Update on Methylene Blue treated Fresh Frozen Plasma

UK Blood Services currently import fresh frozen plasma (FFP) for transfusion to patients born after 1.1.96, as a vCJD risk reduction measure. In order to mitigate the viral risk of imported plasma, the FFP is thawed and treated with a pathogen inactivation system involving the addition of methylene blue (MB). After an illumination step, the MB is removed and the MB FFP refrozen.

The French regulator has recently withdrawn its approval for MB FFP, for reasons explained below. The Joint (UK Blood Services / Health Protection Agency) Professional Advisory Committee (JPAC) has considered whether the component should remain available in the UK, and below are extracts from a position statement that will be published on their website: **www.transfusionguidelines.org.uk**

BACKGROUND

In May 2011 the French regulatory authority Agence Française de Sécuité Sanitaire de Produits de Santé (AFSSAPS) requested the Etablissement Français du Sang (French National Blood Service) to phase out the use of methylene blue plasma (MB FFP), due to concerns about allergic reactions to MB FFP occurring more frequently than with other plasma components. This was completed in February 2012. Their decision was also influenced by 'continuous quality control of blood components identifying a greater variability of fibrinogen concentration in MB FFP as compared with the other therapeutic plasma'.

Therefore the question has arisen as to whether MB FFP should remain as a specified component in the Guidelines for UK Blood Transfusion Services.

Conclusions from UK haemovigilance data

The analysis of UK reactions to MB FFP from SHOT data shows no significant increase in overall reactions or severe allergic reactions when compared to standard FFP, even when including one MB FFP report where the reaction was to mixed components (see Table 1). However, the overall numbers of reports of reactions to MB-FFP are very small and this has to be taken into account, together with the limitations of haemovigilance data reporting which is likely to underestimate at least the more minor reactions.

It is difficult to make a direct comparison of the UK and French data due to the different way the allergic reaction data is presented in the two haemovigilance systems and the different groups of patients and unit sizes included for MB FFP between the countries. More standardised definitions will be a help in the future for comparing haemovigilance data between countries and this is important for the most effective monitoring of reactions to new components.

Table 1 Summary of MB and standard FFP acute transfusion reactions reported to SHOT 2007 - 2011

SHOT report year	MB-FFP reactions				Standard FFP reactions			
	Total reports	Severe reports			Total reports	Severe reports		
		Anaphylactic/ severe allergic	Hypo-tensive	Total		Anaphylactic/ severe allergic	Hypo-tensive	Total
2007	**0**	*0*	*0*	**0**	**20**	*8*	*0*	**8**
2008	**1**	*0*	*1*	**1**	**31**	*13*	*0*	**13**
2009	**1**	*0*	*0*	**0**	**41**	*11*	*0*	**11**
2010	**4**	*2*	*1*	**3**	**40**	*9*	*2*	**11**
2011	**1**	*0*	*0*	**0**	**42**	*9*	*2*	**11**
Total	**7**	***2***	***2***	**4**	**174**	***50***	***4***	**54**

Notes:

- *There were a total of 8 acute transfusion reactions to MB FFP from 2007-2011, but 1 recipient received other blood components and IV contrast media and has thus been excluded from the main analysis*
- *Total acute transfusion reaction numbers to standard FFP are derived from the numbers stated at the start of the Acute Transfusion Reaction (ATR) chapter in the relevant SHOT report, minus any MB FFP, SD FFP or cryoprecipitate cases that had also been included.*
- *Numbers of anaphylactic, severe allergic and hypotensive reactions to standard FFP have been derived from further analysis of the SHOT data from 2007-2011 in order to capture all severe acute transfusion reactions to standard FFP*
- *2009 standard FFP numbers include two children with standard FFP aged 10, 14 yrs (mild reactions)*
- *TACO, TRALI or TAD reports are not included in the analysis (for MB FFP there were no TRALI or TAD reports although there was 1 TACO to MB FFP in an adult in 2009)*

UK Quality monitoring of FFP

Pathogen inactivation of plasma by any of the currently licensed methods results in a reduction in clotting factor activity. The worst affected factors following MB-treatment of plasma are Factor VIII (FVIII), fibrinogen and Factor XI. The specification for MB FFP in the UK requires FVIII to be measured on a routine basis and that >75% units should contain >0.50 IU/ml. There is no requirement to routinely measure fibrinogen in MB FFP.

Table 2 Recent data (June 2012) for FFP from Manchester and Colindale Blood Centres, the two sites in NHSBT that produce MB FFP.

	FVIII:C (IU/ml)	Fibrinogen - Clauss (g/L)
Standard FFP (n=99)	0.92 (0.24) 83%>0.70	2.45 (0.37)
MB-treated FFP (n=127)	0.65 (0.20) 80%>0.50	1.72 (0.34)

Data are mean (SD).

The date in Table 2 show that there is wide variability in the levels of FVIII and fibrinogen in FFP. This is well known and reflects the wide normal range for both of these factors in healthy individuals (0.5-2.0 IU/ml for FVIII and 1.5-4.0 g/L for fibrinogen). Levels of FVIII and fibrinogen are lower in MB-treated FFP by 29% and 30% respectively, compared with untreated plasma. However, the results do not appear to be any more variable as evidenced by the standard deviation, and are consistent with validation data and published studies. Ina more recent study to assess thrombin generation and clot formation in MB FFP, the endogenous thrombin potential and peak thrombin are reduced by 10% and 30% respectively following MB treatment, but this was not associated with a reduction in the rate of clot formation or clot firmness by thrombelastometry.

JPAC RECOMMENDATIONS

1) The UK haemovigilance data have not demonstrated a statistically significant increase in the rate of reactions to MB FFP compared to standard FFP. Although the low numbers of UK MB FFP reactions mean that it is difficult to draw robust conclusions, the data do not support the immediate withdrawal of the use of MB FFP in the UK.

2) In view of the data from France, SHOT will undertake proactive monitoring of future FFP reaction rates and JPAC will review these data and alter the recommendations if necessary.

3) An investigation pathway should be developed in the UK so that recipients of MB plasma with severe allergic reactions are investigated in collaboration with allergy experts.

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