New Zealand Blood Service
The gift of life

BLOOD ISSUES

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Trans-Tasman Therapeutic Goods Agency

The Australian and New Zealand Governments have signed a Treaty to establish a single, bi-national agency to regulate therapeutic products, including medical devices and prescription, over-the-counter and complementary medicines. The Joint Scheme will apply in both New Zealand and Australia and will cover:

- Regulation of the manufacture, supply, import, export and promotion of therapeutic products.
- Setting of standards in relation to the quality, safety and efficacy or performance of therapeutic products and their manufacture, supply, import, export and promotion.
- Post-market monitoring of therapeutic products.
- Enforcement of the requirements of the scheme

The single agency, which will replace the Australian Therapeutic Goods Administration (TGA) and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) will be accountable to both the Australian and New Zealand Governments and is expected to commence operation in 2005. It will require new legislation in both countries and a common set of rules. Both countries will have an equal voice in the oversight of the scheme through the two member ministerial council that comprises the NZ Health Minister and the Federal Health Minister in Australia.

The primary policy objective for the joint scheme is to manage the risks to public health and safety from avoidable harm associated with the use of therapeutic products. It will:

- Regulate therapeutic products for safety, quality and efficacy to ensure that the benefits of use will outweigh the risks if the product is used appropriately.
- Regulate products in accordance with international best practice, adopting a globally harmonised approach where possible.
- Ensure that health and safety objectives are met while minimising costs to businesses and Government and without imposing unnecessary trade barriers.
- Provide increased access to scarce technical resources.

In respect of blood and blood components, the new agency will perform the functions that Medsafe does now, audit and licensing of blood collection and manufacturing sites, evaluation and approval of fractionated products and oversight of recalls. Under consideration is the issue of whether the new agency should also perform regulatory functions such as standards setting in relation to blood.

A working party comprising representatives from NZBS, the Medsafe joint agency project team and the Ministry of Health has been established in order to determine the most appropriate way to manage blood safety issues within the new regulatory environment.

Assigning an NHI number to a Foetus

Occasionally NZBS is required to provide blood for transfusion to a foetus. From a transfusion point of view, the baby needs to be identified as separate from the mother. The reason for this is that blood which has been cross-matched for the baby will not necessarily be compatible with the mother. If samples taken from the foetus are labelled using the mother's details there is a risk that the crossmatched blood may be labelled in the same manner and this raises the possibility that incompatible components could be transfused to the mother. The NZBS information system also requires a separate record for both mother and child to ensure that blood with the baby's blood group is not inadvertently issued to the mother.

National Women's Hospital manages the situation when an intrauterine transfusion is required, by registering the foetus using a pre-allocated NHI number. When the baby is born, the details are updated on the hospital system, by adding the date of birth for example, and the NHI is formally registered. This does require more work for the hospital to ensure that the baby is not re-registered when born and thereby creating duplicate entries, but the increased safety benefits for transfusion are worth the extra effort.

The Transfusion Nurse Specialists will be working with the Transfusion Committees to assist with the development of this process in other hospitals that undertake intrauterine transfusions.

Patient Experiences of Informed Consent for Blood Transfusion

Informed consent for transfusion is a requirement of the New Zealand Code of Health and Disability Services Consumers' Rights. The code requires that patients are provided with information and an explanation of the purpose for which blood components and blood products are being prescribed and that they consent to transfusion. NZBS produces a range of leaflets to support the process of gaining informed consent and these should be available in all sites where blood components and products are transfused.

A study has been carried out in Waikato to ascertain whether patients gave informed consent for blood transfusion, if they were satisfied with the information they were given and what their experiences/concerns of the blood transfusion were.

Using a modified version of a questionnaire by Gray and Murphy (1993), 201 (94 male, 107 female) patients were interviewed. Interviews averaged 15-20 minutes in length and were conducted within 5 days of the transfusion.

Patients who were in intensive care units, high dependency units, delivery suites, paediatric departments or emergency departments were excluded. 70% were acute admissions and 30% were booked or elective admissions.

72% (145) of patients interviewed had signed a consent form. However 18% (27) of this group were not satisfied with the information they were given, suggesting that only 58% (118) of patients gave true informed consent. 16% (33) of the patients could recall receiving the NZBS leaflet and all patients in this group were satisfied with the information they were given. 84% of patients did not receive written information and only a third of this group were satisfied with the information they received.

