Pharmacokinetics of Cefoperazone/sulbactam in Critically Ill Thrombotic Thrombocytopenic Purpura Patients Undergoing Therapeutic Plasma Exchange

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Abstract

AIMS The aim of this study was to investigate the pharmacokinetics of CFP and SUL in critically ill thrombotic thrombocytopenic purpura (TTP) patients undergoing TPE. METHODS Critically ill TTP patients receiving a dose of 3 g CFP/SUL (2.0 g/1.0 g) intravenously every 8 h were included in the study. Serial blood samples were collected at 0, 1, 2, 3, 4, 6, and 8 h at the third infusion with TPE (Session I) and the sixth infusion without TPE (Session II). Effluent samples were also collected at the effluent port of plasma eliminated during TPE. Concentrations of CFP and SUL in plasma and effluent were measured using LC/MS/MS. RESULTS Specific pharmacokinetic parameters were calculated to evaluate the effect of TPE on CFP and SUL. The amount of drug eliminated during TPE (QPE) were 395.75±147.38 and 35.25±11.32 mg, respectively. Percentage eliminated by TPE (fe%) were 11.38±3.18% and 2.74±1.13%, respectively. Calculated percentages of total drug clearance by TPE (%CLPE) were 27.71±10.8% and 6.16±2.16%, respectively. There were no significant differences in pharmacokinetic parameters (AUC0-8, Vd, T1/2a) between session I and session II for both CFP and SUL. CONCLUSIONS A single plasma volume TPE does not remove clinically significant amounts of CFP and SUL. Dosage adjustment in critically ill TTP patients after the procedure is not necessary. CFP is more likely to be removed than SUL during TPE due to its small Vd and high protein binding (Pb). Elevated plasma drug concentration due to organ dysfunction may permit more drug removal during TPE.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

* Patients with TTP are often at risk for multiple nosocomial infections and need to be treated with cefoperazone/sulbactam during TPE.

* Cefoperazone is highly protein bound and sulbactam has a small volume of distribution, which tend to be removed by TPE.

WHAT THIS STUDY ADDS ABOUT THIS SUBJECT

* We quantified the proportion of cefoperazone and sulbactam removed by TPE. Cefoperazone is more likely to be removed than sulbactam.

* No significant differences were observed in PK when compared with and without TPE.

* Dosage adjustment after TPE is unnecessary, and the time interval between TPE and drug infusion is negligible.

Abstract

AIMS

The aim of this study was to investigate the pharmacokinetics of CFP and SUL in critically ill thrombotic thrombocytopenic purpura (TTP) patients undergoing TPE.

METHODS

Critically ill TTP patients receiving a dose of 3 g CFP/SUL (2.0 g/1.0 g) intravenously every 8 h were included in the study. Serial blood samples were collected at 0, 1, 2, 3, 4, 6, and 8 h at the third infusion with TPE (Session I) and the sixth infusion without TPE (Session II). Effluent samples were also collected at the effluent port of plasma eliminated during TPE. Concentrations of CFP and SUL in plasma and effluent were measured using LC/MS/MS.

RESULTS

Specific pharmacokinetic parameters were calculated to evaluate the effect of TPE on CFP and SUL. The amount of drug eliminated during TPE (Q_{PE}) were 395.75±147.38 and 35.25±11.32 mg, respectively. Percentage eliminated by TPE (*fe* %) were 11.38±3.18% and 2.74±1.13%, respectively. Calculated percentages of total drug clearance by TPE (%CL_{PE}) were 27.71±10.8% and 6.16±2.16%, respectively. There were no significant differences in pharmacokinetic parameters ($AUC_{0\text{-}8}$, Vd, $T_{1/2a}$) between session I and session II for both CFP and SUL.

CONCLUSIONS

A single plasma volume TPE does not remove clinically significant amounts of CFP and SUL. Dosage adjustment in critically ill TTP patients after the procedure is not necessary. CFP is more likely to be

removed than SUL during TPE due to its small Vd and high protein binding (Pb). Elevated plasma drug concentration due to organ dysfunction may permit more drug removal during TPE.

Keywords: Pharmacokinetics; Thrombotic Thrombocytopenic Purpura; Cefoperazone; Sulbactam; Therapeutic Plasma Exchange; Removal;

Abbreviations: TTP, thrombotic thrombocytopenic purpura; TPE, therapeutic plasma exchange; CFP, cefoperazone; SUL, sulbactam; PV, plasma volume; Pb, protein binding; Vd, volume of distribution; AUC, area under concentration-time curve; Kel, elimination rate constant; CL, drug clearance; MOF: multiple organ failure.

