New Zealand Blood Service
The gift of life

# BLOOD ISSUES

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## Editorial

This edition of Blood Issues focusses on haemophilia and its treatment. This month sees two significant developments in the management of this disease in New Zealand. Firstly the introduction of Biostate, a high purity Factor VIII concentrate manufactured by CSL Bioplasma in Melbourne from plasma collected by NZBS. Secondly the implementation of the Pharmac tender process for recombinant Factor VIII. These developments will have a major impact on the future management and development of haemophilia services in New Zealand.

The National Haemophilia project group has overseen the two initiatives. This includes input from the District Health Boards, NZBS and the Haemophilia Foundation of New Zealand. The project has been co-ordinated by DHBNZ.

Haemophilia has had a significant impact on the development of blood services internationally. During the 1950s the discovery of cryoprecipitate and its routine manufacture from donated blood provided the first real opportunity to mange bleeding episodes. This was followed by the large scale manufacture of Factor VIII concentrates. Treatment moved from the hospital to the home. People with haemophilia were able to treat bleeds at an early stage. Quality of life and life expectancy improved.

The emergence of HIV in the late 1970s had a devastating impact. Pooling of plasma, the first step in the manufacture of Factor VIII concentrates, became a powerful mechanism for spread of HIV by transfusion. A generation of people with haemophilia became infected. The plasma fractionation industry responded with the introduction of specific viral inactivation steps into manufacturing processes. Regulation of the sector intensified. Paradoxically the devastating impact of HIV in haemophilia became the driver to the development of the modern plasma fractionation industry. The safety record of plasma derivatives available today is excellent. The safety record of AHF-HP was excellent, the two inactivation steps used in the manufacture of Biostate will ensure that is an even safer product.

The enhanced safety and purity profile of Biostate is associated with a lower yield of Factor VIII from plasma. During 2003/4 CSL manufactured approximately 32000 vials of AHF-HP. The same amount of plasma will today produce 23000 vials of Biostate.

Increasing evidence during the early 1990s that hepatitis C was also transmitted by plasma derived coagulation concentrates was a further blow to the sector. The haemophilia community internationally lost confidence in plasma derived products. Recombinant coagulation concentrates became available and younger patients, particularly those who had not been exposed to plasma derived product, gained access to these. As these individuals grow the mix of plasma derived and recombinant product will inevitably change. NZBS needs to actively manage this transition. The first active step in this process was a decision to 'cap' the level of production of Biostate to the demand for intravenous immunoglobulin (Intragam P). In the event that demand for Biostate increases above this level then the increased requirement will be met by the use of recombinant product.

With effect from 1 July the NZBS charge for Biostate will be similar to that of recombinant Factor VIII. Demand for Intragam P is more predictable than that for Factor VIII. The introduction of the cap will therefore assist NZBS collection planning activities. NZBS needs however to ensure that demand for Biostate is closely linked to the manufacturing schedule with CSL Bioplasma. This will require ongoing close co-ordination with the Haemophilia Treater's group.

The change from AHF-HP to Biostate has been actively managed. A number of patients who previously received AHF-HP will have been switched to recombinant product. Communication tools to support the change and to ensure that Biostate recipients are fully informed about the new product have been developed. Residual stocks of AHF-HP have been closely monitored and product distributed to meet anticipated demand.

During early 2005 Pharmac, at the request of the DHB CEOs, initiated a national purchasing tender for recombinant Factor VIII. Prior to this initiative each DHB was responsible for its own procurement of recombinant product. A national approach to purchasing has enabled a significant reduction in the prices for the products. The Haemophilia treater's group and the Haemophilia Foundation were actively involved in the Pharmac process. The new arrangements take effect from 1 July.

The introduction of national co-ordination of haemophila management will enable more accurate monitoring of the level of demand for Factor VIII. Further work is currently been undertaken to support the development of a national haemophila service. The haemophilia project group is leading this work. The DHB CEOs have endorsed the principle of a national service. Further work needs to be carried out to define the mechanics to support this.

