SOLVENT DETERGENT FRESH FROZEN PLASMA - ESTIMATE OF USAGE

The UK Transfusion Services are committed to providing users with the choice of solvent detergent (SD) fresh frozen plasma produced from UK volunteer donors at the earliest possible opportunity. It is envisaged that from early 1998, a proportion of UK donor plasma will be pooled and SD treated, through a contracting arrangement with Octapharma, Vienna. Standard FFP will continue to be produced. An information sheet comparing standard and SD FFP is enclosed. It is envisaged that the costs of SD FFP will be approximately £20/200 ml unit more than standard FFP.

For planning purposes, we need to know as soon as possible what your requirements are likely to be, so that we are always able to meet demand. It would therefore be very helpful if the attached questionnaire could be returned to your supplying blood centre as soon as possible.

Please indicate the patient groups for whom you envisage using SD FFP. It would be helpful if you could estimate how many units of FFP this would amount to, and what percentage of your total FFP you would envisage replacing by SD FFP.

These figures are for planning purposes only at this stage.

I envisage ordering SD FFP for the following patients (delete as appropriate):-

Plasma infusion/exchange for thrombotic thrombocytopenic purpura (TTP)	YES/NO
Patients who need regular FFP eg single clotting factor deficiency where no concentrate available	YES/NO
Disseminated intra-vascular coagulation	YES/NO
Massive transfusion	YES/NO
Liver disease	YES/NO
Warfarin reversal	YES/NO
Cardiac surgery	YES/NO/NOT DONE
Liver transplantation	YES/NO/NOT DONE
Neonates	YES/NO
Other children	YES/NO

TOTAL NO. UNITS ESTIMATED_____ **% OF CURRENT FFP USE**_____

If a virally treated cryoprecipitate preparation were available, what percentage of your current cryoprecipitate usage would you replace? _____

Dr C Hay
Consultant Haematologist
Manchester Royal Infirmary
Oxford Road
Manchester M13 9WL

Signed: [redacted]

Please return to:Dr E M Love
Manchester Blood Centre
Plymouth Grove
Manchester M13 9LL

Not Relevant

Presentation and content

A unit of FFP contains approximately 200-300 ml of plasma from a single donor containing 40-60 ml of anticoagulant mixture. The plasma may be derived from either whole blood or apheresis donation, and in either case is frozen to -30° C or below within 8 hours of collection.

Plasma proteins including coagulation factors in FFP are present in similar concentrations to those in normal plasma. National quality requirements demand that >75% of units have a factor VIII content of >0.7 iu/ml [1], which is assured by a quality monitoring programme.

Donor selection and testing

All blood donors in the UK are accepted under the Medical Assessment of Donors Guidelines [2]. These are designed to exclude donors who are likely to be at risk of acquiring viruses which may be transmitted by transfusion. As a further safety enhancement, FFP is manufactured only from donors who have tested negative for anti-HIV 1+2, anti-HCV, Hepatitis B surface antigen and syphilis in the preceding 6-24 months, as well as in the current donation. In addition, most of the plasma currently collected from regular donors in the 'window period' of an infection (infectious but still seronegative). The approximate risks of viral transmission from single donor blood components from previously tested donors have been calculated from data collected in England and Wales[3]. These are:-

HIV 1+2	0.19 / million donations (95% credibility interval 0.05-0.55)
Hepatitis C	2.4 / million donations* (95% credibility interval 1.8-3.2)
Hepatitis B	5-20 / million donations+

*Calculated prior to implementation of HCV RNA screening.

+Provisional figure; based on limited data on duration of potentially infective periods.

Theoretically, single unit FFP can also transmit the hepatitis A virus (HAV) and parvovirus B19. Based on the observed adult seroconversion rate of 1%, it is estimated that as many as 1 in 5,000 donations may carry HAV [4]. However, 60% of transfusion recipients, particularly the elderly, have protective antibody, reducing the at risk figure to 1 in 12,500. In others

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transmission may be asymptomatic. Only 3 cases of transfusion-transmitted HAV have been reported in England since 1980[7].

For parvovirus B19, estimates of viraemic donations range from 1 in 8,000 -1 in 16,000 [8,9]. Again, because of protective antibody in approximately 60% of recipients, the at risk figure falls to 1 in 20-40,000.

No confirmed cases of bacterial contamination of FFP have been reported to the NBS/PHLS reporting system.

For patients who will need repeated infusions of fresh frozen plasma, vaccination against HAV and HBV should be considered.

