Table 4 Product batches made by UK fractionators derived from plasma donated by individuals who later developed variant Creutzfeldt–Jakob disease[a,b]

Infectivity Classification[c]	Plasma product	Number of implicated batches
Low	Factor VIII (excipient[d])	77
	Albumin 20%	21
	i.m. immunoglobulin	12
Medium	Albumin 4-5%	28
	i.v. immunoglobulin	11
High	Factor VIII	16
	Factor IX	8
	Anti-thrombin	1
	TOTAL	174

[a]Twenty-three plasma donations from nine variant Creutzfeldt–Jakob disease donors, data courtesy of Health Protection Agency.
[b]Excludes fate of two plasma units from two further vCJD cases (see text for explanation).
[c]Risk categories as used in plasma product notification exercise.
[d]Albumin from implicated plasma donation used as excipient (inert substance added to provide bulk) in preparation of batch of Factor VIII.

Three recipients are not known to be dead from ONS flagging to date, and are therefore presumed to be alive. The mean age of these three recipients is 44 ± 20 years. The time elapsed since their transfusion ranges from 13 to 21 years. The fate of a further three recipients is not known. None of the fCJD recipients identified as having received blood from donors who went on to develop fCJD have appeared on the NCJDSU register to date.

vCJD cases with history of transfusion

Eleven vCJD cases were reported to have received past blood transfusions between 1962 and 1999. A further case received a blood transfusion after onset of illness. This case is excluded from further analysis. For two cases, hospital records showed that they had not been transfused. No hospital records could be found for another two cases reported to have been transfused in 1962 and 1971, respectively. Hospital transfusion records were found for seven vCJD cases (64% of those reported as transfused) who had been transfused with components donated by 125 donors (121 identified), with one vCJD case, who also received a solid organ transplant, receiving components from 103 donors. The identity of four donors who donated red cell/whole blood components to two cases (case 2 and case 7, see Table 5) is unknown. Table 5 shows the transfusion date, number of donors and blood components donated, and the interval from transfusion to onset of clinical symptoms of vCJD in these seven recipients. These cases had been exposed to between two and 103 donors, respectively (NB search for donors to case 6 is incomplete). To date, one donor who gave red cells to case 5 and another donor who gave red cells to case 6 are also registered on the NCJDSU database as vCJD cases. These are the donors of the two clinical cases of transfusion-transmitted vCJD referred to previously (see vCJD cases with history of donation).

sCJD cases with history of transfusion

Fifty-two cases of sCJD identified between 1980 and 2000 were reported to have received a blood transfusion, of which 28 received a transfusion after 1980. Transfusion records were found for seven sCJD cases transfused between 1984 and 1997. Donor details were found for 24 donors who donated components transfused to these seven sCJD cases. One of these donors is known to have died, with a cause of death not related to CJD. Twenty donors are not known to have died from ONS flagging to date, and are therefore presumed to be alive. The fate of a further three donors is not known. The mean age of the donors presumed still alive is 51 ± 9 years. None of the traced donors who gave blood to patients who were subsequently diagnosed with sCJD have appeared on the NCJDSU register to date.

fCJD cases with history of transfusion

One case of fCJD identified in 1992 was reported to have received three blood transfusions in 1965, 1970, and 1987 none of which could be traced.

Discussion

This study has identified three instances in which a recipient of a transfusion derived from a 'vCJD' donor has developed infection with vCJD, including two clinical cases and one pre- or subclinical infection [7–9]. These are three different donor/recipient pairs. In view of the small size of the total at-risk recipient population ($n = 66$) and the background mortality rate for vCJD in the general UK population (0·24/million/annum), these observations provide strong evidence that vCJD can be transmitted from person to person through blood transfusion. This finding has had important implications for public health policy nationally and internationally.

