

Blood-derived drugs: viral safety

Médicaments dérivés du sang: sécurité virale

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ABSTRACT

The stable blood products, called since 1995 "the medicines derived from blood", are classified into five categories (albumin, clotting factors, protease inhibitors, immunoglobulins, biological glues). Their manufacture, dispensing, and pharmacovigilance (Correspondants) are provided primarily by the pharmacist. They have a great importance in the compensation of constitutional or acquired deficiency of plasma proteins. Obtaining them from blood donation (voluntary, anonymous and free), requires the application of several successive fractionation, merging, purification, elimination and/or viral inactivation. The main techniques used in fractionation are, precipitation (by cold or ethanol) and chromatography, which also contributes to the reduction of a possible viral load. The viral securisation is a decisive criterion for evaluation of the drug under the authorization of placing on the market. Other recombinant products have been developed ; they have the advantage of being equally effective but safer than plasma products. We propose in our work to review key points on securing viral transmission of medicines derived from blood.

Keywords: blood-derived drugs ; security.

RÉSUMÉ

Les produits dérivés du sang, appelés depuis 1995 « les médicaments dérivés du sang », sont classés en cinq catégories (albumine, facteurs de coagulation, inhibiteurs de la protéase, immunoglobulines, colles biologiques). Leur fabrication, délivrance et pharmacovigilance sont essentiellement faites par le pharmacien. Ils ont une place importante dans la compensation des déficits innés ou acquis en protéines plasmatiques. L'obtention de ces produits à partir de dons de sangs (volontaires, anonymes et gratuits) nécessite l'application de plusieurs procédures de fractionnement, de fusion, de purification et d'élimination et/ou inactivation virale. Les principales techniques utilisées dans le fractionnement sont : la précipitation (par le froid ou l'éthanol) et la chromatographie, qui contribue aussi à la réduction de la charge virale. La sécurisation virale est un critère décisif pour l'évaluation du médicament avant d'autoriser sa mise sur le marché. D'autres produits recombinants ont été développés ; ils ont l'avantage d'être aussi efficaces tout en étant plus sûrs que les produits du plasma. Nous proposons dans notre travail de revoir les points clés sur la sécurisation de la transmission virale des médicaments dérivés du sang.

Keywords: Médicaments dérivés du sang ; sécurité.

الأدوية المشتقة من الدم: السلامة الفيروسية

الملخص:

منتجات الدم المستقرة منذ تسميتها في 1995 بالأدوية المشتقة من الدم، تصنف إلى خمس فئات (الألبومين وعوامل التجلط، مثبطات أنزيم البروتياز، الغلوبولين المناعية، والغراء البيولوجي). يتم الصنع، الصرف، والرقابة الصيدلانية في المقام الأول من قبل الصيدلي. لديهم أهمية كبيرة في تعويض نقص تكويني أو مكتسب لبروتين البلازما. يتم الحصول عليها عن طريق التبرع بالدم (الطوعي، المجهرول والمجانبي)، ويتطلب تطبيق عدة تجزئات متتالية بالإضافة إلى الاندماج، وتنقية، والقضاء على و / أو تعطيل الفيروس. التقنيات الرئيسية المستخدمة في التجزئة هي، الترسيب (بواسطة البرد أو الإيثانول) والتحليل البياني اللوني، مما يساهم أيضا في الحد من التحميل الممكن للفيروسات. السلامة الفيروسية هي معيار حاسم لتقييم الدواء الذي هو قيد الترخيص لطرجه في الأسواق. لماذا تم استحداث منتجات أخرى متوتلة لأنها تتمتع بفعالية مماثلة ولكن أكثر أمانا من منتجات البلازما. اقترحنا في عملنا مراجعة السلامة الفيروسية في الأدوية المشتقة من الدم.

الكلمات الرئيسية: الأدوية المشتقة من الدم، السلامة.

INTRODUCTION

Blood-derived drugs (BDD) are industrially manufactured from human plasma from thousands of blood donations. They are indicated as replacement therapy of constitutional or acquired diseases of hemostasis, or for the treatment of medical or surgical disease states.

