EDINBURGH HAEMOPHLIA TREATMENT POLICY

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To prevent and treat bleeds in individuals with haemophilia it is necessary to raise the plasma level of the deficient clotting factor. For those with mild haemophilia A and some individuals with vWD this may be possible for surgery and minor bleeds in the short term with desmopressin (see below) and has the major advantage of avoiding exposure to a clotting factor concentrate, which before the licensing of recombinant products was derived from human or animal plasma and it conserved stocks of scarce cryoprecipitate, although it was licensed for use in haemophilia and Von Willebrand disease in the 1977's its use in Edinburgh began in 1980.

Prior to 1965 the only treatment for haemophilia was fresh frozen plasma, but it was not possible to raise plasma concentration to a level sufficient to stop bleeding. This was because it was only possible to infuse approximately one litre of plasma before the circulation became overloaded and this, which might only raise the concentration of factor VIII to perhaps 15 – 20%; furthermore repeat infusions could not be administered at frequent intervals.

Cryoprecipitate

The development of cryoprecipitate in the mid 1960's was a very major therapeutic advance for the treatment of haemophilia A and Von Willebrand disease. Cryoprecipitate was prepared by freezing plasma from each single

blood donation and allowing in to thaw at 4 degrees centigrade; a precipitate would remain and this was centrifuged and re-suspended in approximately 50mls of plasma. It was not possible to either assay or standardise the amount of factor VIII in each donation, but on average they contain about 70 iu factor VIII, although there was a large variation between individual packs. To treat an average bleed in an adult patient 15 – 20 packs of cryoprecipitate would be thawed in a water-bath and pooled together before being infused into the patient. This was a messy, wet and time consuming procedure. The other major disadvantage of cryoprecipitate, is that allergic reactions to it were relatively common. Occasionally these reactions could be serious and life threatening. For this reason cryoprecipitate was not suitable for use by patients at home. My clinical experience was that if a patient who had received very little previous blood product therapy was treated with cryoprecipitate over a number of days for a bleed or to cover surgery they became jaundiced. If they received between 5 and 10 infusions of cryoprecipitate, i.e. were exposed to 100/200 individual blood donations there was a high likelihood that they would develop hepatitis. It thus appeared to me that the frequency of hepatitis carriage by blood donors was approximately 0.5% and most of this was due to a putative non-A/non-B virus(S). Many patients with severe haemophilia A treated with FFP and cryoprecipitate up to 1970 became infected with hepatitis B virus and even despite screening blood donors in the 1970's for this virus clotting factor concentrates continued to transmit it because the screening tests were insufficiently sensitive to exclude all hepatitis B virus infection donations.

Factor VIII Concentrates

Factor VIII concentrates derived from pools of plasma to which many individual blood donations had contributed started to be manufactured in the 1970's. Initially pool sizes were small, e.g. 500 donations, but the pool size rose so that in the 1980's some manufacturers had pool sizes, of many tens of thousands of donations. There were manufacturing advantages in producing batches from large volumes of plasma because a smaller percentage was used for quality control purposes and this therefore resulted in a higher yield of factor VIII from the starting plasma. Each batch might result in the production of several thousand bottles of factor VIII concentrate and each contained an identical amount of clotting factor, which could be assayed for the batch as a whole. It was thus possible to give precise doses of factor VIII to patients and thus ensure the correct dose was given to stop or prevent haemorrhage. An additional advantage of concentrates was that allergic reactions were much less common and the bottles could be stored and used at home by patients.

One of the major draw backs of concentrate is that if a single blood donor donation is contaminated with an infectious virus it can potentially result in the whole batch of concentrate being infectious with the potential to transmit the infection to many recipients. It is this amplification system that has been responsible for the early and ready transmission of hepatitis and HIV viruses to patients with such devastating effect.

The initial clotting factor concentrates were relatively impure and contained large amounts of other plasma proteins. These early concentrates were very difficult to solubilise by adding water to the freeze dried "cake" in the bottle. Furthermore the volume of reconstitution was relatively large. The early concentrates were only slightly more purified than freeze dried cryoprecipitate. The volume of a single infusion might be 200 – 300mls of concentrate as compared to 1-5mls with recombinant clotting factors today. One of the difficulties encountered with the low purity concentrates produced by SNBTS in the early 1980's was that its use to cover major orthopaedic surgery could result in an acquired bleeding state due to is content of non-factor VIII proteins.

