World Journal of Gastrointestinal Pharmacology and Therapeutics

Online Submissions: http://www.wjgnet.com/esps/
wjgpt@wjgnet.com
doi:10.4292/wjgpt.v5.i2.50

World J Gastrointest Pharmacol Ther 2014 May 6; 5(2): 50-54
ISSN 2150-5349 (online)

EDITORIAL

Colonoscopy preparation-induced disorders in renal function and electrolytes

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Received: November 18, 2013 Revised: February 19, 2014
Accepted: April 16, 2014
Published online: May 6, 2014

Abstract

Colonoscopy and flexible sigmoidoscopy are commonly used mainly for colon cancer screening and detection, but also in several other situations such as inflammatory bowel disease (for diagnosis and follow up) and gastrointestinal hemorrhage. Bowel cleansing preparations mainly include polyethylene glycol and oral sodium phosphate solutions, with the later being most frequently used due to better toleration from patients. Despite their favourable safety profile these agents have been associated with renal function deterioration and electrolyte disorders, some of which were serious or even fatal. The present paper discusses the complications associated with colonoscopy preparation agents.

Key words: Oral sodium phosphate; Hyperphosphatemia; Hypocalcemia; Phosphate nephropathy

Core tip: Despite the important diagnostic and clinical utility of colonoscopy, serious electrolyte disorders and impaired kidney function have been observed with the agents used for bowel cleansing. The aim of this paper is to present these complications and discuss their prevention and management.

Florentin M, Liamis G, Elisaf MS. Colonoscopy preparation-induced disorders in renal function and electrolytes. *World J Gastrointest Pharmacol Ther* 2014; 5(2): 50-54 Available from: URL: http://www.wjgnet.com/2150-5349/full/v5/i2.50.htm DOI: http://dx.doi.org/10.4292/wjgpt.v5.i2.50

Colonoscopy is widely used worldwide particularly for colon cancer screening and detection. The use of bowel cleansing agents one or two days prior the procedure improves its diagnostic utility. Various preparations have been developed throughout the years, but few of them are currently being used, specifically polyethylene glycol and oral sodium phosphate (OSP) solutions, because of their ease of use and safety profile[1]. As minimal volume of oral intake is required with OSP, this is associated with less patient discomfort, greater compliance and improved colonic cleansing compared with polyethylene glycol[2]. However, serious electrolyte disorders and impaired kidney function have been observed with these agents and particularly with OSP. The aim of this paper is to present these complications and discuss their prevention and management. Disturbances in electrolyte levels with less frequently used bowel cleansing agents are also mentioned.

KIDNEY FUNCTION IMPAIRMENT

Two distinct patterns of kidney injury induced by sodium phosphate preparations (phosphate nephropathy) have been described; early symptomatic and late insidious[3]. In the former patients present acutely with symptoms of hypocalcemia (*e.g.*, abdominal pain, vomiting, muscle cramping, dizziness, lethargy, confusion, seizures, tetany, cardiovascular collapse) within hours to a few days after sodium phosphate administration, either p.os or as en-

ema[4,5]. Acute renal failure along with marked hyperphosphatemia and hypocalcemia are the hallmarks of this clinical entity. The second pattern of kidney injury has an insidious onset and becomes obvious a few days to several weeks or months after sodium phosphate ingestion[6]. The administration of laxatives and sodium phosphate enemas generally increases phosphorus and decreases calcium concentration due to rapid phosphate absorption and binding to serum calcium, respectively[4,7-9]. Interestingly, in a study including 100 adults without predisposing conditions for kidney injury or electrolyte disorders, hyperphosphatemia occurred in 87% of them the day after colonic cleansing[10]. Phosphate concentration correlated inversely with glomerular filtration rate (GFR), total body water and weight[10]. Indeed, well-hydrated adults with normal renal function usually tolerate this amount of phosphate and infrequently develop symptomatic hyperphosphatemia and hypocalcemia[6,11].

Kidney function improved or even returned to baseline within one month in most of the patients with the early symptomatic type of renal injury; however, chronic kidney disease and death have also been reported[3]. The pathological diagnosis remains unknown as no biopsies were performed in these cases. A possible explanation for kidney function deterioration is that excessive hyperphosphatemia is directly tubulotoxic[3].

Predisposing factors for renal injury and hyperphosphatemia are old age, female sex, impaired renal function (which diminishes phosphate clearance), diabetes mellitus, dehydration, decreased bowel motility or vitamin D supplementation which lead to increased intestinal absorption of phosphorus, repeated OSP dosing, hypertension, treatment with inhibitors of renin-angiotensin-aldosterone-system (RAAS) or diuretics and hyperparathyroidism[10,12]. The greater increase in phosphorus levels in the elderly may be related to the subclinical loss of renal function and/or the altered absorption due to increased intestinal transit time[13]. Importantly, if the recommended dose of 60 g (90 mL) of OSP is surpassed or the interval between doses is < 5 h, severe hyperphosphatemia may develop[4,8].

