The choice of safe clotting factor concentrate for treatment of haemophilia in Hong Kong - recommended guidelines

Scientific Committee
of
the Advisory Council on AIDS
Hong Kong

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1. Introduction

Scientific and medical evidence is now sufficiently well established to merit an update in therapeutic policy for the management of haemophilia. The purpose of this paper is to review recent scientific data on coagulation concentrate therapy, and the efficacy and safety of these products.

Concentrates (table I) currently used for various bleeding disorders are listed below with details of manufacturing method and specific activity, and the level of contaminated protein.

Table I : Currently available F VIII concentrate – derived from human plasma

Type	**Production method**	**Sterilisation**	**Specific activity * (u/mg)**	**Contaminating protein**
Plasma (for comparison)			0.017	
Crude (cryoprecipitate)	Cryoprecipitate	None	0.1-0.9	Abundant plasma proteins, in particular fibrinogen & fibronectin.
Second generation concentrates of **intermediate purity (IP)**	Conventional fractionation methods	Yes	1-10	<1% F VIII, contains many plasma proteins - fibrinogen, fibronectin, immunoglobulins and â2microglobulin.
Third generation concentrates of **high purity (HP)**	Conventional chromatographic techniques Immunoaffinity purification (immobilised monoclonal antibodies)	Yes	100-250 (no albumin added, the vWF present stabilizes F VIII). 9-22 (after addition of albumin). 2-15 (final product); prior to albumin addition (for stabilization), the specific activity could be up to 2500-3000.	Trace amounts of fibrinogen & fibronectin. Albumin contain 2-5% impurities. Murine proteins from the monoclonal antibodies may be present in minute quantities.

* specify activity = units of activity per unit of protein content (u/mg)
[appendix (pages 6-11) : high purity factor VIII, factor IX products currently available]

2. Viral safety of clotting factor concentrates

The efforts to reduce the risk of viral disease arising from the use of clotting factor concentrates have been quite successful. However, additional steps need to be taken to further protect the users of these products.

Step One: Mass screening of HBsAg, anti-HCV and anti HIV-1 and -2 to reduce viral burden.

- HBsAg testing screens out over 99% of the infected donors.
- The sensitivity of anti-HCV test is considerably less compared to that of HBsAg. All plasma pool should therefore be considered as potentially HCV contaminated.
- Anti HIV-1 and -2 screening test is highly sensitive. However, all plasma pool should be considered as potentially HIV contaminated because of the "window period".

Step Two: Physical or chemical methods are used to inactivate or remove contaminating viruses. All clotting factor concentrates now undergo at least one viral attenuation process in addition to purification viz:

- Wet heat.
- Dry heat at 80°C for 72 hours (BPL, UK).
- Solvent-detergent treatment to disrupt membranes of lipid enveloped viruses.
- Physiochemical treatment with B-propiolactone and ultraviolet irradiation.
- Immunoaffinity chromatography.

This two-step approach has been highly effective and is essentially safe with respect to transmission of viral infections.

3. General therapeutic recommendations

3.1 Hepatitis B vaccination

All patients who are sero-negative to hepatitis B and are either receiving blood products or could be considered, because of their medical condition, to be eligible for blood product therapy at any stage, should be immunized against hepatitis B. Such patients require regular follow-up of their hepatitis B medical status and revaccination when appropriate.

3.2 Use of DDAVP (Desmopressin acetate)

All patients with moderate/mild haemophilia and mild vWD should preferably be

assessed for response to DDAVP as part of their initial assessment. For such patients, defined efficacy of DDAVP therapy would be highly cost-effective in their management, and would reduce the risks of unnecessary exposure to blood product therapy.

3.3 Use of Cryoprecipitate

Prior to development of effective viral attenuation of commercial lyophilized factor VIII concentrates, cryoprecipitate was considered safer from transmission of viral infections because of the reduced number of donor exposure, ie 4 to 16 donor units per treatment, as compared to exposure to 10,000 to 20,000 donor units per single lot of commercial concentrate. The latest recommendation from the UK Regional Haemophilia Centre Directors Committee (1993) was to discontinue use of cryoprecipitate if viral inactivated concentrates are available.

