OXFORDSHIRE HEALTH AUTHORITY

OXFORD HAEMOPHILIA CENTRE

575

Churchill Hospital,
Headington,
Oxford OX3 7LJ.

11th January, 1982

To all Haemophilia Centre Directors

Dear Colleague,

You are no doubt aware that at least 4 commercial companies are about to introduce preparations of factor VIII and possibly factor IX that have been processed in an attempt to reduce the risk of transmitting hepatitis B and non-A non-B. As far as we know the products have been subjected to a heat treatment process such as pasteurisation after removal of the bulk of fibrinogen but other methods such as treatment with B-propiolactone and UV-light or differential adsorption-elution may be used. Although initial production batches may have been tested for infectivity by injecting them into chimpanzees it is unlikely that the manufacturers will be able to guarantee this form of quality control for all future batches. It is therefore very important to find out by studies in human beings to what extent the infectivity of the various concentrates has been reduced. The most clear cut way of doing this is by administering those concentrates to patients requiring treatment who have not been previously exposed to large pool concentrates. Those patients are few in number but a study along those lines is being carried out at Oxford to determine the infectivity of factor VIII concentrates produced by the Plasma Fractionation Laboratory, Oxford and Blood Products Laboratory, Elstree. This study shows that it is possible to demonstrate infectivity using quite small numbers of previously untreated patients. It is very important also to find out as soon as possible whether the manufacturing methods used to reduce the hepatitis risk has resulted in a product with undesirable characteristics such as high content of denatured protein, reduced factor VIII recovery in vivo, reduced factor VIII $\frac{1}{2}$-life in vivo, increased incidence of factor VIII antibodies or of immune complex disease.

Although there is no doubt that the introduction of 'hepatitis-safe' products would constitute a major advance we hope you will agree with us that their use on a 'named patient' basis would be undesirable and might seriously hinder controlled studies in the future. There are several reasons for thinking this:-

1. The best way of assessing efficiency and observing recovery of activity, side effects etc., is by properly conducted clinical studies. Since a number of products are likely to be introduced in the next few months a core of 'at risk' patients will be needed for this assessment. It is for the treatment of such patients that producers will make their products available. If patients at risk are treated on a 'named patient' basis they will be unavailable for clinical trials and the results will be of anecdotal value only.

2. For the purposes of a Product Licence the manufacturers are required to set out to the Regulatory Authority in the U.K. the evidence of product efficacy and safety and details of processing, batch to batch reproducibility toxicity tests etc., which help to ensure quality control. In addition there would be a requirement for samples of each batch or batch protocol to be submitted if requested to the Regulatory Authority for assessment at NIBSC. Manufacturers could be laible if subsequent batches failed to meet the original product protocols and import of such products could be prohibited. Although it will not be possible for the Regulatory Authority to check infectivity of batches as an ongoing control, measurement of total protein, clottable protein, factor VIII antigens and activity ratio etc., will help to ensure that the materials have been properly processed. Even if factor VIII concentrates are subjected to similar pasteurization processes as those used to sterilise albumin and other simple plasma protein fractions they may not withstand denaturation to the same extent. Formal trial of efficacy and on-going monitoring of quality control is thus important.

3. Use of a product on a 'named patient' basis is often justifiable but by-passes these regulatory controls which have been established in the interests of patients.

We are therefore writing to let you know that the Hepatitis Working Party are discussing plans for Clinical Trials of these products as they become available and will if necessary request exemption from a clinical trials certificate in respect of individual products in order to expedite trials. We hope that the companies concerned will collaborate in these trials and will offer appropriate supplies of their concentrate as well as financial support.

Unfortunately there is insufficient time available to air these problems at the next meeting of the Haemophilia Centre Directors but if you have any observations we would be most grateful to learn of them as soon as possible.

With all best wishes,

Yours sincerely,

A.L. Bloom C.R. Rizza