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14 March 1988

Professor John D Cash
National Medical Director
Scottish National Blood Transfusion Service
Headquarters Unit
21 Ellen's Glen Road
EDINBURGH
EH17 7QT

To go with litigation papers.

Dear John

SNBTS RESPONSE TO HIV CONTAMINATION OF BLOOD PRODUCTS

Further to your request for details of SNBTS actions in response to the emergence of AIDS, I have now assembled the enclosed summary of key events.

There is much supportive documentation of these events should this become necessary.

With kind regards

Yours sincerely

DR R J PERRY
Director

Enc

SUMMARY OF SNBTS RESPONSE TO HIV CONTAMINATION OF PFC COAGULATION FACTORS

1. FVIII HEAT TREATMENT DEVELOPMENTS

Early 1982	-	In response to known hepatitis risk of FVIII concentrates, PFC initiated development programme for solution heating of FVIII (publications appended). BPL (Elstree) were exploring dry heat as an option on a collaborative basis with PFC.
1983/1984	-	International debate as to causative agent of AIDS. Consensus view that causative agent was an infectious agent (virus) emerged in mid-1984.
Oct 1984	-	Report from SEBTS of seroconversion of haemophiliac cohort.
Oct 1984	-	SNBTS carried large stock of FVIII (unheated/12 months supply). PFC immediately examined tolerance of this material to withstand dry heat. Established that product would tolerate 68 °C/2hrs.
Oct 1984	-	Present at conference (Groningen) where first virus inactivation results were announced (US) from CDC/Cutter study within one day of results being obtained. Indicated that dry heat at 68 °/1hr inactivates approximately 4 logs virus.
Nov 1984	-	Initiated studies of improved heating of FVIII (68 °/24hrs).
Oct - Dec 1984	-	Heat treatment and clinical trial of existing FVIII stocks.
Dec 1984	-	Issue of heated FVIII to Haemophilia Centres/RTC's.
Jan 1985	-	Recall of all FVIII stocks (RTC and Haemophilia Centres), heat treatment and re-issue on batch dedication basis.
Jan 1985	-	New heating process developed (68 °/24hr) and implemented for all <u>new</u> batches of FVIII.
Jan 1985 - Autumn 1985	-	Routine issues of 68 °/2hr product.
Autumn 1985 - Apr 1987	-	Routine issue of 68 °/24hr product on batch dedication basis.
Mid 86 - Apr 87	-	Development and manufacture of 3rd generation product 75 °/80 °/72hrs (Z8).

Apr 1987 - Present - Routine issue of Z8 on batch dedication basis.

It is noteworthy that as a direct consequence of high stock levels in December 1984 it was possible to exchange and transfuse heated product into the supply sysstem whilst maintaining supply. Also high stock levels and ability to implement a heating programme rapidly meant that product derived from plasma collected in 1983 was subjected to a significant heat treatment process. To my knowledge this was not accomplished elsewhere in the world. In England and Wales for instance, only product derived from plasma collected from early 1985 was subject to heat treatment.

2. FIX HEAT TREATMENT DEVELOPMENTS

1975-1982	-	Explored possibility of polyethylene glycol (PEG) precipitation to reduce product thrombogenicity and increase virus safety.
Oct 1982	-	Initiated development programme for solution heating of FIX concentrates to inactivate virus contaminants.
Feb 1983	-	Initiated project to study thrombogenicity of heated FIX.
Oct 1984	-	Initiated development work on dry heated product as preferred option to solution heating.
Feb - Oct 1985	-	Clinical evaluation and detailed study of product (heated) thrombogenicity. Commercial purchase of heat treated FIX.
Feb 1985	-	Animal studies of heated FIX initiated.
Oct 1985	-	FIX (80°/72hrs) issued for routine use.
Oct 1985 - Present	-	FIX (80°/72hrs) issued routinely throughout Scotland and Northern Ireland.

3. BATCH HISTORY OF FVIII BATCH NO 023110090 ASSOCIATED WITH HIV TRANSMISSION TO SHS HAEMOPHILIACS

This batch was associated with the transmission of HIV to approximately 15 Edinburgh Haemophiliacs. The details of these seroconversions have been extensively reported in the literature by Dr Ludlam.

FVIII Batch No 023110090 was manufactured in November 1983 from plasma collected in the Autumn 1983. Clearly this preceded the availability or introduction of plasma donation testing or product treatments to inactivate HIV (eg heat treatment) either in the UK or internationally.