The risk of developing vCJD infection in the surviving recipient population is significant but cannot be precisely estimated because of variables including the timing of blood donation in relation to clinical onset in the donor, the influence of the codon 129 genotype of donor and recipient and the effect of the introduction of leucodepletion in 1999. Furthermore, the currently observed number of infections in the recipient population may be an underestimate as some surviving recipients may yet develop vCJD and there is limited available information on the outcome in the cohort of

Table 5 Donors (n = 125) of labile blood components given to variant Creutzfeldt–Jakob disease cases[a] (n = 7) with identifiable past hospital transfusion records

Case	Transfusion date	Number of donors of labile blood components transfused	Blood component donated to vCJD recipient	Interval from transfusion to onset of illness
1	1993	38	Cryoprecipitate (4) Fresh frozen plasma (11) Platelets (8) Red cells (14) Whole blood (1)	4 years, 9 months
1	1993	65	Cryoprecipitate (12) Fresh frozen plasma (25) Platelets (17) Red cells (11)	4 years, 6 months
2	1983	2[b]	Red cells	15 years, 11 months
2	1993	3	Fresh frozen plasma	6 years, 3 months
3	1994	4	Red blood cells	5 years, 4 months
4[c]	1999	5	Red blood cells (2) Red blood cells (Leucocyte-depleted) (3)	8 months
5[a]	1996	5[d]	Red blood cells	6 years, 6 months
6[a]	1997	1+[e]	Red blood cells	7 years, 10 months
7	1982	2[b]	Whole blood	13 years, 11 months

[a]Two of these cases linked to donors already on the National CJD Surveillance Unit (NCJDSU) register as vCJD cases [7,9].
[b]Component details traced, but donors not identifiable.
[c]Timing of clinical illness excludes blood transfusion as the source of infection in this case.
[d]One of the donors already on NCJDSU register as vCJD case, others presumed not to be source of infection.
[e]One donor already on NCJDSU register as vCJD case. Search for 40+ donors to Case 6 not complete, as of 1 March 2006.

deceased recipients; a significant proportion of these individuals may not have survived long enough to express clinical disease even if infected. The minimum incubation period in CJD transmitted from person to person by a peripheral route is 4·5 years in kuru and growth-hormone-related CJD [10,11] and only nine deceased recipients survived for longer than this period. An investigation of the hospital records of the deceased recipients is underway, and to date, none had clinical features of vCJD pre-mortem. However, the identification of the individual with 'preclinical' vCJD infection was dependent on post-mortem examination of peripheral lymphoreticular tissues, and, to date, no equivalent tissues have been available in the deceased transfusion recipients. Extrapolating from the three observed infections in the total recipient population is likely to lead to an underestimate of the overall risk of transfusion transmission of vCJD, although the introduction of leucodepletion in 1999 may have reduced the risk to recipients transfused after this date.

A further important variable in estimating individual risk is the time from blood donation to clinical onset in the donor and, although evidence from animal studies in relation to this issue is conflicting [12–14], it is likely that an extended gap between blood donation and clinical onset in the donor will reduce the risk of transfusion transmission. All tested clinical cases of vCJD have been methionine homozygotes at codon 129 of *PRNP*, but the individual with 'pre-clinical' transfusion transmitted infection was heterozygous at this locus [8], indicating that individuals with this genotype are susceptible to secondary infection with vCJD. Except for the three cases infected through blood transfusion, the codon 129 genotypes of the recipient population are not known. Although the relative risk of secondary infection in relation to the codon 129 genotype is uncertain, a recent study in a transgenic mouse model suggests that individuals with all human codon 129 genotypes may be susceptible to secondary infection with vCJD, with a hierarchy of risk from methionine homozygotes to heterozygotes to valine homozygotes [15]. Risk may vary according to genetic background, but it cannot be assumed that some recipients will possess an absolute genetic barrier to infection.

The analysis of vCJD cases with a history of blood transfusion has identified over 100 donors to these cases, although the great majority were linked to one vCJD case who had undergone an organ transplant. A risk assessment has suggested that these donors are themselves at significant risk of developing vCJD and these individuals have been informed of this risk and have been advized not to act as blood or organ donors. To date, none of these individuals have developed vCJD, with the exception of the two donors linked to the two clinical cases of vCJD described above.

