL factor VIII concentrate, 8Y, and who have never before received a large pool concentrate.

Primary End Point:

3.1 Biochemical evidence of acute hepatitis.

Secondary End Points:

3.2 If hepatitis develops, incubation period, severity,

symptomatology, duration, cause.

- 3.3 Serological evidence of transmission of Human Immunodeficiency Virus, Hepatitis A virus, Hepatitis B virus, Cytomegalovirus, Epstein-Barr virus and Human parvovirus.

4. PRODUCT

The 8Y concentrate to be used in this study will be manufactured from the plasma of unremunerated N.B.T.S. donors at the Blood Products Laboratory, Elstree. Only normal production batches will be used, all prepared from large plasma pools (5-25,000), individual donations having been serologically screened for anti-HIV and HBsAg. Donations will not have been screened by ALT or anti-HBc.

5. ADMISSION CRITERIA

- 5.1 The clinical investigator believes the patient needs treatment with factor VIII concentrate and that 8Y is likely to be at least as safe as other available products.
- 5.2 No previous exposure to blood or any blood products.
- 5.3 Serum transaminase (AST and/or ALT) should be within the local normal range immediately before treatment with VIII concentrate.
- 5.4 No other evidence of liver disease before treatment with factor VIII concentrate.
- 5.5 Anti-HIV negative before treatment with factor VIII concentrate.
- 5.6 HBsAg negative/anti-HBs negative (unless previously vaccinated) before treatment with factor VIII concentrate. It is recommended that hepatitis B vaccination be carried out before entry to the study.
- 5.7 Informed consent obtained from patient and approval obtained from local Ethical Committee.

## 6. FOLLOW-UP & SAMPLING FREQUENCY

The minimum follow-up period will be 26 weeks (6 months) after first exposure to a new batch. Blood samples will be obtained, and patients clinically reviewed:

- immediately before treatment with concentrate (blood samples should be obtained preferably on more than one occasion to give a base line).
- at least every 2 weeks for the first 16 weeks
- thereafter at least every 4 weeks until 26 weeks

At each visit sufficient blood will be taken for:

- plasma ALT/AST, with an additional aliquot to be stored and used for repeat analysis, should this prove necessary
- 2 ml serum, stored frozen, for virology studies.

Full blood count and T-cell subset analysis should be carried out at the beginning and end of the study.

Serum samples will be retrospectively examined for serological evidence of viral transmission by initially testing entry and exit samples. If hepatitis occurs (clinical or biochemical), or seroconversion is detected, intermediate samples will be examined.

Action to be taken on finding raised transaminase:

1. Notify co-ordinator immediately.
2. Independent analysis of ALT/AST on stored aliquot of same plasma sample.
3. Recall patient for further blood samples as soon as possible.
4. In consultation with the co-ordinator, arrange examination of stored intermediate samples.

## 7. LABORATORY TESTS/METHODS

Biochemical liver function tests will be carried out locally, laboratories providing details of methodology and normal ranges. Where one or other of

ALT or AST tests is not routinely carried out locally, samples of stored plasma should be provided to the co-ordinating Centre for central analysis. All serological studies will be carried out centrally at PHLS Colindale.

#### 8. DEFINITIONS

Acute hepatitis will be defined as a rise in serum AST or ALT to exceed  $2\frac{1}{2}$  times the upper limit of normal in at least 2 post-infusion samples taken within 2 weeks or less of each other. Other diagnostic criteria and definitions will be as previously described.<sup>(4)</sup>

#### 9. BATCH CONTROL

Studies using other products have shown that batch variability may be a problem. For this reason and also because the pilot study using 8Y product indicated a low overall risk of NANBH, an objective of this study will be to examine a large number of different batches. Each patient will normally receive only a single batch of product during the 26 weeks observation period, but patients needing heavy treatment may be treated with more than one batch. The study will not be concluded until at least 20 batches have been satisfactorily tested.

#### 10. ANALYSIS OF DATA/PATIENT NUMBERS

Some patients entered the study may have to be retrospectively excluded from analysis if it later becomes apparent that admission criteria have not been met or if the follow-up protocol has not been adequately complied with. However, all patients initially entered will be included and reasons for withdrawal discussed in the final analysis.

If any patient entered into the study or being followed less formally in other studies develops NANBH or other evidence of viral transmission the co-ordinator will be informed and will consider termination of the study. Ignoring the possibility of batch variability and applying the 'rule of three' for zero numerators,<sup>(13)</sup> 60 patients without evidence of NANBH

would need to be studied to show with 95% confidence that the product carries less than 5% risk of transmitting NANB. Because it may be impracticable to achieve this number, the initial aim will be a for a minimum of 20 patients.

#### 11. GENERAL ORGANISATION/LIAISON

This will be a multicentre study, co-ordinated by Dr. C.R. Rizza (Oxford Haemophilia Centre) and Dr. F.B.A. Kernoff (Royal Free Hospital Haemophilia Centre).

A data collection Centre will be established at Oxford, where a nominated member of staff (probably a Research Nursing Sister) will carry day to day responsibility for proper data collection, adherence to the protocol, and assisting with the practicalities of sampling and transport.

The co-ordinators will undertake to inform all study participants immediately if they become aware of adverse effects attributable to infused product.