Following the reports of product infectivity, attempts were made to identify the specific donation(s) which led to the product being infective. These were unsuccessful.

Attached is a summary of the action taken by Dr McClelland and Dr Cuthbertson to effect a batch recall after initial notification by Dr Ludlam of seroconversions.

Batch No 023110090 was in all other respects compliant with the product specification at that time and there were no noteable events during the manufacturing process.

4. PACKAGE INSERTS - AIDS WARNINGS

At no time during the manufacture of non-heated products did we include a specific warning in our insert leaflets that FVIII (or FIX) carried a risk of HIV transmission. Reference to the possibility of hepatitis transmission has always been included, latterly updated to include HIV. I enclose the various texts used for inserts since 1983 and the chronological sequence of their introduction.

5. GENERAL CONCLUSIONS

(i) PFC has been pursuing the development of virus inactivation procedures since before 1982.

(ii) HIV was not established unequivocally as the causative agent of AIDS until at least mid-1984.

(iii) SNBTS made heat treated FVIII available to all Haemophiliacs in December 1984.

(iv) Heat treated imported products were not licenced (by DHSS) in the UK until February 1985 although limited material was available on a named patient basis before that time.

(v) All plasma collected after 1983 (approximately) was processed to heated product.

(vi) By all international standards, the SNBTS took prompt action to reduce the risk of HIV transmission to Haemophiliacs.

(vii) Prior to 1985 the PFC did not include AIDS warnings in package inserts (or other formal product documentation) since there was no firm scientific evidence to support or justify such a warning.

DR R J PERRY
11 March 1988

SOME NOTES ON PFC/SNBTS STRATEGY FOR ELIMINATING THE RISK OF INFECTION FROM COAGULATION FACTOR CONCENTRATES

1. INTRODUCTION

The possibility that human plasma products can transmit infectious agents has been known since the mid-1940's. When coagulation factor concentrates were developed in their modern form (early 1970's) this risk was well appreciated and research into this problem has been underway at PFC since that time. Our first project (supernine 1971-82) concentrated on the possibility of removing viral contaminants by precipitation with PEG.

The technique was not straightforward and could not be easily applied to FVIII concentrates. It was also difficult to be sure that complete removal of all viral contaminants would be achieved routinely at full-scale. For these reasons the project was shelved in the early 1980's in favour of studies on heat treatment, as soon as we become aware that heating of clotting factors might be feasible.

Our initial heating studies (late 1981 - October 1984) concentrated on pasteurisation (ie heating in solution) but we maintained an awareness of an alternative method that emerged later of heating in the freeze dried state via colleagues at BPL/PFL who began investigating this mode of heating in mid-1984. This level of awareness meant that we were able to switch to dry heating studies and introduce this treatment very rapidly as soon as it was known that HIV in FVIII concentrates would be inactivated by this technique (November 1984). Application of this knowledge to FIX concentrates was delayed pending safety studies in animals. This particular requirement was recognised from the beginning of the heat treatment project and steps to set up an appropriate animal study were initiated in February 1983, but the study did not begin until February 1985 due to the difficulty of finding suitable facilities.

2. Heating in Solution

We became aware during 1981 that the pasteurisation of coagulation factors was being developed by Behringwerke. The manuscript that I obtained which described this work (Heimberger et al Drug Res. 31 : 619-622, 1981) was written in German. I passed it to Alex Macleod to see if W. Zolg with whom he was collaborating at Edinburgh University could assist in translating it. By helping with the translation Alex became interested in the subject and began some preliminary experimental work in late 1981 or early 1982. Further data concerning HB infectivity studies in chimpanzees was then obtained by me at the ISBT meeting in Budapest in August 1982 and this encouraged us to continue to pursue the topic. At the 1982 ISBT Congress Hyland also reported that they were heat treating FVIII but the method was not disclosed.

The whole area of virus inactivation of coagulation factors was reviewed in my report of the Congress and this led us to continue pursuing the study of heating in solution as this was the only heating method for which data were available to demonstrate that virus was indeed being inactivated. The principal problem with the method (US patent 4297 344, 1981) was that the published FVIII yield was only 8%. To maintain self-sufficiency this would have to be increased by 3-4 fold. Therefore in October 1982 we began to

investigate alternative stabilisers (based on the observation of Gekko et al, J. Biochem 90: 39-50, 51-60, 1981) to try and improve the yield over heating. Results of our work were submitted to the ISTH in December 1982 and were presented at the ICTH meeting held in Stockholm in July 1983.

