bcc Mr. P.J. Hedley

GRO-C

NEWCASTLE HEALTH AUTHORITY

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14th December, 1984

Dear Douglas,

AIDS : The Use of Heat-Treated Factor VIII

I thought you would wish to see the attached paper before it is considered by my Authority next week. The DMT sought clinical advice on the implications of AIDS for the use of Factor VIII. The position can be summarised as follows:

For new patients and patients without AIDS antibodies

We think it would be indefensible to give such patients untreated Factor VIII. Were any such patients subsequently to contract AIDS we would be in a very vulnerable position in legal and public relations terms bearing in mind current knowledge. This applies to the use of untreated Factor VIII supplied from Elstree - although it is "cleaner" than commercial imported Factor VIII, it cannot be guaranteed to be free of contamination by AIDS virus.

For patients who already have AIDS antibodies

You will see that studies elsewhere indicate that a substantial proportion of haemophiliacs possess AIDS antibodies. Figures will soon be available for the Newcastle patients. Since the incubation period for AIDS is so long one cannot tell for how many of the patients the presence of antibodies indicates previous exposure but acquired immunity and for how many patients the presence of antibodies is indicative of the disease incubating. Theoretically, to expose such patients again to the AIDS virus from contaminated, untreated Factor VIII, does not lead to a significant new risk - either they are immune or they are already developing the disease. However such a policy would be difficult to present in public relations terms both to individual patients and to the public at large. Furthermore continued use of untreated Factor VIII for such patients would expose the patients' relatives to some additional risk.

The position of relatives

AIDS can be transmitted by heterosexual intercourse as well as by homosexual activity. It can also be transmitted via the blood (the patient's blood or exposure of the relatives own blood to contact with contaminated Factor VIII). This means that the relatives of all patients

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have almost as direct an interest as the patients themselves in steering clear of contact with possibly contaminated Factor VIII. People with Factor VIII antibodies have to take special precautions in sexual intercourse and must be scrupulously careful in their body contact with and handling of relatives and children. Thus from the relatives' point of view, any continued use of untreated Factor VIII represents an unacceptable risk.

Cost of the New Policy

Heat treatment of Factor VIII reduces its efficacy and thus more of it is needed to achieve the same effect as untreated Factor VIII. The cost of this consequence is estimated at between £150,000 to £250,000 per annum.

It is difficult to be more precise since usage is highly sensitive both to the incidence among haemophiliacs of major bleeds and to the extent to which in any one year haemophiliacs need to undergo surgery. A single patient needing a splenectomy, for example, requires many thousands of units of Factor VIII at a cost of several thousand pounds.

Factor VIII Funding Hitherto

As you may know the RHA some years ago provided specific funding for Factor VIII. The record of funding (uplifted for inflation) and expenditure in recent years is as follows:

	Funding £	Expenditure £
1981/82	392,969	254,096
1982/83	425,499	243,566
1983/84	475,300	306,555

In 1984/85 expenditure is projected to be about £450,000.

This time last year when Newcastle sought Regional support for the underfunding on renal and cardiothoracic services we netted off the consistent underspending on Factor VIII in calculating our net funding deficiency on Regional services. During 1984/85 we have had to restore most of that netted off figure to the Factor VIII budget in order to contain the higher level of expenditure. In the present year there will more or less be a break-even between Regional funding for Factor VIII and expenditure.

Cost Trends in Future Years

It is difficult - for reasons already explained - to predict precisely future patterns of expenditure. However, we think that usage of Factor VIII is likely to increase as an increasing number of haemophiliacs become older, requiring surgery of various kinds.

Conclusion

In the light of this analysis we think it is most probable that the use of heat treated Factor VIII will result in a rate of expenditure exceeding the funding made available by the Region. The DMT has advised the Authority that this issue will need to be discussed with the Region since the Haemophilia Service is genuinely Regional in its responsibilities. The DMT

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did not think it could advise the Authority to make its change of policy on the use of Factor VIII conditional on a prior RHA commitment to fund the extra cost. This is one of those rare circumstances where patient safety, family health, public policy and legal considerations all coincide to compel a decision to be made first, with any argument about money being undertaken subsequently.

We hope Regional officers will agree to explore with us ways in which the District can be adequately and realistically funded for Factor VIII.

