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CASE REPORTS

LIFE-THREATENING ELECTROLYTE DISTURBANCES FROM A COMMONLY PRESCRIBED DRUG – SODIUM PHOSPHATE BASED ENEMA

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ABSTRACT

Laxatives are commonly used medication in patients of all age groups. Sodium phosphate based enema is one of them. While they are often prescribed, medical practitioners may not be familiar with the content of them and their related potential toxicity. We report a case of life threatening toxicity in a young child without underlying renal disease after she was given repeated doses of sodium phosphate enema, and discuss about the acute management of phosphate-containing laxatives toxicity, as well as the growing concern for safety of this kind of medication.

ARTICLE HISTORY

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Introduction

Laxatives are commonly used medication in patients of all age groups. Sodium phosphate- based enema is one of them. It is easily available over-the-counter with no prescription required. Medical practitioners may not be familiar with the content of each laxatives and their related potential toxicity. There are a few reported cases of sodium phosphate based enema toxicity in children. Although majority of them had a complete recovery, permanent morbidity or even death has been reported in some cases. (1)

Case Report

A 15-month-old girl with body weight of 8.6kg suffering from chronic constipation presented to the emergency department (ED) with limb stiffness for 1 hour after she was given ¾ tube of phosphate containing enema. Previously she had been extensively worked up for constipation including water soluble contrast enema and rectal biopsy which were normal. She had been prescribed fleet enemas for her constipation by her pediatrician. On presentation in the ED, she was conscious but she rapidly became unresponsiveness. Glasgow Coma Scale (GCS) was 4/15 (E1V1M2). Pupils were 4mm in size with sluggish response. She developed seizures with generalized hypertonia. Oxygen saturation was 88% in room air. Blood pressure was 68/39 mmHg. Diazepam 2.5mg was given per rectal but there was large amount of bowel output soon after the rectal suppository. Lorazepam 1mg was then given after intravenous access was secured. However the anti-epileptics failed to abort the seizures. She was intubated and needed inotropic support. Repeated doses of lorazepam were given. Initial blood tests revealed profound hypocalcemia 0.96mmol/L (reference range 2.12-2.59mmol/L), hyperphosphatemia 6.76mmol/L (reference range 1.10-1.95mmol/L) and hypokalaemia 2.1mmol/L (reference range 3.5-5.0mmol/L). There was also metabolic acidosis with pH 7.28, pCO2 4.1kPa, bicarbonate 14.1mmol/L, base excess -11.2mmol/L and also hypernatremia 150mmol/L (reference range 136-145mmol/L). The first renal function showed creatinine level of 50umol/L (reference range 21-36umol/L) and a urea of 7.2mmol/L (reference range 1.8-6.4mmol/L). In view of the initial laboratory findings, boluses of intravenous 10% calcium chloride, 14.9% potassium chloride and also 8.4% sodium bicarbonate were given in attempt to quickly correct the electrolyte disturbances and metabolic acidosis. The seizures were then aborted.

Further history was then taken from parents. It was discovered that within 5 days before admission, 3 doses of sodium phosphate based enema (a total of 1.75 tube, 133 ml per tube) were given to the child. The last dose of ¾ tube enema was given 2 hours before admission with poor result. Each tube of the phosphate containing enema delivers 190mmol sodium and 163mmol phosphate, therefore, a total of 33mmol/kg phosphate was given to the child within the past few days, and about 120mmol phosphate was just given to the child immediately before admission with rectal retention. The diagnosis of sodium phosphate enema toxicity was made. The clinical symptoms of seizure and hypertonia were explained by the severe hypocalcemia induced convulsion and carpopedal spasm.

Further boluses of calcium chloride and potassium chloride were given as guided by blood results. She was hydrated with intravenous fluid containing 40mmol/L potassium and 18mmol/L calcium. She was noted to have progressive abdominal distension and therefore repeated rectal wash-out was performed and yielded 900ml watery stool per wash. The calcium, phosphate and potassium levels were corrected to a safe level soon after admission and then gradually normalized (table 1). The creatinine and urea levels also returned to normal with fluid replacement. The urine output remained satisfactory. Symptoms of carpopedal spasm and hypotension also resolved with correction of calcium level. This patient did not require renal replacement therapy. She was extubated within 48 hours and the remaining course was unremarkable.

