New Zealand Blood Service
The gift of life

BLOOD ISSUES

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Editorial

Two main themes continue to occupy the clinical team within NZBS. The first relates to potential changes to the regulatory environment in which NZBS operates. The second relates to the relationship between NZBS and the DHB sector and development of systems and projects to improve this.

In New Zealand blood and blood products are treated as medicines. NZBS is therefore subject to the requirements of the Medicines Act 1981 and Medicines Regulations 1984. Every year each main NZBS site is inspected by NZBS auditors. Successful performance in the inspection results in a 'Licensee to Manufacture Medicines' being issued. The license lists the products that each site is able to produce.

In December 2003 the Australian and New Zealand Ministers of Health signed a treaty to support establishment of a TransTasman Regulatory Agency. The new agency is due to commence activities in July 2005 and will replace the current regulatory authorities in each country, Medsafe (New Zealand) and the Therapeutics Goods Administration (Australia). Responsibility for audit and licensing of Blood Centres will fall with the new Agency. NZBS is currently involved in discussions with Medsafe and the TGA to determine how the new arrangements will work. The range of products provided by NZBS will not however change.

Earlier this year Medsafe issued a consultation document on a 'Review of the Regulation of Human Tissue and Tissue based Therapies'. The outcome of the consultation process is awaited. It seems however inevitable that a system to regulate tissues will emerge from the process. Interestingly the Australian Therapeutics Goods Agency has also initiated a review in this area and there are considerable similarities in some of the options discussed in both the New Zealand and Australian documents. NZBS provides significant tissue banking services. The outcome of the review will inevitably impact on these.

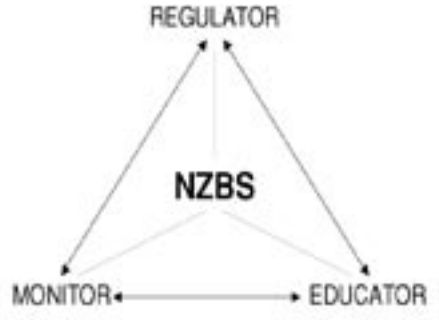
This edition of Blood Issues focusses on a number of the projects that NZBS has initiated to increase our support for DHB managed blood banks. The Clinical Oversight programme has been designed in conjunction with IANZ and aims to ensure that the requirements of the new laboratory standard (ISO 15189) regarding clinical oversight are met. This is an exciting development that provides an opportunity to increase overall consistency across the blood banking sector.

Peter Flanagan
National Medical Director

DHB Clinical Oversight Programme

NZBS has statutory responsibility for the collection and distribution of blood and is consequently appointed to ensure that DHBs maintain efficient blood banking and cross-matching systems. All providers of blood transfusion services are obliged to ensure that their practices, policies and procedures meet evidence based standards. NZBS also has a significant role in defining standards for these practices, policies and procedures. In recognition of its responsibilities NZBS currently provides a range of clinical audits, site visits and regionally focussed meetings. These functions are undertaken by a variety of NZBS medical, nursing, quality and laboratory personnel. Delivery of these services is inconsistent from region to region and until now have not come under the umbrella of a co-ordinated national programme.

NZBS provides three key roles to the transfusion medicine community i.e. regulator, monitor and educator and these are represented in the diagram below.



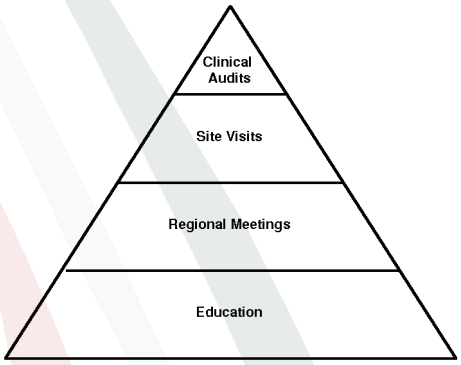
The roles are interrelated but in a hierarchical sense the regulator role assumes primary importance as this provides the context in which the others operate. When considered together all three roles effectively demonstrate the 'clinical oversight' process. Maintenance of standards inevitably requires collaboration between NZBS, transfusion service providers i.e. DHBs and the national accrediting agency International Accreditation New Zealand (IANZ). In one example of this IANZ increasingly requires DHBs to seek clinical, and in some cases technical, oversight from NZBS. This is particularly so for smaller, provincial blood banks, where clinical and technical specialist transfusion medicine support is minimal or non-existent.

