Pharmacokinetics of amphotericin B after accidental overdose in an adult critically ill patient treated with plasmapheresis: A case report

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Abstract

Amphotericin B is a broad-spectrum antifungal agent that is used in the treatment of systemic fungal infections. We describe the case of a 62-year-old female patient with recent aneurysmal subarachnoid hemorrhage who was treated for suspected ventriculitis and a fungal coinfection. Instead of liposomal amphotericin B (L-AmB), 465 mg (5 mg/kg) amphotericin B deoxycholate (DOC) was inadvertently administered, leading to refractory shock with multiple organ failure and requiring mechanical ventilation. Since an overdose of amphotericin B can lead to fatal consequences and has a half-life of 15 days, plasmapheresis was started. The serum concentration decreased from 1.32 µg/mL to 0.62 µg/mL before plasmapheresis, demonstrating a mean half-life of 49 hours. After two plasmapheresis sessions, the serum concentration further dropped to 0.26 µg/mL, demonstrating a mean half-life of 17 hours. In contrast, the third plasmapheresis session had no effect on serum concentration. The patient made a full recovery, potentially facilitated by enhanced amphotericin B elimination through plasmapheresis. Positive outcomes were previously reported in two adult patients treated with plasmapheresis. However, other reports without plasmapheresis described fatal outcomes in adult patients, albeit with a twofold overdose compared to the two patients successfully treated with plasmapheresis. Moreover, plasmapheresis itself carries risks such as hypocalcemia, metabolic alkalosis, and coagulation deficits. Consequently, the role of plasmapheresis in amphotericin B overdose is still debated.

Introduction

Amphotericin B is a broad-spectrum antifungal agent that is used in the treatment of systemic fungal infections [1]. It exerts its effect by disrupting the fungal cell wall synthesis by binding to ergosterol on cytoplasmic membranes [1]. Amphotericin B is considered highly toxic via several mechanisms. First, Amphotericin B can exert a direct cytotoxic effect by interacting with cholesterol in human cell membranes, leading to increased cell permeability and consequently cell death. Second, Amphotericin B infusion promotes proinflammatory cytokine release [2]. Adverse effects are dose-dependent and include fever, hemolysis, thrombocytopenia, renal failure, electrolyte disorders, hepatic failure, cardiac dysrhythmias, seizures and anaphylactoid shock [1]. Attempts have been made to improve tolerability and increase efficacy, such as binding amphotericin B to carriers. There are several carrier agents, including a non-lipid formulation with sodium deoxycholate (DOC) (recommended therapeutic dose 0.25-1 mg/kg/day) and lipid formulations, including amphotericin B lipid complex (ABLC) (3-5 mg/kg/day), liposomal amphotericin B (L-AmB) (3-5 mg/kg/day) and amphotericin B colloidal dispersion (ABCD) (4 mg/kg/day). Due to the significant differences in safety and dosing between the formulations, medication errors can have serious consequences for patients. In adult patients, four case reports have been documented where the non-lipid formulation was erroneously administered instead of the intended liposomal formulation [3-6]. Among these cases, only two report non-lethal outcomes in patients treated with plasmapheresis. However, these reports lack critical data on amphotericin B pharmacokinetics pre- and post-plasmapheresis [5,6]. We present data of amphotericin B

pharmacokinetics after an accidental overdose with non-lipid amphotericin DOC 5 mg/kg instead of L-AmB 5 mg/kg in a critically ill patient. Furthermore, we report information on serum levels of amphotericin B before and after plasmapheresis, adding to the body of evidence with regard to the pharmacokinetics of amphotericin B.