Plasma derived from vCJD cases has been used in the production of plasma derived products, including clotting factors and immunoglobulin. To date, there is no evidence that vCJD has developed in a recipient of these products. However, the potential incubation period from a presumed low dose exposure by a peripheral route may be prolonged and current observational data cannot exclude the possibility of transmission of vCJD through plasma products. A risk assessment carried out in the UK suggested that, on worst case assumptions, some plasma products could be associated with an additional risk of developing vCJD in relation to the background population risk through exposure to BSE and since 1999 plasma for the production of plasma products has been imported to the UK from other countries. In contrast to labile blood components, plasma products are manufactured using a production process, some steps of which may reduce TSE infectivity [16]. Together with the estimated relatively low levels of initial infectivity in plasma used in fractionation, the risks from plasma products are probably much lower than the risks from transfusion of labile blood components.

An important question raised by the evidence of transfusion transmission of vCJD is whether other human TSEs may be transmissible through this mechanism. Cumulative evidence in sCJD over many years does not suggest that sCJD is transfusion transmitted [17]. Case-control studies have not demonstrated an increased risk of sCJD through a past history of blood transfusion [18–20] and lookback studies have not linked blood transfusions derived from sCJD blood donors to sCJD cases [21,22]. However, the case-control methodology may be compromised by control selection (some studies of CJD used hospital based controls) and this type of research cannot exclude rare transfusion transmission events. The lookback study of sCJD (and fCJD) from the TMER study provides only limited evidence, not least because of the difficulties in tracing blood donations made years or decades in the past, and there is only one study of sCJD equivalent to the TMER study of vCJD [22]. This has not provided evidence of transfusion transmission of sCJD, despite prolonged periods of follow-up in a proportion of cases. There is however a need to continue the study of blood transfusion and sCJD, and this will become of particular importance should highly sensitive tests for infectivity in blood be developed [23]. There is recent evidence of prion protein deposition in peripheral tissues in sCJD, including muscle [24]. However, the increased lymphoreticular involvement in vCJD in comparison to sCJD may be associated with an increased risk of transfusion transmission of vCJD.

The TMER study has provided compelling evidence that vCJD is transmissible through blood transfusion, representing the first evidence of transmission of human TSEs through this route and via material sourced from a peripheral tissue rather than the high level infectivity tissues of the central nervous system. The manifest implications for public health of transmission transfusion of vCJD have led to measures to minimize the risk from blood transfusion [25] and plasma products derived from cases incubating vCJD and many of these actions were taken years in advance of the evidence for transfusion transmission, both in the UK and many other countries. Although there is uncertainty about the potential for transfusion transmission of vCJD to lead to a self-sustaining epidemic, the introduction of a policy of deferring transfusion recipients as blood donors in the UK has minimized this possibility. Other actions to reduce the risk, such as the introduction of filtration devices, are under consideration in the UK, but the identification of vCJD cases with a history of blood donation in France, Ireland, Spain and Saudi Arabia indicates that this issue has an international dimension. One determinant of the risk is the population prevalence of vCJD infection, which is almost certainly highest in the UK, but the identification of secondary transmission of vCJD underlines the importance of international surveillance systems both for human and animal prion diseases.

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医薬品
医薬部外品　研究報告　調査報告書
化粧品

識別番号・報告回数		回	報告日 年　月　日	第一報入手日 2007 年 3 月 2 日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称			研究報告の公表状況	Variability of parvovirus B19 to inactivation by liquid heating in plasma products Hattori, S. et al., Vox Sanguinis, 92, 121-124 (2007)	公表国 日本	
販売名（企業名）						

