New Zealand Blood Service
The gift of life

BLOOD ISSUES

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Iron and the Blood Donor

Blood Services are dependent on the continued support of blood donors. Many donors can safely donate up to four times a year with no adverse consequences. In some donors however, regular donation will lead to a reduction in iron stores and ultimately iron deficiency. Blood Services have a responsibility to maintain the health of donors and there is increasing international awareness of the issue of donation-induced iron deficiency. Mechanisms to reduce the likelihood of this occurring are required.

How much iron is required?

Each millilitre of packed red blood cells (RBC) contains a milligram of iron and each donation of whole blood results in the loss of about 200 – 250 mg of iron. It then follows that four blood donations of whole blood over a twelve month period could result in an annual loss of 1 gram of body iron or, on average, an additional loss of 2.7 mg daily over and above 'physiological' losses.

Average daily iron requirements are about 1mg for adult males and post-menopausal females, 1.8 mg for adolescent males, 2.4 mg for adolescent females and 2.8 mg for adult pre-menopausal females. Healthy, adult male donors on an adequate diet may be able to tolerate annual losses of 1 gram of body iron but other categories of donors may not. Such, otherwise healthy, donors may be at risk of becoming iron-deficient or developing iron-deficiency anaemia solely as a result of blood donation.

What is iron deficiency?

Iron deficiency can be defined in a number of ways, each of which represents an increasing level of severity. There is some preliminary data that raises the possibility that physical, cognitive and behavioural impairment might be associated with iron deficiency even in individuals with a normal haemoglobin. Iron deficiency can be sufficient to lead to iron-deficient erythropoiesis but not sufficient to cause the haemoglobin to fall or the severity of iron deficiency can be such that it causes the haemoglobin to fall.

Risk factors for iron deficiency include post-menarche, pre-menopausal females, females with a history of irregular periods, menorrhagia, use of intrauterine device, bleeds at other sites such as frequent nose bleeds, recent migrants, vegetarians, and endurance athletes. In one study amongst post-menarche, pre-menopausal women in New Zealand, iron intake varied from 9.6 to 10.5 mg daily, the proportion of women with non-anaemic iron deficiency ranged from 0.7 to 12.6%; and iron deficiency anaemia was found in 1.4 to 5.5%. Another study in a group of 21 year old New Zealanders found that 0.97% of males and 6.7% of females were iron deficient (serum ferritin <12 ug/L), iron deficiency anaemia was found in 0% of males and 2.2% of females.

Blood Donors and Iron Deficiency

In a study in the United States in the 1980's, 8% of male and 23% of female blood donors had reduced iron stores (based on low serum ferritin). A similar but more recent study from Germany showed that 26% of regular donors were iron deficient with serum ferritin levels of <15ug/L and that 12% had iron deficiency anaemia.

It is believed that iron-replete blood donors start to show a significant decline in ferritin levels after 6 – 10 donations over a 2 year period. A fall in serum ferritin, though a reliable indicator of iron deficiency, is a relatively late and insensitive indicator of developing iron deficiency. Normal and high ferritin values do not necessarily mean adequate iron stores for a number of reasons. Commonly measured red cell indices such as Haemoglobin, (Hb) Mean Cell Volume (MCV) and Mean Cell Haemoglobin (MCH) also change late in the course of developing iron deficiency. It may well be that iron deficiency develops after fewer than 6 to 10 donations or indeed that some donors are iron deficient to start with despite conventionally-measured indices in the normal range.

Iron Supplementation

Assuming an additional iron loss equivalent to 2.7 mg daily in those donating four whole blood donations annually and absorption of about 10% of an oral dose of iron, approximately 27 mg of oral elemental iron daily would appear to be sufficient to maintain iron stores in whole blood donors. Supplements however should not be prescribed without baseline iron studies, on the basis of an abnormal full blood count alone or following a certain number of donations.

Drawbacks of and concerns about iron supplements for regular blood donors include poor compliance, side effects (especially gastrointestinal), the potential for poisoning in children and the potential for causing iron overload amongst members of populations with a known high carrier rate of haemochromatosis-causing mutations.

Proposed Study of New Zealand Blood Donors

Little is known about the iron status of New Zealand blood donors today. Clearly, this information is required to make informed decisions about donor eligibility, frequency of blood donation and testing. NZBS is planning to undertake an initial observational study on 5000 blood donors at two NZBS sites – Christchurch and Waikato. It is proposed that the study will look at serum ferritin levels in blood donors and analyse what effect three important variables – age, sex and prior donation history has on these levels. The study proposal which has been approved by the NZBS is currently under review by the National Ethics Committee. Information gained from the study will be useful for further work in developing a risk model for iron deficiency in blood donors and will help to tailor donation, testing and possibly iron supplementation schedules for blood donors.