4. Specific recommendations: HIV viral safety

4.1 Patients who are HIV seropositive

In HIV seropositive haemophilia patients requiring blood products therapy, high purity (HP) factor VIII/IX products should replace IP materials to restrict immunosuppression.

4.2 Patients who are HIV seronegative

- There is now considerable evidence that improved viral-depleting processes and donor screening practices have resulted in factor VIII products with greatly reduced risk for transmission of HIV. No seroconversions to HIV have been reported with any of the factor VIII products currently marketed in the United States/UK, including products that are heated in aqueous solution (pasteurized), solvent-detergent treated, and/or immunoaffinity purified. Thus, each of these methods appear to have greatly reduced risk of HIV transmission as compared to older methods of viral inactivation.

- ***Recombinant Factor VIII (rFVIII)***
  While there have been no reported seroconversions to HIV-1, HIV-2 or hepatitis B or C viruses due to the use of currently marketed, viral-inactivated, plasma-derived products, there is always the possibility of human viral transmission. Recombinant factor VIII (rFVIII), produced by well-established hamster cell lines, which have been transfected with a gene for human factor VIII, is stabilized in

human albumin. The risk of human viral contamination is regarded as lower than that of plasma-derived factor VIII products.

4.3 Patients with factor IX deficiencies

In all patients with factor IX deficiency requiring blood product therapy, it is recommended that HP factor IX concentrates be adopted as soon as practically possible within the constraints of availability and licensing. Patients with mild factor IX deficiencies undergoing surgery should be treated with HP factor IX concentrates in preference to fresh frozen plasma.

4.4 Patients with vWD

For the management of symptomatic vWD, it is recommended that IP concentrates should be progressively replaced by more specific HP materials subject to the assessment of data from on-going clinical trials.

* **Relationship between purity and immunoimpairment:** *There is considerable controversy over the issue. Evidence that HP concentrates induce less alterations in parameters of cell-mediated immunity exist, but is by no means conclusive. The UK Regional Haemophilia Director Committee favours the use of HP to IP concentrates, in particular for HIV positive patients in their 1993 recommendation.*

References

1 The National Haemophilia Issue (MASAC) Revised May 8, 1993.

2 Recommendations on choice of therapeutic products for the treatment of patients with haemophilia A, B and vWD (UK Regional Haemophilia Centre Directors Committee) Blood coagulation and fibrivologous Vol. 3, 1992.

3 Viral safety of clotting factor concentrates, seminars in Thrombosis and Haemophilia statistics Vol. 19, No. 1, 1993.

TABLE I. FVIII PRODUCTS LICENSED IN THE U.S.

A. RECOMBINANT (R) VIII PRODUCTS

Product Name	Manufacturer	Method of Viral Depletion/ Inactivation	Specific Activity⧗ Final	Specific Activity⧗ Discounting Albumin	Hepatitis Safety Studies in Humans With this product
Recombinate ä	Baxter	See below **	1.65 to 19 iu/mg Protein	3,000 + *	Yes
Kogenate®	Miles	See below ***	8-30	3,000 + *	Yes

* Representative sample from in-process materials prior to addition of albumin.

** The production process for Recombinate ä contains a number of steps, (immunoaffinity chromatography, exposure to virucidal solutions, pasteurization, etc.) which are capable of inactivating or removing viruses. The process has been validated to inactivate or exclude > 1 x 10^1 log of model enveloped and non-enveloped viruses.

*** The production process for Kogenate® combines anion and immunoaffinity chromatography with heat treatment step. This process has been validated for a 12 log reduction of relevant model viruses.

