

IN CONFIDENCE

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 SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

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Minutes of Meeting of Coagulation Factor Study Group held in Headquarters Unit on 27th February 1986

Present: Dr J D Cash (in the chair)
 Dr F E Boulton
 Dr J Dawes
 Dr P Foster
 Dr D Pepper
 Dr R Perry
 Dr C Prowse

1. INTRODUCTION

ACTION

Apologies were received from Dr G S Gabra and Dr B Cuthbertson.

2. MINUTES OF PREVIOUS MEETING (21st November 1985)

The following amendments were agreed to the previous minutes:

p1. 3A(ii) end of para 1: insert after process. Concern was expressed over the (temporary) cessation of plasma VIII:C monitoring at certain centre(s).

p2. 3A(ii), para 4: 'Vox Sanguinis report from Canada, should'

p3. 3B(v) should read 'Cardiff Studies on Lots 4013 and 4014.'

p4 3Bc(i)

para 2: amend to 'Dr Pepper commented on PFC's findings'

para 3: omit initial 'Acidified.'

p4 3Bc(ii) para 2: delete 2nd sentence and replace by 'A range of viruses had been spiked into FIX and irradiated at 2.5M Rad (arranged by De Pepper). All test viruses had been completely inactivated. It was agreed that Dr Cuthbertson and Dr Pepper should carry out further experiments.'

p5 d(i), para 3: replace (5/week) by (17/week)

p5 d(iii), line 1: replace 'has' by 'had'
 line 6: amend to ... Scotland there may be difficulties in doing this at

PFC, however it was noted that given appropriate resources the technology/process could be developed within PFC; the question of licensing could then be assessed.

line 11: amend to 'results of immunodepletion studies to produce VIII deficient plasma'.

p5 e(i), line 1 - amend to: 'Dr Boulton said 3 patients in Edinburgh, 4 in Cardiff and 2 in Belfast had received heat treated FVIII and been studied in detail.'

p6, 4, para 2, line 4 amend to 'lipid-FVIII complexes do not bind to inhibitor. Therefore'.

3. MATTERS ARISING

a) FFP Specification

(i) Drs Gabra and Boulton still pursuing validation results (FVIII and platelets) from Regional Centres and will also sound out reactions to centralising factor VIII assays.

GG, FEB

(ii) Dr Gabra had sent a draft manuscript on plasma FVIII quality assessment aimed at Vox Sanguinis. This requires
 Comments from the Group
 Data from 1985 QA exercises
 Data on Edinburgh Packs vs Line Study
 Data from Regional Plasma VIII Assays

ALL
 CP
 CP
 GG, FEB.
 CP

(iii) Dr Foster tabled a summary of FVIII assays on thawed Feedstock plasma (Jan 1985 to early 1986). Concern was expressed over discrepancies between PFC and EBTS, FVIII assays and meaning of frozen plasma 'platelet' count. Action agreed:
 Follow up on PFC/EBTS FVIII discrepancy
 Assay BTG in PFC plasma
 EBTS to send recent in house FVIII and platelet count data on unfrozen plasma to R Perry
 EBTS to compare 'platelet' counts and BTG in plasma before and after freezing

CP, FEB
 JD

CP

FEB, CP, JD

b) Centralised Factor VIII Assay System

C Prowse tabled a report on requirements for a proposed central facility. This seems a viable option and the chromogenic assay appears most economic on this scale. The acceptability of such a central facility to be investigated. If accepted by Regional Directors a pilot study of line-sample transport would be required.

GG, FEB
(JDC)

CP

c) Fractionation Update(i) Overview

Dr Perry commented on recent studies on improvements in freezing and freeze-drying conditions that allow more rigorous heating of FVIII, but commented that such changes also result in less viricidal action. Current plans for changes in FVIII product:

- Phase I: current 68°/24h: 7 months stock
- Phase II: improved freezing: 68°/72h:
3 months stock
- Phase III: improved freezing + Zn treat
to allow smaller fill volume
(0.6iu/mg) and improved freeze-
drying: 80°/72h manufacture from
April '86. Issue from Jan '87.
- Phase IV: Hi purity PFC product (50 iu/mg).
80°/72h early large scale viallings
from April '86. (no vWf, this may
be available as side product).

Actions required:

further model virus studies
Trial infusions to haemophiliacs and
v. Willebrand's disease patients to determine
recovery/half-life to be discussed with
Dr Ludlam for Phase III and IV products
(available around April).

