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A model comparing how rapidly transfusion of solvent detergent plasma restores clotting factors versus infusion of albumin-saline

Petra Jilma-Stohlawetz [a,b], Friedrich W. Kursten [c], Michaela Horvath [a], Gerda Leitner [a], Jana List [a], Jana Marcek [d], Peter Quehenberger [b], Michael Schwameis [d], Johann Bartko [d], Bernd Jilma [d,*]

[a] Department of Blood Group Serology and Transfusion Medicine, Medical University of Vienna, Vienna, Austria
[b] Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria
[c] Clinical Research and Development Department, Octapharma Pharmazeutika Produktionsges.m.b.H, Vienna, Austria
[d] Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria

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ABSTRACT

Background: A recent randomized controlled trial demonstrated the bioequivalence between universally applicable and AB0 compatible transfusion plasma in healthy volunteers. There was a limited change in coagulation factor levels and inhibitors before and after plasmapheresis and subsequent plasma transfusion. The aim of this extension trial was to investigate the true capacity of these plasma products to restore baseline levels of coagulation factors and inhibitors after plasma depletion in comparison to haemodilution induced by infusion of albumin solution.

Materials and methods: Fourteen healthy subjects, who completed both plasma transfusion periods, underwent an additional plasmapheresis (600 mL) followed by an infusion of 1200 mL albumin (3.125%) in a third period.

Results: The fibrinogen levels, as well as other clotting factors (FII, FV, FVII and FXI), decreased by 10% after plasmapheresis, and subsequent infusion of albumin solution further aggravated this drop in clotting factors to approximately 20–25%. The clotting factors with a long half-life were not even restored 24 hours after infusion of albumin solution, whereas those with a short half-life were replenished by endogenous synthesis within 24 hours. In contrast, transfusion of either plasma product rapidly restored all clotting parameters and inhibitors (protein S and plasmin inhibitor) immediately after transfusion.

Conclusion: This study demonstrates that albumin solution induces an enhanced dilution of clotting factors and inhibitors, whereas both plasma products quickly compensated for the experimental loss of these plasma proteins.

1. Introduction

A recent randomized, double blind trial (hereafter referred to as the core study) demonstrated the bioequivalence between a pharmaceutical grade, universally applicable, pathogen safeguarded plasma (*Uniplas LG*) and its parent compound (*Octaplas LG*) in healthy individuals. This core trial also demonstrated the absence of haemolytic transfusion reactions after transfusion of universal plasma [1].

However, the changes in coagulation factor levels and inhibitors throughout the procedure of plasmapheresis (PPh; 600 mL of plasma was removed) and subsequent transfusion of 1200 mL plasma was rather small. For example, the observed decrease in fibrinogen averaged 13% after PPh,

* Corresponding author. Department of Clinical Pharmacology, Medical University of Vienna, Währingergürtel 18-20, A-1090 Vienna, Austria. Tel.: +43 (0)1 404002981; fax: +43 (0)1 404002998.
E-mail address: Bernd.Jilma@meduniwien.ac.at (B. Jilma).

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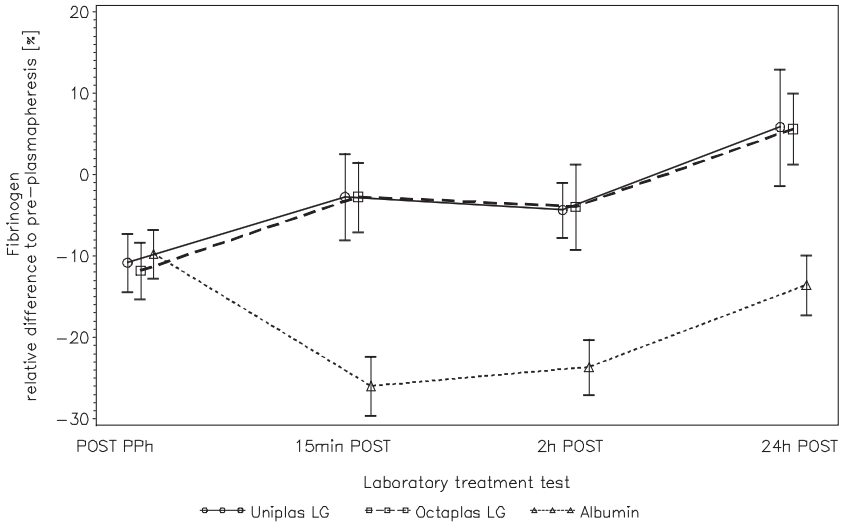

