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What can be learned in the snake antivenom field from the developments in human plasma derived products?

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ABSTRACT

Human plasma-derived medicinal products and snake antivenom immunoglobulins are unique and complex therapeutic protein products. Human plasma products are obtained by fractionating large pools of plasma collected from blood plasma donors. They comprise a wide range of protein products, including polyvalent and hyperimmune immunoglobulins, coagulation factors, albumin, and various protease inhibitors that are transfused to patients affected by congenital or acquired protein deficiencies, immunological disorders, or metabolic diseases. Snake antivenoms are manufactured from pools of plasma collected from animals, typically horses, which have been immunized against snake venoms. Transfusing antivenoms is the cornerstone therapy to treat patients affected by snakebite envenoming. Over the last thirty years, much technical and regulatory evolution has been implemented to ensure that this class of biologicals meets modern quality requirements. The purpose of this review is to compare the main developments that took place in plasma production, protein fractionation, pathogen safety, quality control, preclinical and clinical studies, and regulations of these products. We also analyze whether both fields have been influencing and cross-fertilizing each other technically and in regulatory aspects to reach modern safety and efficacy standards at global levels, and how experience in the human plasma fractionation industry can further impact the manufacture of snake antivenom and that of other animal-derived antisera.

1. Introduction

Human plasma-derived products and animal plasma-derived antivenoms are important protein therapeutics that play a critical role in the treatment of human diseases. Human plasma is the source of a wide range of about 20 proteins, which are used as therapy of severe bleeding, thrombotic immunological, or metabolic disorders, bacterial or viral infections, or blood losses associated with trauma (Table 1) (Burnouf, 2007). There are about 70 human plasma fractionators in the world, and the volume of plasma fractionated yearly has been steadily increasing over the years to reach now close to 42 millions liters. Most of the largest human plasma fractionators are located in developed countries; many countries of the world (especially in Africa, Middle-East, South-East Asia, and South America) do not have access to the plasma fractionation technologies. Plasma products include purified concentrates of immunoglobulin G, albumin, various coagulation factors (such as Factor VIII, Factor IX, fibrinogen, fibrin glue), protease inhibitors and anticoagulants, and immunoglobulin M (Burnouf, 2007). Plasma products are most often used for substitutive therapy in situations of threatening congenital or acquired plasma protein deficiencies. Apart from normal immunoglobulins and albumin, several human plasma products are transfused to treat rare diseases and can be regarded as orphan drug products. Several human protein products are on the World Health Organization Model List of Essential Medicines, highlighting their clinical importance for human health. Human plasma is also the source material for the manufacture of close to ten hyperimmune immunoglobulin preparations that are used to protect or treat patients against bacterial or viral infections, or even risks associated with alloimmunization against red blood cell D (rhO) antigen (Table 2) (Hsu and Safdar, 2011; Radosevich and Burnouf, 2010). Many of the proteins fractionated from human plasma are not produced, at least from the time being, from synthetic sources. However, coagulation Factor VIII and Factor IX are examples of coagulation factor

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Table 1
Main classes of human plasma-derived products and clinical use (apart from IgG) (*Abbreviation: IV, intravenous*).

Class	Proteins	Main clinical use
Coagulation factors (IV use)	Fibrinogen, Factor V; Factor VII; Factor VIII; Factor IX, Factor X, Factor XI, Factor XIII, Von Willebrand factor	Substitutive therapy of congenital deficiency in a single coagulation factor
Combined coagulation factors (IV use)	Prothrombin complex	Treatment of complex coagulation factor deficiency
Combined coagulation factors (topical use)	Fibrin sealant/Fibrin glue	Haemostatic and sealing surgical agent
Anticoagulant	Antithrombin; Protein C	Substitutive therapy of congenital deficiency
Protease inhibitors	Alpha 1-antitrypsin; C1-esterase	Substitutive therapy of congenital deficiency
Albumin	Albumin	Plasma expander; fluid resuscitation

Table 2
Human plasma-derived immunoglobulin products (Abbreviations: IM, intramuscular; IV, intravenous; SC, sub-cutaneous).

