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Exceptional Case

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Iso-osmolar hyponatremia from polyethylene glycol

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ABSTRACT

Understanding and applying pathophysiological concepts to patient care is an important skill for physicians in the clinical setting. Here, we present a case that demonstrates how the application of common physiological concepts relating to the widely accepted hyponatremia algorithm led to an accurate diagnosis of hyponatremia. This case documents iso-osmolar hyponatremia caused by orally administered polyethylene glycol absorption in the gastrointestinal tract. Herein, we discuss the workup and differential diagnosis for iso-osmolar hyponatremia in juxtaposition with the pathophysiological mechanisms unique to this case. We discuss these pathophysiological mechanisms based on the patients' laboratory data and responses to therapeutic interventions.

Keywords: hyperkalemia, hyponatremia, ileus, iso-osmolar, osmolality, polyethylene glycol, sarcoidosis

INTRODUCTION

Polyethylene glycol (PEG) 3350 is described as 'a mixture of nonabsorbable, nonmetabolized polymers' that when administered orally acts as a 'pure osmotic agent' in the gastrointestinal (GI) tract (based on the manufactures' clinical review application for over-the-counter use) [1]. The compound is a polymer of ethylene oxide with the formula: $HOCH_2(CH_2OCH_2)_nCH_2OH$ and is commonly used clinically as an osmotic laxative. The '*n*' in the formula can vary from 4 to 136 units of ethylene oxide [2]. The number that is seen after its name represents the average molecular weight of PEG molecules in the solution. For example, PEG 3350 contains molecules averaging 3350 g/mol (3350 Da or 3.350 kDa). This agent was approved by the Federal Drug Administration in 1998 for adults with occasional constipation and in 2005, it was approved for over-the-counter use. This widespread use of PEG is also supported by the American Gastroenterology Association, where it is broadly recommended as a first-line agent for constipation [3]. Although there was initial concern that this compound might be absorbed into the bloodstream producing systemic effects [4], this possibility has since been assumed to represent only a theoretical risk. We describe a case of iso-osmolar hyponatremia due to PEG absorption into the systemic circulation and discuss the workup, physiology and risk factors associated with the subsequent and unique downstream consequences. In this review, the abbreviation PEG will refer to PEG 3350 packaged without electrolytes, and

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A

Complete blood count

Admission: WBC 13.2 x 10^9/L, Hgb 11.2 g/L, Plt 485 x 10^9/L

Day 10 (consult day): WBC 11.2 x 10^9/L, Hbg 11.6 g/L, Plt 512 x 10^9/L

Basic metabolic panel

Admission: Na 131 mmol/L, K 4.9 mmol/L, Cl 97 mmol/L, TCO_2 23, BUN 20 mg/dl, Cr 0.96 mg/dl, glucose 137 mg/dl, Ca 8.6 mg/d

Day 10 (consult day): Na 123 mmol/L, K 5.5 mmol/L, Cl 92 mmol/L, TCO_2 22 mmol/L, BUN 20 mg/dl, Cr 1.0 mg/dl, glucose 88 mg/dl

Other laboratory results

Cortisol 18.2 mcg/dl, magnesium 1.4 mg/dl, phosphorus 4.4mg/dl, osmolality (serum) 277 mosm/kg H_2O, blood Na measured using direct electrode 127.9, blood K measured using direct electrode 5.42 mmol/l, albumin 3.1 g/L, uric acid 3.9 mg/dl

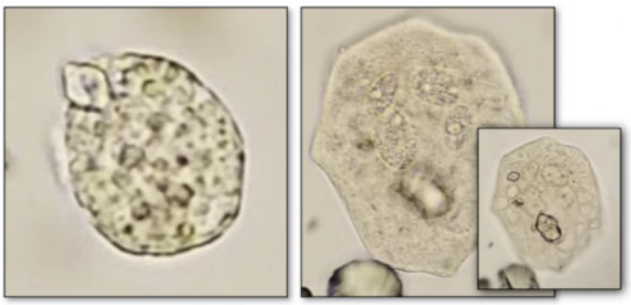
Urine analysis

Urinalysis: pH 6.5, specific gravity 1.020, WBC 0–5, RBC 0–3

Urine sediment: Many large macrophage-like vacuolated renal tubular epithelial cells, unknown polarizing crystals, no casts

Other urine labs: Urine Na 100mmol/L, urine K 38.1 mmol/L, urine Cl 68 mmol/L, urine Cr 121 mg/dl, osmolality (urine) 525 mosm/kg H_2O -> 787 mosm/kg H_2O

