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一般的名称			研究報告の公表状況	Preparation of soluble infectious samples from scrapie-infected brain: a new tool to study the clearance of transmissible spongiform encephalopathy agents during plasma fractionation Vito Angelo Berardi, et al. Lancet 2006; 46: 652- 8	公表国 イタリア	
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研究報告の概要

英国で血液感染による変異型クロイツフェルト・ヤコブ病が 2 例報告されて以来，プリオンと関わる血液，血液成分，及び血漿由来製剤の安全性が大きく懸念されている。感染性海綿状脳症(TSE)に感染した齧歯類の脳の一部をスパイクした血液成分や血漿由来製剤からのプリオンの除去，あるいは不活性化を可能にする方法の開発が取り組まれた。しかしながら，スパイクには恐らく血液感染とは関連のない病原性プリオンタンパク質 (PrP^{TSE})の凝集体が含まれており，この集合体の存在により試験が無効になる可能性がある。これを明らかにするため，筆者らは以下の実験を行った。
スクレーピーのハムスター263K 株の脳組織を 10%リン酸緩衝食塩水で懸濁し，低速遠心分離後，上澄み液を収集し，30 分間２５ 220,000×g で高速遠心分離を行った。高速遠心による浮遊物 (S^{HS})と沈殿物を収集し，ウエスタンブロット法によりプロテイナーゼ耐性 PrP^{TSE}を，離乳ハムスターへ脳内接種し感染性を測定した。実験では，相当量のプリオン感染力(脳組織の 10%懸濁液の mL あたりの 50%致死量 105 以上)がスクレーピーのハムスター263K 株の S^{HS}分画でみられたが，その効果は PrP^{TSE}の凝集体を含む分画よりも低かった。一方，この分画はなにも含んでいないか，含んだとしても僅か微量の PrP^{TSE}の凝集体であることが確認された。本実験で示された PrP^{TSE}の凝集体を含まない感染性物質を調製する簡便な方法は，ヒト血液成分及び血漿由来製剤におけるプリオン除去，または不活化確認試験に用いるのに適当なスパイク物質を調製する上で有用であると考えられた。

使用上の注意記載状況・その他参考事項等

BYL-2006-0215

報告企業の意見	今後の対応
弊社の血漿分画製剤の製造工程において，2004 年の Position statement で欧州医薬品審査庁が推奨する，プリオン除去及び感染性評価の開発を行った。その結果，各製品の製造過程で，少なくとも 4log のプリオン除去が可能であることが確認されている。	現時点で新たな安全対策上の措置を講じる必要は無いと考える。引き続き関連情報の収集に努める。

Preparation of soluble infectious samples from scrapie-infected brain: a new tool to study the clearance of transmissible spongiform encephalopathy agents during plasma fractionation

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BACKGROUND: Concern about the safety of blood, blood components, and plasma-derived products with respect to prions has increased since the report of two blood-related infections of variant Creutzfeldt-Jakob disease in the United Kingdom. Efforts were directed toward the development of procedures able to remove or inactivate prions from blood components or plasma-derived products with brain fractions of transmissible spongiform encephalopathy (TSE)-infected rodents as spiking materials. These spiking materials, however, are loaded with pathological prion protein (PrP^{TSE}) aggregates that are likely not associated to blood infectivity. The presence of these aggregates may invalidate these studies.

STUDY DESIGN AND METHODS: Brains from 263K scrapie–infected hamsters were suspended in 10 percent phosphate-buffered saline. After low-speed centrifugation, the supernatant was collected and ultracentrifuged at 220,000 × *g* at 25°C for 30 minutes. The high-speed supernatants (S^{HS}) and pellets were collected; the proteinase-resistant PrP^{TSE} was measured by Western blot and infectivity by intracerebral inoculation into weanling hamsters.

