Safety of plasma-derived factor concentrates
An example of pharmacovigilance with fibrinogen and factor XIII concentrate

M. Spannagl\textsuperscript{1}, Ch. Joch\textsuperscript{2}, B. Heindl\textsuperscript{1}
\textsuperscript{1}Department of Anaesthesiology, Munich University Hospitals, Munich, Germany
\textsuperscript{2}CSL Behring GmbH, Marburg, Germany

Keywords
Plasma products, pharmacovigilance, inactivation process, donor screening

Summary
Elaborate measures for donor selection and the production of clotting factor concentrates have led to a high safety standard of these products. A multimodal approach to eliminate unwanted contents has been established by strict screening of possible donors and various inactivation procedures within the production process. The systematic registration of adverse events shows very few allergic and non-allergic reactions to plasma derived clotting factor concentrates. In none of the registered cases transmission of infections could be verified. The worldwide registration of such adverse events is not yet sufficiently established, since adequate structures are lacking in some countries. According to estimates, far less than half of occurring adverse events are registered in Germany. A European solution in the form of an official register is about to be introduced.

Production and quality of factor concentrates

Ever since the transmission of pathogenic viruses by the transfusion of plasma products in the 1990s, great efforts have been made to maximise the safety of these products. Elaborate and comprehensive measures to increase safety have been introduced not only in collecting the starting material but also in the manufacture of plasma products. Safety measures implemented today for the collection of whole blood or plasma include:

- careful selection of donor facilities (exclusion of high-risk areas),
- supervision of donor facilities by the authorities,
- careful screening of donors (exclusion of high-risk donors),
- high proportion of long-term donors (double-checking of first-time donors),
- standardised testing of each donation (infectious diseases serology),
- quarantined storage of individual donations,
- establishment of quality management systems (seamless EDP documentation of the donor, the processes, and the blood donation).

Following release of the individual donations and plasma pooling, manufacturers undertake company-specific steps for virus reduction and inactivation (e.g. solvent/detergent processes, pasteurisation, steam or dry heating, nanofiltration). These are basically monitored by the following means:

- testing the plasma pool for viral infections before and after the inactivation steps (immune serology and DNA/RNA testing to exclude pathogenic sources),
- comprehensive quality management system implemented during production,
- monitoring by health authorities (e.g. batch release by the Paul Ehrlich Institute).

Without doubt, this multimodal approach has led to the almost complete prevention of transmission of infections by plasma concentrates. Nevertheless, the expense involved in collecting the starting material and production costs have now become so great that the cost-benefit ratio of the immense financial outlay per viral infection prevented needs to be looked at more closely from the perspective of healthcare politics and society. A minimal, but not really quantifiable, risk nevertheless remains due to unknown or not yet adequately characterised infectious agents (e.g. prions).

In Germany in 2002, 2.1 million litres of plasma were made available for the production of clotting factors, inhibitors, and albumin, of which 1.3 million litres remained on the German market. It is interesting that, by extending and upgrading donor facilities in recent years, Germany has turned from being a net importer of plasma to being a net exporter (9). A large number of units of highly-concentrated single factors or combinations of several factors are now being used in routine clinical practice (Tab. 1). Only factors V and XI are not yet produced in concentrated form, but are available for replacement only as natural components of fresh plasma.

Single factors and defined combinations of factors are isolated and purified from the pooled plasma of 1000 to 10 000 donors. It is necessary to pool and mix several thousand individual donations in order to obtain as broad a spectrum of antibodies as possible in the case of polyvalent immunoglobulins. Plasma can be collected from whole blood donations or by plasmapheresis. By means of various precipitation procedures (e.g. cryoprecipitation) and purification processes (e.g. ion-exchange immunoaffinity chromatography) very pure single factors can be isolated from the plasma (Fig. 1).

Factor concentrates for clinical use are usually available as readily-soluble lyophilisates.

