Confidential

SURVEY OF COMMERCIALLY-PRODUCED AND NHS-PRODUCED FACTOR VIII CONCENTRATES

It is the intention that in the foreseeable future the UK demand for freeze-dried factor VIII Concentrate will be met by the blood fractionation units of the NHS. It is also policy, in keeping with the aims of WHO and other countries who share our medical standards and ethics that the raw material, fresh-frozen human plasma, should be collected from voluntary donors within the UK. It is also the intention at present not to embark on a programme of plasmapheresis. Most of the concentrate produced will be of intermediate purity which is obtained from a yield of factor VIII activity in the range of 30-35%. It would be possible to obtain a high purity concentrate but the yield would be low, over 80% of factor VIII activity being lost during production. At present the view prevails that the greatly increased cost of collection and the low yield of factor VIII are seldom justified. The Department has been advised by an Expert Group that there will be a need for about 10% of high purity concentrate, the remainder being of intermediate purity. A demand for some cryoprecipitate will continue.

This paper is concerned with the available forms of freeze-dried factor VIII Concentrate, the advantages and disadvantages of these and the resulting clinical preferences. As the declared intention is to make the NHS independent of commercial producers of the therapeutic agent it is essential to produce within the NHS concentrates which are as acceptable and as effective as those made commercially.

PREPARATIONS OF FACTOR VIII

For many years the only treatment for bleeding in haemophiliacs was transfusion of fresh blood or plasma. Their use was limited by the large volumes needed to raise the circulating factor VIII to haemostatic levels. In 1964 Judith Pool developed a method of preparing cryoprecipitate which is still the most widely used preparation of factor VIII. It is made in the Regional Transfusion Centres from fresh-frozen plasma and distributed on demand to clinicians. Its main disadvantage is that the activity can vary considerably from Centre to Centre and from batch to batch. Unless held at suitably low temperatures and infused shortly after thawing activity may be diminished.

A concentrate of factor VIII prepared from fresh-frozen plasma has been available since mid-1950s but there has been little demand until recent years possibly due to the effectiveness and availability of cryoprecipitate. During the last few years there has been a greatly increased demand for the freeze-dried concentrate. It is thought probable that the advent of home-treatment and the obvious advantages of the concentrate for this regime has to a large extent resulted in the quite sudden increase in demand.

FREEZE-DRIED FACTOR VIII CONCENTRATES

Several forms of freeze-dried factor VIII Concentrate are available to clinicians in the UK for the treatment of haemophilia A and other disorders in which the concentration of circulating factor VIII is reduced. Producers of factor VIII fall into two categories,- commercial and NHS, and the plasma from which factor VIII is produced is correspondingly derived from two different sources: NHS products are prepared from blood or plasma given by volunteer donors within the Blood Transfusion Services; it is likely that commercially produced factor VIII is almost entirely produced from plasma collected by plasmapheresis at paid-donor sessions.

COMMERCIAL SERVICES OF FREEZE-DRIED FACTOR VIII CONCENTRATE

Product licences have been granted to three overseas commercial firms enabling each to sell its product in the UK but restricting the market available to the firms to designated Haemophilia Centres. Supplies are more than adequate to meet UK demands, but the product is expensive.

At present 3 products are available:

'HEMOFIL'	made by	Hyland Division of Travenol Laboratories Ltd. Belgium and USA.
'KRYOBULIN'	made by	Immuno AG, Vienna.
'PROFILATE'	made by	Abbott Scientific Products Division, California, USA.

A fourth firm will shortly be given a product licence and a fifth is likely to apply for one.

NHS SOURCES OF FREEZE-DRIED FACTOR VIII CONCENTRATE

Within the NHS, three laboratories produce factor VIII Concentrate. The products are distributed without charge, in Scotland, through Regional Transfusion Centres to Haemophilia Centres; in England and Wales to Haemophilia Centres in response to direct requests but also to other clinicians.

The NHS production units are:

Blood Products Laboratory, Elstree.	Director: Dr W d'A Maycock
and its branch	
Protein Fractionation Laboratory, Oxford.	Head of Laboratory: Dr. Ethel Bidwell.
Protein Fractionation Centre, Liberton.	Scientific Director: Mr J G Watt.

The three NHS production units make freeze-dried factor VIII Concentrate by the same process which is that described by Newman et al based on cryoprecipitation and purification of the cryoprecipitate by washing. The washed precipitate is then dissolved, dispensed and freeze-dried.

There are quite considerable differences in the final product.

[Ref: Newman et al (1971) Methods for the production of clinically effective intermediate and high-purity factor VIII Concentrate. British Journal of Haematology, 21, 1-20]

CLINICAL PREFERENCES FOR THE AVAILABLE FACTOR VIII CONCENTRATES

A limited survey among users of factor VIII Concentrates (14 clinicians in 9 centres) has revealed clear preferences, usually for one product.

