Pharmacokinetics and optimal exposure of antifungal drugs in critically ill patients

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Chapter 7

Plasma concentrations of caspofungin at two different dosage regimens in a patient with hepatic dysfunction

Abstract

*The currently recommended dosage regimen of caspofungin (50 mg/day) was developed for patients with invasive candidiasis. With invasive aspergillosis, successful outcomes occur in less than half the patients. We evaluate the pharmacokinetics in a patient with elevated liver enzyme levels after liver transplantation, who received caspofungin for the treatment of aspergillosis. Plasma concentrations of caspofungin were monitored at 2 different dosage regimens. The area under the concentration-time curve (AUC) at a dosage of 70 mg was 191 mg*hr/L and was associated with an increase in liver enzymes. After dose reduction to 50 mg with an AUC of 100 mg*hr/L, liver enzymes normalized. In conclusion, caspofungin plasma concentrations may be helpful to evaluate exposure and reduce the need for off-label dosing.*

7.1 Introduction

Invasive aspergillosis (IA) is a rapidly progressive disease and an important cause of morbidity and mortality in immunocompromised patients [1,2]. The guideline of the Infectious Diseases Society of America for the treatment of IA recommends the use of voriconazole as primary therapy. In patients who are refractory to or intolerant of voriconazole, a lipid formulation of amphotericin B or caspofungin can be used. The currently recommended dosage regimen of caspofungin in adults with a body weight $\leq$ 80 kg consists of an intravenous loading dose of 70 mg on day 1, followed by a daily maintenance dose of 50 mg. Although this dosage regimen was developed for patients with invasive candidiasis (IC) [3], it is evaluated for the treatment of IA. These studies have shown a favourable response of 33-42% [4,5]. Caspofungin is concentration-independent and highly bound to plasma proteins. The unbound fraction in plasma varies from 3.5% in healthy volunteers to 7.6% in patients with IC [6,7]. Caspofungin is generally well tolerated; the most frequently reported adverse effects are elevation in liver enzyme levels, gastrointestinal upset,

and headaches [1].

7.2 Case report

A 60-year-old woman (weight: 65 kg) was admitted to our hospital for liver transplantation. Tacrolimus and mycophenolic acid were administered as immunosuppressive therapy. Alkaline phosphatase (ALP) concentration was 180 IU/L (normal $<$ 120 IU/L), aspartate aminotransferase (AST) concentration was 205 IU/L (normal $<$ 40 IU/L), alanine aminotransferase (ALT) concentration was 258 IU/L (normal $<$ 45 IU/L), and gamma-glutamyl transpeptidase (GGT) was 66 IU/L (normal $<$ 40 IU/L) on day 6 after transplantation. Albumin concentration was 2.2 g/dL (normal 3.5-5.5 g/dL) and the Child-Pugh score (CPS) was 9.

Four days after the transplantation, the patient suffered from respiratory insufficiency and was intubated. Six days after transplantation, *Aspergillus fumigatus* susceptible to voriconazole and amphotericin B was isolated from sputum. In addition, the thoracic computed tomography scan showed several lesions distinctive for pulmonary IA and the patient was diagnosed with probable IA.

Voriconazole was started in an intravenous loading dose of 6 mg/kg twice daily followed by a reduced dose of 3 mg/kg twice daily, because liver enzyme levels were elevated. On day 27 after the transplantation, liver enzymes were still elevated, ALP was 329 IU/L, AST 40 IU/L, ALT 19 IU/L, and GGT 612 IU/L. Furthermore, the trough concentration of voriconazole (0.2 mg/L) was subtherapeutic and therefore therapy was switched to caspofungin. Amphotericin B was considered not suitable for this patient because of her estimated glomerular filtration rate of 34 mL/min.

With the intent of maximizing the potential effectiveness and with the known safety at higher dosages described in the literature [8–11], a daily dose of 70 mg caspofungin was chosen. With existing moderate increase in liver enzyme levels, plasma concentrations of caspofungin were assessed on day 5 of therapy by a validated HPLC fluorescence detection method at the department of Clinical Pharmacy, Nijmegen. The 24-h area under the concentration-time curve (AUC), which was calculated based on the linear-log-trapezoidal rule, was 191 mg*hr/L (Fig. 7.1).

Notably, it is the unbound fraction that exhibits pharmacologic effects. Therefore, the free drug AUC (fAUC) was calculated. Considering an unbound fraction of 7.6%, the fAUC was 14.5 mg*hr/L. The minimum inhibitory concentration (MIC) of the *Aspergillus fumigatus* isolated from our patient was 0.05 mg/L, which is similar to MICs described in the literature [12]. The above resulted in a calculated fAUC/MIC ratio of 290.

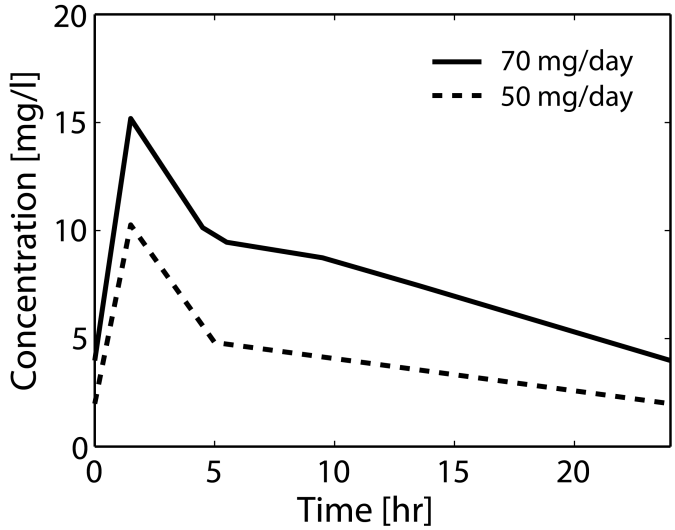

Figure 7.1: *The 24-h area under the concentration-time curve of caspofungin with a dosage of 70 mg and 50 mg/day.*

