Case-Control Study and Case Series of Pseudohyperphosphatemia during Exposure to Liposomal Amphotericin B

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Pseudohyperphosphatemia due to an interaction between liposomal amphotericin B and the Beckman Coulter PHOSm assay occurs sporadically and remains underrecognized in clinical practice. This retrospective case-control study compares the incidences of hyperphosphatemia in adult inpatients exposed to liposomal amphotericin B or a triazole. A case series of patients with confirmed pseudohyperphosphatemia is described. A total of 80 exposures to liposomal amphotericin B and 726 exposures to triazoles were identified. Among subjects without chronic kidney disease and no concomitant acute kidney injury, hyperphosphatemia occurred more often during liposomal amphotericin B therapy than during triazole therapy (40% [14/35 cases] versus 10% [47/475 cases] of cases; \( P < 0.01 \); adjusted odds ratio, 5.2 [95% confidence interval [CI], 2.3 to 11.9]). Among individuals with chronic kidney disease and no concomitant acute kidney injury, hyperphosphatemia also occurred more often during liposomal amphotericin B exposure (59% [10/17 cases] versus 20% [34/172 cases] of cases; \( P < 0.01 \); adjusted odds ratio, 6.0 [95% CI, 2.0 to 18.0]). When acute kidney injury occurred during antifungal exposure, the frequencies of hyperphosphatemia were not different between treatments. Seven episodes of unexpected hyperphosphatemia during liposomal amphotericin B exposure prompted a confirmatory test using an endpoint-based assay that found lower serum phosphorus levels (median difference of 2.5 mg/dl [range, 0.6 to 3.6 mg/dl]). Liposomal amphotericin B exposure conveys a higher likelihood of developing hyperphosphatemia than that with exposure to a triazole antifungal, which is likely attributable to pseudohyperphosphatemia. Elevated phosphorus levels in patients receiving liposomal amphotericin B at institutions using the Beckman Coulter PHOSm assay should be interpreted cautiously.

Amphotericin B is a polyene antifungal indicated for the treatment of invasive fungal infections, including aspergillosis, candidiasis, cryptococcosis, and zygomycosis (1). Several generic formulations of this drug are available in the United States, including amphotericin B deoxycholate, or conventional amphotericin B (CamB), amphotericin B colloidal dispersion (ABCD), and amphotericin B lipid complex (ABLC; Ablecet). The liposomal formulation of amphotericin B (LAmB; AmBisome) may be preferred over other formulations due to a more favorable side effect profile and enhanced tissue penetration, but it is still associated with hypokalemia, likely attributable to increased tubular permeability to monovalent cations, and hypomagnesemia, for which the mechanism is less certain (1–3). Although the drug is known to cause hyperphosphatemia as well, several reports of hyperphosphatemia and pseudohyperphosphatemia have been published (1–4).

