# Solvent/detergent plasma for prevention of bleeding in recessively inherited coagulation disorders: dosing, pharmacokinetics and clinical efficacy

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Background and Objectives. This open-label multicenter trial of solvent/detergent (SD) plasma involving 17 patients with recessively inherited coagulation disorders (one afibrinogenemia, four FV, six combined FV and FVIII, one FX and five FXI deficiencies) evaluated the pharmacokinetics of the deficient factors and hemostatic efficacy.

Design and Methods. *In vivo* recovery (IVR) of the deficient coagulation factor was determined in a non-bleeding state in all patients and the mean values for FV, FVIII, FX, FXI and fibrinogen were 1.3, 1.2, 1.5, 1.3 and 1.5 dL/kg, respectively. The mean plasma half-life of FV, FVIII and FX was 18, 43 and 33 hours, respectively. All patients underwent replacement therapy for elective procedures at risk of bleeding (surgery in 14 cases and vaginal delivery in two patients), except one treated for a central nervous system surgical emergency.

Results. Treatment courses with SD plasma were judged fully effective in 13/16 cases (81%). In the remaining three cases, mild bleeding occurred after major surgery in a FV deficient patient with a factor level of 43% and in a FXI deficient patient when factor levels were between 20% and 41%; and after minor surgery in a patient with FV and FVIII deficiency when factor levels were 41% and 18%, respectively. Bleeding was controlled by continuing or increasing treatment with SD plasma.

Interpretation and Conclusions. These results suggest that, even though the current absolute risk of blood-borne infections associated with fresh-frozen plasma is relatively small, SD plasma should be preferred in patients with recessively inherited coagulation disorders who need replacement therapy when virus-inactivated single-factor concentrates are not available.

Key words: solvent/detergent plasma, inherited coagulation disorders.

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Recessively inherited coagulation disorders (RICD) are rare, their clinical spectrum is not well characterized and treatment strategies are not well defined.[1] Only one recombinant product is licensed for factor VII (FVII) deficiency (recombinant activated FVII). Plasma-derived single-factor concentrates (fibrinogen, FVII, factor XI, factor XIII) are licensed and available in some countries but not in many others; concentrates of the prothrombin complex factors are often used for prothrombin and factor X (FX) deficiencies, whereas only fresh frozen plasma (FFP) is available for factor V (FV) and combined FV and factor VIII (FVIII) deficiency. In RICD, important determinants of replacement therapy such as the plasma half-life and the hemostatic levels of the deficient coagulation factors are not as well defined as in hemophilia A and B.[1] Another important aspect of replacement therapy in RICD is viral safety. When available, virus inactivated factor concentrates are the treatment of choice because they carry a lower risk of infection than FFP[2,3] and have the additional advantages of a small infusion volume and fewer allergic reactions. The risk of blood-borne infections from FFP can be minimized by adopting virus inactivation methods.[4] In order to quench the infectivity of lipid-enveloped viruses while preserving the activity of coagulation factors the solvent/detergent (SD) method has been successfully applied to pooled plasma, providing for the first time a virus-inactivated *batched* FFP.[5] Satisfactory results concerning tolerability and safety of SD plasma in different clinical settings are reported[6,7] but relatively little information is available on its clinical use in RICD.[8,9] This multicenter, open-label study had the goals of evaluating the pharmacokinetics of the deficient factors in patients with RICD treated with SD plasma and correlating the hemostatic efficacy of SD plasma with the factor levels attained and maintained during treatment. Secondary goals of the study were the assessment of viral safety and tolerability of SD plasma.

## Design and Methods

### SD plasma

SD plasma (Octaplas®, Octapharma, Vienna, Austria) is prepared from pooled FFP (700-1500 donors per batch) with ABO specificity. The product is virus inactivated using

the solvent (TNBP)/detergent (Triton X-100) technology. Briefly, FFP is thawed rapidly and treated for 4 hours with 1% TNBP and 1% Triton X-100 at 30°C. TNBP is then removed by extraction with castor oil and Triton X-100 by reverse-phase hydrophobic chromatography. After sterile filtering and bag filling, the resulting product is rapidly frozen in 200 mL bags. Octaplas® was generously provided by the Italian distributor (Kedrion, Castelvecchio Pascoli, Italy) for the whole study period.