Yours sincerely,

GRO-C: Chris Spry

District General Manager

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NEWCASTLE DISTRICT HEALTH AUTHORITY

REPORT OF AN AD-HOC GROUP TO CONSIDER THE USE OF HEAT-TREATED FACTOR VIII CONCENTRATE

At the request of the District Administrator (Mr. C.Spry) and the Chairman of the Hospital Medical Committee (Dr. C.B. Henderson) we met on December 4th 1984 to consider the necessity and implications of using heat-treated factor VIII concentrates in treating patients attending the Health Authority's Haemophilia Centre at the Royal Victoria Infirmary.

Background. The Haemophilia Centre at the Royal Victoria Infirmary cares for patients with haemophilia in the Northern Region. This condition is due to a genetic defect in the production of one of the coagulation factors (factor VIII) required for the normal clotting of blood. Consequently patients with the disorder are at risk of severe bleeding either spontaneously, after minor injury, or after surgery, depending on the severity of their condition.

The mainstay of treatment of patients with haemophilia is to administer factor VIII intravenously either as human factor VIII concentrate, human cryoprecipitate, or animal factor VIII. For clinical and practical reasons most patients with haemophilia are treated with human factor VIII concentrate: 30-40% of the material used in the Haemophilia Centre is UK-derived factor VIII obtained free of charge from the National Blood Transfusion Service, but the remainder is purchased from a variety of commercial sources. All human factor VIII preparations, however, are obtained from donors. Although both NHS and commercial factor VIII concentrates are satisfactory forms of replacement therapy, material from both sources has the potential to transmit infections from donors to recipients. This danger is aggravated by the fact that factor VIII concentrates are prepared by pooling plasma fractions from a large number of donors: consequently, even a very small number of infected donations can produce widespread contamination of the final product. Until recently, the most important contaminants were hepatitis viruses.

Considerable efforts are therefore made to establish that donors are healthy, that they do not have known infective agents in their blood, and that the quality of the final product is satisfactory. For a number of reasons, NHS factor VIII is substantially less likely to contain infective agents than that obtained from commercial sources which is ultimately derived from donors in North America. Whilst it has been the policy of the Health Authority and the Haemophilia Centre to use NHS factor VIII wherever possible, supplies are limited and it is anticipated that the UK will not become self-sufficient before 1986. We believe that this date may also be overoptimistic.

Consumption of factor VIII concentrates, and their cost, within the Authority, over the past few years are shown below:

	Units (million)	Cost (£)
1982/83	4.9	279,000
1983/84	4.1	275,000
1984/85 (end October)	3.8	301,000

Annual fluctuations in usage (reflected in the number of units used per year) are due to the development of inhibitory antibodies in some patients, and the large quantities required if even a small number of haemophilic patients require major surgery. The increase in costs are due to price rises of the commercial products. The RVI pharmacy department, in consultation with the Director of the Haemophilia Centre, have made substantial efforts to obtain commercial factor VIII at the most economic price but the world-wide shortage of the material does not provide much scope for price negotiation.

Acquired Immunodeficiency Syndrome (AIDS). This disease has only been recognised for the past four to five years. Recent evidence suggests that it is caused by one or more retroviruses, and that infection with the agent results in depression of the immune system. Consequently, patients are susceptible to overwhelming infections from other viruses, bacteria and fungi. Knowledge of the natural history of AIDS is very incomplete, and there is no known effective treatment for patients suffering from the disorder. Epidemiological evidence, however, has shown that it may be transmitted during homosexual and (less commonly) heterosexual intercourse, and by transfusion of blood containing the putative AIDS virus. The disease appears to have a median incubation period of 2 years but it may be as long as 5 years in some individuals.

90 individuals are believed to have died from AIDS in the UK including 2 heterosexual haemophilic patients. Because of the known haematogenous transmission of AIDS, haemophiliacs are at clear and special risk of contracting the disease. 74% of haemophiliacs in the USA, 53% of West German haemophiliacs, and 34% of London haemophiliacs have antibodies to the putative AIDS virus (HTLV III & LAV) indicating previous exposure to viral antigen either as live or dead virus. It is not known at present what proportion of haemophiliacs attending the Northern Regional Centre have anti-viral antibodies but this information will be available soon: there is no reason to believe that the incidence will be less than that in London haemophiliacs and we know that one patient has contracted the disease in Newcastle. The clinical implications of the presence of anti-viral antibodies

are uncertain except to indicate previous exposure to living or dead virus. It is also uncertain whether antibody positive patients would be protected against further exposure to the AIDS virus. At the present time there is no test for the AIDS agent which can be used to screen factor VIII preparations for potential infectivity. Whilst the likelihood of contracting AIDS seems greatest from the use of commercial factor VIII, NHS factor VIII cannot be regarded as completely free of risk.