The first case of severe hyperphosphatemia was in a child with acute lymphocytic leukemia who was treated with LAmB for a mixed fungal infection (4). It was postulated that the electrolyte abnormality was caused by a sudden load of exogenous phosphorus coupled with inadequate clearance by the kidneys. Later, Bailey and Chan proposed the possibility of an artifactual elevation of serum phosphorus during LAmB therapy after two patients were found to have falsely elevated phosphorus levels subsequently shown to be normal by treating the serum samples with a lipemic cleansing agent (5). An ensuing case series described 4 pediatric patients who developed hyperphosphatemia while receiving LAmB (6). In that report, transitioning from LAmB to ABLC at the onset of hyperphosphatemia led to normalization of the serum phosphorus level, leading the authors to conclude that any interference with the PHOSm assay must be specific to the liposomal formulation. Another group reported that ultrafiltration of the serum may be an effective method to obtain a more accurate serum phosphorus measurement (7). Two in vitro studies demonstrated a dose-dependent, linear rise in phosphorus measurements when serum was spiked with LAmB. A 0.0072- to 0.0090-mmol/liter increase in phosphorus correlated with a 1-mg/liter increase in LAmB concentration (8, 10). No effect was observed using a comparable placebo molecule without active drug, leading the authors to conclude that active drug in the liposomal formulation (LAmB) is involved in the assay interference (10). In 2008, pseudohyperphosphatemia caused by LAmB was detailed in a product corrective action statement released by Beckman and Coulter, Inc., to hospital laboratories that use Synchron chemistry systems to measure serum phosphorus by the PHOSm assay. The product information for AmBisome was updated in 2012 to reflect...
the possible assay interference (1); http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/050740s021ltr.pdf. Jensen et al. found that LAmB interfered with the PHOSm assay, a timed-rate phosphorus assay, but not the PHS assay, an endpoint-based phosphorus assay (10). The influence on the rate of formation of the phosphomolybdate complex correlated with the presence and amount of LAmB. Jensen et al. believed that a carbohydrate formulation component, mannitol, employed by the PHOSm assay to regulate the rate of the reaction, might participate directly or indirectly in the mechanism of LAmB interference. They also suggested that the amphotericin B moiety in the liposome structure might independently increase the rate of the complex formation reaction. The PHS assay also contains mannitol, but no substantial shift in the endpoint absorption of the phosphomolybdate complex was evident, despite the changes in rate early in the assay. Despite this opportunity to avoid inaccurate serum phosphorus measurements, practitioners remain largely unaware of this issue, and many questions remain unanswered regarding the clinical implications of this phenomenon.

A recent study evaluating pediatric oncology patients found a 43% incidence of hyperphosphatemia in patients receiving LAmB, compared to 13% for patients receiving the lipid complex formulation of amphotericin (ABLC) (11). Furthermore, in a pediatric cohort in which pseudohyperphosphatemia was defined as an elevated serum phosphorus level without a decline in serum calcium and with normal renal function, it was concluded that as many as 50% of those treated with LAmB may develop pseudohyperphosphatemia, with no observed effect of dose or duration of therapy (12). However, limited data are available for adult populations and in comparison to non-amphotericin B-based antifungals. Differentiating hyperphosphatemia from pseudohyperphosphatemia is important because incorrect diagnosis may lead to unnecessary and potentially harmful treatment. Therefore, gaining a better understanding of the incidence of LAmB-induced pseudohyperphosphatemia is of interest to clinicians and clinical laboratorians. In the present study, we assessed the incidence of hyperphosphatemia in an adult population receiving LAmB in comparison to that for a population receiving triazole antifungals. We hypothesized that treatment with LAmB confers a significantly elevated likelihood of developing hyperphosphatemia compared to that with triazole antifungals. In addition, we searched for cases of patients with confirmed pseudohyperphosphatemia in our institution.

**MATERIALS AND METHODS**

**Study design: main cohort.** Upon approval of the Institutional Review Board at the Medical University of South Carolina, and in accordance with the principles of the Declaration of Helsinki, a retrospective cohort study of all patients who received intravenous LAmB, fluconazole, or voriconazole from 30 July 2006 through 30 August 2011 was conducted. Limited use of other amphotericin B products at our institution during the study period precludes comparison of LAmB with other formulations of the drug. Patient data, including demographic information, medications administered, and laboratory results, were retrieved from the Clinical Data Warehouse. Patients were included if they were between the ages of 18 and 89 years and had received LAmB or a triazole for at least 48 h during the study period.