Introduction

Thrombotic Thrombocytopenic Purpura (TTP) is a type of thrombotic microangiopathy, whose typical clinical manifestations include severe thrombocytopenic purpura, microangiopathic hemolytic anemia, neuropsychiatric symptoms, occasionally fever or renal damage. The main pathogenesis of TTP is associated with severe deficiency of ADAMTS-13 (von Willebrand factor-cleaving protease). TTP is considered as a rare and life-threatening hematologic critical illness with a mortality rate of up to 10 to 20 percent, even if diagnosed timely and treated properly. Currently, the first-line treatment for the acute episode of TTP is based on daily therapeutic plasma exchange (TPE). TPE is a therapeutic apheresis procedure for removal of pathologic substances, including anti-ADAMTS-13 antibodies, ADAMTS-13 immune complexes, and ultra-large VWF multimers. The replacement fluid is usually a large volume of fresh-frozen plasma containing ADAMTS-13, in order to maintain oncotic pressure and compensate for blood loss [1]. The application of TPE has greatly reduced the mortality of TTP patients and should be started as soon as possible.

The basic procedure for TPE can be performed through a highly permeable microporous filter with hemodialysis equipment or centrifugation with an apheresis device. According to the guidelines, one exchange procedure requires the replacement of approximately 1 to 1.5 plasma volume (PV) [2,3]. Similar to the mechanisms by which TPE clears pathologic substances, drugs that do not bind to proteins are more likely to be cleared from plasma compartment, resulting in sub-therapeutic doses and may affect therapeutic efficacy. The amount of drug eliminated by TPE is determined by pharmacokinetic properties of the drug and TPE-specific factors, such as the time between initiation of TPE and infusion of drug; plasma exchanged volume and TPE procedure frequency. The pharmacokinetic properties, especially volume of distribution (Vd) and protein binding (Pb), were considered to be the most dominant factors in determining whether a drug is susceptible to removal by TPE [7]. Drugs that exhibit a higher Pb (>80%) and smaller Vd (<0.2 L kg^{-1}) are more likely to be eliminated by TPE [5,6,7]. Amphotericin B liposomal, for instance, with a small Vd (0.1-0.16 L kg^{-1}) and high Pb (95%) can be significantly removed by TPE. A study has shown that supplemental doses are needed after TPE as therapeutic concentration fell below minimum inhibitory concentration [8].

Patients with critically ill TTP are often at high risk for multiple nosocomial infections and need to be treated with a combination of antibiotics during TPE in the intensive care unit (ICU). Beta-lactam antibiotics present similar pharmacokinetic properties and are widely used in current clinical practice. Most β-lactam antibiotics including ceftazidime, cefepime, and ampicillin showed poor removal by TPE [9, 10]. Cefoperazone/sulbactam (CFP/SUL) is a combination containing extended spectrum beta-lactamases (ESBL) inhibitor antibiotic widely used for the treatment of complicated several bacterial infections, such as extended-spectrum β-lactamase producing Enterobacteriaceae and carbapenem resistant Acinetobacter baumannii. Cefoperazone is highly protein bound (70-93%) with an average Vd of 0.28L kg^{-1} and a $T_{1/2}$ of 1.7 hours, while sulbactam has a low Pb of 40%, a small Vd of 0.14L kg^{-1}, and $T_{1/2}$ of 1 hour in subjects with normal renal and hepatic function. TPE has the potential to remove a certain amount of CFP or SUL. To the best of our knowledge, no information is available about the amount of CFP and SUL removed or pharmacokinetics changes during TPE. This is the first report to evaluate the effect of TPE on the pharmacokinetics of CFP/SUL, aim to provide relevant clinical suggestions for the optimization of antibiotic dosing regimens.

Materials and methods

Patients

This was a prospective, single-center study conducted in the Hemato-oncological intensive care unit of the first affiliated hospital of Harbin Medical University between Mar 2020 and June 2021. Critically ill TTP patients with suspected or confirmed infections who received CFP/SUL as an empirical or targeted therapy became candidates for this research. Patient characteristics and clinical data, including demographic data (sex, age, high weight), type of infection, and organ function characteristics were collected.

