

EXPERT GROUP ON THE TREATMENT OF HAEMOPHILIA

Note of the meeting held at DHSS on 20th March 1973

PRESENT:

Dr J J A Reid - Chairman
 Dr Rosemary Biggs
 Professor E K Blackburn
 Professor A S Douglas
 Dr W d'A Maycock
 Dr C Rizza
 Mr G John, Supply, DHSS
 Dr I S Macdonald, SHHD
 Dr D P Thomas, B2, DHSS
 Mr W A Walters, HS2B, DHSS
 Mr I G Gardiner, B4, DHSS, Secretary
 Dr Sheila Waiter, B4, DHSS, Secretary

Several significant advances in the treatment of haemophilia have taken place in recent years. Various therapeutic materials are now available. The most recently developed is human freeze-dried anti-haemophilic globulin concentrate which is expensive and may be in limited supply. Nevertheless, it appears to be the therapeutic agent of choice in the majority of cases, and would be used widely if available in larger quantities.

A short time before this meeting took place, product licences were granted to two firms which import freeze-dried AHG concentrate from overseas, making it available to hospitals and haemophilia centres. The Department decided to assemble a group of experts to advise generally on the likely trends in treatment of haemophilia and, more specifically, to make proposals on which realistic planning for the future can be based.

The terms of reference of this group are as follows:

"To advise the Department on trends in methods of treatment of haemophilia and allied conditions; and to consider possible future requirements for the treatment of the condition and the consequences for the supply of therapeutic agents".

Following introductory remarks by the Chairman, the group considered papers which had been prepared by Dr Biggs and Dr Maycock. A general discussion followed and the main points are summarised in this note. At the conclusion of the meeting, several recommendations were made to the Department. These are also enumerated.

1. THE SIZE OF THE PROBLEM.

The number of individuals suffering from haemophilia in the U.K is not known. It was agreed that the number registered with haemophilia centres (1,754) is an under-estimate. Based on

the generally accepted ratio of 5/100,000 in the U.K., a figure of 3,000 can be used as a reasonable estimate for forward planning. There was originally a central register of haemophiliacs but this was discontinued; there might be advantages in resuming national registration but there are no plans to do this at present.

2. PRESENT TREATMENT

Haemophilia is caused by the lack from the blood of an essential coagulation factor: factor VIII. Various therapeutic agents contain factor VIII, and each has advantages and disadvantages in its use. These were discussed by Dr Biggs in her paper. It is agreed by clinicians that the preferred treatment of episodes of bleeding before and during surgical procedures is with the more purified products, namely cryoprecipitate and AHG Concentrate.

3. COMPARISON OF THERAPEUTIC MATERIALS

Cryoprecipitate is currently the most commonly used therapeutic agent. In 1972, figures from a summary of questionnaires sent to Directors of haemophilia centres indicate that cryoprecipitate from 230,000 donations of blood (in England and Wales) was issued, while human AHG concentrate from 30,000 donations of blood (England, Wales and N. Ireland) was issued. There are disadvantages to using cryoprecipitate compared with AHG Concentrate

- (a) Cryoprecipitate is presented frozen and must be kept in deep-freeze until immediately before use.
- (b) The process of making up the material is tedious and could be abused by non-experts.
- (c) The yield of factor VIII is variable from batch to batch of cryoprecipitate. This was clearly demonstrated in table III of Dr Bigg's paper. It is possible to bring the post-infusion level of plasma factor VIII to a particular desired level but in practice this will be difficult with variable potency of the therapeutic agent.

Freeze-dried concentrate is presented in bottles, each containing about 400 units of factor VIII activity. The bottles should be kept at 4-10°C and have a very significantly longer life than cryoprecipitate kept under ideal conditions. The material at present available is of variable solubility but that of good solubility is very convenient to use, easy to make up and the dose can be determined accurately. Adverse reactions following infusions of freeze-dried AHG concentrate are rare.

A possible disadvantage arises from the fact that AHG concentrate is prepared from a larger pool of donations, and in theory therefore, the risk of hepatitis is greater. About 1 in 800 of the donors who present to the transfusion service is a carrier of hepatitis B antigen.