Weak D, Partial D and Du

The D antigen of the Rh blood group system is particularly immunogenic. The distinction between Rh(D) positive and Rh(D) negative is generally straightforward with the majority of the individuals clearly being either Rh(D) positive or Rh(D) negative when typed with commercially available anti-D reagents. However for a small percentage of individuals Rh(D) typing does not produce clear-cut results. The existence of weak D types is well known and is reported to occur in 0.2% to 1% of the Caucasian population. There are two distinct types of what is commonly called 'weak D':

Weak D - typified by reduced expression of normal D antigen (quantitative difference). People with Weak D cannot make antibodies to D.

Partial D - where one or more epitopes is missing from the D antigen (qualitative difference). This occurrence is much rarer than Weak D. People with partial D can make antibodies to those parts of the D antigen not present on their own red cells.

In the past, the term "Du" has been used and this caused significant confusion because sometimes it was used for both Weak D and Partial D, and sometimes for Weak D alone.

The context in which Rh(D) typing is required is important, as this determines how results are interpreted. For example, in pretransfusion testing individuals with inconclusive results are treated as Rh(D) negative and receive Rh(D) negative blood until such time as a definitive Rh(D) type is determined. In antenatal (or perinatal) testing a woman with weak or discrepant D typing results is treated as Rh(D) negative and given anti-D immunoglobulin if indicated. Cord bloods with inconclusive results should be considered Rh(D) positive when deciding whether or not anti-D immunoglobulin is required for the baby's mother.

Once a definitive Rh(D) status is obtained the situation changes. In general, weak D individuals can be treated the same as Rh(D) positives whether it be in pretransfusion, antenatal/perinatal or cord blood situations, whereas the treatment of partial D individuals depends on the situation.

Women with partial D in the antenatal setting or patients with partial D requiring transfusion should be considered Rh(D) negative. Conversely a partial D infant with an Rh(D) negative mother should be treated as Rh(D) positive in respect of the mothers candidacy for anti-D immunoglobulin (but receive Rh(D) negative blood if requiring transfusion).

Use Of Frozen Components For Rh(D) Negative Individuals

The NZBS Policy 'Blood Component Support Of Rh(D) Negative Individuals' (111PO32) has recently been brought into line with the latest (2004) edition of the British Committee For Standards in Haematology (BCSH) 'Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant'.

Historically the red cell contamination present in frozen components from Rh(D) positive donors was thought to present a possible risk of alloimmunisation or boosting preformed anti-D if the plasma was transfused to an Rh(D) negative recipient. Previous NZBS policy required that Rh(D) negative frozen plasma components should be used for Rh(D) negative recipients and in particular for premenopausal women. When Rh(D) positive plasma components were given to Rh(D) negative recipients an injection of anti-D immunoglobulin was also normally required to prevent possible alloimmunisation. This requirement was based on the 1992 BCSH 'Guidelines for the use of fresh-frozen plasma'. The rationale being that frozen plasma components have a small degree of red cell contamination, with the red cell stroma remaining (after freezing and thawing) said to be capable of "*... inducing Rh immunisation and can boost anti-D levels in subjects with preformed anti-D*".

With our current understanding of the nature of frozen plasma components, the BCSH now recommends, and NZBS policy reflects, that "*...Fresh frozen plasma of any Rh(D) type may be given regardless of the Rh status of the recipient. No anti-D prophylaxis is required if Rh(D) negative patients receive Rh(D) positive FFP..*". Although not explicitly stated in the original guidelines document a subsequent erratum issued by BCSH indicates that the recommendation also applies to cryoprecipitate and cryosupernatant.

The BCSH guidelines state that frozen plasma components may be transfused regardless of RhD type and are based on a recent UK study that showed levels of intact red cells were undetectable following freeze-thawing and red cell mircoparticles present were negative for RhD antigen. As a consequence, sensitization following transfusion of Rh(D) positive units is most unlikely. This data supports the BCSH guidelines that state that frozen plasma components may be transfused regardless of RhD type. It then follows that no Anti-D prophylaxis is required if Rh(D) negative patients receive Rh(D) positive fresh frozen plasma or cryoprecipitate.

vCJD – Introduction of Extended Donor Deferrals

NZBS closely monitors developments relating to vCJD and the actions taken by other international blood services. A stakeholder group has been established to consider developments and provide advice to the service on the need for extension of current measures aimed at reducing the risk of transmission of the disease by transfusion in New Zealand.

In 2000 NZBS introduced measures to prevent people who had been resident in the United Kingdom for a cumulative period of 6 months or more between 1980 and 1996 from donating blood. 1 in 10 active blood donors in New Zealand were lost by this measure. In 2001 NZBS introduced new systems to remove white cells from donated blood prior to transfusion. This is known as "Universal leucodepletion". The UK has also introduced this. None of the cases of transfusion associated disease in the UK to date had received leucodepleted blood components. In 2003 NZBS introduced a measure whereby people who had received a transfusion in the United Kingdom since 1980 were prevented from donating blood.

