Pediatr Blood Cancer 2008;51:59–61

Sevelamer Hydrochloride: A Novel Treatment of Hyperphosphatemia Associated With Tumor Lysis Syndrome in Children

Shaker Abdullah, MD,[1] Manuel Diezi, MD,[2] Lillian Sung, MD, PhD,[1] L. Lee Dupuis, RPh, MScPhm, FCSHP,[1,3] Denis Geary, MD, FRCP(C),[4] and Oussama Abla, MD[1]*

Background. Sevelamer is a phosphate-binder used effectively for the treatment of hyperphosphatemia in patients treated with dialysis. ***Objectives.*** To describe the safety of sevelamer in children with hyperphosphatemia secondary to tumor lysis syndrome and the serum phosphate concentrations observed following its administration. ***Procedure.*** A retrospective chart review of all children with leukemia/lymphoma diagnosed between November 2002 and April 2004 who received sevelamer during their initial admission was conducted. We monitored the effects of sevelamer on serum phosphate concentration, calcium/phosphate product and renal function at hours 24, 48, and 72 from sevelamer initiation. ***Results.*** Thirteen patients received sevelamer during the study period. Their median age was 13 years (range 2.7–17.9) and eight were boys. Nine children had acute lymphoblastic leukemia, one had acute myeloid leukemia and 3 had non-Hodgkin's lymphoma. The most frequently used dose of sevelamer was 400 mg orally twice daily. The median duration of sevelamer therapy was 2 days (range 1–7). Two children were excluded from the efficacy analysis due to concurrent use of dialysis. Mean serum phosphate levels decreased after sevelamer administration, in eleven patients, from a baseline 2.2 mmol/L ± 0.4 (95% CI, 1.7–3.1) to 1.1 mmol/L ± 0.2 at hour 72 (95%CI, 0.6–1.5). The only toxicity attributed to sevelamer was mild vomiting in three patients. ***Conclusions.*** Sevelamer appears to be effective and tolerable for the treatment of hyperphosphatemia associated with tumor lysis syndrome. Pediatr Blood Cancer 2008;51:59–61. © 2008 Wiley-Liss, Inc.

Key words: children; hyperphosphatemia; sevelamer; tumor lysis

INTRODUCTION

Hyperphosphatemia is a well-known complication of tumor lysis syndrome following induction therapy for leukemia/lymphoma [1]. Malignant lymphoblasts contain four times more intracellular phosphate compared with mature lymphocytes [2]. Release of phosphate occurs from 24 to 48 hr following initiation of chemotherapy and can lead to hyperphosphatemia when the renal threshold for phosphate excretion is exceeded. The subsequent precipitation of phosphorus as calcium phosphate in the renal tubules may lead to acute renal failure [2]. Untreated severe hyperphosphatemia can lead to metastatic calcifications of the vessels and soft tissues [3].

Hemodialysis is the treatment of choice for severe hyperphosphatemia, although continuous peritoneal dialysis or continuous venovenous hemofiltration (CVVH) have been successfully employed [4,5]. Initial management of mild to moderate hyperphosphatemia includes dietary or intravenous phosphorus restriction and the administration of oral phosphate binders. These drugs bind phosphorus in the gastrointestinal (GI) lumen forming insoluble products that are not readily absorbed [3]. The most commonly used phosphate binders contain either aluminum or calcium. Aluminum hydroxide has an unpleasant taste, whereas calcium salts, such as calcium carbonate and calcium acetate, can potentially cause hypercalcemia and an increased calcium–phosphate product. If the latter exceeds 80 mg/dL (6.5 mmol/L), it may lead to nephrocalcinosis, vascular calcifications, and increased risk of mortality [3].

Sevelamer hydrochloride (RenaGel, Genzyme) is a phosphate binder that does not contain aluminum or calcium. It is an insoluble cationic polymer not absorbed by the gut, which is effective in lowering serum phosphate concentrations in adults [6,7] and children receiving hemodialysis [8]. The following is the first report describing a single institution's experience with the use of sevelamer in children with hyperphosphatemia associated with tumor lysis syndrome. Our objectives were to describe the safety of sevelamer given as a phosphate binder to pediatric patients with this metabolic complication and to describe the serum phosphate concentrations observed following its administration.

