New Zealand Blood Service
The gift of life

BLOOD ISSUES

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Editorial

In June 2003 the NZBS cosponsored a national workshop in Wellington on issues relating to haemophilia management. The main outcome of the workshop was the establishment of a project group tasked to take responsibility for the development of a proposal to DHBNZ for the national co-ordination and management of Haemophilia Services. The project group has met on a number of occasions during the last two years. Significant progress has been made on a number of fronts. Two particular initiatives will soon be completed.

The first initiative relates to the introduction of Biostate. This is a new high purity Factor VIII product derived from plasma collected by NZBS. Biostate is suitable for treatment of both Haemophilia A and von Willebrand's disease. It is a proven product having been licensed and used in Australia for almost two years. The Biostate manufacturing process incorporates two specific viral inactivation steps (solvent detergent treatment and dry heat) as opposed to the single step used in manufacture of AHF-HP (the current product). The safety record of AHF-HP is excellent, the two inactivation steps used in the manufacture of Biostate will ensure that it is an even safer product. In common with other high purity Factor VIII products, the yield of Biostate is reduced when compared to other products including AHF-HP. This means that less Biostate is produced per litre of plasma than was the case with AHF-HP. The haemophilia project group in discussion with the haemophilia treaters and HFNZ has made the decision to use this as an opportunity to increase the availability of recombinant Factor VIII in New Zealand.

The second initiative relates to a national procurement process for recombinant Factor VIII. This project was managed by Pharmac with involvement for the national haemophilia group. The aim is to coordinate the purchase of recombinant FVIII in order to improve confidence in continuity of supply and also to ensure that the product is purchased in a cost efficient manner. The outcome of the tender process is not yet known. It is however anticipated that new arrangements will be introduced early in the 2005/06 financial year.

Management of these two initiatives will be a significant logistic challenge. NZBS is coordinating the transition from AHF-HP with CSL, the treaters and HFNZ. This process will be taking place at the same time as the impact of the recombinant tender is announced and implementation of this progressed. The national haemophilia group will play a key role in coordinating the many activities that will be needed to achieve a positive outcome to these changes.

Peter Flanagan
National Medical Director

Introduction of the National Haemovigilance Programme

On 1 January 2005 NZBS began its National Haemovigilance Programme with a pilot conducted at Auckland City, Waikato and Tauranga Hospitals. By piloting the programme it is hoped to iron out any major wrinkles before it is released to the wider blood transfusion community.

NZBS is introducing the National Haemovigilance Programme to monitor adverse events occurring during the transfusion process. The programme meets requirements identified in the Council of Europe Guide. It is modelled on similar schemes successfully operating in the UK and Eire.

The aim is for the national haemovigilance programme to monitor adverse events occurring across the whole 'vein to vein' process i.e. from the collection of blood or blood components from donors through to the transfusion of these products to patients at the bedside.

Full national introduction of the programme will begin once information from the pilot has been reviewed and final sign off received from the NZBS Clinical Advisory Group.

Capturing Events Other Than Transfusion Reactions

A major task of the haemovigilance programme will be to capture data about adverse events other than 'traditional' transfusion reactions for example transfusion of incorrect or inappropriate blood or blood components. When a person receives blood intended for another patient or blood where special requirements such as providing irradiated or CMV-negative components are not met, unless there is a major incompatibility the patient may not experience any obvious side effects. However it is important to recognise and report these potentially serious events.

In common with other types of event the transfusion of an incorrect blood component represents a system failure which needs to be identified and corrected to prevent similar events happening in the future. Whilst these events might be reported through a hospital's quality management system this information often does not reach the hospital's blood bank or NZBS.

If maximum benefit is to be obtained from the national haemovigilance system then it will be important to ensure that all transfusion related incidents or events are reported to the hospital's Transfusion Safety Officer (normally the blood bank Charge Scientist). This individual will be the key link into the national programme and will subsequently notify the National Haemovigilance Office. NZBS will work with hospitals to ensure that adverse events are appropriately reported in a timely manner.

All Hospital Staff Encouraged to Report Transfusion Related Adverse Events

Blood transfusion is a complex process involving a variety of staff groups in the hospital such as those from the laboratory, nurses, doctors and orderlies. Any failure in the transfusion chain has the potential to cause significant harm or even death for patients. All personnel involved in the transfusion process must be encouraged to be vigilant and report any untoward events that they may observe whether or not transfusion has actually occurred. Reports of adverse events should initially be made to the hospital's Transfusion Safety Officer.