In April 2006 NZBS introduced additional measures based on concerns relating to the increasing number of cases of vCJD reported in France and Ireland. The measures reflect those introduced earlier relating to travel/residency and transfusion in the United Kingdom. Prospective donors who have visited or lived in France or the Republic of Ireland, or received a blood donation in France or the Republic of Ireland since 1980 will be permanently deferred from donating blood in New Zealand. NZBS anticipates that about 0.25% of current donors will be lost by these new measures.

Further information on the new deferrals is available on the NZBS website (www.nzblood.co.nz)

Fractionated Plasma Products Update

Zoster Immunoglobulin

Zoster immunoglobulin presents unusual problems for maintaining an adequate supply of plasma from which it can be made. Most of the plasma comes from older individuals who have suffered a recurrence of infection with the Varicella-zoster virus. The virus that causes chicken pox normally remains in the body after an acute infection taking up residence in the nerve cells and re-emerging many years later when the person is run down. The new episode of infection affects a localised area of skin supplied by infected nerve cells and this secondary or recurrent infection is called "shingles" or herpes zoster. With the development of anti-viral medicines, patients suffering an outbreak of shingles have had the infection partially suppressed and usually do not develop antibody titres that are sufficiently high to provide source plasma for the manufacture of Zoster immunoglobulin.

From time to time NZBS has been unable to collect enough source plasma to manufacture its own Zoster Immunoglobulin and has had to obtain stocks of Australian Zoster Immunoglobulin to ensure continuity of supply. The current stock of NZBS Zoster Immunoglobulin will expire on the 21st June 2006 and a recently purchased batch of Zoster Immunoglobulin from the Australian Red Cross Blood Service (ARCBS) will be its replacement. The plasma for this product is sourced from Australian blood donors.

The labelling will appear different to the NZBS product as it has the ARCBS logo on it, a hyphenated suffix –VF added to the trade name and Australian registration details, but in all other aspects it is identical to the NZBS product.

ARCBS Zoster Immunoglobulin and Section 29 of the Medicines Act

Plasma products are defined as medicines under the Medicines Act 1981 which regulates the use of medicines in New Zealand. The Act requires that in order for a medicine to be marketed an application with supporting documentation must be made for the consent of the Minister. The Minister's consent is notified in the New Zealand Gazette, at which time the medicine along with a set of indications, dosage instructions and routes of administration is regarded as being approved. Proposed changes, including new indications and changes to the data sheet also have to be applied for. Because of this requirement for seeking and obtaining consent, there are effective and safe medicines that are available in other countries, but do not have approval in New Zealand.

As there is a need to provide access to some unapproved medicines, Section 25 of the Medicine's Act permits registered medical practitioners to procure, administer and arrange the administration of an unapproved medicine. ARCBS Zoster Immunoglobulin is an example of a medicine that is unapproved for use in New Zealand.

Section 29 of the Medicine's Act permits an authorised supplier (in this case NZBS) to supply medicines that have not been approved to medical practitioners. A requirement of Section 29 of the Act is that NZBS must notify the Director-General of Health of that supply in writing, naming the medical practitioner and the patient, describing the medicine and the date and place of supply.

Use of Intragam P as protective treatment for Chicken Pox

Protective treatment against chicken pox infection can also be obtained by the use of Intragam P. The titre of antibody against varicella-zoster virus in Intragam P is assessed by CSL Bioplasma and the dose of Intragam P that is required to give a protective treatment against chicken pox infection can be calculated. Information relating to the appropriate dose of Intragam P to be used in the treatment of varicella-zoster virus can be provided by your local Transfusion Medicine Specialist.

Biostate®

CSL have commenced the manufacture of a 500IU vial formulation for Biostate® and the first batch is now available. There are new temperature storage conditions that Medsafe have approved for both this and the 250IU formulation.

The new storage conditions are "*Store at 2-8˚C (Refrigerate. Do not freeze). Biostate can be stored below 25˚C for a single 6 month period (Do not return to refrigeration).* The shelf life remains at 24 months when stored at 2-8˚C.

The ability to store Biostate® below 25˚C will enhance convenience for end-users and patients for home storage and travel.

Second Viral Inactivation Step for Intramuscular Immunoglobulins

CSL Bioplasma has incorporated a second viral reduction step in the manufacturing process of the intramuscular immunoglobulin products, Normal Immunoglobuin, Hepatitis B Immunoglobulin, Rh(D) Immunoglobulin, Tetanus Immunoglobulin and Zoster Immunoglobulin. The current manufacturing process is based on Cohn ethanol precipitation and includes pasteurisation as the viral inactivation step. The second viral reduction step occurs when the product is passed through a nanofilter membrane that retains viruses but allows the passage of proteins of interest. Products derived from this process will be recognised by the addition of the hyphenated suffix –VF to the tradenames.