Factors mentioned as being of significance are:

1. Availability of the product
2. Cost of the product
3. Presentation, including availability of a selection of dose sizes, inclusion of needles, filter needle, syringe, diluent.
4. Volume of diluent required
5. Solubility of product
6. Activity of reconstituted product
7. Risk of transmission of viral hepatitis
8. Presence of blood iso-agglutinins
9. Levels of fibrinogen and other proteins

1. Availability of the product

There is a more than adequate supply of commercially produced factor VIII Concentrate. Haemofil is the product most commonly bought; more Kryobulin is now being bought, there has been little uptake of Profilate.

NHS concentrate is in short supply but production rates are increasing. It is still necessary for the BPL, Elstree and PFC, Liberton to 'ration' their concentrates. The situation is better in Oxford where Dr Bidwell's laboratory is able to supply a greater proportion of the Haemophilia Centre's needs for concentrate. When PFC, Liberton is fully commissioned and BPL, Elstree working to full capacity (twice the present production rate) it is anticipated that the UK demand for factor VIII Concentrate will be met from NHS sources.

2. Cost of factor VIII Concentrates

The commercial products are priced according to the declared factor VIII activity; the pack include needles, filter needle, syringe, diluent etc.

Current prices

'HEMOFIL'	12p per unit
'KRYOBULIN'	12p per unit
'PROFILATE'	10p per unit

Concentrate produced by the NHS is issued free of charge to clinicians. However it costs £3 to £5 to collect 1 donation of blood and if infusions must be given the cost of a giving set (£) and needles, syringe and diluent must be added to the estimated cost of 6p per I.U. factor VIII. For comparison it has been estimated that the cost of production of factor VIII as cryoprecipitate is 2p per I.U.

[From a study by: Dr Felicity Carter et al, University of Strathclyde]

3. Presentation

	Sizes of vials (average)	Diluent	Other contents of pack
'HEMOFIL'	250 I.U.	Sterile water for injection U.S.P. 10ml	Needle Filter needle 12ml Luer syringe
	800 I.U.	?	
		Water for injection B.P.	
'KRYOBULIN'	100 I.U.	10ml)	Syringe Filter 3 needles
	250 I.U.	20ml) -	
	500 I.U.	40ml)	
	1000 I.U.	100ml	Transfer tube Giving set with filter
'PROFILATE'	Content as stated: usually	Water for injection U.S.P.	
	250 I.U.	25ml	?
BPL, ELSTREE	Dispensed in small transfusion bottle: (400ml)	Water for injection B.P.	
	250 I.U.	50ml	None
PFC, LIBERTON	Vials with content (declared) in range:	Water for injection B.P.	
	160 I.U. to 300 I.U.	15ml	None

PFC etc Both planning

BPL, OXFORD - As BPL, Elstree. ~~but currently trying~~ to reduce volume of diluent required.

4 & 5. Volume of diluent required and Solubility of product

The concentrates available demonstrate a wide range of solubility. Clinicians prefer the required volume of diluent to be small so that a haemostatic dose of factor VIII can be given in small volume by syringe. The generally held view is that if larger volumes of diluent are used and an infusion required then the product could not be recommended for home therapy.

7. correct

The time taken to dissolve is also variable between products and for the NHS products it also varies quite widely between batches.

	Volume for 250IU dose (common in home therapy)	Volume for 750IU dose (commonly used for 'on demand' treatment in hospital)	Time taken to dissolve contents of one vial
'HEMOFIL'	10ml	30ml	5 to 10 minutes
'KRYOBULIN'	20ml	60 to 80ml	Up to 20 minutes
'PROFILATE'	25 ml	75 ml	10 to 15 minutes
BPL, ELSTREE	50ml	150ml	Very variable 10 to 35 minutes
PFC, LIBERTON	15 to 30ml	45 to 90ml	10 to 15 minutes
BPL, OXFORD	Under review	Under review	

6. Activity of reconstituted product

No comparative study has been published but several centres assay the factor VIII content of individual vials from time to time and assay the levels of factor VIII activity pre- and post-treatment. There has been criticism of Hemofil, with low results of in vitro assays. Several factor VIII standards are available. Hyland, makers of Hemofil, have their own; Edinburgh use BS4 and there is an International Standard. It may be that use of differing standards accounts for variation in assay levels.

Kryobulin produces the expected clinical response.

The BPL, Elstree and Oxford products are usually of the stated potency and produce the anticipated clinical response.

The PFC, Liberton product does not always produce the expected haemostasis and factor VIII content has been found to be as low as 50% of the stated content.

7. Hepatitis

The risk of acquiring hepatitis, and in particular hepatitis B, following infusion of factor VIII Concentrates has recently been highlighted. The commercial products are prepared from large pools of fresh human plasma which may contain the causative agents of viral hepatitis.

This is especially likely if the sources of the raw material are paid donors or donors from geographical areas where the diseases are more prevalent. It is not possible to subject the Concentrate to any treatment known to diminish the risk of transmission of hepatitis, ~~since such treatments greatly increase the loss of factor VIII activity during preparation.~~

The commercial products available in the UK carry a warning that a risk of acquiring hepatitis, although small, accompanies the infusion of these blood products. It is now obligatory for commercial firms to test individual donations of blood or plasma for HBsAg and to batch test the final product by radioimmunoassay (RIA).