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
過去の研究から，ヒトパルボウイルス B19 は液体-熱不活化に対して，溶液の組成に大きく依存する複雑な感受性を示すことが明らかとなっている。また，これらの研究では，ヒトパルボウイルス B19 のモデルとして一般的に用いられる動物パルボウイルスは必ずしも適切ではないという事実を強調している。本稿では液体-熱処理時の，ハプトグロビン中及び抗トロンビン製剤中のヒトパルボウイルス B19 の感受性を明らかにしている。60℃にてさまざまな培養時間で培養後，各試料中に残存する感染性を，細胞ベースアッセイによって測定した。その結果，ハプトグロビン溶液中で緩徐ではあるが実質的（最大では完全）な不活化が可能であったが，一方，抗トロンビン溶液中では限定的な不活化しか確認できなかった。しかしながら，この結果は，多くのパラメータ（pH 値，クエン酸塩濃度及び塩化ナトリウム，ならびにそれぞれの溶液で用いられる安定剤）がヒトパルボウイルス B19 の熱感受性に影響することを考慮すると単純なものではないと考えられる。したがって，著者らはそれぞれの実験条件の下，慎重に評価することを提言している。	BYL-2007-0277

報告企業の意見	今後の対応
弊社の血漿分画製剤に使用されるミニプール血漿においては，ヒトパルボウイルス B19 に対する NAT を実施しており，10E5 IU/mL 以上が確認された場合は，そのミニプール血漿は製造工程から除去している。現在の科学水準では，ヒトパルボウイルス B19 を確実に不活化する方法は存在しないため，感染リスクを完全に排除することはできないと考える。	今回，得られた情報は感染リスクの変化を示唆するものではないことから，現時点で新たな安全対策上の措置を講じる必要はないと考える。引き続き情報収集に努める。

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ORIGINAL PAPER

Variability of parvovirus B19 to inactivation by liquid heating in plasma products

S. Hattori,[1] M. Yunoki,[1,2] M. Tsujikawa,[1] T. Urayama,[1,2] Y. Tachibana,[1] I. Yamamoto,[1] S. Yamamoto[1] & K. Ikuta[2]

[1]*Infectious Pathogen Research Group, Hirakata Research Laboratory, Research & Development Division, Benesis Corporation, 2-25-1 Shodai-Ohtani, Hirakata, Osaka 573-1153, Japan*

[2]*Department of Virology, Research Institute for Microbial Diseases, Osaka University, 3-1 Yamadaoka, Suita, Osaka 565-0871, Japan*

Vox Sanguinis

Background and Objectives Previously, we reported that although human parvovirus B19 in albumin and intravenous immunoglobulin preparations was rapidly inactivated during liquid heating, in contrast to other parvoviruses such as canine parvovirus, sensitivity to heat was highly dependent on the composition of the solution. In this study, we aimed to further elucidate the sensitivity to heat of B19 in haptoglobin and antithrombin (previously named antithrombin III) preparations during liquid heating.

Materials and Methods Two different solutions collected immediately before heat treatment of haptoglobin and antithrombin preparations were spiked with B19 and subsequently treated at 60 °C for 10 h. B19 DNA-positive, anti-B19 IgG/IgM-negative plasma was used as a source of B19. The residual infectivity in each sample was measured using a B19 cell-based infectivity assay with an mRNA polymerase chain reaction.

Results B19 in different plasma preparations showed different heat-sensitivity patterns during liquid heating: (i) slow inactivation in haptoglobin preparations, and (ii) only limited inactivation in antithrombin preparations. The kinetics of inactivation was greatly different from that in our previous studies in which the virus was shown to be rapidly inactivated in albumin and intravenous immunoglobulin preparations.

Conclusion B19 has unique properties in terms of heat sensitivity, depending on the composition of the solution during liquid heating. This finding may indicate the need for caution when interpreting the sensitivity of B19 to heat.

Key words: heat sensitivity, parvovirus B19, plasma products, viral inactivation, viral safety.