Specificity	Antibody potency assessment in plasma	Formulation	Most frequent mode of administration	Clinical indications
Polyvalent	None – At least 1000 donors/plasma donations should contribute to each batch	Liquid	IM	Prevention of hepatitis A, measles, rubella, chicken pox and other infections
Polyvalent	None – At least 1000 donors/plasma donations should contribute to each batch	Freeze-dried or liquid	IV, SC	Replacement therapy in humoral immune deficiency states; immune modulation in auto-immune disorders; inflammatory disorders
D (Rho)	Quantitative assay (e.g. autoanalyser-based assay or flow-cytometry method)	Freeze-dried or liquid	IM or IV	Prevention of the haemolytic disease of the new-born
HBs	Quantitative assay of hepatitis B surface antigen (e.g. RIA or ELISA)	Liquid	IM	Prevention of hepatitis B infection
HBs	Quantitative assay of hepatitis B surface antigen (e.g. RIA or ELISA)	Freeze-dried or liquid	IV	Prevention of Hepatitis B infection (e.g. after liver transplant)
Tetanus	Neutralization assay or quantitative assay correlated to the neutralization assay	Liquid	IM	Prevention of tetanus
Varicella-Zoster	Quantitative assay (e.g. ELISA, immunofluorescence or complement fixation)	Liquid	IM	Prevention or treatment of chicken-pox infection
HAV	Quantitative assay	Liquid	IM	Prevention of hepatitis A
CMV	Quantitative assay (e.g. ELISA, immunofluorescence or complement fixation	Liquid or freeze-dried	IV	Prevention of CMV infection (e.g. after bone marrow transplantation)
Rabies	Rarely performed	Liquid	IM	Prevention of rabies infection

glycoproteins that used to be obtained exclusively from human plasma, but are now also commercially available as synthetic proteins prepared by recombinant technologies using genetically-modified mammalian or human cell lines expressing these proteins (Burnouf, 2011).

The plasma of animals, most often horses, which have been immunized by venom preparations obtained from one or several snake species is the source material for the manufacture of antivenom immunoglobulins (Gutierrez et al., 2011; WHO, 2010, 2016). Antivenoms are the only effective and dedicated therapy to treat envenoming, a major tropical disease due to snakebites. The number of envenoming is estimated to be between approximately 500′000 and 1′800′000 each year, and to lead to up to over 100′000 deaths in rural areas of Africa, Asia, Latin America and Oceania (Gutiérrez et al., 2017; Kasturiratne et al., 2008). There are about 45 manufacturers of antivenom immunoglobulins in the world, most of them now located in developing areas of the world, since several, located in industrialized countries, have stopped this production activity (Gutierrez et al., 2007). The manufacturing processes of antivenoms immunoglobulins and immunoglobulin fragments has been described in detail**s** in recent excellent WHO Guidelines and other publications (Gutierrez et al., 2011; WHO, 2010, 2016).

Human plasma products and antivenoms are proven, well-established, essential biological products. They share similarities, but also substantial differences in manufacturing processes. Production methods of both classes of biologicals are aiming at ensuring optimal quality and safety profiles, at optimal yields and minimal cost. However, there has been, so far, relatively little cross-fertilization in the respective fractionation expertise of human plasma products and antivenoms, probably because few manufacturers are producing both classes of products. The purpose of this publication is therefore to review how the developments that have been seen in the human plasma fractionation industry in the last 30 years may benefit the field of antivenom, especially in aspects related to production and control of plasma raw material, fractionation methods, product quality profile, virus safety, and good manufacturing practices (GMP).

2. How is human plasma collected?

2.1. Biochemical features of human plasma

Human plasma is a unique biological material that comprises hundreds of functionally active proteins. Its total protein content is close to 60 mg/mL. Most abundant proteins are albumin (35–40 mg/mL), immunoglobulins (8–12 mg/mL), and fibrinogen (1.5–3 mg/mL). In addition, other therapeutically relevant proteins include coagulation factors, protease inhibitors, pro/anti-coagulant proteins typically present at a dose of a few milligrams or micrograms/mL. Currently, more than 20 distinct protein therapeutics