Exclusion criteria included any of the following: (i) a serum phosphorus level of >4.7 mg/dl at the time of antifungal initiation; (ii) receipt of a phosphorus binder at the time of antifungal initiation; (iii) a baseline estimated glomerular filtration rate (eGFR), calculated using the four-variable modified diet in renal dysfunction (MDRD) equation, of <20 ml/min/1.73 m² of body surface area; (iv) absence of a baseline value for serum creatinine or phosphorus; (v) continuous renal replacement therapy; or (vi) concurrent treatment with a triazole and LAmB (13). In addition, phosphorus values associated with a hemolysis index of 2.0 or greater and those measured within 24 h of phosphorus supplementation were excluded. Patients were stratified by baseline eGFR and the presence of concomitant acute kidney injury (AKI) into groups with eGFRs of >59 ml/min (no chronic kidney disease [CKD]) and those with eGFRs of 20 to 59 ml/min (CKD), with or without AKI. AKI was defined as a 50% rise in the serum creatinine value as recorded on the date of the peak phosphorus level with respect to the baseline serum creatinine value (14).

Baseline values were defined as the closest values preceding therapy, no more than 7 days prior to drug initiation, and follow-up values were those recorded between the first and last days of continuous drug administration during the encounter. Additionally, data were collected regarding administration of phosphate binders, evidence of in vivo hemolysis, phosphorus supplementation, and administration of parenteral nutrition. Serum phosphorus values were measured using the PHOSm assay as part of the Synchron DxC 800 chemistry system, with a reference range of 2.5 to 4.7 mg/dl. This colorimetric assay measures serum phosphorus based on the reaction of phosphorus anions with ammonium molybdate under acidic conditions, which results in the generation of a molybdenum phosphorus complex that exhibits a visible absorption envelope (15). To avoid detecting minimal and clinically insignificant changes in serum phosphorus levels, hyperphosphatemia was defined by values of >5.0 mg/dl, and severe hyperphosphatemia was defined by values of >7.0 mg/dl.

**Cases of documented pseudohyperphosphatemia.** Upon provider notification to a laboratorian that a patient was receiving LAmB and pseudohyperphosphatemia was suspected, a serum sample was sent to an external laboratory that used the kinetics-based phosphorus assay of the Siemens Dimension RXL chemistry system (reference range of 2.5 to 4.9 mg/dl). For each of those cases, the medical record was reviewed to extract relevant clinical information regarding medical diagnoses, medication administration, laboratory results, and microbiology results.

**Statistical analysis.** Descriptive statistics were applied to variables of interest. The incidences of hyperphosphatemia and severe hyperphosphatemia were compared among the triazole group and the LAmB group by using chi-square tests. For relationships that showed statistical significance, logistic regression models were used to determine if adjusting for a change in calcium, defined as (lowest calcium on day of highest phosphorus — baseline calcium)/baseline calcium, and use of phosphorus binders (except for patients with a baseline eGFR of >60 ml/min and no AKI) had any effect on the relationship between the group and the incidence of elevated phosphorus. For the analysis of groups with eGFRs of 20 to 59 ml/min, the baseline eGFR was included as a covariate in the adjusted logistic regression models. The incidences of 50% and 100% relative increases were also compared using chi-square tests.

**RESULTS**

A total of 806 cases were included in the final analysis (Fig. 1). The median patient ages of the groups ranged from 50 to 62 years, and baseline serum calcium and phosphorus values were within the normal reference ranges for all groups (Table 1). A total of 80 LAmB exposures were identified, whereas 726 triazole exposures were included as controls. Overall, the incidence of hyperphosphatemia was 52.5% for LAmB-treated patients and 17.2% for triazole-treated patients ($P < 0.01$). Severe hyperphosphatemia was also more common among LAmB-treated subjects (17.5% versus 2.0%; $P < 0.01$). The distribution of serum phosphorus values is shown in Fig. 2. Among patients with hyperphosphatemia during LAmB treatment, the peak occurred at a median of 4 days of therapy (range, 2 to 27 days), and the average dose was...
5.2 mg/kg of body weight/day (range, 2.5 to 9 mg/kg/day) among patients with a documented weight (n = 25). Phosphorus values fluctuated after the initial onset of hyperphosphatemia. In some patients, hyperphosphatemia resolved while therapy continued, while others demonstrated episodic or persistent hyperphosphatemia until discontinuation of LAmB.

