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Acute Hyponatremia Induced by Bowel Preparations for Colonoscopy: Identification of Patients at Risk

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Abstract

Introduction: Iatrogenic acute hyponatremia has been observed following bowel preparation for colonoscopy and is believed to be associated with hypo-osmotic preparations.

Aim: To review cases of hyponatremia attributed to bowel preparations for colonoscopy reported to the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS).

Methods: All adverse event (ADR) reports to the FAERS reported between March 2008 and May 2014 were reviewed. The data was filtered to cases using the term "colonoscopy" with primary ADRs of "hyponatremia" and/or seizure". Bowel preparations reviewed (including alternative spellings of brand names) included: *OsmoPrep™, MoviPrep™, SuPrep™, Visicol™, Magnesium citrate, Golytely™, MiraLAX™, Trilyte™, Gavilyte™,* and *Colyte™*. Complete reports of all cases were obtained from the FDA using the Freedom of Information Act (FOIA).

Results: We reviewed 40 cases of colonoscopy preparations with primary diagnosis of hyponatremia; 15 hyponatremia cases also reported seizures. We also reviewed 17 cases with primary ADRs of seizures without hyponatremia. Serum sodium levels were available in 27 of 40 hyponatremia cases with a mean value of 118 mEq/L. The average serum sodium level in hyponatremic patients developing a seizure was 115 mEq/L. *OsmoPrep™, MoviPrep™ and SuPrep™* accounted for the majority of hyponatremia cases (35%, 32.5% and 10% respectively). Two patients with hyponatremia died from seizures followed by cerebral edema. Predisposing factors for hyponatremia induced by colonoscopy preparations include female gender (72.5%); excess fluid ingestion (17.5 %), hypothyroidism (15%), thiazide diuretics use (10%), SSRI use (7.5%) and combination of more than one preparation (5%).

Conclusions: Acute hyponatremia is an uncommon but serious complication of a variety of colonoscopy bowel preparations. Identification of patients at risk, avoiding combinations of preparations and limiting excess fluid intake are strategies to prevent iatrogenic hyponatremia from colonoscopy preparation.

Introduction

Colonoscopy is a common procedure utilized for both diagnostic and therapeutic purposes in daily clinical settings. According to the data from the Centers for Disease Control and Prevention (CDC), more than 10 million colonoscopies are performed annually the U.S. alone [1]. The overall risk of serious complications following colonoscopy is low. In a review of 12 studies with 57,742 screening colonoscopies, serious harm occurred in 2.8 per 1,000 examinations and over 85 % of the complications occurred in the setting of polypectomy [2].

An excellent bowel preparation is essential for diagnostic accuracy and safety of the colonoscopy procedure.3,4 Bowel preparations should empty the entire colon of all fecal material without any damage of the colonic mucosa. The ideal bowel preparation should be effective, tolerable, inexpensive and convenient to use [3-6]. Bowel preparations should also not cause discomfort or fluid and electrolytes imbalance. The preparation agents may be isosmotic (e.g. Polyethylene glycol (PEG) preparation), hyposmotic (e.g. a combination of PEG-3350 and sports drink), hyperosmotic (e.g. sodium sulfate, magnesium citrate, sodium phosphate) or a combination of iso- and hyper-osmotic (e.g. combination of sodium picosulfate and magnesium citrate). Our group reported fluid and electrolytes shifts occurring after hyperosmotic colonoscopy preparations shortly after their acceptance on the market [7]. Bowel regimens are also variable in regard to ingested fluid volume and include high volume (4 liters/128 oz) or low volume (2 liters/64 oz) preparations. Not all of the regimens are approved for use by the Food and Drug Administration (FDA) [6]. Over-the-counter

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preparation regimens involving mixing with sports drinks, *MiraLAX™ + Gatorade* combination, are hyposmolar regimens not approved by the FDA [8]. Concerns regarding with the risk of hyponatremia from these preparations have been voiced in the medical literature [9-11]. A 2001 study published in The Lancet reported an incidence (7.5%) of hyponatremia after colonoscopy [12]. The administration of bowel regimens can predispose to the development of hyponatremia by a number of mechanisms which result in relative increase in the ratio of body water to sodium. Acute hyponatremia can produce detrimental neurological complications culminating in seizures, coma and death [13].