26% (53) of patients had concerns about blood transfusions, with viral infections being the most prominent worry for patients. Of those patients interviewed only 15% questioned the clinician. 93% of this group were satisfied with the answers received. Patients offered 330 comments with 55% being positive, 22% being negative and 23% were considered to be neutral. There were no significant differences between Maori and European groups.

In relative terms this study was a small one, however it provides a baseline of patient's perceptions towards blood transfusions and it indicates that a sizeable proportion of patients are given insufficient information to alleviate their concerns or make an informed consent.

vCJD Development in the United Kingdom

In December 2003 it was announced in the UK that a patient who had recently died with vCJD had received a blood transfusion in 1996 prior to precautionary measures being implemented. The donor showed no signs of vCJD at the time of donation, but developed the disease three years later in 1999 and subsequently died.

It is therefore possible that the disease was transmitted from donor to recipient by blood transfusion. It is also possible that both individuals separately acquired vCJD by eating BSE infected meat or meat products. Although it is possible that vCJD was transmitted from donor to patient, the link has not yet been proven. This report from the United Kingdom is of concern and NZBS is closely monitoring the situation.

Review of vCJD Precautionary Measures in New Zealand

In September 2003 a workshop was held by NZBS to review progress made on precautionary measures to reduce the risk of TSE transmission by blood and blood products. The focus of the review was in three main areas:

- Significant developments in relation to the understanding of vCJD and the risk relating to transmission by blood and blood products as well as the response of the international community to this.
- A review of the BSE epidemic in Europe and measures introduced to reduce the risk of animal to human transmission by food.
- A review of the systems implemented by NZBS to improve risk management around supply.

Data on the pattern of the vCJD epidemic in the United Kingdom suggests that it may have reached its peak. By late 2003, 143 cases have been identified in the UK, 6 in France and one each in Italy, Canada, the USA, Hong Kong and Ireland. The rate of case accrual is no longer increasing, however it is too early to be confident that the period of major risk has ended. The number of cases of vCJD occurring outside of the UK remains small and there is no evidence that this is increasing at this stage.

The Australian authorities have recently reviewed their position on precautionary measures and protection of the blood supply and this has resulted in a common position in New Zealand and Australia. In the last twelve months NZBS has made significant progress in improving plasma collection and the development of a contingency plasma supply at CSL.

Recommendations arising out of the workshop were that the current position regarding vCJD precautionary measures should be maintained and that NZBS should continue to take active steps to ensure that effective risk management systems are in place for the continued supply of fractionated plasma products derived from blood donated in New Zealand. The position will be actively monitored and formally reviewed in twelve months or as soon as possible in the event of significant developments

Cord Blood

A program which has been established with the co-operation of the Auckland Obstetric Centre and the National Women's Hospital invites pregnant women to consent to the donation of a sample of the cord blood of their babies. The sample of cord blood is used as a diagnostic reagent in serological diagnostic testing of adults and older children. The blood that is used would otherwise be discarded.

Cord red cells react weakly to Anti-I and strongly with Anti-i. Within the first 18 months of life this pattern is reversed with adult red cells reacting strongly with Anti-I and weakly with Anti-i. Adult red cells that fail to react with Anti-I are very rare, so cord cells become important as a source of material when testing for the presence of Anti-i.

These red cells are used to test for the presence of antibodies in the blood of some patients, such as Anti-i, which is associated with infectious mononucleosis and some patients with dyshaemopoetic states. It is also used as a negative control in tests to detect Anti-I associated with polyagglutination in haemolytic uraemic syndrome, some forms of pneumonia, and in neonates with necrotising enterocolitis.

The collection from at least 3 donors is necessary to prepare a batch panel of cord red cells that are suitable to use as a diagnostic reagent. The cells must be relatively fresh and they have a maximum shelf life of

about 6 weeks. It has been estimated that the cost of importing from a commercial source would represent a significant financial outlay each year.

The consenting process for the mothers is similar to that for a blood donor. Although the cord red cells will not be transfused to patients the distribution of them as a reagent to laboratories in New Zealand requires that the sample is tested for and has non-reactive serology to HIV, HBV and HCV.

NZBS wishes to thank everyone who is involved in this important community health project. The willingness of pregnant women to donate the cord cells of their babies, the assistance of the obstetricians in consenting pregnant women to allow for the testing of infectious disease markers and the midwives who are involved in arranging the collection of the cord blood samples have all made this possible.