Virus inactivation studies were begun at PFC in February 1983 and these demonstrated substantial stabilisation of virus in the pasteurisation for clotting factors in comparison to traditional method of pasteurising albumin.

Modified heating conditions were established to try and improve the degree of virus inactivation as much as possible without loss of too much factor VIII activity and small quantities of material were prepared for a preliminary clinical evaluation. A pilot-scale study of scale-up was then initiated and this was still in progress in 1984 when the project was shelved as soon as information became available that heat treatment in the freeze dried state might be effective in inactivating HIV.

Throughout this period this work was reviewed and supported by the SNBTS factor VIII study group which included both senior SNBTS scientists and expertise from outwith the SNBTS.

There is currently some concern in the USA over the effectiveness of some dry heating regimes and as a consequence most USA manufacturers are now abandoning the dry heat method in favour of pasteurisation despite the much reduced yield that they are believed to be experiencing according to the original Berhingwerke method.

3. Dry-Heating

We first became aware of the concept of heating in the freeze dried state from the work of Rubenstein submitted to the ISBT congress in Budapest in 1982 (the poster was not presented but the abstract was published). However there were no data at this time on the ability of the method to destroy virus(es). We learnt in mid-1983 that others were pursuing this method (eg Armour), and became aware that the technique was limited by product solubility with the less pure products being more severely constrained than the more highly purified products. Some high purity concentrates (s.a. 1 iu/ml) could be heated at 68 °C for 72 hours while intermediate purity material from BPL (0.5 iu/ml) could only withstand heating at 68 °C for 24 hours. The SNBTS concentrate was less pure than that of BPL (to maximise yield) and was not expected to withstand heating for even this length of time. Hence there was considerable doubt about the effectiveness of the dry heat method particularly as it might be applied to the established SNBTS product.

This position changed in November 1984 when we learnt that the HIV virus in factor VIII concentrates was relatively heat sensitive (Groningen symposium) with the report that HIV spiked into concentrate was reduced from 5 logs to 1 log HIV after heating at 68 °C for 1 hour. This information was reported at the Groningen meeting within hours of the results being obtained by CDC (this data was never formally published). On return to PFC we learnt that our current factor VIII product could withstand heating for up to 2hrs at 68 °C and we embarked immediately on a programme of heating all stocks of FVIII in this manner. There were over 10 months supply of FVIII in stock and we were able to heat batches manufactured from mid-January 1984 to the end of October

1984 (production was cancelled for Nov/Dec to carry out various modifications to the building and plant). The time lag from the date of a blood donation through to plasma entering fractionation is usually some 2-3 months hence all donations collected from about October 1983 have been heat treated in a manner which could be expected to inactivate HIV. This significantly predates a) the general acceptance that AIDS is caused by a virus, b) any information concerning the heat sensitivity of HIV, c) any knowledge held by anyone concerning the inactivation of HIV by any method.

Despite the fact that the preliminary CDC data suggested that heating at 68 °C for 2hr might be adequate to destroy HIV we continued with an intensive programme of work (also during Nov-Dec 1984) to discover if we could modify our FVIII concentrate so that more substantial heating could be achieved. We discovered that a modification to the product formulation would allow heating to be extended to 24hrs and this processing change was introduced in January 1985 (ie as soon as we started-up production following the Groningen symposium).

We then continued to carry out further studies on dry heating and this led to the design of a new factor VIII concentrate suitable for more severe heating (ie 75-80 °C/3 days). Production of the 68 °C/24hr product ceased in mid-1986 to be replaced by this more advanced product which carried more security concerning freedom from HIV infection and possibly from other potential infectious agents.

The manufacture of heat treated FIX concentrates was delayed until mid-1985 pending preliminary results from animal studies which were carefully designed to assess the safety of the product vis-a-vis thrombogenic side effects.