Raising Awareness Of The Need For Haemovigilance

For haemovigilance to be successful there needs to be an awareness of the programme and what it hopes to achieve. NZBS will be developing educational material not only highlighting the haemovigilance programme but also those areas where errors occur during the transfusion process and how these events should be reported when discovered.

Haemovigilance – A Role In Standardising Practices

The introduction of a formal haemovigilance programme is also an important step in standardisation of a number of existing processes used to monitor, analyse and report adverse events associated with transfusion. For example, transfusion reactions, donor incidents, specimen labelling errors, blood bank errors all fall under the umbrella of haemovigilance and NZBS will standardise reporting of these in line with international practices.

Recent Developments Relating to vCJD And Transfusion

The number of cases of vCJD reported to the UK CJD Surveillance Centre (UKCJDSU) continued to fall during 2004 with a total of 148 deaths from definite or probable vCJD having been reported as of February 2005. 9 deaths occurred during 2004 compared to 18 in 2003 and 6 cases of definite/probable vCJD cases are still alive. The number of cases reported outside the United Kingdom remains low with nine cases having been reported in France and a single case in each of Ireland, Italy, Canada and the USA. The vCJD cases reported in France and Italy had not had a history of residence in the UK, unlike the cases reported in Ireland, Canada and the USA that had a history of UK residence during the late 1980s.

Using the best fitting model the most recent quarterly analysis of the incidence of vCJD onsets and deaths in the UK indicates that although a peak in incidence has been passed, this does not exclude the possibility of future peaks. There is the possibility of epidemics in other genetic subtypes and also human to human spread. All clinical cases of vCJD reported to date are homozygous for methionine at codon 129 but the possibility that future cases may occur in other genetic subtypes is reinforced by the second report of possible transfusion transmission of vCJD. In this instance the recipient of red cells from a donor who subsequently developed vCJD died of unrelated causes. The presence of prion protein in the spleen and a cervical lymph node was demonstrated at post-mortem and in this case the recipient was not symptomatic and was heterozygous for methionine/valine at codon 129.

Paul Clarke and Azra Ghani have published projections on the future course of the epidemic of primary vCJD in the UK which suggest that the primary peak of the epidemic may have passed and that estimates for future cases are significantly lower than was the case 3 to 5 years ago. The two cases of probable transmission of vCJD by transfusion involved red cell transfusion and no cases of transmission linked to plasma product use have yet occurred. In response to these two cases the UK Department of Health reviewed its approach to notification of risk to recipients of blood products manufactured from pools that included donations from individuals who subsequently developed vCJD. In conjunction with Det Norske Veritas, the UK CJD Incidents Panel assessed the risk of various products and developed a framework for communication to recipients and clinicians. The UK government informed countries to which implicated product had been exported and Medsafe confirmed that New Zealand did not receive any of this product.

Some years ago CSL Bioplasma initiated a research programme aimed at understanding the ability of its manufacturing systems to remove prion protein and this work is undertaken in close collaboration with the Australian regulator, the Therapeutic Goods Agency. The prion clearance capability for Factor VIII is of particular interest because coagulation factor concentrates were identified by Det Norske Veritas as the product with the highest risk. NZBS continues to actively monitor the situation and formally reviews developments relating to vCJD and transfusion on an annual basis.

A workshop was held in March 2005 to review the progress made by NZBS since the last vCJD workshop held in September 2003 and the results of a survey of New Zealand Donor travel patterns and transfusion history were presented. The NZBS travel survey undertaken in 2004 identified that the proportion of donors who have travelled to the UK during 1980 and 1996 has reduced significantly from previous surveys and the residual risk, based on cumulative stay in UK/Europe has consequently changed. NZBS has also implemented a risk management strategy aimed at improving confidence in supply of product following a pool withdrawal that is based on a target of four months supply of fractionated product and four months supply of plasma available for fractionation following each major pool. Indications are that this strategy is now in place.

The stakeholders at the workshop reviewed the content of the wording of the vCJD risk statement in the NZBS Fresh Blood Components Informed Consent leaflet and recommended that this wording should be changed to read

"The risk of acquiring CJD/vCJD from transfusion remains very low and has never been reported in New Zealand. Rare transfusion related cases have been reported in the UK."

