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Pharmacokinetics of caspofungin in a critically ill patient with liver cirrhosis

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Dear Editor,

We would like to report the pharmacokinetics (PK) of caspofungin in a critically ill patient with Child B9 liver cirrhosis. Caspofungin is the first echinocandin approved for the treatment of invasive fungal infections caused by *Candida* and *Aspergillus* spp [1]. Because it is generally well tolerated and appears to have limited interaction with other drugs, caspofungin is potentially an important agent in the treatment of invasive fungal infections in critically ill patients, especially in those not tolerating treatment with voriconazole due to severe liver insufficiency [1].

Case history

A 53-year old man (85 kg) was admitted to the intensive care unit (ICU) because of respiratory failure and septic shock due to spontaneous bacterial peritonitis. He has a past medical history of alcoholic liver cirrhosis (Child-Pugh score B9) and was recently diagnosed with acute myeloid leukemia (AML-M2). Three weeks prior to admission he was treated with high dose cytarabine. On admission, physical examination revealed high fever, low blood pressure, ascites and acute respiratory failure. Blood analysis showed neutropenia, acute renal failure and high C-reactive protein level. Liver function tests revealed a total bilirubin level of 3.54 mg/dL (nl < 1), aspartate transaminase level of 104 U/L (nl < 32) and alanine transaminase level of 140 U/L (nl < 31). He required orotracheal intubation, mechanical ventilation, administration of vasopressors and renal replacement therapy. Chest X-ray showed signs of pneumonia. Meropenem 1g once daily was empirically associated.

A progressively increasing serum *Aspergillus* antigen and a computed tomography scan of the chest was compatible with invasive pulmonary aspergillosis for which treatment was started with caspofungin. Given the poor prognosis of invasive aspergillosis and good safety profile of caspofungin, it was decided to administer a full dose of 70 mg once daily, as required for patients with a body weight exceeding 80 kg, in contrast to a reduced dose recommended in patients with moderate liver cirrhosis [2].

Caspofungin steady state trough (C_{24h}) and peak (C_{1h}) plasma levels were determined on days 13 and 14 of treatment with a previously validated HPLC-UV method [3]. Troughs and peaks were 3.81 and 3.88 mg/L and 8.01 and 9.07 mg/L, respectively on days 13 and 14. PK parameters were calculated on the mean trough and peak levels as described previously and shown in Table I [3]. The patient's liver function tests remained stable during treatment with caspofungin, and the serum *Aspergillus* antigen gradually decreased, which was interpreted as a good antifungal response without systemic toxicity. The lesions on chest X-ray improved as well.

Discussion

The recommended dose for treating invasive fungal infections is 70 mg on day 1 followed by a maintenance dose of 50 mg/day [1]. However, a dose reduction to 35 mg daily following the 70 mg loading dose is recommended for patients with moderate hepatic insufficiency (Child-Pugh score B7-9), as the area under the curve (AUC_{0-24}) of caspofungin is significantly increased in this population [1,4]. The phase I PK studies addressing dosing recommendations in patients with hepatic insufficiency were however undertaken in

patients with chronic and stable hepatic insufficiency, without acute episodes of illnesses [4]. There are no data on the pharmacokinetics of caspofungin in critically ill, mechanically ventilated patients with underlying liver cirrhosis.

In Table I, PK parameters as calculated in our patient were compared to the ones calculated after single and multiple doses of 70 mg in healthy subjects, to trough levels described in 40 surgical ICU patients and to the PK parameters as calculated after multiple dosing in patients with moderate liver failure [4-6]. As shown, the AUC_{0-24} is comparable to the one reported in healthy subjects; accumulation due to decreased hepatic metabolism resulting in a significantly higher systemic exposure (C_{1h} , C_{24h} , AUC_{0-24}) was not seen. Moreover, it seems that using a standard dose of caspofungin in severely ill patients with underlying moderate liver disease is probably needed to avoid underdosing. Reducing the dose in our patient, as recommended for patients with Child-Pugh score B7-9 liver failure, would probably have resulted in too low caspofungin systemic exposure and therapeutic failure. Possible explanations for this result are PK alterations typically seen in ICU patients, e.g. capillary leak due to sepsis leading to a higher distribution volume or lower albumin levels leading to a more rapid elimination by the kidney or hemodialysis.

In critically ill patients with life-threatening invasive fungal infections, benefits and risks of adjusting caspofungin dose in accordance to the recommendations for patients with chronic liver failure have to be carefully assessed. Therapeutic drug monitoring can potentially assist in these particular situations in preventing drug related toxicity or underdosing leading to therapeutic failure.

Table I Pharmacokinetic parameters compared to previously reported results

| | C _{24h} , mean (mg/L) | C _{1h} , mean (mg/L) | AUC ₀₋₂₄ * (mg.h/L) | Vd (L/kg) | Cl (ml/min) | t _{1/2} (h) |
|---|-----------------------------------|----------------------------------|-----------------------------------|--------------|----------------|-------------------------|
| Case | 3.84 | 8.54 | 148.6 | 0.16 | 7.8 | 19.9 |
| PK parameters in healthy subjects (MD 70 mg) [5] | 2.61 | 15.42 | 144.27 | NR | 9.85 | 10.70 |
| SICU patients (MD 70 mg-50 mg) [6] | 0.52-4.08 | NR | NR | NR | NR | NR |
| PK parameters in patients with moderate HI (Child-Pugh score B7-9) (SD 70 mg) [4] | 2.81 | 12.10 | 210.18 | NR | 5.55 | 15.07 |

*AUC₀₋₂₄ calculated in the patient case from mean peak and trough concentrations; AUC₀₋₂₄ in ref. 4 and 5 was calculated from 12 concentrations. MD, multiple dose; SD, single dose; HI, hepatic insufficiency; SICU, surgical intensive care unit; C_{24h}, trough level; C_{1h}, peak level; AUC, area under the curve; Vd, distribution volume; Cl, clearance; t_{1/2}, half-life; NR, not reported

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Chen SC, Slavin M, Sorrell TC (2011) Echinocandin antifungal drugs in fungal infections. *Drugs* 71:11-41.
2. Caspofungin acetate. European Public Assessment Report – Scientific Discussion. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000379/WC500057186.pdf (Cited: December 28, 2010)
3. Spriet I, Annaert P, Meersseman P et al (2009) Pharmacokinetics of caspofungin and voriconazole in critically ill patients during extracorporeal membrane oxygenation. *J Antimicrob Chemother* 63:767-770.
4. Mistry GC, Migoya E, Deutsch PJ et al (2007) Single- and multiple-dose administration of caspofungin in patients with hepatic insufficiency: implications for safety and dosing recommendations. *J Clin Pharmacol* 47: 951-961.
5. Stone JA, Holland SD, Wickersham PJ et al (2002) Single-and multiple dose pharmacokinetics of caspofungin in healthy men. *Antimicrob Agent Chemother* 46: 739-45.
6. Nguyen TH, Hoppe-Tichy T, Geiss HK et al (2007) Factors influencing caspofungin plasma concentrations in patients of a surgical intensive care unit. *J Antimicrob Chemother* 60:100-106.