Among subjects without CKD or AKI (group 1), hyperphosphatemia occurred more often during LAmB therapy than during triazole therapy (40% [14/35 subjects] versus 10% [47/475 subjects] of cases; P < 0.01) (Fig. 3). Severely elevated serum phosphorus levels (>7.0 mg/dl) were also more common during LAmB therapy (6% [2/35 subjects] versus <1% [1/475 subjects] of cases; P < 0.01). In the adjusted analysis, LAmB-treated patients remained more likely to have high serum phosphorus levels (odds ratio, 5.2 [95% confidence interval {CI}, 2.3 to 11.9]; P < 0.01) and severe hyperphosphatemia (odds ratio, 29.1 [95% CI, 2.5 to 341.5]; P < 0.01) compared to triazole-treated patients. Also, LAmB-treated subjects were more likely to have a >50% increase in the serum phosphorus level (60% [21/35 subjects] versus 19% [88/475 subjects] of cases; P < 0.01) (Fig. 4).

Among individuals with CKD and no concomitant AKI (group 3), hyperphosphatemia also occurred more often during LAmB therapy (67% [2/3 subjects] versus 12% [4/33 subjects] of cases; P = 0.05) (Fig. 3). Similarly, severe hyperphosphatemia was more common during LAmB therapy in this group (18% [3/17 subjects] versus 2% [4/172 subjects] of cases; P < 0.01). Again, LAmB-treated patients remained more likely to have hyperphosphatemia (odds ratio, 6.0 [95% CI, 2.0 to 18.0]; P < 0.01) and severe hyperphosphatemia (odds ratio, 8.6 [95% CI, 1.6 to 45.2]; P = 0.01) in the adjusted analysis, and they were more likely to have a >50% increase in the serum phosphorus level (65% [11/17 subjects] versus 21% [36/172 subjects] of cases; P < 0.01) (Fig. 4).

In the presence of concomitant AKI (groups 2 [no CKD] and 4 [CKD]), no difference in the incidence of hyperphosphatemia was observed, except for the incidence of severe hyperphosphatemia in group 4, which occurred more often in patients receiving LAmB (67% [2/3 subjects] versus 12% [4/33 subjects] of cases; P = 0.05) (Fig. 4). When relative changes were analyzed for these groups, LAmB-treated subjects in group 2 (80% [20/25 subjects] versus 57% [26/46 subjects] of cases; P = 0.01), but not those in group 4 (67% [2/3 subjects] versus 48% [16/33 subjects] of cases; P = 0.5), were more likely to have a >50% increase in the serum phosphorus level.

Administration of parenteral nutrition at the time of the high phosphorus value occurred more commonly in the triazole group. In group 1, 18 (38%) patients with hyperphosphatemia while receiving a triazole were concurrently prescribed parenteral nutrition, compared to 1 (7%) patient receiving LAmB. Similarly, for groups 2, 3, and 4, the numbers of patients were 4 and 1 (17% and 6%), 9 and 1 (26% and 10%), and 2 and 0 (11% and 0%), respectively.

Case reports. All 7 instances of a confirmatory test being per-

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**TABLE 1 Patient demographics and baseline values**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LAmB therapy (n = 20)</th>
<th>Triazole therapy (n = 521)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>50 (39, 62)</td>
<td>57 (44, 67)</td>
</tr>
<tr>
<td>No. (% of females)</td>
<td>21 (35)</td>
<td>251 (48)</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>38 (28.5, 45.5)</td>
<td>40 (30, 52)</td>
</tr>
<tr>
<td>Phosphorus level (mg/dl)</td>
<td>3.2 (2.6, 3.7)</td>
<td>3.2 (2.7, 3.8)</td>
</tr>
<tr>
<td>Calcium level (mEq/dl)</td>
<td>8.3 (7.9, 8.6)</td>
<td>8.1 (7.7, 8.6)</td>
</tr>
</tbody>
</table>

All values are reported as medians (1st, 3rd quartiles) unless otherwise noted. NA, not applicable.
formed using the Siemens Dimension RXL chemistry system phosphorus assay revealed artifactual elevation (Fig. 5). LAmB doses ranged from 3 to 8 mg/kg/day. The degrees of false elevations of serum phosphorus levels ranged from 0.6 to 3.6 mg/dl (median, 2.5 mg/dl). The details of these cases are available in the Appendix.

