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Anidulafungin-induced Hepatotoxicity and Dose Reduction: A Case Report

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Authors' contributions

This work was carried out in collaboration between all authors. Author LWL wrote the draft of the manuscript. Author LWL managed the literature searches. Author ALK designed the figures, managed literature searches and contributed to the correction of the draft. Authors TTT, JT and WL provided the case, the figures and supervised the work. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Anidulafungin, the newest echinocandin antifungal recently approved by the U.S. FDA, is unique among echinocandins as it undergoes biotransformation rather than being metabolized. In general, patients who received anidulafungin demonstrated low rates of adverse events. Hepatotoxicity is uncommon with anidulafungin and to date; there is no information on hepatic dose adjustments and it is also unknown if the adverse events are dose-related. We describe a patient who developed raised alkaline phosphatase (ALP) upon exposure to a high maintenance dose of anidulafungin at 200 mg every morning. Our patient has a persistent active mitral valve *Candida* endocarditis, complicated with recurrent candidemia. Patient received multiple courses of anti-fungal agents but breakthrough while on oral anti-fungal suppressive therapy. Prior to the initiation of high dose anidulafungin therapy, patient's liver function tests were all normal. One month after

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the initiation of high dose anidulafungin, repeat blood tests revealed a raised ALP level to 3 times the upper normal limit. As prolonged anti-fungal therapy is necessary, the maintenance dose of anidulafungin was reduced to 100 mg every morning, even though patient remained well. Three months after dose reduction, patient's serum ALP levels showed a steady decrease to 1 time the upper normal limit. In this patient that we have reported – taking into consideration of the temporal relationship of events, coupled with the probability scoring using the Naranjo Algorithm, it is probable that anidulafungin may exhibit dose-related hepatotoxicity resulting in elevated serum ALP levels and such adverse events may be mitigated with dose reduction.

Keywords: Anidulafungin; hepatotoxicity; adverse effects; dose reduction.

1. INTRODUCTION

Echinocandins represent the fourth class of antifungal agents available for the treatment of systemic fungal infections. They are a valuable class of antifungal agents that inhibit fungal β(1,3)-D-glucan synthesis and are currently used for the treatment of *Candida* and *Aspergillus* infections [1]. Anidulafungin (Eraxis; Pfizer) is the newest echinocandin antifungal to be approved by the US Food and Drug Administration (FDA) for the treatment of esophageal candidiasis, candidemia and deep-tissue candidiasis. Anidulafungin is a semisynthetic lipopeptide synthesized from fermentation products of *Aspergillus nidulans.* Anidulafungin has potent in vitro fungicidal activity against a broad range of *Candida* species and is also effective against species of *Candida* that are intrinsically resistant to azoles (*Candida krusei)*, amphotericin B (*Candida lusitaniae)*, or other echinocandins (*Candida parapsilosis)* [2].

Anidulafungin is unique among echinocandins because it slowly degrades in human plasma, undergoing a process of biotransformation rather than being metabolized. In addition, anidulafungin does not require dosing adjustments in patients based on age, sex, weight, disease state, and concomitant drug therapy, renal or hepatic insufficiency [3]. Reliable, safe dosing of anidulafungin, without the need for drug monitoring, is supported by a lack of variability in anidulafungin pharmacokinetics in patients with a wide spectrum of mucosal and invasive fungal infections, regardless of patient's age, weight, gender and race [2]. In general, patients who received anidulafungin demonstrated low rates of adverse events; with no alterations in liver function test values in various safety studies conducted.

Hepatotoxicity is uncommon with anidulafungin and to date; there is no information on hepatic dose adjustments to alleviate the adverse event of raised liver enzymes, especially raised alkaline phosphatase (ALP) in patients initiated on anidulafungin. It is also unknown if these adverse events are dose-related. We describe a patient who developed raised ALP upon exposure to a high maintenance dose of anidulafungin at 200 mg every morning. Patient's serum ALP levels improved after reducing the dose of anidulafungin.

2. CASE REPORT

A 61-year-old Chinese lady presented in late November 2014 with clinical complaint of 10 days of fever at a maximum temperature of 39 degrees celsius, accompanied with chills and rigors. Extensive work up revealed a persistent active mitral valve *Candida* endocarditis, complicated with recurrent candidemia. She has multiple drug allergies – facial rash with cloxacillin and an unknown allergic reaction to mefenamic acid. Her past medical history included chronic kidney disease secondary to obstructive uropathy, which was relieved with the creation of bilateral percutaneous nephrostomy. She also had cervix cancer for which she underwent surgical removal of the tumor and adjuvant radiotherapy. Of note, she has a history of rheumatic heart disease with mitral regurgitation and mitral stenosis, complicated by *Candida albicans* infective endocarditis (IE) and fungaemia in 2013. She was treated with 6 weeks of anti-fungal agent and repeated blood cultures were negative for both bacterial and fungal growth. Subsequently, patient was initiated on oral fluconazole as suppressive therapy since February 2014 [Minimum Inhibitory Concentration (MIC) of *Candida albicans* to fluconazole was 2 mcg/ml (sensitive)].

