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SCIENTIFIC COMMITTEE ON MEDICINAL PRODUCTS AND MEDICAL DEVICES

Opinion
On
Update of the Opinion given by the Scientific Committee on Medicinal Products and Medical Devices on The Risk Quantification For CJD Transmission Via Substances of Human Origin

Adopted by
The Scientific Committee on Medicinal Products and Medical Devices
On 16 February 2000

In October 1998 the SCMPMD issued an "Opinion on the Risk Quantification for CJD Transmission via Substances of Human Origin". It concluded that there is no epidemiological evidence to indicate the transmission of the classical forms of CJD (sporadic, familial, iatrogenic) by blood and blood products. As the experience with variant CJD (vCJD[1]) is limited a similar statement could not be made for vCJD.

The SCMPMD also discussed measures which could be assumed to reduce the risk of transmission by blood and blood products if a risk exists at all (possibly for vCJD). Consideration was given to donor deferral, leukodepletion and recall of plasma products. While the SCMPMD endorsed the CPMP recommendation to withdraw plasma derived products only if a donor to a plasma pool is subsequently strongly suspected of having vCJD, the effect of leukodepletion in reducing the theoretical risk of vCJD transmission was viewed with caution. With respect to donor suitability, the SCMPMD supported the exclusion criteria listed in the Council Recommendation 98/463/EC on the suitability of blood and plasma donors and the screening of donated blood in the European Community (O.J. L203 21.07.98, p. 14) and did not propose additional criteria. It recommended the deferral of donors with a positive result from a validated test for TSE infectivity, if such a test became available.

During 1999 three important pieces of information became known:

1. In February 1999, a report entitled "Assessment of the Risk of Exposure to vCJD Infectivity in Blood and Blood Products" was finalised by Det Norske Veritas Limited (DNV) which performed this study for the UK Spongiform Encephalopathy Advisory Committee (SEAC) and the UK Department of Health (DoH). It concluded with a discussion of possible measures which could have an effect in reducing the theoretical risk of vCJD transmission. Two measures were considered to have significant potential benefit (quoted from the DNV report):

   "**Leucodepletion**. Leucodepletion appears to have significant benefit in reducing risk of vCJD infection through blood transfusion, although the degree of benefit is extremely uncertain. Since there are some scenarios where leucodepletion has significant benefit, and considerable uncertainty about those scenarios where it does not have benefit, it would be prudent to adopt leucodepletion as a risk reduction measure."

   "**Elimination of UK Plasma Products.** Eliminating UK plasma products will clearly eliminate any risk there may have been from infectivity in these products, assuming there is no vCJD in the source country. However, the degree of benefit is highly sensitive to several uncertain assumptions. The uncertainty here is not in how effective the measure would be, but the magnitude of the risk from vCJD in plasma products that it is mitigating. Since there are some scenarios where the risk is significant, the UK plasma product ban could be considered prudent in the absence of better information."

[1] In the SCMPMD Opinion of October 1999 as well as in a wealth of literature the term "new variant CJD" (abbreviated nvCJD) is used. However, there is now increasing agreement to call this disease "variant CJD" (abbreviated vCJD). Therefore, in this text the term "variant CJD" (vCJD) is used unless "new variant CJD" (nvCJD) is contained in a quotation. It should be always borne in mind that the terms "variant CJD" (vCJD) and "new variant CJD" (nvCJD) refer to the same disease.

2. On March 22 and 23, 1999, the World Health Organization convened a "Consultation on Diagnostic Procedures for Transmissible Spongiform Encephalopathies: Need for Reference Reagents and Reference Panels". During this meeting, a new test method was presented, claiming to be able to detect prion protein in the blood of infected animals. This test stimulated great interest, particularly regarding the question as to whether or not it could be used for the screening of blood donors.

3. On August 17, 1999, Health Canada requested with Directives D99-01 and D99-02 (http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/btox.html) of August 17, 1999, to exclude "from donating blood all persons who have spent time in England, Scotland, Wales, Northern Ireland, Isle of Man and the Channel Islands amounting cumulatively to a period of 6 months or more between the years 1980 and 1996, inclusive". The exclusion should be introduced as soon as operationally feasible, but not later than six months from the date of these Directives.