We reviewed cases of bowel preparations with the occurrence of hyponatremia and/or seizures reported to the Food and Drug Adverse Event Reporting System (FAERS). We focused on the characteristics that may predispose to the development of hyponatremia.

Materials and Methods

The FAERS is a publicly accessible database, used for post-marketing safety surveillance for all FDA-approved drugs and therapeutic agents. The adverse events are voluntarily reported by physicians, pharmacists and other healthcare professionals as well as drug manufacturers, patients, and attorneys. The database was searched for cases of bowel preparation associated with the term "colonoscopy" with reports of a primary ADR diagnosis of "hyponatremia" or a primary diagnosis of "seizure". The individual files were downloaded for the period between March 2008 and May 2014. The types of bowel preparations utilized in the reported cases included *OsmoPrep™, MoviPrep™, SuPrep™, Visicol™, Magnesium citrate, Golytely™, MiraLAX™, Trilyte™, Gavilyte™, and Colyte™*. Complete reports of all cases from the FAERS database were obtained from the FDA using the Freedom of Information Act (FOIA). The cases were reviewed individually and analyzed to establish authenticity and to remove duplicated cases. All the reports underwent careful examination to confirm the occurrence of hyponatremia and/or seizures after colonoscopy bowel preparation. The reports were further evaluated and the information was gathered on age, gender, type of bowel preparation implicated, hyponatremia, other reported electrolytes abnormalities, potential contributing factors for hyponatremia and underlying disease states. Furthermore, serum sodium levels were collected if reported and the neurologic complications such as seizures were recorded. Concurrent medications including selective serotonin inhibitors (SSRIs) and thiazides diuretics were also recorded.

Results

We reviewed 40 cases that were reported to have a primary diagnosis of the ADR of hyponatremia and 17 cases reported to develop seizures without hyponatremia. Fifteen (37.5%) of hyponatremia cases also developed seizures. None of these patients were reported to have hyponatremia prior to the use of the bowel preparation. Serum sodium levels were available in 27 of 40 hyponatremia cases and ranged from 103 to 128 mEq/L (normal serum sodium = 135-145 mEq/L) with a mean value of 118 mEq/L. The average serum sodium level in hyponatremic patients developing a seizure was 115 mEq/L (Figure 1). The most common reported preparations associated with hyponatremia were *OsmoPrep™* (14cases, 35%), *MoviPrep™* (13 cases, 32.5%) and *SuPrep™* (4 cases, 10%), (Table 1).

Two patients with hyponatremia following colonoscopy preparation died from cerebral edema and seizures. Both of these patients were found to have ingested MoviPrep™.

The patient characteristics of the hyponatremia cases are shown in Table 2. The factors that were associated with the development of hyponatremia included female gender (72.5%), fluid ingestion in excess of recommended amounts (17.5 %), hypothyroidism (15%), thiazide diuretics use (10%), use of selective serotonin reuptake Inhibitors (SSRI) (7.5%), cirrhosis (5%) and the combined use of more than one bowel preparation (5%). Only 2 patients with primary reports of seizure without hyponatremia following colonoscopy preparation had prior history of seizure disorder.

Discussion

Bowel preparation agents using a variety of regimens are generally regarded as safe and well tolerated if the agents are appropriately prescribed and the preparation instructions are correctly followed [14-17]. Despite their overall safety profile, there are known gastrointestinal (GI) and non-GI related adverse events associated with their use. GI complications include nausea, vomiting, abdominal distension, and ileus. Other known complications include electrolyte abnormalities including hyponatremia, seizures, encephalopathy, exacerbation of congestive heart failure and pancreatitis. Phosphate nephropathy followed by chronic renal failure is uniquely associated with the use of sodium phosphate containing colonoscopy preparations and has limited their use [18-26].

Our group has determined that renal adverse drug reactions (phosphate nephropathy, renal failure) from sodium phosphate-based colonoscopy preparation are more common in women. Lower body weight is another risk factor for kidney injury from sodium phosphate-based colonoscopy preparations [27].