TTP was diagnosed based on current expert statements regarding the ICU management of patients with TTP [11]. The study was approved by the ethics committee of the participant hospital, and the study was conducted in adherence to the Declaration of Helsinki. Written informed consent was obtained from the patient designated decision-maker.

Therapeutic Plasma Exchange settings

TPE was carried out via a continuous-flow centrifugation system using the Fresenius Blood Cell Separator (Fresenius COM.TEC, Germany). Extracorporeal blood flow was maintained at 20˜40 ml min^{-1}. At the end of TPE, the blood was returned with 0.9% sodium chloride physiological solution. Fresh frozen plasma was used as volume replacement solutions. Sodium citrate (pH 5.0±0.5) was used in a 1:14 v/v ratio with blood as anticoagulant therapy.

Sample collection

Cefoperazone/sulbactam (Sulperazon, Pfizer, New York, USA) with cefoperazone 2.0 g/sulbactam 1.0 g in a 3-g ampoule was given to patients. A dose of 3.0 g CFP/SUL for adults was added to 100 mL of 0.9% normal saline solution and was administered by intravenous injection using an infusion pump at the usual rate for 60 min every 8 h. Each TPE session began 10 min after the end of the CFP/SUL infusion. 3 mL blood anticoagulated with EDTA were collected from median cubital vein. To evaluate the effect of TPE on the pharmacokinetics of CFP and SUL, whole blood samples were collected during two sessions.

Session I, the third dose of CFP/SUL was administered on the first day with TPE. Serial venous blood samples were collected at time 0 (trough concentration), time 1 (peak level, 10 min before TPE), and time 2, 3, 4, 6, 8 h after the start of drug infusion. An aliquot was also taken from the effluent port of plasma eliminated during TPE.

Session II, before the following day's TPE, a series of venous blood samples were collected respectively at the same time points at the sixth CFP/SUL administration without TPE.

Whole blood samples were centrifuged at 4°C at 3000 rpm for 10 min, and then the plasma was separated. All plasma samples were stored at -80°C until analysis.

Measurement of drug concentrations

Concentrations of CFP and SUL in plasma were simultaneously determined by liquid chromatography method with tandem mass spectrometer detection (LC-MS/MS). Ceftiofur was used as internal standard (IS). The plasma samples were extracted by protein precipitation. An aliquot of 200 μL plasma with 20 μL IS (100 μg mL^{-1}), was added with 400 μL acetonitrile. The mixture was then vortexed for 1 min and centrifuged at 13,500 rpm for 5 min at 4. The supernatant was injected into the LC-MS/MS system.

The LC-MS/MS system consisted of an AB ExionLC system and an AB SCIEX QTRAP QUADTM 4500MD (Applied Biosystems Sciex, Ont, Canada). The chromatographic separation was performed using a Waters Symmetry C18 column (150×4.6 mm, 5 μm). The column temperature was set at 40. The analysis was carried out using linear gradient elution with mobile phase acetonitrile-0.1% (v/v) formic acid in ammonium formate solution (10 mM), at a flow rate of 1 mL min^{-1}. The linear gradient was as follows: 0-1 min, 10% acetonitrile; 1-7 min, 10% to 90% acetonitrile; 7-8 min, back to the initial state. The total elution time was 8 min. The analytes were detected in negative electrospray ionization mode. Multiple reaction monitoring (MRM) was used to monitor precursor to product ion transition of m/z 644.1-528.1 for cefoperazone, m/z 231.9-140.1

for sulbactam, and *m/z*521.9-127.0 for IS. Ion spray voltage was at 4500 V and capillary temperature was at 550. Declustering potential (DP) was at 30 V for cefoperazone and IS, 12 V for sulbactam. The collision energy (CE) was optimized at 15 eV for cefoperazone, 17 eV for sulbactam, and 30 eV for IS, respectively. Dwell time was set at 100 ms for all the analytes.

The calibration curves ranged from 10 to 500 μg $mL^{-1}$for cefoperazone and 2 to 100 μg mL^{-1} for sulbactam, respectively. The accuracy and precision of QC samples were within ±10%.

Pharmacokinetic calculations

Specific pharmacokinetic parameters were used to evaluate the effect of TPE on CFP/SUL including the amount of drug eliminated during TPE (Q_{PE}); the fraction eliminated by TPE (*fe* %); Apparent volume of distribution (Vd); Area under the plasma level versus time curve (AUC); Elimination rate constant (Kel); Half-life ($T_{1/2}$) and Drug clearance (CL).

