letters

TO THE EDITOR

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Current clinical uses of intravenous immunoglobulin

Editor – El-Shanawany *et al* (*Clin Med* July/August 2006 pp 356–9) emphasise the differences between several preparations of intravenous immunoglobulin (IVIG) in the context of limiting the risk of infections and reactions. A further important factor is that preparations from different donor pools may vary significantly in their specific antibody profiles, which has implications for the use of IVIG as replacement therapy, which is essentially a form of passive immunisation.

This was demonstrated to us when we treated a patient with West Nile encephalitis and long-standing chronic lymphatic leukaemia with IVIG derived from Israeli donors, and observed a dramatic improvement.[1] Subsequent examination of West Nile virus (WNV) antibody titres revealed high levels in immunoglobulin derived from Israeli sources, where the disease is endemic and frequently asymptomatic, while sources in the USA had undetectable levels. This was followed by other case reports of efficacy in humans.[2] Experiments in mice infected with WNV revealed both prophylactic and therapeutic efficacy of plasma and IVIG prepared from healthy Israeli donors, but not from US donors.[3,4] Clinical trials of IVIG in WNV infection are currently being planned by the National Institutes of Health.[5]

This finding may also be generalisable as a model for treating other infectious, particularly viral, diseases with no specific treatment. IVIG is prepared from specific healthy blood donor panels who have the desired antibodies generated by past natural infection. The generated antibodies are active against a number of viral epitopes and have proved their efficacy, in that the donors have been infected and returned to health. The use of such IVIG, generated naturally or by deliberate infection, has also been proposed as a means of defence against bioterrorism using infective agents for which no antimicrobial therapy exists.[6]

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In response

Shimoni *et al* raise an interesting point regarding antibody titres in IVIG against infectious agents which are limited in their geographical distribution. West Nile virus (WNV) is common in the Middle East, Africa and Asia and has more recently emerged in North America.[1] Antibody titres in IVIG against WNV are greater when plasma is obtained from populations where the disease is endemic and of high prevalence.[2] Differences in disease-specific IgG levels become especially relevant when IVIG is being used to treat a particular pathogen. In general pathogen-specific immunoglobulins are not usually specifically produced from selected donors, but are sourced from the batches used to make normal IVIG that contain the highest levels of relevant antibody.

In IVIG replacement therapy, batch-to-batch variation is rarely an issue. However, we accept that there are significant batch-to-batch variations in many different antibody titres.[3] It is very difficult to control for this, although some legislation is now in place for certain antibody specificities, for example anti-D.[4] It is not usually practicable to routinely measure the patients' specific IgGs and match this to antibody titres in IVIG batches. There may be occasional exceptions in replacement therapy for specific antibody deficiency syndromes (SPAD), but not usually for common variable immunodeficiency (CVID) where measurement of IgG levels and clinical assessment is currently the norm for determining the adequacy of replacement treatment.

To ensure standardisation of IVIG, the manufacturers subject each batch to a range of assays including checking that not less than 95% of the product is IgG, and that the distribution of IgG subclasses, and Fc function are normal. Levels of prekallikrein activator and haemagglutinins are also monitored. In addition, levels of specific IgG against a range of infectious agents (including diphtheria, measles and polio) must meet minimum titres. Counterintuitively, the final product must also contain a minimum titre against

hepatitis B surface antigen, though the plasma source will have been checked for the presence of hepatitis B virus by polymerase chain reaction.

The allocation of IVIG varies from country to country. Australia, Spain and the USA on the whole use IVIG derived from plasma from donors from their own country. With the proviso that the products are otherwise similar, this decision makes good sense given the differences in endemic diseases and vaccination protocols between countries. Another significant difference is the method of collecting plasma; in the UK this has been performed on an altruistic voluntary basis while in the US donors are paid. This may result in an increase in the proportion of donors from lower socioeconomic groups in the USA. There is debate as to which method of plasma collection is safer with regard to the risk of potential transmission of infection; however, plasma from all sources is subjected to a rigorous series of checks. During the production of IVIG there are serial steps to inactivate and/or clear any viruses/transmissible agents which may be present in the plasma. The emergence of new viruses such as severe acute respiratory syndrome coronavirus and the spread of established viruses such as WNV to new geographical areas may have an impact on the selection of plasma/product to ensure that appropriate cover is provided.

In the UK, plasma is currently sourced from the USA because of directives resulting from concern regarding possible variant Creutzfeldt-Jakob disease (vCJD) transmission. At present, blood donations from those resident in the UK for three months or more between 1980 and 1996, or who received a blood transfusion or surgery in the UK, are prohibited from being used for the production of IVIG. However, current production processes have been shown to remove prions down to undetectable levels in the final IVIG product.[5] Given the current worldwide shortage of IVIG, with major problems in obtaining adequate supplies in the UK, even for indications which are both licensed and life threatening, it is vital that the ban on UK plasma is urgently revisited and that any decisions regarding risk assessment are made based on the scientific evidence base available. The current ban on the use of UK plasma is also inconsistent with the ongoing use of UK packed cells, albumin and colloid plasma substitutes produced with gelatine obtained from bovine bone products.

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Skin cancer: prevalence, prevention and treatment

Editor – Dr Sharpe's editorial on skin cancer (*Clin Med* July/August 2006 pp 333–4) is a good overview of the subject for non-dermatologists. Despite the editorial requirement for brevity, his failure to specifically mention Mohs micrographic surgery (MMS) misses an opportunity to bring this little known treatment to the attention of our general medical colleagues. This highly specialised form of cutaneous surgery has an important role in the management of selected cutaneous squamous cell carcinoma[1] and published national guidelines recognise MMS as the treatment of choice for high risk, invasive facial basal cell carcinoma.[2] Mohs surgery, in which tumours are excised under total microscopic control, was pioneered in the USA and is increasingly available in specialised dermatology units in the UK. For the most difficult lesions, it offers tumour removal with maximal preservation of normal tissue together with cure rates which surpass those offered by radiotherapy or formal excision with wide margins. Of particular interest to readers of this journal, MMS is a surgical technique exclusively practised by physicians.

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Skin cancer and surgical margins for basal cell carcinoma

Editor – I enjoyed reading Sharpe's informative editorial (*Clin Med* July/August 2006 pp 333–4) which rightly highlights the burden that skin cancer care creates in the UK with over 50,000 recorded basal cell carcinomas (BCCs). However, I feel clarification is needed regarding BCC excision as an error in marking surgical margins of just 1 mm can adversely affect cure rates. Sharpe states that the recommended minimum clearance margin is 3 mm for most BCCs.[1] However, in clinical practice, for predetermined surgical margins around BCC most surgeons would take at least 4 mm. The reason for this is that 3 mm margins will clear approximately 85% of well-defined previously untreated BCC less than 20 mm in diameter on the face, whereas 4 mm margins achieves >95% clearance.[2] If the goal of BCC excision is complete extirpation of the tumour then margins of 3 mm are