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ADVISORY COMMITTEE FOR THE NATIONAL BLOOD TRANSFUSION SERVICE

WORKING PARTY TO ADVISE ON PLASMA SUPPLIES FOR SELF-SUFFICIENCY IN BLOOD PRODUCTS IN ENGLAND AND WALES

P R E L I M I N A R Y R E P O R T

MEMBERSHIP OF THE WORKING PARTY

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1. Raw material for the preparation of plasma products can be considered under two headings:

1.1 Normal human plasma for coagulation factor concentrates, normal immunoglobulins and albumin products.

1.2 Antibody-containing human plasma for specific immunoglobulins.

Since the supply of normal human plasma has the greatest impact upon the Regional Transfusion Centres and the Blood Products Laboratory, it was agreed that this aspect would be considered initially.

2. Before the volume of plasma required for self-sufficiency in the various products can be determined it is necessary to determine the amount of each product required for clinical practice.

In essence this is reduced to the need for two groups of products, factor VIII concentrates (FVIII) and albumin, since there is self-sufficiency at present in other coagulation factors and normal immunoglobulin.

2.1 Requirement for FVIII. Representatives of the Haemophilia Directors estimate that by the mid-1980's the annual requirement for FVIII will reach 100 M units for the United Kingdom. Forecasting beyond that time could not be accurate but it was considered that by the 1990's the need for FVIII could reach 150 M units per year.

2.2 Requirement for albumin. The present production of P.P.F. is in the order of 50 Kg. per 1 M of the population per year. In the interim expansion at BPL in 1982 this will be increased to 80-90 Kg. per M per year. The quantity of this product purchased is unknown, nor is the clinical need. In certain European countries its usage reaches 350-375 Kg. per M per year. If sufficient plasma is collected to provide, say, 100 M units FVIII there will be sufficient raw material to provide 250 Kg. per M per year. It is likely that this is considerably in excess of the usage rate at present. For this reason the Working Party agreed that the supply of normal human plasma should be based upon that required to satisfy the needs of FVIII. It recognised, however, that further enquiries with respect to the need for and the use of albumin should be made and propose to ask members of the Advisory Committee to conduct these enquiries in their respective regions.

3. It was agreed that the estimates for plasma supply should be based upon that required to produce 100 M units. Although this total was estimated for the U.K. for the mid-1980's (see section 2.1) it was considered to be unnecessary to correct this for that required in Scotland or to consider a figure higher than this since estimates were vague for a longer period.

4. Type of FVIII preparation required. The Working Party has examined the various products available and considered the advantages and disadvantages of each, which are discussed in Appendix I.

Small pool frozen or freeze-dried cryoprecipitate has advantages for patients requiring infrequent treatment since exposure to a large number of donations of plasma is avoided and with this a lessened risk of the transmission of hepatitis. In those countries where this is the primary FVIII product there is no obligation to attain standards required by an independent agency; it would be difficult to produce a similar product in the U.K. However, because of the importance further consideration is being given to the preparation of this product and to this end a questionnaire has been sent to various international fractionation centres.

Large pools increase exposure of the patient, but this can be reduced in the future by using donations obtained by plasmapheresis from a selected group of donors whose medical history is kept under close observation. With this in mind, it is the opinion of the Working Party that the intermediate purity concentrate is the product of choice for the major therapy of haemophilia A.

This view was also given by the representatives of the Haemophilia Directors who considered that it may be necessary to have up to 10% each of the total factor VIII as small pool freeze-dried cryoprecipitate and high purity concentrate.

It was agreed that, although the above proportions of the various products were not fully agreed they served as a good basis for the determination of plasma needs.

Therefore, in the total of 100 M units FVIII:

Freeze-dried cryoprecipitate	=	10 M units per year
Intermediate purity concentrate	=	80 M units per year
High purity concentrate	=	10 M units per year

5. Yields of FVIII. In addition to volume it is necessary to consider the possible yield of FVIII per Kg. plasma. After careful consideration the Working Party proposes the following:

Freeze-dried cryoprecipitate	=	350 units per Kg.
Intermediate purity concentrate	=	225 units per Kg.
High purity concentrate	=	90 units per Kg.