Other side effects

Acute mild allergic reactions to FFP are common (up to 1%), and severe reactions rare (0.1%). The risks of red cell haemolysis due to passive transfer of anti A,B are minimised by prescribing ABO compatible FFP where possible, (group AB is the 'Universal Donor'), and also by testing and labelling group O donations for high titre anti -A,B.

Rarely, the presence of potent anti-HLA or anti-granulocyte antibodies in the donor may give rise to transfusion related acute lung injury (TRALI)[10], with clinical features resembling adult respiratory distress syndrome. Similarly, severe thrombocytopenia due to passive transfer of platelet antibodies has been reported.

FFP contains intact and fragmented red cells, leucocytes and platelets. These may be responsible for some of the side effects. Because of the red cell content, children and women of childbearing age who are RhD negative should receive FFP from RhD negative donors.

SOLVENT DETERGENT (S/D) FFP (Information supplied by Octapharma Limited).

Trade name: OCTAPLAS
Solvent/Detergent (SD) treated human plasma; frozen, ABO blood group specific.

Pharm. form.: Bags of 200ml solution for parenteral administration by the intravenous route only.

Qualitative and quantitative composition:

Name of ingredient

Active ingredients
Human plasma proteins

Other ingredients
Sodium citrate dihydrate (anticoagulant)
Sodium dihydrogenphosphate dihydrate (buffer) 0.1-0.2g
Glycine (osmolality regulator)

Presentation, content and efficacy

SD FFP is manufactured from plasma donations collected by the UK Transfusion Services using the same donor selection criteria as with standard FFP. The plasma is tested for anti-HIV 1+2, HBsAg and anti-HCV both by the Transfusion Services in the UK and by Octapharma in the plasma pool prior to solvent/detergent (SD) treatment. The initial plasma pool is also tested for hepatitis A by PCR. The final product is again tested for the same viral markers.

Thawed standard plasma pools of 380 litres (600-1,500 donations) are filtered through a 1 µm filter, in order to remove cells and cell debris, and are subsequently subjected to virus inactivation using the SD treatment. The solvent (1% Tri (N-Butyl) Phosphate, TNBP] and detergent [1% Triton X-100] are then removed by oil extraction and solid phase extraction using chromatography respectively, leaving residual levels of ≤2 µg TNBP/ ml and ≤5 µg Triton X-100/ml.

Toxicological studies indicate that these residual levels should present no clinical problems. The plasma pool is then subjected to sterile filtration (0.2 µm) before the aseptic filling in standard, sterile blood bags. The final product is labelled, quickly refrozen (≤-60°C) and stored at a temperature of ≤-30°C. The SD FFP bag is over-wrapped with a sealed polyamide/polyethylene film which ensures clean thawing before use.

The production of SD FFP is well documented and fully validated according to GMP guidelines. The production is performed in a pharmaceutical facility which is regularly inspected and approved by national and international authorities. A fully validated in-process and final quality control system has been introduced which ensures the quality of each and every unit of SD FFP.

Unlike conventional FFP, SDFFP is a standardised product with identical levels of coagulation factors in every unit from the same batch. A randomised study of liver disease/liver transplant patients revealed equivalent correction of coagulation abnormalities by conventional and SD FFP[11]. The product has a standardised filling volume of 200 ml, and the active ingredients are standardised through optimised integration of approximately 1,000 donations.

Fabrik/200 ml

Homogenisation of total protein, coagulation factor and inhibitor levels within the physiological range, has been

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Not Relevant

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Standard FFP and SD FFP compared

	Standard FFP	SD FFP
Source	UK donors, single pack format	UK donors: pools of up to 380 litres (600-1,500 donations)
Donor Testing	Mandatory UK markers. Must have also tested negative in previous 6-24 months	As for FFP
Virus risk		
HIV 1 + 2	1 : 5.26 million	No transmissions to date of these 3 viruses in any SD treated products, including FFP.
Hepatitis C	1 : 416,000	
Hepatitis B	1 : 50-200,000	
Hepatitis A	1 : 12,500	Zero to date, ab neutralises
Parvovirus B19	1 : 20 - 40,000	Zero to date, ab present
Coagulation factor content	Variable between units	Constant within batch
Testing requirement	75% units >0.7 iu/ml VIII	>0.5 iu/ml each clotting factor
Residual SD	None	Residual levels not toxic (animal evidence)
Allergic reactions		
mild	1%	Probably less frequent
severe	0.1%	
Adverse reactions due to antibody		Pooling reduces all of these risks
red cell	avoidable	
TRALI	rare	
thrombocytopenia	very rare	
Cell fragments	Present: RhD match if possible	Absent, no need to RhD match
Licence	Not required	Licensed, batched product
Indications	See BCSH Guidelines	As for FFP. May have advantages in TTP
Usage	300,000 units/year in UK	3,000,000 units used in Europe 1991-1997

The difference between these formulations of FFP is such that well informed clinical judgement is needed to decide which product should be prescribed to each patient. This table is designed as an aide memoir to use after reading the information sheets that accompany it.