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Introduction

Human parvovirus B19 (B19) is not highly pathogenic to healthy individuals; however, this virus does present a certain level of risk, because it may cause serious pathological conditions in pregnant women and immunosuppressed individuals. As B19 has no envelope, it is resistant to detergent or organic solvent treatments. In addition, B19 is a small virus (18–26 nm in diameter), which means that it is not easy to eliminate by filtration. Liquid-heat treatment, i.e. pasteurization, considered a highly reliable method of inactivating viruses, has been introduced into the manufacturing process for the production of various plasma derivatives. Investigations using model animal parvoviruses suggested that viruses like B19 are heat resistant, indicating that the potential for inactivation of this virus in plasma products may be limited [1]. In addition, the European Agency for the Evaluation of Medical Products and Japanese Ministry of Health, Labor and Welfare have issued guidance for risk evaluation of non-enveloped viruses in plasma products [2,3].

Interestingly, recent reports have shown that under liquid-heating conditions in albumin preparations and heat-treated/

Correspondence: Mikihiro Yunoki, PhD, Infectious Pathogen Research Group, Hirakata Research Laboratory, Research & Development Division, Benesis Corporation, 2-25-1, Shodai-Ohtani, Hirakata, Osaka 573-1153, Japan
E-mail: yunoki.mikihiro@mk.m-pharma.co.jp

PEG-treated intravenous immunoglobulin (IVIG) preparations, B19, unlike other animal parvoviruses such as canine parvovirus (CPV) and porcine parvovirus (PPV), was highly heat sensitive and was rapidly inactivated [4–6]. Unexpectedly, however, during heat treatment, the B19 in a sucrose solution was not inactivated rapidly [5]. In addition, B19 was also resistant to inactivation by dry heating [5]. Therefore, in this study, we aimed to elucidate further the sensitivity to heat of B19 in haptoglobin and antithrombin (previously named antithrombin III) preparations by liquid heating.

Materials and methods

Test materials

Plasma collected according to the regulation in the USA, and negative for anti-human immunodeficiency virus (HIV) 1/2 IgG, hepatitis B virus (HBV) surface antigen, anti-hepatitis C virus (HCV) IgG, and negative for HIV RNA, HBV DNA and HCV RNA additionally, but positive for B19 DNA (negative for anti-B19 IgG), was used (Plasma ID: P4). This plasma sample was the same as the one used previously for an evaluation of heat sensitivity in albumin and IVIG preparations [5,6]. Two different solutions collected immediately before heat treatment of haptoglobin and antithrombin preparations were used (Haptoglobin Injection-Yoshitomi and Neuart®, respectively; Benesis Corporation, Osaka, Japan).

B19 infectivity assay

The infectivity of B19 in the samples was titrated using KU812 cells (JCRB0104; Health Science Research Resources Bank, Tokyo, Japan) and subsequently viral mRNA in positive wells was detected with reverse transcriptase–polymerase chain reaction (RT-PCR) systems. Briefly, the KU812 cells were inoculated with 10-fold serial dilutions of B19 and cultured in RPMI-1640 medium containing 10% fetal bovine serum, 6 IU/ml erythropoietin (Sankyo Co., Ltd, Tokyo, Japan), 100 U/ml penicillin, 100 μg/ml streptomycin (Invitrogen Corp., Carlsbad, USA), 1 mM sodium pyruvate (Invitrogen Corp.), and an ITS-X supplement (Invitrogen Corp.) for 4 days [5]. Wells were monitored for the presence or absence of viral mRNA, and the viral titre remaining after heat treatment was calculated according to the Kärber method [7]. We used two different PCR systems. For the experiment using haptoglobin preparations, RNA was extracted and viral mRNA was amplified as described previously [5]. For the experiment using antithrombin preparations, total RNA was extracted from the infected cells (ABI PRISM 6100 system; Applied Biosystems, Foster City, CA, USA) and employed for amplification of the B19 VP2 exon region with the sense primer B19-21 5′-TGGCAGACCAG-TTTCGTGAA-3′ (nt 2162–2181), antisense primer B19-22 5′-CCGGCAAACTTCCTTGAAAA-3′ (nt 3086–3067) and probe B19-F23 5′-FAM-CAGCTGCCCCTGTGGCCC-3′ (nt 3048–3065), using a TaqMan One-step RT-PCR Master Mix Reagents Kit and ABI 7500 Real-Time PCR system (Applied Biosystems) [8]. These primers and the probe were optimized for the ABI system based on previous designs.

