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9th February, 1983.

Mr.J.G.Watt,
Plasma Fractionation Centre,
Scottish National Blood Transfusion Service,
Ellen's Glen Road,
Edinburgh. EH17 7QT.

Dear John,

Thank you for your telephone call.

Dr.Davidson in fact is sending out an amendment to say that the batch No. DEFIX is 648 and not 684 as per his letter.

In addition I want to assure you that we now believe that the odd reaction that [redacted] had was probably a response to intravenous pethidine which he had taken as a single bolus rapidly for the control of pain following his replacement joint. He should therefore not be included as a reaction. I hope this clears up the matter.

Yours sincerely,

Dr.C.D.Forbes.

Received: 14 FEB 1983
File No: Adverse Reactions DEFIX 648
Mr Watt
Dr Berry

RJP MPORH AR FVIII 1983

REPORT ON ADVERSE REACTIONS ASSOCIATED WITH FACTOR VIII CONCENTRATE
(Batch nos. 616, 617, 680 and 683) and
FACTOR IX CONCENTRATE
(Batch No.648)

FACTOR VIII INCIDENT

On 29th September 1982 Dr Forbes (Glasgow Royal Infirmary) wrote to Dr Cash describing an unusual apparent adverse reaction to FVIII concentrate supplied by P.F.C. The reaction was described as epileptiform seizures following administration to a severely affected haemophiliac. No batch numbers were quoted in this initial report though it was stated that the same batch(es) was used in other patients without reaction. Dr Cash subsequently wrote to Dr Forbes requesting batch details of the implicated material (5th October) but this information was not forthcoming. No further action was taken at this stage since there was inadequate batch information either directly from Dr Forbes or through Dr Cash. It is understood that Dr Cash had assumed that Dr Forbes had also, as normally expected, informed West R.T.C.

On the 11th January there followed a further report from Dr Forbes describing similar epileptiform seizures in another patient following infusion of P.F.C. Factor VIII concentrate. Again the report was sent directly to Dr Cash, who immediately alerted P.F.C. of this second incident. Batch numbers quoted in Dr Forbes' letter referred to a G.R.I. numbering system and the P.F.C. batch numbers of the implicated material were eventually received by telephone from Dr Small via Dr Forbes' secretary. A recall procedure of all implicated batches from both this and the previous incident was activated by P.F.C. and as a matter of course the D.H.S.S. Medicines Inspectorate were informed. Immediate laboratory investigation of associated library samples was not undertaken since the paucity of clinical information may have led to a poorly designed investigation on limited amounts of material. To date, no formal examination of library samples has taken place, though batch records have been carefully examined and indicate a normal analytical and product profile.

Further action on these specific 'adverse reactions' was pre-empted by yet another seemingly related reaction to Defix.

FACTOR IX INCIDENT (I.F.)

On 2nd February 1983 a verbal report from Dr Crawford of Glasgow Blood Transfusion Service was received at P.F.C. A mild haemophilia B patient on home therapy, commenced injection of a vial of Defix (reported batch No. 648) and collapsed during the early stages of the injection. After admittance to Glasgow Royal Infirmary the patient recovered rapidly with no apparent further symptoms. Further discussion with Dr Davidson (Consultant Haematologist, G.R.I.) indicated that less than 5ml had been injected when the patient collapsed following symptoms resembling a fit. The patient remained unconscious for approximately one hour. The remainder of the syringe contents were returned to the vial (by parents) and sent to The Blood Transfusion Service at Law Hospital.

On receipt of the above information P.F.C. immediately implemented a recall procedure on batch 648. All material supplied by P.F.C. was accounted for.

Dr Davidson subsequently confirmed the reaction and recall instructions in a letter to Dr Crawford (3rd February 1983) though in this letter the implicated batch is quoted as 684.