BC, PF

FEB

Comments:

Freeze-drying conditions differ between ~~B&L~~ PFL
and Elstree for FVIII product. All, except
two initial batches, material for clinical
trials in E&W now from Elstree. Publication
of PFC results is planned at an appropriate
time.

PF

(ii) Citrate Studies

Dr Prowse reported favourable results for donations collected in half strength citrate regarding platelet and red cell storage by in vitro assay, and confirmed benefits of this for plasma FVIII stability. Autologous cell transfusion studies are being planned. It was suggested that effects of 24h hold of whole blood at room temperature (and 4°C) prior to processing on plasma and cell quality be investigated. A letter to Dr Aronson at the BoB yielded the information that anti-coagulants are only required to yield red cells with less than 1% lysis and a 24h survival exceeding 70%. Obviously there are other (unwritten) requirements. JDC informed the group that CPDA1 is now licensed to allow holding of blood at room temperature for up to 8h after donation, prior to platelet and red cell component production.

CP

CP

(iii) NE Plasmapheresis study and developments in E/W

NE study - Dr Prowse summarised data to hand on plasma quality obtained in the three completed legs of this study. Agreed to write to Dr Smith summarising available Scottish data.

CP

E/W - Dr Prowse summarised results obtained on the fractionation of filtration apheresis plasma as presented at the recent BPL meeting. Dr Lane is coming to PFC on 17th March to plan further work. R Perry to discuss plan with JD, CP etc prior to that date. In view of possible activating effects of membranes attempt to obtain urine for FpA assay from filtration apheresis donors (? via Dr Urbaniak).

RP

JD

d) White Cell Release Studies

Samples have been collected and are currently being assayed.

JD

e) Cardiff Studies on Lots 4013 and 4014

4 infusions (2 of each batch) had been given to one patient in Cardiff. Results support one-stage more valid for labelling than two-stage and suggest a more biphasic disappearance curve for unrecalcified product. Samples to be solicited from Cardiff for CAg assays (Dr Greedharry). Agreed to shelve any further studies until later products

CP, FEB

available. Publication to be encouraged as part of wide-range paper on FVIII process.

f) Von Willebrand Factor Concentrate

Agreed that Dr O'Brien's data on in vitro bleeding time test was of interest but uncertainty as to interpretation. Still only the single planned infusion of Phase I FVIII product done on vWd patient. Agreed that studies on infusion of cryoprecipitate and Phase III product should be pursued if possible. For the future vWf concentrate might be a side-product of the high purity FVIII process. Dr O'Brien should be offered this when available.

FEB

g) Viricidal Options

Dr Robin Weiss will be collaborating with PFC/BPL on HTLVIII studies. Dennis Aw (Dr Peutherer's department) is visiting his laboratory to learn methods.

Further studies with model viruses are being performed at PFC in relation to freeze-drying variations and the effects of irradiation (see below).

BC

Dr Pepper reported the effects of different radiation doses on the activity of FVIII and FIX from Oxford. 0.5Mrad would appear the maximum allowing reasonable retention of activity. Further studies combining heat and irradiation planned. Also irradiation only on newer PFC products. He also reported Miles-Cutter patent publication on chemical inactivation using copper phenanthroline but felt this was not a viable option at present.

DSP

h) Factor VIII Assay Group

Dr Prowse summarised results for the four 1985 exercises, which continue to be good, and went over items planned for discussion at the Assay group meeting due to be held on 20th March 1986, to include future plans.

Artificial substrate had been prepared at PFC but not freeze-dried. Agreed that current PFC priorities would not allow this to a reasonable standard. Alternative sites for freeze-drying (SAPU, HQ Lab) could be investigated, but possibility of centralisation may change priorities.

CP

Immunodepleted plasma is currently being studied to 200 ml scale. If successful, to be freeze-dried in HQ Lab and circulated.

CP

i) Clinical Trials of Heat Treated Factor VIII

No further formal studies since last meeting. Question of serial follow-up samples to be pursued.

JDC

Plans (n=3/product) required for recovery and survival studies on Phase III (to include vWd if possible) and IV products in or after April. Dr Dawes requested serial urine samples (to 24h) be collected in any such studies.

FEB

Also proposed Phase IV product be infused to dogs prior to patient study, as well as Phase II products as control. This would probably require 3,000-5,000 iu per animal due to high basal VIII levels, and a change in protocol to allow half-life determination (see recent paper from Chapel Hill in P.N.A.S.)