T Activation

Polyagglutination refers to the agglutination of altered red cells by a large proportion of ABO-compatible adult sera. The causes of red cell membrane alteration are microbial activity (bacteria or viral), certain forms of aberrant erythropoiesis, and inherited conditions. In the microbially induced forms, enzymes are produced which remove carbohydrate residues and expose hidden antigens (cryptantigens).

The first type of polyagglutination was described as early as 1925. This initial type of polyagglutination has become known as 'T activation'. In classical T activation, the T antigen is exposed through the action of neuraminidase which removes the terminal N-acetyl-neuraminic acid (also known as sialic acid) from red cell membrane structures. Much of the cryptic T antigen on red cells is carried on the MN and Ss sialoglycoproteins.

Infections that can cause T activation include anaerobic bacteria (e.g. Clostridia species), pneumococci, and influenza virus. Other variants, such as Th and Tx activation, are less common than classical T activation. Tk and Tn activation are considered distinct entities. Tk activation is the result of the action of a bacterial enzyme, β-galactosidase, whereas Tn is due to a clonal red cell mutation and is not related to microbial action.

Most adult human plasma contains anti-T. This is thought to arise from prior exposure to gram negative bacteria and some vaccines which contain a substance which is either identical or very similar to T. Most anti-T in human serum are IgM antibodies which can result in agglutination in tests performed in saline at room temperature. Some sera will also contain IgG anti-T (which can agglutinate cells under special conditions).

Confirmatory Testing

Routine blood banking tests tend not to detect the presence of T activation on red cells. Typing of polyagglutinable red cells is generally uncomplicated when monoclonal reagents are used. These monoclonal reagents lack the contaminating polyagglutinins found in older polyclonal reagents.

When polyagglutination is suspected, NZBS performs two tests in parallel. The first test is used to confirm the presence of polyagglutination while the second attempts to subclassify it. The red cells of interest are incubated with several cord blood sera and normal group AB adult sera. Cord sera would normally not contain the implicated antibodies. Therefore, reaction of the patient's red cells with the adult sera but not the cord sera would be consistent with polyagglutination.

There are several points to remember during such testing. Firstly, the naturally occurring antibodies in adult serum varies between individuals and necessitates the use of sera from several different people. Secondly, polyagglutinins are unstable and the use of fresh adult sera is ideal. Thirdly, an autocontrol is required since other autoantibodies which react at room temperature may give a false positive result. Usually the autocontrol is non-reactive in true polyagglutination.

Specific tests are needed to confirm T activation. Normal adult sera contain not only anti-T, but also antibodies which react with other types of polyagglutinable cells. The use of such sera would therefore not be specific. A better approach is to use lectins which are proteins derived from plants, invertebrate animals, and lower vertebrates. They bind specifically to carbohydrate determinants and can agglutinate red cells by binding their surface oligosaccharides.

A battery of lectins can be used to differentiate the various types, but a screening test using a two-lectin panel of *Arachis hypogaea* (peanut) and *Glycine soja* (wild soya bean) detects most of the causes of polyagglutination: T, Th Tk, Tn, and Tx. *Arachis hypogaea* and *Glycine soja* would be expected to give positive reactions with classical T-activated red cells. The term 'T variant' has been used to describe red cells reacting with *Arachis hypogaea* but not *Glycine soja*.

Different degrees of T-activation occur in vivo depending on the amount of neuraminidase produced. If a large amount of neuraminidase is present, the strongly T-activated red cells may even react with sera that contain weak anti-T. Conversely, small amounts of neuraminidase may produce red cells which will only react with potent anti-T. Thus, laboratory testing may not provide consistent results on samples taken at different times.

Clinical Significance

From a transfusion perspective, the main concern is the infusion of plasma (all derived from adult donors) which might react with the susceptible red cells of the patient. Most reports of haemolysis have been in association with necrotising enterocolitis in infants. However, it is often difficult to attribute haemolysis to any one cause since several potential culprits are usually present.

Once the bacterial or viral infection is controlled the T activation usually resolves. Measures to reduce the risk include: avoidance of unnecessary transfusion, the use of washed cellular components (red cells and platelets) and the selection of FFP which has low reactivity against T-activated cells.

Specially Prepared Blood Components

The following are not available generally and a special request to the NZBS Medical Officer on call must be made before these components will be supplied.