Additional recommendations arising out of this workshop were that :

- NZBS should actively investigate the feasibility of reinforcing current precautionary measures and in doing so should ensure that any measures implemented will manage transfusion and travel risks in a consistent manner. It was agreed that any new measures should not adversely impact on NZBS' ability to supply.
- Further consultation should take place once NZBS has concluded its investigations and undertaken an impact assessment of proposed new measures.
- NZBS should continue to ensure that current risk management systems are maintained and developed appropriately to assure the continued supply of fractionated plasma products derived from blood donated in New Zealand. This risk management approach will include the maintenance of contingency supplies of plasma and/or finished products derived from New Zealand donated plasma sufficient to overcome the impact of withdrawal of a batch of plasma.

References

Paul Clarke and Azra C. Ghani J.R.Soc Interface doi=10.1098/rsif.2004.0017. Published online October 2004.

Incidence of variant Creutzfeldt-Jakob Disease Onsets and Death in the UK htt)p://www.cjd.ed.ac.uk www.cjd.ed.ac.uk

EMEA CHMP Position Statement on Creutzfeldt-Jakob Disease and Plasma derived and Urine derived Medicinal Products http://www.emea.eu.int www.emea.eu.int

Transfusion In Autoimmune Haemolytic Anaemia – A Guide For Clinical Staff

Many patients with Autoimmune Haemolytic Anaemia (AIHA) develop anaemia that is severe enough to require blood transfusion. This is often the case for patients who rapidly develop severe anaemia or have an underlying disease like symptomatic coronary artery disease.

Many clinicians are reluctant to transfuse these patients. The main reason for this is the presence of a broadly reactive autoantibody in the patient's serum, which makes it virtually impossible to find a unit of blood that is crossmatch compatible. This adds a degree of uncertainty about the safety of transfusion of serologically incompatible blood.

Although the presence of an autoantibody is known to reduce the half-life of the transfused blood, the survival is almost as good as the patient's own red cells and haemolytic transfusion reactions are rare. On the other hand if the incompatibility is due to a clinically significant alloantibody a haemolytic transfusion reaction can be expected. It is important to remember that as long as the presence of any alloantibody has been identified and the selected blood is negative for that antigen, transfusion of blood is not significantly more risky than any other blood transfusion. The difficulty lies with the detection and identification of alloantibodies in the presence of an autoantibody that reacts with all red blood cells (RBC). It also makes it impossible to provide crossmatch compatible RBCs.

A number of serological approaches have been developed to provide suitable blood for AIHA patients. All of these are aimed to avoid and/or to detect alloantibodies of Rhesus, Kell, Duffy, Kidd and MNSs blood group systems which may cause clinically significant haemolysis. Possible approaches are outlined below:

Transfusion Of RBCs That Match All Clinically Significant Blood Groups (Transfusion Of Phenotypically Matched Blood)

In routine transfusion, endeavours are made to match ABO and Rh(D) blood groups. If the patient is negative for any of the other blood groups and transfused with RBCs that are positive for that blood group the patient may develop antibody against that blood group. On the other hand if the patient is positive for the blood group the patient is incapable of producing an antibody against that blood group. If in addition to ABO and Rh (D) the other blood groups of Rhesus, Kell Duffy, Kidd and MNSs system are matched when selecting blood for transfusion adequate safety will be provided. The transfusion of blood that matches all these blood groups will also prevent formation of any significant alloantibody.

Although this approach looks attractive it does have a few problems. The patient's red cells are positive for the direct antiglobulin test (cells are coated with autoantibody) and it is often difficult to determine all the important blood groups. It is also often very difficult to get the RBCs that match all the required blood groups, particularly when they are required at short notice.

Dilution Procedure

Occasionally the autoantibody is weaker than the alloantibody. If the serum is diluted in these situations to the extent that the autoantibody is no longer detectable and then tested against a panel of reagent cells it is possible to identify the alloantibody. Unfortunately in most situations this rather simple approach does not work.

Adsorption Procedures

In an adsorption procedure autoantibodies are eluted from patients red cells using a variety of reagents. These red cells are then mixed with the patient's serum to adsorb out the autoantibody. The alloantibodies will not be adsorbed by the patient's own red cells (as the patient lacks the corresponding antigen) and will be left behind in the serum. This serum is used to exclude the presence of an alloantibody or to identify the alloantibody that may be present and is also used for crossmatching.

Autoadsorption is not useful in recently transfused patients and on occasions not enough of the patient's red cells are available for autoadsorption. In these situations adsorption is carried out with several allogenic red cells of varying phenotype (blood groups). Adsorption with allogenic red cells will remove the autoantibody that reacts with all red cells but will not remove an alloantibody if the adsorbing cell is negative for that particular blood group. For example if the patient has an autoantibody and anti-Kell, adsorption with a Kell negative blood will remove the autoantibody leaving behind anti-Kell in the serum.