P. R. FOSTER
11/3/88

DOCUMENTS APPENDED

1.	1981	Translation of Behringwerke paper by W Zolg and A Macleod
2.	28/1/82	Minutes of First Meeting of SNBTS FVIII Study Group
3.	9-10/2/82	Report of first meetings of Safety Action Group
4.	30/3/82	Minute of FVIII Study Group
5.	30/3/82	Report of Safety Action Group
6.	3/6/82	Minute of FVIII Study Group
7.	15/6/82	Report of Safety Action Group
8.	23/6/82	Report of Safety Action Group
9.	August 82	Extracts from PF report of ISBT Congress
10.	14/10/82	Minutes of FVIII Study Group
11.	14/10/82	Notes recording first expts using Sorbitol for pasteurisation of FIX concentrate
12.	12/11/82	Memo concerning patent situation
13.	12/11/82	Correspondance from JKS acknowledging information concerning use of sorbitol for pastuerisation
14.	16/12/82	Correspondance from DSP on Same
15.	18/12/82	Letter from JGW to JDC concerning patent situation
16.	Dec 82	Abstract submitted to ISTH
17.	11/1/83	Memo from PF concerning prepn of small quantity of pasteurised FVIII for preliminary clinical evaluation
18.	12/1/83	Report of Safety Action Group
19.	7/2/83	Meeting to initiate programme of animal testing for heated FIX concentrate.
20.	August 83	Abstract submitted to BBTS meeting
21.	Dec 83	Abstract submitted to ISBT congress noting stabilising effect of sugars on virus
22.	August 84	Research disclosure summarising our work on pasteurisation
23.	1-2/11/84	Notes of Groningen meeting with first information that modest dry heating might inactivate HIV

24.	20/2/85	Memos concerning heat treatment of FIX re attempts to shorten timescale of animal testing.
25.	1/4/85	Memo concerning problem with in vitro thrombogenicity results on heated FIX
26.	20/5/83	Notes on meeeting to proceed with prepn of heated FIX for clinical trial.
27.	Feb 86	Abstract submitted to ISBT

HISTORY OF FACTOR VIII LEAFLETS

In 1983 the leaflet was coded as PFC 35B (A). A review of the leaflet text was initiated in April 1985. The PFC number had been changed to 55L. (B).

A further review was undertaken in March 1987 when the new product Z8 was introduced, the code number changing to 3L (C).

Last order PFC 35B made 14.3.84 (T0962/L).

First order PFC 55L made 13.6.85 (Y0228/678).

First order PFC 3L made 24.4.87 (800309/678).

The first possible date the PFC 55L leaflet could have been used would be 31.7.85.

When the PFC 3L arrived the remaining PFC 55L were discontinued from use. This was 19.5.87.

Further Information Labels

The original labels were made using the Markem machine.

These were attached to the vials shoulders and cap. (A)

The purchase of the Zeta printer allowed the information to be printed on circular labels. These were affixed to the cap flip top. (B)

Since the start of heat treatment each vial has carried a heat treated sticker and the box outers have carried a similar statement on both box ends.

Initially the label said heat treated but in 1984 a standard label pattern was introduced with specific temperatures and times stated. (C & D)

The heat treatment operation is fully documented in Productions Monthly Report - 11/84 to 5/85.

(A BRYCE fviii/1a)

Approved to Fabricate

A, B, C + D

All characters red except line 2 of D which is black

A

HEAT TREATED

B

HEAT
TREATED

C

THIS PRODUCT
HAS BEEN
HEAT TREATED

D

HEAT TREATED
HEATED TO [illegible] FOR [illegible] HOURS

D.

The temperature and number of hours in line 2 are variable figures. These are inserted when batch is being furnished.

HUMAN ANTIHAEMOPHILIC FACTOR – FACTOR VIII CONCENTRATE

(LYOPHILISED)

Description

This concentrate which is rich in coagulation factor VIII is prepared from frozen indated human plasma by the Scottish National Blood Transfusion Service at the Protein Fractionation Centre, Edinburgh. The method of preparation is based on extraction from controlled cryoglobulin precipitate (1, 2) recovered from plasma volumes requiring up to 4000 donations of plasma.

All plasma used for preparation of factor VIII concentrate is derived from blood collected from volunteer donors and has been screened for the presence of the HB surface antigen using a radioimmunoassay and the preparation has also been examined by more sensitive techniques applied in at least two laboratories external to the place of manufacture. Nevertheless none of these tests are of sufficient sensitivity to eliminate the possibility of transmitting hepatitis. Methods for examination of the product continue to be developed but the risk of transmission cannot be disregarded.

Factor VIII concentrate contains natural blood group antibodies derived from the plasma of origin. The amounts present are not significant except in circumstances where very large volumes are being administered over a long period (as in major surgery). In such circumstances patients of the blood groups A, B or AB should be observed for evidence of intravascular haemolysis.

