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CLINICAL INVESTIGATION

Hyperphosphatemia in Pediatric Oncology Patients Receiving Liposomal Amphotericin B

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OBJECTIVE After transitioning our front-line amphotericin product to the liposomal formulation, we observed an increased incidence of hyperphosphatemia. We aimed to determine the incidence of hyperphosphatemia in children with oncologic disorders receiving an amphotericin B product and to establish whether the incidence varies depending on amphotericin formulation.

METHODS This retrospective review of the medical record was conducted at a tertiary, free standing children's hospital. Pharmacy data revealed 159 patients receiving an amphotericin product between November 2006 and December 2008. Doses of amphotericin, serum phosphorous, calcium and creatinine concentrations were recorded at daily time points during the 10 days following both initiation and discontinuation of amphotericin. Administration of phosphate binders and total parenteral nutrition was noted. The incidence of hyperphosphatemia, defined as a serum value greater than the age-adjusted upper limit of normal, was compared among the amphotericin groups.

RESULTS One hundred thirty-nine amphotericin recipients had a serum phosphorus measurement during amphotericin therapy. Final analysis included 117 children, of which 64 (55%) were oncology patients. Deoxycholate (mean maximum dose 1 mg/kg), lipid complex (mean maximum dose 4.8 mg/kg) and liposomal amphotericin (mean maximum dose 4.9 mg/kg) were used in 24 (20.5%), 37 (31.6%) and 56 (47.9%) of all patients, respectively. Hyperphosphatemia developed in 27% (32/117) of all patients, and in 33% (21/64) of oncology patients. Similar to within all recipients, among oncology patients, 45% (n=18) of liposomal recipients demonstrated hyperphosphatemia compared to 13% of those receiving lipid complex (n=3, p=0.007). No oncology patient received deoxycholate.

CONCLUSION Nearly 45% of children with oncologic disorders receiving liposomal amphotericin developed hyperphosphatemia. The incidence is significantly greater for the liposomal formulation than either of the other amphotericin formulations.

INDEX TERMS amphotericin, antifungal, electrolyte, hyperphosphatemia, pediatric oncology

ABBREVIATIONS ABLC, Abelcet; AMBD, amphotericin B deoxycholate; AMBL, AmBisome; CaXP, serum calcium-phosphorus product

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BACKGROUND

Fungal infections are of particular concern in immunocompromised patients, and greatly contribute to morbidity and mortality in children with oncologic disorders. Amphotericin B is an antifun-

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gal agent with activity against many fungi subspecies including *Candida* spp., *Aspergillus* spp. and *Cryptococcus* species.^{1,2} Due to its wide spectrum of activity, amphotericin B remains a mainstay of antifungal treatment despite the extensive toxicity profile that limits its usefulness in certain patients. Currently, a lipid formulation, either amphotericin B lipid complex (Abelcet, Enzon, Bridgewater, NJ; ABLC) or amphotericin B liposome (AmBisome, Gilead Sciences, Foster City, CA; AMBL), is preferred in oncology patients due to decreased toxicity. The liposomal formulation is favored in our institution.

Although not considered a common side effect of amphotericin therapy, hyperphosphatemia has been previously characterized in 5 children receiving AMBL.^{3,4} Reports in adults have implicated liposomal amphotericin as a cause of a pseudohyperphosphatemia. An interaction with the assay equipment was hypothesized to result in a pseudo rather than real phosphorous elevation.⁵⁻⁸ After transitioning the amphotericin formulation at our institution to AMBL, we observed more frequent hyperphosphatemia. Our objective was to determine the incidence of hyperphosphatemia in children with oncologic disorders receiving an amphotericin B product and to establish whether the incidence varies depending on amphotericin formulation.

METHODS

This retrospective study was approved by the institutional review board at Indiana University-Purdue University, Indianapolis, Indiana. All patients, 18 years and younger, who received amphotericin B deoxycholate (XGen Pharmaceuticals, Big Flats, NY; AMBD), amphotericin B lipid complex (ABLC), or liposomal amphotericin B (AMBL) from November 2006 through December 2008 at Riley Hospital for Children, Indianapolis, Indiana were eligible for inclusion. Causes for exclusion included: lack of baseline serum phosphorus measurement, elevated baseline phosphorus, no serum phosphorus measurement during the first 10 days of amphotericin therapy and hyperphosphatemia with concomitant nephrotoxicity during amphotericin therapy. Hyperphosphatemia was defined as a serum phosphorus concentration greater than the age-adjusted upper limit of normal at our institution. Nephrotoxicity was defined as a greater than 25% increase in two consecutive serum creatinine concentrations from the baseline value.

Data collected included age, weight, gender and baseline serum creatinine, calcium and phosphorus concentrations. Information regarding amphotericin

B included formulation, dose and duration of therapy. Additionally, we documented administration of phosphate binder, phosphorus supplement, and/or parenteral nutrition. Serum creatinine, phosphorus and calcium values were recorded during the first 10 days following both initiation and discontinuation of amphotericin therapy. The serum calcium-phosphorus product was calculated in hyperphosphatemic patients by multiplying the serum calcium and phosphorus values.

