Ceftriaxone Dosing in a Critically Ill Patient With Hypoalbuminemia During Continuous Venous Hemofiltration

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Ceftriaxone Dosing in a Critically Ill Patient With Hypoalbuminemia During Continuous Venous Hemofiltration: Emphasis on Unbound Pharmacokinetics

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Keywords

unbound plasma concentration, ceftriaxone, pharmacokinetics, hypoalbuminemia, continuous venovenous hemofiltration

Ceftriaxone is a β-lactam antibiotic with extensive protein binding (85% to 95%).[1,2] Low albumin levels commonly found in critically ill patients may increase the ceftriaxone unbound fraction and affect pharmacodynamic target attainment.[2–4] We assessed the effect of unbound ceftriaxone plasma concentrations on the pharmacokinetic-pharmacodynamic targets in a critically ill patient requiring continuous venovenous hemofiltration (CVVH) and present a new ceftriaxone dosing recommendation.

A 76-year-old female patient (body mass index 28 kg/m^2) was admitted to our intensive care unit with Gram-negative septic shock due to *E coli*. Her APACHE IV score at admission was 121, indicating a mortality risk of 81%. Serum albumin concentration was 10 g/L (normal 5-50 g/L), and hematocrit was 0.21 (normal 0.35-0.45). She received intravenous ceftriaxone at the standard dose of 2000 mg once daily and developed renal failure (Kidney Disease Improving Global Outcomes stage 3) requiring CVVH at day 11.

CVVH was conducted using the AN69ST hemofilter with a surface area of 1 m^2 following the regional citrate anticoagulation CVVH protocol.[5] Blood flow and ultrafiltrate rates were set at 180 and 0 mL/min, respectively. Prismocitrate 18/0 at 1440 mL/h and Phoxilium at 1600 mL/h were infused as prefilter and postfilter dilutions, respectively, with an effluent flow rate of 3040 mL/h.

Ceftriaxone, plasma, prefilter, postfilter, ultrafiltrate, and urine samples were collected over 40 hours at 8 different time points. Total and unbound concentrations of ceftriaxone were measured using validated liquid chromatography–tandem mass spectrometry and calculating the sieving coefficient (SC).[6] A 2-compartment model was used for pharmacokinetic analysis.

Total ceftriaxone concentrations ranged between 36.0 and 139.6 mg/L, and unbound ceftriaxone concentrations ranged between 21.2 and 102.9 ml/L. The median unbound ceftriaxone fraction was 67.8% (interquartile range 58.9-73.7). Total ceftriaxone clearance was 40.6 mL/min. Clearance by CVVH was 40.0 mL/min, which accounted for approximately 99% of total ceftriaxone clearance. The volume of distribution was 16.1 L, and median SC was 0.74 (interquartile range 0.63-0.82). The residual renal clearance was 0 mL/min.

Our case demonstrates that extreme hypoalbuminemia greatly impacts pharmacokinetics during CVVH treatment and translates into higher concentrations of ceftriaxone exposure (Figure 1). In our patient the standard recommended dose of ceftriaxone, 2000 mg, administered intravenously resulted in unbound concentrations approximately 5 times greater than the present EUCAST (European Committee on Antimicrobial Susceptibility Testing) minimum inhibitory concentration (MIC) breakpoint of 1 mg/L for *E coli* (90% to 100% $fT_{4x\ MIC\ -5x\ MIC}$).[7] Simulations based on total ceftriaxone concentrations and 95%

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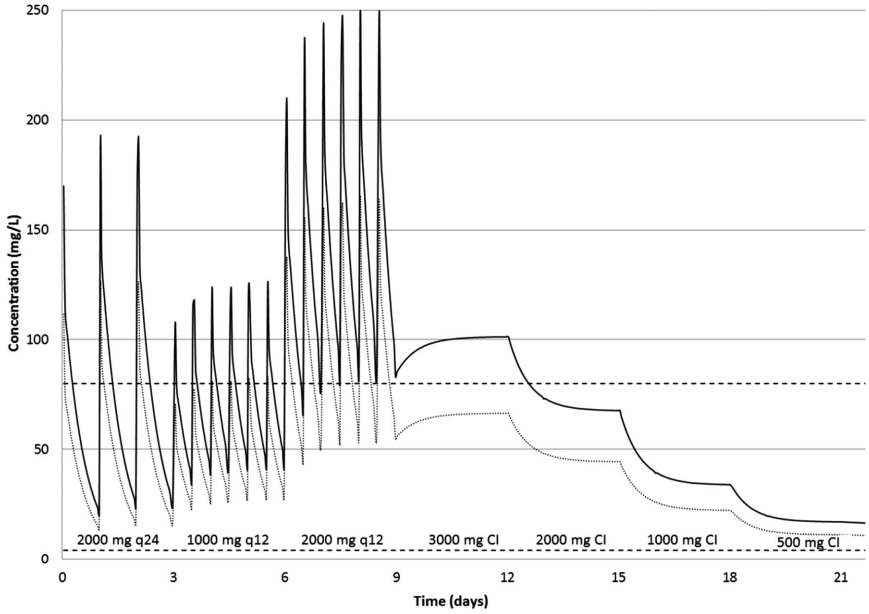