The D.H.S.S. Medicines Inspectorate were informed of this further epileptiform reaction to P.F.C. product and in view of the apparent similarity in symptoms/

symptoms of both FVIII and FIX reactions a meeting was arranged between D.H.S.S., P.F.C., Law B.T.S., Dr Forbes and Dr Davidson with a view to clarifying the nature of the reactions and establishing a rational and scientific investigation of the implicated products.

NOTES OF MEETING AT GLASGOW ROYAL INFIRMARY (4th February 1983)

Present:	Dr R Crawford	(BTS)
	Dr R Perry	(PFC)
	Mr D Haythornthwaite	(DHSS)
	Dr Forbes	(GRI)
	Dr Small	(GRI)
	Dr Davidson	(GRI)

Dr Forbes indicated that only one patient was associated with documented (and anecdotal) reports of adverse reaction to FVIII concentrates NY 616, 617, 680 and 683 though three seizures occurred at different times. Only one patient and one specific incident was associated with Defix 648.

Dr Small summarised the case history of the haemophiliac A patient.

[redacted] ('A' Patient)

On three separate occasions during 1982 this patient whilst undergoing hospital treatment had self-administered rapid infusions of Factor VIII, previously reconstituted in the haematology department and had subsequently suffered epileptiform seizures approximately one hour after infusion. Infusion times were estimated at less than five minutes. All other infusions throughout the year were uneventful.

The patient was a known alcohol abuser with a history of allergy and occasional bronchospasms. He had a previous head injury though there was no history of epileptiform seizures. A brain scan indicated no apparent abnormalities though and E.E.G. suggested some possibility of an underlying brain disorder. He received treatment regularly with dihydro-codeine and was suspected of drug abuse.

In conclusion, Dr Forbes considered there to be inadequate information or evidence on which to implicate the product as the cause of the seizures. He suggested that it was an idiosyncratic reaction from an unusual patient following unusually rapid infusions.

It was agreed therefore that no further action was indicated except for a general alertness to reactions of this nature in the future.

The patient has died subsequently but a post-mortem was not performed.

[redacted] ('B' Patient)

This patient was described as a 'well adjusted' mild haemophiliac on home therapy.

During the course of an injection of Defix (648) he collapsed after approx. 5ml had been infused. He remained unconcious for one hour but there were no other recorded abnormalities (by either parent or later by clinicians).

Contrary to the initial verbal report there was no epileptiform seizure and it was therefore a dissimilar reaction to those above.

It was agreed that there was inadequate evidence to support a product defect although to conclude the incident report it was agreeed that Law Blood Transfusion/

Transfusion Service search for immunological reactions and P.F.C. examine the vial contents for incorrect resolution.

General Comments

(a) Dr Forbes stated that, in view of communication problems highlighted by this incident he had arranged for future adverse reaction reports and product defects to be reported simultaneously through three separate mechanisms.

1. To Dr Davidson
2. To Law B.T.S. (Designated Officers)
3. To P.F.C.

(b) The question of dried product reconstitution was discussed with Dr Davidson and he indicated that all material supplied for use on the ward was reconstituted in his laboratory prior to despatch. He did not at present record the batch number of the W.F.I. used for this purpose though agreed to look at this possibility.

Dr Davidson also agreed that, following the introduction of a new FVIII packaging system, storage of VIII + water as a matched pair would be possible and desirable.

(c) The Medicines Inspector (D Haythornethwaite) agreed that there was inadequate evidence of product defect and considered that all material could be re-issued for use.

It has subsequently been decided that the FVIII implicated should be re-issued though the circumstances and inexplicable reaction of [redacted] to Defix (Batch 648) should at this stage not be discounted as a batch related phenomena and thus FIX Conc. 648 should be recalled. This is particularly prudent in view of the relative 'abundance' of replacement batches.

Important Postscript

The preceeding report presents the information available up till 4th February 1983 and attempts to present an objective assessment of discussions held on 4th February 1983. However, on re-examination of pertinent letters from Dr Forbes to Dr Cash, two separate patients are referred to as having epileptiform seizures. This is contrary to Dr Forbes reassurance on 4th February 1983 that all FVIII related incidents were associated with one patient [redacted].