Human blood can be vector of viral infectious agents if the donation is made during the viremic phase (AIDS and hepatitis, etc.). Preventing contamination of plasma-derived therapeutics, the manufacturing process involves the mixing of thousands of

blood donations, and requires the combination of protective measures, which effectiveness has increased significantly in recent years [1].

The units used in the manufacture of plasma products are collected from a population of selected donors, excluding those whose behavior or history (travel in countries where the prevalence of an infectious agent is high) are identified as holders of risk factors. In addition, the search for direct viral markers (viral antigen) or indirect markers (antibodies) of the AIDS (HIV 1 and 2), hepatitis B and C, and HTLV retroviruses is performed on each donation blood and positive units are destroyed [2].

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Before the industrial fractioning, samples of plasma units are mixed, and a search for the presence of the viral genome (currently required in Europe for hepatitis C) is performed, allowing the removal of a positive donation [3]. After industrial mixture, the plasma pool (with a volume of 2000 liters or more), is itself controlled and then subjected to fractioning and purification steps for each plasma product, comprising one or more steps of inactivating or eliminating the AIDS virus and hepatitis B and C in particular [4].

Inactivation technologies most commonly used are the treatment by solvent-detergent and pasteurization. Nanofiltration (viral removal by filtration) is increasingly used as additional security. With the selection of donors and these measures, virus transmission by plasma products has become an exceptional event.

However, the risk of emergence of new infectious agents requires maintaining great vigilance and response capability for the rapid implementation of effective prevention [5].

TRANSFUSION RISK OF BLOOD-DERIVED DRUGS

Various pathogenic infectious agents may be present in the blood. Bacterial and parasitic agents, as well as strictly intracellular viruses, do not create a risk of infection for plasma products, in particular because of their destruction during the fractioning steps. The specific case of prions is discussed later [1, 6].

The characteristics of pathogenic viruses transmitted by plasma-derived drugs are summarized in the table below (table 1) [7].

Table 1: Features and risks of transmission proved (in the absence of viral inactivation treatment) of potentially present in human blood virus [8].

Virus	Family	genome	Envelope	Size (nm)	Theoretical risk of transmission
Epstein-Barr	Herpes	dsDNA	E	120-220	-
cytomegalovirus	Herpes	dsDNA	E	180-200	-
Human herpesvirus 8	Herpes	dsDNA	E	120-200	-
Human immunodeficiency	retro	ssRNA	E	80-100	(+)
Human T Cell Leukemia I & II	retro	ssRNA	E	80-100	-
Simian foamy	retro	ssRNA	E	80-100	(-)
SARS	Corona	ssRNA	E	60-220	(-)
West Nile	Flavi	ssRNA	E	40-60	(-)
hepatitis G	Flavi	ssRNA	E	40-60	(+)
Hepatitis C	Flavi	ssRNA	E	40-50	(+)
dengue	Flavi	ssRNA	E	40-50	(-)
TT	Circo	ssDNA	E	30-50	(+)
Hepatitis B	Hepadna	dsDNA	E	40-48	(+)
hepatitis E	HEPE	ssRNA	BO RN	35-39	(+)
hepatitis Delta	Delta	ssRNA	E	36	(+)
Hepatitis A	Picornia	ssRNA	BO RN	27-32	(+)
parvovirus B19	Parvo	ssDNA	BO RN	18-26	(+)

BLOOD-DERIVED DRUGS SECURITY MEASURES

Microbiological security remains the primary concern of manufacturing; it relies on three essential steps: the quality of the plasma, control of manufacturing processes, inactivation and/or viral removal, and specific traceability to drugs related plasma [9].

Quality of plasma

At the Blood donation viral safety is ensured by: the voluntary gift, the medical screening of donors, unit biological control of the donation. July 1, 2001 was introduced on nucleic acid testing (NAT), research on HIV and HCV. Upon receipt of plasmas in "French Laboratory of Fractioning and Biotechnology (LFB)", biological control of viral markers is performed on a limited number of samples and validated. Plasma batches obtained after thawing are systematically tested [10, 11].