Porcine parvovirus infectivity assay

ST cells (porcine testis cell line; ATCC CRL-1746) were inoculated with 10-fold serial dilutions of the NADL-2 strain of PPV (ATCC VR-742) and cultured in minimum essential medium supplemented with 10% fetal calf serum for 10 days. Wells were monitored for the presence or absence of viral cytopathic effects, and the viral titre remaining after heat treatment was calculated according to the Kärber method [7].

Heat treatment of B19 and porcine parvovirus

Heat treatment of B19/PPV was performed as described previously [5]. Briefly, the B19-positive plasma sample was diluted with 10 volumes of PBS. The diluted B19-positive plasma was precipitated by ultracentrifugation at 150 000 *g* for 3 h and the resulting particulate fraction was resuspended in 2 volumes using the intermediate product. The samples containing B19 were then aliquotted and incubated in a water bath at 60 °C, or 37 °C for the control, for preset periods of time. After immediate cooling, the remaining infectivity titre of B19 was measured as described above. PPV experiments were also performed in the same way.

Results

To evaluate the ability of heat treatment to inactivate B19 in the product's intermediate, the virus was inoculated into two different samples. After being heated at 60 °C for 10 h, the samples for kinetic experiments on the heat inactivation of B19 were taken at preset time points. The B19 was inactivated by 6·3 logs and 2·1 logs after 10 h by liquid heating of haptoglobin and antithrombin preparations, respectively, whereas PPV was inactivated by 3·2 logs and 2·1 logs, respectively. No inactivation of B19 was observed on heating at 37 °C for 10 h in the control (data not shown). The kinetics of inactivation in the haptoglobin preparations differed between B19 and PPV, i.e. the infectivity of B19 was reduced near detection limit at 5 h, whereas the infectivity of PPV remained even at 10 h (Fig. 1). On the other hand, the kinetics of inactivation in the antithrombin preparations was comparable and the levels of infectivity remaining even after inactivation for 10 h were similar (Fig. 1).

Discussion

We previously reported that B19 was inactivated rapidly in albumin and IVIG preparations during liquid heating at

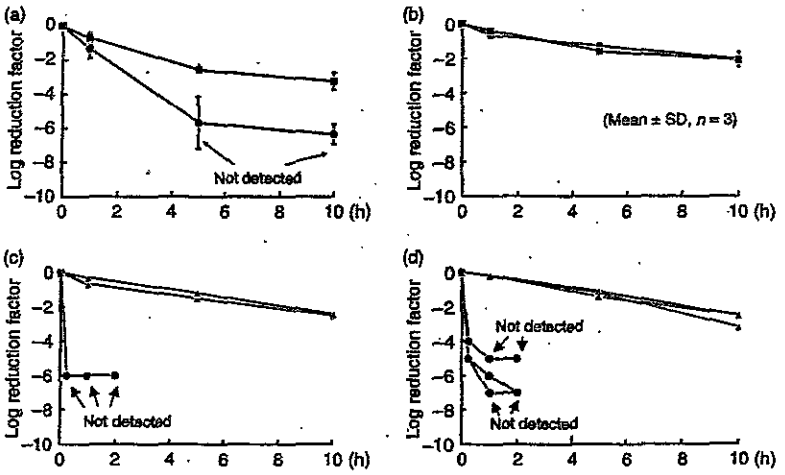

Fig. 1 Heat inactivation kinetics of parvovirus B19 in several plasma products. B19 was introduced into plasma samples, that were collected immediately before heat treatment of haptoglobin (a) and antithrombin (b) preparations. The samples containing B19 were then aliquotted and incubated in a water bath at 60 °C, or 37 °C for the control, for preset periods of time (0, 1, 5, and 10 h). The infectivity of B19 remaining after heating (●) was measured. In the haptoglobin preparations, no infectivity was detected in two of three independent experiments after 5 and 10 h of heat treatment. Porcine parvovirus (■) was also evaluated for comparison. The inactivation kinetics of B19 and CPV (▲) in albumin and intravenous immunoglobulin preparations are shown in (c) and (d), respectively. The results in (c) and (d) are derived from references [5,6], respectively, with minor modifications.