The reconstituted product contains not more than 60gl l total protein less than 200 m. mol/l sodium ions and not more than 50 m. mol/l citrate ions.

Storage

Factor VIII concentrate should be stored in the dark at temperatures below 5°C. Maintenance of potency is best achieved at temperatures below −35°C but at least 90 per cent of the stated potency should be recoverable after 12 months storage at temperatures between 0 and 5°C. The accompanying vial of water for reconstitution cannot be stored safely below 0°C.

Resolution from the Dry State

If the material has been stored below freezing point it should be allowed to remain at room temperature for at least 15 minutes before resolution is commenced. The volume of water stated on the label, which is calculated to provide a solution approximately isotonic with human plasma, should be added by aspiration from the accompanying vial and added to the dry powder using a syringe, employing strict aseptic techniques. The addition of water should be a gentle process. The bottle containing the mixing solution should be rolled gently on a flat surface using the palm of the hand so that at least three complete revolutions occur. It should then be allowed to stand without further agitation.

Within twenty minutes the solution should be seen to have become slightly opalescent but with no solid material visible. If a clot or gel is seen to form the solution should not be used for clinical administration but should be returned and a report made of the incident to the Transfusion Centre or Haemophilia Treatment Centre from which the product was obtained.

Where more than one container is required to provide a clinical administration there may be advantage in pooling the contents of several containers but this should be done using care to avoid microbiological contamination. The volume of the concentrate collected into one pool should not be greater than will be administered within a period of two hours following resolution.

Reconstituted factor VIII concentrate solution should not be stored.

Administration

Factor VIII concentrate should be administered as soon as practicable after solution is complete and should continue slowly at a rate not exceeding 3ml/minute. A slower rate is to be recommended for the first administration of a series. The administration should be by intravenous injection or infusion using plastics or siliconised glass equipment. A catheter or butterfly needle may be used for injection. Continuous infusion over long periods is to be avoided and the product should not have addition made to it nor should it be added to other infusion fluids.

The actual volume of solution required for any administration depends on the haemophiliac status of the individual patient and the purpose of treatment. As a general guide it can be stated that, in a patient without active haemorrhage, an infusion of 1 international unit per kilogramme body weight will produce an average increase of about 2 IU/100 ml of plasma. Presence of abnormally low response in absence of blood loss from the circulation may indicate the presence in the patient of an antibody specific to factor VIII. Treatment will require to be repeated at varying intervals to maintain the required concentration of factor VIII activity in the plasma. Intervals between administration are usually 4, 8, 12 or 24 hours as appropriate.

Side Effects

Complications in the use of factor VIII concentrate are rare. Apart from the general complications of hepatitis and intravascular haemolysis (see above) some patients may occasionally experience slight irritation at the site of injection. A transitory headache or nausea following the administration of factor VIII concentrate has also been reported and for individual patients this appears to be related to a particular batch of the product.

References

1. Newman, J., Johnson, A. J., Karpatkin, M. H. and Puszkin (1971) British Journal of Haematology 21:1-20.
2. James, H. L. and Wickerhauser, M. (1972) Vox Sanguinis 23:402-412.

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P.F.C.358 Waddie & Co.

Prod.Lic.3473/0007

(LYOPHILISED)

Description

This concentrate which is rich in coagulation factor VIII is prepared from frozen indated human plasma by the Scottish National Blood Transfusion Service at the Protein Fractionation Centre, Edinburgh. The method of preparation is based on extraction from controlled cryoglobulin precipitate (1, 2) recovered from plasma volumes requiring up to 4000 donations of plasma.

All plasma used for preparation of factor VIII concentrate is derived from blood collected from volunteer donors and has been screened for the presence of the HB surface antigen using a radioimmunoassay and the preparation has also been examined by more sensitive techniques applied in at least two laboratories.

The product has been heat treated at 68°C for twenty-four hours in the dried state (3) but it cannot be assumed that the product is non-infective.

Factor VIII concentrate contains natural blood group antibodies derived from the plasma of origin. The amounts present are not significant except in circumstances where very large volumes are being administered over a long period (as in major surgery). In such circumstances patients of the blood groups A, B or AB should be observed for evidence of intravascular haemolysis.

The reconstituted product contains not more than 60g/l total protein, not more than 40g/l sucrose, less than 200 m.mol/l sodium ions and less than 50 m.mol/l citrate ions.

