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**研究報告の概要**

フランスでのヤギの BSE 確認が、小反芻動物が飼料を介した経時的な曝露により BSE を維持するのかという議論をヨーロッパで活発化させている。TSE フリーの生後 6 ヵ月の雌の子ヒツジ 30 匹に BSE 汚染ウシ脳が経口投与された。約 6 ヵ月後に BSE 投与のヒツジの群れの中に同様の BSE 非投与の子ヒツジ 20 匹が加えられ、TSE フリー飼料を用いて自然に成熟するまで同じグループとして厳格に飼育された。最初に投与された 30 匹中 24 匹が 655～1,056 日の間に BSE に感染し、これらの雌ヒツジから産まれた 2 匹も BSE で生後 73 日目、親ヒツジへの投与から数えて 655 日後に死亡した。このことから実験的なヒツジの群れの間での BSE 汚染飼料による BSE 伝播及びヒツジの子宮又は分娩による BSE 伝播が確認された。なお、後に加えられた 20 頭については現在まで（群れに入れてから 3 年間）感染は認められていないが、水平感染はないと結論するのは時期尚早である。

**使用上の注意記載状況・その他参考事項等**

現在販売していないため、添付文書を作成していない。

| 報告企業の意見 | 今後の対応 |
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| ヒツジを用いた実験の結果、BSE垂直感染が示唆された報告である。<br>本剤はヒトフィブリノゲン、ヒトトロンビン、塩化カルシウム及びウシアプロチニンを主成分とする生理的組織接着剤であるが、このうちウシアプロチニンはウシ肺から製造される。2003年12月、米国のウシにBSEが発生した際に、「ウシ等由来原材料を使用した医薬品、医療用具等の一部変更承認申請等におけるリスク評価等の取り扱いについて」（平成15年8月1日付薬食審第0801001号、薬食安第0801001号）の別添「カナダでのBSE発生の確認を踏まえた医薬品等のBSEリスク評価の考え方について」（平成15年7月8日付 伝達性海綿状脳症調査会資料）に基づき、アプロチニン液（ウシ肺由来）のリスク評価を行った結果、一定の安全性は確保されていると評価した。 | 本製品は、発売する予定はなく、承認整理する方針である。 |

# Natural transmission of BSE between sheep within an experimental flock

SIR, – The recognition of bovine spongiform encephalopathy (BSE) in a French goat (Eloit and others 2005) has heightened the debate in Europe as to whether BSE has been maintained in small ruminants following historical exposure via feed. Key to the debate and associated risk assessments, especially in the UK, is whether BSE can transmit naturally between infected sheep. Here, we report preliminary evidence that natural transmission can take place between sheep in an experimental flock.

Thirty six-month-old ewe lambs of the PrP ARQ/ARQ genotype from transmissible spongiform encephalopathy (TSE)-free sources were dosed orally with 5 g of BSE cattle brain inoculum. This genotype has previously been shown to be fully susceptible to this inoculum. Approximately six months after infection, the BSE-dosed sheep were mixed with 20 matched undosed animals of the same age and genotype, and kept as a single group under strict biosecurity. Normal intensive commercial practices were followed as far as possible, while avoiding iatrogenic spread of infection.

The ewes were bred from 18 months of age by natural mating using breed/genotype-matched sires from the same TSE-free flocks that had been introduced to the unit. Placental cotyledons were collected at birth. All sheep had unrestricted access to the lambing area to maximise the potential for transmission of disease. Clinical observation, weight recording and tonsil and third eyelid biopsies were used to monitor disease progression. At clinical end point, the sheep were euthanased and examined postmortem, and tissues were collected for a range of immunohistochemical (IHC) and biochemical tests.

Twenty-four of the original 30 dosed sheep reached clinical end point between 655 and 1056 days postinfection (dpi), with a mean (sd) incubation of 797 (105) dpi. Two of the lambs born in 2003 also died of BSE. The first clinical disease in the flock occurred in a dosed ewe, the dam of lamb 2, just 73 days after the birth of its lamb, with clinical end point at 655 days after dosing. The dam of lamb 1 reached clinical end point 198 days after its birth. The first positive tonsil biopsies occurred in these dosed ewes at 369 dpi and in lambs 1 and 2 at 546 days of age. IHC examination of tissues from lambs 1 and 2 using monoclonal antibodies R145 and P4 showed the typical reduction in intracellular labelling with P4 in the obex previously associated with BSE (Fig 1). Lymphoid tissues also showed the typical BSE-associated pattern of reduced labelling of tingible body macrophages with the P4 antibody (Fig 2).

**FIG 1: Vagus nucleus in the obex of lamb 1 stained with P4, showing abundant extracellular labelling with very little or no labelling of neurons or microglia. x 230**

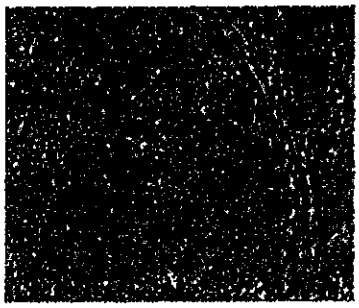

**FIG 2: Secondary follicle in the tonsil of lamb 1 stained with P4, showing immunolabelling of follicular dendritic cells within the light zone but no labelling of tingible body macrophages within the dark or light zones. x 230**

To date (June 2005), 22 lambs from the 2003 lamb crop born to both dosed and undosed ewes remain alive at 781 to 786 days of age and there are no clinical cases in the original undosed ewes three years after their introduction.

Although scrapie is known to transmit between sheep under natural and experimental conditions, there have been no previous reports of BSE being transmitted naturally between sheep. Foster and others (2004) failed to demonstrate transmission, but this may be explained by lower infection pressures in their experimental design and the use of less susceptible genotypes. At this stage in our study, it is impossible to determine whether infection was acquired from the dam in utero or during the perinatal period, but the incubation period of the affected lambs suggests infection occurred at or just before birth. Previous studies in experimentally infected sheep of the same genotype resulted in incubation periods of 628 to 1132 dpi in animals dosed orally with 5 g of the same inoculum at six months of age (Bellworthy and others 2005) and 525 to 723 dpi in lambs dosed orally with 1 g of the inoculum at two weeks of age (S. J. Bellworthy, unpublished data). The incubation period in the lambs in the present study would preclude the extremely unlikely potential of iatrogenic infection associated with tonsil biopsy. The absence of disease in unrelated, but susceptible, lambs introduced both before and after the first lambing period suggests that transmission may have been restricted to mother and lamb, rather than also horizontally, but it would be premature to conclude at this stage of the study that horizontal transmission had not occurred. Age and closeness of contact may play critical roles in determining likelihood of transmission, although in studies with scrapie we have demonstrated that adult sheep do become infected following introduction to an infected flock, albeit with longer incubation periods than lambs. Horizontal or vertical transmission is clearly a major factor in the spread of scrapie, and transmission may even occur in the absence of direct sheep-to-sheep contact. It remains to be seen whether this is confirmed also with BSE in sheep.

This is the first confirmation that BSE can transmit either in utero or perinatally in sheep. It indicates that if BSE had entered the sheep population at the start of the BSE epidemic, it could have propagated within the flock if the level of infection was sufficient in the presence of susceptible sheep. However, an extensive survey of the UK flock has shown no evidence of the classic BSE phenotype (Stack and others 2005).

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