**DISCUSSION**

Hyperphosphatemia is a serious condition that can result from a multitude of causes, including rhabdomyolysis, tumor lysis syndrome, acute and chronic kidney disease, hypoparathyroidism, acromegaly, and excessive phosphorus administration (10, 16). Standard treatment involves dietary phosphorus restriction and administration of phosphate binders. Hemodialysis is reserved for extreme cases. The most widely recognized cause of spurious elevations of serum phosphorus levels is related to interference caused by serum samples containing paraproteins, such as the case of Waldenstrom’s macroglobulinemia and multiple myeloma. Other triggers include hyperlipidemia, hyperbilirubinemia, and hemolysis (17,18). Pseudohyperphosphatemia may result in improper treatment and inadvertent reductions of serum phosphorus levels to levels below the normal range (16). Therefore, recognition of pseudohyperphosphatemia is important to ensure avoidance of iatrogenic hyperphosphatemia.

The present study demonstrates that exposure to LAmB is associated with a higher likelihood of development of hyperphosphatemia than that with exposure to triazole antifungals. No known cause of hyperphosphatemia was identified as a possible etiology of the observed increased incidence. This finding, taken together with our 6-patient series of confirmed pseudohyperphosphatemia cases as well as previous reports of spurious elevations of serum phosphorus levels during LAmB exposure (4–11), indicates that an artifactual elevation of serum phosphorus is likely to explain the increased incidence of hyperphosphatemia during LAmB exposure in the main cohort. In addition, the results indicate that an elevated serum phosphorus level may not be a rare event, with incidences ranging from 40 to 60% depending on the presence or absence of CKD. Because elevated serum phosphorus levels were also found in 10 to 20% of subjects under triazole antifungal exposure, one could speculate that 30 to 40% of hyperphosphatemic events might be attributable to pseudohyperphosphatemia. The incidence of hyperphosphatemia was unexpectedly high among patients receiving a triazole. As each record was inspected, it was apparent that many of these patients were receiving parenteral nutrition, which likely contributed to the unexpected results. Excluding patients receiving parenteral nutrition altogether could introduce selection bias; nonetheless, this effect may have diminished the detection of a statistically significant difference in the subgroups with AKI (groups 2 and 4).

It is unclear whether renal dysfunction affects the likelihood of a spuriously elevated serum phosphorus level. Three patients described by Sutherland et al. and 4 adults detailed in this report had AKI (6). True hyperphosphatemia associated with AKI may have masked a higher incidence of artifactualy elevated serum phosphorus levels among subjects exposed to LAmB who acquired AKI concomitantly. The doses of LAmB utilized during the episodes of
elevated serum phosphorus in our cohort varied between 3 and 10 mg/kg/day; therefore, no clear dose dependency could be ascertained. Potentiation of the interference by an unknown molecule that accumulates during renal dysfunction may also occur, but this hypothesis requires further investigation. Since the metabolism of amphotericin B is not well established, some other mechanism of drug accumulation may also affect the presence and degree of pseudohyperphosphatemia.

The precise mechanism for the spurious elevation of serum phosphorus during exposure to LAmB remains incompletely understood. Jensen et al. conducted a careful examination of previously postulated mechanisms for the drug-assay interaction, such as those related to pH, lipidic structure, or phosphorus content. Their study led them to conclude that the interference caused by LAmB in the PHOSm chemistry assay results from a LAmB-dependent alteration of the kinetic performance of the reagent system (10). They also found that ultrafiltration of serum samples containing LAmB by use of LipoClear or Microcon-30 filter units generates reliable measurements of phosphorus levels with the PHOSm assay.