   In a concerted action, the US Food and Drug Administration (FDA) issued, also on August 17, 1999, a guidance document (http://www.fda.gov/cber/guidelines.htm) entitled, "Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Creutzfeldt-Jakob Disease (nvCJD) by Blood and Blood Products". In this document, the current list of donor deferral criteria has been extended. As a new measure, "FDA recommends that donors who have spent six months or more cumulatively in the United Kingdom from 1980 through 1996 (i.e., from January 1, 1980 through December 31, 1996) be indefinitely deferred". The new guidance was to be immediately implemented. FDA interprets immediate implementation to mean as soon as feasible, but not later than April 17, 2000.
   In the meantime, a number of other countries, notably Japan and New Zealand, have also introduced this new exclusion criterion.

The SCMPMD feels obliged to consider the new information and to consider amending its Opinion of October 1998 with respect to the following three issues: 1. Leukodepletion; 2. Screening assays; 3. Exclusion of donors at risk for infection by ruminant derived material.

1. Leukodepletion

As extensively summarised in the SCMPMD Opinion of October 1998, TSE infectivity is predominantly associated with the buffy coat, i.e. with the white cell compartment of the blood, in most animal systems where it is found in peripheral blood. This conclusion has been confirmed by a recent study in mice infected intracerebrally with the Fukuoka-1 strain of human TSE (Brown et al. 1999). The same study showed that with the onset of clinical signs the titre of infectivity increased sharply. Concomitantly, infectivity was also found in the plasma. This infectivity was only marginally removed by high speed centrifugation. The conclusion was that this remaining infectivity was not associated with cells or particles.

It is not known which type of leukocytes (lymphocytes, granulocytes, monocytes and others) harbour TSE infectivity. A study in 1997 (Klein et al.) was understood by

some to show that B-lymphocytes may be the carrier of TSE infectivity. Later, it was demonstrated that the role of B-lymphocytes is to contribute to the maturation of follicular dendritic cells (Klein et al. 1998, Brown et al. 1999), and not as a carrier of infectivity (within the limit of sensitivity of the infectivity tests, Raeber et al. 1999). There is now general agreement that the follicular dendritic cells which are stationary cells in lymphatic tissues like lymph nodes and spleen play a crucial role for TSE replication in those tissues.

In preparations of blood components white blood cells are usually unwanted contaminants which can cause a number of adverse reactions (febrile non-haemolytic reactions, alloimmunisation and others, for review see Klein et al. 1998). Therefore, for a number of years different techniques have been used in order to remove leukocytes from red cell and platelet concentrates, e.g. the removal of buffy coat (for red cell preparations) or the use of filters. These filters consist either of microporous polyurethane sheets or of synthetic fibres. While the mechanism of removal by microporous membranes is simply a mechanical sieving effect trapping the cells in small holes, the effect of fibrous filters depends on the adhesion of the cells to the fibres (so called depth filtration). The type of the forces which mediate adhesion (ionic, non-ionic, or receptor mediated) is not known (Callaerts et al. 1993). The use of such filters does not remove completely white blood cells but reduces their number by a factor up to 10^4, therefore, the widely used term "leukodepletion" is not accurately reflecting the real effect. The effectivity of at least some filter types differs for different cell types (Mogi et al. 1993).

Whether such filters, by removing white blood cells, also remove TSE infectivity is assumed, but has not been experimentally shown. The only study, known to the SCMPMD, which examines the effect of leukofiltration on TSE infectivity was recently published by Brown et al. (1999). Leukofiltration was used in an attempt to remove TSE infectivity from plasma which is more or less devoid of white blood cells. There was not a significant reduction in infectivity and, in one of three experiments, infectivity was significantly increased. However, leukofiltration can routinely be applied to whole blood before separation of the plasma, which might prevent shedding of prions from cells into the plasma. However, the design of these experiments does not reflect the intended use of leukodepletion which will be applied to whole blood before separation of plasma. It is expected that in such a situation leukocytes are removed before they may shed prion into the plasma or break down into debris. The hypothesis that leukofiltration causes a destruction of leukocytes, thereby probably enhancing TSE infectivity, is neither proven nor disproved. It is also not known whether different filters have differing effects on the removal of TSE infectivity and it is not known whether infectivity would be sufficiently reduced to render a presumptively infectious blood unit non-infectious.