Storage

Factor VIII concentrate should be stored in the dark at temperatures below 5°C. Maintenance of potency is best achieved at temperatures below −35°C but at least 90 per cent of the stated potency should be recoverable after 12 months storage at temperatures between 0 and 5°C. The accompanying vial of water for reconstitution cannot be stored safely below 0°C.

Resolution from the Dry State

If the material has been stored below freezing point it should be allowed to remain at room temperature for at least 15 minutes before resolution is commenced. The volume of water stated on the label, which is calculated to provide a solution approximately isotonic with human plasma, should be added by aspiration from the accompanying vial and added to the dry powder using a syringe, employing strict aseptic techniques. The addition of water should be a gentle process. The bottle containing the mixing solution should be rolled gently on a flat surface using the palm of the hand so that at least three complete revolutions occur. It should then be allowed to stand without further agitation.

Within twenty minutes the solution should be seen to have become slightly opalescent but with no solid material visible. If a clot or gel is seen to form the solution should not be used for clinical administration but should be returned and a report made of the incident to the Transfusion Centre or Haemophilia Treatment Centre from which the product was obtained.

Where more than one container is required to provide a clinical administration there may be advantage in pooling the contents of several containers but this should be done using care to avoid microbiological contamination. The volume of the concentrate collected into one pool should not be greater than will be administered within a period of two hours following resolution.

Reconstituted factor VIII concentrate solution should not be stored.

Administration

Factor VIII concentrate should be administered as soon as practicable after solution is complete and should continue slowly at a rate not exceeding 3ml/minute. A slower rate is to be recommended for the first administration of a series. The administration should be by intravenous injection or infusion using plastic or siliconised glass equipment. A catheter or butterfly needle may be used for injection. Continuous infusion over long periods is to be avoided and the product should not have addition made to it nor should it be added to other infusion fluids.

The actual volume of solution required for any administration depends on the haemophiliac status of the individual patient and the purpose of treatment. As a general guide it can be stated that, in a patient without active haemorrhage, an infusion of 1 International unit per kilogramme body weight will produce an average increase of about 2 IU/100 ml of plasma. Presence of abnormally low response in absence of blood loss from the circulation may indicate the presence in the patient of an antibody specific to factor VIII. Treatment will require to be repeated at varying intervals to maintain the required concentration of factor VIII activity in the plasma. Intervals between administration are usually 4, 8, 12 or 24 hours as appropriate.

Side Effects

Complications in the use of factor VIII concentrate are rare. Apart from the general complications of hepatitis and intravascular haemolysis (see above) some patients may occasionally experience slight irritation at the site of injection. A transitory headache or nausea following the administration of factor VIII concentrate has also been reported and for individual patients this appears to be related to a particular batch of the product.

References

1. Newman, J., Johnson, A.J., Karpatkin, M.H. and Puszkin (1971) British Journal of Haematology 21:1-20.
2. James, H.L. and Wickerhauser, M. (1972) Vox Sanguinis 23:402-412.
3. MMWR Vol 33 No 42 1984 Page 589-591.

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P.F.C.55L Waddle & Co. 5/4/85 Prod.Lic.3473/0007

HUMAN ANTIHAEMOPHILIC FACTOR – FACTOR VIII

CONCENTRATE (Z8; HEAT TREATED)

Description

This concentrate which is rich in coagulation factor VIII is prepared from frozen indated human plasma by the Scottish National Blood Transfusion Service at the Protein Fractionation Centre, Edinburgh. The method of preparation is based on extraction from controlled cryoglobulin precipitate (1, 2) recovered from plasma volumes requiring up to 4000 donations of plasma.

All plasma used for preparation of factor VIII concentrate is derived from blood collected from volunteer donors and has been screened for the presence of the Hepatitis B surface antigen using a sensitive immunoassay and the preparation has also been examined for this antigen by more searching techniques applied in at least two laboratories. In addition, product, plasma pools and individual plasma donations are tested for the presence of antibody to HIV. The product has been heat-treated at 80°C for 72 hours in the freeze dried state. This treatment is expected to inactivate viruses associated with the Acquired Immune Deficiency Syndrome (HTLVIII, LAV, ARV) (3, 4, 5). The effect of this heat-treatment on Hepatitis B, and Hepatitis, non A non B has still to be elucidated and therefore, this product cannot be assumed to be non-infective with regard to the hepatitis viruses.

Storage

Factor VIII concentrate should be stored in the dark at temperatures between 2°C to 5°C.