RESULTS: A substantial amount of prion infectivity (more than 10^5 LD_{50} per mL of a 10% suspension of brain tissues) is present in the S^{HS} fraction of 263K scrapie–infected hamster brains. Concomitantly, this fraction contains none or only traces of PrP^{TSE} in its aggregate form.

CONCLUSION: This study describes a simple and fast protocol to prepare infectious material from 263K scrapie–infected brains that is not contaminated with PrP^{TSE} aggregates. This S^{HS} fraction is likely to be the most relevant material for endogenous spiking of human blood in validation experiments aimed at demonstrating procedures to remove or inactivate TSE infectious agents.

The occurrence of two blood-related infections of variant Creutzfeldt-Jakob disease (vCJD) in the United Kingdom[1,2] and the finding that approximately 10 percent of vCJD cases were blood donors before the appearance of clinical signs[1] are cause of increasing concern for the safety of blood transfusion and, as a consequence, of blood components or plasma-derived products. There is strong evidence that vCJD is caused by the consumption of bovine spongiform encephalopathy (BSE)-contaminated meat products, but the occurrence of human-to-human transmission of vCJD has now raised the possibility that other cases might be related to blood transfusions rather than meat consumption. BSE and vCJD, together with scrapie in sheep and goats, sporadic and genetic CJD, Gerst-

ABBREVIATIONS: BSE = bovine spongiform encephalopathy; LD_{50} = doses required to kill 50 percent of inoculated animals; NaPTA = sodium phosphotungstic acid; PK = proteinase K; P^{HS} = high-speed pellet; P^{NaPTA} = pellet after sodium phosphotungstic acid precipitation; PrP^{TSE} = pathological prion protein; PrP^{27-30} = 27- to 30-kDa fragment of protease-resistant prion protein; S^{LS} = low-speed supernatant; S^{HS} = high-speed supernatant; TSE = transmissible spongiform encephalopathy; TBST = Tris-buffered saline (pH 8) with 0.05 percent Tween 20; vCJD = variant Creutzfeldt-Jakob disease.

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mann-Sträussler-Scheinker disease, and sporadic or familial fatal insomnia, belong to the group of transmissible spongiform encephalopathy (TSE) or prion diseases that are progressive degenerative disorders of the central nervous system with fatal outcome.[3] The majority of vCJD cases have occurred in the United Kingdom (n = 159)[4] or in patients who spent months in the United Kingdom before the development of disease. However, vCJD has also occasionally been reported in patients who were not British and never traveled to the United Kingdom, suggesting that these patients were infected in their own country.[5-8] Moreover, a preliminary prospective study in the United Kingdom has indicated that there are about 3000 individuals in the age group 10 to 30 years who might carry prion infectivity in the lymphoreticular tissues[9] and, possibly, in the blood. The findings that vCJD patients carry infectivity in blood up to 3 years before the appearance of clinical signs[1] and that no test is yet available for the screening of vCJD-infected people[10,11] have focused the efforts for the safety of blood toward procedures that may remove or inactivate the infectious agent in blood, blood components, or plasma products. These validation experiments are usually performed either with blood taken from TSE-infected rodents or with human blood spiked with TSE-infected rodent brains.[12] Blood of TSE-infected rodents, however, contains only up to 10^2 infectious doses per mL,[13,14] and even the complete removal of these low levels of infectivity does not guarantee the efficacy of the treatment and the safety of blood.[12] Spiking blood with TSE-infected brains greatly increases the amount of infectivity and therefore overcomes the low-level infectivity naturally carried in rodent blood, but the criticism of these validation studies is that the nature of prions in the brain may substantially differ from that present in the blood.[12] Most of the infectivity in the brain is associated with the abnormal prion protein (PrP^{TSE}) in its aggregate form, whereas in blood it is likely that infectivity is associated to a much more soluble fraction of PrP^{TSE}. This substantial difference in the physicochemical structure of PrP^{TSE}-associated infectivity may influence the efficacy of procedures able to inactivate or remove prion infectivity.