Baseline characteristics were analyzed via repeated measures analysis of variance (ANOVA). A Fisher's exact analysis was used to compare the incidence of hyperphosphatemia treatment between the three amphotericin groups. P-values of <0.05 were considered statistically significant. Statistical analyses were conducted using Statistical Package for Social Sciences version 16.0 (SPSS, Inc., Chicago). Data are presented as mean \pm standard deviation.

RESULTS

Electronic pharmacy records revealed 159 children who received an intravenous (IV) amphotericin product during the study period. Of these, 139 had a phosphorus measurement during amphotericin therapy and 117 were included in final analysis. Additional exclusions were for age (n=10), no baseline phosphorus measurement (n=2), elevated baseline phosphorus (n=4), and concomitant nephrotoxicity (n=6). Sixty-four (55%) were patients being treated for oncologic disorders with a mean age of 88.3 ± 63.5 months and weight of 26 ± 18 kg. Forty-eight percent of oncology patients were male. Table 1 illustrates amphotericin formulation distribution.

Hyperphosphatemia developed in 27% (32/117) of all amphotericin recipients. The incidence among the oncology (33%, n=21) and nononcology (21%, n=11) population was similar (p=0.145). Among oncology patients, hyperphosphatemia developed more frequently in recipients of AMBL (45%) than in those treated with ABLC (13%; p=0.007). No oncology patient received AMBD. This difference in hyperphosphatemia was not observed outside of the oncology population (Table 2).

Hyperphosphatemia after AMBL was similar among oncology (45%) and nononcology patients (37.5%; p=0.608). The incidence of hyperphosphatemia was not different in those receiving total parenteral nutrition and nonrecipients (p=0.948). No patient received supplemental phosphorus. There was no difference in the doses (mg/kg) of ABLC (4.85 ± 0.61 and 4.62 ± 1 ; p=0.444) or AMBL (4.95 ± 0.81 and 4.87 ± 1.4 ; p=0.789) in

Table 1. Amphotericin formulation distribution among all patients

Formulation	Number (%) of Recipients	Median (Range) Age in Months	Mean Max Dose (mg/kg)
AMBD	24 (20.5%)	1 (1–197)	1
ABLC	37 (31.6%)	47 (2–215)	4.8
AMBL	56 (47.9%)	68 (1–213)	4.9

ABLC, amphotericin B lipid complex; AMBD, amphotericin B deoxycholate; AMBL, liposomal amphotericin B

patients with and without hyperphosphatemia, respectively. Table 3 describes mean phosphorus values in oncology patients with hyperphosphatemia and the mean percent above the age-adjusted upper limit of normal.

A similar proportion of the AMBL (42%) and ABLC (50%) recipients under 12 years of age developed a serum calcium-phosphorus product (CaXP) greater than $65 \text{ mg}^2/\text{dL}^2$ ($p=\text{NS}$). For patients older than 12 years of age, a serum CaXP greater than $55 \text{ mg}^2/\text{dL}^2$ was observed in 60% of AMBL recipients, but was not noted in the ABLC recipients. The median (range) percent change in serum calcium for patients with hyperphosphatemia was zero (–21.43% to 43.02%).

The mean delay between amphotericin initiation and hyperphosphatemia onset was 4.1 ± 2.2 days (range: 1–9). Resolution of hyperphosphatemia occurred within 10 days of amphotericin discontinuation in 11 (61%) AMBL and 2 (67%) ABLC recipients. No patient required phosphate binders

Table 2. Hyperphosphatemia incidence among amphotericin formulations

Formulation	Patients (%)
Nononcology patients (n=53) *	
AMBD (n=24)	2 (8.3%)
ABLC (n=13)	3 (23.1%)
AMBL (n=16)	6 (37.5%)
Oncology patients (n=64) †	
ABLC (n=24)	3 (13%)
AMBL (n=40)	18 (45%)

ABLC, amphotericin B lipid complex; AMBD, amphotericin B deoxycholate; AMBL, liposomal amphotericin B

* $p=0.042$ for AMBD vs. AMBL and $p=0.454$ for ABLC vs. AMBL
† $p=0.007$ for ABLC vs. AMBL

Table 3. Phosphorus concentrations in patients with hyperphosphatemia

Amphotericin Formulation	Upper Limit of Normal*	Mean Highest Phosphorus (mg/dL)	Mean Percent Above Limit of Normal
ABLC	5.2 (n=1)	5.8	11.5%
	5.5 (n=1)	5.9	7.3%
	6.5 (n=1)	6.8	4.6%
	Total (n=3)	6.2	7.8%
AMBL	5.2 (n=6)	6.2	18.6%
	5.5 (n=7)	6.2	12.7%
	6.5 (n=3)	7.7	19%
	6.8 (n=2)	7.2	5.9%
	Total (n=18)	6.9	18.3%

ABLC, amphotericin B lipid complex; AMBL, amphotericin B liposome; ULN, upper limits of normal

* upper limits of normal serum phosphorus based on age: 4 mo-1 yr = 6.8 mg/dL; 1–5 yrs = 6.5 mg/dL; 5–10 yrs = 5.5 mg/dL; and 10–20 yrs = 5.2 mg/dL

or other intervention to decrease phosphorus concentrations.