So far, the available scientific data is ambivalent. In contrast to the classical forms of CJD, infectivity may be present in peripheral blood of vCJD cases (as extrapolated from models of small laboratory animals with a peripheral distribution of the pathological form of the prion protein similar to that in vCJD patients) and this infectivity may be predominantly associated with white blood cells (again inferred from models of small laboratory animals). Therefore, it might be of benefit to remove white blood cells as completely as possible in order to diminish infectivity. However, with respect to vCJD there are a number of caveats: lack of experimental proof (in

animal model system) of the effect of leukodepletion on TSE infectivity, lack of knowledge on which cell types carry the infectivity and to which degree they can be removed, unknown effects of different filter types, and lack of validation. For this reason, the SCMPMD cannot make a clear-cut recommendation with respect to the general introduction of leukodepletion, unless a number of studies has been performed to answer the open questions. The SCMPMD recommends supporting of such research..

It is realised that it will take at least two years until those studies has been finished. In the meantime, it might be advisable to introduce leukofiltration as a precautionary step, as it is assumed that it will contribute to diminishing infectivity in blood. A recommendation for the general use of leukofiltration would be in line with the belief that many if not all transfusion recipients would benefit from the removal of white blood cells for other reasons.

2. Screening assays

It is assumed that although there is no proven or even probable case of transmission by blood or blood products the identification and exclusion of donors in the preclinical phase of CJD or vCJD would contribute to an increase in the safety margin and, probably, an increase in the confidence in blood and blood products by potential recipients. Therefore, the SCMPMD in its Opinion of October 1998 emphasised the need for "the development of a simple readily available ex vivo diagnostic test for preclinical nvCJD/CJD". In addition it stated: "When a validated test for TSE infectivity in donor blood becomes available, it should be implemented in routine donor screening as soon as possible and donors found to be positive should be excluded from donation. Member States should, in the interest of public health, warrant availability of TSE tests for blood screening in collaboration with possible patent holders."

During the "WHO Consultation on Diagnostic Procedures for Transmissible Spongiform Encephalopathies: Need for Reference Reagents and Reference Panels" held in Geneva on March 22 and 23, 1999, M.J. Schmerr presented results of a new assay that may be able to detect the pathological form of prion protein in blood of animals in the clinical as well as in the preclinical phase of TSE (scrapie in sheep and chronic wasting disease in deer, Schmerr 1999, Schmerr et al. 1999). The basic reaction is the competition of the proteinase K treated sample with a labelled peptide derived from the sequence of prion protein binding to an antibody raised against this peptide (Schmerr et al. 1998). The test material is extracted from buffy coat prepared from a sample of peripheral blood. From the relation between free and bound peptide as determined by capillary electropheresis the amount of competing protein, i.e. protease resistant prion protein, is calculated.

In contrast to other tests used for the detection of TSE infected animals or for confirmation of CJD/vCJD in humans the assay proposed by Schmerr uses for the first time as test material a body fluid, namely blood, which is easily available. In this respect, this assay fulfils a prerequisite for a screening assay which could be used in the blood donation setting. However, it has to be stressed that this assay is far from being validated either in animals or in humans. On the contrary, preliminary tests with human material performed in several laboratories have not yet validated this test.

There is no doubt that the assay has the potential to be developed into a screening assay, but this development will need a number of carefully designed studies. Use in donor screening will not be possible until there is more information on the sensitivity, specificity and validity of the assay.

The SCMPMD repeats its recommendation to support efforts in the development of easily applicable screening tests for CJD/vCJD.

The SCMPMD would also like to draw the attention to an ethical aspect of the expected introduction of a screening assay for CJD/vCJD. The information of a positive test result would confront the individual with the diagnosis of an inevitably fatal disease without any reliable prediction of the duration of the preclinical phase. Such information could cause severe psychological stress and would demand careful counselling. In such a situation, it would not be surprising if donors would stop donating if such a test for CJD/vCJD were introduced. If the number of those donors is high the introduction of a screening assay would lead to a significant loss of donors who would have to be replaced by first time donors who are at higher risk of well known blood borne infections. This situation should be considered well in advance.