The potential implications of our findings in clinical practice are illustrated by cases 3 and 4. These patients received phosphate binders to correct the laboratory abnormality; had the pseudohyperphosphatemia continued unrecognized, it is possible that the patients would have developed hypophosphatemia, which can lead to ominous clinical consequences. Moreover, once the serum phosphorus levels decreased to baseline values, serum samples were not reanalyzed by the Siemens Dimension RXL chemistry system. Therefore, the possibility of incorrectly reporting truly low phosphorus levels as normal levels cannot be discarded. Thus, a lack of clinician awareness of this drug-assay interaction could result in excessive laboratorial testing and patient harm induced by inappropriate therapies.

Our study is not without important limitations. Due to the small sample size of group 4, the results for this group must be viewed cautiously. Also, serum samples from the main cohort were not verified with a confirmatory assay to document the spurious nature of the values. Therefore, pseudohyperphosphatemia is a probable explanation for the observed findings, but not a definite one. Nevertheless, pseudohyperphosphatemia was confirmed for a small subset of patients. Furthermore, no plausible alternative explanation exists to account for the increased incidence of high serum phosphorus levels during LAmB exposure. In addition, the retrospective nature of our study diminished our ability to search for a direct relationship between phosphorus binder usage and individual serum phosphorus determinations or to evaluate the impact of the increased hyperphosphatemia during LAmB exposure on other meaningful outcomes, such as costs associated with additional testing, diagnostic work-up, and monitoring. Despite these limitations, this study is the first to quantify the excess of hyperphosphatemia cases among general adult patients receiving LAmB in comparison with those receiving other, non-amphotericin B-based antifungal therapy. Furthermore, the characterization provided herein of the timing and degree of hyperphosphatemia and the evidence of its resolution despite con-

*FIG 4 Relative increases in serum phosphorus levels in subjects presenting without concomitant AKI (A and B) or with concomitant AKI (C and D). *, P < 0.01 between treatment groups.*
Pseudohyperphosphatemia with Liposomal Amphotericin B

Antimicrobial Agents and Chemotherapy
November 2015 Volume 59 Number 11 aac.asm.org

Continuation of therapy may guide clinical decision-making of practitioners involved in the care of subjects treated with LAmB.

Pseudohyperphosphatemia can occur during therapy with LAmB when serum phosphorus values are measured with the PHOSm assay. Awareness of this phenomenon among clinicians must be raised. The effect may not be predictable in its occurrence, onset or severity, or dose dependency. Further study is needed to elucidate any relationship between pseudohyperphosphatemia and CKD or AKI and to determine whether spurious normohyperphosphatemia masking true hypophosphatemia can also occur in patients exposed to LAmB. In order to prevent adverse events, laboratories using the Beckman Coulter PHOSm assay should be notified automatically when patients receive LAmB. Although the benefit has not been examined rigorously, ensuring that blood samples are drawn distal to or away from the drug infusion site, and at a time when LAmB concentrations are at their nadir, may reduce assay interference. Finally, providers should consider using alternative assays, such as an endpoint-based assay, or using a method to filter lipid layers prior to analyzing the sample.

APPENDIX

All 7 instances of a confirmatory test being performed using the Siemens Dimension RXL chemistry system phosphorus assay revealed artifactual elevation (Fig. 5). LAmB doses ranged from 3 to 8 mg/kg/day. The degrees of false elevations of serum phosphorus levels ranged from 0.6 to 3.6 mg/dl (median, 2.5 mg/dl). The cases are detailed here.