In this article, we show that fractions of 263K scrapie–infected brains retain a high level of prion infectivity without being associated with the aggregate form of PrP^{TSE}. This fraction might be useful in the validation studies of pharmaceuticals products derived from blood or urine collected from human or BSE-susceptible ruminants.

MATERIALS AND METHODS

Extraction of water-soluble scrapie infectivity

263K scrapie–infected hamster brains were suspended in 9 vol of sterile phosphate-buffered saline (PBS; pH 7.4) and homogenized by use of a Teflon-glass Potter tissue grinder. The homogenate was dispersed with 10 sonication pulses (Vibra Cell, Sonics & Materials Inc., Newtown, CT) while kept on ice and then centrifuged at $825 \times g$ for 15 minutes at 25°C (GS-6R, rotor GH-3.7, Beckman Coulter, Fullerton, CA). Low-speed supernatant (S^{LS}) was sonicated as above and ultracentrifuged at $220{,}000 \times g$ for 30 minutes at 25°C (Optima TL-100, rotor TLA 100.3, Beckman Coulter, Fullerton, CA). This high-speed supernatant (S^{HS}) was collected and the high-speed pellet (P^{HS}) was sonicated in sterile PBS to obtain a 10 percent suspension (gram-equivalents of brain/PBS). In Replicate 2, sonication was never performed. These three fractions (S^{LS}, S^{HS}, and P^{HS}) were stored at –70°C until assayed. The S^{HS} fraction of Replicate 3 was examined by transmission electron microscopy after negative staining.

Western blot measurement of the 27- to 30-kDa fragment of protease-resistant prion protein

Fractions S^{LS}, S^{HS}, and P^{HS} were thawed and treated for 60 minutes at 37°C with proteinase K (PK; Sigma Chemical Co., St. Louis, MO) at a final enzyme concentration of 50 µg per mL. The digestion was stopped by adding protease inhibitors (Complete, Roche Diagnostics GmbH Roche Applied Science, Mannheim, Germany) in accordance with the manufacturer's instruction.

Sodium dodecyl sulfate–polyacrylamide gel electrophoreses and Western blot assays were performed according to Lee and coworkers[15] with some modifications. After PK treatment, the samples were serially diluted in half-log steps in NuPAGE gel loading buffer, boiled for 10 minutes in a water bath, and electrophoresed on 12 percent NuPAGE Bis-Tris gels (Invitrogen Corp., Carlsbad, CA) for 60 minutes at 125 V. The nitrocellulose membrane (Hybond ECL, Amersham Biosciences Europe GmbH, Freiburg, Germany) was soaked in Towbin transfer buffer for 5 minutes before "sandwich" assembly and semidry transfer for 60 minutes at 125 mA at 4°C. The membrane was blocked for 60 minutes at 37°C in 3 percent nonfat dry milk (Bio-Rad, Hercules, CA), dissolved in Tris-buffered saline (pH 8) with 0.05 percent Tween 20 (TBST), and incubated overnight at 4°C with 3F4 monoclonal anti-hamster 27- to 30-kDa fragment of protease-resistant prion protein ($PrP^{27\text{-}30}$) antibody[16] (provided by H. Diringer) diluted 1:2000 in TBST. The membrane was rinsed with TBST (five changes of solution in 25 min), incubated for 90 minutes at room temperature with an alkaline phosphatase–labeled goat anti-mouse IgG (Perkin-Elmer Sciences, Wellesley, MA) diluted at 1:5000 in TBST, and rinsed again. Bands were revealed by the CDP-star chemiluminescence detection kit (Applied Biosystems, Foster City, CA) and

recorded onto sensitive films (Hyperfilm ECL, Amersham Biosciences).