For some years now, in addition to the careful screening of blood donors as well as molecular genetic and serological testing to detect the presence of viral infections, all factor concentrates with marketing authori-
In cases of complicated disorders of haemostasis (e.g. perioperative coagulopathy with massive transfusion) the use of factor concentrates may be considered in order to elevate critical factor levels (e.g. of fibrinogen) rapidly – something that cannot be achieved with fresh frozen plasma (FFP).

Undesirable effects
Thromboembolic complications

Plasma of healthy people contains procoagulant and anticoagulant factors in a physiological relation to each other – the clotting tendency and fibrinolysis are in equilibrium. So replacement therapy with fresh frozen plasma does not lead to a procoagulant situation with the risk of thrombosis and embolism. Administration of clotting factor concentrates, however, results in the one-sided replacement of procoagulant components. There have been repeated reports of thromboembolic events (e.g. disseminated intravascular coagulation and thrombosis) following the administration of prothrombin complex (PPSB) products (10). Recent work shows that an increased prothrombin content of PPSB may be responsible for the complications (7).

Thromboembolic events have also been described with the use of rFVIIa. The incidence of such events after giving rFVIIa to acutely bleeding trauma patients is reported as about 4% (1).

Immunological reactions
ABO incompatibility, TRALI and allergic reactions

Isolation and purification of factor concentrates means that they can be used irrespective of the patient’s blood group.

There are no case reports of transfusion-related acute lung injury (TRALI) following administration of clotting factors. As well as the production from pooled plasma, purification steps minimise the alloantibodies. This means that it is extremely unlikely that factor concentrates cause TRALI. The same reasoning applies to allergic and pseudoallergic reactions.

Development of inhibitors

Inhibitors are IgG antibodies that develop against a procoagulant factor (e.g. FVIII), especially as the result of replacement therapy for inherited coagulopathies (e.g. haemophilia A). Their inhibitory action increases the risk of bleeding and makes it very difficult to give further effective treatment. Inhibitors appear in a significant percentage after the first treatment (particularly with replacement therapy for people with haemophilia A); the median time is between nine and eleven days. Development of inhibitors in patients transfused at intervals with FFP or factor concentrates as part of the perioperative management of coagulopathy is theoretically possible, and the production of specific inhibitors has very rarely been reported in other than the treatment of haemophilia, e.g. development of antibodies to thrombin and factor V after the application of fibrin sealant (19).

Infections

Human plasma may be contaminated with a great many infectious agents. Viruses are
Safety of factor concentrates

- The most common, especially HIV, hepatitis A/B/C and parvovirus B19 (Tab. 2). In Germany, careful screening of donors, serological testing of the plasma and four to six months’ storage in quarantine have lowered the probability of disease transmission with FFP to about 1:1 million for hepatitis B and 1:20 million for HIV and hepatitis C.

- One or more steps to inactivate enveloped viruses are built into the production processes of factor concentrates. This method reliably removes HIV, hepatitis B and hepatitis C viruses. In recent years there have been no further notifications of infections with these viruses transmitted by inactivated plasma and plasma products.

- The case is somewhat different for non-enveloped pathogens (e.g. hepatitis A and parvovirus B19) which may lead to serious infections in pregnant women and immunosuppressed patients. Standard production process measures may be of limited value against these viruses, so isolated reports of the transmission of hepatitis A and parvovirus B19 with factor concentrates still appear in the literature from time to time (14, 17).

- The possibility of transmission of variant Creutzfeldt-Jakob disease (vCJD) by blood products is a very topical subject. In Great Britain in 2003 and 2004, there was a report of one case each year of the apparent transmission of vCJD by transfusion of packed red blood cells from an infected donor (11, 13). In keeping with today’s scientific knowledge, the main infectivity comes from prions bound to leucocytes; very much lower concentrations of prions are found in the plasma.

- Leucocyte depletion of blood donations reduces the risk of infection. Even though an infection transmitted by plasma is extremely unlikely, it cannot be completely ruled out for this type of transfusion. Certain steps in the production of factor concentrates, such as fractionation, chromatography and filtration, result in the considerable reduction of artificially-added prions. This means that in the light of current knowledge, the transmission of vCJD by factor concentrates is highly unlikely.

