Pond Street
Hampstead
London NW3 2QG

Telephone
01-794 0500
Ext. GRO-C

The Royal Free Hospital

HAEMOPHILIA CENTRE & HAEMOSTASIS UNIT

Ref: PBAK/cb

21st October 1986

Arb-T.
Dr Mowe.-
We need to discuss urgently.
GRO-C 28/10.

Dr Alison Smithies
Principal Medical Officer
DHSS
Hannibal House
London SE1 6TE

Dear Alison

re: NHS 8Y FACTOR VIII STUDIES

Further to our conversation on 22nd September, I have now produced a draft version of a revised 8Y Protocol which is attached for your interest.

I have discussed the whole matter with Charles Rizza and I think we are in agreement about the need for a new, tighter study. Hopefully, and in collaboration with Jim Smith, we shall be able to produce an agreed final Protocol in the near future.

You will see that I have focused on four main points:

1) That there should be more clinician involvement in study design, and more effort made to foster a sense of 'belonging' among study participants;
2) That the Protocol should be tightened to bring it into line with international commercial studies;
3) That funding needs should be recognised and met;
4) That legal and ethical problems, previously largely ignored, should be resolved, with no double standards for NHS and commercial products.

The new Protocol design will certainly limit patient accrual, but I think very little is to be gained by continuing as at present.

At the risk of labouring the point, the proper performance of this kind of study is dependent upon the support and skills of those with a major professional commitment to haemophilia care. Virtually all research of consequence comes from Reference Centres. Without central acknowledgement of the contribution of these Centres, there is a real

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24 Oct 1986
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risk of disintegration of this valuable resource. Your support would be much appreciated.

With all best wishes

Yours sincerely

GRO-C

P B A Kernoff MD MRCP MRCPath
Consultant Haematologist

Enc.

NHS 8Y FACTOR VIII : 2nd PROSPECTIVE STUDY

OUTLINE PROTOCOL

1. TITLE OF PROJECT

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

2. BACKGROUND

Some 15-25% of multitransfused haemophiliacs have liver biopsy evidence of chronic active hepatitis or cirrhosis, and recent evidence suggests that liver disease is an increasingly common cause of death.

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 a first exposure to conventional unheated concentrates, acute post-infusion NANBH is a virtual certainty, implying invariable contamination of these products. Because there are no reliable serological tests for NANB, attempts to eliminate this contamination have largely focussed on the possibility of sterilizing concentrates by chemical or physical means.

Although conventional 'dry heating' protocols are probably effective against human immunodeficiency virus (HIV), clinical studies in 'first exposure' recipients have shown that the incidence of NANBH still remains close to 100%. This implies that dry heating under the conditions normally employed is insufficiently aggressive to inactivate NANB agents. 'Wet heating' appears to be more effective in NANBH neutralization, but sizable reductions in final yield of factor VIII make application in the voluntary sector impracticable.

The product to be assessed in this study is 'dry heated', but much more intensively (80^{o}C for 72 hrs) than has been the case with the conventionally treated products, referred to above, which have been evaluated in formal clinical trials. A pilot clinical study using the 8Y product (14 batches) in 13 patients who had never previously been exposed to large donor pool concentrates showed no evidence of NANBH transmission, suggesting that the heating process was effective in neutralizing NANB agent(s). However, the protocol used in this pilot study had several design weaknesses. In particular, several of the patients had previously been treated with substantial quantities of cryoprecipitate; not all patients had normal liver function tests at entry; the frequency of follow-up was sub-optimal in several instances; and one patient, not formally entered into the study, had marked rises in transaminases on a single sampling occasion, which are at present unexplained.

The purpose of this second study is to re-assess the 8Y product under the more stringent clinical trial conditions which are now internationally accepted to be necessary if product safety is to be proved beyond reasonable doubt.

3. OBJECTIVES

The purpose of this study is to assess the incidence of NANBH and other viral transmission in patients receiving a first lifetime exposure to NHS 8Y factor VIII concentrate.