What Is The Usual Approach?

Although the use of phenotypically matched RBCs (matched for all-important blood groups) is an option it is often not practical. Adsorption procedures are the main method for selecting blood for transfusion to AIHA patients. Partial phenotyping and matching is often undertaken as it reduces the risk of developing alloantibodies and helps to identify any alloantibody that may develop. Testing for alloantibodies in a patient with AIHA and finding suitable RBCs for transfusion usually takes 4-6 hours and some times even longer. Clinical staff should contact NZBS as soon as it is evident that a patient with AIHA may need blood transfusion. In an emergency situation it may be necessary to start transfusion before all the investigations have been completed. Although the presence of an alloantibody is common in transfused AIHA patients it is worthwhile to remember that if the patient has not been transfused in the past, nor has been pregnant, it is very unlikely that an alloantibody is present.

What Is Meant By "Least Incompatible"?

When blood is issued for an AIHA patient it is often labelled as "least incompatible". This rather ambiguous term is used to indicate that the blood is incompatible by conventional crossmatch due to the presence of an autoantibody or an antibody that is not clinically significant. Other terms such as "best match available" and "suitable for transfusion" have been suggested as an alternative but neither is completely satisfactory. It is important that the clinicians understand the significance of "least incompatible", understand that each AIHA patient will have a different problem and that close communication between NZBS and the clinicians is important to provide appropriate transfusion support for these patients.

Establishment of Trans Tasman Regulatory Authority Delayed

In January 2005, The New Zealand and Australian Governments signalled that the establishment of the new Trans Tasman Regulatory Authority was to be delayed until July 2006. Information on the new structures was provided in the November 2004 edition of Blood Issues. The delay will provide more time to determine the preferred system for the future regulation of blood components in New Zealand.

Safety Related Changes to Intragam® P

CSL Bioplasma have recently made three safety-related changes to the Precautions and Adverse Reactions sections of the Product Information and Datasheet for Intragam® P.

- Thrombotic events have been reported in association with IVIG therapy. Risk Factors include advanced age, immobility, impaired cardiac output and conditions associated with increased plasma viscosity, such as hypertriglyceridaemia and monoclonal gammopathies.

- Patients of blood group A or AB receiving high dose IVIG (>0.4 g/kg) every 4 weeks) especially those with reduced bone marrow reserve or post haemopoietic stem cell transplantation appear to be more susceptible. Patients receiving high dose IVIG (>0.4 g/kg every 4 weeks) should have a pre-infusion ABO blood group determined and have their haemoglobin monitored in the days following therapy for evidence of clinically significant haemolysis.

- Patients who receive IVIG for the first time, when there has been a long interval since the previous infusion or in rare cases, when the human normal immunoglobulin product is switched may experience a higher frequency of adverse events, including those of a minor nature.

Reactions to IVIG tend to be related to the infusion rate and are most likely to occur during the first hour of the infusion. It is recommended that the patient's vital signs and general status are monitored regularly throughout the infusion.

Progesa Implementation Completed

Shortly following Easter, the Counties Manukau DHB Blood Bank went live on Progesa. This means that all main DHB Blood Banks across New Zealand are now using the same IS system for managing blood stocks and for issue of blood products to patients.

Progesa is now a valuable national tool.

It enables the centralised production of information on blood product use by DHB. This can assist our understanding of trends in blood product use and the investigation of apparent differences in activity. The NZBS Demand Management programme is based on this.

It enables NZBS to electronically block release of blood products. If a donor becomes ill shortly following donation then NZBS can immediately block release of the components manufactured from the donor. Very few countries have the ability to do this through a single system.

Progesa is an international system. It is used in many countries including Scotland, Canada and Ireland. The Australian Red Cross Blood Service has recently started to implement it. In most countries however its use is restricted to the collection and manufacturing activities of blood services. Electronic communication between the Blood Service and hospital blood banks in these countries remains problematic.

Implementation of Progesa in New Zealand started in July 1999. Manufacturing activities were fully active by October 2000. The first hospital blood bank went live in April 2000. Now that Counties Manukau has gone live, implementation of the national network is complete.

A Few Wise Words To Close

"Blood transfusion is like marriage; it should not be entered upon lightly, unadvisedly or wantonly, or more often than is absolutely necessary"

R W Beal 1976