60 °C, whereas B19 in a sucrose solution was not inactivated quickly [5]. In the present study, we found that the heat sensitivity of B19 in haptoglobin as well as antithrombin preparations during liquid heating at 60 °C was substantially different from previous results determined under equivalent heating conditions with albumin and IVIG preparations. Thus, B19 showed different inactivation kinetics during liquid heating, depending on the product: (i) rapid inactivation within a few hours; (ii) slow inactivation that takes 10 h; and (iii) little inactivation even after heating for 10 h (i.e. comparable with the inactivation kinetics obtained with CPV or PPV as a model virus). Liquid heating of these samples was performed with the stabilizers used in the preparation of the products. Such stabilizers had been selected based on their abilities to stabilize plasma proteins and to inactivate viruses. In this study, we used a haptoglobin preparation containing glycine and an antithrombin (AT) preparation containing sodium chloride/trisodium citrate dihydrate, as stabilizers, as described in the Materials and methods. On the other hand, liquid heating for the albumin and IVIG preparations reported in our previous papers was performed with sodium caprylic acid/acetyl tryptophan and D-sorbitol, respectively, as stabilizers. Thus, we could not identify which component of the stabilizers for the haptoglobin and antithrombin preparations plays a role in the reduction in B19's heat sensitivity, because there is no component included in the stabilizers for these preparations but not in those for the albumin and IVIG preparations. Concentration of citrate during heat treatment was generally 0·5–1·0 M [9]. Our manufacturing condition was located in this range. However, our preliminary experiments suggest that the B19 heat sensitivity was influenced by several constituents such as concentration of citrate, sodium, chloride, and pH, during AT heat treatment (data not shown). This finding suggests that the parameter of B19 stabilizing during heat treatment is not so simple and it seems to be complex. Thus, B19 heat sensitivity during heat treatment should be evaluated in each process conditions avoiding an over estimation for the B19 inactivation. We are now trying to identify the components of the stabilizers that contribute to the decrease in the sensitivity of B19 to heat.

Umemori *et al.* [10] presented that even after heat treatment at 60 °C for 10 h, a B19-containing albumin preparation remained infective as assayed using Niigata embryonal carcinoma (NEC) and KU812 cells. However, comparable results, i.e. inactivation to near the limits of detection [10], or below the limit of detection in our previous study [5], were also obtained in the present study. This slight difference may be derived from the use of a cold spot using heat-block system [10] vs. complete sinking into a water bath [5,6]. The sensitivity of B19 to heat was also shown to be influenced by the residual moisture in the sample preparations during dry heating [5,11]. These findings strongly suggest that the sensitivity of B19 is highly dependent on the conditions during heating. Therefore, it is necessary to design a study for the evaluation of safety with respect to contamination by and/or elimination of B19 during the manufacturing process, especially when heating steps are investigated.

Canine parvovirus or PPV has been used at many facilities as a model for B19. We confirmed that these two viruses are useful for modelling B19 as they are more resistant to liquid heating than B19. Similarly, Prikhod'ko [12] also proposed that PPV is a useful model for B19 in dry heating. However, attention should be given to the sensitivity of B19 to heat which could be affected by the stabilizer used, as found in this study. We do not know the mechanism behind the clear difference in sensitivity to heat between B19 and other

parvoviruses. One explanation is a possible difference in the structure of VP2 because of a partial deletion in the gene for this protein in B19 [13,14]. Further studies are required to understand the mechanism behind this phenomenon, and ensure the safety of blood derivatives.