This ambiguity is to be resolved before terminating the investigation or re-issuing product.

8/2/83

RJC/LC/7.2.83

AN INVESTIGATION INTO REPORTED ILL-EFFECTS FOLLOWING USES OF SNBTS FACTOR VIII INTERMEDIATE CONCENTRATE BATCHES NY 616, NY 617, NY 680 and NY 683

Following interviews with Dr. C. Forbes, Dr. G.D.O. Lowe, Dr. M. Small, Dr. J.F. Davidson and Mr. I. MacAdam it was concluded:-

(a) There is no evidence of a product defect.

(b) The reactions were associated with very rapid injection.

(c) The patient was unusual and had a large number of clinical problems including, possibly a neurological abnormality. No other patient was involved.

(d) Reported opiate abuse by the patient has not been shown to have been a factor.

(e) The existing reporting and investigating system for transfusion reactions may not always work as it is designed to do.

(f) See Appendix.

Narrative: [redacted] was a patient with severe haemophilia A. Among other problems he suffered from asthma and eczema. The symptoms were occasionally and irregularly aggravated by the use of blood products. There was no evidence that this was batch specific. Following a head injury some years ago there were no clinically detectable neurological signs and a brain scan was normal.

The patient was a heavy drinker and had been dependent on dihydrocodeine orally for some time. It is also possible

RJ Crawford report AR FVIII 1983

though uncertain that he may also have been using illicit opiates by injection. As he was unreliable he had been removed from the home therapy programme and all the treatments in question were self administered in hospital. The factor VIII vials were reconstituted in the blood products laboratory using a laminar air flow work station. The vials were then agitated in a 37°C water bath until the contents were fully dissolved and were then despatched to the ward.

On three separate occasions, in 1982 separated by a number of months he injected factor VIII rapidly (on one occasion he injected 35 iu/Kg within a few minutes) and the injections were following 40 minutes to one hour later by major convulsive seizures. Intervening treatments were no more eventful than was usual for him viz pruritus once every couple of weeks and occasional bronchospasm. Neurological assessment showed no change in the normal brain scan. The neurologist suggested that the EEG was compatible with underlying seizure disorder and advised that the effect of giving the factor VIII slowly should be studied before using anticonvulsants. This policy was found satisfactory.

The patient died in January, 1983 of status asthmaticus unrelated to therapy. No necropsy was carried out.

Brief histories of the relevant batches have been made available by Dr. Davidson. None has been associated with reported reactions.

Robert J. Crawford
7.2.83

APPENDIX

On the 7th February, 1983 Dr. Perry told me that in spite of the clinicians' denials there was a letter in Dr. Cash's files from Dr. Forbes dated 11th January indicating that [redacted] had a major convulsive seizure after factor VIII and intravenous pethidine on the 8th January.

In view of the interviews on the 4th of February Mr. Watt has asked Dr. Forbes to confirm the whole situation in writing before any further action by the SNBTS.

Robert J. Crawford,
7.2.83

RJC/LC/7.2.83

AN INVESTIGATION INTO REPORTED ILL-EFFECTS FOLLOWING THE USE OF SNBTS FACTOR IX CONCENTRATE (DE FIX) BATCH DE 648

Following interviews with Dr. C. Forbes, Dr. G.D.O. Lowe, Dr. M. Small, Dr. J.F. Davidson and Mr. I. MacAdam it was concluded:-

(a) There is no evidence of a product defect.

(b) The reaction was totally different from the seizures following factor VIII.

(c) Only one patient was involved.

(d) There is no evidence that drugs e.g. chlorpheniramine were being used.

(e) Investigations currently planned relating to analysis of the returned vial should be completed in spite of the fact that the vial was sampled at the RTC.

(f) The planned antibody screens on the patient's serum should be completed.