The current study of ADR reports to the FAERS describes the occurrence of hyponatremia secondary to a variety of bowel

Bowel preparation	Primary Diagnosis	
	Hyponatremia (n=40)	Seizures without Hyponatremia (n=17)
OsmoPrep™	14 (35%)	3 (17.6%)
MoviPrep™	13 (32.5%)	5 (29.4%)
SuPrep™	4 (10%)	1 (5.9%)
Visicol™	1 (2.5%)	3 (17.6%)
Magnesium citrate	1 (2.5%)	0
Golytely™	1 (2.5%)	2 (11.8%)
MiraLAX™	4 (10%)	2 (11.8%)
Trilyte™	1 (2.5%)	0
Gavilyte™	0	1 (5.9%)
Colyte™	1 (2.5%)	0

Table 1: Cases of Primary Diagnosis of Hyponatremia and Cases of Primary Diagnosis of Seizure without Hyponatremia According to Bowel Preparation Regimens

Gender	Female – 29 (72.5%), Male – 10 (25%), Unreported – 1 (2.5%)
Age group	30-39 Yr – 3 (7.5%), 40-49 Yr – 2 (5%), 50-59 Yr – 14 (35%), 60-69 Yr– 12 (30%), 70-79 Yr – 2 (5%), 80 Yr and above – 1 (2.5%),Unreported age – 6 (15%)
Other electrolytes abnormalities	Hypokalemia – 20 (50%), Hypocalcemia – 6 (15%)
Thiazide diuretics	4 (10%)
SSRI	3 (7.5%)
Excess fluid ingestion†	7 (17.5%)
Hypothyroidism	6 (15%)
Mixed use of more than one bowel preparation*	2 (5%)
Cirrhosis	2 (5%)

Table 2: Characteristics of patients who developed hyponatremia secondary to bowel preparation (n=40)

†3 cases of *MoviPrep™*, 2 cases of *OsmoPrep™*, 1 case of *Visicol™*, 1 case of *SuPrep™*

*One reported case used a combination of *MiraLAX™* and bisacodyl and the other used both *MoviPrep™* and magnesium citrate.

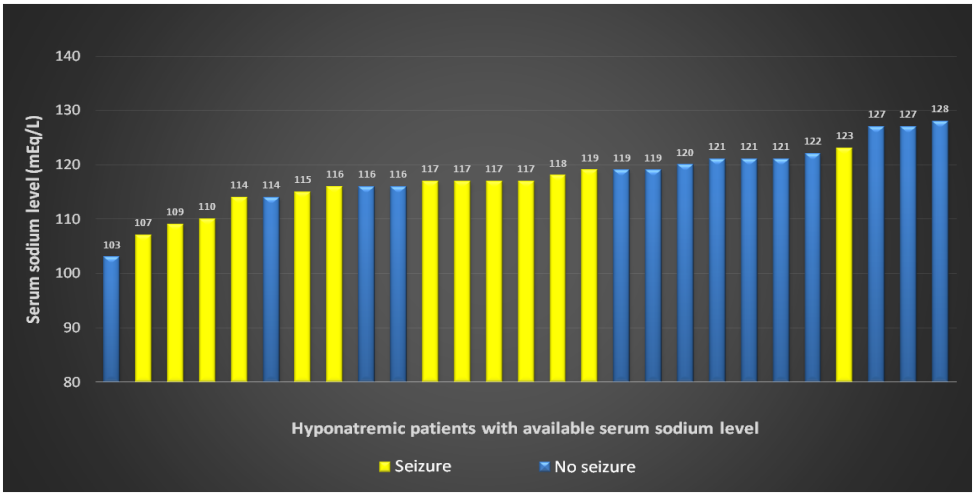

Figure 1: Hyponatremic patients with reported serum sodium level

regimens. In our study, *OsmoPrep™* and *MoviPrep™* accounted for nearly 70% of hyponatremia cases. *OsmoPrep™* is a low volume hyperosmotic regimen containing monobasic and dibasic sodium phosphate compounds whereas *MoviPrep™* is a low volume isosmotic regimen composed of polyethylene glycol (PEG) and ascorbic acid. The latter component of *MoviPrep™* also contributes to the cathartic effect of the preparation [17].