B. IMMUNOAFFINITY PURIFIED FVIII PRODUCTS DERIVED FROM HUMAN PLASMA

Product Name	Manufacturer	Method of Viral Inactivation	Specific Activity⧗ Final	Specific Activity⧗ Discounting Albumin	Hepatitis Safety Studies in Humans With this product	With another product, but similar viral inactivation method
Monoclate P	Armour	Pasteurized (60°C, 10 h)	@5-10	3,000+	Yes (ongoing)	Yes
Hemofil M	Baxter-Hyland	Solvent-detergent (TNBP/Triton X-100) 25°C, ³ 10 h	@2-11	3,000+	Yes(3)	--
Coagulation FVIII, Method M	(Manufactured by Baxter-Hyland for Am Red Cross)	Solvent-detergent (TNBP/Triton X-100) 25°C, ³ 10 h	@2-11	3,000+	No	Yes(3)

⧗ NOTE: The degree of product purity is reflected by the specific activity of FVIII (units/mg protein). Since most FVIII concentrates (including recombinant FVIII) have human serum albumin added as a stabilizer, most persons look at the specific activity discounting albumin. The immunoaffinity purified FVIII.

C. INTERMEDIATE PURITY AND HIGH PURITY FVIII PRODUCTS DERIVED FROM HUMAN PLASMA

Product Name	Manufacturer	Method of Viral Inactivation	Specific Activity⧗ Final	Specific Activity⧗ Discounting Albumin	Hepatitis Safety Studies in Humans With this product	Hepatitis Safety Studies in Humans With another product, but similar method
Profilate OSD	**Alpha**	**Solvent-detergent (tri(n-butyl) phosphate (TNBP) and polysorbate 80) 27°C, 6 h**	**@6-10**		**No**	**Yes**
Koate-HP	**Cutter**	**Solvent-detergent (TNBP+polysorbate 80), ³ 24°C, 6 h**	**@9-22**	**50**	**No**	**Yes**
NY Blood Center FVIII-SD	**NYBC, Melville Biologics**	**Solvent-detergent (TNBP and Cholate) ³ 24°C, 6 h**	**@1**		**Yes(1)**	**--**
Humate P	**Behringwerke (distributed by Armour)**	**Heated in solution (pasteurized), 60°C, 10 h**	**@1-2**		**Yes(2)**	**--**
Melate SD	**N.Y. Blood Center Melville Biologics**	**Solvent-detergent (TNBP + polysorbate 80) ³ 24°C, 6 h**	**@50-150**		**No**	**Yes**

⧗ NOTE: The degree of product purity is reflected by the specific activity of FVIII (units/mg protein). Since most FVIII concentrates (including recombinant FVIII) have human serum albumin added as a stabilizer, most persons look at the specific activity discounting albumin. The immunoaffinity purified FVIII.

FVIII PRODUCTS LICENSED IN THE U.S. (Continued)

D. PORCINE FVIII

Product Name	Manufacturer	Method of Inactivation	Specific Activity Final	Hepatitis Safety Studies in Humans	
				With this product	With another product, but similar method
Hyate C	Porton/Speywood	None	>50	No (but no report of transmission of human viruses)	No

TABLE II. F IX PRODUCTS CURRENTLY LICENSED IN THE U.S.

A. COAGULATION F IX PRODUCTS

Product Name	Manufacturer	Method of Viral Depletion/ Inactivation	Specific Activity Final	Hepatitis Safety Studies in Humans: With this product	Hepatitis Safety Studies in Humans: With another product, but similar viral inactivation method
AlphaNine	Alpha	Heated in N-Heptane solution, 60 ℃, 20 h and affinity chromatography	@84	No	Yes (with HCV transmission in 1980's)
AlphaNine SD	Alpha	TNBP and Polysorbate 80 24°-30 ℃, >24 h, and affinity chromatography	@190	No	Yes
Mononine	Armour	Monoclonal antibody column, Sodium Thiocyanate, Ultrafiltration	160+	Yes[4]	--