Narrative: [redacted] is a nineteen year old patient with Christmas disease. He has been on prophylactic factor IX therapy since childhood. On the 28th of January, 1983 he returned from work and started to inject some factor IX from a vial of batch DE 648.

He is reported to have collapsed unconscious after injecting between 2 and 5 ml. Neither he nor his family were available for interview but the clinical history obtained on hospital admission indicated that his body was flaccid, not convulsed.

There was no reason to suspect circulatory collapse or any change in his respiratory status. He was unconscious for one hour and on admission to hospital he was oriented but drowsy. He vomited twice. No clinical abnormality was found and he made a rapid recovery.

Subsequently he had a supervised injection of factor IX from another batch without ill-effect. As his last supply of FIX was given to him on the 26th November, 1982 and this belonged to batch 648 it is almost certain that this was not his first exposure to the batch.

There are no specific reports of use of this batch of material in Glasgow Royal Infirmary but Law Hospital reports having used 2 vials without ill-effect, Monklands Hospital used 2 vials without ill-effect and the Southern General Hospital had a total of 5 vials and no ill-effects were reported, the case records have yet to be reviewed.

Robert J. Crawford
7.2.83

FINAL REPORT ON ADVERSE REACTIONS ASSOCIATED WITH P.F.C. FACTOR VIII (BATCH NO's 616, 617, 680 AND 683) AND DEFIX (BATCH NO 648)

C O N T E N T S

SUMMARY AND CONCLUSIONS ON ADVERSE REACTIONS ASSOCIATED WITH FACTOR VIII BATCH NOS. 616, 617 680, 683 AND DEFIX 648

SUMMARY

A series of apparent adverse reactions associated with PFC Factor VIII concentrate (Batch No's 616, 617, 680 and 683) were respectively reported to PFC (via Dr Cash) by Dr Forbes. The first of these reports was received in October 1982 and described epileptiform seizures following administration of FVIII concentrate. No batch details or clinical history was submitted at this stage and apart from a literature review on the clinical significance of particulate debris in parenteral products no further action was indicated.

In January 1983, a further report was received from Dr Forbes describing similar epileptiform seizures in a different patient following infusion of PFC FVIII. In the light of this related though independent reaction an inherent product defect was suspected and all material implicated in this and the previous reaction was identified and recalled.

On 2nd February, a further report was received from West of Scotland Blood Transfusion Service describing an adverse reaction to Defix 648. Early reports of this reaction suggested similarities between this and the previous FVIII reactions. In view of this the batch was immediately recalled and DHSS Medicines Inspectorate (D. Haythornthwaite) was informed. Moreover, the lack of detailed clinical data on all reported reactions and the possibility of widespread product defect indicated the need for detailed and urgent investigation of all apparently related incidents.

This investigation which took the form of an interview with Dr C. Forbes, Dr G. D. O. Lowe, Dr M. Small, Dr J. F. Davidson and Mr I. MacAdam in the presence of Dr R. Crawford, Mr D. Haythornthwaite and Dr R. Perry took place on 4th February 1982.

Conclusions drawn from this investigation and subsequent correspondence can be summarised as follows:-

(a) There is no evidence of a systematic product defect (FVIII or FIX). Factor VIII (616, 617, 680 and 683) will be reissued. Defix 648 will not be reissued (unexplained reaction).

(b) Epileptiform seizures were associated with unusually rapid infusion and or unusual patient history in the case of FVIII related reactions.

(c) Despite early correspondence implicating PFC VIII in epileptiform seizures in two separate patients subsequent information confirmed that such reactions were confined to one patient only (D.R.)

It was the report of similar reactions in two separate patients that led to the escalation of the investigation leading to the meeting on 4th February.

(d) These reported reactions highlight the need for an organised and documented system of adverse reaction reporting and investigation which hitherto have either been not formally documented or implemented.

As a pharmaceutical manufacturer, the PFC is responsible for ensuring the safety and efficacy of all blood products issued from this centre and in the event of product defects or adverse reactions/

reactions has a well defined responsibility to investigate all reports of defects and reactions associated with PFC blood products. Any response to such reports will be conditioned by the nature of the information received either directly from the physician or indirectly through the RTC.