### Patients and study design

This open-label, single-arm multicenter clinical study in patients with RICD conformed to international standards of good clinical practice and all patients gave written informed consent according to the Declaration of Helsinki. The study was promoted by the Association of the Italian Hemophilia Centers (AICE) and was intended to enroll patients with RICD who needed replacement therapy for bleeding episodes or for surgical procedures. The need for replacement therapy, the dosage regimens of SD plasma and the use of antifibrinolytic drugs or other hemostatic agents were decided by the attending clinicians on the basis of the individual bleeding history and the level of deficient factor in plasma, type and severity of hemorrhage and type of surgery. SD plasma was chosen as a therapeutic option when no specific concentrate was licensed or available in Italy.[2] Vaccinations against hepatitis A (HAV) and B viruses or booster doses of the vaccines were recommended in non-immunized patients. Whenever possible a single-dose pharmacokinetic study was initially performed in non-bleeding patients in order to identify the dosage of SD plasma for treatment of bleeding or for surgical prophylaxis. All patients were hospitalized during each treatment course with SD plasma and underwent out-patient visits during a 12-month follow-up period.

### Coagulation assays

Coagulation factor activities were measured in plasma samples and Octaplas® batches. FV:C and FX:C were measured by one-stage prothrombin time-based assays; FVIII:C and FXI:C were measured by one-stage activated partial thromboplastin time-based assays. Fibrinogen was measured by functional assay based on fibrin polymerization time using a commercial kit (Laboratoire Stago, Asnieres, France; sensitivity threshold 5 mg/dL).

### Pharmacokinetics and coagulation monitoring

Pharmacokinetic studies were carried out in a non-bleeding state by infusing a test dose of SD plasma (15-20 mL/kg b.w. at a maximum rate of 10 mL/min) after a wash-out period from any previous treatment lasting more than four times the half-life of the deficient coagulation factor, i.e. at least 8 days for combined FV and FVIII or FX deficiencies, 12 days for FXI deficiency and 15 days for afibrinogenemia. Plasma samples for functional assays of deficient factors were obtained before the infusion, 10 min, 30 min, 1h, 3h, 6h, 18h, and 24h after the end of the infusion and then daily until the deficient factor level returned to baseline values. Pharmacokinetic data were analyzed using both the model-independent methods of Longo *et al.*[10] and Matucci *et al.*[11] and the compartmental method according to one- and two-compartment open models.[12] Area under the curve (AUC), clearance, volume of distribution area (VdArea), mean residence time (MRT), terminal half-life and $\alpha$ and $\beta$ distribution half-life were calculated using a single-dose pharmacokinetic program (PKRD 5.03) developed by Messori *et al.* [13] The incremental *in vivo* recovery (IVR) was calculated as the ratio between the maximum post-infusion level of the deficient factor measured within the first 60 min after the end of the infusion and the amount of factor administered according to the following formula:

$$IVR\ (dL/kg) = \frac{maximum\ level\ (U/dL) - baseline\ level\ (U/dL)}{dose\ of\ factor\ administered\ (U/kg)}$$

Fibrinogen levels and doses were expressed in mg/dL and mg/kg, respectively. IVR was determined in all patients after the first infusion of SD plasma, including those who did not undergo the pharmacokinetic study.

During each treatment course, the level of the deficient factor was measured before (trough level) and after each infusion of SD plasma or once a day when the intervals between infusions were longer than 24 hours.

### Efficacy assessment

The efficacy of treatment with SD plasma during and after surgery or delivery was evaluated by the surgeons and attending physicians and rated as *effective* when actual blood loss did not exceed the expected amount and no bleeding complication occurred, *partially effective*, when blood loss exceeded that expected by less than 50% or when mild bleeding complications were observed, or *ineffective*, when blood loss was more than 50% of that expected or clinically relevant bleeding complications occurred and alternative replacement treatment and/or blood transfusion were required.