Figure 1. Dose simulation graphs based on 2-compartment analysis showing the result of concentration-time curves of total and unbound ceftriaxone plasma concentrations in a critically ill patient with hypoalbuminemia receiving CVVH and treated using several dosing regimens of ceftriaxone. The x-axis shows the dose regimens of intravenous ceftriaxone administered intermittently (ceftriaxone 2000 mg once daily, ceftriaxone 1000 mg twice daily, ceftriaxone 2000 mg twice daily) or via continuous intravenous infusion (CI) over 24 hours (respectively 3000 mg, 2000 mg, 1000 mg, and 500 mg). The y-axis shows the calculated total and unbound concentrations of ceftriaxone. The graph with the solid line represents simulations based on the total plasma concentration. The graph with the dotted line represents simulations based on measured unbound ceftriaxone concentrations. The median unbound fraction was set at 67.8% as was found in our patient. The upper horizontal dashed line represents the ceftriaxone target concentration of 80 mg/L based on total drug concentration in a patient with a normal unbound fraction corresponding to 95% protein binding. The lower horizontal dashed line represents the PK/PD threshold of unbound ceftriaxone of 1 mg/L and target attainment of 4×100% *f*T above the present EUCAST MIC breakpoint for *E coli*. CI indicates continuous infusion of 500-3000 mg/day; CVVH, continuous venovenous hemofiltration; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibiting concentration; PD, pharmacodynamics; PK, pharmacokinetic; q12, twice daily; q24, once daily.

albumin binding (Figure 1) showed the discrepancy between measured and predicted unbound concentrations. Unbound ceftriaxone dosing simulations indicate target attainment with a dosing regimen of 500 mg/24 h by continuous intravenous infusion, thereby preventing potential toxic side effects and ineffective therapy (Figure 1). High unbound plasma ceftriaxone concentrations may also have accounted for the higher SC values found in our analysis.[6,8,9] We can expect the measurement of unbound antibiotic concentrations to increase in Western countries because of the increased demand for individualized patient care and personalized antibiotic dosing schedules.

Our data emphasize the importance of using unbound concentrations of ceftriaxone to determine dosage regimens in patients with hypoalbuminemia who are receiving CVVH. Pharmacokinetic modeling revealed unbound ceftriaxone pharmacokinetic/pharmacodynamic target attainment for *E coli* following 500 mg/24 h by continuous intravenous infusion.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

References

1. Garot D, Respaud R, Lanotte P, et al. Population pharmacokinetics of ceftriaxone in critically ill septic patients: a reappraisal. *Br J Clin Pharmacol*. 2011;72(5):758-767.
2. Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. *Clin Pharmacokinet*. 2011;50(2): 99-110.
3. Wong G, Briscoe S, Adnan S, et al. Protein binding of β-lactam antibiotics in critically ill patients: can we successfully predict unbound concentrations? *Antimicrob Agents Chemother*. 2013;57(12):6165-6170.
4. Schleibinger M, Steinbach CL, Topper C, et al. Protein binding characteristics and pharmacokinetics of ceftriaxone in intensive care unit patients. *Br J Clin. Pharmacol.* 2015;80(3): 525-533.
5. Janssen PK, Foudraine NA, Burgers DM, Neef K, le Noble JL. Population pharmacokinetics of cefuroxime in critically ill patients receiving continuous venovenous hemofiltration with regional citrate anticoagulation and a phosphate-containing replacement fluid. *Ther Drug Monit*. 2016;38(6):699-705.

6. Meenks SD, Foudraine NA, Janssen PKC, le Noble J. Pharmacokinetics and dose individualization of ceftriaxone in a hepatically impaired, critically-ill patient receiving continuous venovenous hemofiltration. *Int J Clin Pharmacol Ther*. 2018;56(3):148-150.
7. The European Committee on Antimicrobial Susceptibility Testing. 2019. Eucast Clinical Breakpoints Tables Version 9.0. http://www.eucast.org. Accessed June 1, 2019.
8. Choi G, Gomersall CD, Tian Q, Joynt GM, Freebairn R, Lipman J. Principles of antibacterial dosing in continuous renal replacement therapy. *Crit Care Med*. 2009;37(7):2268-2282.
9. Harvey B, Johnson TN, Yeomanson D, Mulla H, Mayer AP. Ceftriaxone pharmacokinetic properties during continuous veno-veno haemofiltration using an in vitro adult, paediatric and neonatal model. *Perfusion*. 2014;29(1):32-38.