Red Cells Washed – Leucocyte Depleted

A unit of leucodepleted red cells which has been washed with an approved wash solution and resuspended in an approved additive solution. The unit has ≤ 0.5g of residual protein. This component should be used as soon as possible after processing. If storage is unavoidable, the component should be stored at a temperature of 4°C ± 2°C and must be used within 24 hours.

Platelets Apheresis Washed Leucocyte Depleted

Preparation of this component is not available at all centres. A unit of leucodepleted platelets which has been washed with an approved platelet additive solution. The washing process will reduce the total residual plasma protein to ≤ 0.5g per unit. This component should be used as soon as possible after preparation. If the component is produced using a closed system, it may be stored for up to 24 hours at a temperature of 22C° ± 2°C with continuous gentle agitation. If an open process is involved, it must be used within 6 hours of preparation.

Plasma Fresh Frozen – Leucocyte Depleted

Segments attached to bags of Fresh Frozen Plasma (FFP) can be thawed and tested against red cells treated with neuraminidase (to stimulate the classical form of T activation). Each segment of FFP can be titred (usually at doubling dilutions) and the least reactive units selected for transfusion.

Quality Assurance and Blood Transfusion

The collection, testing and manufacture of blood components and products takes place in a highly regulated and monitored environment to provide confidence that a safe and effective product is produced. NZBS is inspected, regulated and licensed by Medsafe to ensure that the safety of blood components and products transfused to patients is maintained. The first step in the process begins with donation from voluntary and unpaid donors. A system of voluntary non-remunerated blood and plasma donation is safer because the incidence and prevalence of transfusion-transmissible infections is invariably lower. A voluntary system also permits the use of donor education and selection procedures that encourage unsuitable donors to self-exclude or self-defer ensuring that fewer units of blood have to be discarded due to evidence of infectious disease markers.

All potential donors (both regular and new) undergo a thorough selection process to determine whether they are in good health. This ensures that the donor is protected against damage to his/her own health and that the recipient is protected against the transmission of disease, drugs or contaminated products. A strict standardised and validated procedure for preparation of the phlebotomy site ensures that bacterial contamination of the collected blood does not occur and the collection process is monitored to ensure that blood flow is uninterrupted. If the flow is intermittent and accompanied by discomfort it will compromise the quality of the donation making it unsuitable for the preparation of platelet components.

The bags in which the blood is collected must meet a set of standards and a representative sample from each batch is checked before use to ensure that they meet the standard, that the packs are not damaged and that the labels are correct. This check continues throughout the whole process of collection and manufacturing.

All donations are tested for ABO and Rh(D) blood groups (new donors are tested twice), anti HIV, anti Hepatitis C, Hepatitis B surface antigen and Syphilis. Testing for HIV RNA and Hepatitis C RNA is carried out to reduce the window period for these two transfusion transmitted infections. To ensure that low levels of antigen or antibody are detected only validated tests and reagents which have been confirmed to have high sensitivity are used.

A proportion of the blood components are tested regularly so that they meet standardised criteria. For example an adult dose of platelet should have more than 2.4 x 10e11 platelets, less than 5 x 10e6 white cells and the pH at expiry should be between 6.4 and 7.4. Some components are also cultured to monitor any bacterial contamination. To preserve the efficacy of the product and to prevent bacterial contamination the whole blood or component is stored in a controlled environment from the time it is collected from the donor to the time that a finished component is transfused to a patient.

Quality assurance of blood transfusion does not end when the component or product leaves the Blood Service. A quality management system is needed whenever blood component therapy is given and includes adequate documentation in both the transfusion process and outcomes. All institutions that transfuse blood components and products should implement national and local policies and written procedures for all aspects of the transfusion process. Correctly used, blood components and products can save lives and provide clinical benefit to many patients.

NZBS Chief Executive Officer

Dr Graeme Benny has been appointed as Chief Executive Officer of NZBS and will commence employment on 3 March 2004.

Dr Benny has considerable experience of senior healthcare management, having been a General Manager at both Counties Manukau and Auckland Healthcare. For the past three years he has been General Manager Operations at Metlifecare. He has a very good understanding of the public health sector and will bring his considerable knowledge and experience of working with District Health Boards and the Ministry of Health.

He has a Ph.D in Clinical Biochemistry and has many years experience in the development and production of fractionated blood products.