

Ceftaroline removal during plasmapheresis



Eliminación de ceftarolina durante la plasmaféresis

Ceftaroline is a broad-spectrum cephalosporin indicated for the treatment of complicated skin-structure infections and community-acquired pneumonia. Its effect depends on the cumulative percentage of time over the interval by which the free antimicrobial concentration exceeds the MIC.^{1,2}

Plasmapheresis removes abnormal cells or substances in the blood that are associated with or cause a certain disease. Depending on the characteristics of the drug plasmapheresis could affect its clearance rate.³

We report a case of a 72-year-old female (weight 53 kg, body mass index: 20.7 kg/m²) with no known allergies, and a history of hypertension, dyslipemia and double aortocoronary bypass. In October 2018, was admitted to the emergency department due to dyspnea and cough during the previous 5 days. Upon admission, she presented tachycardia and hypotension. Also blood tests revealed an elevated serum creatinine (SCr) level of 1.97 mg/dL and a white blood count of 20.000 cells/mm³. Based on the X-ray results, she was diagnosed with a bilateral bronchopneumonia. Her initial clinical condition status was deteriorated and was admitted to the Intensive Care Unit, receiving ceftriaxone 2 g q24h and levofloxacin 500 mg q12 h. An induced sputum culture was obtained, where MRSA was isolated (MIC $\leq$ 4 mcg/mL for linezolid). Then, treatment with levofloxacin was modified to linezolid 600 mg q12h and ceftriaxone was maintained.

Clinical evolution declined with respiratory failure, agitation, decreased urinary output, anemia and thrombocytopenia. After respiratory worsening and persistence of anemia and thrombocytopenia, microangiopathic hemolytic anemia secondary to possible severe MRSA pneumonia was suspected. The diagnosis was confirmed with other laboratory data: negative Coombs test, increased lactate dehydrogenase 1115 U/L, haptoglobin < 2.44 mg/dL, presence of 4–5% of schistocytes and ADAMS-13 levels 13%. The patient was diagnosed with thrombotic thrombocytopenic purpura and the antibiotic treatment was changed to ceftaroline. In addition, five sessions of plasmapheresis were prescribed. The patient presented resolution of all signs and symptoms of infection after twelve days of treatment including platelet count and recovery of renal function.

Unlike extracorporeal oxygenation techniques and renal replacement therapy,^{4,5} there is no information on the PK behavior of ceftaroline in patients during plasmapheresis.⁶

To assess the potential influence of plasmapheresis on ceftaroline PK, consecutive blood samples were taken on day 10 (plasmapheresis session) and 11 (without plasmapheresis). Blood samples were analysed by high performance liquid chromatography. Once ceftaroline plasma concentrations (CPC) were obtained, pharmacokinetic parameters were calculated. Ceftaroline doses were adjusted according to the renal function of the patient and plasmapheresis sessions. CPC described in Fig. 1.

Plasma exchange could indirectly alter drug therapy. Prolonged exchange sessions and a larger volume of plasma collected may be the main reasons for altered drug clearance.³ Some factors that influence drug clearance during plasmapheresis are high plasma protein binding (PPB) (>75%) and low volume of distribution (Vd) (<0.3 L/kg).³ Only some information on drug removal during this technique is available from previously published studies, and information on antimicrobials is limited. A review by Kintzel et al.⁷ concluded that drugs that remain in the intravascular compartment are more susceptible to be removed by plasmapheresis than those with an extensive cellular and tissue distribution.

Another study by Vay et al.⁸ found no alteration in voriconazole plasma concentrations (Vd 4.6 L/kg) after plasmapheresis in a critically ill patient. Ibrahim et al.³ observed that ceftriaxone (PPB = 96%; Vd = 0.1 L/kg) needed to be administered with a difference of 15 h from plasmapheresis.

Our results showed that ceftaroline (PPB < 20%; Vd = 0.3 L/kg) clearance was two-fold higher during plasmapheresis (3.79 h vs. 6.67 h). In fact, ceftaroline half-life has been reported to be approximately 2.5 h in healthy subjects.^{1,2} Taking into account that the patient presented renal impairment during plasmapheresis (SCr = 2.31 mg/dL, normal range: 0.7–1.2 mg/mL), half-life should have risen to higher values, but in our patient, half-life was closer to normal renal function values.