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Table 1. Laboratory findings of renal function and electrolytes levels at intervals after admission

Time since admission	1hr	3hr	5hr	9hr	16hr	22hr	27hr	34hr	Normal reference range
Na (mmol/L)	150	151	149	149	148	147	151	147	136-145mmol/L
K (mmol/L)	2.1	2.2	2.2	2.5	3.3	3.5	3.4	4.2	3.5-5.0mmol/L
Ca (mmol/L)	0.96	1.19	1.54	1.56	1.59	1.87	1.91	2.05	2.12-2.59mmol/L
iCa^{2+}(mmol/L)	0.46	0.64	0.75	0.82	0.92	1.02	1.04	1.14	1.13-1.32mmol/L
PO4 (mmol/L)	6.76	2.36	2.11	1.57	1.01	0.80	0.70	0.66	1.10-1.95mmol/L
Mg (mmol/L)	0.63	0.63	0.64	0.64	1.00	0.96	0.91	0.87	0.7-0.95mmol/L
Creatinine (umol/L)	50	33	26	23	22	18	21	16	21-36umol/L
Urea (mmol/L)	7.2	5.5	5.0	4.1	3.1	2.4	2.1	1.7	1.8-6.4mmol/L
pH	7.28	7.41	7.43	7.44	7.38	7.41	7.46	7.42	7.35-7.45
Base excess (mmol/L)	-11.2	-1.0	1.0	0.1	-4.8	-5.6	-0.8	-1.2	-2.0-2.0mmol/L
HCO_3- (mmol/L)	14.1	23.6	25.0	23.9	19.3	17.6	22.2	22.6	22-26mmol/L

Note: Na- Sodium; K- Potassium; Ca- Calcium; iCa^{2+}- Ionised calcium; PO4- Phosphate; Mg- Magnesium; HCO_{3-}- Bicarbonate.

Table 2. Different preparations of osmotic laxatives. The electrolyte content, recommended paediatric dosage and mechanism of action. (12-13)

Drug	Content	Dosage form	Paediatric dosage	Mechanism of action	Remarks
Lactulose Liquid	100ml contains: - 67g lactulose - <10g galactose - <6g lactose	Liquid	1-11months: 2.5ml BD 1-4 years: 2.5-10ml BD 5-17 years: 5-20ml BD	Being a synthetic disaccharide, lactulose is not absorbed in the small intestine nor broken down by enzymes. Therefore, it is retained in the colon for water absorption through osmosis, leading to the formation of softer stool	Caution in lactose intolerant patients
Sodium phosphate	133ml 1 bottle contains: - 19g monobasic sodium phosphate - 7g dibasic sodium phosphate Sodium content per delivered dose: 4.4g	Enema	Avoid in Children <2 years old 2-5 years: ¼ bottle daily 5-11 years: ½ bottle daily 12 years or older: 1 bottle daily	Promotes evacuation of the bowel by increasing bulk volume and water content of stool	FDA received reports of severe dehydration and changes in serum electrolytes levels from taking more than the recommended dose of sodium phosphate products, resulting in serious adverse effects on organs, such as the kidneys and hear, and in some cases resulting in death
	Children Enema 66.6ml 1 bottle contains: - 9.5g monobasic sodium phosphate - 3.5g dibasic sodium phosphate Sodium content per delivered dose: 2.2g		Avoid in children <2 years old 2-5 years: ½ bottle daily 5-11 years: 1 bottle daily		

Drug	Content	Dosage form	Paediatric dosage	Mechanism of action	Remarks
	Phospho-Soda Buffered Saline Mixture 45ml Each 15ml contains: - 7.2g monobasic sodium phosphate - 2.7g dibasic sodium phosphate	Liquid	Avoid in children <5 years old 5-9 years: 7.5ml per dose, max 1 dose per day 10-11 years: 15ml per dose, max 1 dose per day 12 years or older: 15ml per dose, max 3 doses per day		
Sodium citrate enema	Each 5ml tube contains: - 450mg Sodium citrate - 45mg Sodium laurylsulfoacetate - 3.125g Sorbitol Also contains glycerol, sorbic acid and purified water to 5ml	Enema	Neonate: 1ml per kg <3 years: ½ tube 3 years or older: 1 tube	It is a fast acting enema which works to soften bowel motions and gently assist bowel emptying without irritating the lining of the bowel	
Polyethylene glycol	4000 Powder 10g/ sachet	Powder for re-constitution	Recommended in Children >8years: 1-2 sachets daily, preferably taken as a single dose in the morning	High molecular weight (4000) macrogols are long linear polymers which retain water molecules by means of hydrogen bonds. When administered by the oral route, they lead to an increase in volume of intestinal fluid	