More information on Biostate and the other coagulation factor concentrates can be obtained from the NZBS website www.nzblood.co.nz.

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National Medical Director

## What is Haemophilia?

Haemophilia is the name given to two important inherited disorders affecting the blood coagulation system. They are deficiency of factor VIII, (haemophilia A) and deficiency of factor IX, (haemophilia B). The two diseases have the same clinical problems and can only be distinguished by testing for the specific factor deficiencies. The conditions typically affect males because the genes controlling production of coagulation factors VIII and IX are present on the X chromosome. As males have only one X chromosome, the presence of an abnormal Factor VIII or IX gene will result in a deficiency of the particular factor. Females with one affected chromosome will have only a mildly reduced factor level because the second X chromosome will usually carry normal coagulation factor genes.

Reduced levels of a coagulation factor such as factor VIII or factor IX result in slower clotting, a weak "thrombin burst" and physically weak clots. As a result, clots are easily disrupted by physical movement. Bleeding from an injury will start and stop repeatedly over many days, unless the amount of coagulation factor present is increased to an adequate level. The concentration of coagulation factors in the blood of "normal" individuals varies from 50% to 150% of the average level in the normal population (defined as 100%). Levels of factor VIII or IX above 30% are needed to stop bleeding from most moderate or major injuries, though in the case of muscle injuries the levels should be above 50%. Bleeding in some critical sites such as in the central nervous system may require even higher levels.

Where a person with haemophilia has factor VIII or IX levels between 5-30%, clinical bleeding problems are not common in everyday life. They occur only after significant trauma such as sprains and lacerations, etc. Where factor levels are below 1-2%, bleeding problems may be spontaneous or follow minimal trauma. This is severe haemophilia and results in the typical problems of frequent bleeding affecting joints and muscles. Spontaneous haemophilic bleeding into a joint causes inflammation that eventually results in destruction of cartilage and severe and disabling 'haemophiliac arthropathy'. Joint cartilage is progressively damaged and eventually lost. The lining synovial membrane becomes inflamed, thickened, and prone to further trauma and bleeding on the slightest provocation. The connective tissue surrounding the joint (the joint capsule) also becomes thickened and scarred, limiting joint movement. As a result, the affected person develops chronic joint pain and limitation of movement.

The main joints affected by haemophilia are the "hinge" joints of the ankle, knee, wrist and elbow but others can also be affected. The hip and shoulder are better protected by large muscle groups and are not often a site of bleeding. Bleeding problems if untreated in childhood will lead to chronic disabling joint disease by early adult life with severe loss of opportunities for social interaction and employment.

Bleeding into muscles although less common, can lead to severe permanent problems. Muscle bleeding is more difficult to control for reasons that are not fully clear. A large muscle haematoma may eventually lead to fibrosis with permanent limitation of movement and sometimes calcification at the affected site. Severe muscle bleeds at some sites may create a risk for a compartment syndrome with muscle necrosis and sometimes also severe nerve injury, leading to such problems as foot drop or loss of innovation to the intrinsic muscles of the foot or hand. Rarely, bleeding at other sites may be critical, such as haematuria, retro peritoneal haematoma, pharyngeal bleeding, or bleeding into the eye or brain.

## Treatment of Haemophilia

Treatment for Haemophilia requires replacement of the missing coagulation factor. People with severe haemophilia A or B need regular prophylactic intravenous injection of factor VIII (FVIII) or IX respectively, to prevent spontaneous joint and other bleeding that would produce chronic disability. The enormous advance of the past twenty years has been the improved joint status of younger people with haemophilia as a result of effective prophylaxis. This outcome and the improved safety of all products has resulted in vastly improved life outcomes.