Q_{PE} was calculated as total volume of efluent port (V_{ep})×concentration of CFP or SUL concentration from effluent port (C_{ep}); In the equation: $Q_{PE}= V_{ep}\times C_{ep}$[12].

fe % can be calculated as Q_{PE}/TBS × 100%. Total Body Stores (TBS)=Vd×concentration before plasma exchange [13].

Kel=(ln C_a-ln C_b)/(T_b-T_a). T_b-T_a, duration of two blood collection time points, ln C_a and ln C_b, natural log of plasma drug concentrations at the corresponding time points T_a and T_b. Kel_{Total}=(ln C_1-ln C_3)/(T_3-T_1). ln C_1, natural log of plasma concentration at start of TPE. ln C_3, natural log of plasma concentration at the end of TPE; $Kel_{Patient}$=(ln C_1-ln C_3)/(T_3-T_1) on session II [4]; Definitions, the Elimination rate constant during TPE (Kel_{Total}) represents the contribution of durg removed due to TPE and patient; The contribution of durg eliminated due to patient is $Kel_{patient}$. $T_{1/2}$ can be calculated as 0.693/Kel [4].

Drug clearance while off TPE ($CL_{patient}$) was calculated for the values of $Kel_{Patient}$×Vd [13, 14]. The Drug clearance due to TPE (CL_{PE}) was calculated using the equation: $CL_{PE}=Q_{PE}/AUC_{PE}$. AUC_{PE}, the AUC during TPE [12, 13]. Total drug clearance (CL_{Total}) = CL_{PE}+$CL_{patient}$; The proportion of %CL_{PE} was determined by $CL_{PE}/CL_{Total}\times 100\%$. Creatinine clearance (Ccr) was calculated using the Cockroft-Gault equation [15].

Data were analyzed using the SPSS statistic version 22 (IBM; New York, NY, United). The Paired-samples t-test was used to compare the pharmacokinetics of the day with and without TPE. Calculated values of <0.05 were considered to be statistically significant. The correlation between plasma drug concentration before TPE and Q_{PE} were analyzed by Pearson's correlation coefficient.

Results

Four critically ill TTP patients with confirmed or suspected infections receiving cefoperazone/sulbactam monotherapy were enrolled. The median age was 55 years. **Table 1** lists the demographic clinical features in these patients. Of the 4 patients, mean (±SD) serum albumin concentration was 34.75±1.64g L^{-1}, mean total bilirubin (TBIL) was 49.2±13.53 μmol L^{-1} and mean creatinine clearance (Ccr) was 55.5±12.36 μmol L^{-1}. Patient 2 and 3 had a Ccr of 36 and 54 ml min^{-1}, respectively. The Ccr of patient 1 and 4 were above 60 mL min^{-1}. Three patients recovered and one patient died of sepsis. Mean duration and plasma volume exchanged per session were 96±10 min (85 112 min) and 1970+-36 mL (1910 2000 ml), respectively.

The Q_{PE} of CFP was 395+-147 mg (268 645 mg) and *fe* % was 11.38+-3.18% (8.43˜16.75 %). For SUL, the Q_{PE} was 35+-11 mg (20˜51 mg) and*fe* % was 2.74+-1.13 % (1.35˜4.28 %)**(Table 2)** . Noteworthy, a positive correlation was found between the amount of drug removed and plasma drug concentration of CFP and SUL before TPE, but there were no statistically significances (r= -0.895, p=0.056 for CFP, and r= -0.821, p=0.179 for SUL) **(Figure 2).**

Kel_{Total} and $Kel_{patient}$ were described in **Table 2** , respectively. For CFP, Kel_{Total} and $Kel_{patient}$ were 0.4+-0.14 and 0.26+-0.13 h^{-1}, which correspond to $T_{1/2}$ of 3.73+-1.27 and 3.24+-1.57 h; estimated Kel_{Total} and

$Kel_{patient}$ for SUL were 0.65+-0.15 and 0.46+-0.2 h^{-1}, which correspond to $T_{1/2}$ of 1.71+-0.26 and 1.72+-0.26 h, respectively. **(Figure 1).**The average Kel_{Total} for CFP and SUL were estimated to be 0.5-fold higher than that for $Kel_{patient}$. However, no significant differences were found in $T_{1/2a}$ for CFP and SUL between the two sessions (P=0.974 and P=0.967). The fraction of CFP and SUL eliminated due to TPE ($\%CL_{PE}$) were 27.71+-10.8% and 6.16+-2.16%, respectively.