Discussion

Our patient had an alarming presentation of acute phosphate intoxication from the use of osmotic sodium phosphate based enema. The clinical symptoms including change in level of consciousness, carpopedal spasm, seizure and hypotension are due to severe hypocalcemia secondary to hyperphosphatemia. Metabolic acidosis is a consistent feature in severe hyperphosphatemia, and it may occur as the kidneys attempt to excrete the excessive phosphate load even in the absence of seizure or cardiac arrest. (2) It may be resulted from excessive bicarbonate loss from diarrhea, and the excessive phosphate may also be present in form of inorganic acids in the body. Hypokalaemia has been reported in other cases of phosphate enema intoxication in both adults and pediatric patients as well. (3-4,8) In our case it is likely due to the excessive gastrointestinal loss resulted from the osmotic enema, as evident by the large amount of watery stool from rectal wash-out. Other mechanism of hypokalemia, may be related to the increased renal potassium loss due to secondary hyperaldosteronism in response to intravascular volume contraction. (4) Excessive gastrointestinal fluid loss can account for the hypernatremia caused by dehydration, and the excessive sodium load from the enema.

The management of toxicity resulting from phosphate-containing enema involves avoiding further absorption of enema from gastrointestinal tract, increasing rate of elimination of excessive phosphate load from body and also correction of the significantly deranged electrolytes levels. Rectal wash out should be performed as soon as possible, especially when there is suspicion of enema retention. Phosphate elimination can be promoted by aggressive hydration and diuresis. In case of pre-existing renal impairment, renal replacement therapy may need to be considered as well. While intravenous boluses of calcium are important to quickly correct the life-threatening hypocalcaemia level, caution has to be taken as it can cause metastatic calcification and acute renal failure due to calcium-phosphate crystals precipitation in renal tubules in the background of hyperphosphatemia. Correction of metabolic acidosis with intravenous sodium bicarbonate has to be considered cautiously too, as increasing alkalosis can result in further lowering of ionised calcium level as

well by increasing the binding of calcium ion to plasma proteins, hence further exacerbate the symptoms. The use of alkalising agent may also lower the threshold for precipitation of calcium phosphate complexes in renal tubules and interstitium and in turn increases the risk of renal failure. (6)

Clinicians have long been aware that caution has to be taken when prescribing phosphate containing enema to patient with underlying renal failure. However, from the reported cases in children, many of them do not have pre-existing renal problems. (5,7-9) Toxicity may even occur in children with no underlying renal abnormalities when given doses within therapeutic range. (7,9) Significant colonic absorption of phosphate can occur if there is stasis of the enema, resulting in potentially life-threatening complications. Therefore, it is very important to educate the carer not to repeat doses when there is poor result and to watch out for enema retention, especially in very young children. Pediatricians should be aware of the potential toxicity of sodium phosphate based laxatives and be familiar with the composition of different types of osmotic laxatives (table 2). Children with poor gastrointestinal transit, conditions which increased intestinal permeability, pre-existing renal disease, pre-existing electrolytes disturbances and inadequate fluid intake are at risk to develop complications.

There is a growing concern for safety of phosphate-containing oral laxatives or enema for all age groups. In 2003, Desmeules et. al. first described a new entity named as 'phosphate nephropathy', which is nephrocalcinosis induced by a high phosphate load as the sole causative factor. (6) Since then many more cases of phosphate nephropathy were reported after the use of oral sodium phosphate solutions as pre-procedural preparation for colonoscopy. The belief that phosphate-containing enema is comparatively safe as there is limited systemic absorption of the enema from rectum, is probably not sustained, when there were more and more cases of life-threatening sodium phosphate enema toxicity being reported in the literature. It is also reasonable to postulate that, given the same electrolyte disturbance caused by phosphate-containing enema as the oral sodium phosphate solution, the enema form can also impose risk of acute or chronic renal failure by causing phosphate nephropathy. This postulation has been supported by few studies that have been published recently. One study was published in 2012 reporting fatalities and severe complications from use of sodium phosphate enemas in a single centre in Israel. (10) Autopsy of one of their patient, who died from complication of sodium phosphate enema complication, demonstrated calcium phosphate precipitation in renal tubular lumens. There is another retrospective cohort study published in 2016 comparing the decline in estimated glomerular filtration rate following use of sodium phosphate enemas versus use of polyethylene glycol (PEG) alone for screening colonoscopy. (11) The results showed that greater proportion of patients use sodium phosphate enemas versus PEG and had long-term eGFR declines.

Physicians should be more aware of its potential complications when prescribing this widely used medication, and to consider use of other safer options especially in paediatric age group.

Compliance with Ethical Standards

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