DISCUSSION

Pediatric oncology patients experience electrolyte abnormalities for varied reasons and prompt recognition can be critical. Based on observational experiences, we aimed to determine if different liposomal amphotericin formulations were associated with differing rates of hyperphosphatemia. We found that nearly 45% of children with oncologic disorders developed hyperphosphatemia during AMBL therapy. Hyperphosphatemia incidence is significantly higher with the liposomal formulation than the other available formulations.

Hyperphosphatemia is a common problem in those with kidney disease, and is a manifestation of tumor lysis syndrome. However, little has been reported about any significance of hyperphosphatemia in pediatric cancer patients without renal insufficiency. Severe hyperphosphatemia can contribute to rhabdomyolysis, hemolysis, decreased oxygen transport and respiratory failure in those with chronic kidney disease.^{9,10}

Importantly, excess serum phosphorus binds calcium in the body and vasculature. A serum CaXP greater than $55 \text{ mg}^2/\text{dL}^2$ results in soft tissue and cardiovascular calcification increasing both morbidity and mortality.⁹ The National Kidney Foundation Kidney Disease Outcomes Quality Initiative recommends that serum CaXP be maintained less than $55 \text{ mg}^2/\text{dL}^2$ in those over 12 years of age and less than $65 \text{ mg}^2/\text{dL}^2$ in younger children.¹¹ It is both impressive and concerning that 47% of our ABL recipients had a calcium-phosphorus product in excess of these recommendations. Mean peak phosphorus values ranged from 6% – 19% above the upper limit of normal for oncology ABL recipients. How this elevation affects the calcium-phosphorus product and subsequent alteration in morbidity and mortality warrants investigation.

Hyperphosphatemia due to ABL has been previously described in 5 children (age 8 – 18 years).^{3,4} Four reports included children with malignancy. In all cases, hyperphosphatemia was observed after initiation of ABL. These elevations were observed as early as 1 day after initiation of ABL. In 1 child, hyperphosphatemia occurred intermittently throughout a month of amphotericin therapy.⁴ Our findings are similar in that hyperphosphatemia onset occurred between 1 and 9 days after initiation of ABL.

Sutherland and colleagues note the use of the Synchron LX-20 (Beckman Coulter Inc., Brea, CA) analysis method.⁴ Case reports of 6 adults and laboratory studies have implicated ABL as an etiology of pseudohyperphosphatemia due to an interaction between the ABL and the Synchron LX-20 method.^{5–8} It has been proposed that elevated phosphorus may be due to degradation of the liposomal vehicle of ABL causing interference with Synchron LX-20.⁶ Within our institution, serum phosphorus is measured using a different apparatus, the Synchron DxC (Beckman Coulter) system, which leads to question if the hyperphosphatemia is real or if this is a machine interaction with the Synchron systems. It is important to note that despite a phosphorous elevation, there was no significant reduction in serum calcium concentration. Such a decline would have supported true hyperphosphatemia over pseudohyperphosphatemia. We did not aim to determine if the hyperphosphatemia we observed after transitioning to ABL was a pseudohyperphosphatemia, rather we simply wished to characterize the incidence of hyperphosphatemia among amphotericin formulations. Future investigation to determine true versus pseudohyperphosphatemia is warranted. Clinicians should be aware of this potential phosphorus elevation and the institution-

al-analysis methods used while carefully evaluating the patient clinical status in order to avoid inappropriate interventions aimed at hyperphosphatemia treatment.

A limitation to this study is that it was a retrospective chart review. Although all included patients had at least one phosphorus value drawn during amphotericin B therapy, not all patients had daily measurements. While 45% of our ABL recipients developed hyperphosphatemia, 13% of our ABLC patients developed this as well. This difference was not observed in the nononcology population. A larger sample size may have yielded additional findings given the relative infrequent use of ABLC use in our oncology population.

CONCLUSION

Nearly 45% of children with oncologic disorders developed hyperphosphatemia while receiving therapy with ABL. The incidence of hyperphosphatemia is higher with the liposomal formulation than the other available formulations. Clinicians should be aware of this and the analytical method used within their institution to optimally manage patients with hyperphosphatemia. Our findings represent important potential adverse data that is often difficult to ascertain through voluntary post-marketing reporting. Further investigation is warranted to determine the significance of this finding and whether it represents a true or pseudohyperphosphatemia.

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