Case study

A 62-year old woman with a recent history of an aneurysmal subarachnoid hemorrhage with an extraventricular drain (EVD) as treatment for hydrocephalus was admitted to the intensive care unit (ICU) for suspected ventriculitis. Upon arrival to the ICU, the patient had a low Glasgow Coma Scale (GCS) score of 6 and a fever of 40^0C, blood pressure was 190/80 mm Hg, heart rate 107 beats/min. Further physical examination was without abnormalities. Initial laboratory results revealed serum leukocytes of 13.8 x 10^9/l. A previous liquor culture was positive for*Acinobacter baumanni spp.*. She had to be intubated and mechanically ventilated due to her low GCS. The EVD was removed and she was treated with 3000 mg meropenem daily for 14 days. An external lumbar drain was placed 24 hours later. Her GCS did improve to E4M6V4 and she could be extubated after 10 days in the ICU. Two days later, a subsequent liquor culture became positive for *Candida albicans*species, raising suspicion of a ventricular fungal coinfection, for which L-AmB 5mg/kg once-daily and flucytosine 25 mg/kg four times daily was started after consultation with the clinical microbiologist. She received a first dose of 465 mg L-AmB and flucytosine 2330 mg. The next day, the patient inadvertently received the same dose amphotericin B DOC intravenously over 60 minutes instead of the prescribed L-AmB. She reported abdominal pain and general malaise within two hours. She was vomiting and in respiratory distress, had a fever of 39.5°C, her GCS dropped to E4M6V2 and systolic blood pressure dropped below 100 mmHg. She was in shock, had to be re-intubated and mechanical ventilation, fluid infusion, vasopressors and inotropics had to be started. Laboratory results revealed anemia (Hemoglobin 3.9 mmol/L, mean corpuscular volume 90), thrombocytopenia (platelets 138 x 10^9/L), acidosis (serum pH 7.16, bicarbonate 16 mmol/L, lactate 12.7 mmol/L), renal failure (serum creatinine 167 µmol/L, urea 12.3 mmol/L) and hepatic failure (serum aspartate aminotransferase 710 mmol/L, alanine aminotransferase 371 mmol/L) within 24 hours. As usual causes for new onset clinical deterioration, such as sepsis, were considered unlikely due to the clinical course, an adverse drug reaction was therefore suspected and antifungal medication was immediately discontinued. We performed an extensive medication review, and discovered the medication error in four days. Upon the discovery of the medication error, plasmapheresis was started as amphotericin B DOC has a half-life of 15 days, assuming toxic levels were still present. Her plasma was calculated at 5 L. Three plasmapheresis sessions with a substitution volume of 5000 mL per session were done over a time course of three days. The serum amphotericin B concentration was 1.32 µg/mL 50 hours after the amphotericin B DOC administration and dropped to 0.85, 0.68 and 0.62 µg/mL at t = 72, 93 and 103 hours after the amphotericin B DOC dose, respectively (Figure 1), without the use of extracorporeal elimination techniques. The half-life was 35, 65 and 75 hours between t = 50 - 72 hours, t = 72 - 93 hours and t = 93 - 103 hours after dose. The mean half-life in the first 103 hours after administration was 49 hour and slightly increased over time. Serum concentrations amphotericin B further dropped to 0.48 and 0.26 µg/mL after the first and second plasmapheresis sessions (t = 111 and 124 hours after dose), demonstrating a half-life of 17 hours. Consequently, amphotericin B redistributed modestly from tissue to serum with an increase in amphotericin B concentration to 0.28 µg/mL (t = 144 hours). The third plasmapheresis had no effect on serum concentration (0.29 µg/mL at t = 149 hours). Over the entire course of plasmapheresis sessions, the amphotericin B half-life was 42 hours. Following plasmapheresis, the patient required CVVHDF therapy for renal failure for five days, which had no effect on amphotericin B serum levels. She remained hemodynamically stable during her time in the ICU. She was extubated 20 days after the erroneous dose and was subsequently discharged to the general ward 24 days after the medication error, where she made a full recovery.

Discussion

We described a case of an accidental 20-fold overdose with amphotericin B DOC due to a medication error in a critically ill patient. The patient developed shock, anemia, thrombocytopenia, renal failure,

acidosis and hepatic failure. She was treated with supportive care, plasmapheresis and CVVHDF and made a full recovery. In this case report, we reported the pharmacokinetics of amphotericin B extensively, demonstrating a significant shorter half-life than described in literature (49 hours versus 15 days), without the use of extracorporeal elimination techniques [7,8]. The half-life only marginally decreased to 42 hours with plasmapheresis, with two of the three plasmapheresis sessions demonstrated a decrease in amphotericin B serum levels.