DOI 10.1002/pbc.21478

PATIENTS AND METHODS

This retrospective study was approved by the Research Ethics Board at The Hospital for Sick Children in Toronto, Canada. Children ≤18 years of age diagnosed with acute leukemia or lymphoma between November 2002 and April 2004 and who received sevelamer during their admission for induction treatment were identified from pharmacy records. Demographic and clinical data were obtained from their medical records. We specifically obtained the following information: serum phosphate, calcium and creatinine concentrations at hours 0, 24, 48, and 72 from the start of sevelamer therapy, dates of initiation and discontinuation of sevelamer, administered sevelamer dose, concurrent use of other phosphate binders, rasburicase administration or dialysis, extent of oral intake during sevelamer treatment, any modification in the intravenous (IV) fluid rate, adverse effects attributable to sevelamer and reported difficulties with sevelamer administration. Hyperphosphatemia was defined as serum phosphate concentration above the upper limit of normal for age at our institution (2.20 mmol/L for children <1 year of age; 2.1 mmol/L, 1–4 years; 1.81 mmol/L, 4–8 years; 1.71 mmol/L, 9–14 years and 1.52 mmol/L for children >14 years of age). Severe hyperphosphatemia was defined as a serum phosphate concentration exceeding 3.2 mmol/L. The calcium/phosphate product was calculated by multiplying the phosphate and calcium concentrations in mmol/L.

[1]Divisions of Hematology/Oncology, The Hospital for Sick Children, Toronto, Canada; [2]Hemato-Oncologie Pédiatrique, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [3]Department of Pharmacy, The Hospital for Sick Children, Toronto, Canada; [4]Divisions of Nephrology, The Hospital for Sick Children, Toronto, Canada

*Correspondence to: Oussama Abla, Hematology/Oncology, Hospital for Sick Children, 555 University Avenue, Room 9420 Black, Toronto, ON, Canada M5G 1X8. E-mail: oussama.abla@sickkids.ca

Received 16 August 2007; Accepted 27 November 2007

Data Analysis

Descriptive statistics were used to describe patient demographic data. In order to determine whether serum phosphate declined over time, daily serum concentrations were examined for 3 days after sevelamer administration using a linear mixed model. Analyses were conducted with SAS software (version 9.1; SAS Institute, Inc., Cary, NC).

RESULTS

During the study period, 79 pediatric patients were diagnosed with acute lymphoblastic leukemia (ALL), 26 with acute myeloid leukemia (AML) and 30 with non-Hodgkin's lymphoma (NHL). Thirteen of these children received sevelamer for the treatment of hyperphosphatemia secondary to tumor lysis. Their median age was 13 years (range 2.7–17.9) and eight were boys. Nine children had ALL (6 precursor-B, 1 mature-B and 2 T-cell); one patient had relapsed AML and 3 had NHL. The most frequently administered dose of sevelamer was 400 mg twice/day orally. The median duration of sevelamer therapy was 2 days (range 1–7), and the median number of sevelamer doses administered was 5 (range 2–20). Sevelamer was administered with food in five children and on an empty stomach in two patients. The extent of food intake was not documented in the medical records of the remaining six patients. There was no change in IV fluid administration rate in most patients; however, two children had their IV hydration rate increased by 25% during sevelamer therapy. There was no concurrent use of aluminum or other oral phosphate binders during sevelamer treatment in any of the 13 children.

Two patients were excluded from the efficacy, but not toxicity analyses due to concurrent use of dialysis. Among the remaining eleven children, two had received aluminum hydroxide prior to sevelamer administration without benefit. Clinical parameters reflecting serum phosphate, calcium–phosphate product and renal function in these patients are presented in Table I. In these 11 patients, serum phosphate concentrations declined significantly over time (beta coefficient for time −0.33, standard error 0.06; $P = 0.0003$). The mean serum phosphate decreased from a baseline level of 2.2 mmol/L ± 0.4 SD (95% confidence interval, 1.7–3.1) to 1.3 mmol/L ± 0.3 at hour 24 (95% CI, 0.9–2.0) and to 1.1 mmol/L ± 0.2 at hour 72 (95% CI, 0.6–1.5). The mean serum calcium/phosphate product decreased from a baseline level of 4.5 mmol/L ± 0.9 SD (95% CI, 2.9–6.3) to 3.3 mmol/L ± 1.2 at hour 24 (95% CI, 1.7–5.8) and to 2.5 mmol/L ± 0.8 at hour 72 (95% CI, 1.5–3.8). A 34–50% decrease in serum creatinine concentration was observed in three children who had received sevelamer; these children had not received rasburicase nor had any increase in the rate of IV hydration administration.

Sevelamer was overall well tolerated by all 13 children; mild vomiting attributed to sevelamer was documented in 3 patients. The sevelamer tablets were able to be swallowed by all patients, including the youngest one (2 years old).

DISCUSSION

We have reviewed the use of sevelamer in pediatric patients with hyperphosphatemia related to tumor lysis syndrome. Sevelamer appears to be effective in lowering serum phosphate concentrations and the calcium–phosphate product in most patients, with minimal side effects.