Fig. 1. Time courses of fibrinogen levels. Differences of fibrinogen levels relative to baseline (i.e., pre-plasmapheresis [PPh]) before and after transfusion of bioequivalent plasma products or infusion of albumin solution up to 24 hours post-infusion. Data are presented as means ± SD.

although a 25% decrease in plasma coagulation factors was expected. Likewise, fibrinogen increased by only 6% after transfusion of 1200 mL plasma (Fig. 1), although a greater rise in fibrinogen was expected based on the concentration of clotting factors in the plasma products (90% of normal). As both plasma products were active treatments and similar in terms of protein content and plasma colloid-osmotic pressure, the active-control design of the study did not provide any control to explore possible changes in plasma proteins throughout such a procedure.

We hypothesized that fluid redistribution may have occurred following PPh and/or plasma transfusion, and was responsible for the lower than expected observed effects in both directions. To address this issue experimentally, the core study was augmented by a third control period (extension arm), in which volunteers received an infusion of 1200 mL albumin solution after PPh, instead of plasma. Hence, the aims of the extension study and the overall analysis of the three periods were to validate the experimental model and setup to increase assay sensitivity, in order to investigate the true capacity of these plasma products to restore coagulation factor levels and inhibitors after experimental plasma depletion.

As albumin supports plasma colloid-osmotic pressure, it is often administered as a resuscitation fluid [2]. However, there is no clear consensus over the choice of resuscitation fluid. Fluid resuscitation with albumin was associated with higher mortality rates than was resuscitation with saline in a post-hoc study of patients with traumatic brain injury [3]. However, the use of albumin-containing solutions was associated with lower mortality compared with other fluid resuscitation regimens in a meta-analysis of studies with septic patients [4]. Finally, no substantial difference between crystalloids and colloids was seen in any important patient-centred outcome in 6997 critically ill patients [5]. Thus, it was also of interest to compare the effects of an infusion of 1200 mL albumin solution with plasma on coagulation parameters from the perspective of albumin as a potential resuscitation fluid.

2. Subjects and methods

The core study and subsequent amendments were approved by the Ethics Committee of the Medical University of Vienna and the national authority (Österreichische Agentur für Gesundheit und Ernährungsmittelsicherheit: AGES), and was conducted in compliance with the regulations of Good Clinical Practice (CPMP/ICH/135/95), and the Declaration of Helsinki 2008. All subjects re-consented in writing before inclusion into the extension study arm.

2.1. Study design and subject population

The objectives of this extension study were to compare the recovery of clotting factors and inhibitors of *Uniplas LG* and *Octaplas LG*, reported in the core study, with that of albumin solution (primary objective) and to compare the safety and tolerability of the pathogen safeguarded plasmas with those of an albumin infusion (secondary objective).

Subjects with blood group O were excluded, because they were not expected to be at risk of incompatibility after transfusion of *Uniplas LG*. Exclusion criteria and enrolment criteria for the extension arm (third period) were the same as for the core study [1], with the additional requirement that all subjects entering the extension arm had to have completed the core study. Thus, only subjects who had received full amounts of both plasma products (i.e., 1200 mL *Uniplas LG* and 1200 mL *Octaplas LG* [both Octapharma PPGmbH, Vienna, Austria]) in the core study were eligible for the extension study arm. This subgroup of eligible, healthy subjects underwent similar procedures as in the previous core study where they had received the two plasma products in a randomized sequence (randomization faxed from a central

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