Apart from the additional Viral Inactivation Step and the tradename change, the products are identical to the previous products in terms of their physical, chemical and immunological properties. The new range of intramuscular immunoglobulins will be phased in as they are manufactured by CSL Bioplasma and the first product expected to arrive in NZBS with the two viral inactivation steps is Normal Immunoglobulin in July 2006. The second viral inactivation step has already been introduced in Australia, as shown by the labelling for Zoster Immunoglobulin that has been sourced from ARCBS.

WinRho® SDF

WinRho® SDF is not registered for the treatment of immune thrombocytopenic purpura (ITP) in New Zealand, however there are on occasions overseas residents who travel in New Zealand and who carry their overseas sourced fractionated products with them. Clinicians and health care professionals need to be aware that Disseminated Intravascular Coagulation (DIC) may be a rare but potentially severe complication among patients who are being treated for ITP with WinRho® SDF.

Among patients in the USA treated for ITP with WinRho® SDF there have been reports of signs and symptoms consistent with intravascular haemolysis that include back pain, shaking, chills, fever and discoloured urine occurring, in most cases within four hours of administration. Potentially serious complications of intravascular haemolysis that have also been reported include clinically compromising anaemia, acute renal insufficiency or DIC that have in some cases been fatal.

The FDA licensed WinRho® in 1995 for the treatment of immune thrombocytopenic purpura (ITP) in Rh(D) positive nonsplenectomised children with acute ITP, children and adults with chronic ITP and children and adults with ITP secondary to HIV infection. It is currently the only Rh(D) Immunoglobulin licensed for this indication in the United States. The FDA also approved WinRho® for suppression of Rh isoimmunisation and it is used for the treatment of "off-label" thrombocytopenias (e.g. secondary thrombocytopenia) to an unknown extent.

During the clinical trials of WinRho®, two cases involving "acute-onset haemoglobinuria consistent with intravascular haemolysis" were noted. Since then additional cases have been submitted to the FDA and have been previously reported. These reports described data on 15 patients, 11 of whom experienced additional complications; 6 developed sufficient decreases in haemoglobin to require transfusion, 8 experienced onset or exacerbation of renal insufficiency, 2 of whom underwent dialysis; 1 died from pulmonary oedema and respiratory distress secondary to exacerbated anaemia; and 6 experienced 2 or 3 of these complications concurrently. The review of these reports suggested that patients receiving WinRho® SDF for ITP or secondary thrombocytopenia should be closely monitored for signs and symptoms of those or other potential complications of haemoglobinaemia, notably disseminated intravascular coagulation (DIC).

Between 1995 and 2004 FDA received six reports of DIC associated with 'acute haemolysis', 1 child who recovered without sequelae and 5 adults, all of whom died. The attending clinicians made the assessment that acute haemolysis or DIC caused or contributed to each death.

BayHep B

NZBS has supplied the Hepatitis B immunoglobulin 2171U/ml product BayHep B 0.5ml as a preparation for neonates when the CSL product is unavailable. The name of this product has recently been changed to HyperHEP™ 0.5ml and prescribers will notice this change once stocks of BayHep B in the blood banks are depleted and are replaced with HyperHEP B™.

The name of the manufacturing and packing site has changed to Talecris Biotherapeutics and the way in which the potency of the finished product is expressed has also changed to reflect the use of a new standard in the potency assay. The labeling of the product has been changed to reflect the name and company change and the change in the finished product potency. In all other aspects HyperHep B™ is the same product as BayHep B. The NZBS Transfusion Nurse Specialists have communicated this information to the Lead Maternity Carers and any queries relating to this change should be directed to them in the first instance.

Mix2Vial Filter Transfer set for Coagulation Factor Concentrates

CSL Bioplasma have made changes to the preparation device for the reconstitution of the coagulation factor concentrates, Biostate®, MonoFIX®-VF, Prothrombinex™-HT and Thrombotrol®-VF. This change relates to the inclusion of a "Mix2Vial" filter transfer set used to transfer the Water for Injection from the glass vial to the product vial containing the freeze dried coagulation product. The first coagulation factor concentrate product to demonstrate the change is Biostate® and a transparent sticker has been placed on top of the carton to alert the user that the product contains a new reconstitution device.

Do not use the product if the seal of the lid is not intact, if there are any concerns about the integrity of the Mix2Vial™, or if the vial does not contain a vacuum. If any of these events occur, please return the product to NZBS.

Reporting of Adverse Events to Fractionated Products

NZBS closely monitors reports of adverse reactions following administration of fractionated blood products. If a patient suffers such an event then please contact the hospital blood banks where the product was issued. Blood Bank staff will ensure that the report is sent to NZBS for review.