Case 1. A 29-year-old man with a history of testicular cancer and subsequent development of germ cell tumor of the chest, and with a postchemotherapy status, was admitted for nausea, vomiting, and abdominal pain. An echocardiogram showed a large mobile mass in the right atrium. LAmB treatment was initiated at 6 mg/kg/day when growth of Candida albicans was reported for blood cultures on hospital day 2. The patient presented with a serum creatinine level of 1.6 mg/dl and was fluid resuscitated with oral and intravenous fluids. The serum phosphorus level on admission was 4.1 mg/dl. On day 4 of LAmB therapy, the phosphorus level peaked at 6.2 mg/dl, while the confirmatory assay measured the serum phosphorus level as 4.9 mg/dl (measured 5 h 7 min after the dose was administered). All other electrolytes were within normal limits. Despite continued treatment with LAmB until discharge on hospital day 18, kidney function and the serum phosphorus level remained within the normal ranges throughout the remainder of the hospitalization.

Case 2. A 48-year-old woman with AIDS and a history of progressive multifocal leukoencephalopathy and cryptococcal meningitis presented to the emergency department after having a seizure. The patient was treated with lorazepam and phenytoin. LAmB treatment was initiated at 5 mg/kg/day. Her phosphorus level peaked at 5.9 mg/dl on day 7 of LAmB therapy, at which time the external laboratory reported a confirmatory result of 4.3 mg/dl (measured 19 h 59 min after the dose was administered). Her phosphorus level was intermittently elevated until day 12 of LAmB, and she was discharged on hospital day 15.

Case 3. A 54-year-old man was admitted to the hospital for treatment of cryptococcal meningitis. Along with flucytosine treatment, LAmB treatment was initiated at 6 mg/kg/day. His serum phosphorus level was 3.6 mg/dl on admission and increased to 6.3 mg/dl by the 3rd day of therapy. To correct the hyperphosphatemia, the patient received 667 mg of calcium acetate plus 800 mg of sevelamer carbonate that day, 1,920 mg of aluminum hydroxide gel (30 ml) on day 4 of LAmB therapy, and 1,920 mg of
aluminum hydroxide gel plus 800 mg of sevelamer carbonate on the 5th day of therapy. Despite this therapy, his serum phosphorus level increased to 7.4 mg/dl. That day, a serum sample analyzed at the external laboratory revealed a serum phosphorus level of 3.8 mg/dl (measured 5 h 55 min after the dose was administered). His serum creatinine level had also increased, from 0.8 mg/dl on admission to 1.6 mg/dl. Because AKI was attributed to LAmB, the dose was decreased to 3 mg/kg/day. The patient was given additional intravenous fluids and continued LAmB therapy after discharge. He was readmitted 15 days later for diverticulitis. At that time, his serum creatinine level was 2.7 mg/dl. On the 3rd day of this admission, his serum phosphorus level was 6.4 mg/dl, but a sample sent to the external laboratory revealed a phosphorus value of 3.4 mg/dl (measured 9 h 55 min after the dose was administered). The patient was aggressively volume resuscitated. LAmB therapy was discontinued on hospital day 5, and fluconazole was initiated at 400 mg daily. Subsequently, his serum creatinine level trended down to 2.0 mg/dl, and his phosphorus level trended down to 5.1 mg/dl at the time of discharge on hospital day 7.

Case 4. A 49-year-old man with newly diagnosed type 2 diabetes and a hemoglobin A1c value of 17.6% was transferred to the hospital for treatment of left maxillary invasive fungal sinusitis with bony destruction. In addition to aggressive surgical treatment, vancomycin, piperacillin-tazobactam, caspofungin, and LAmB (8 mg/kg/day) therapies were initiated upon admission. Positive fungal cultures resulted in a diagnosis of mucormycosis. His baseline serum creatinine level was 1.0 mg/dl but rose to 1.7 mg/dl by day 3, and his serum phosphorus level increased over the same period, from 4.6 mg/dl to 8.4 mg/dl. No confirmatory measurement was taken at that time. The LAmB dose was decreased to 4 mg/kg/day, and the patient was aggressively volume expanded in an attempt to improve kidney function. However, his serum creatinine level continued to increase, to 3.0 mg/dl. On day 6, his serum phosphorus level was 5.7 mg/dl, but a sample analyzed at the external laboratory yielded a serum phosphorus level of 5.1 mg/dl (measured 43 h 6 min after the dose was administered). The patient received 2 doses of calcium acetate at 2,001 mg on hospital days 6 and 7. Subsequently, LAmB treatment was discontinued, posaconazole treatment was initiated, and the patient was discharged.

