Optimising the Safety of Blood Products

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Without blood and blood products, the treatment of severe haemorrhage seems to be difficult or impossible, and haemato-logical conditions like haemophilia and leukaemia cannot be treated effectively. However, it has been known for a long time that blood and blood products may transmit infectious agents. Of major interest are viruses inducing hepatitis (hepatitis B and C virus; HBV, HCV) and the human immunodeficiency viruses (HIV-1/-2). The screening of each blood or plasma donation for the presence of the virus markers hepatitis B surface antigen (HBsAg) and HIV-1/-2 and HCV antibodies reduced the number of blood-borne infections for recipients of blood products prepared from pooled plasma, and especially for those receiving single donations.

The infection of large numbers of haemophilic patients with blood-borne viruses, transmitted by factor concentrates produced from large pools of plasma, has prompted the introduction of virus inactivation steps. Following the introduction of inactivation steps, the blood products appeared to be safe, but nevertheless some batches of factor concentrates or immuno-globulins transmitted HIV (PPSB in 1989), HAV (factor VIII in 1992), HCV (immunoglobulins in 1994) or HBV (PPSB in 1994). These unexpected transmissions of blood-borne viruses showed that the capacity for virus inactivation or elimination steps was limited and that, despite the screening of single donations for viral markers, infectious donations must have been incorporated into the starting plasma pool. In 1989, the Committee for Proprietary Medicinal Products (CPMP) released guidelines for the validation of virus safety of blood products [CPMP/268/95: 'Validation of virus removal and inactivation procedures' (III/8115/89): CPMP/269/95: 'Medicinal products derived from human blood and plasma' (III/8379/89)]. Starting from these early attempts to increase the safety of blood products, CPMP and national authorities [Paul Ehrlich Institut and Bundesgesundheitsamt, BAnz No. 84, May 4, 1994, p. 4742] published updates of such guidelines based on the experience with earlier guidelines. Furthermore, requests for the quality assurance of the starting material were increased. With the reduction of the virus load in the starting

material in mind, testing of plasma pools was introduced. This testing seemed to be a valuable step to reduce the virus load in the plasma pools since it was observed that some pools used for the production of clotting factor concentrates and immunoglobulins contained antibodies against HIV or HCV. These findings implied that either the plasma/blood donations were not properly tested for the presence of antibodies, or that donations tested positive for HIV or HCV were not eliminated after detection of their reactivity but incorporated into the plasma pool.

For the plasma pool testing, the pooled plasma or the pooled cryo-precipitate is the source for the screening for HIV and HCV antibodies as well as for HBsAg. As no test systems have been

evaluated for testing pools of plasma, the test procedures must be validated for the specificity and sensitivity for testing pools.

In the article 'How Accurate is Serologic Testing...' by Rabenau et al. [1] in this issue, the question is addressed how accurately commercial test kits can detect antibodies against HIV and HCV or HBsAg in pooled plasma. These authors have spiked plasma with HBsAg, anti-HIV and anti-HCV, and wanted to show whether the test systems used were sufficiently sensitive to detect the antibodies and HBsAg in experimentally contaminated plasma pools. Both antibody test systems seemed to be sensitive enough to detect contaminated plasma pools. As expected, antibodies directed against HBsAg present in plasma pools complexed experimentally added HBsAg. Only after dissociation of the immune complexes, the contaminating HBsAg could be detected.

This information is of value for the producers in order to improve testing of plasma pools. Although testing of plasma pools for markers which could detect GLP (or GMP) failures can contribute to reducing the virus load in the starting material for the production of blood derivatives, there remains the problem of donations in the window period which can have a high virus load.

For those immunoglobulins which do not have an efficient inactivation step included into this production process, a

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PCR testing for HCV is required. Attempts are undertaken to introduce also PCR for the screening of blood and blood products in order to reduce the risk of transmitting HIV, HCV and HBV by cellular products and also to reduce the virus load in plasma pools.

The main arguments against PCR testing are its cost-intensiveness and the question of quality control; however, it seems possible to overcome both problems in the near future. International and national institutions are working on the problem of quality assessment of PCR for HBV, HCV and HIV, and it seems to be only a question of time to solve this problem. The discussion about the increasing costs of the testing and the question at which points of the production process PCR should be applied is still going on. Plasma pool testing with PCR would be one step to increase the safety of blood derivatives by reducing the virus load of the pools.

Reference

1 Rabenau H, Schütz R, Berger A, Doerr HW, Weber B: How accurate is serologic testing of plasma pools for hepatitis B virus surface antigen, anti-human immunodeficiency virus 1 and 2, and anti-hepatitis C virus? *Infusionsther Transfusionsmed* 1996;23:124-130 (this issue).

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