Sodium phosphotungstic acid precipitation of the S^{HS} fraction

To recover PrP^{TSE} in fraction S^{HS}, the sample was mixed with 1 volume of 4 percent sarkosyl and processed with sodium phosphotungstic acid (NaPTA; 0.3%) and $MgCl_2$ (12.75 mmol/L) as published by Wadsworth and associates[17] with the only modification consisting in the precipitation of the final pellet by ultracentrifuge at 220,000 × *g* for 30 minutes at 25°C (Optima TL-100, rotor TLA 100.3). The pellet (P^{NaPTA}) was then sonicated in sterile PBS to obtain a 10 percent suspension (gram-equivalents of brain/PBS) and stored at –70°C until assayed.

Infectivity bioassay

Groups of 7 to 10 Syrian hamsters were anesthetized and then inoculated intracerebrally with 50 µL of fractions S^{LS}, S^{HS}, P^{HS}, and P^{NaPTA}. Animals were maintained in coded plastic cages with water and food ad libitum and regularly scored for clinical signs of scrapie disease as previously described.[18] Incubation periods (mean ± SD) were measured and infectivity titers were estimated by applying these values to a dose incubation curve drawn after an endpoint titration.[19] An inverse relation exists between dose and incubation period in the 263K strain in hamsters, which gives a mean incubation period of 155.5 days for 1 LD_{50} intracerebral unit in 0.05 mL of a 10 percent brain homogenate.[19] Animals were housed at the animal facility of the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) under the supervision of the Service for Biotechnology and Animal Welfare of the ISS who warrants the adherence to national and international regulations on animal welfare.

RESULTS

Western blot analyses of 263K scrapie–infected brain fractions

As expected, a great amount of partially PK-resistant PrP^{TSE} (PrP^{27-30} Fig. 1) and infectivity (approx. 8 log LD_{50}/mL 10% brain suspension) is present in the supernatant (S^{LS}) after low-speed centrifugation of 263K scrapie–infected brain homogenates in PBS. The majority of PrP^{27-30} and infectivity is then recovered in the pellet after ultracentrifugation (P^{HS}). As shown in Table 1, the difference

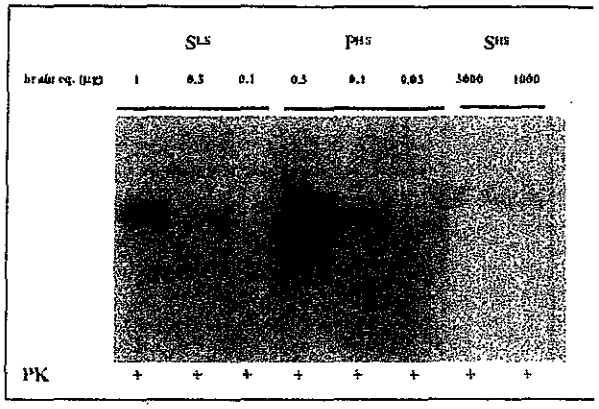

Fig. 1. Western blot analysis of PrP^{27-30} in low-speed (S^{LS}) and high-speed (P^{HS} and S^{HS}) fractions prepared from 263K scrapie–infected brain (Replicate 3). The samples were treated with PK, diluted in half-log steps in NuPAGE gel loading buffer, and resolved on a 12 percent NuPAGE Bis-Tris gels. After the transfer to nitrocellulose membrane and incubation with monoclonal antibody 3F4, PrP^{27-30} was visualized by chemiluminescence on sensitive films. PrP^{27-30} was not measurable in S^{HS}, indicating that virtually all the aggregate form of PrP^{TSE} was precipitated after centrifugation at 220,000 × *g* for 30 minutes.