In Morocco, the safety of plasma is provided by a range of facts, both administratively and regulatory. These facts are translated especially during the last ten years by a strengthening in the quality of donations through the establishment of a pre-donation information, medical donor selection, biological control, and monitoring post-donation [12].

Mastery of fractioning processes, inactivation and/or viral removal

Mastery of fractioning processes: Fractioning is a separation of plasma proteins that contributes to the purification of BDD in reducing the risk of transmission of pathogens. It is ensured by two process types: One is the ethanol precipitation, resulting in the separation of albumin and immunoglobulins (ethanol has a bacteriostatic effect and contributes to the viral removal by precipitation of virus and inactivation of enveloped viruses. Studies using unconventional transmissible agent models have also shown efficacy in their elimination) [13]. The other is cryoprecipitation, which consists of thawing plasma at a temperature between + 2 and + 4° C, resulting in the separation of the cryoprecipitate, rich in factor VIII, von Willebrand factor and fibrinogen (cryoprecipitation has a low degree of viral clearance, but does not lead to viral inactivation). [14]

Viral inactivation: These processes were essential to eliminate the risk of HIV transmission, HBV and HCV, and for preventing the transmission of emerging viruses such as West Nile virus [15].

The existing complementarities between NAT tests and viral reduction methods are evidenced especially in reducing the risk of transmission of resistant non-enveloped viruses such as parvovirus B19. All plasma products must be subject to at least an effective treatment and validated its ability to inactivate viruses. In practice, and in accordance with the recommendations of the regulatory authorities, most plasma products are subject to two validated selective treatments for inactivation and/or elimination of viruses [10].

Princept treatment, often a chemical process (solvent-detergent or SD) or heat (pasteurization), generally has the function of the inactivation of the most pathogenic viruses (HIV, HBV, and HCV), while the second (dry heating, nanofiltration), is the inactivation or removal of non-enveloped viruses (HAV and parvovirus B19) [16, 17]. The

processes of nanofiltration membranes (15 to 75 nm) allow efficient retention of viruses, and are generalized to a number of increasingly important plasma products [5, 18]. There have been no cases of HIV, HBV or HCV transmission, by a plasma product virally inactivated by validated procedures, for nearly 15 years (table 2) [1].

Table 2: Special features of the main methods of reducing viral plasma products [19].

processes	Principle	targeted virus	Characteristics
Applied current split			
Solvent detergent	Incubation of a few hours in the presence of TNBP and one or more detergents (Tween 80, Triton X-100) 20-37 ° C	wrapped	Ineffective against non-enveloped viruses No or little risk of denaturation of plasma proteins SD agents must be removed (usually by chromatographic or oil extraction processes) Applicable in practice to the full range of plasma products
Pasteurization	Heating a solution at 60 ° C for ten hours, generally in the presence of stabilizers (sugars, polyols, amino acids)	Non-enveloped	Parvovirus B19 may show resistance to the treatment, according to the composition of the medium Possibility from 10 to 30% loss of biological activity for coagulant fractions applied to certain coagulant fractions, fibrinogen, antithrombin, alpha 1-antitrypsin and immunoglobulins
acid pH	Incubation at an acid pH (close to 4) for several hours at 25-37 ° C	Some enveloped and non-enveloped viruses	Reserved for immunoglobulin G
Caprylic acid (octanoic acid) (<pH 5.5)	Incubation at a pH below 5.5 for 30 to 60 minutes at 20-22 ° C.	wrapped	Reserved for immunoglobulin G
nanofiltration	Filtration of a protein solution on multilayer membrane of a porosity of 15 to 75 nm.	Non-enveloped wrapped	Viral removal is performed by size exclusion based on the size differential viruses and nanofilters applicable in practice to the entire range of plasma products, including high molecular weight
Treatment on the final bottle			
Pasteurization	Heating a solution at 60 ° C for ten hours in the final bottle in the presence of stabilizers fatty acids	Non-enveloped wrapped	Reserved to albumin
Dry Heating	Heating a lyophilized product at 80 ° C for 72 hours, or at 100 ° C for 30 minutes, generally in the presence of amino acids and / or sugars and / or polyols	Wrapped enveloped virus non-	Parvovirus B19 may show resistance to this treatment Possibility from 10 to 20% loss of biological activity for lesfractions coagulant applied primarily to certain coagulant fractions