The NHS products are prepared from small pools of plasma obtained from voluntary donors. Each donation is tested for HBsAg by a method of reversed passive haemagglutination (RPH) or RIA. Each 5 litre pool and each batch of the final product is tested for HBsAg by RIA. It is accepted that no test is 100% certain to identify all infective material and a risk therefore persists albeit very small, of transmitting hepatitis B. However this risk is considerably less than that accompanying the use of commercial products. It should progressively fall as the number of antigen positive individuals in the donor pool in the UK falls following the introduction of more sensitive tests for HBsAg on all donations and exclusion of HBsAg individuals. Some clinicians accept the risk of using Hemofil, claiming that the benefits of using a high purity product outweigh the risk of transmitting hepatitis particularly for the severely affected patient who is less susceptible following repeated and frequent treatment. Others prefer to use an NHS product regardless of the relative inconvenience of using these products to avoid the risk.

8. Blood Group Iso-agglutinins

A few cases have been reported of intravascular haemolysis and progressive anaemia for which no other cause can be found following repeated and massive doses of factor VIII Concentrate. It is unlikely that plasma from donors with high-titre anti-A or anti-B would be included in the NHS plasma pool as these donors are usually known and their plasma used as a source of anti-A and anti-B but in the event that a concentrate did contain unusually high levels of these antibodies the dilution in the circulating blood volume would minimise their adverse effect. When large doses of factor VIII Concentrate are given repeatedly the risk of haemolysis being produced is increased.

The commercial producers warn clinicians of the possibility and suggest that patients of blood groups A, B and AB should be monitored for signs of intravascular haemolysis and falling haematocrit values when they must be given massive doses of factor VIII. One centre (Manchester) is at present investigating the levels of anti-A and anti-B in Hemofil and Kryobulin.

Ref.1. Rosali, L A et al (1970) Haemolytic anaemia due to anti-A in concentrated antihemophilic factor preparations. Transfusion, 10, 139-141.

2. Seeler, R A (1972) Haemolysis due to anti-A and anti-B in factor VIII preparations. Archives of Internal Medicine, 130, 101-103.

9. Fibrinogen levels

The levels of fibrinogen and other proteins in Hemofil are reduced during production. Theoretically, hyperfibrinogenaemia could follow the administration of large doses of factor VIII Concentrate but in practice high levels are tolerated well and do not produce adverse effects following administration of either commercially - or NHS - produced factor VIII Concentrate.

SUMMARY OF USERS' VIEWS

Only a small group of users was approached but they were fairly consistent in their preferences which are summarised below:

1. Users like the ease of reconstitution of the commercial products and the resulting small volume of a haemostatic dose of factor VIII even for adult patients. This is particularly true of Hemofil.

2. For home therapy a small volume dose is essential. Some patients on home therapy use cryoprecipitate but the majority are on high or intermediate purity concentrates. a small dose (approximately 250u) of Hemofil given early often produces haemostasis.

3. The risk of transmission of viral hepatitis, particularly following the use of Hemofil and particularly to the less severely affected haemophiliac is recognised. All the clinicians interviewed would for this reason prefer an NHS product, a few consider the risk of infection acceptable as the product is effective; some patients are reported to have refused commercial concentrates following recent publicity.

4. The presentation is important.
The needles, filter, vacuum packing which reduces frothing of Kryobulin is particularly praised.

The 400ml bottles issued by BPL, Elstree and PFC, Oxford are criticised. Storage is difficult. In the event of having to set up an infusion some centres have no means of supporting the inverted bottle (blood/infusion fluids are generally dispensed in plastic packs with loops for hanging: few wards have clips to fit the base of the small transfusion bottle).

? PF Laboratories

5. Ease of reconstitution
Hemofil is on average the quickest and easiest; the factor VIII concentrates produced by BPL, Elstree and PFC, Oxford take the longest time to reconstitute and pool if a large dose is required.

CONCLUSIONS

Clinical preference is for the commercial products based on ease of reconstitution and delivery but there is every indication that NHS products of comparable solubility and ease of reconstitution and of consistently high potency would be used to the exclusion of commercial products.

Effort must be directed towards producing a product available in a small range of dose sizes of consistent potency, soluble in a small volume of diluent. There is no evidence that the levels of fibrinogen and other protein should be reduced but this development could be examined.

It is recognised that yield will drop as high purity is attained, but the aim should be to produce concentrate of intermediate purity, with the solubility of the commercial products otherwise it will be difficult to persuade clinicians to change from commercially produced to NHS produced concentrate.

Cost will be an incentive, also the safety of the product, but attention must be paid to presentation.

There will be a need for about 10% of high-~~priority~~ purity factor VIII Concentrate to treat patients with factor VIII inhibitors and babies.