In severe haemophilia A, prophylactic doses of Factor VIII are usually injected three times weekly (Mon, Wed, Fri) or every second day. The time interval is related to the clearance rate for FVIII which is T1/2 – 12 hrs. After injection of Factor VIII significant amounts will be present for about 36-48 hours but will be negligible after 72 hours. In general, if the factor level is kept above 5% during active daytime hours there is very little risk for abnormal bleeding to occur, even in active young boys. This can be achieved by a factor dose of the order of 15-25iu/kg given every 48 hours, with the dose injected at the beginning of the day. Apart from the prophylactic use of Factor VIII, it is occasionally also needed to treat traumatic bleeding episodes or to provide support during surgery.

Occasionally, problems arise during treatment. A small group of children have a more rapid clearance of coagulation factor and will not be protected for as long after each dose. Using much larger doses is one approach but costs rapidly become very high. A clinically effective strategy is to give factor injections more frequently, ie each day, but is accompanied by greater personal stress for the affected child and his parents.

About 15% of people with Haemophilia A develop an antibody against FVIII that inhibits the coagulant activity. FVIII antibodies typically appear within the first few years of treatment. About half of the affected individuals have high titre inhibitors that prevent effective treatment with FVIII. Alternative treatments in this situation are expensive and difficult and include use of recombinant factor VIIa (Novoseven®) or FEIBA® which can bypass the action of factor VIII when bleeding episodes occur and/or to attempt to produce immunological tolerance to suppress the antibody.

Since the early 1990's all children in New Zealand with Haemophilia A have been treated with recombinant factor VIII from commercial sources. FVIII concentrates made from blood and plasma donations given by NZ blood donors and manufactured for NZBS by CSL Bioplasma are used to treat adult patients who have

had prior treatment with plasma-derived products. With the improved treatments now in use, a larger amount of FVIII is needed and the total amount of plasma-derived FVIII is insufficient for effective treatment of all patients. Currently, plasma-derived FVIII provides about 40% of all New Zealand FVIII requirements.

## Safety of Coagulation Factors

The modern management of haemophilia started in the 1960s with the development of cryoprecipitate and accelerated in the 1970s with the increasing availability of plasma derived coagulation factor concentrates. Ready availability of coagulation factor concentrates made home therapy, early control of bleeding and prophylactic treatment for haemophilia a reality and a success story. But it soon became apparent that this success had a cost. Coagulation factor concentrates are prepared from plasma pooled from thousands of donors and it was inevitable that these pools would be contaminated with bloodborne viruses from untested donors. In the USA and Europe during the 1980's, 60 –80% of Haemophiliacs treated with coagulation factor concentrates from untested blood donors became infected with the HIV virus.

The presence of the HIV virus in the community was a turning point for the blood transfusion services and the plasma fractionators. Since then there have been significant advances in the development of safer plasma derived coagulation factor concentrates and the development of recombinant coagulation factors that have a very good safety record. In spite of these developments the use of coagulation factors is not without risk and the following is a summary of risks associated with plasma derived and recombinant coagulation factors.

### Plasma Derived Coagulation Factors

Currently, the safety of blood products depends on a three pronged approach; appropriate donor selection, screening tests for pathogens in the donated blood and pathogen reduction during or after production. These measures are aimed to reduce the viral load in the source plasma and to eliminate any virus that may escape the donor selection and screening process. Over the last few years these processes have improved significantly with the introduction of new measures such as Nucleic Acid Testing for viruses and the use of more than one method of pathogen inactivation. Plasma derived coagulation factors that are currently available are very safe. There has been no confirmed report of HCV or HIV transmission since these measures have been introduced. However Parvovirus B19 for which donated blood is not routinely screened and which is resistant to most viral inactivation processes is an example of a virus that can be transmitted through the use of plasma derived coagulation factors.