Resolution From the Dry State

The material should be allowed to remain at room temperature for at least 15 minutes before resolution is commenced. For reconstitution, 20 ml of Water for Injections should be added by aspiration from the accompanying vial and added to the dry powder using a syringe, employing strict aseptic techniques. To provide a solution approximately isotonic with human plasma, this recommended reconstitution volume must be used. The addition of water should be a gentle process. The bottle containing the mixing solution should be rolled gently on a flat surface using the palm of the hand so that at least three complete revolutions occur. It should then be allowed to stand without further agitation.

Within thirty minutes the solution should be seen to have become slightly opalescent but with no solid material visible. If a clot or gel is seen to form the solution should not be used for clinical administration but should be returned and a report made of the incident to the Transfusion Centre or Haemophilia Treatment Centre from which the product was obtained.

Where more than one container is required to provide a clinical administration there may be advantage in pooling the contents of several containers but this should be done using care to avoid microbiological contamination. The volume of the concentrate collected into one pool should not be greater than will be administered within a period of two hours following resolution.

Reconstituted factor VIII concentrate solution should not be stored.

Administration

Factor VIII concentrate should be administered as soon as practicable after solution is complete and should continue slowly at a rate not exceeding 3 ml/minute. A slower rate is to be recommended for the first administration of a series. The administration should be by intravenous injection or infusion using plastic or siliconised glass equipment. A catheter or butterfly needle may be used for injection. Continuous infusion over long periods is to be avoided and the product should not have addition made to it nor should it be added to other infusion fluids.

The actual volume of solution required for any administration depends on the haemophilic status of the individual patient and the purpose of treatment. As a general guide it can be stated that, in a patient without active haemorrage, an infusion of 1 international unit per kilogramme body weight will produce an average increase of about 2 iu/100 ml of plasma. The presence of an abnormally low response in the absence of blood loss from the circulation may indicate the presence in the patient of an antibody specific to factor VIII. Treatment will require to be repeated at varying intervals to maintain the required concentration of factor VIII activity in the plasma. Intervals between administration are usually 4, 8, 12 or 24 hours as appropriate.

Side Effects

Complications in the use of factor VIII concentrate are rare. Apart from the general complications of hepatitis and intravascular haemolysis (see above) some patients may occasionally experience slight irritation at the site of injection. A transitory headache or nausea following the administration of factor VIII concentrate has also been reported and for individual patients this appears to be related to a particular batch of the product.

References

1. Newman, J., Johnson, A. J., Karpatkin, M. H. and Puszkin (1971) British Journal of Haematology 21 : 1-20.
2. James, H. L. and Wickerhauser, M. (1972) Vox Sanguinis 23:402-412.
3. MMWR Vol 33 No. 42 1984 Page 589-591.
4. Levy, J. A., Mitra, G. A., Wong, M. F., Mozen, M. M., (1985) : Lancet 1 : 1456-1457.
5. McDougall, J. S., Martin, L. S., et al (1985) : J. Clin Invest 76 : 875-877.

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE
PROTEIN FRACTIONATION CENTRE
21 ELLEN'S GLEN ROAD
EDINBURGH EH17 7QT

July

~~29-11~~-84 Letter to TDs:-

a. Leaflet (Blue)

"Important Message to Blood Donors" leaflet to be issued in every call-up letter.

All donors issued with a leaflet at sessions.

Local organisers to distribute leaflet in advance to those who don't get call-up letter.

Leaflet to be enclosed with new donor registration book.

b. Questionnaire

Each donor asked to sign a statement, prior to blood withdrawal, "I have read the SNBTS AIDS leaflet (Important Message to blood donors) and confirm that, to the best of my knowledge, I am not in one of the defined transfusion - related risk groups.

Sept 85 REVISED LEAFLET ISSUED - (Red)

19-08-86 CoGp - abandon single leaflet: send out (a) health check including up to date exlusions) and a general info leaflet.

18-11-86 Revision of Donor Exclusion categories

08-12-86 Issue of revised donor exclusion categories; to be in use by 31-12-86. (Revision 2)

09-01-87 Revision 3. Issued to TDs 09-01-87 (8/1/87 CoGp)

Decisions

a. Abandon Red leaflet (New info etc) - out of date

b. Use Self Exclusive criteria

c. Issue general leaflet (as per J Gillon

27-02-87 Revision 4 issued to TDs for use from 04-05-87

26-03-87 Revision 5 issued to TDS for use from 04-05-87