TABLE 1. Endpoint titration of PrP^{27-30} in different fractions (S^{LS}, S^{HS}, and P^{HS}) of 263K scrapie–infected brain

Replicate number	Fraction	Log dilutions (weight-equivalents of brain tissue) 0.5 (3 mg)	1 (1 mg)	4 (1 µg)	4.5 (0.3 µg)	5 (0.1 µg)	5.5 (0.03 µg)	6 (0.01 µg)	Difference (log) between S^{LS} and S^{HS}
1	S^{LS}			+	+	–			≥4.5
	S^{HS}	–	–						
	P^{HS}			+	+	+	–		
2*	S^{LS}			+	–				≥4.0
	S^{HS}	–	–						
	P^{HS}			+	–				
3	S^{LS}			+	+	+	–		≥5.0
	S^{HS}	–	–						
	P^{HS}			+	+	+	+	–	
4	S^{LS}			+	+	+	–		4.5
	S^{HS}	+	–						
	S^{NaPTA}†	–							
	P^{NaPTA}	+	–						

* No sonication was performed in this replicate.
† S^{NaPTA} = supernatant after sodium phosphotungstic acid precipitation.

between the amount of PrP^{27-30} in S^{LS} and P^{HS} was either null (Replicate 2) or no more than 0.5 log (Replicates 1 and 3) and it was not influenced by the use of sonication for the dispersion of samples (compare Replicates 1 and 3 with Replicate 2). Concordantly, PrP^{27-30} was either not measurable (Fig. 1, Replicate 3) or present at a very low amount (Fig. 2, Replicate 4) in the supernatant after ultracentrifuge (S^{HS}, Table 1), indicating that virtually all the aggregate form of PrP^{TSE} was precipitated by 220,000 × *g* for 30 minutes. In other words, the ultracentrifuge reduces the amount of PrP^{TSE} aggregates in the supernatant of more than 10,000 times (Table 1). Examination of the S^{HS} fraction of Replicate 3 revealed amorphous proteinaceous material and no delimiting membranous structure. In Replicate 4, the small amount of PrP^{TSE} was completely precipitated by NaPTA precipitation (P^{NaPTA}; Fig. 2). In the other replicates, PrP^{TSE} was not recovered even after NaPTA precipitation.

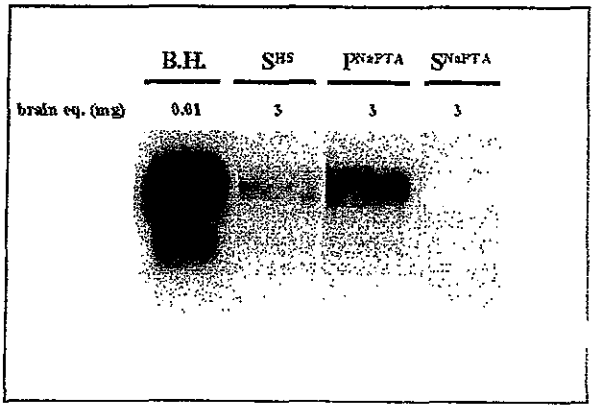

Fig. 2. Western blot analysis of PrP^{27-30} in S^{HS} fraction before (S^{HS}) and after (S^{NaPTA}) NaPTA precipitation (Replicate 4). The samples were treated with PK, resolved on a 12 percent NuPAGE Bis-Tris gels, and transferred to nitrocellulose membrane. After incubation with monoclonal antibody 3F4, PrP^{27-30} was visualized by chemiluminescence on sensitive films. PrP^{27-30} traces in the S^{HS}, were recovered in the pellet after NaPTA precipitation (P^{NaPTA}). PK-treated 263K-infected Syrian hamster brain homogenate (B.H.) was loaded as positive control.

Infectivity measurement of 263K scrapie–infected brain fractions

Virtually all infectivity present in the S^{LS} fraction is recovered in the pellet after ultracentrifugation (P^{HS} fraction). A substantial amount of infectivity is also found in the S^{HS} fraction, however. The mean incubation periods of hamsters inoculated with aliquots of S^{HS} fractions were, respectively, 15.9, 18.5, and 25.6 days longer than the corresponding S^{LS} fractions (Table 2), which corresponds to an estimate lost of infectivity titer ranging from 30 to 200 times.