Another concern is that of variant Creutzfeldt-Jacob Disease (vCJD). Although the steps taken by the New Zealand Blood Service such as leucoreduction, the exclusion of donors who have had a transfusion in the United Kingdom, or who have lived or travelled in UK for six months or more between 1980 and 1996 and the manufacturing process of coagulation factors from plasma significantly reduces the amount of prion protein that could possibly be present, there is a fear that it may be transmitted through the use of plasma derived coagulation factors and other plasma products such as albumin. Recent reports of possible transmission of vCJD by fresh blood components have added to this concern.

### Recombinant Coagulation Factors

Recombinant FVIII (rVIII) preparations have been available since the early 1990s and recombinant FIX (rIX) has been available since the late 1990s. No human or animal protein is used during production or purification of rIX but animal cells are used for its production. Early rVIII preparations were formulated in human albumin and the presence of albumin introduced the possible risk of vCJD. Current products (so-called second and third generation rVIII) either have no exposure to human albumin during manufacturing and formulation or are only used for cell culture. However, animal cells are used in the manufacturing process of rVIII and rIX and may contain animal proteins.

Recombinant coagulation has a very good safety record and has virtually eliminated the risk of transfusion transmissible diseases. The recovery of rIX and B domain deleted rVIII however is not as good as plasma-derived products following transfusion. There is no doubt that the development of an inhibitor is the most serious complication of replacement therapy in Haemophiliacs today. There has been concern that rVIII might be more immunogenic than plasma derived FVIII. A number of long term prospective trials has shown that the risk of inhibitor formation is no greater with most rVIII than with plasma derived products. Allergic reactions and thrombosis also remain a major concern and both recombinant and plasma derived coagulation factors have been implicated for these complications.

### Options

When considering the options, the safety, the availability and the cost of the product must be taken into account. Safety is the primary concern for all patients who use coagulation factor concentrates. Both types of products have the potential for transmission of infectious agents and no product can guarantee complete safety. There is no scientific basis that can demonstrate one product as safer than the other, so choice is based more on perception and emotion than on scientific facts.

Availability of the product when it is required is another important issue for the patients. The production capacity of recombinant clotting factors is increasing but is still limited and a recent severe shortage of rVIII highlighted the importance of availability from a variety of sources. The average cost of recombinant clotting factors is still higher than the average cost of plasma derived products but with the introduction of new techniques of purer preparation and double viral-inactivation for plasma products, this gap is shrinking.

## Biostate®

Biostate® is manufactured by CSL Bioplasma from plasma collected in New Zealand and from July 2005 replaces AHF-HP as the plasma derived Factor VIII product that is distributed by NZBS. Biostate® will be provided only when supplies of AHF-HP have been fully utilised. Biostate® and

AHF are two distinct medicines and each will be provided on a prescription only basis.

The factor VIII in Biostate® is purified from cryoprecipitate using selective precipitation and chromatography steps. The manufacturing process of Biostate® includes solvent detergent (tributyl phosphate and polysorbate 80) treatment and dry heat treatment (80C for 72 hours) steps to reduce the potential for viral transmission. The solvent detergent, dry heat treatment and partitioning steps used in the manufacture of Biostate® have been shown to be effective virus inactivation/removal steps in vitro for the relevant viruses HIV and hepatitis A (HAV) and also with model viruses for hepatitis B (HBV) and hepatitis C viruses (HCV). The virus inactivation/removal steps in the manufacture of Biostate® also have some effect on parvovirus B19.

Biostate® is presented in packs of 250 IU and 500IU factor VIII for reconstitution with 5ml or 10ml Water for Injections respectively. When reconstituted as recommended, each vial nominally contains 50 IU of factor VIII, and approximately 100IU/ml von Willebrand factor:Ristocetin co-factor (VWF:Rco) activity. In the absence of the added albumin, the specific activity of Biostate® has been determined to be nominally 50 IU/mg total protein. When expressed as per mg clottable protein (fibrinogen), the specific activity of Biostate® in the absence of the added albumin averages 150IU/mg. The levels of fibrinogen and other proteins such as fibronectin, immunoglobulins (IgA, IgM IgG) and TGF-β in Biostate® are all significantly lower than the levels commonly found in plasma.