### Assessment of viral safety

At study entry, all patients underwent serological examinations to assess their status with respect to HCV, HBV, HAV, HIV and human B19 parvovirus. Serological markers for each of these blood-borne infections were monitored after the first exposure to SD plasma according to the timing of seroconversion for each virus. Markers for HBV, HCV and HAV were determined at weeks 4, 8, 12, 16, 26, 38 and 52; serum alanine aminotransferase, at weeks 0, 1, 2, 4, 8, 12, 16, 26, 38 and 52; HIV antibodies, at weeks 8, 16, 26, 38 and 52; parvovirus B19 antibodies and hemoglobin levels, at weeks 0, 1, 2, 4 and 12. Serum HCV-RNA was tested by reverse transcription-polymerase chain reaction at study entry. HCV antibodies were tested by second-generation enzyme immunoassays. HBV markers, HIV-1 and HIV-2 antibodies, anti-HAV and anti-B19 parvovirus IgM and IgG were tested by commercial enzyme immunoassays.

**Table 1.** Demographic and clinical features of the 17 patients with RICD.

| | *Deficient coagulation factor* | | | | | *All patients* |
|---|---|---|---|---|---|---|
| | *Fibrinogen* | *FV* | *FV+FVIII* | *FX* | *FXI* | |
| N. of patients (M:F) | 1 (M) | 4 (1:3) | 6 (1:5) | 1 (M) | 5 (2:3) | 17 (6:11) |
| N. of patients with severe factor deficiency | 1 | 2 | – | 1 | 4 | 8 (47%) |
| Median age, years (range) | 20 | 33 (19-65) | 39 (23-49) | 55 | 33 (13-53) | 39 (13-65) |
| Median weight, kg (range) | 68 | 72 (50-120) | 69 (56-80) | 75 | 52 (40-100) | 68 (40-120) |
| Anti-HAV neg, | 0 | 3 | 2 | 0 | 0 | 5 (30%) |
| Anti-HBs neg, | 0 | 2 | 2 | 1 | 2 | 7 (41%) |
| Anti-HCV neg, | 0 | 4 | 4 | 1 | 5 | 14 (82%) |
| Anti-HIV neg, | 1 | 4 | 6 | 1 | 5 | 17 (100%) |
| Anti-B19 neg, | 0 | 0 | 0 | 0 | 1 | 1 (6%) |

## Results

### Patients

Seventeen patients with RICD (one with afibrinogenemia, four with FV deficiency, six with combined FV and FVIII deficiencies, one with FX deficiency and six with FXI deficiencies) from five Hemophilia Centers were enrolled in the study (Table 1). Eight patients (47%) had severe factor deficiency, i.e., undetectable levels of the deficient factor in plasma (FV, FX and FXI <1%, fibrinogen < 5mg/dL). Four patients (24%) had been previously treated with FFP, two (11%) with coagulation factor concentrates, four (24%) with both and seven (41%) had not previously received plasma or plasma-derived products. All patients needed replacement therapy for procedures at risk of bleeding (elective surgery in 14 and vaginal delivery in two patients), except one treated in a emergency with SD plasma for the removal of a subdural cyst. The planned surgery was not ultimately performed in the FX deficient patient after the pharmacokinetic study had been carried out because judged unnecessary.

### Pharmacokinetics

This study was performed in seven patients (three with combined FV and FVIII deficiencies, three with FV deficiency and one with FX deficiency) using a median dose of SD plasma of 18 mL/kg (range: 15-20). Table 2 shows the data concerning the pharmacokinetic parameters of FV, FVIII and FX including IVR, which was determined in a non-bleeding state in all 17 patients. A complete pharmacokinetic study was not carried out in patients with FXI deficiency (n=5) and afibrinogenemia (n=1), but the calculated IVR was 1.3±0.7 dL/kg and 1.5 dL/kg, respectively.