6. Amount of plasma required. Quantities of plasma will be given in Kg. since this is the unit of measurement normally used at BPL. (1 Kg. plasma is approximately 1 litre).

Assuming total of 100 M units FVIII and yields as stated above:

10 Kg. freeze-dried cryoprecipitate requires	28,500 Kg. plasma
80 Kg. intermediate purity concentrate requires	350,000 Kg. plasma
10 Kg. high purity concentrate requires	110,000 Kg. plasma
Total	488,500 Kg. plasma

It was agreed that the aim should be to obtain annually 500,000 Kg. plasma which must be separated from the red cells and frozen within 18 hours after collection.

7. Methods for obtaining 500,000 Kg. plasma annually.

7.1 Yield of plasma from donations of whole blood

During 1980 2.032 M donations of whole blood were collected by the RTCs. Enquiry of the R.T.Ds. has established that the additional donations which would have been required to satisfy clinical need were an additional 125,000 donations. It is difficult to forecast the need for red cells in the mid-1980's but the Working Party considered that a total of 2.2 M donations was a reasonable estimate.

Also, it has been estimated that the plasma from 51% of the donations could be separated within 18 hours provided that adequate facilities and staff were available. This will realise some 200,000 Kg. plasma for fractionation.

7.2 Methods to produce balance of 300,000 Kg. fresh plasma

7.2.1 Increasing the collection of whole blood

If plasma was separated pro-rata from an increased collection of whole blood, it would require 5.5 M donations annually. This would, inevitably, lead to waste and the Working Party do not consider this to be a viable proposition.

7.2.2 Introduction of plasmapheresis

Several countries use plasmapheresis, i.e. separation of plasma from red cells of the donor with return of the red cells to the donor, as a source of plasma for the fractionation of plasma for coagulation factors.

Plasmapheresis can be conducted in two ways:

(a) Manual procedures: These have been well tried for the collection of antibody-specific plasma. However, in order to collect 500 Kg. plasma per donation the time required is 1-1½ hours. This has been put forward as a disadvantage in the recruitment of large panels of such donors, although it is used successfully in Belgium.

(b) Machine procedures: Several machines have been devised which are efficient in separating plasma from red cells. Some employ a continuous procedure and require two needles to be inserted into the veins of the donor, while others are discontinuous and can be used with one venepuncture. 500 Kg. plasma can be collected in about 35 minutes which is attractive from the point of view of donor recruitment.

The Working Party recommend that the balance of 300,000 Kg. fresh plasma is collected by plasmapheresis. This will require the establishment of Plasmapheresis Centres in the regions and the recruitment of donor panels to service them. Machine procedures were, in general, preferred but manual pheresis could be undertaken in favourable circumstances.

8. Collection of plasma by pheresis

W.H.O. recommendations limit the volume of plasma collected annually from a donor to 15 Kg. It was agreed that this volume should not be exceeded. From the pilot study at Leeds RTC it was concluded that a maximum of 5 donations (2.5 Kg.) per year may be preferable from the viewpoint of retaining donors on the panel. It was considered that 30 donations per year to obtain 15 Kg. plasma would be unlikely to be achieved and the maximum would be 10 Kg. (20 donations). The effect on the number of donors required on donor panels to yield 10 Kg. and 2.5 Kg. plasma per year is shown in Table 1.

The recruitment of the donors for plasmapheresis will be the subject of further consultation but even at the level of 3.2 per 1000 of the population this should not prove insuperable if resources are made available.

9. Establishment of Plasmapheresis Centres

The general view of the Working Party was that such Centres were probably best established in urban conurbations. However, it was agreed that Centres in small towns should not be ruled out since this had proved successful in Belgium.

Combination of such Centres with therapeutic plasmapheresis units was considered to be undesirable.