JD, CP

j) Phospholipid/Factor VIII Complexes

Dr Pepper reported:

- i) Ultracentrifugal separation of complexes will be performed soon, now the appropriate centrifuge is being installed.
- ii) Addition of NIBSAC phospholipid to current products reduces VIII:C_{Ag} reaction in human antibody 2 site-IRMA and in MAb IRMA using ESH3 or 4 but appreciable effect on 2 site MAb ELISA. Effects of phospholipase addition in these assays not readily interpretable.
- iii) NIBS report effects of MAb ESH3 and 4 in Bethesda type activity assay are altered by phospholipid addition.
- iv) A panel of human inhibitors (6 Cardiff, 4 St Thomas's) have been obtained. Plan to study effect of phospholipid on their inhibitory activity.

DSP

DSP

k) Factor IX Concentrate

- i) Dr Boulton has been pursuing the possibility of infusing FIX to non-haemophilic patients. None as yet but Dr Finlayson's return may help. J Dawes requested urine samples from any such studies.

FEB

- ii) Dr Foster reported that improved freeze-drying could reduce FIX losses in process

but might also lead to reduced virus killing. Model virus studies are being performed. Any novel product should be tested in dogs prior to volunteer studies.

BC

iii) Dog Studies

The paper on the earlier FIX studies should be submitted to Br J Haematol in the next month. Studies on Oxford FVII (+ heat) are complete. Dose response studies, using Edinburgh FIX + heat + ATIII, will start at 200 u/Kg using material reconstituted in half volume. Subsequent dose to be determined thereafter. Once dose-response done consider doing Oxford 'hot' FIX from filtration apheresis plasma (if available from J Smith), local hot-hot material from PFC and possibly Cutter commercial material at appropriate doses. Factor VIII infusions also need to be slotted into this programme, if survival studies are feasible. Current blotting order may be:

CP

CP
contact

JS

PF

JD

- (1) 200 u/Kg SNBTS FIX
- (2) ? Cryo
- (3) ? SNBTS HOT-HOT FIX
- (4) PFL Apheresis FIX (or FXI)
- (5) 400 u/Kg SNBTS FIX
- (6) Phase IV factor VIII
- (7) Cutter FIX
- (8) PFC new FIX

4. ANY OTHER COMPETENT BUSINESS

- (i) Dr Mayne has anecdotal evidence heated FIX is not as effective in treatment of inhibitor patients. In an effort to determine what is missing C Prowse has arranged for Protein C, VIIa and IXa assays to be done on FIX ± Heat by Steve Walters in Oxford. This batch was used in the dog studies and shows prolongation of TGT₅₀ but not NAPIT after heating. CAG assays should also be done.

CP

CP

- (ii) Four homozygous factor VII deficient dogs (2 belonging to SNBTS) from the closing ICI colony will be housed at Garscube. Suggestions for appropriate uses welcomed.

ALL

- (iii) FPLC and other studies on heat-induced damage to protein continue and may now involve collaboration with Dr Stanworth in Dept. Immunology, Birmingham on physical methods.

DSP, RP

(iv) Serial follow up studies for viral markers and immune system malfunction in haemophiliacs receiving heat-treated products are being pursued.

JDC, FEB

(v) Professor Cuschieri has requested if SNBTS could produce 'fibrin glue'. Other centres in Scotland have also expressed interest in such a product. Any product would need to be heat treated and contain fibrinogen, FXIII and (? human) thrombin.

RP

5. DATE OF NEXT MEETING

10.30 a.m., SNBTS HQ UNIT, Monday 23rd June.

C V PROWSE
1 March 1986

Tabled Papers

1. G Gabra: Manuscript entitled 'The Value of Quality Assurance of Factor VIII:C Assays in the Production of Fresh Frozen Plasma for Fractionation.'
2. P Foster: 'FFP Quality 1985 and Part of 1986'.
3. C Prowse: 'Feasibility of Centralising Feedstock Plasma Factor VIII Assays.'
4. C Prowse: 'Results of in vitro studies of components prepared in half-strength citrate'.
5. C Prowse: 'Summary of results obtained on plasma from N.E. plasmapheresis study'.
6. F Boulton: 'Results of Volunteer Infusions in Cardiff using FVIII prepared with and without calcium'.
7. C Prowse: 'Summary of 1985 FVIII QA exercises'.