### Treatments

Overall, nine batches of Octaplas® were used in the clinical study (five of blood group A, one of group B, two of group O and one of group AB), one or two batches per patient. The details on the clinical use of SD plasma in the 16 treated patients are given in Table 3. The median duration of treatment courses was 4 days; SD plasma was infused at the median dose of 18 mL/kg (range: 6-29), corresponding to a median volume of plasma of 1200 mL per infusion (range: 400-2000). Each unit of SD plasma (200 mL) was infused over a period of 30-60 minutes while the next bag was thawed. All patients were given repeated infusions (median: 4 per patient) at time intervals ranging between 6 and 96 hours, with the exception of two patients who received a single dose of SD plasma prior to minor surgical procedures. In order to prevent bleeding complications, all patients with combined FV and FVIII deficiency, except one who had a baseline FVIII level of 47%, were also treated with FVIII concentrates (two patients), desmopressin (DDAVP, one patient) or both (two patients). Antifibrinolytic amino acids were administered to 4/16 patients (25%). Owing to a transient shortage of fibrinogen concentrate, the afibrinogenemic patient was treated with SD plasma from the day before surgery until post-operative day 2 and switched to a fibrinogen concentrate when it became available in the amount needed, in order to facilitate home treatment at discharge (day 8).

### Clinical efficacy and plasma levels of deficient factors

Treatment courses with SD plasma were judged effective in 13/16 patients (81%) and partially effective in the remaining 3 patients, who had mild bleeding at the surgical sites. The levels of deficient coagulation factors attained in plasma during effective and partially effective courses are given in Table 3. Intraoperative bleeding occurred in a FV deficient patient (patient 9) who underwent central nervous system surgery with a FV level of 43% after SD plasma was infused at the dose of 18 mL/kg. A patient with combined FV and FVIII deficiency (patient 1) treated with SD plasma (18 mL/kg/day) and DDAVP (0.3 μg/kg/day) had excessive bleeding from the drainage the day after laparoscopy and multiple peritoneal biopsies, at a time when FV and FVIII levels were 41% and 18%, respectively. Subsequently, FVIII levels were increased and maintained above 50% by switching the patient to FVIII concentrate (36 U/kg/day) in association with SD plasma (18 mL/kg every 18-48 h). Excessive

**Table 2.** The pharmacokinetics of FV, FVIII and FX in seven patients with RICD (three with combined FV and FVIII deficiency, three with FV deficiency and one with FX deficiency) treated with a single dose of SD plasma.

| *PK parameters* | *FV mean + SD* | *FVIII mean + SD* | *FX* |
|---|---|---|---|
| *In vivo* recovery* (dL/kg) | 1.3±0.4 | 1.2±0.6 | 1.5 |
| Area under the curve (U h/L) | 4932±2835 | 5620±1628 | 13535 |
| Clearance (mL/h/kg) | 5.8±4.0 | 2.4±0.8 | 1.2 |
| Mean residence time (h) | 24.9±13.7 | 56.3±16.7 | 45.2 |
| Terminal half-life (h) | 18.3±10.3 | 42.6±12.6 | 33.1 |
| VdArea# (mL/kg) | 109.9±30.2 | 146.2±68.8 | 59.2 |
| α half-life§ (h) | 1.4±1.2 | 4.6 ±4.6 | 7.8 |
| β half-life◊ (h) | 17.6±9.2 | 98.4±92.5 | 34 |

*#VdArea: volume of distribution area; §Distribution phase, according to the two-compartment model; ◊Elimination phase, according to the two-compartment model.*

bleeding from the drainage occurred 48-72 hours after bilateral mastectomy in a FXI deficient patient (patient 12) whose FXI levels had remained between 20% and 41% during the 7-day treatment course with SD plasma (29 mL/kg/day) associated with oral tranexamic acid. No surgical bleeding was observed in the remaining four FXI deficient patients who received lower doses of SD plasma (range: 8-20 mL/kg) and whose median FXI levels were maintained between 9% and 54%.

### Adverse reactions

Three of 17 patients (18%) who had previously had allergic reactions to FFP were pretreated with steroids and/or antihistamines prior to the administration of SD plasma. An extensive rash during each infusion of SD plasma was observed in only one of these patients (6%), in whom the infusion often needed to be stopped despite premedication and treatment with steroids and antihistamines.