Although ceftaroline clearance rate was higher during plasmapheresis, CPC were still considered therapeutic, according EUCAST clinical breakpoint values for MRSA (MIC = 1 mcg/mL).⁹

In conclusion, a significant clearance of CPC during plasmapheresis was observed. Although further pharmacokinetic studies are needed to fully elucidate ceftaroline PK, this antibiotic should be used with caution when using extracorporeal clearance therapies. Therapeutic drug monitoring should be performed to achieve effective antimicrobial plasma concentrations during plasmapheresis.

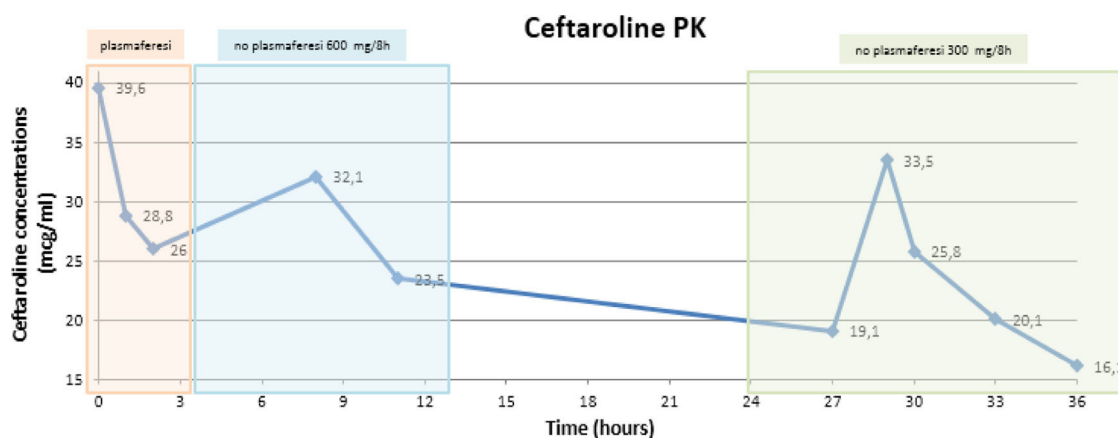


Fig. 1. Ceftaroline plasma levels.

References

1. Grau S, Sorlí L, Luque S. Farmacocinética y farmacodinamia de ceftarolina. *Enferm Infecc Microbiol Clin.* 2014;32 Suppl. 2:15–20. Ediciones Doyma, S.L.
 2. Kiang TKL, Wilby KJ, Ensom MHH. A critical review on the clinical pharmacokinetics pharmacodynamics, and clinical trials of ceftaroline. *Clin Pharm.* 2015;54:915–31. Springer International Publishing.
 3. Ibrahim RB, Liu C, Cronin SM, Murphy BC, Cha R, Swerdlow P, et al. Drug removal by plasmapheresis: an evidence-based review. *Pharmacotherapy.* 2007;27:1529–49.
 4. Riccobene T, Jakate A, Rank D. A series of pharmacokinetic studies of ceftaroline fosamil in select populations: normal subjects, healthy elderly subjects, and subjects with renal impairment or end-stage renal disease requiring hemodialysis. *J Clin Pharmacol.* 2014;54:742–52.
 5. Chung SJ, Lim TP, Kwa AL. Intravenous ceftaroline 200 mg administered every 8 h is safe and adequate for methicillin-resistant *Staphylococcus aureus* bloodstream infections in end-stage renal failure patients on haemodialysis: a case study. *Int J Antimicrob Agents.* 2015;46:720–1.
 6. Gonçalves-Pereira J, Póvoa P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of β -lactams. *Crit Care.* 2011;15.
 7. Kintzel PE, Eastlund T, Calis KA. Extracorporeal removal of antimicrobials during plasmapheresis. *J Clin Apher.* 2003;18:194–205.
 8. Vay M, Foerster KI, Mahmoudi M, Seeßle J, Mikus G. No alteration of voriconazole concentration by plasmapheresis in a critically ill patient. *Eur J Clin Pharmacol.* 2019;75:287–8.
 9. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 10.0; 2020. <http://www.eucast.org>
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