10. Estimate of cost of collecting additional donations of whole blood and 300,000 Kg. plasma by pheresis

10.1 Cost of additional 125,000 whole blood donations:

Capital cost	£250,000.
Collection cost (£6 per unit)	£750,000.
Processing cost (£7 per unit)	£875,000.
Total	£1,875,000.

Thus, cost in first year is £1,875,000
and annual recurring cost of £1,625,000.

10.2 Cost of plasmapheresis

Three estimates have shown the cost to be approximately £50 per Kg. plasma.

Therefore the annual cost of obtaining 300,000 Kg. is £15,000,000.

These costs do not include:

(a) cost of additional donor recruitment
(b) cost of additional separation of plasma from whole blood within 18 hours from the 70,000 Kg. at present achieved
(c) cost of setting up plasmapheresis centres.

The costs involved in collecting the plasma must be balanced against the value of the products obtained from the plasma. Table 2 shows what could be obtained from one Kg. plasma and what will probably be required. Admittedly, production costs have to be added to that of plasma collection but the overall savings are clearly demonstrated.

11. Regional self-sufficiency

If it is assumed that the usage of FVIII concentrates will be pro-rata to population, the amounts of plasma to be collected by each region by plasmapheresis and the estimated number of plasmapheresis units is shown in Table 3. This assumes that 10,000 Kg. (approx.) will be collected in an eight-bedded unit per year.

However, it is known that the use of FVIII is not the same in each region which will lead to anomalies. Thus some regions would have to expend large sums to achieve self-sufficiency while others could achieve this state relatively easily. Until self-sufficiency is reached, every region has an incentive to produce as much fresh plasma as possible; thereafter there is no incentive unless surplus plasma can be offered elsewhere with suitable financial recompensation. Also, the situation may arise where an RTC cannot provide sufficient plasma due to lack of facilities which cannot easily be remedied. It is clear that further consideration must be given to this aspect.

TOTAL AMOUNT PLASMA REQUIRED PER YEAR Kg.	PLASMA PER DONATION Kg.	NO. DONATIONS AT 10 Kg. PER YEAR (20 donations)	ESTIMATED NO. OF DONORS ON PANELS*	NO. DONATIONS AT 2.5 Kg. PER YEAR (5 donations)	ESTIMATED NO. OF DONORS ON PANELS*
300,000	0.5	30,000	40,000 i.e. 0.8 per 1000 of population	120,000	160,000 i.e. 3.2 per 1000 of population

* Estimate is base on recruitment of 30% more donors than actually donate per year to compensate for non-attendances. This could be greater than estimated if donors were asked to donate 20 times per year.

TABLE 1.

REGION	POPULATION M.	PLASMA REQUIRED PER YEAR Kg.	NO. OF PLASMAPHERESIS CENTRES
Northern	3.0	18,000	2
Yorkshire	3.1	18,600	2
Trent	4.7	28,200	3
East Anglia	1.9	~~6,000~~ 11,400	1
N.W. Thames	3.4	20,400	2
N.E. Thames	3.4	20,400	2
S.E./S.W. Thames	6.5	39,000	4
Wessex	2.4	14,400	1-2
Oxford	2.3	13,800	1-2
S. Western	3.4	20,400	2
W. Midlands	5.2	31,200	3
Mersey	3.2	19,200	2
N. Western	4.5	27,000	3
Wales (Cardiff)	2.2	13,200	1-2
			(Total 29-32)

TABLE 3

APPENDIX I

1. Fresh-frozen plasma is prepared at RTCs. and whilst it is a valuable source of coagulation factors it cannot play a part in the treatment of haemophilia A.

2. Frozen cryoprecipitate is presented for clinical use in the transfer pack in which it is prepared. It is prepared in RTCs. but it is difficult to have a national programme based on this product because:

   2.1 the high yield is not always attained in large-scale production and lack of confidence in the FVIII content leads to over-ordering and waste.

   2.2 there is a significant incidence of adverse reactions due to the presence of residual plasma.