Treatment aims at phosphate absorption reduction by oral phosphate binders, increased phosphate clearance and correction of dehydration and subsequently hypocalcemia. Whether calcium supplement should be used is a matter of debate, as renal calcium-phosphate precipitation may further deteriorate renal function[4]. The rapid correction of hypocalcemia and hyperphosphatemia seems to be able to prevent chronic kidney injury and return renal function to baseline.

The second type of phosphate nephropathy is frequently discovered incidentally at follow-up or due to the occurrence of nonspecific symptoms, such as malaise, nausea or vomiting. In fact, the true incidence of this entity remains unknown as it often goes under recognized. Affected patients present with gradual onset renal insufficiency and low-grade proteinuria, usually < 1 g/d. Phosphorus and calcium levels are normal or near normal at the time of diagnosis[3].

Phosphate nephropathy after OSP administration seems to be a direct consequence of the acute phosphate load and subsequent increase in serum phosphorus level. The decrease in plasma calcium associated with OSP-induced hyperphosphatemia is the result of calcium binding to the elevated phosphorus, leading to the tubular deposition of calcium phosphate[4]. Calcium-phosphate product (CPP) is generally regarded as an indicator of the risk of calcium phosphate precipitation in the kidney. The normal range for CPP is 21-46. A mean peak of 71.28 is transiently reached after OSP administration[14].

It has been suggested that the tubular fluid in the loop of Henle becomes supersaturated in calcium and phosphate ions after OSP administration, resulting in the production of a solid-phase material, probably immature apatite[15]. The calcium phosphate crystals potentially stimulate inflammatory reactions and cellular damage[16,17].

These assumptions appear to be confirmed histopathologically. In patients with the late-onset phosphate nephropathy the histologic hallmark is nephrocalcinosis. This is characterized by abundant renal parenchymal deposits of calcium phosphate in distal tubules and collecting ducts along with chronic tubulointerstitial injury; in contrast, glomeruli and blood vessels remain almost intact[3]. Interestingly, acute tubular cell injury has been observed in tubules both with and without calcium phosphate deposition[3].

We should note that despite the normal baseline renal function, patients frequently have risk factors for kidney function deterioration and/or electrolyte abnormalities. In fact, nephrocalcinosis is frequently encountered in patients with a propensity for hypercalcemia, such as hyperparathyroidism, increased bone turnover, excess intake of vitamin D or calcium, hypercalcemia of malignancy, sarcoidosis and distal renal tubular acidosis[9]. Furthermore, when urine is concentrated, the urinary level of CPP rises exponentially, increasing the risk of calcification. Therefore, excessive fluid loss without sufficient hydration predisposes to phosphate nephropathy after OSP administration.

The largest case series comes from Markowitz et al who presented 21 cases of biopsy-proven phosphate nephropathy associated with OSP administration prior colonoscopy. The baseline creatinine of the patients was 1.0 mg/dL and reached 3.9 mg/dL at a median of one month after the procedure[9]. Serum calcium was within normal limits, while phosphorus was increased in at least a third of patients (data was available for 16 out of 21 patients), in some of whom excessively so (*e.g.*, 10.2 mg/dL)[9]. In the follow-up period (mean 16.7 mo) 4 patients developed end-stage renal disease requiring renal replacement therapy, one of whom subsequently underwent renal transplantation. In 16 of the remaining 17 patients an improvement in renal function was observed at the end of follow-up, with a mean serum creatinine of 2.4 mg/dL. We should note, though, that only 4 patients reached a serum creatinine < 2.0 mg/dL and none returned to baseline[9]. The aforementioned histologic changes of nephrocalcinosis were observed in all biopsies[9].

ELECTROLYTE DISORDERS (OTHER THAN HYPERPHOSPHATEMIA)

Hypocalcemia

A decrease in calcium concentration of 0.3-0.8 mg/dL occurs in all patients after OSP administration due to the subsequent hyperphosphatemia[5]. Elderly patients are particularly prone to develop hypocalcemia due to impaired kidney function, vitamin D deficiency and reduced intestinal absorption[18]. Calcium levels are usually normalized within 24 h[19].

Hypokalemia

A frequent electrolyte disorder associated with OSP use is hypokalemia, with an incidence of 20%-30%[2], which, importantly, is doubled (56%) in hospitalized patients over 65 years old[18]. Potassium losses are gastrointestinal and renal. The former are due to sodium and potassium exchange across the colonic epithelium and/or diarrhea; the latter may be accompanied by metabolic acidosis because of concurrent bicarbonate loss[5,20]. Potassium is excreted by the kidneys as a consequence of hyperphosphaturia-induced luminal electronegativity[21] and volume contraction-induced secondary aldosteronism[4,22]. We should note that the combination of hypokalemia and hypocalcemia increase the risk of QT interval prolongation. Furthermore, in the presence of cardiac disease and/or arrhythmia ventricular tachycardia may be triggered by OSP-induced hypokalemia[23].