Considering the severity of the infection and the good tolerability of caspofungin by our patient, we decided to maintain the dosage at 70 mg/day. Afterwards, the ALP concentration further increased to 605 IU/L, AST was 33 IU/L, ALT 30 IU/L, and GGT 483 IU/L on day 39 after transplantation. No other hepatoxic medication was given to the patient, nor was new medication introduced at this time. No clinical symptoms of cholestasis or other liver disease were present and were therefore excluded as underlying causes of the elevated liver enzymes.

The dosage of caspofungin was decreased to 50 mg/day and, in the following days, the ALP concentration decreased to 175 IU/L, AST to 25 IU/L, AST to 14 IU/L, and GGT to 79 IU/L. At steady state, plasma concentrations of caspofungin were measured. The calculated AUC was 100 mg*hr/L (Fig. 7.1) and the corresponding fAUC was 7.6 mg*hr/L, which resulted in a fAUC/MIC ratio of 152. Treatment with caspofungin was continued in a dosage of 50 mg/day and liver enzyme levels remained stable since the time of the last measurement.

After a total of 7.5 weeks of caspofungin treatment, the patient was mobilized for upcoming discharge. The antifungal treatment at discharge was continued with voriconazole orally, as liver function had normalized [1].

7.3 Discussion

We described a case of IA treated with caspofungin at 2 different dosage regimens. Although caspofungin is proven to be an effective antifungal agent in the treatment of IA, successful outcomes occur in less than half the patients receiving caspofungin in the currently recommended dosage regimen [4, 5, 13]. Furthermore, the tolerance of caspofungin at higher dosages has been studied. The use of caspofungin in a dosage of 70-150 mg/day in patients with IC and IA was well tolerated and the incidence of drug-related adverse events was similar between the standard and high-dose regimens. No serious drug-related adverse events or discontinuations of the study therapy because of drug-related adverse events were reported [8–11]. Considering the severity of the infection, the reported response rate, and the encouraging safety experience at higher dosages, a dose of 70 mg caspofungin per day was chosen with the aim of maximizing the effectiveness of the treatment.

However, 2 weeks after the start of the caspofungin treatment, the ALP concentration further increased and GGT remained elevated. No interacting or hepatotoxic comedication was used and no clinical symptoms of cholestasis or other liver disease were present.

Elevation in liver enzyme levels has been reported as a side effect of caspofungin [1, 2]. The use of a higher dosage of caspofungin than recommended may have contributed to the hepatotoxicity in our patient. Patients with a CPS of 7-9 should receive a maintenance dosage of caspofungin of 35 mg/day [12, 14]. For reasons mentioned earlier, together with the intolerance of the primary antifungal therapy, the dosage of caspofungin was decreased from 70 to 50 mg instead of 35 mg/day. After adjusting the dosage of caspofungin to 50 mg, liver enzyme levels decreased and remained stable.

The fAUC/MIC was calculated during both dosage regimens. *In vivo* pharmacodynamic studies have demonstrated that the AUC/MIC ratio is a good indicator of the caspofungin exposure-response relationship [15]. A mean fAUC/MIC associated with the stasis endpoint for caspofungin of 22 for *Candida albicans* was found [15]. The fAUC/MIC ratio in our patient was far above this stasis endpoint in both dosage regimens. Nevertheless, caspofungin has a fungicidal activity against *Candida* species and a fungistatic activity against *Aspergillus* [12]. The target fAUC/MIC for caspofungin in the treatment of IA could be different from that for IC and has yet to be established.

The calculated AUC at the dosage of 70 mg (191 mg*hr/L) in our patient was higher than the AUC established in healthy volunteers at similar dosage (130-144 mg*hr/L) [16]. The AUC at the dosage of 50 mg (100 mg*hr/L) in our patient corre-

sponded with the AUC measured in healthy volunteers (87-108 mg*hr/L) [15–17]. A similar exposure (116 mg*hr/L) is reached in patients with a CPS of 7-9 who received a dosage of 35 mg [17]. If our patient had received a dose of 35 mg, the exposure would probably have been lower than could have been expected based on the results from that study. Therefore, 50 mg could be preferred over 35 mg in this case.

When comparing both dosage regimens in our patient, the decline in AUC of almost 50% after the dosage of caspofungin was decreased from 70 to 50 mg/day is notable. We hypothesise that 2 factors may have contributed to the increased AUC at 70 mg: a slight nonlinear pharmacokinetic behaviour [16], and the decreased clearance caused by hepatic insufficiency [14].

7.4 Conclusion

In conclusion, the empirical choice for a higher dosage of caspofungin may have resulted in hepatotoxicity in a patient with already elevated liver enzyme levels. A dosage of 50 mg/day would probably have been safer. Furthermore, no evidence yet available displays an improved effectiveness at higher dosages. Based on our findings, we recommend monitoring for side effects when a higher dosage of caspofungin than currently recommended is administered. Caspofungin plasma concentrations may be helpful to evaluate exposure and reduce the need for off-label dosing. More clinical studies in specific populations are necessary to examine the influence of patient characteristics on the pharmacokinetics and pharmacodynamics, and thereby on the effectiveness and tolerability of caspofungin treatment.

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