The co-ordinators will also be responsible for preparing a final report for publication in a scientific journal. This report will be presented under the authorship of the '8Y Study Group' but will list all physicians who have contributed patients.

#### 12. FUNDING

The agreed costs of the study will be met by BPL. Costs will include those arising from: employment of a Research Nursing sister or clinician, secretarial assistance, transportation of staff, patients and samples, sample testing, attendance of participants at administrative and scientific meetings.

Estimate of approximate costs for 60 patients: £10,000 pa.

Anticipated duration of study : 2 years minimum.

13. ETHICAL/LEGAL CONSIDERATIONS

BPL factor VIII concentrate, 8Y, is an unlicensed product, used by physicians on a 'named patient' basis under the provisions of the Medicines Act, 1968. A clinical trials exemption certificate (CTX) will be applied for by BPL and the study will not start until this has been obtained.

The Treasury has given approval to compensation arrangements along the lines of the ABPI procedures<sup>14</sup> in the event of any injury being sustained by patients taking part in the study.

Institutional Ethical Committee approval and informed patient/parent consent must be obtained by participating physicians before patients are entered into the study.

Data concerning the production process and in-vitro/animal evidence of safety and efficacy will be made available to investigators by BPL Elstree.

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U.K. HAEMOPHILIA CENTRE DIRECTORS

CONSENT FORM FOR NHS 8Y FACTOR VIII STUDY

1. Explanation of the purpose of this research

Either to prevent or stop bleeding, you/your child need(s) treatment with factor VIII concentrate. All factor VIII treatment with factor VIII concentrates, whether made by the NHS or imported from abroad, are prepared from plasma obtained from several thousand donors. Although all donors are carefully screened before their plasma is accepted, and all concentrates are heated to destroy any HIV virus (AIDS virus). The risk of transmission of other viruses has not yet been entirely eliminated.

The main problem which remains to be overcome is the elimination of the chance of transmission of the virus which causes non A, non B hepatitis (NANBH). With the main objective of removing the risk of NANBH, the factor VIII concentrate which is being used in this study has been purified and heated by new methods. It is expected to have a reduced or absent risk of virus transmission. The only way to prove this, however, is to carry out regular blood tests in people who have received treatment with this new concentrate. Because people who have never previously been treated with concentrate (such as you/your child) are thought to be at most risk of NANBH, the study is at present limited to this group.

2. Plan of the study

Before treatment with factor VIII, a blood sample will be taken and the first of 3 injections of a course of hepatitis B vaccine will be offered (if you/your child have not previously been vaccinated against hepatitis B). After treatment with factor VIII, a blood sample and brief clinical examination will be needed at least every 2 weeks for 4

months and then once a month for a further 2 months. The amount of factor VIII you/your child need(s) will depend on circumstances, and for at least 6 months after the first injection any more treatments which are needed will be with the same type of concentrate.

3. Alternative possibilities for treatment

Why treatments other than factor VIII concentrate are not felt to be appropriate in you or your child's case will be explained. If you choose not to participate in this study, we shall in any event recommend frequent clinical and blood test follow-up.

4. Potential benefits

Judging from the freedom from ill-effects observed using many batches of this material, preliminary studies using many batches of this 8Y concentrate suggest that it has fewer risks than products which were previously available for the treatment of haemophilia. If this is confirmed both you/your child and other patients will benefit.

5. Potential risk and discomforts

All products made from human blood carry a risk of transmission of infection. Although experience with this concentrate has so far been very good a thorough study in many (perhaps at least 60) patients in different hospitals is required and until this is done it cannot be assumed to be without risk. Like other factor VIII concentrates, it may occasionally cause transfusion reactions. The need for frequent blood tests after treatment may be inconvenient and mildly uncomfortable.

6. Any questions you may have

Either Dr. Rizra, or any of the medical or nursing staff of the Haemophilia Centre who are involved in this study, will be glad to

answer any questions you may have, now and at any time in the future.

7. Confidentiality

Records relating to this study will be kept in the Haemophilia Centre and will be made available to professional staff involved in the study. Copies of records, with names removed and code numbers inserted, will be made available to the Blood Products Laboratory, Elstree (the manufacturer of the concentrate) and also (on request) to collaborating investigators in other hospitals. It is possible that officials from the Department of Health may also wish to inspect the records. At the end of the study, results will be reported in a scientific journal. The identity of patients will not be disclosed in this report, which will be given to you on request after it has been published.

8. Reimbursement of expenses

Any reasonable expenses you may incur as a result of participation in this study will be reimbursed.

9. Your right not to participate

You are free not to participate in this study. If you do agree to participate you may withdraw your consent and discontinue participation at any time without jeopardizing your medical care in any way. We shall let you know the findings of the study as it progresses, so you will always be aware of any new information which becomes available which may affect your decision to continue participation.

Statement of Consent

I have read the above and understand the nature of the study and the possible risks. I am willing to participate/I am willing to let my child ..... participate in the study.

Name..... Witness' name .....

\*Signature..... Witness' signature .....

\* Optional as some local Ethics Committees prefer patients not to sign the statement of consent.

Copy 1 to be filed in patient's study record

Copy 2 to be given to patient or his parents

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