In September 2014, she again presented with recurrent candidemia (*Candida albicans*) secondary to mitral valve IE. The sensitivity testing reported an MIC of 32 mcg/ml to

fluconazole (resistant), 0.015 mcg/ml to caspofungin (sensitive) and 0.15 mcg/ml to posaconazole (sensitive). As such, patient was switched to high dose Caspofungin 100 mg every morning for 6 weeks, before starting on oral posaconazole 400 mg twice daily as suppressive therapy. In this current admission where patient had recurrent candidemia despite using oral posaconazole, she was once again re-initiated on high dose Caspofungin 100 mg every morning. The repeated sensitivity testing of the *Candida albicans* isolated in blood culture reported a higher MIC of 64 mcg/ml to fluconazole (resistant), 0.06 mcg/ml to caspofungin (sensitive), 4 mcg/ml to voriconazole (resistant), and ≤0.015 mcg/ml to anidulafungin. In view of recurrent candidemia with breakthrough while on fluconazole and posaconazole suppressive therapies, the infectious disease physician explored the option of combination anti-fungal therapy. Our pharmacy research laboratory then performed two anti-fungal combination therapies via in vitro synergy tests using the E test method – anidulafungin with posaconazole (Fig. 1) and caspofungin with posaconazole (Fig. 2). Based on the in vitro synergy tests results using the E test method, combination therapy was not used given the limited synergistic effect exhibited. Taking into consideration of the creeping caspofungin MIC of *Candida albicans* isolated, decision was made to initiate patient on anidulafungin, which is more potent than caspofungin, and at high dose of 200 mg once every morning, for a planned duration of 10 weeks of effective anti-fungal therapy, counting from the initiation of high dose caspofungin 100 mg every morning in this admission.

Prior to the initiation of high dose anidulafungin therapy, patient's liver function tests – serum liver enzymes [alkaline phosphatase (ALP), alanine transaminase (ALT) and aspartate transaminase (AST)] were all normal. However, one month after the initiation of high dose anidulafungin, repeat blood tests revealed a raised ALP level to 3 times the upper normal limit. As patient was asymptomatic and otherwise well, the dose of anidulafungin was kept at 200 mg every morning. Regular weekly monitoring of serum liver enzymes showed gradual decrease in ALP levels and levels stabilized at 1.5 times the upper normal limit for 2 months before a slow increase of ALP to 2 times the upper normal limit. Taking into consideration the need for prolonged anti-fungal therapy in this patient, the maintenance dose of anidulafungin was reduced to 100 mg every morning, even though patient remained well. Three months after dose reduction, patient's serum ALP levels showed a steady decrease to 1 time the upper normal limit. Patient remained stable throughout the course of anidulafungin therapy and did not develop any other adverse events secondary to anti-fungal therapy. Of note, patient was not on any other long term medication other than the above-mentioned anti-fungal therapy.

Fig. 1. Interaction between Anidulafungin and Posaconazole by the E-test method

Fig. 2. Interaction between Caspofungin and Posaconazole by the E-test method

3. DISCUSSION

Anidulafungin has unique pharmacokinetic properties among echinocandins as it undergoes slow chemical degradation to produce a ring-opened peptide that lacks antifungal activity. Anidulafungin also has negligible renal clearance (<1%) and is not a clinically relevant substrate, inducer, or inhibitor of cytochrome P450 enzymes [4]. Various studies [1–7] have demonstrated that the use of anidulafungin is associated with low incidences of adverse events, however, in these studies, the dose of anidulafungin used was 100 mg every day. At present, scarce data are available to describe the use of high dose anidulafungin (with doses exceeding 100 mg every day as recommended by the drug monograph). In a phase I study conducted in a group of thirty healthy volunteers, they received escalating doses of anidulafungin (150-mg load/75-mg maintenance up to 260-mg load/130-mg maintenance) for 10 days to determine a maximum tolerated dose of anidulafungin [8]. Some transaminase elevations were seen at the highest dose, but no patient experienced any dose limiting toxicities and thus no maximum tolerated dose was determined. Currently, there are also no published data to suggest that the adverse events associated with anidulafungin are dose-related and if dose reduction of anidulafungin may alleviate some of these adverse events.

In order to demonstrate a causal relationship between a drug and an identified adverse event, we used the Naranjo Algorithm to derive a probability score. The Naranjo Algorithm, or Adverse Drug Reaction (ADR) Probability Scale, is a method by which to assess whether there is a causal relationship between an identified untoward clinical event and a drug using a simple questionnaire to assign probability scores. The ADR is assigned to a probability category from the total score as follows: *definite* if the overall score is 9 or greater, *probable* for a score of 5-8, *possible* for 1-4 and *doubtful* if the score is 0. The Naranjo criteria do not take into account drug-drug interactions [9]. In the patient we have described above, we obtained a score of 8 based on the Naranjo Algorithm. This implies that the adverse drug reaction (raised serum ALP levels in our patient) followed a reasonable temporal sequence after a drug, as a recognized response after exposure to the drug. The drug reaction was confirmed by withdrawal (in this case, dose reduction), and could not be reasonably explained by the known characteristics of the patient's clinical state.