In 1980 the majority of patients in Edinburgh were being treated with cryoprecipitate being prepared by SNBTS from Scottish blood donors. As described earlier a small number of patients were receiving home therapy with NHS factor VIII concentrate the remaining concentrate was used in hospital either for surgery or for patients who were allergic to all infusions of cryoprecipitate.

Hepatitis

By the later part of the 1970's it was clear that many patients exposed to blood products had chronic and variable abnormalities of their liver function tests. Acute hepatitis A and B were excluded as causes by appropriate blood tests. This hepatitis therefore became known non-A/non-B hepatitis. Until 1989 there was no reliable test to identify how many other viruses might be causing this hepatitis. There was a view that hepatitis following use of commercial concentrates was more severe than

that following use of NHS concentrates. It was also considered that the chances of an NHS concentrate transmitting hepatitis was rather less than a commercial one. There was also some evidence that commercial concentrates might contain at least two viruses responsible for non-A/non-B hepatitis. Furthermore it was not clear whether the hepatitis caused by NHS concentrates was the same or different from the causative agent in commercial concentrates.

My predecessor, Dr S H Davies, had a policy of not using commercial concentrates because of the uncertainty about hepatitis viruses in the concentrates derived from plasma collected in the United States and elsewhere. I did my upmost to continue this policy when I became responsible for the service in the 1980. The disadvantage of this policy was that there was relatively little factor VIII concentrates available and this significantly delaying the introduction of home treatment for many eligible patients. I impressed upon SNBTS my desire to have more factor VIII concentrate. At that time it was the need to generate as much factor VIII concentrate as possible, which drove the blood transfusion service to collect as many donations of whole blood as possible; at that time the need for plasma (for factor VIII concentrate manufacture) was the principal driver for blood donor recruitment and donation whereas today, because of the use of recombinant factor VIII, it is the need for red cells to treat bleeding and anaemia.

One of the disadvantageous of factor VIII concentrate compared to cryoprecipitate was the yield of factor VIII from starting plasma is substantially lower compared to plasma being converted to cryoprecipitate. Thus the demand for plasma to fractionate into factor

VIII concentrate rose sharply in Edinburgh after 1980 because I wished to use more factor VIII concentrate to treat the patients and the yield from starting plasma compared to cryoprecipitate was much less and these were the twin reasons for requiring a sharp increase in plasma supply in the early 1980's.

To try and ensure that patient's attending the Edinburgh Haemophilia Centre only received cryoprecipitate or NHS derived concentrates when visiting another Haemophilia Centre they were individually told to request either cryoprecipitate or an NHS concentrate and to avoid a commercial concentrate if possible. To emphasise the importance of this each patient was supplied with a small statement to this effect, which was placed in their haemophilia card, which they could show to get treatment at another Centre.

Because of the relative scarcity of NHS factor VIII concentrate during 1981 and 1982 a small amount of commercial concentrate was purchased, but it was purchased for treating a small number of patients with specific haemostatic therapeutic difficulties.

In attempt to reduce recipient exposure to multiple batches of factor VIII a "batch dedication" system was devised in 1984. In this there were three parallel batches of factor VIII concentrate, which were given to patients based on their surname i.e. individuals with a surname beginning with a letter in the first third of the alphabet were given concentrate from "bin 1", middle third of the alphabet from "bin 2" and the last third of the alphabet from "bin 3". This simple to operate system reduced the batch exposure of an individual patient by about one third.

In December 1984 immediately following the decision made at the Elstree meeting on the 10th December arrangements were made by SNBTS to dry heat treat vials of finished product at 68 degrees for two hours. Arrangements were made for patients to return their home stocks of factor VIII and they were issued with heat treated concentrate. This allowed all patients in Edinburgh to continue not only on NHS concentrate, but one that was heat treated. Despite the modest heat treatment it was effective in preventing further HIV transmission in Scotland (despite it being discovered retrospectively that several batches of concentrate contained HIV infected plasma donations).

