American Journal of Case Reports

ISSN 1941-5923
© Am J Case Rep, 2017; 18: 463-466
DOI: 10.12659/AJCR.902862

Received: 2016.12.15
Accepted: 2017.02.14
Published: 2017.04.28

Hyperphosphatemia, a Cause of High Anion Gap Metabolic Acidosis: Report of a Case and Review of the Literature

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 74
Final Diagnosis: Metabolic acidosis due to hyperphosphatemia
Symptoms: Abdominal pain
Medication: —
Clinical Procedure: —
Specialty: Nephrology

Objective: Rare disease

Background: Hyperphosphatemia is a common problem in patients with kidney failure. It is usually mild and rarely severe enough to cause metabolic acidosis on its own. Besides kidney failure, use of phosphate containing enemas, rhabdomyolysis, and tumor lysis syndrome are common causes of severe hyperphosphatemia.

Case Report: A 74-year-old man with a history of diabetes mellitus type II, arterial hypertension, and end stage renal disease, who was on hemodialysis and who had undergone hemicolectomy for ischemic bowel disease, and had not eaten for several days, developed severe metabolic acidosis, with an anion gap (AG) of 31 meq/L, uncorrected for serum albumin. At that time he had a high level of beta-hydroxybutyrate and severe hyperphosphatemia (16.5 mg/dL). Metabolic acidosis and hyperphosphatemia were corrected with hemodialysis, confirming the role of hyperphosphatemia in the development of high AG metabolic acidosis.

Conclusions: Although our patient had many reasons to develop high AG metabolic acidosis, hyperphosphatemia played a significant role in his acidosis. Severe hyperphosphatemia is rarely mentioned as a cause of high AG acidosis. It should be added to the long list of causes of this metabolic disorder. Physiological basis of acid base changes are discussed.

MeSH Keywords: Acid-Base Equilibrium • Acidosis • Hyperphosphatemia

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/902862

Background

In hemodialysis patients, metabolic acidosis is associated with a high anion gap (AG) due to the inability of the kidney to excrete the daily acid load of 1 to 1.5 meq/kg of body weight [1]. This problem is primarily due to low glomerular filtration rate and the inability of the kidney to excrete fixed acids such as sulfate, urates, and phosphates. Other factors, like, impaired ammonia production and secretion due to tubulointerstitial fibrosis, hyperkalemia, and aldosterone resistance also contribute to this problem. Occasionally, loss of bicarbonate from the gastrointestinal tract due to diarrhea or ingestion of acid from endogenous or exogenous sources can be the cause of metabolic acidosis. Phosphorus excretion helps with the disposal of the acid, although, unlike ammonia secretion that can increase several folds with acidosis, phosphorus excretion rate does not change much and therefore its contribution to acid/base homeostasis is limited. Dialysis patients commonly have hyperphosphatemia, but they can't use phosphorus to excrete hydrogen ions. Most dialysis patients who take phosphate binders and follow a phosphorus restricted diet, have mild to moderate hyperphosphatemia, with blood levels somewhere between 4 to 6 mg/dL and severe hyperphosphatemia, levels >10 mg/dL is uncommon. Severe hyperphosphatemia can be seen with dietary indiscretion, Fleet enema use [2,3], vitamin D intake and rhabdomyolysis [4]. Even in these situations, AG is usually increased by 5 to 6 meq/L and very high AGs are uncommon. Herein, we describe a case of severe hyperphosphatemia with a high AG.

Case Report

A 74-year-old Hispanic man who had been diagnosed with ischemic bowel disease and had undergone right hemicolectomy in another hospital came to our institution for a second opinion after being told by the first hospital they couldn't help him anymore. His past medical history included diabetes mellitus type II, arterial hypertension, coronary artery disease, peripheral arterial disease leading to bilateral leg amputation and end stage renal disease. He had been undergoing hemodialysis treatment, three times a week, for four years. On admission to our hospital, he was alert, awake, normotensive and afebrile, but he was having abdominal pain and he was not able to eat. Due to this, he was kept on intravenous fluids and he was not taking phosphate binders. On admission, his serum phosphorus was 8.6 mg/dL, serum albumin 2.6 g/dL, and AG 16 meq/L. Two days after admission to our hospital, we noted increasing serum PO4 and AG levels. Four days after admission and before his second dialysis treatment, his serum phosphorus level was 16.5 mg/dL, uric acid 16 mg/dL, albumin 2.7 g/dL, and AG of 31 meq/L without and 34 with albumin correction. After undergoing hemodialysis treatmen, his serum phosphorus and AG decreased to 3.3 mg/dL and 12 meq/L, respectively. Blood drawn prior to the dialysis treatment showed: serum ketones 1+, beta-hydroxybutyrate 3.0 meq/L and L lactate 1.6 meq/L. CPK levels were checked twice and they were normal, 144 and 218 IU/L (normal range 49 to 397). Table 1 shows laboratory data when hyperphosphatemia and high AG were developing. Later on during his hospital stay, he underwent computed tomographic (CT) angiography of abdomen that showed atherosclerotic stenosis of the superior mesenteric artery at its origin from the aorta that was balloon dilated and stented. He also had surgery for relief of bowel obstruction secondary to bowel adhesions. Afterward, he improved somewhat but he continued to be weak. He was discharged home two months later and he expired seven months after his discharge from the hospital.