As anticipated, 10% of cases were described with the use of *SuPrep™*, a hypo-osmolar preparation. A publication issued by UK National Patient Safety Agency (NPSA) reported 218 patient safety incidents associated with the use of bowel cleansing preparations over a 5-year period. 6% of the 218 incidents caused moderate patient harm and one patient death was reported. These data are derived from a voluntary reporting system, similar to FAERS in the U.S. Hyponatremia was a significant adverse effect highlighted in the NPSA report [17]. An observational study was undertaken to assess the incidence of hyponatraemia in colonoscopy patients then published in 2001 by The Lancet. In the study, 40 patients (14 women, 26 men, mean age 57·4 years) were assessed before and after colonoscopy with 20 gastroscopy patients (10 women, 10 men, mean age 55·8 years) serving as controls. On the morning of procedure, the colonoscopy patients drank 2–3 liters of bowel preparation solution containing polyethylene glycol and balanced electrolytes. Serum levels of sodium and arginine vasopressin (ADH) were collected in all patients before and after the procedure. The study found 3 (7.5%) of 40 colonoscopy patients had a serum sodium concentration of 130 mEq/L or lower in association with elevated ADH levels. By contrast, gastroscopy patients in the control group developed neither hyponatremia nor elevated ADH levels [12]. Except for this small study in The Lancet, the incidence of hyponatremia in after bowel preparation for colonoscopy has not been reported, as most of the literature is based on individual case reports. The methodology employed in data collection using the FAERS also does not allow for determination of the incidence of this condition, due to the voluntary nature of ADR reports to the FDA [27].

The association of hyponatremia with individual colonoscopy preparations can also not be determined using this method. Nonetheless, our study emphasizes that hyponatremia may occur following a variety of colonoscopy preparations and is not limited to hypo-osmolar preparations.

PEG is a non-absorbable agent that passes through the bowel without significant net absorption or secretion and therefore typically does not result in fluid and electrolyte shifts [6]. The total net gain or loss of water and sodium from bowel clearance with PEG is unlikely to exceed 700 ml or 30 mmol respectively and therefore the clinical impact of those changes are minimal [4]. In contrast, sodium phosphate regimens are hyperosmotic promoting pronounced fluid and electrolytes shifts and colonic evacuation by drawing large amount of water (1-1.8 liters of water per 45 ml of preparation) [28]. A pharmacokinetic study of sodium phosphate based colon cleansing solution found elevated serum phosphate levels (mean serum phosphate at 120 min was 7.8 ±0.5 mg/ dL) in smaller individuals (less than 55 kg) after ingestion of the solution [29]. Hyperosmotic colonoscopy preparations, especially those containing sodium phosphate should generally be avoided and are contraindicated in patients with chronic kidney disease, congestive cardiac failure, cirrhosis [28].

PEG-based isosmotic bowel regimens can be either high volume (4L) preparations such as PEG mixed with balanced electrolyte solution (PEG-ELS) or newer low volume (2L) preparations such as *MoviPrep™, Halflytely™ or MiraLAX™*. The latter two are usually co-administered with bisacodyl. Bisacodyl used as an adjunct to PEG-based preparations, has been reported to be associated with abdominal cramping and ischemic colitis [30-31].

Although PEG-ELS are generally well tolerated, 5% to 15% of patients do not complete the preparation because of poor palatability and/or large volume [6-14]. Accordingly, low volume PEG based regimens are more desirable for patients who cannot tolerate high volume preparations.

However, patients who opt for low volume preparations tend to drink more water or clear liquids than instructed. According to one European study, it is found that 82.1% of patients who took PEG + Ascorbic acid regimen drank at least 1 L or more additional water or clear liquids, while 66.1% of patients who took sodium phosphate regimen drank 2 L additional water or clear liquids [32]. Not all of the ingested water stays within the bowel lumen and part of it will be absorbed and therefore overzealous drinking of water can lead to water intoxication and hyponatremia [17]. This finding is confirmed in our study. We demonstrated that 7 of 40 hyponatremia cases, (17.5%), drank additional water or hypotonic fluids beyond the recommended amounts. A new finding in our study is the risk of hyponatremia is increased when low volume preparations are combined with other preparations.

Concerns about iatrogenic hyponatremia from the use of over-the-counter PEG-based hyposmolar regimens have been cited in the medical literature. A common form of these regimens is *MiraLAX™* + Gatorade combination (238 grams of PEG-3350 without electrolytes mixed in 64 ounces of Gatorade) which is not FDA approved. This preparation has achieved popularity because of lower volume and improved palatability compared to standard high volume PEG and electrolyte solution regimen as well as cost saving [8]. However, *MiraLAX™ + Gatorade* regimen is not an osmotically balanced

solution and its safety has not been evaluated in sufficiently large studies [9]. A recent case series identified severe hyponatremia and serious adverse events, including cardiac arrhythmias and ICU admissions in 14 low-risk patients who used *MiraLAX™ + Gatorade* bowel preparations [10]. In addition, a study based on an endoscopic database of over 8,400 patients found a higher incidence of severe hyponatremia with *MiraLAX™ + Gatorade* versus osmotically balanced PEG bowel preparations [11].