Factor IX Concentrate

Patients with haemophilia B, a deficiency of factor IX treatment with a product containing factor IX. Historically this was fresh frozen plasma, but during the 1970's concentrates containing factor IX began to be manufactured. These concentrates initially also included factors II, VII and X in addition to factor IX. One of the major drawbacks of these early concentrates was that they contained activated clotting factors, which predisposed the recipient to either disseminated intra-vascular coagulation and/or thrombosis. I had a patient who developed both these complications during a post-operative period in the early 1980's. Because the prevalence of haemophilia B is very much less (about 1/5) than haemophilia A, and because the yield of factor IX in concentrate is higher from starting plasma, there has been a more plentiful supply per patient of factor IX containing concentrates for haemophilia B compared to factor VIII for haemophilia A.

During the 1980's NHS Commercial plasma fractionators moved towards manufacturing clotting factor concentrates of higher purity i.e. more units of factor VIII per mg of protein in the final vial. This was because higher purity concentrates dissolved more readily and required a smaller volume of diluent. This was important for the treatment of babies in whom it can be difficult to give injections of clotting factor concentrate, because of the small veins buried in chubby arms. Higher purity products were also less likely to give rise to allergic reactions or give rise to an acquired coagulopathy secondary to the non-factor VIII proteins. The other stimulus for the production of higher purity concentrates was that they were more suitable for viral inactivation by "dry" heating. Heat applied to a low purity concentrate was more likely to render the freeze dried concentrate difficult to solubilise when water was added to reconstitute it.

By the mid-1980's it was clear that there needed to be a Scottish National co-ordinated approach to the development and adequate supply of factor VIII concentrate of suitable quality for treating patients with haemophilia. To promote this the Scottish Home and Health Department invited me to establish and chair a Factor VIII Working Party for Scotland and Northern Ireland. It was a tripartite committee consisting of representatives of Haemophilia Directors, Senior SNBTS Personnel (General Manager, Mr David McIntosh, Director of PFC Dr Bob Perry, Director of Research Dr Peter Foster and Scottish Home and Health Department (Dr Aileen Keel). Later the remit of the Working Party Expanded to include other clotting factor concentrates and it was therefore renamed Coagulation Factor Working Party for Scotland and

Northern Ireland. The Working Party estimated the increasing national annual requirement for factor VIII concentrate and agreed a specification for the product. It was agreed to develop a high purity iron exchange concentrate virally inactivated by the solvent/detergent method. This venture was undertaken in collaboration with the Plasma Fractionation Facility at Lille in France. Whilst the manufacturing facility at PFC was adapted for the new technology Scottish plasma was shipped to Lille for fractionation and bottling and returned for use in Scotland. The high purity concentrate, Liberate, underwent full pharmacokinetic evaluation and obtained a full product license.

After development of the high purity factor VIII concentrate discussions were initiated to specify and develop a high purity, single factor IX, concentrate i.e. without factors II, VII and X. This proved harder to achieve partly because of solubility difficulties with the final product. Eventually a satisfactory concentrate was developed, which underwent full pharmacokinetic and clinical evaluation (under a CTX) and received a product license under the name of HIPFIX.

With the licensing of the first recombinant factor VIII concentrate in 1995 I was keen to see its introduction for patients in Scotland. With the generous support and some start-up funding from SNBTS a "recombinant factor VIII consortium" was established consisting of the directors of Edinburgh and Glasgow Comprehensive Care Centres, Scottish Health Board Representatives, NSD and Public Health Medicine under the chairmanship of the General Manager of Lothian Health Board. This ensured there was an orderly and progressive increase in the proportion of recombinant concentrate available within Scotland. There were nationally agreed criteria as to the order in which the concentrate

should be made available to different groups of patients (criteria available). By 2002 all patients in Scotland were being offered recombinant factor VIII and IX to treat their haemophilia. This programme was very considerably in advance of the more piecemeal introduction of recombinant factor VIII and IX into England.

Although the majority of patients with haemophilia A and B attending the Edinburgh Centre are now treated with recombinant VIII and IX concentrate a very small number of patients are treated with plasma derived concentrate either because of adverse reactions to recombinant factor IX concentrate or to induce immune tolerance in patients with anti-factor VIII antibodies. Plasma derived concentrates are also used to treat von Willebrand Disease, factor XI deficiency (factor XI concentrate), factor X deficiency (prothrombin complex concentrate containing factors II, IX and X), fibrinogen deficiency is treated with plasma derived fibrinogen concentrate.