Hypernatremia

Oral ingestion of isotonic bowel cleansing agents does not by itself affect plasma sodium concentration[14], but in patients with impaired renal handling of water or in old patients with decreased thirst[24], the risk of hypernatremia exists. In fact, mild, asymptomatic hypernatremia is quite common after OSP use, especially in the elderly. It occurs due to intestinal absorption of sodium from OSP (the standard dose of OSP contains 434 mEq of sodium), dehydration and colonic shifting between sodium and potassium[4,22]. Severe hypernatremia (in the range of 166 mEq/L) and acute kidney injury was demonstrated in a patient with Alzheimer's and Parkinson's diseases who took 45 mL of OSP, probably because of insufficient fluid intake[25]. Hypernatremia may also complicate the use of the osmotic cathartics lactulose and sorbitol which are used in the treatment of hepatic encephalopathy and drug intoxications, respectively[26,27]. In these cases, water is lost in excess of sodium plus potassium (*i.e.*, hypotonic losses), thus leading to increased plasma sodium.

Hyponatremia

Hyponatremia after colonoscopy preparation may occur as a consequence of intravascular volume depletion (mainly from diarrhea) and subsequent excessive thirst, increased water intake together with the bowel preparation agent, renal disease or syndrome of inappropriate antidiuretic hormone release (SIADH)[28,29]. ADH release during bowel preparation may be triggered from nausea, pain or anxiety[30]. Hyponatremia after OSP has been sporadically observed due to excessive free water intake[31]. Importantly, the affected patients had other risk factors for hyponatremia, *e.g.*, treatment with thiazide diuretics, RAAS inhibitors or antidepressants[31]. In contrast, polyethylene glycol administration has been associated with serious cases of hyponatremia. Specifically, a 73-year-old woman who had ingested polyethylene glycol experienced gastrointestinal disturbances and tonic-clonic seizures which were attributed to hyponatremia and reversed with lorazepam and correction of sodium levels[30]. This patient was currently treated with a selective serotonin re-uptake inhibitor (SSRI) and thyroxine for hypothyroidism, but thyroid stimulating (TSH) levels were slightly elevated. Both SSRIs and hypothyroidism are causes of hyponatremia, while nausea is a major stimuli for ADH release. We should stress, though, that hyponatremia has been reported in patients with moderate to severe hypothyroidism. Thus, the imperfect treatment of hypothyroidism does not seem to have affected sodium levels in this patient. Of note, age is another contributing factor for SIADH. In fact, in 60% of 50 hospitalized patients no reason other than age was identified as a cause of SIADH in one study[32]. Overall, polyethylene glycol induced severe hyponatremia in a background of SSRI use and old age in this case.

Two other patients who experienced nausea, abdominal distension and diarrhea and consumed large amounts of fluids after polyethylene glycol administration, exhibited symptomatic hyponatremia (unconsciousness, seizures)[33]. The first one was currently taking thiazides and the second one had end stage renal disease and was receiving regular hemodialysis.

Sodium picosulfate/magnesium citrate (Picolax) has also been associated with hyponatremia and indeed in patients without risk factors for sodium concentration abnormalities[34,35].

Hypomagnesemia

Lower intestinal tract fluids contain up to 15 mEq/L of magnesium; therefore, in cases of protracted diarrhea which frequently happens during colonoscopy preparation, magnesium depletion may occur. Indeed, laxative abuse, even if these contain magnesium, has been associated with hypomagnesemia due to excessive intestinal magnesium loss[36,37].

Hypermagnesemia

Picolax has been associated with hypermagnesemia, which was attributed to the magnesium load delivered within the agent[38-40]. This electrolyte disorder does not seem to have serious clinical consequences[38,39]. Other cleansing agents that do not contain magnesium do not confer an increased risk for hypermagnesemia.

PREVENTION OF ADVERSE EFFECTS

Several precautions may prevent from phosphate ne-

phropathy and electrolyte disturbances in patients undergoing colonoscopy. The OSP dose may be minimized and the interval between OSP doses may be lengthened; these strategies do not diminish the efficacy of the procedure[41,42]. Of major importance is the sufficient fluid administration to avoid volume depletion and its deleterious consequences. It is also prudent to perform biochemistry tests, including renal function and electrolyte levels, in order to treat any disorders before administering OSP and proceeding to colonoscopy. In cases of significant renal dysfunction and/or electrolyte disorders, the use of OSP should probably be reconsidered. Some authors have suggested the use of alternative agents, at least in the place of the second OSP dose, which seems to be the main culprit for phosphate nephropathy development[5].

CONCLUSION

Despite the valuable clinical utility of colonoscopy, its preparation possesses excess risk for kidney impairment and electrolyte disorders, particularly in certain patient populations. Taking into account that these adverse effects may be permanent and sometimes life-threatening, it would be prudent to take simple precautions in patients at risk or even avoid the procedure if the associated risk of serious adverse events is considered higher than its benefit.

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