Progress with heat treatment of human plasma products

Heat treatment or pasteurisation of blood products is directed towards inactivation of a group of transmissible viruses which result in sub-clinical or clinical hepatitis in a proportion of treated patients. Currently, albumin fractions are pasteurised at 60°C for ten hours to inactivate hepatitis B virus and there is the assumption that this heat process also inactivates the group of viruses responsible for non-A non-B hepatitis. Long-standing use of pasteurised albumin products without the complication of hepatitis suggests that the pasteurisation process is effective.

Pasteurisation of other blood products has not been developed to this extent because these products are not amenable to the heat treatment process:- examples are fibrinogen, factor VIII, factor IX, which are all known to transmit hepatitis B and non-A non-B viruses.

Immunoglobulin produced by ethanol precipitation in Cohn Fraction II is not pasteurised but in long-standing wide use has acquired only a marginal anecdotal association with transmission of hepatitis virus. The earlier assumption that virus in immunoglobulin would be immune-complexed and therefore inactivated is more likely to account for the lack of transmission of infection rather than the view that the virus is not fractionated in with Cohn Fraction II immunoglobulin intermediates.

Virus transmission in haemophiliacs

Hepatitis B transmission in large-pool factor VIII and factor IX concentrates is recognised in haemophilia patients but the incidence has been effectively reduced by screening of plasma to exclude source material from hepatitis B antigen carriers. The absence of markers for non-A non-B hepatitis virus does not allow for this screening of source material and epidemiological evidence suggests that large-pool concentrates are universally associated with effective transmission of non-A non-B hepatitis virus.

The severity of non-A non-B hepatitis in haemophiliacs probably associated with the co-existent impaired immune responsiveness of these patients has motivated plasma fractionation organisations to re-examine means whereby hepatitis virus can be inactivated in large-pool concentrates. Heat treatment of blood products is still primarily directed at the inactivation of transmissible viruses causing hepatitis in recipients.

AIDS

The syndrome of acquired immune deficiency currently under investigation is likely to include in its aetiology transmission of an infective virus and the possible phenomenon of reactivation of an existing virus in individuals concerned. In limited numbers, AIDS sufferers have included individuals receiving human blood-based fractions. This aetiological observation has promoted more activity in the area of blood products pasteurisation with the empirical view that a virus is involved and, as with hepatitis virus, is likely to be partially or completely inactivated by heat.

Means of heat treatment of blood products

Heat treatment represents only one pathway by which viruses may be inactivated. Nonetheless, it is the most favoured route at present. Heat treatment may take place during the process of blood product purification, i.e. during a wet process step or heating a finished freeze dried product can be attempted. Heat transfer in the wet state is more homogeneous and efficient and to satisfy reliability in manufacture is to be preferred; however, wet treatment is associated with more molecular damage of heat unstable proteins than occurs by the dry-heat route.

Wet-heat pasteurisation of blood products at BPL is now available with albumin fractions, anti-thrombin III, factor XIII, and is likely to be successful during this calendar year with factor IX. The loss of yield of factor IX incurred may be tolerated within the considerable excess of source material available to the fractionation facility.

Wet-heat of factor VIII intermediate concentrate is likely to require a longer programme of work if a satisfactory reliable method is to be developed which does not carry unacceptable penalties related to loss of yield of factor VIII activity. Progress with this procedure will be reported to the Authority.

Dry-heat: the majority of commercial manufacturers are currently depending upon dry-heat of the finished factor VIII concentrate to reduce the infectivity of the product relative to transmission of hepatitis. The associated claims (which are entirely unfounded in scientific and quality control terms) are that the heat process will inactivate the putative virus transmission causing AIDS.

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Appreciating pressure under which users are currently operating in the management of haemophilia, BPL has undertaken preliminary studies to assess yield of factor VIII intermediate concentrate after dry-heat. It has been shown possible to maintain greater than 95% of factor VIII activity in the finished product after heating at 75°C for ten hours or heating at 60°C for 24 hours. Both these presentations of heat exceed the requirements established for virus inactivation by wet-heat with albumin products (60°C for ten hours).

Since this form of product treatment will allow BPL to present to clinical managers of haemophilia a product carrying equivalent weight of claims for safety as those of rival commercial organisations, this product is being advanced with high priority to enable manufacture to become routine by the late summer 1983.

To introduce the product, the full co-operation of the haemophilia directors will be required since a non-human primate testing facility is not available to BPL accepting that this system of testing may not be appropriate with regard to hepatitis or AIDS transmitting viruses.

Introduction of an extra stage in the process of purification of factor VIII may impose costly intermediate reorganisation of manufacturing and equipment for which there is no budgeted sum. It is assumed that this contingency will be met recognising the political sensitivity of AIDS transmission in the UK caused by treatment with blood products.

R. S. LANE,
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