   2.3 the product is not convenient to store, transport and infuse particularly for home or self-therapy.

   2.4 there are difficulties in ensuring adequate quality assurance and control.

3. Freeze-dried cryoprecipitate:

   3.1 Small pool (8-12 donations) is produced in the Central Laboratories as the primary FVIII product in Finland, Switzerland and the Netherlands. The aim is to obtain a high yield and minimum donor exposure. However, all production methods involve multiple aseptic connections without terminal sterilising filtration of the product and spin-freezing of a relatively dilute solution of FVIII before drying introduces intractable problems of hygiene and thus maintenance of good manufacturing practice (GMP) required in the U.K. will be very difficult.

   3.2 Large pool. Two approaches have been used:

   (a) In Belgium, about 1000 cryoprecipitates, prepared at RTCs. are transported to the fractionation centre, pooled aseptically without sterilising filtration, the pool dispensed in 50-100 ml. volumes, spin-frozen and freeze-dried.

   (b) In France, about 1000 donations of plasma undergo cryo-precipitation in an 'open' process and the redissolved cryoprecipitate filtered through sterilising membranes before spin-freezing and freeze-drying.

   Advantages over small pools are greater consistency of the product and are potentially more secure and a representative sample can be taken for quality control. However, sterilising filtration is expensive in yield and 10% may be lost in rigorous quality control and the GMP problems of spin-freezing remain.

TABLE 1.

Factor VIII product	Pool size dons.	FVIII iu/ml	Sp. act. iu VIII/ mg protein	Yield iu VIII/ kg plasma	Advantages	Disadvantages
Fresh frozen plasma	1-4	0.7	0.011	700	Available in RTCs. Minimum pool size.	"Reactions". Hypervolaemia. ABO matching required. Frozen storage required. Variable, poor quality control.
Frozen cryoprecipitate	1-12	2-5	0.1-0.2	300-400	Available in RTCs. High yield of factor VIII. Minimum pool size.	"Reactions". Variable potency ? over-use. Frozen storage required. Difficult reconstitution. Poor quality control.
Freeze-dried cryoppt.						
(a) small pool	1-12	5-10	0.1-0.2	250-350	Stored +5°. High yield of factor VIII.	High capital investment and revenue costs, therefore centralization. Q.C. compromises for small pools.
(b) large pool	>500	5-10	0.1-0.2	250-350	Stored +5°. High yield of factor VIII. Less variable potency.	GMP problems. Larger pool for HB transmission. Aseptic production or difficult sterilisation by filtration.
"Intermediate" purity concentrate	>500	15-20	0.3-0.5	200-250	Stored +5°. Good potency, solubility for HT. Precise statement of potency. Low risk of reactions. Isoagglutinins etc. predictable. Good GMP and QC potential.	Only feasible as part of central comprehensive fractionation. High capital investment in cold rooms, driers. (Large pools). Reduced yield of cryo (starts from large-scale cryo).
"High" purity concentrates	>>1000	20-30	>0.5	?125	As Intermediate, but slightly greater potency and convenience. Potential improvements in solubility, reduction in e.g. isoagglutinins, ?HB, fibrinogen.	As Intermediate. Very large pools inevitable. Higher "purity" rarely significant. High cost in plasma resources.

4. Intermediate purity concentrates. These concentrates begin with large-pool (500-5000 donations) cryoprecipitation of plasma. The cryoprecipitate is processed to give high potency (15-20 units per ml.), stability, solubility and safety. For each of these attributes there is a penalty in FVIII yield. It has been estimated at BPL that approximately 27% of the initial FVIII activity is lost in this preparation which does not occur in freeze-drying large pool cryo-precipitate. Methods are being examined to reduce these losses.

5. High purity concentrate. Further purification is expensive in yield of FVIII. The product has greater potency for a given volume and potentially has improved solubility and reduction in contaminants such as fibrinogen. It has to be prepared from large plasma pools.

The characteristics of the above FVIII products and the advantages and disadvantages of each are shown in Table 1.