Heat-treated factor VIII concentrates. A number of manufacturers of factor VIII concentrates possess Clinical Trial Certificates for the preparation and administration of heat-treated factor VIII. Heat-treatment of factor VIII was initially introduced in order to inactivate at least some of the viruses causing hepatitis. Heat treatment has also been shown to inactivate some retroviruses and it seems likely, on theoretical grounds, that heat-treatment will inactivate the AIDS virus. The use of heat-treated factor VIII, however, poses five potential problems:

1) No heat-treated commercial factor VIII is currently available with a Product Licence. For the time being, therefore, any use of commercial heat-treated material within the Authority must be carried out under the "named-patient" provisions of Section 8 of the Medicines Act. Informal discussion by one of us (MDR) with the Licensing Authority indicates that there are no objections to this course of action.

2) Heat treatment of factor VIII results in some loss of biological activity. On theoretical grounds, therefore, factor VIII degradation products produced by the heat treatment might produce adverse effects. Informal discussion by one of us (MDR) with the staff of the National Institute for Biological Standards suggest that, in practice, such problems have not arisen.

3) Heat-treated factor VIII from commercial sources costs substantially more than conventional material. At present, manufacturers of heat-treated factor VIII are quoting prices of 12p./unit or 14p./unit, compared with 8p./unit for non-heated factor VIII. Substitution of heat-treated commercial factor VIII for conventional commercial products would increase our costs for factor VIII by approximately £61,000 during the current financial year. Over a full year we estimate that at currently quoted proces the additional costs of changing completely to heat-treated factor VIII would amount to £150,000 to £250,000 per annum depending on usage.

4) Substantial stocks of conventional commercial factor VIII are held by the Authority and by patients in their homes. The stock value of material in the RVI pharmacy (28.11.84) is £33,149. Manufacturers have, however, indicated that they will accept this material for credit, or for heat-treatment.

5) Use of heat-treated factor VIII will, because of the loss of activity incurred during the process, exacerbate the world shortage of the material. We believe, however, that this is a problem for national and international heatlh agencies which should not prejudice the treatment offered by the Health Authority to haemophiliac patients within the Region. In offering our advice to the Authority we have therefore not taken this into account.

Conclusion and advice. Our conclusions and advice are as follows:-

1) From the available evidence a change from using conventional commercial factor VIII to using commercial heat-treated factor VIII appears to carry little risk, but offers substantial advantages. It should be appreciated however that these advantages, though likely, are not proven and we cannot exclude the possibility that even heat-treated commercial factor VIII concentrates do not transmit AIDS.

2) We believe, on balance, that the use of NHS factor VIII should be discontinued until after April 1985 when material from this source will also undergo prior heat-treatment. One of us (P.J.) has received assurances from the Director of the Blood Products Laboratory at Elstree that the Authority will be able to "role over" its allocation of NHS factor VIII concentrate until after April 1985. The temporary discontinuation of NHS material, over the next three months, will not therefore have any financial implications over a full year.

3) We advise the continued use of cryoprecipitate.

4) In the light of available knowledge, we cannot identify groups of haemophilic patients who would be likely to benefit from heat-treated commercial factor VIII, or who would be likely to be at special risk from conventional commercial factor VIII, apart from those without previous exposure to any factor VIII concentrate.

5) In formulating our advice we have not taken into account the economic consequences of changing to heat-treated commercial material. We believe that this decision must be for the Authority and its Officers.

6) If the Authority is able to identify funds for the changes that we believe can be justified on clinical grounds, we further recommend that:

a) the Health Authority inform the Licensing Authority (Medicines Division, DHSS) of its intention to use commercial heat-treated factor VIII on a "named patient" basis.

b) The District Pharmaceutical Officer continues to negotiate with individual companies for the most cost-effective supplies of heat-treated material.

c) The position is reviewed at the end of the current financial year when further scientific and commercial information may have become available.

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Dr. Peter JONES, (Director, Haemophilia Centre)

Professor R. MADELEY (Professor of Virology)

Dr. A.G. BIRD (Consultant Immunologist)

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Mr. P.HOPLEY, (District Pharmaceutical Officer)