Pharmacokinetics of CFP and SUL were also compared on both sessions **(Table 3).**$AUC_{0\text{-}8}$ of CFP on session I and session II were 1532.8+-768.95 and 1411.4+-789.43 mgxh L^{-1}, respectively (p=0.855). $AUC_{0\text{-}8}$ of SUL on session I and session II were 110.47+-36.22 and 115.12+-39.81mgxh L^{-1}, respectively (p=0.887) **(Table 3)** . There were little differences in pharmacokinetic parameters ($AUC_{0\text{-}8}$, Vd, and $t_{1/2}$) between session I and session II. We noticed that the maximal peak concentration of session I was higher than that of session II, it was thought to be the cause of the pharmacokinetic instability. We did not observe a redistribution phenomenon occurred at two hours after the TPE procedure

(Figure 1).

Discussion

To our knowledge, this is the first research to investigate the effect of TPE on CFP and SUL pharmacokinetics in critically ill TTP patients. The TPE specific properties and pharmacokinetic characteristics of the drug are two key factors determining drug elimination during TPE. The time between the drug infusion and TPE initiation are two factors that affect the amount of drug extracted from TPE. Researches have shown that the closer the time between drug infusion and TPE initiation, the greater the amount of drug removed by TPE [10]. In our presented four cases, TPE was initiated 10 min after intravenous infusion, at which point the majority of drugs would be primarily present in the intravascular space, and could therefore be removed by TPE [4,16]. Besides, volume of exchange is another significant TPE specific parameter driving the amounts of drug be removed by TPE. The treatment target for a plasma exchange procedure should be 1 to 1.5 PV, equivalent to a removal of approximately 63% and 78% of plasma contents respectively [17]. An increase in volume of exchange can increase a greater amount of drug extracted. In this study, the average volume of exchange is approximately 1970+-36.74 mL, corresponding to nearly one PV.

The pharmacokinetic properties of Vd and Pb are considered to be the most dominant factors determining whether a drug is susceptible to removal by TPE. Low Pb and high Vd always correlate with drug's distribution in tissues and cells and therefore are unsusceptible to removal by TPE. In contrast, drug with small Vd (¡0.2 L kg^{-1}) and high Pb (¿80%) are more easier to be removed during TPE due to the greater distribution of the drug in the vascular space [12,17]. In our study, we found that approximately 2000 mL exchange yielded a higher Kel_{Total} than the $Kel_{patient}$ without TPE , suggesting that TPE lead to increases in the rate of CFP and SUL elimination. $Q_{PE}$and *fe* % seems to be the most reliable parameters for the determination of the amount of drug removed via TPE. The fraction eliminated by TPE (*fe* %) was significant for CFP as 11.38+-3.18% (range 8.43˜16.75%). SUL is eliminated by TPE with only 2.74+-1.13% (range 1.35˜4.28%) from effluent port of depleted plasma. The *fe* % of CFP is over 4-fold higher than that of SUL. The calculated smaller Vd (0.14+-0.03 L $kg^{-1}$for CFP vs. 0.48+-0.15 L kg^{-1} for SUL) and higher Pb (70-93% for CFP vs. 38% for SUL, obtained from non-critically ill patients) may contribute to the remarkable increased fraction eliminated by TPE. In addition, it was suggested that a 30% increase in $\%CL_{PE}$ could be considered a clinically significant effect [13]. $\%CL_{PE}$ of CFP and SUL were about 27% and 6%, respectively. It is suggest that CFP is more likely to be removed than SUL during TPE. However, CFP and SUL removal by TPE may not be clinically significant.

There were only slight differences in parameters between session I and session II in those four patients**(Table 3)** . Unexpectedly, $AUC_{0\text{-}8}$ and Vd of CFP on session I were slightly increased than those on session II, contrary to our expectations. There are many aspects needed to be considered. First, it seems that TPE did not alter the pharmacokinetic behavior of CFP and SUL significantly. Then, the relatively elevated peak concentration at session I might due to pharmacokinetic instability might increase the $AUC_{0\text{-}8}$. Finally, the number of patients included in our trial is limited and two of four critically ill patients with severe infection

or septic shock received aggressive fluid resuscitation. Overhydrating status may lead to pharmacokinetics changes, such as AUC and Vd [18].