Prior to the initiation of anidulafungin, patient was exposed to prolonged courses of high dose caspofungin 100 mg every morning. Compared to anidulafungin and micafungin, caspofungin has a slightly higher frequency of liver-related laboratory abnormalities of 1 to 15%. [10–11] Furthermore, in a systematic review on the tolerability and hepatotoxicity of antifungals, the pooled estimate percentage of patients with elevation of liver enzyme levels not requiring stopping of treatment was 7.0% (95% confidence interval 4.1 – 9.9) for caspofungin, as compared to 2.0% (95% confidence interval 0.3 – 3.7) for anidulafungin. The Adjusted Wald method was used for point estimate and confidence interval. Despite on prolonged course of high dose caspofungin, patient only had occasional elevations of serum ALP (maximum of 1.5 times the upper normal limit) during regular blood tests, but the serum ALP had normalized prior to the initiation of anidulafungin. Moreover, as patient was not on any other long term medications, the elimination of drug-drug interactions or hepatotoxicity induced by other drugs thereby increases the probability that the raised serum ALP levels were most likely attributable to the use of anidulafungin. Presenting temporal relationship of events, coupled with the probability scoring using the Naranjo Algorithm, it is probable that anidulafungin may exhibit dose-related hepatotoxicity resulting in elevated serum ALP levels and such adverse events may be mitigated with dose reduction. Nevertheless, more studies are needed to confirm this observation.

4. CONCLUSION

Anidulafungin, the newest echinocandin antifungal recently approved by the U.S. FDA, is unique among echinocandins as it undergoes biotransformation rather than being metabolized. As such, it does not require dose adjustment in patients with renal or hepatic insufficiency. Though it was demonstrated in various studies to have low rate of adverse events and negligible drug interactions, in this patient that we have reported – taking into consideration of the temporal relationship of events, coupled with the probability scoring using the Naranjo Algorithm, it is probable that anidulafungin may exhibit dose-related hepatotoxicity resulting in elevated serum ALP levels and such adverse events may be mitigated with dose reduction.

CONSENT

All authors declare that written informed consent was not obtained as only anonymous patient data was used.

ETHICAL APPROVAL

This case report was reviewed and approved by the Singhealth institutional ethics review board (CIRB 2015/2269).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Sucher AJ, Chahine EB, Balcer HE. Echinocandins: The newest class of antifungals. Ann Pharmacother. 2009; 43:1647-57.
2. Vazquez JA, Sobel JD. Anidulafungin: A novel echinocandin. Clin Infect Dis 2006; 43:215-22.
3. Dowell JA, Stogniew M, Krause D, Damle B. Anidulafungin does not require dosage adjustment in subjects with varying degrees of hepatic or renal impairment. J Clin Pharmacol. 2007;47:461-470.
4. Liu P, Ruhnke M, Meersseman W, Paiva JA, Kantecki M, Damle B. pharmacokinetics of anidulafungin in critically ill patients with candidemia/ invasive candidiasis. Antimicrob Agents Ch. 2014;57(4):1672-76.
5. Reboli AC, Rotsein C, Pappas PG, et al. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med. 2007; 356:2472-82.
6. Kett DH, Shorr AF, Reboli AC, Reisman AL, Biswas P, Schlamm HT. Anidulafungin compared with fluconazole in severely ill patients with candidemia and other forms of invasive candidiasis: Support for the 2009 IDSA treatment guidelines for candidiasis. Critical Care. 2011;15:R253.
7. Mootsikapun P, Hseuh P, Talwar D, Co VM, Rajadhyaksha V, Ong M. Intravenous anidulafungin followed optionally by oral voriconazole for the treatment of candidemia in Asian patients: Results from an open-label Phase III trial. BMC Infectious Diseases. 2013;13:219.
8. Thye D, Shepard B, White RJ, et al. Anidulafungin: A phase 1 study to identify the maximum tolerated dose in healthy volunteers. Presented at: 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; Chicago, Ill. Abstract A-36; 2001.
9. Naranjo CA, Busto U, Sellers EM et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239245.
10. Kolfa G, Ruhnke M. Pharmacology and metabolism of anidulafungin, caspofungin and micafungin in the treatment of invasive candidiasis – Review of the literature. Eur J Med Res. 2011;16:159-66.
11. Wang J, Chang C, Young-Xu Y, Chan KA. Systematic review and meta-analysis of the tolerability and hepatotoxicity of antifungals in empirical and definitive therapy for invasive fungal infection. Antimicrob Agents Ch. 2010;54(6):2409-2419.

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