TABLE I. Parameters of Sevelamer Efficacy in 11 Patients*

Patient number	Serum PO_4 concentration pre-sevelamer (mmol/L)	Serum PO_4 concentration hour-24	Serum PO_4 concentration hour-48	Serum PO_4 concentration hour-72	Ca/PO_4 pre-sevelamer (mmol/L)	Ca/PO_4 hour-24	Ca/PO_4 hour-48	Ca/PO_4 hour-72	Serum creatinine pre-sevelamer (μmol/L)	Serum creatinine hour-72	Receipt of rasburicase
1	2.1	1.51	1.19	1.33	5.01	3.71	2.87	3.16	54	47	No
2	2.08	0.88	0.8	0.9	4.24	1.83	1.69	1.89	42	33	Yes
3	1.97	1.95	1.44	0.98	4.31	3.85	3.19	2.17	36	31	No
4	2.8	1.72	1.29	0.66	5.88	3.44	2.64	1.45	117	60	No
5[b]	2.54	1.11	0.91	1.03	5.28	2.24	1.87	2.37	88	64	No
6	2.3	1.11	1.08	1.08	4.8	3.2	1.84	2.05	47	29	No
7	1.72	1.11	1.26	N/A	3.8	2.9	2.75	N/A	64	N/A	No
8	2.02	1.11	1.24	0.95	2.92	1.72	2.07	1.79	77	51	No
9	1.89	1.11	1.71	1.35	3.78	3.34	2.76	3.73	41	25	Yes
10	1.96	1.11	1.09	1.52	4.62	4.08	2.49	3.54	82	82	No
11[b]	3.09	1.11	2.45	1.5	6.24	5.81	4.9	3.2	30	18	Yes

PO_4, phosphate; Ca/PO_4, calcium–phosphate product; N/A, not available.
*The patients who underwent concurrent dialysis are not shown; [b]Patients number 5 and 11 had their IV hydration rate increased by 25%.

Standards of care for the management of hyperphosphatemia associated with tumor lysis syndrome include aggressive hydration with isotonic saline, avoiding urinary alkalinization, the avoidance of intravenous and oral phosphate solutions and the administration of oral phosphate binders [1,2]. Furthermore, in the presence of hyperphosphatemia it is preferable to avoid calcium-based phosphate binders due to the risk of precipitating metastatic calcifications [9]. Several studies have shown sevelamer to be an effective oral phosphate-binder in adult patients treated with hemodialysis [7,10,11]. Preliminary data suggest that sevelamer can also be safely given to children with end-stage-renal-disease. Mahdavi et al. [8] showed that the drug was effective in reducing the serum phosphate concentration and the calcium–phosphate product in children undergoing dialysis. More recently, a randomized cross-over trial comparing sevelamer with calcium acetate in children with chronic kidney disease was conducted. Sevelamer and calcium acetate were equally effective in lowering serum phosphate concentrations and the calcium–phosphate product, however a lower rate of hypercalcemia was observed with sevelamer [9]. In both pediatric studies [8,9], sevelamer was well tolerated except for an increased incidence of metabolic acidosis observed in 18% of the children in the latter study [9]. Other side effects reported include abdominal pain, diarrhea, nausea-vomiting, muscle cramps, hypocalcemia, headache, hyperparathyroidism [9], and hypermagnesemia [12]. None of our patients developed hypermagnesemia or hypocalcemia, and since this is a retrospective study we were not able to fully evaluate the presence of metabolic acidosis.

Sevelamer does, however, have a few limitations. First, the capsules must be swallowed whole which could be problematic for younger children. Second, its maximal phosphate-binding capacity occurs at a gastric pH of 7, thus agents such as histamine H-2 antagonists or proton pump inhibitors may interfere with its action [13]. Third, sevelamer is generally more expensive than aluminum hydroxide. Based on our institution's current acquisition costs, sevelamer is almost 14 times more expensive than aluminum hydroxide.

Other novel phosphate binders include lanthanum, nicotinamide and iron-containing preparations [14]. Lanthanum carbonate was shown to be effective and tolerable as a phosphate binder in adult hemodialysis patients. However, pediatric experience with lanthanum has not been reported nor has it been given in the setting of tumor lysis syndrome. Clinical studies with this drug are warranted [14].

Our study suggests that sevelamer can be an effective and well-tolerated therapy for tumor lysis-induced hyperphosphatemia in children. However, the small number of patients and the retrospective nature represent major limitations of this study. While it is theoretically possible to have conducted a case-control study to evaluate the effect of sevelamer on tumor-lysis associated hyperphosphatemia, matching patients with respect to diagnosis, tumor burden and hydration would have been very difficult. In addition, since patients who received sevelamer did so because the clinical team perceived them to be at risk of clinically significant hyperphosphatemia, this selection process precludes truly relevant matching. However, without a control group we cannot demonstrate the contribution of sevelamer in reducing serum phosphate concentrations beyond the contribution of the other interventions used for tumor lysis syndrome such as aggressive hydration. Despite these limitations, our paper provides valuable information particularly in describing the use of sevelamer in children with tumor lysis syndrome. Prospective studies with sevelamer in children with this metabolic complication are needed. Ideally, these trials should assess the efficacy, tolerance and cost-effectiveness of sevelamer in a randomized fashion with other phosphate binders such as aluminum hydroxide.

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