The enrichment factor for infectivity versus PrP^{TSE} (calculated as the difference between the reduction factor for PrP^{TSE} and the reduction factor for infectivity) ranged from more than 200 times in Replicate 2 up to 1000 times in Replicate 1 (Table 2). Virtually all infectivity in S^{HS} was recovered in the pellet (P^{NaPTA}) after NaPTA precipitation.

DISCUSSION

In blood of TSE-affected rodents or sheep, a substantial proportion of infectivity is associated with plasma.[20-22] If the distribution of infectivity in human blood is the same as in animals, then plasma-derived products might be at risk of transmitting vCJD. Usually, precautions against the risk of infection in medicinal products, including plasma-derived pharmaceuticals, consist of source deferrals, screening of donors, and inactivation or removal of the infectious agent. In TSE diseases, however, the first two lines of defense are poorly practicable because blood is infectious during the long asymptomatic phase of

TABLE 2. Bioassay measurement of infectivity in different fractions (S^{LS}, S^{HS}, and P^{HS}) of 263K scrapie–infected brain

Replicate number	Fraction	Number of days (± SD) in incubation periods (number)	Estimated titer (log LD_{50}/mL of 10% brain suspension)	Difference (log) between S^{LS} and S^{HS}	Enrichment factor (infectivity/PrP^{27-30})
1	S^{LS}	55.8 ± 1.0 (8)	8.4	1.5	$\geq 10^{3.0}$
	S^{HS}	71.7 ± 2.3 (9)	6.9		
	P^{HS}	56.4 ± 2.7 (10)	8.3		
2*	S^{LS}	56.5 ± 2.0 (10)	8.3	1.7	$\geq 10^{2.3}$
	S^{HS}	75.0 ± 0.0 (9)	6.6		
	P^{HS}	59.1 ± 6.9 (10)	8.0		
3	S^{LS}	62.3 ± 0.7 (7)	7.7	2.3	$\geq 10^{2.7}$
	S^{HS}	87.9 ± 1.9 (7)	5.4		
	P^{HS}	Not done			
4†	S^{HS}	85.6 ± 4.2 (7)	6.6		
	P^{NaPTA}	87.7 ± 4.6 (7)	6.4		

* No sonication was performed in this replicate.
† Samples were 10-fold diluted respect to other replicates.

disease[1,2] and no tests are yet available for an early preclinical diagnosis[3,8] or for the screening of blood.[10,11] Thus, efforts are directed to implement procedures able to remove or inactivate TSE agents. Validation studies performed in the past years suggest that TSE agents can be removed by the processes used to manufacture plasma products. There is uncertainty, however, on the complete validity of these experiments mainly because it has been questioned whether the TSE agents in exogenous infectious materials used to spike human blood share the same physicochemical characteristics of the vCJD and other TSE agents in blood.[12,23] A comparison of different spiking preparations showed that brain homogenate, caveolae-like domains, and microsomes partition similarly, whereas purified PrP^{TSE} had significantly different partitioning properties.[23] Obviously, the best spiking material would be infectious human plasma,[24] but all attempts to transmit the disease with whole blood or buffy coat from human patients to experimental animals have so far failed.[25,26] The next best is to use blood from TSE-infected rodents. There is long-lasting evidence that blood of hamsters with experimental scrapie,[14,27] mice with experimental Gerstmann-Sträussler-Scheinker disease[20,28] or vCJD,[13] and sheep with natural scrapie[21] or experimental BSE[21,29] is infectious. Their blood contains too little infectivity to ensure the efficacy of removal procedures, making mandatory the use of exogenous spiking materials to perform reliable validation studies. Then, considering that removal may be influenced by the state of prion aggregation,[30] what is the most appropriate spiking material for the validation of the processes used for manufacturing plasma products? Brain homogenate may not be relevant because it contains large cell and membrane debris, high lipid content, and other brain molecules. Neither are highly purified PrP^{TSE} aggregates since they are not likely to be present in blood. Any attempt to measure PrP^{TSE} in blood or concentrates of blood components, such as buffy coats, has been frustrating, and claims of success have not been successively confirmed.[10] PrP^{TSE} in buffy coat of diseased 263K scrapie–infected hamsters is detectable after at least 144 cycles of protein misfolding cyclic amplification.[31] Theoretically, microsomal membrane fraction is a better spiking material,[12] although data from rodents infected with a mouse-adapted strain of human Gerstmann-Sträussler-Scheinker disease have shown that plasma is free of membranous structures,[32] that filtration or high-speed centrifugation does not eliminate infectivity from plasma,[42] and that in plasma of vCJD-infected mice, infectivity is reduced by PK treatment.[33] These data suggest that in plasma the infectious agent is very small, unsedimentable, and poorly aggregated.