Virus removal

Introduced in France in the early 1990s, nanofiltration is now

applied to many plasma products worldwide (table 3) [20]. This is the only specific treatment viral elimination recognized for its strength, based on the processes of nanofiltration membranes (15 to 75 nm), or equivalent, for effective retention of viruses [21]. In addition to its efficacy in viral elimination (and probably that of prions), it has the additional benefit of not to induce disturbances of protein (activation, neoantigens training) and performance is, without exception, greater than 90-95% [22, 23].

Validation of the effectiveness of inactivation steps and viral removal

This efficiency is defined by the viral reduction factor obtained after applying the concerned process. It is assessed by overloading, across the virology laboratory, the product with a virus, with measurement of the initial viral titer and residual viral titer obtained after treatment with the process. Thus, the reduction factor is the logarithm of the ratio between the initial charge and the final charge. All these techniques for disposal and/or viral inactivation however, have limitations and none can guarantee itself a top viral safety of manufactured products [24]. It is recommended to use in the manufacture of BDD, two distinct and complementary techniques, which at least has to be efficient on the naked viruses. The combination of inactivation steps of the increasingly complex purification steps of the manufacturing processes must allow obtaining microbiologically safe products with a level of biological safety that complies with the requirements [25]. Since their application during the manufacture of BDD, no cases of infection with HIV, HBV and HCV were observed. However, according to the circular 98/231 of 9th April 1998, informing the BDD receiving patients about the real or theoretical risks of these treatments should be made by the prescribing physician before administering any of these drugs [2].

Traceability

The term traceability means the ability to trace the history, application or location of an item or activity by means of recorded information. The traceability of medicinal products derived from plasma, defined by the decree of 6th May 1995 on pharmacovigilance exerted on medicinal products derived from plasma, enables the link between the donation and a given batch of drugs, and the link between a lot of drug and the patient. Traceability has two objectives: to locate the BDD in the distribution chain to quickly activate if necessary, a measure of withdrawal. The second is to conduct ascending (from the patient to the donor) or descending investigations (from donor to patient) [26]. The requirement is made to report any adverse pharmacovigilance center linked to the use of medicinal products derived from plasma. *A priori* information on patients known or theoretical risks of medicinal products derived from plasma should be routinely made by prescribers (circular of the Health Branch [DGS] of 9th April 1998). Afssaps may have to take steps to "precautionary" recalls or linked to a risk for the health of the patient [27].

SPECIAL MEASURES FOR SECURING AGAINST PRIONS

It was decided, on behalf of the precautionary principle, a number of measures to increase the safety of plasma. Are excluded from blood donation, the donors at risk of Jakob disease creutzfeldt (JDC), those who have been transfused or

Table 3: Key features of BDD used in the treatment of hemorrhagic and thrombotic diseases [2].