### Viral safety

During the 12-month follow-up period, all 17 patients remained seronegative for HIV. No seroconversion was observed in patients susceptible to hepatitis virus infections (5 to HAV, 7 to HBV and 14 to HCV). Parvovirus B19 antibodies remained undetectable in the only susceptible patient during the follow-up period.

## Discussion

RICD are typically orphan diseases, often neglected by health care providers, advocacy organizations and drug manufacturers. In the last decade, the development of SD plasma has prompted clinical studies[8,9,14-16] to evaluate its use in different clinical settings, including patients with RICD.[8,9] This study with SD plasma provides for the first time pharmacokinetic profiles of deficient coagulation factors in patients with RICD and information on dose regimens used to handle surgical operations, one of the most common reasons for treatment in RICD.[1,3] The levels of deficient factors were monitored during treatment to ascertain the relationship between the factor levels attained and maintained in plasma and the occurrence of bleeding. The study included mainly patients with FV deficiency, for whom no specific concentrate is available, and patients with FXI deficiency, because no concentrate is licensed in Italy for their treatment.

Detailed data on FV, FVIII and FX pharmacokinetics were obtained. A comparison between our results and other pharmacokinetic data obtained with FFP in RICD is difficult because of the paucity of studies in the literature. Our data on FV half-life are consistent with previous reports of values of 12-16 hours,[17-18] although values ranging as widely as between 4.5 and 36 hours have been reported.[1,19] The IVR of FV in our study is similar to that reported after SD plasma infusion in patients with RICD.[9] Data on IVR and half-life of FX have been reported after the infusion of FFP and SD plasma[8,20] and our results are consistent with them, indicating a biological half-life of FX ranging from 20 to 40 hours[20] or longer.[8] Our FVIII data after the administration of SD plasma in patients with combined FV and FVIII deficiency show a longer half-life, a reduced clearance and a slightly lower IVR in comparison with those reported in single-dose pharmacokinetic studies with FVIII concentrates in severe hemophiliacs.[21,22] The FVIII concentration in plasma compared to that in concentrates, the volume infused and the modality of administration (prolonged plasma infusion compared to concentrate bolus injection) may account for these differences. No relevant differences were found between our and previous studies with FFP[23] or SD plasma[8,9] in IVR for FXI and fibrinogen. Even though these pharmacokinetic data provide useful general information for the clinical management of patients with RICD, individual factor monitoring is warranted to adjust treatment regimens in order to reach and maintain hemostasis and at the same time minimize the risk of fluid overload.

No bleeding complication was observed in eight patients with FV or combined FV and FVIII deficiencies who had FV levels between 13% and 35% during treatment with SD plasma, consistently with the minimum hemostatic threshold of 15% reported by others.[1,3] The occurrence of mild intra-operative bleeding in a patient with a FV level as high as 43% was promptly controlled by surgical measures and attributed to local causes. Only one patient with combined FV and FVIII deficiency and a baseline FVIII level of 47% received exclusively SD plasma. DDAVP and/or FVIII concentrates were associated with SD plasma in the remaining patients with the combined deficiency to further raise FVIII levels.[24] Surgery was uncomplicated in four FXI deficient patients who maintained FXI levels between 9% and 54%. On the other hand, one patient bled after mastectomy in spite of FXI levels maintained between 20% and 41%. A surgical cause for this bleeding episode could not be ruled out and the occurrence of bleeding in FXI deficiency is often unpredictable and not clearly related to factor levels in plasma. For this reason, hemostatic levels of FXI as high as 30% to 45% have been suggested for minor and major surgery.[3,25] With regard to our surgical experience with SD plasma in FXI deficient patients it should be considered that invasive surgery, i.e., pinealoma removal, was successfully managed maintaining FXI levels higher than 45%, while levels lower than 30% were maintained during less invasive procedures. The afibrinogenemic patient needed two

**Table 3.** Treatment regimens, levels of deficient factors during treatment and clinical outcome in 16 patients with RICD given SD plasma to prevent bleeding complications.