References.

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demonstrated in extensive studies, whereas single donor FFP is highly variable in this respect. A minimum of 0.5 IU/ml is guaranteed also for the labile clotting factors (Factor V and VIII). Normally values 0.7-0.9 IU/ml are obtained for all clotting factors. The content of fibrinogen is approximately 2.5 mg/ml and the APTT is approximately 33 seconds.

The clinical indications and recommended dosages for SD FFP are identical to those for standard FFP. The same is true for the administration of the product. SD FFP is effective when used in plasma exchange procedures for thrombotic thrombocytopenic purpura (TTP)[2] and may have some advantages in this setting.

Infectious risks

In addition to the donor selection and screening procedures described for standard FFP, samples from FFP units will also be tested in 'mini-pools' for HCV RNA when this requirement is implemented, probably during 1998. Plasma will then not be sent for SD treatment until the results of such testing are available. The initial plasma pools and final products are also tested for anti-HIV 1+2, HBsAg and anti-HCV.

The SD method provides reliable inactivation of enveloped viruses such as HIV, HBV and HCV which addresses the limitations of the donor selection and screening such as "denial" of recent risk behaviour, sensitivity and specificity of tests, and testing, reporting and release errors. The SD method has been applied to many therapeutic products derived from human plasma and has established an impressive world-wide safety record. The efficacy of the SD method as used in the SD FFP manufacturing process has been extensively validated. These studies clearly demonstrate the reproducibility, the non-selective mode of action and the robustness of this method, which, taken together, contribute to the very high safety margin towards enveloped viruses.

Non-enveloped viruses such as HAV and Parvovirus B19 are not specifically inactivated by the SD method. Therefore, the risk of transmission of such viruses may theoretically be greater than with single donor FFP. However, plasma pools for SD FFP manufacture contain a specified minimum antibody level which has been shown to be neutralising for HAV. In addition, the initial plasma pool is tested for HAV PCR.

Parvovirus B19 antibodies should also be neutralising, but the theoretical possibility of transmission cannot be totally excluded. Parvovirus B19 transmission may cause hydrops fetalis with subsequent fetal loss during pregnancy, and may precipitate aplastic crises in patients who are immunocompromised or with underlying haematological diseases. Therefore, as with all other products derived from human blood or plasma, SD FFP should only be given to such patients if strongly indicated, and in all recipients, the risk of HAV and Parvovirus B19 should be weighed against the benefits of total inactivation of HIV, HBV and HCV by the SD treatment.

When medicinal products prepared from human blood or plasma are administered, infectious diseases due to the transmission of infectious agents cannot be totally excluded. This applies also to pathogens of hitherto unknown origin.

Appropriate vaccination (e.g. against HAV and HBV) for patients in regular receipt of medicinal products derived from human blood or plasma should be considered.

Non-Infectious risks

Allergic reactions towards human plasma proteins are not abolished by the SD treatment. However, adverse reactions attributable to passive transfer of red blood cell (haemolytic transfusion reaction), leukocyte (transfusion-related acute lung injury) or platelet antibodies (passive post-transfusion purpura) are likely to be minimised, due to testing of the irregular red blood cell antibodies and the dilution effect of the pool.

Because intact cells and cellular debris are removed by 1 µm filtration and destroyed by the SD process, adverse reactions attributable to blood cells (e.g. fever and immunisation) do not occur during or after the use of SD FFP. Therefore, no specific product is required for Rh(D) negative patients.

Usage

More than 3,000,000 units of SD FFP from more than 4,000 batches have been used to treat 1,000,000 patients throughout Europe from 1991 to 1997. During this period there have been:

- No documented unexpected adverse reactions;
- No viral or bacterial transmissions, including HAV and Parvovirus B19.

SD FFP has replaced standard FFP totally in Austria, Belgium, Luxembourg, Norway and Portugal, and is also in extensive use in France, Germany, Netherlands and South Africa. The product will soon be introduced in Spain, UK and USA.

Not Relevant