Additionally, TTP is considered as a life-threatening critical illness and often associated with severe complications such as hypoalbuminemia and multiple organ dysfunction (MOF). Hypoalbuminemia might cause decreased drugs binding resulting in less distribution of drugs in the vascular space, in favor of tissue distribution, especially for CFP with a larger Pb [19]. Besides, positive correlation was observed between Q_{PE} and plasma drug concentration before TPE, however it failed to reach statistical significance. SUL is mainly excreted by kidney (84%) while most of CFP is excreted via bile. Organ dysfunction is an important factor leading to elevated plasma drug concentration. In our cohort, the largest amount of CFP removed (645 mg) was noted in the patient with impaired bile excretion (TBIL 71.9 μmol L^{-1}, DBIL 31.5 μmol L^{-1}). Similarly, the largest amount of SUL (51 mg) removed in the patient with impaired renal function (Ccr 36 mL min^{-1}, serum creatinine 156 μmol L^{-1}). It is suggested that elevated plasma drug concentration and extended half-life due to organ dysfunction allow more drug removal by TPE. It is more remarkable when drug distribution half-life ($T_{1/2a}$) is longer than 2 hours of the TPE procedure duration [20]. In our cohort, $T_{1/2a}$ of CFP and SUL showed a prolongation compared with previous parameters in noncritically ill patients (˜1.7 h for CFP and ˜1 h for SUL). $T_{1/2a}$ of CFP is longer than 2 hours, which is one of the reasons why its *fe* % is higher than that of SUL.

The pharmacokinetics of CFP/SUL vary widely among critically ill patients. Therefore, it would be worthwhile to carry out further studies to confirm these results.

Conclusion

In general, we firstly describe the pharmacokinetics of CFP and SUL in critically ill TTP patients undergoing TPE. Results confirmed that Vd and Pb are the two dominant factors determining drug elimination by TPE. CFP is more likely to be removed than SUL during TPE due to its a small Vd and high Pb. However, the amount of CFP and SUL removed by TPE may not be clinically significant, and dosages should not be adjusted in critically ill TTP patients undergoing TPE.

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Competing interests

None declared.

Compliance with ethical standards

Ethics approval was obtained from the ethics committee of the participant hospital, and the study was conducted in adherence to the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Conflict of interest

The authors declare no conflict of interest.

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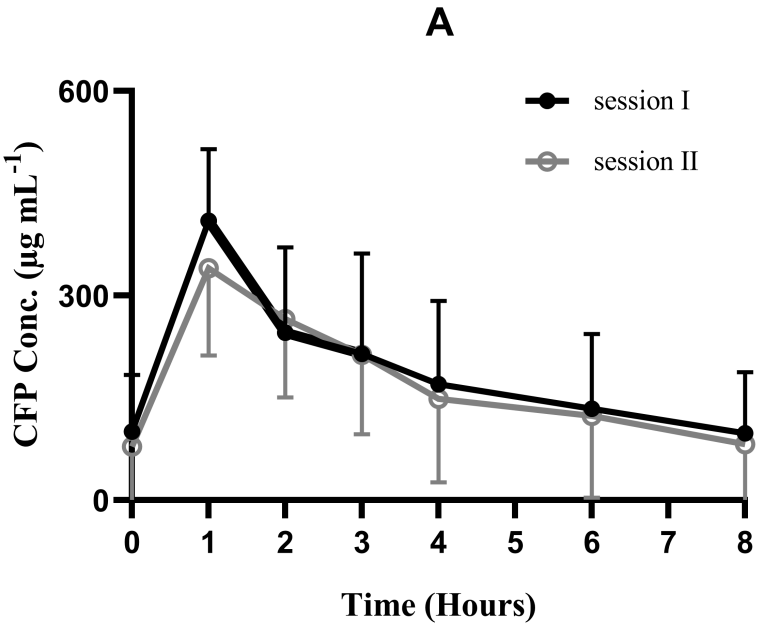

