Amphotericin B Pharmacokinetics During Extracorporeal Membrane Oxygenation: A Case Report

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ABSTRACT

Amphotericin B treatment during extracorporeal membrane oxygenation is at times necessary for the treatment of secondary fungemia or, less commonly, to treat a primary fungal infection. The impact of the extracorporeal circuit on the pharmacokinetics of amphotericin B have not been described in vivo. This case report describes the pharmacokinetics of amphotericin B in a patient receiving extracorporeal membrane oxygenation support for respiratory failure secondary to Blastomyces dermatitidis pneumonia. Amphotericin B concentrations were established and maintained at therapeutic levels with standard dosing despite the presence of a membrane oxygenator and intermittent replacement of extracorporeal circuit components. This suggests that no adjustments in the dosing of amphotericin B are necessary during extracorporeal membrane oxygenation.

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INTRODUCTION

Amphotericin B, a polyene macrolide antifungal agent, is the drug of choice for the treatment of several types of invasive fungal infections (1). Patients supported with extracorporeal membrane oxygenation (ECMO) are at risk for fungal bloodstream infections due to the presence of large intravascular cannulas, the debilitating nature of their underlying illness, and the prolonged duration of support that is often necessary. Although the occurrence of fungal bloodstream infections during ECMO is uncommon, it greatly increases patient morbidity and mortality. Furthermore, certain fungal infections, such as Blastomyces dermatitidis pneumonia, have a low incidence of extra-pulmonary involvement and a high rate of recovery, but may lead to acute respiratory distress syndrome (ARDS) and respiratory failure (2). In such cases, the use of ECMO as a supportive therapy may be justified. Thus, definite indications exist for the use of amphotericin B during ECMO support. However, despite these indications, there is little information available on the pharmacokinetics of amphotericin B during ECMO. We evaluated the pharmacokinetics of amphotericin B during ECMO in a patient with ARDS secondary to pulmonary blastomycosis to learn more about the optimal use of this medication under these circumstances.

CASE DESCRIPTION

A 15 year old, 100 kilogram black male with ARDS secondary to pulmonary blastomycosis was referred to the Pediatric Intensive Care Unit at Georgetown University Medical Center for ECMO support. Veno-arterial ECMO was initiated after bedside cannulation with a 29 french femoral venous cannula and a 19 french femoral arterial cannula. A standard roller head extracorporeal circuit was employed as previously described (3) and included a roller head pump, polyvinyl chloride tubing, and two membrane oxygenators.

The patient received ECMO support for 20 days. Intravenous amphotericin B treatment was begun the day prior to the initiation of ECMO. On the first day of treatment, two 1 mg test doses of amphotericin B were administered, followed by 25 mg given over four hours. Two 100 mg doses separated by nineteen hours were given on the second day, and 100 mg doses over four hours were subsequently given daily. This rapid increase in dosing to the standard 1 mg/kg/day amphotericin B dose has been associated with improved survival from ARDS secondary to blastomycosis (1, 2). The total dose of amphotericin B administered was 2,072 grams. Amphotericin B administration was well tolerated by the patient. The patient did develop moderate renal insufficiency, a common toxicity related to amphotericin B administration, although the critical nature of the patient's illness may have also contributed to this finding.

Amphotericin B levels were obtained throughout the course of ECMO, including 30 minutes prior to dosing (trough) and 1 hour after the completion of a dose (peak), as suggested by the reference laboratory. Furthermore, levels were obtained when the membrane oxygenators and the entire ECMO circuit were electively changed unrelated to amphotericin B dosing. Blood samples for levels were drawn from an arterial catheter for patient determinations and from the ECMO circuit's post-oxygenator manifold for circuit determinations. Samples were centrifuged and frozen until analysis. Amphotericin B level determinations were performed using a bioassay technique, with a lower limit of sensitivity of 0.1 micrograms per milliliter.

Manipulation of the ECMO circuit included replacement of both membrane oxygenators on day 5 of ECMO (day 6 of amphotericin B), replacement of the entire circuit on ECMO day 9 (day 10 of amphotericin B), replacement of one membrane oxygenator and a change of circuit tubing from 3/4 inch to 1/2 inch size on the venous side of the circuit on ECMO day 12 (amphotericin B day 13), and replacement of the entire circuit on ECMO day 17 (amphotericin B day 18). Membrane oxygenators were exchanged when a deterioration in gas exchange by the oxygenators became evident. Replacement of the entire ECMO circuit occurred when excessive fibrin collections developed in the arterial and venous tubing. The size of the circuit tubing was changed to improve venous drainage.

ECMO was discontinued after 20 days when only modest improvement in the patient's pulmonary status had been noted and signs of severe neurologic impairment were present. The patient expired soon after the discontinuation of ECMO.

PHARMACOKINETIC RESULTS

Amphotericin B levels are shown in Table 1. Peak levels from both the patient and the circuit were always in the reference range of 0.5 to 4.0 micrograms per milliliter, while trough levels were higher than the reference range of 0.2 to 1.0 micrograms per milliliter. On day number 10 of amphotericin B treatment, the entire ECMO circuit was electively replaced. As shown in Table 1, levels from the patient and the circuit obtained 60 minutes before and 90 minutes after the circuit change were essentially unchanged. The ECMO circuit was also electively replaced on the eighteenth day of amphotericin B treatment, 15 hours after dosing. Ninety minutes after changing the circuit, amphotericin B levels were consistent with previously obtained trough levels.