3. Exclusion of donors at risk for TSE infection by ruminant derived material

Until the end of 1998 vCJD cases were observed only in the United Kingdom (UK), with one single exception. Therefore, residency in UK was described as one of the known risk factors for vCJD (the others being young age (i.e. below 53 years) and homozygosity of methionine at codon 129 of the prion protein gene). The exclusion of donors who resided for some time in the UK could, therefore, be considered as contributing to minimising the theoretical risk of vCJD transmission by blood and blood products.

The first recommendation of this kind was given by the Ottawa based Bayer Advisory Council on Bioethics which stated in his working paper "Creutzfeldt-Jakob disease, blood and blood products: A bioethics framework" (1998):
"The differences between classical CJD on the one hand and nvCJD on the other create differences in the quality of the hypothetical risk. As discussed earlier, the new variant form appears to have crossed the species barrier from cattle. It has an earlier age at onset, and the load of pathological prions is much greater than in classical forms of the disease. The anatomical distribution of nvCJD infectivity is also different, which raises the plausible possibility that it is more likely to have infectivity in the blood. Therefore, nvCJD is the wild card that warrants special vigilance. The disease appears to be isolated, at present, to parts of Europe. The number of people in affected countries who are currently incubating the disease is unknown. The Council therefore recommends:

> 20. That persons who, at any time since 1980, have resided in a geographic area with a significant incidence of BSE or nvCJD not be permitted to contribute blood or plasma until the hypothetical risk of accepting donations from such persons can be evaluated."

This statement did not take into account that the exclusion of donors may cause a shortage in the supply of blood and blood products as was experienced in the USA following the recommendation to withdraw all blood products which were produced from plasma pools to which a donor contributed who was subsequently recognised of suffering from CJD or being at risk for CJD. Therefore the US and Canadian authorities aimed at finding an acceptable balance between reduction of theoretical risk of vCJD transmission and the impact on the blood supply.
For this reason a survey was performed to gather information on the percentage of US donors who stayed for some time in UK and on the length of this stay between 1 January 1980 and 31 December 1996. On the basis of the number of persons staying for defined time intervals in UK[2] the overall theoretical risk was calculated as the sum of (number of persons) times (average number of days staying in UK). The contribution of groups of individuals living for a certain time period in UK to the overall risk was calculated. For example, persons staying for more than 5 years in the UK contributed 49.2% to the overall risk while persons staying there for only 1 to 3 days contributed only 0.2%. At the same time, the loss of blood donors was estimated depending on the period of UK residence taken as the exclusion criterion.

On the basis of these data the rule cited above was chosen as the best compromise. According to the calculations an exclusion of potential donors who stayed cumulatively for more than 6 months in the UK reduced the theoretical overall risk of vCJD transmission by approximately 90% while affecting only 2.2% of the donor population.

The decision is based on two assumptions:

a) The risk of acquiring vCJD (and to be infectious afterwards) is directly proportional to the length of stay in the UK in the period 1980 to 1996
b) The risk of acquiring vCJD exists only in UK and does not exist in North America

There are a number of comments on these assumptions:

a) All available data support the hypothesis that vCJD is caused by the same agent as bovine spongiform encephalopathy (BSE) (Collinge et al. 1996, Hill et al. 1997, Bruce et al. 1997, Scott et al. 1999). Therefore, it is plausible to assume that this agent is transmitted to humans by exposure to material derived from subclinically or clinically infected cattle, most probably to food containing bovine derived material. There is no proof of this hypothesis, but there is no more plausible explanation. The risk of exposure to contaminated bovine material was definitely high between 1980 and 1990 when additional measures to protect consumers were taken. As these measures were not fully enforced during the early nineties it is reasonable to include the years up to 1996 in the risk period.

   There is no information on the infectious dose to humans nor on the amount of infectivity in different types of food. Therefore, no judgement can be made as to

[2] The survey asked for the cumulative stay in UK and in the Republic of Ireland. However, in the final decision of the US and Canadian authorities the Republic of Ireland was not included in the list of regions where a stay gives cause for exclusion.

whether the risk was ubiquitous and exposure to contaminated food was inevitable, as to whether infectivity was low and only repetitive exposure led to infection or to whether the probability of exposure to contaminated material per unit time was low and increased with the length of stay in the area of risk. Under some assumptions, there would be a linear relationship between risk of exposure and length of stay.

b) It became obvious during 1999 that the risk for vCJD is not restricted to UK. Until February 7, 2000, 52 patients died from confirmed or probable vCJD in the UK. In addition, approximately 10 patients, still alive, are strongly suspected of suffering from vCJD (information from the CJD surveillance unit in Edinburgh). One case of vCJD has been observed in the Republic of Ireland, but this individual stayed for 5 years in the UK and could have contracted the infection there. However, in France two cases of vCJD have now been confirmed and a third case is suspected; none of them had ever travelled to the UK. The French cases demonstrate that there is a risk of acquiring vCJD independent of residence in the UK.