Primary End Point:

3.1 Biochemical evidence of acute hepatitis.

Secondary End Points:

3.2 If hepatitis: severity, duration, symptomatology, incubation period, cause.

3.3 Serological evidence of transmission of HIV, HAV, HBV CMV, EBV, HPV.

4. PRODUCT

The 8Y concentrate to be used in this study will be manufactured from volunteer donor plasma at the Blood Products Laboratory, Eltree. Only normal production batches will be used, all prepared from large plasma pools (3000 donors), 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 Patient needs treatment with VIII concentrate.

5.2 No previous exposure to VIII concentrate.

5.3 Treating physician believes that 8Y product is likely to be at least as safe for patient as other available products.

5.4 Previous lifetime exposure to other blood products 10 or less donor units. This is equivalent to a maximum chance of previous NANBH of approximately 3%.

5.5 Biochemical liver function tests normal before treatment with VIII concentrate.

5.6 No other evidence of liver disease before treatment with VIII concentrate.

5.7 Anti-HIV negative before treatment with VIII concentrate.

5.8 HBsAg negative/anti-HBs negative (unless previously vaccinated) before treatment with factor VIII concentrate.

5.9 Informed consent obtained; institutional Ethical Committee approval obtained.

5.10 (Optional). A course of hepatitis B vaccine should be started before the first infusion of VIII concentrate is given.

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 (preferably, on more than one occasion);
- at least every 2 weeks for the first 16 weeks;
- at least every 4 weeks until 26 weeks

From each blood sample, the following are needed:

- biochemical liver function tests, including AST and ALT;
- 2 ml serum, stored frozen in 0.5 ml aliquots.

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

7. LABORATORY TESTS/METHODS

Biochemical liver function tests will be carried out locally, laboratories providing details of methodology and normal ranges. Where ALT is not routinely carried out, either special arrangements will be made locally or samples of stored serum provided to the co-ordinating Centre for central analysis.

All serological studies will be carried out centrally, probably at PHLS Colindale.

8. DEFINITIONS

Acute hepatitis will be defined as a rise in serum AST and /or ALT to exceed 2 1/2 times the upper limit of normal in at least 2 post-infusion samples taken within 4 weeks of

each other. Other diagnostic criteria and definitions will be as described in Brit. J. Haemat, 1985, 60, 469.

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 no more than 2 patients will be treated with the same batch. Exceptionally, patients needing heavy treatment may need to be treated with more than one batch.

10. ANALYSIS OF DATA/PATIENT NUMBERS

Some patients entered into the study may have to be retrospectively excluded if it later becomes apparent that admission criteria have not been met. However, all patients initially entered will be included in the final analysis, on an 'intention to treat' basis. Also, any patients not entered into the study who are reported, on the basis of clinical or random testing, to have developed evidence of NANBH or other viral transmisssion possibly attributable to 8Y infusion will also be included in the analysis.

Ignoring the possibility of batch variability, and applying the 'rule of three' for zero numerators (JAMA, 1983, 249, 1743), 60 patients without evidence of NANBH will need to be studied to achieve a 95% probability that the product is free of this risk. Because it may be impracticable to achieve this number, a minimum of 20 patients will be aimed for in the first instance.

If any patient entered into the study develops NANBH, cessation of the study will need to be considered in the light of the status at that time of similar studies using other products.

11. GENERAL ORGANISATION/LIAISON

This will be a multicentre study, co-ordinated by Dr C R Rizza (Oxford Haemophilia Centre) and Dr P 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, assisting with the practicalities of sampling and sample and patient transport.

At not less than 6 monthly intervals, the co-ordinators will be responsible for preparing interim reports on the status of the study, which will be presented for discussion at regular meetings of all study participants. 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 costs of the study will be met by BPL or other NHS agencies. Costs will include those arising from: employment of a Research Nursing Sister, or physician; secretarial assistance; transportation of staff, patients and samples' sample testing; attendence of participants at administrative and scientific meeting.

Estimate of approximate costs : £20,000 pa.
Anticipated duration of study : 2 years minimum.

13. ETHICAL/LEGAL CONSIDERATIONS

NHS 8Y factor VIII concentrate 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.

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

BPL, or other NHS agencies, will indemnify participating physicians against litigation arising as a consequence of this study. Also, BPL will adhere to British Pharmaceutical Industry guidelines in respect of patient compensation for injury (BMJ, 1983, 287, 675).

PK. 26.9.86.