To address these issues NZBS has developed its DHB Clinical Oversight Programme and all DHBs have been invited to participate in the programme which will formally commence in January 2005. The programme supplements activities specified in the pre-existing supply agreements between NZBS and each DHB, has been endorsed by IANZ and is complementary to the IANZ accreditation process for blood banks or laboratory services. IANZ has indicated that participation in the programme will be deemed to meet the clinical input requirements for transfusion medicine, as well as providing an appropriate transfusion medicine contribution to the laboratory director role defined in NZS/ISO 15189.

In formulating the programme the following principles were felt to encapsulate its requirements:

- Promotion and implementation of evidence based standards in transfusion medicine
- Identification and management of areas of non-compliance with standards and procedures for transfusion through the provision of transfusion medicine support
- Identification of optimal utilisation
- Identification of problems arising from the transfusion of blood and blood products by the DHBs.

The four key elements of the resulting programme are activities which have been identified as being poorly performed; Clinical audit of DHB transfusion policies and procedures; Site visits; Regional meetings and Education. These operate in a hierarchical manner as shown by the diagram below. Clinical audit is supported by the programme of site visits, regional meetings and seminars with the whole programme resting on a foundation of education.



Clinical Audit of DHB Transfusion Policies and Procedures

The programme provides for one clinical audit every two years of all DHB hospitals where transfusion is carried out. Audit by NZBS personnel may need to be limited to larger sites such as DHB 'base' hospitals while DHB blood bank staff audit the smaller sites using an NZBS format. An example of this is that NZBS would audit Whangarei Hospital who in turn would audit Bay of Islands, Dargaville and Kaitaia hospitals.

Site Visits

One formal site visit per year to laboratories of all DHB hospitals where pretransfusion testing is performed is proposed. Site visits will normally be a full day visit with clearly defined terms of reference. A full report of each site visit will be provided with requests for corrective actions and/or recommendations. In addition to support from site visits NZBS also provides 24 hour/7 day access to Transfusion Medicine Specialists (TMS) via telephone. Further support over and above this one site visit will be provided wherever possible following a specific request from a DHB. An example of this would be NZBS representation at Hospital Transfusion Committee meetings.

Regional Meetings/Seminars

Three 'customer focussed' regional meetings per year will be organised by the NZBS centres in Auckland, Waikato, Wellington and Christchurch. Wherever possible workshops or seminars will also be held in conjunction with regional meetings. These will cover specific topics such as refrigeration, Progesa or major policy or procedural changes. There will be standard terms of reference adopted for these meetings and minutes will be provided to all regional blood banks. Regional meetings and/or seminars are intended to supplement the site visit programme. Attendance will be monitored by both NZBS and IANZ as evidence of participation in the oversight process.

Education

NZBS will maintain and where necessary develop appropriate educational and training resources. NZBS with the physical and intellectual resources at its disposal is ideally placed to provide guidance to the transfusion medicine community in respect of transfusion related education. How this should occur is not well understood and is an area that needs further exploration.

Blood Bank Stocks Project

The NZBS Blood Bank Stocks Project has been established to review the current systems for supply of blood components and product to DHB blood banks. The aim is to define a model that utilises historic issue data extracted from the NZBS Blood Management System (Progesa) to set future blood bank stock levels for individual blood banks. Although the model will be initially applied to red cells it is anticipated that the principles developed will subsequently be applied to all blood components and products.

NZBS has utilised principles adopted by the English National Blood Service (NBS). This approach however, whilst robust, does not adequately address the specific geographic and logistic issues found in New Zealand. Furthermore, district hospitals in England tend to be significantly larger than many of the main DHB sites in New Zealand and an alternative strategy may be more appropriate. Key principles have been identified on which the proposed blood stocks model will be based.

- Stock level definitions such as minimum and ideal stocks originally set in 1999 will be utilised as a baseline for comparison
- Logistics data which includes frequency of supply and geographic location will be taken into account
- Extraction of historical issue data from Progesa will be used to identify mean daily issuing requirements and to review the level of variability
- Stock levels will be determined for each blood bank using standard inventory management principles wherever possible.

In determining the appropriate stock levels for each blood bank it is important to understand the dynamics behind these levels. The primary requirement is to ensure that there is sufficient stock of the appropriate freshness or expiry date available to meet anticipated issue

requirements at any point in time. This is in turn dictated by both the routine clinical supply of blood components and products and the unpredictable requirements of emergencies. The ability to maintain appropriate stock levels will depend on a number of factors including geographical location in relation to supplier, transport issues and re-supply frequencies. A valid model must include these factors.