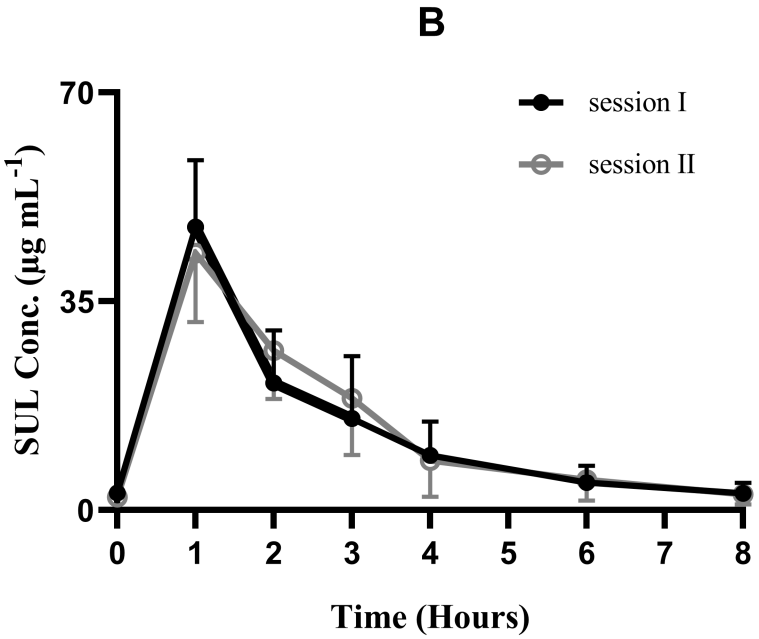

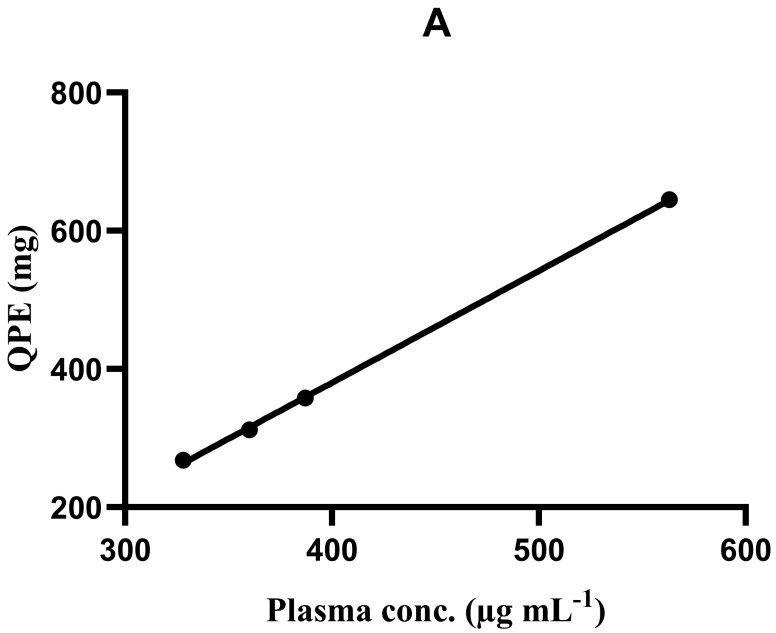

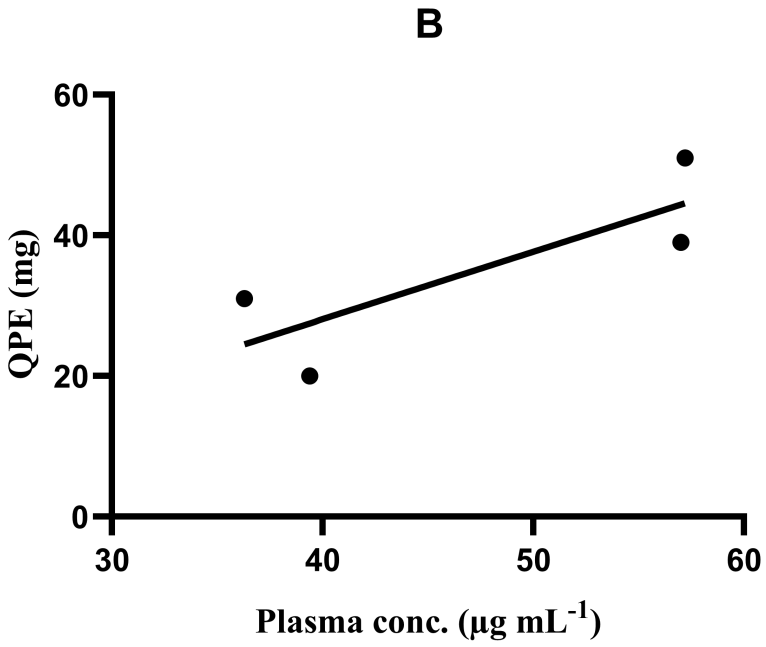

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