Case 5. A 10-year-old girl with acute myeloid leukemia was admitted to the hospital for a bone marrow transplant. Her hospital course was complicated by a *Candida tropicalis* fungemia related to her central venous catheter. LAmB treatment was initiated at 5 mg/kg daily, and the catheter was removed. The patient remained on LAmB after discharge; however, she was readmitted 2 weeks later for a chief complaint of lethargy and decreased appetite. Prior to LAmB, her serum creatinine level was 0.3 mg/dl. It increased to 0.6 mg/dl on day 3 and was 1.0 mg/dl on day 23 of treatment, at which time her serum phosphorus level was within normal limits. The phosphorus level rose to 7.1 mg/dl on day 30. Her serum creatinine level trended back to 0.6 mg/dl on day 34, and her phosphorus level remained within normal limits to below the normal range. Subsequently, on day 56 of LAmB treatment, her serum phosphorus level peaked at 7.3 mg/dl (on day 6 of hospitalization), but it was measured as 5.5 mg/dl at the external laboratory (measured 14 h 15 min after the dose was administered), confirming a false elevation. LAmB treatment was continued after discharge, and no laboratory measurements were available after LAmB discontinuation.

Case 6. A 12-year-old boy with recurrent acute myelocytic leukemia was admitted to the hospital for fever secondary to respiratory syncytial virus. His hospital course was complicated by a central venous catheter infection. Initially, he was treated with voriconazole for empirical fungal coverage. However, on day 93 of his hospital stay, voriconazole treatment was discontinued and LAmB treatment was initiated at a dose of 3 mg/kg daily. His serum creatinine level was consistently around 0.3 mg/dl throughout the hospitalization. His serum phosphorus level was within normal limits until day 25 of LAmB therapy, when his serum phosphorus level began trending up, to a peak of 8.6 mg/dl on day 36. On day 35 of LAmB therapy, his serum phosphorus level was 7.8 mg/dl as measured by the PHOSm assay but was 5.3 mg/dl at the external laboratory 45 h 20 min after the dose. The LAmB dose was decreased to 1 mg/kg three times per week; however, the serum phosphorus level remained elevated. The LAmB dose was increased to 5 mg/kg daily on day 41, and his phosphorus level continued to be elevated, in the range of 6 to 7 mg/dl, until his death on day 56.

ACKNOWLEDGMENTS

N. M. Bohm and K. C. Hoover had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. N. M. Bohm and K. C. Hoover conceived the study idea and executed the project, including verification of data; J. C. Q. Velez provided insight regarding study design and analysis; Y. Zhu provided data regarding measurements of hyperphosphatemia from outside laboratories and expert description of the affected laboratory assay; and A. E. Wahlquist contributed to the study design and provided statistical analysis. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. N. M. Bohm takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data acquisition and data analysis conducted by A. E. Wahlquist were supported by the South Carolina Clinical & Translational Research Institute (SCCTR), with an academic home at the Medical University of South Carolina, through National Institutes of Health (NIH) Clinical and Translational Science Award (CTSA) grant UL1TR000062. J. C. Q. Velez has served on an advisory board for Mallinckrodt Pharmaceuticals. No other authors have relevant financial interests, activities, relationships, or affiliations that would present a conflict of interest.

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