Other factors influencing stock requirements will be:

- how much stock is issued to locations outside the blood bank e.g. ward refrigerators, satellite blood banks,
- how much stock is held prospectively reserved or crossmatched for patients
- whether or not red cells are issued electronically crossmatched on demand.

Geographically isolated blood banks such as those at Gisborne and Greymouth may need proportionately higher stocks compared with Auckland City or Wellington Hospitals which are close to their supplier and can therefore be restocked more frequently. The outcome of consultation with stakeholders together with the review of supply practices and delivery schedules will inevitably result in changes to the underlying assumptions used in the final construction of the preferred model and the stock levels ultimately chosen for each site.

A number of benefits will arise from the use of an agreed model. Firstly it will allow stock levels to be evaluated on a regular basis ensuring that changes in local activity are reflected in the agreed levels. Review could be undertaken on an annual basis and in response to an increase in the number of urgent orders received by NZBS. The model will also allow stock levels to be reset in the event that the pattern of routine orders is changed. NZBS has initiated a review of its overall logistic processes. This review will identify the optimal methods for routine, urgent and emergency supply of Blood Banks and this may result in a review of current supply patterns. In the event that this happens the model will be used to reset levels in an objective and consistent manner.

New stock levels will be established utilising the model identified from this consultation. NZBS acknowledges that there may be exceptional factors that will need to be taken into consideration for some DHBs and that might require levels modification to the outputs of the agreed model. It will be important that any such variations and the rationale for them are documented. NZBS will be keen to understand the type of issues that might require variations to be established.

Safety Related Changes to the Product Information (PI) and Datasheet for Intragam® P

In January 2004 CSL Bioplasma and NZBS issued a safety alert relating to a report of a patient who experienced hypoglycaemia associated with the use of Intragam® P. The hypoglycaemia was due to insulin treatment for a falsely elevated blood glucose level thought to be caused by maltose in Intragam® P. Maltose is added as a stabiliser (10gm/100ml) and contributes to the isotonicity of the product. Maltose interferes with capillary blood glucose monitoring by some types of glucose meters. The case report of falsely elevated capillary blood glucose levels in a patient receiving Intragam® P involved the Advantage (Roche) glucose meter that uses Accu-Chek Advantage test strips. Subsequent to that report, CSL have made changes to the Product Information (PI) and datasheet.

The changes are in the form of an additional paragraph which has been inserted at the end of the section "Precautions". The paragraph reads: Interference with glucose estimations. The maltose present in Intragam® P may interfere with some blood glucose measurements, resulting in the overestimation of blood glucose results. If this glucose measurement is used to guide treatment hypoglycaemia may occur. Only certain glucose tests using glucose dehydrogenase have been implicated, so when monitoring glucose levels in patients receiving Intragam® P, information from the manufacturer of the glucose meter and/or test strips should be reviewed to ensure that maltose does not interfere with the blood glucose reading.

For further information about this change or to report an adverse reaction to a blood product please contact your local Transfusion Medicine Specialist.

Autologous Serum Eye Drops

Autologous Serum Eye Drops (25%) (ASED) are a licensed therapeutic product prepared by the Blood Processing Department of the New Zealand Blood Service (NZBS) in Auckland. Since the first batch was produced in December 2000, there has been an increasing demand for provision of ASED. The method of preparation conforms to the Principles of Good Manufacturing Practice for collection and preparation of blood components and products and is summarised below:

- The patient completes the blood donor questionnaire and signs the consent for collection and testing of blood.
- At least 250 ml of whole blood is collected into a sterile dry bag.
- The unit rests at room temperature for several hours until there is clot formation, is centrifuged, the serum expressed and the unit centrifuged again. The collected serum is blast frozen and the clotted red cells are discarded. This process takes place in a closed system.
- Once the screening infectious serology tests are confirmed as negative, the serum is thawed and mixed with sterile balance salt solution (saline:serum 3:1)
- In a clean room laminar flow cabinet the serum solution is filtered and dispensed in 5ml aliquots into sterile eyedropper bottles.
- The bottles are labelled and can be stored for up to six months if maintained at - 20°C. Sterility testing is undertaken and the drops are dispensed once the culture results confirm no growth after 14 days incubation.
- The drops are available for use by the patient 18 working days after blood collection. The patient is provided with an information sheet about the storage

of the eye drops (stored in the fridge and discarded within 7 days), use of the eye drops and the reporting of adverse events.