Postman	Product (marketing laboratory)	Purification methods	Specific methods of disposal and / or viral inactivation	Storage
VIII	FACTANE® (LFB)	Ion exchange chromatography and adsorption	Nanofiltration and solvent detergent treatment	2° -8° C 30 months <25° C 6 months; protected from light ; do not freeze
VIII	Hémophil M® (Baxter)	Affinity chromatography with monoclonal antibodies and ion exchange chromatography	Treatment by solvent-detergent	2-8° C 2 years; do not freeze
VIII	Monoclate P® (Aventis Behring)	Affinity chromatography with monoclonal antibodies	Pasteurization at 60° C for 10 h	2° -8° C, with <25° C 6 months; do not freeze
IX	Betafact® (LFB)	Ion exchange chromatography and adsorption	Nanofiltration and solvent detergent treatment	2° -8° C with 30 months <25° C 6 months; protected from light ; do not freeze
IX	Mononine® (Aventis Behring)	Affinity chromatography with monoclonal antibodies	ultrafiltration	2° -8° C, with <25° C 1 month; do not freeze
VWF	Wilfactin® (LFB)	Affinity chromatography and ion exchange and adsorption	Nanofiltration at 35 nm and dry heating to 80° C for 72 h and solvent-detergent	Temperature <25° C 3 years; protected from light ; do not freeze
VWF VIII +	Wilstart® (LFB)	Affinity chromatography and ion exchange and adsorption for VWF and FVIII	For VWF, nanofiltration at 35 nm and dry heating to 80° C for 72 h and solvent-detergent	2° -8° C 30 months <25° C 6 months; protected from light ; do not freeze
fibrinogen	Clottagen® (LFB)	Adsorption chromatography and	Treatment by solvent-detergent	<25° C 3 years; protected from light ; do not freeze
VII	VII-F® LFB (LFB)	Ion exchange chromatography and adsorption	Treatment by solvent-detergent	° - 8° C 2 years; away from the light, do not freeze
XI	Hemoleven® (LFB)	Ion exchange chromatography	Nanofiltration and solvent detergent treatment	2° -8° C 2 years; protected from light ; do not freeze
XIII	Fibrogammin®(Aventis Behring)	multiple rainfall	Pasteurization 10 h at 60° C	2° -8° C; do not freeze
PPSB	Kaskadil® (LFB)	Ion exchange chromatography and adsorption	Treatment by solvent-detergent	<25° C 3 years; protected from light ; do not freeze
CCAC	Feiba® (Baxter)	Ion exchange chromatography and ethanol precipitation	Steam treatment in two steps (60° C for ten to 190 mbar, then 80° C for 1 hour to 370 mbar)	2° - 8° C, with <30° C for 6 months; do not freeze
protein C	Protexel® (LFB)	Adsorption chromatography and	Solvent detergent	2-8° C 2 years; protected from light ; do not freeze
protein C	Ceprotrin® (Baxter)	Affinity chromatography and ion exchange	Solvent-detergent and steaming	2-8° C 2 years; protected from light ; do not freeze
AT	Aclotine® (LFB)	Adsorption chromatography and	Pasteurization	<25° C 2 years; protected from light ; do not freeze

transplanted, and recall the batch of products from which a plasma donor is suspected or diagnosed to be suffering from vJDC. Other measures have been taken, such as the exclusion of donors who have stayed more than one cumulated year in the UK between 1980 and 1996, and the systematic plasma de leukocytation [22,28, 29].

Furthermore, it was demonstrated that the manufacturing process of plasma-derived therapeutics, including removal steps might greatly reduce the theoretical infectivity vis-à-vis vJDC. This elimination seems to be explained by the characteristics of hydrophobicity and aggregability of the infectious agent [30-32]. In addition, the steps of nanofiltration on multilayer membrane with a porosity of 75 nm or less, already widely used for virus removal, also seem highly effective in removing prions, probably by steric exclusion and trapping mechanism in the filter [33, 34]. vJDC transmission risk by plasma products therefore seems very minor, even if it is relative scientific value of these experimental studies, because the current misunderstanding of the nature of the infectious agent in the blood cannot judge their predictive value. The risk of transmission of prions through blood has been subject to a recent international consultation coordinated by WHO [35,36].

Finally, at the request of the expert group convened by the Afssaps, filtration at 15 nm, already effective for certain factors and immunoglobulins will be widespread [19].

CONCLUSION

The reduction in viral load is achieved through the application of one or more method(s) of physical neutralization (dry heating, pasteurization, ultrafiltration), and/or chemical procedures (solvent detergent, pepsin-PH4, thiocyanate sodium), corresponding to the specific viral inactivation steps. All these steps cannot guarantee alone complete viral safety of finished products. For a given process, the viral safety is the ability of the process to eliminate/inactivate viruses. At least two stages, an inactivation must be validated.

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