| *Pt.* | *Deficient factor* | *Baseline factor level, %* | *Reason for treatment* | *N. of doses* | *Median dose, mL/kg (range)* | *Median interval between doses, hours (range)* | *Treatment duration, days* | *Median factor level, % (range)* | *Outcome* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | FV<br>FVIII | 17<br>6 | laparoscopy and biopsies* | 7 | 18 (14-18) | 36 (18-54) | 10 | 34 (24-42)<br>30 (14-67) | Partially effective |
| 2 | FV<br>FVIII | 15<br>35 | carpal tunnel syndrome° | 4 | 18 (6-18) | 50 (27-52) | 6 | 30 (21-42)<br>47 (39-75) | Effective |
| 3 | FV<br>FVIII | 12<br>16 | hemorrhoidectomy ^ | 2 | 18 (16-21) | 48 | 3 | 27 (22-39)<br>34 (24-45) | Effective |
| 4 | FV<br>FVIII | 18<br>47 | cholecystectomy§ | 6 | 14 (12-15) | 24 | 6 | 32 (24-40)<br>61 (52-75) | Effective |
| 5 | FV<br>FVIII | 14<br>12 | vaginal delivery* | 4 | 20 | 24 | 4 | 33 (23-57)<br>49 (19-124) | Effective |
| 6 | FV<br>FVIII | 20<br>37 | Cesarean section^ | 4 | 20 | 24 | 4 | 37 (31-49)<br>72 (39-94) | Effective |
| 7 | FV | <1 | gastric by-pass§ | 4 | 12 (9-14) | 24 (24-96) | 7 | 23 (10-37) | Effective |
| 8 | FV | <1 | vaginal delivery | 2 | 15 (10-20) | 48 | 3 | 13 (6-18) | Effective |
| 9 | FV | 20 | subdural cyst removal | 4 | 18 | 48 (8-48) | 7 | 39 (30-43) | Partially effective |
| 10 | FV | 27 | lipoma removal§ | 1 | 20 | – | 1 | 35 (27-43) | Effective |
| 11 | FXI | <1 | varicocele and phimosis | 2 | 19 | 48 | 3 | 15 (5-29) | Effective |
| 12 | FXI | <1 | bilateral mastectomy § | 7 | 29 | 24 | 7 | 33 (20-41) | Partially effective |
| 13 | FXI | <1 | ovarian cyst removal | 2 | 14 (8-20) | 6 | 1 | 9 (7-12) | Effective |
| 14 | FXI | <1 | arthroscopy | 1 | 12 | – | 1 | 9 (8-11) | Effective |
| 15 | FXI | 30 | pinealoma removal | 3 | 18 (15-20) | 72 (48-96) | 7 | 54 (48-90) | Effective |
| 16 | Fibrinogen | <5 mg/dL | cholecystectomy | 4 | 12 (6-21) | 24 mg/dL (6-48) | 4 | 98 mg/dL (64-163) | Effective |

** Desmopressin and FVIII concentrates were associated; ° Desmopressin was also administered; ´ FVIII concentrates were also administered; §antifibrinolytics were also administered*



infusions of SD plasma to achieve fibrinogen levels of at least 100 mg/dL for major surgery; factor levels were maintained postoperatively above 50 mg/dL, the recommended hemostatic threshold.[1,3]

Treatment with SD plasma of RICD was well tolerated and safe, confirming the results obtained in larger series of patients with other diseases.[6,7] Hence, even though the current absolute risk of blood-borne infections associated with FFP is relatively small (less than 1 in 100,000 for the hepatitis viruses and HIV taken together),[4] SD plasma should be preferred to FFP in patients with RICD who need replacement therapy and cannot benefit from single-factor concentrates.

*ES, MM and PMM conceived and designed the study; MEM, MM, MS, AT and GB contributed to the collection, interpretation and analysis of clinical and laboratory data; ES, MEM and MM wrote the article and PMM revised it critically. All authors approved the final version of the manuscript. The authors declare that they have no potential conflicts of interest.*

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