In many reported reactions the initial safe response is to recall all implicated material and to reissue subsequently in the light of investigation. This is an expensive and time consuming exercise and in some instances can be avoided by the provision of fuller details at the outset of the investigation. The ensuing investigation may also be facilitated and progressed more efficiently if clearer lines of communication exist. These observations certainly apply to this series of investigations as evidenced by the appended correspondence.

Recommendations

In response to these and other similar reported reactions it is proposed that an organised and documented policy for reporting and acting on adverse reaction notification be agreed and implemented within the SNBTS as a matter of urgency and in furtherance of this proposal a draft SNBTS Standard Operating Procedure is appended for discussion.

Such a proposal is submitted with the support of the Medicines Inspectorate who, having been involved in this investigation, has expressed satisfaction with the eventual outcome but disquiet with the lack of defined procedures.

→ John Watt.

SEIZURES AFTER FVIII INFUSION

M Small MRCP Registrar in Medicine
W F Durward MRCP Consultant Neurologist
C D Forbes MD FRCP Senior Lecturer in Medicine

University Department of Medicine and Department of Neurology
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SEIZURES AFTER FVIII INFUSION

Allergic reactions to blood products are not uncommon but to our knowledge the precipitation of grand mal seizures after infusion of factor VIII concentrates has not been noted previously. We now report the case of a 26 year old haemophiliac who sustained 3 epileptiform seizures following factor VIII replacement therapy for muscle haemorrhage.

CASE REPORT

The patient was a severe haemophiliac who had received frequent large quantities of factor VIII, in the form of cryoprecipitate or specific concentrates since the age of 12 years. On a few occasions he had experienced allergic reactions following an infusion which usually consisted of marked pruritis or very rarely bronchospasm. He had no family history of epilepsy but had sustained a head injury 2 years previously while under the influence of alcohol. A skull x-ray and radionuclide brain scan and cerebral flow study were normal at that time. In July 1981, while an in-patient, he had a grand mal seizure 40 minutes after the infusion of 2000 units of Edinburgh factor VIII concentrate (35 U/kg). It was noted later that he had injected the concentrate himself rapidly over about 2 minutes. Five months later he again had a tonic clonic seizure, in hospital, lasting 4-5 minutes, and terminated by intravenous diazepam. This followed the rapid infusion of 1000 units of factor VIII one hour before. In June of 1982 a further seizure lasting 2 minutes was associated with the rapid self administration of 2000 units of factor VIII, one hour prior. Brain scans following these 3 episodes were negative and at no time was any abnormality detected in CNS examination. An EEG performed after

the last seizure showed a suggestion of an underlying seizure disorder but no focal abnormality was detected. Anti-convulsant therapy was never instituted. The patient was also a severe brittle asthmatic and unfortunately died recently at home in status asthmaticus. A post-mortem examination was not obtained.

COMMENT

We feel that the temporal relationship of the seizures to the administration of factor VIII on 3 occasions makes this the most likely aetiological factor in precipitating the seizures. Unusual intravascular particulate material has been noted in the cerebral white matter of a haemophiliac treated with large quantities of factor VIII concentrates (1) and perhaps such particle deposition in a brain with an underlying seizures tendency may have been sufficient stimulus to evoke these seizures. EEG abnormalities in adult haemophiliacs occur with a normal frequency (2) and the fact that seizures, following factor concentrate infusions, have not been noted before may be due to the unusual situation in this patient who, despite repeated warnings, occasionally injected his concentrate over the period of 1-2 minutes.

1. Ghatak N R, Husain M M.
Unusual intravascular material in the brain.
Am J Clin Pathol 1976; 65: 508-512.

2. Forbes C D, Renfrew S.
Electroencephalography in Haemophilia and Christmas disease.
Haemostasis 1975; 4: 36-39.