The concentration of serum that has been used ranges from 20% to 100% but most of the published data is based on the use of 20% ASED. Dilution of serum has additional benefits such as improved compliance (less sticky to apply) and the production of a greater yield of ASED from one collection. Tsubota et al[1] showed that 20% autologous serum gives adequate viscosity and a relatively high concentration of growth factors that are stable when stored at 4°C for 1 month and for 3 months in the freezer.

Indications For Use

- Severe keratoconjunctivitis sicca (KCS) or dry eye that can occur in autoimmune conditions such as Sjogren's Syndrome and Rheumatoid Arthritis.
- Severe persistent epithelial defects (PED) defined as "corneal epithelial defect persisting more than two weeks without improvement despite conventional treatment such as artificial tears or extended wear soft contact lenses"[1]. Causes of PED include neurotrophic ulcers (diabetes mellitus, herpes zoster opthalmicus and herpes simplex keratitis) Stevens-Johnson Syndrome (SJS), ocular cicatricial pemphigoid (OCP), chemical or ocular surface burns and limbal stem cell deficiency[2].
- Severe dry eye associated with chronic graft-versus-host disease (cGVHD) following allogeneic haematopoietic stem cell transplantation[3].
- Post-radiation keratopathy
- Post-penetrating keratoplasty
- Any severe ocular surface disorder that does not respond to conventional treatment.

Mechanism of Action

Lack of tear production results in deprivation of essential tear components such as epidermal growth factor (EGF), vitamin A, antibacterial factors[4] (eg lysozyme, complement and IgG) fibronectin, basic fibroblast growth factor (bFGF)[5], hepatocyte growth factor[6] and transforming growth factor ß[3]. Serum contains components and growth factors that are thought to promote wound healing and maintain the ocular surface epithelium. Factors play a role in the migration, proliferation and differentiation of corneal epithelium.

Efficacy

Various studies have been undertaken involving ASED which have been small and largely consist of unblinded uncontrolled case studies. Apart from one study which examined the efficacy of ASED in patients with superior limbic keratoconjunctivitis instead of surgical therapy, the majority of patients were refractory to or also received concurrent conventional treatment. The overall response rate was approximately 64% (for PED and KCS) and positive responses were noted within 1-2 weeks of commencement of treatment and invariably within 1 month. Cessation of serum drops and crossover to placebo/arm conventional treatment demonstrated a deterioration following improvement after serum. A full list of these studies and references is available from NZBS.

Adverse Effects

Caution is recommended in treating patients with scleromalacia and/or ocular vasculitis, with ASED following the report of corneal limbal thinning a patient with scleral vasculitis associated with rheumatoid arthritis[7]. There is one case report of immunoglobulin deposition in the cornea of a patient with PED[8]. Likewise Poon et al[5] observed a small peripheral corneal infiltrate in a patient with rheumatoid arthritis after 1 day of serum drops. One patient treated with ASED for severe dry eye associated with GVHD developed eczema around the eyelids, leading to discontinuation of treatment[3].

Bacterial contamination is an important risk as the ASED do not contain any anti-microbial agents. Lagnado et al assessed the level of contamination of sterial serum eye drops used in an inpatient setting. Cultures of the first and last drop from each bottle (which was used 2 hourly over a 24 hour period) were performed. 13 of 134 samples were contaminated in a total of 6 patients. Only 1 of the 6 positive cultures was from first drop samples, suggesting contamination after bottle opening. There was no clinical or microbial evidence of infection, however all patients were also on preservative-free chloramphenicol drops. Possible adverse effects related to phlebotomy include bruising, soft tissue injury, nerve injury, arterial puncture and syncope/dizziness. There is always a possibility that serum may contain components that are detrimental to the ocular surface. TGF-ß (transforming growth factor ß) is known to have anti-proliferative effects and high concentrations may suppress wound healing[10]. There have been no reports to date on the effects of prolonged application of ASED

Summary

The beneficial effects of ASED for severe dry eye and PED in patients that are refractory to conventional treatments have been reported in a number of small and predominantly non-comparative studies. Response rates are variable, however an improvement is usually seen within 4 weeks of treatment in approximately 64% of cases. The majority of the data is based on a 20% concentration of serum. Patients must be educated about the risk of bacterial contamination and accordingly advised on the use and handling of drops. Generally ASED is a safe and important adjuvant therapy in patients with ocular surface disorders.

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6. Matsumo Y, Dogru M, Goto E, et al Autologous serum application in the treatment of neurotrophic keratopathy. Opthalmology 2004 Jun; 111(6):1115-20

7,8,9,10 A complete copy of the Review and full list of References is available from NZBS