A PubMed search using the terms 'amphotericin B' and 'overdose' revealed nine case reports with 11 pediatric and four adult patients (table 1) [3-6,9-13]. The case reports demonstrate a high mortality rate: only five patients survived the overdose. Of the adult patients, two case reports documented fatal outcomes without plasmapheresis [3,4]. Conversely, two case reports in adults with plasmapheresis reported positive outcomes [5,6]. However, it is worth noting that the amphotericin B DOC overdose in the non-plasmapheresis patients was twice as high as in the plasmapheresis treated patients, which likely contributed to the fatal outcomes. Moreover, pharmacokinetics of amphotericin B were hardly described in these case reports, making it difficult to isolate the sole effect of plasmapheresis.

Little is known about the pharmacokinetics of amphotericin B. After introduction into the intravascular compartment, amphotericin is quickly distributed into the extravascular compartment, followed by a longer equilibrium period [1,14]. Trough concentrations are reached in 24 hours [5]. Amphotericin B has no known metabolites. Amphotericin B undergoes biphasic elimination with a terminal half-life of up to 15 days, which is originally only reported in two adult patients [7,8]. The primary route of elimination is not known. Serum levels are not influenced by hepatic or renal failure [14]. Due to its substantial size (924 Da), high protein binding, lipophilic nature, and large volume of distribution (approximately 4 L/kg), Amphotericin B is deemed unsuitable for dialysis, including CVVHDF [14]. Plasmapheresis can be used to eliminate drugs that are too large and have a high rate of protein binding [14]. However, plasmapheresis is a high-risk procedure, with risks of hypocalcemia, metabolic alkalosis and coagulation deficits. Because of the toxic characteristics of amphotericin B, the reported long half-life of the drug, and earlier case reports of similar medication errors with deadly outcome, plasmapheresis was recommended upon the discovery of the medication error, four days after its occurrence. Drug levels of amphotericin B were monitored extensively pre- and post-plasmapheresis using Ultra Performance Liquid Chromatography with Diode-Array Detection (UPLC-DAD).

Irrespective of plasmapheresis, our patient may have survived the accidental overdose of amphotericin B for several reasons. Unlike the majority of reported cases where young children were involved (9 out of 13 cases), our patient was older. Additionally, our patient received a lower cumulative dose of amphotericin B DOC (5 mg/kg), whereas the majority of cases (8 out of 15) involved either doses exceeding 5 mg/kg or multiple overdoses. Remarkably, the first amphotericin B serum concentration, 50 hours after the medication error, was 1.32 µg/ml, and already within the therapeutic range (reference range 1.2 – 2.4 µg/ml) [1]. Instead of the half-life of 15 days previously documented in case reports, the mean half-life of amphotericin B in our patient pre-plasmapheresis was 49 hours, but fluctuated significantly, which may indicate biphasic elimination. Plasmapheresis may have enhanced the elimination of amphotericin B as the mean half-life decreased to 42 hours, also with great fluctuation. It is questionable whether the patient would have also recovered without plasmapheresis.

Due to the potential confusion regarding L-AmB and amphotericin B DOC administration, our institution has taken action. As a result of recommendations of a root cause analysis, amphotericin B DOC was banned from our hospital. Only L-AmB is now available.

Conclusion

We described a patient who survived a 20-fold overdose of amphotericin B DOC due to a medication error. We described a much shorter terminal half-life (49 hours vs. 15 days) of amphotericin B than previously reported. Plasmapheresis may have marginally enhanced the elimination of amphotericin B However, the role of plasmapheresis is still under debate.

Author contributions

JAH van Oers completed the main body of the manuscript. All authors made decisions about the entire treatment process and provided the main idea for writing the final article. JAH van Oers, JD Workum, and TCC Jaspers participated in the collation of data, generated the table and figure and reviewed the literature. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author on request.

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Table 1

Legends : a = Patients in these case reports were treated with plasmapheresis.

Figure 1.

Legend s: Amphotericin B concentrations (y-axis) in time (x-axis). The black line represents the Amphotericin B concentrations. The vertical bars with vertical lines represent the three plasmapheresis sessions. The grey area represents the time on continuous veno-venous hemodiafiltration (CVVHDF).

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`Table 1 Reports of patients with amphotericin B DOC overdose.docx` available at https://authorea.com/users/655711/articles/661390-pharmacokinetics-of-amphotericin-b-after-accidental-overdose-in-an-adult-critically-ill-patient-treated-with-plasmapheresis-a-case-report