   If it is accepted that humans are infected through exposure to bovine derived material the appearance of vCJD cases outside of UK is not a surprise. During the eighties and early nineties large amounts of bovine derived material (including live cattle) were exported from UK to other Member States and elsewhere. Though it may only be a chance observation, it has been calculated that in the eighties 5% to 10% of bovine material in French food came from importation from the UK and that this figure is reflected in the ratio of confirmed and probable vCJD cases in France and UK ($3/62 \approx 1/20 = 5\%$), assuming that bovine derived material in UK food was nearly 100% from UK origin and taking into account that the population in France and UK are approximately the same (58.7 millions vs. 59.0 millions).

   From UK exportation data it is known that bovine derived material, with great differences in quantity, was exported to a number of Member States. It cannot yet be excluded that there is a substantial risk of vCJD in countries in which significant amounts of this material entered the food chain. However, this risk may be smaller than expected from the UK exportation data from these countries to certain countries if there is a significant trade of bovine derived materials to other countries. On the contrary, Member States for which the UK exportation data list small figures, the risk may be higher than expected if they have (unknowingly) imported such material via other Member States. The extent of this trade is not known to the SCMPMD, but these figures would be important in estimating the endogenous vCJD risk in different Member States and subsequently the reduction of the overall risk for vCJD by any donor exclusion criteria.

   As the UK exportation data to the USA are very small it can be assumed that there is a negligible endogenous vCJD risk. However, it may be questionable to assume that the vCJD risk in North America is posed only by travellers to UK. If the risk of residence in certain Member States besides the UK is taken into consideration (according to the above figure), a 120 months (10 years) stay in France would be equivalent to a six month stay in the UK.

Despite the cases of vCJD in France, there is no doubt that the highest risk of vCJD is associated with residence in UK. The exclusion criteria proposed by the US and Canadian authorities are a compromise in an attempt to minimise the theoretical vCJD transmission risk (measured as person * days in the UK) without seriously compromising the number of donors. The importance of vCJD risk endogenous to the different Member States has already been discussed. It has to be assumed that the effect of the exclusion criterion may also be influenced by travel behaviour which may differ for European blood donors. It is expected that the number of Europeans staying for a short time in the UK is much higher than for US citizens and that this figure may be different for different Member States. The proposed exclusion criteria may, therefore, have different effects on the reduction of the theoretical risk in North America and Europe.

The adverse effects of any exclusion criterion on the donor population is not only the possibility of a shortage in supply. Excluded donors have to be replaced by new donors, most probably by first time donors. This replacement creates an additional risk as the prevalence of blood borne infectious diseases in first time donors is significantly higher than in repetitive donors. Any new exclusion measure, therefore, has to be balanced against the calculable risk of HIV, HBV and HCV transmissions by window donations of first time donors.
On the basis of these deliberations the SCMPMD recommends a careful consideration whether the exclusion of donors who stayed for a defined period of time in areas with increased risk of exposure to the BSE agent would provide an increase in safety balanced to its negative impact on supply and donor population. In order to be able to make the optimal decision three sets of data have to be collected and evaluated:

1. The travel pattern of European donors which may differ between Member States.
2. The exposure to UK bovine derived material in food between 1980 and 1996 in different Member States.
3. The prevalence of HIV, HBV and HCV in first time donors in different Member States.

The data to items 1 and 3 could best be obtained by questionnaires which should be answered by a statistically representative set of blood collection centres and their donors throughout the European Community. In order to enhance comparability the questionnaires in the different Member States should be harmonised. The data of exposure to UK bovine derived material may be compiled by Community services using trade statistics. The SCMPMD would be ready to contribute to the evaluation and interpretation of the collected data.

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