### Pharmacovigilance

In contrast to the extensive efforts made to ensure high safety standards for plasma
products, comprehensive systematic recording of all adverse reactions is not carried out in all countries. Recording of suspected adverse drug reactions in Germany is based on a spontaneous reporting system, i.e. mainly on voluntary notification by members of the healthcare professions. It is well known that the estimated number of unreported cases of adverse reactions is high in voluntary reporting systems – even life-threatening adverse drug reactions are only reported by one in five doctors. Since the introduction of the transfusion law, there has been a legal obligation for doctors to report suspected serious adverse drug reactions directly and without delay, so that the grey zone of unreported cases should become smaller in the future (8).

The division into serious and non-serious adverse reactions is made on the basis of definitions in the German Drugs Law (Arzneimittelgesetz, AMG): hospitalisation required or prolonged, intervention necessary to prevent permanent impairment or damage, permanent or severe disability, life-threatening nature, death, congenital abnormality. The Federal Republic of Germany does not have any central registration of adverse drug reactions, e.g. a patient register.

Other countries with government-funded health services (e.g. the NHS in the United Kingdom) can call on many years of experience with centralised documentation. At the present time, the European Medicines Agency (EMEA) is trying to introduce an adverse reaction database covering the whole of Europe (EudraVigilance) to improve this situation.

As drug manufacturers are obliged by the AMG to notify any adverse reactions of which they become aware directly to the authorities within a defined period, and because systematic data collection by the authorities is difficult, pharmaceutical companies’ pharmacovigilance is one of the most reliable sources for evaluating adverse reactions to plasma concentrates after sale (6).

It is interesting to note that large-scale phase 4 postmarketing studies have also recently been required for newly-approved products (e.g. activated recombinant protein C) to provide systematic data on effectiveness and safety under conditions of routine practice. Overall, structured recording of adverse drug reactions in pharmacovigilance registers is a useful tool for evaluating the safety of preparations after they have been granted marketing authorisation. In the following paragraphs we discuss the manufacturer-based registers of fibrinogen and factor XIII concentrates – available in Germany from a single manufacturer – as examples to demonstrate the safety of these two products.

A highly concentrated human fibrinogen (Haemocomplettan® HS) from CSL Behring was granted marketing authorisation in 1986. From the beginning of 1996 until the end of 2005 there were 24 notifications of suspected known adverse reactions for this fibrinogen concentrate. Assuming administration of an average minimum dose of 2 g and worldwide use of approximately 800 000 g, the estimated number of administrations is 400 000 and thus a rate of one suspected adverse reaction per 16 666 administrations.

Within the same period, more than 1000 million units of factor XIII concentrate (Fibrogammin® P) were sold throughout the world. With a standard dose of 1250 IU, the 31 suspected cases give a rate of one adverse
reaction per 25,806 administrations. All suspected cases notified were documented and reported regardless of causality assessment. Suspected infections (n = 12 for Haemocomplettan® HS, n = 14 for factor XIII Fibrogammin® P) were carefully evaluated—a causal relationship with the blood product administered was ruled out in every case (Tab. 3).

Conclusions

The examples given above show the difficulties of implementing comprehensive registers of adverse drug reactions. And even following the successful establishment of such registers, questions remain as to the correct interpretation and appropriate consequences.

The time-consuming and expensive measures for obtaining fresh plasma and inactivating viruses in plasma products have led to a degree of safety in the clinical use of these products that has never been achieved before. Despite this, the appropriateness of these measures should be demonstrated in the sense of acceptable cost-effectiveness.

The final link is the meaningful determination of indications: the fewest adverse effects and the lowest costs can be achieved only if products are used with clear indications and their clinical effectiveness is closely monitored.

References


Correspondence to:
Dr Michael Spannagl
Senior Consultant Transfusion Medicine and Haemostasis
Munich University Hospitals
Ziemessasse 1, 80336 Munich, Germany
Phone +43/(0)89/51 60 22 86
Fax +43/(0)89/51 60 21 48