A compartmental pharmacokinetics model of the patient and the ECMO circuit was developed using an established computer software program. This program employs numerical methods to estimate the parameters of pharmacokinetic models using.
observed drug concentrations. In this model, central and peripheral compartments were used to describe the patient, and two compartments representing each of the membrane oxygenators were used to describe the ECMO circuit. In the model, drug was not eliminated from the ECMO compartments, but it could accumulate. When the ECMO membrane oxygenators were changed, the amount of drug accumulated in these compartments was reset to zero. In this way, the amount and rate of amphotericin B accumulation in the membrane oxygenators, as well as the pharmacokinetics of amphotericin B in the patient, could be described.

Figure 1 shows the observed and predicted concentrations of amphotericin B. There is good agreement between the observed values and the values predicted by the pharmacokinetic model. Furthermore, no major deviations in the observed or predicted amphotericin B concentrations are noted on days when the ECMO membrane oxygenators were replaced.

Parameters of the model are given in Table 2. The rate constant for drug distribution between the plasma and the ECMO circuit is very fast, while amphotericin B distribution between the patient’s central and peripheral compartments is much slower. The estimated volume of the ECMO circuit is very small as compared to the patient’s central compartment.

DISCUSSION

The development of a systemic fungal infection during ECMO is associated with a poor prognosis and often necessitates the termination of ECMO support. Establishing and maintaining therapeutic amphotericin B levels is essential for any attempted treatment of fungemia during ECMO to be successful. Furthermore, pulmonary blastomycosis resulting in ARDS and ECMO support is potentially treatable with amphotericin B (2). Despite this, little information exists on the pharmacokinetics of amphotericin B during ECMO.

ECMO could be expected to have a great impact on amphotericin B pharmacokinetics. For instance, the increase in circulating blood volume during ECMO could impact on amphotericin B’s volume of distribution. Furthermore, the exposure of blood to a large plastic surface area could result in the adsorption of amphotericin B. One in vitro study suggested that in isolated ECMO circuits, a greater than ten percent reduction in amphotericin B levels occurs within 10 to 14 hours (4). To our knowledge, no in vivo study of this problem has been performed.

The effect of ECMO on the pharmacokinetics of other medications has been examined. In experiments involving fentanyl in an in vitro model (5) and midazolam in an in vivo model (6), saturation of the ECMO circuit could not be obtained despite high dose infusions of the medications. In contrast, a study which evaluated membrane oxygenators of different design found that silicone membrane oxygenators could be saturated in vitro with fentanyl at a concentration of 130 ng/cm² (7). Neonatal ECMO patients receiving vancomycin have been found to have a larger volume of distribution, lower drug clearance, and a longer drug half-life then neonates not receiving ECMO (8). Furthermore,
an *in vitro* examination of phenytoin and diazepam pharmacokinetics during ECMO (9) suggested that a significant proportion of both drugs are bound to the circuit’s polyvinyl chloride tubing. Thus, no single pharmacokinetic model of ECMO that is applicable to all drugs can be described.

The current study suggests that there are no significant changes in the pharmacokinetics of amphotericin B secondary to the ECMO circuit. Amphotericin B levels remained within a clinically acceptable range using a standard dosing regimen. Furthermore, no clinically important alteration in amphotericin B levels occurred when the ECMO circuit was changed. In addition, the rapid distribution of drug from the patient to the ECMO circuit suggested by the rate constants and the small volume of distribution of the ECMO circuit indicates that minimal amounts of amphotericin B bind to or accumulate in the membrane oxygenator.

Amphotericin B may be either fungistatic or fungicidal, depending on the concentration of the drug and the sensitivity of the organism (1). Drug blood levels are influenced by factors related to administration (dose, frequency, and rate of infusion) and tissue levels are influenced by amphotericin B’s high degree of protein binding, which results in high lung tissue concentrations. In uncomplicated cases of pulmonary blastomycosis, cure rates of up to 97% can be achieved when a cumulative dose of 2 grams has been delivered (10). When the course of the illness becomes complicated with the development of ARDS, the mortality rate increases to 50% (2). Currently, there is no information available relating blood levels, or perhaps more importantly pulmonary lung tissue levels, of amphotericin B to survival from pulmonary blastomycosis with ARDS. Such information might be important in directing therapeutic interventions. Furthermore, it is possible that the degree of pulmonary bypass achieved during ECMO could decrease the amount of amphotericin B delivered to the lung tissue and impact on recovery. This study does not address this question.

Amphotericin B has a high degree of binding to erythrocytes (1). Since hemolysis occurs during ECMO, it is possible that amphotericin B levels would be greater than otherwise expected. This study is unable to determine whether such an effect is present. However, hemolysis would not be expected to significantly alter pharmacokinetic parameters such as drug half-life or clearance. It is possible that hemolysis could impact on the volume of distribution for amphotericin B, but this cannot be assessed by the available information.

In this single patient study, the pharmacokinetics of amphotericin B during ECMO are well described by a two compartment model, with the ECMO circuit not contributing to the apparent volume of distribution. Therefore, no dosing adjustments appear to be necessary when amphotericin B is administered during ECMO. It is possible that these findings would be altered in smaller patients where the volume of extracorporeal blood approaches the patient’s blood volume. Evaluation of amphotericin B levels in these patients during ECMO is warranted to further expand our knowledge.

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**REFERENCES**