Discussion

Anion gap (AG) represents the difference between anion and cation concentrations in the serum, but because not all ions in the blood are measured, it is usually expressed in the form of a gap between sodium and potassium versus those of chloride and bicarbonate concentrations. The difference or the gap is related to unmeasured anions and cations, like albumin,

Table 1. Serum electrolytes, phosphorus levels and AG values from admission to day 4, when patient had his second dialysis treatment.

Number of days after admission	Na meq/L	K Meq/L	Cl Meq/L	CO2 Meq/L	PO4 Mg/dL	Albumin g/dL	AG Meq/with no correction
1	137	4..3	98	32	8.6	2.6	7
3	134	5.8	94	17	10.9	2.6	23
4 Pre dial	145	4.9	90	24	16.5	2.7	31
4 Post dial	139	3.7	106	21	3.3	2.7	12

Table 2. Anion gap values in dialysis patients with severe hyperphosphatemia >10 mg/dL.

Name	Na	K	Cl	CO2	BUN	Cr	Ca	PO4	AG
1	140	5.6	101	22.0	104	13.9	7.0	13.3	17.0
2	142	4.2	106	21.0	87	10.09	7.6	11.0	15.0
3	132	6.8	97	21.0	67	7.63	7.0	15.9	14.0
4	139	3.6	97	18.0	79	22.6	6.5	10.8	24.0
6	140	4.7	98	20.7	95	14.7	9.7	11.3	21.3
7	134	7.0	94	14.0	112	9.6	8.9	12.8	26.0
8	140	3.9	98	21.0	152	11.4	7.3	10.3	21.0
9	129	4.4	95	20.0	53	6.1	7.8	10.0	14.0

Electrolyte and AG values are in meq/L, BUN, creatinine, glucose in mg/dL and albumin in g/dL.

phospates, sulfates, urates, lactate, calcium, and magnesium. In people with normal kidney function and endocrine physiology, and using the current laboratory methodology that uses ion selective electrode, the normal AG is 7.0±4 meq/L or a range of 3 to 11 meq/L [5–8]. In dialysis patients, AGs are higher and somewhere around 12.0 meq/L. The charge contribution of Pi is both concentration and pH dependent. The effect of pH, however, is negligible and so the use of pH 7.40 when the actual pH is unknown does not create a significant error. Pi charge can be calculated based on the fact that at physiological pH of human plasma, 80% of PO4 in serum is in the form of disodium hydrogen phosphate ($PO4HNa^2$) and 20% is in the form of mono-sodium-hydrogen phosphate (PO4H2Na). PO4H2Na can accept only one hydrogen ion while PO4HNa2 can accept two hydrogen ions. Due to this, five molecules of PO4 have nine available charges or 9/5 or 1.8 meq/L per each molecule of Pi (phosphorus). Of note, laboratory measures serum phosphorus and not phosphate. To calculate the Pi charge, one has to multiply phosphorus concentration in mg/dL×10, to convert it to mg/L, then divide the result by 31 (atomic weight of phosphorus), to convert it to mmol per liter. Once the mmol concentration of Pi is known, it should be multiplied by 1.8 to get the charge of Pi as meq/L [9].

In our patient with a serum Pi of 16.5 mg/dL, or 5.6 mmol/L, the contribution of Pi to AG would be 5.6×1.8 or 9.29 meq/L. Adding the concentration of lactic acid, 1.6 meq/L, and beta-hydroxybutyrate, 3.0 meq/L, albumin 8.4 meq/L (2.8×3.0) [10], the total contribution of known anions to AG will be 21.79 meq/L. To find out if high Pi level was associated with a high AG, we looked at nine chronic dialysis patients who had severe hyperphosphatemia, >10 mg/dL (Table 2). In these patients, the mean AG was 18.6±4.25 meq/L with a range of 14 to 26 meq/L. Thus, considering that normal AG range is 3 to 11 meq/L, the increase in AG or delta gap was 34–11=23 meq/L. The sum of measured anions in our patient (21.79 meq/L) explains 64% of the total AG. In other words, the measurable anions can't explain 36% of the change in the gap. Where do these other ions come from? Even if one assumes that sulfates, like indoxyl sulfate and p-cresyl sulfate, and urates were released from cells due to ischemia, their contribution, at best, would be very small and in the order of 1 to 2 meq/L [11–13]. Other anions that possibly contributed to AG but not measured include: aspartic, succinic, homovanilic, and pyroglutamic acids.