B. F IX COMPLEX CONCENTRATES

		Method of Viral Inactivation			
Konyne 80	Cutter	Dry heat, 80 ℃, 72 h	Not Available	No	Yes[5]
Proplex T	Baxter-Hyland	Dry heat, 68 ℃, 144 h	@47	No	No
Profilnine HT (wet method)	Alpha	Heated in N-Heptane solution 60 ℃, 20 h	@4.5	No	Yes[6] (with HCV transmission in 1980's)
Bebulin	Immuno	Vapor heated (10h, 60 ℃, 1190 mbar pressure plus 1 h, 80 ℃, 1375 mbar)	@2	Yes[7]	--

C. ACTIVATED F IX COMPLEX CONCENTRATES

Autoplex T	Baxter-Hyland	Dry heat, 68 ℃, 144 h	@5	No	No
FEIBA VH	Immuno	Vapor heated (10 h, 60 ℃, 1190 mbar plus 1 h, 80 ℃, 1375 mbar)	@0.8	No	Yes[8]

UK Regional Haemophilia Centre Directors

Table 1. Factor VIII concentrates in UK

Product (manufacturer)	LIC series (type & pence) donor pool	Viral inact. purification	Sp. act. iu/mg (scicatiles)	Cost[>] p/iu
Monoclate P (Armour)	Fail (HP-3) Paid donors	Promission MAb Immunoaffin Chromatography	5-10 (>3000) (Human serum albumin)	37-45
ISM (Kini course vicis BPL — Baxter tack)	Transitional (named patient for 250 i.u vials) (HP-3) Voluntary donors	S/D MAb Immunoaffin Chromatography	5-10 (>2000) (Human serum albumin)	37-44
Kogenate (Cutter/Bayer)	CTX (HP-4) No donors	S/D Gene insertion MAb Immunoaffin Chromatography	5-10 (Human serum albumin)	N/A
SNBTS HP VIII (CRTS Lille concract with SNBTS)	CTX named patient (HP-3) Voluntary donors	S/D Ion exchange Chromatography	>200 None	Central funded free issue
Factor VIII VHP (CRTS Lille)	Named patient (CTX pending) (HP-3) Voluntary donors	S/D Ion exchange Chromatography	>200 None	30-40
Ocavi (Ocupharses)	CTX Named patient (HP-3) Paid donors	S/D Ion exchange Chromatography	>200 None	30-40
Koate HS (Cutter/Bayer)	CTX (HP-3) Paid donors	S/D Gel exclusion Chromatography	>150 None	N/A
8Y (BPL)	Full (IP-2) Voluntary donors	Superheat Conventional	<10 None	19-24
Z8 (SNBTS)	Full (IP-2) Voluntary donors	H.T. Conventional	<10 None	Central funded free issue
Profilase S.D. (Alpha)	Full (IP-2) Paid donors	S/D Conventional	<10 None	16-24
Humate P (Behring)	Full (IP-2) Paid donors	Pasteurization Conventional	<10 None	26-36

S/D—solvent/detergent
[>]cost dependent upon bulk purchase, regional contract, etc.

Table 2. Factor IX concentrates in UK

Product (manufacturer)	LIC series (type & pence) donor pool	Viral inact. purification	Sp. act. iu/mg (scicatiles)	Cost[>] p/iu
Defix (SNBTS)	Full (IP-1) Voluntary donors	H.T. Conventional	<10 None	Central funded free issue
9A (BPL)	Transitional (IP-2) Voluntary donors	Superheat Conventional	<10 None	26-27
Factor IX VHP (CRTS Lille)	Named patient (HP-3) Voluntary donors	S/D Ion exchange Chromatography	>100 None	30-40
Mononine (Armour)	CTX (HP-3) Paid donors	Sodium thiocynate MAb Immunoaffin Chromatography	>200 None	N/A
Alpha Nine (Alpha)	CTX (HP-3) Paid donors	S/D Ion exchange Chromatography	>200 None	N/A

S/D—solvent/detergent

[>] cost dependent upon bulk purchase, regional contract, etc.