The present policy of rejecting donations which give a positive test for hepatitis B antigen will reduce the incidence of virus in the blood used to make plasma pools. In practice, studies in several centres have shown that the incidence of hepatitis among severely affected patients who have been treated with the freeze-dried preparation is not very much higher than that at centres not using freeze-dried concentrate and this suggests that the development of hepatitis in these multitransfused patients may be dose-related. It was agreed that the theoretically increased risk of acquiring hepatitis (which does not seem to be borne out in practice) should not be a deterrent to using the freeze-dried preparation and in any case this complication will decrease with universal screening of donors for hepatitis antigen.

A survey quoted by Dr Biggs indicates that the incidence of anti-factor VIII anti-bodies in about 6% of patients does not seem to be related to the type of therapeutic material used.

At a meeting of the Haemophilia Centre Directors in 1972 there was a consensus of opinion in favour of freeze-dried concentrate, and this was confirmed in a survey, undertaken by Dr Maycock, of the opinions of clinicians. The limiting factors are the capacity for production (and the cost) of this preparation.

4. FUTURE REQUIREMENTS OF THERAPEUTIC AGENTS

During 1972 considerably more cryoprecipitate than freeze-dried concentrate was issued in terms of donations of blood.

It was generally agreed that 400,000 donations would be required to treat UK sufferers from haemophilia of all degrees of severity, and more if strenuous efforts were made to clear surgical waiting lists and if home treatment or eventually prophylactic treatment became accepted ways of dealing with the problems of haemophiliacs. Life-saving surgery has been undertaken for some time using the therapeutic agents which are available, but clinicians must now look to the possible improvement in the quality of life of boys and men who suffer from haemophilia.

Since more freeze-dried AHG concentrate has become available from two foreign sources the prospects of improved management of day-to-day bleeding episodes using this therapeutic agent has become realistic. If the anticipated annual uptake of 20 million units of the freeze-dried AHG concentrate is to be met from foreign commercial sources the cost will be of the order of £2 million p.a. (assuming the cost to be 10p per unit).

At present, UK production is considerably less than the required amount of the freeze-dried preparation. It was agreed that there was an immediate need to discuss the advisability of central purchase and distribution of the two commercially produced preparations. There is also a pressing need to seek ways of increasing UK production with the intention of reducing and as soon as possible ending purchase from foreign sources.

Freeze-dried AHG concentrate is made at the Blood Products Laboratory, Elstree; at the Plasma Fractionation Laboratory, Oxford,

and at the Blood Products Laboratory, Edinburgh. It is essential the production and distribution of the therapeutic agents concerned should be considered as a U.K. exercise.

In any consideration of increased UK production of freeze-dried AHG concentrate, the immediate problems are those of the organisation and cost of increasing donations of either whole blood or plasma (by plasmapheresis) and the difficulties, including cost, of increasing the capacity of the laboratories at present engaged in production.

Close co-operation between England (including Wales and N.Ireland) and Scotland will be required in order to co-ordinate and optimise blood collection and transport, the fractionation processes, distribution of the therapeutic agents, and utilisation of other blood fraction by-products.

RECOMMENDATIONS BY THE EXPERT GROUP

1. DHSS should give early consideration to central purchase of freeze-dried AHG concentrate from the firms who have recently been granted product licences.
2. Distribution to other haemophilia centres and hospitals should be through the Regional centres, 3 of which are in Oxford, Manchester and Sheffield in England, 1 in Scotland (Edinburgh or Glasgow) and 1 in London (to be decided). The establishment of such a distribution scheme would be a pre-requisite of Recommendation 1 in order to ensure the most effective use of available material.
3. At the same time the U.K. should aim to become self-sufficient as soon as possible by increasing home production of freeze-dried AHG concentrate.
4. The Regional Transfusion Directors should be consulted about the consequences of Recommendation 3 in terms of increased demands upon the Blood Transfusion Services throughout the U.K. Discussions should take place between DHSS and the directors about problems of decreasing production of cryoprecipitate, increasing production of fresh-frozen plasma for fractionation and the possibly increased collection of plasma by plasmapheresis.
5. There should be further meetings of this expert group, at times to be arranged. Several subjects need to be discussed further, including home treatment, and, in due course, prophylactic treatment.
6. The expert group membership might be expanded to include representatives of each of the Regional haemophilia centres, a representative of the Regional Transfusion Directors, and possibly a SAMO. It was also suggested that the National Medical Director of the Scottish National Blood Transfusion Association and Mr Watt of the Edinburgh BPL should be invited to join the group.