Hyponatremia is commonly defined as a serum sodium concentration below 135 mEq/L [33-34]. Hyponatremic state with serum sodium level above130 mEq/L usually does not cause any clinical symptoms. The symptoms of hyponatremia typically manifest when there is acute and marked reduction in the serum sodium concentration. Nausea and malaise, which are the earliest manifestations, may be seen when the serum sodium concentration falls below 125 to 130 mEq/L. If the serum sodium concentration falls below 115 to 120 mEq/L and further, headache, lethargy, obtundation, seizures, encephalopathy, cerebral edema, stupor, coma and respiratory arrest will ensue [13, 35, 36]. Bowel regimens may cause hyponatremia via several overlapping mechanisms. One of these mechanisms is the production of osmotic diarrhea. This causes volume depletion and high and low pressure baroreceptor-mediated nonosmotic stimulation of ADH secretion. The end result of high ADH state is free water retention resulting in hyponatremia [37]. Other mechanisms of bowel cleansing agents-induced hyponatremia include overenthusiastic consumption of large amount of water, concomitant parenteral hypotonic fluid administration, renal failure and increased ADH-release states induced by several non-osmotic stimuli including pain, nausea, and abdominal manipulation related to the colonoscopy procedure [12,17,38]. Our study raises the possibility that concomitant medications such as thiazide diuretics and SSRIs may also contribute to the development of hyponatremia. Thiazide-induced hyponatremia has an underlying complex mechanism and is thought to result from the combination of sodium loss induced by the diuretic and enhanced water re-absorption due to both ADH-dependent and ADH-independent pathways [39,40]. Various SSRIs can predispose patients to develop hyponatremia by causing SIADH [41]. An additional new finding in our study is that hyponatremia from colonoscopy preparations is a more common occurrence in female patients, as 72.5% of cases reported to the FAERS occurred in females. Hyperphosphatemia and calcium-phosphate nephropathy from sodium phosphate containing colonoscopy preparations are also more common in females. This has been attributed to lower overall body weight and smaller amount of total body water and vascular volume in females [27,29]. Pre-existing co-morbid states such as hypothyroidism and cirrhosis of the liver appeared as contributing factors to the occurrence of hyponatremia in our study group. Although incompletely understood, hypothyroidism-induced hyponatremia is thought to be related to decreased ability to excrete free water [42, 43]. A variety of factors are implicated in the predisposition of cirrhotic patients to develop hyponatremia and the most important factor is diminished effective circulatory volume and arterial vasodilatation [44,45].

The occurrence of seizures occurring in patients undergoing colonoscopy and attributed to colonoscopy preparations has not received attention in the medical literature. Reports to the FAERS appear to implicate a variety of colonoscopy preparations in this form of ADR (Table 1). The mechanism of seizure development in colonoscopy patients without hyponatremia is unclear and possibly multifactorial. Colonoscopy is a procedure involving the use of pharyngeal anesthesia and sedation [46]. Lidocaine and fentanyl are frequently used agents for colonoscopy and they can provoke seizures. Patients may be on concomitant medications such as antibiotics, antidepressants and antipsychotics which can also provoke seizures [47]. Concurrent acute medical illnesses and metabolic disturbances such as hypoglycemia, hyperglycemia, cerebral vascular accident, cerebral anoxia, hypocalcemia, hypomagnesemia may also provoke seizures in colonoscopy patients without hyponatremia [48, 49]. Further elucidation and research is needed to better understand the pathogenesis of seizures in that subset of patient population.

In summary, the exact incidence of iatrogenic hyponatremia induced by bowel preparation is unknown, although the condition appears to be rare based on the small number of reports to FAERS. Physicians should be aware of its occurrence and complications. Acute hyponatremia can result in neurologic damage and even death. Female patients appear to be at higher risk. Written instructions should include avoidance of excess free water intake. Combination of more than one colonoscopy preparations may also represent a risk for the development of hyponatremia and should be avoided.

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