In this scenario, the S^{IIS} fraction purified from 263K scrapie–infected hamster brains may be an appropriate spiking material for these studies. S^{IIS} fraction contains at least 10,000-fold the infectivity found in blood of TSE-infected rodents; it is virtually free from PrP^{TSE} aggregates, membranous fractions, and detergent contaminants, which interferes with the efficacy of TSE removal during the production of plasma derivatives.[12,34,35] The finding that in S^{IIS} fraction TSE infectivity is dissociated from PrP^{TSE} aggregates is not surprising, although the primary consequence of an infection with a TSE agent is the conformational change of the cellular PrP into a pathological conformer (PrP^{TSE}), rich in β-sheet structures, which tends to aggregate into amyloid fibers[36] and cosegregates with infectivity.[37] Exceptions to this rule, i.e., the presence of infectivity without the formation of PrP^{TSE} aggregates, have been reported,[38–42] and blood might simply be another condition where this divergence occurs. Likely, the infectivity in S^{IIS} is associated with dimer or small aggregates of PrP^{TSE} that remain in solution after ultracentrifuge, but precipitate in the presence of NaPTA and Mg^{2+}, which form complexes with PrP^{TSE} but not with cellular prion protein.[43]

It is therefore likely that an efficient removal of infectivity through nanofilters or depth filtrations[44–46] is achieved only when infectivity is associated to PrP^{TSE} in its aggregate form, but that these procedures may not be so effective when applied to naturally infected blood or plasma units. In conclusion, this study shows a simple and fast method for preparing a suitable spiking material to use in validation experiments aimed at proving removal or inactivation of prion infectivity in the preparation of blood components or pharmaceuticals derived from human plasma.

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医薬品　研究報告 調査報告書

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研究報告の概要	使用上の注意記載状況・その他参考事項等
変異型クロイツフェルト・ヤコブ病(vCJD)は、献血の際に血液で検査する方法が未だ実用化されていないため、例えば、欧州滞在歴のある方などvCJD伝播のリスクが否定できない方について、問診により献血制限を行う暫定的な措置が講じられている。 今般、ヒト胎盤エキス(プラセンタ)注射剤を使用した方の取扱いについても、以下の措置を講じることとなった。 (1) 同注射剤によるvCJD感染事例は報告されていないが、輸血や臓器移植と同様にヒト由来の臓器から製造されていることから、vCJD伝播の理論的なリスクが否定できないため、念のための措置として、その使用者について問診により献血を制限する。 (2) 日本赤十字社においては、1カ月後を目途に措置を実施する予定。	重要な基本的注意 現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的なvCJD等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

報告企業の意見	今後の対応
ヒト胎盤エキス(プラセンタ)注射剤 からのvCJD伝播の理論的なリスクが否定できないため、念のための措置の情報である。 現時点まで血漿分画製剤からのvCJD伝播の報告はない。	今後ともvCJDに関する安全性情報、規制情報等に留意していく。