In our patient the predialysis anion gap was 31 meq/L, but it decreased to 11 meq after dialysis treatment, indicating that not only Pi, but other anions removed by dialysis contributed to the increase in AG. The nature of these anions remains unknown. As reported by others, AG >30 meq/L is usually due to organic acidosis such as diabetic ketoacidosis or lactic acidosis [14,15], rhabdomyolysis, or methanol or ethylene glycol poisoning. Rare causes include severe hyperphosphatemia due to phosphate intoxication or leukemia [16]. With the use of Fleet enema for bowel cleansing, serum Pi levels as high as 60 mg/dL have been reported [17–19]. Kirschbaum [20] described a 74-year-old woman with no previous history of kidney disease, who developed severe hyperphosphatemia (serum Pi of 62.5 mg/dL (20.1 mmol/L or 36.2 meq/L), hypernatremia, metabolic acidosis, and an AG of 56 meq/L after accidentally ingesting a bottle of Fleet enema. In this case, Pi and albumin accounted for 89% of the increase in AG.

Our patient was a diabetic who developed severe hyperphosphatemia [21] and a high level of beta-hydroxybutyrate. No blood gases were drawn when these events were unfolding but the magnitude of AG left no doubt about the severity of his acidosis. Hyperphosphatemia developed because he had ESRD and he was unable to take phosphate binders. He also had ketoacidosis induced by starvation after being NPO for a few days, but we don't think starvation played a significant role in the development of acidosis [22]. It is well known that

starvation ketoacidosis, when of short duration, is self-limiting, with serum bicarbonate stabilizing usually around 18 to 20 meq/L. Starvation, however, can cause severe acidosis if it is prolonged to two weeks or longer [23]. We believe his acid base picture was a mixed one of metabolic acidosis due to a combination of hyperphosphatemia, starvation ketosis, ESRD, and metabolic alkalosis due to suction of his gastric contents. The ratio of change in his AG versus bicarbonate, delta AG/delta bicarbonate points to this fact. Although other causes of high AG acidosis, like diabetic ketoacidosis, lactic acidosis, rhabdomyolysis, and tumor lysis syndrome should be considered, there was no convincing evidence to believe that any of these entities existed. He had only 1+ ketones in his serum and we measured beta-hydroxybutyrate that was found to be modestly elevated. Of note plasma C-peptide level was measure during his hospitalization and it was within the normal range. In addition CPK levels were measured twice and they were normal, thus ruling out the possibility of rhabdomyolysis. Similarly, there was no evidence to support suspicion of tumor lysis syndrome (TLS). He had no known malignancy and he was not exposed to any agent that could cause TLS. Although he had undergone right hemicolectomy, we don't think short bowel syndrome played any role in his acidosis. Experiments in dogs have shown DL lactate causes more hyperphosphatemia compared to L-lactate [15,24].

Conclusions

Hyperphosphatemia can cause high anion gap (AG) metabolic acidosis mainly through generation of acidic compounds that neutralize bicarbonate. This happens primarily with severe hyperphosphatemia resulting from consumption of phosphorus, such as use of Fleet enema in patients with kidney failure and sometimes in people with normal kidney function. Our patient developed severe metabolic acidosis that could be attributed to hyperphosphatemia, starvation, ischemic bowel disease, and ESRD. Severe hyperphosphatemia is rarely mentioned as a cause of wide gap metabolic acidosis [25] and it should be added to the long list of causes of this common acid/base disorder. Berend et al. [26] proposed use of the term, GOLD MARRK as a mnemonic for causes of high AG acidosis. We propose the mnemonic, GOLD PARK, to include hyperphosphatemia as a cause of high AG acidosis, where, G stands for glycols, O for 5-oxoproline, L for lactic acidosis, D for D-lactic acidosis, P for hyperphosphatemia, A for alcohols and acetyl salicylic acid, R for renal failure and rhabdomyolysis, and K for ketoacidosis (diabetic, alcoholic or starvation induced).

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