Although the product contains von Willebrand Factor (vWF) as measured by an in vitro indicator of its activity VWF:Rco, no clinical trials have been conducted with Biostate® in patients with von Willebrand's disease (VWD).

**Adverse Events**

Biostate® should be used with caution in patients with a known allergy to factor VIII concentrates, or human albumin. Allergic, anaphylactic reactions or fever are rarely observed in patients receiving factor VIII preparations. If any adverse event occurs while Biostate® is being administered, the rate of injection should be slowed or stopped to alleviate symptoms.

Patients congenitally deficient in factor VIII may develop antibodies to factor VIII following treatment. The reported prevalence for the formation of neutralising antibodies (inhibitors) in patients receiving plasma derived factor VIII is approximately 10-20%, although inhibitor development was not detected in 30 patients who participated in the safety and efficacy trial with Biostate®.

If very high doses are used in patients with blood groups A, B or AB, the patient should be monitored for signs of intravascular haemolysis. Prior to using Biostate® for the first time, the hepatitis A and hepatitis B antibody status of recipients should be tested. Immunisation with hepatitis A or hepatitis B vaccines is recommended for patients with no antibodies to these viruses.

## Prothrombinex™– HT

Prothrombinex™– HT has been manufactured since 1990 by CSL Bioplasma from plasma collected in New Zealand. It contains the factors II, IX and X and is prepared by adsorption of coagulation factors onto an ion exchange medium followed by selective elution. The eluate solution is sterilised by filtration, freeze dried and heated in the dry state in the final container at 80°C for 72 hours to reduce the potential for viral transmission.

When reconstituted as recommended, each vial of Prothrombinex™-HT contains factor IX 500IU, factors II and X approximately 500IU each, antithrombin III 25IU and heparin 200IU. The heparin is of porcine origin. It is indicated in the prophylaxis and treatment of bleeding in patients with single or multiple congenital deficiency of factor IX, II or X and in patients with single or multiple acquired prothrombin complex factor deficiency requiring partial or complete reversal (eg. reversal of warfarin anti-coagulant therapy).

Because of the potential risk of Prothrombinex™-HT induced thrombosis, Prothrombinex™-HT should not be used for prophylaxis or treatment of haemorrhage in patients with haemophilia B if a highly purified factor IX preparation is available.

## MonoFIX®-VF

MonoFIX®-VF has been manufactured since 1999 by CSL Bioplasma from plasma collected in New Zealand and is a highly purified form of factor IX. The factor IX in MonoFIX®-VF is purified using ion-exchange and heparin affinity chromatography to remove other vitamin K-dependent factors such as factors II, VII and X. The manufacturing process includes a solvent detergent (tributyl phosphate and polysorbate 80) treatment and a virus filtration step to reduce the potential for viral transmission, particularly of Hepatitis A virus.

MonoFIX®-VF is indicated for the treatment of haemorrhages, for use in surgery and as prophylaxis in patients with haemophilia B. It is not indicated for the treatment of factor II, VII or X deficiencies because it does not contain therapeutic levels of these coagulation factors and it is not indicated for the treatment of haemophilia A patients with factor VIII inhibitors.

## Information about Biostate and other Coagulation Factor Concentrates

NZBS and CSL Bioplasma produce a range of materials that provide information for health professionals about Biostate®, Prothrombinex™ and MonoFIX®-VF. A Biostate® Monograph and Product Information is available in electronic format on the NZBS website or in hard copy format from NZBS National Office. Ph (09 523 5744).

Informed Consent leaflets called "Your Guide to Blood Transfusion – Coagulation Factor Concentrates" that provide information about Biostate®, Prothrombinex™ and MonoFIX®-VF are available from the Transfusion Nurse Specialists in Auckland, Waikato, Palmerston North, Wellington, Christchurch and Dunedin or from NZBS National Office.