Generally, measures against viral contamination (e.g. from HIV, HBV, HCV, and B19, etc.) consist of donor screening, viral elimination during processing, nucleic acid amplification tests of final products, and postmarketing surveillance. In our antithrombin preparation, treatments with heat and the Planova 15N filter (15 ± 2 nm; Asahi Kasei Medical Co. Ltd., Tokyo, Japan) were introduced to inactivate/remove the virus, in addition to some other forms of purification which also contribute to viral inactivation/removal [15]. Importantly, a French group reported a case in which B19 was possibly transmitted from an antithrobmin preparation produced by another manufacturer [16]. Although there had been no report of transmission from our antithrombin preparation even before we introduced the use of donor screening and the Planova 15N filter, the data obtained in this study suggest the significance of the stabilizers used for individual products as well as the significance of other steps to eliminate the remaining virus, such as the use of a Planova 15N filter.

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研究報告の概要

輸血と関係した新たなvCJD疾患(4例目)が、最近診断された。
この最も新しい患者は、後にvCJDを発症したドナーからの輸血を受けた後、約9年経ってvCJDと診断された。同じドナーからの輸血は、以前に確認された1症例とも関連があった。この患者は未だ生存中であり、専門家の治療を受けている。輸血と関係したこの4番目のvCJD感染症例により、輸血を介したヒトの間におけるvCJD感染リスクが高まっている。4症例は全て、成分輸血に関係したものであり、血漿分画製剤による治療に関連した症例は今まで報告されていない。
患者は、後にvCJDを発生したドナーから、英国で輸血を受けたことが知られている少人数（30人未満）の生存者の内の1人である。これらの全ての人は、すでにvCJDの潜在的な曝露を知らされており、ヘルスケア手法（例えば外科）によってvCJDを他の人々に伝播する機会を減らすための特定の措置をとるよう要請された。Health Protection Agency（HPA）は、後にvCJDを発症したドナーから輸血の曝露を受けた患者のケアを行なっている医師と連絡を取っている。これは、彼らはこの新しい事態を知らされ、最新の情報と輸血によるリスクについての専門家の助言を受けることができるよう保証することを目的としている。
HPA感染症センターの部長であるPeter Borriello教授は、「vCJDのこの新しい症例は、ドネーションの時にはvCJDに感染していたことに気付いていなかったに違いないドナーから輸血を受けた小人数のグループに対するリスクについて、我々の懸念を増大させる。しかし、この新しい症例は、如何なる方法によっても、他の人々のリスクについての我々の理解を変えることはない。それどころか、それは血液によるvCJD感染の伝播リスクを減らすために既にとられている予防措置の重要性を、更に強いものにしている。」と述べた。
NHS血液及び移植部の医学部長であるAngela Robinson博士は、「輸血は、しばしば重篤な患者の、生命を救い又は延命するために行われ、必要時に受ける輸血の利点は、常にリスクに対するバランスが図られなければならない。それにもかかわらず、我々の主な関心は、治療のために使用された血液の品質を維持することを通しての我々の患者の安全性である。」と述べた。
vCJDは、稀な疾患であり、今日まで英国で報告されたvCJD症例の2%未満が、輸血と関係していた。

使用上の注意記載状況・その他参考事項等

代表として献血ヴェノグロブリン-IH ヨシトミの記載を示す。
2. 重要な基本的注意
(1)略
1)略
2)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
第4例目のvCJDの輸血感染が確認されたとの報告である。 これまで血漿分画製剤によってvCJD、スクレイピー及びCWDを含むプリオン病が伝播したとの報告はない。しかしながら、万一vCJD感染者の血漿が本剤の原料に混入した場合には、製造工程においてプリオンを低減し得るとの報告があるものの、製剤から伝播する可能性を完全には否定し得ない。そのため、弊社の血漿分画製剤の製造工程におけるTSE感染性低減に関する検証実験を加速し、自社データを早期に取得し、工程評価を行い、必要に応じて工程改善を実施する予定である。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。