B



C

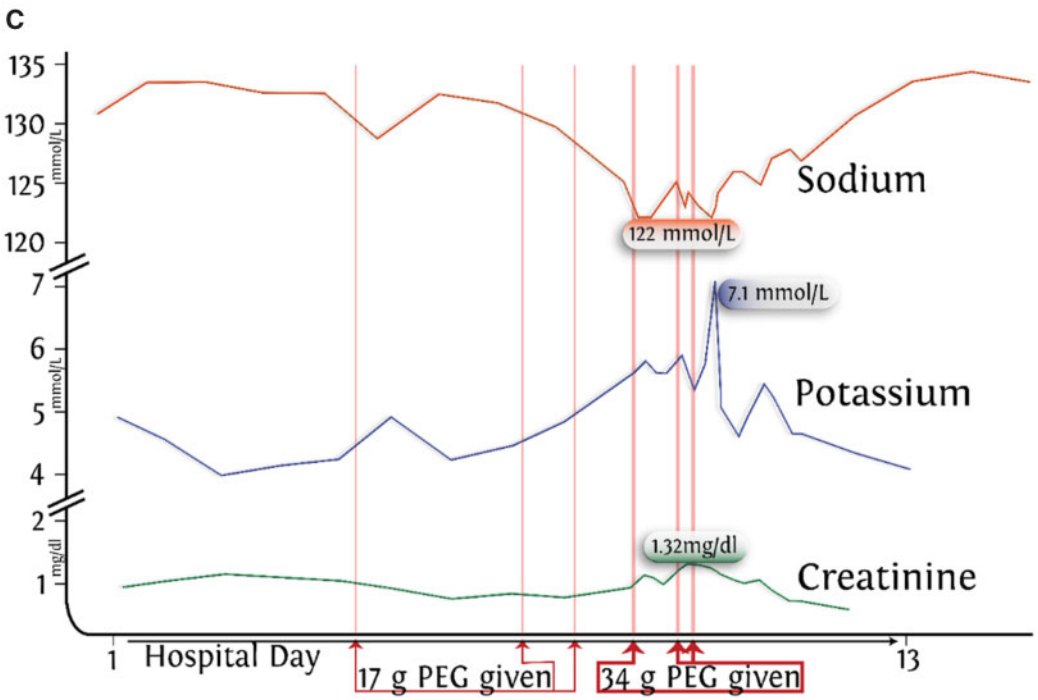


FIGURE 1: Patient's labs, urine sediment and timeline. (**A**) Patient's laboratory results during inpatient admission. (**B**) Photomicrograph of patient's urinary sediment examination, unpolarized. (**C**) Patients hospitalization during the first 13 days (x-axis) demonstrating the relationship between patient's sodium, potassium and creatinine as they relate to PEG dose (thin red arrows = 17 g PEG dose; thick red arrows = 34 g PEG dose). Both a temporal and dose-dependent relationship is reliably seen; sodium decreases and potassium increases after each PEG dose. When PEG is discontinued, the electrolyte abnormalities and creatinine fluctuations also resolved. WBC, white blood cells; Hgb, hemoglobin; Plt, platelets; Na, sodium; K, potassium; Cl, chloride; TCO_2, total carbon dioxide; Cr, creatinine; Ca, calcium; RBC, red blood cells.

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if another compound or brand is discussed it will be labeled appropriately, as the size influences its pharmacokinetics.

CASE PRESENTATION

A 69-year-old, 72 kg man with advanced pulmonary sarcoidosis presented to the emergency department with increasing shortness of breath. Past medical history included active and advanced pulmonary sarcoidosis and a subtotal colectomy due to a concerning polyp. Patient denied tobacco, alcohol or illicit drug use and had no known drug allergies. On exam, the patient had conversational dyspnea, course crackles greater in the mid and upper lung fields, his heart had a regular rhythm although tachycardia was present, his abdomen was soft and non-tender and no lower extremity edema was present. Laboratory data (Figure 1A) demonstrate mild hyponatremia on admission. The patient was diagnosed with pneumonia and broad-spectrum antibiotics were started. Two days later, the patient developed an ileus and consultation by General Surgery recommended medical management with PEG. This treatment continued for 2 days but without a bowel movement. Accordingly, the dose of PEG was increased to 34 g twice daily from 17 g twice daily. Apart from the antibiotics, the patient's shortness of breath was treated additionally with furosemide in the early hospital course. Subsequent laboratory data, 10 days into the hospitalization, revealed worsening hyponatremia and hyperkalemia; nephrology was consulted. An outline of the patient's timeline of results is presented in Figure 1C along with input and output information (Supplementary data, Table S1).

WORKUP AND DISCUSSION

When a patient presents with hyponatremia, the expectation of a low-serum osmolality needs to be confirmed with the actual measurement of serum osmolality. A widely accepted formula for the calculation of the serum osmolality is serum osmolality ($mOsm/kg\,H_2O$) = serum sodium [Na^+(mmol/L)] × 2 + serum blood urea nitrogen (mg/dL)/2.8 + serum glucose (mg/dL)/18. After calculating the expected serum osmolality and measuring the actual serum osmolality, the osmolar gap can be estimated by subtracting the calculated value from the measured value. An osmolar gap of $<10\,mOsm/kg\,H_2O$ is considered normal. In this case, the patient had a calculated serum osmolality of $258\,mOsmol/kg\,H_2O$ and a measured osmolality of $277\,mOsm/kg\,H_2O$ on Day 10, yielding an osmolar gap of $19\,mOsm/kg\,H_2O$ (elevated).

Iso-osmolar or hyperosmolar hyponatremia is caused by the addition of an 'effective solute' (e.g. glucose, mannitol or sucrose) to the serum. The term 'effective' refers to the ability of the compound to pull water across a biological membrane, also called osmosis, and these effective solutes can be differentiated from 'ineffective solutes' such as alcohol and urea. Once iso-osmolar hyponatremia and an osmolar gap were diagnosed in this case, we immediately began searching for potential effective solutes that might be present in the serum. The most plausible substance was PEG (see below). Apart from the biochemical plausibility, this diagnosis is further supported by the temporal and dose-dependent correlation of the laboratory results, and the direct correlation between PEG initiation and discontinuation and changes in the serum sodium and potassium for two separate time periods of its use without change or adjustment of any other medications (Figure 1C). Excessively high concentrations of PEG in the GI tract can be absorbed when contact time is prolonged, as in this case where an ileus was also present along with active sarcoidosis further increasing small intestine permeability.

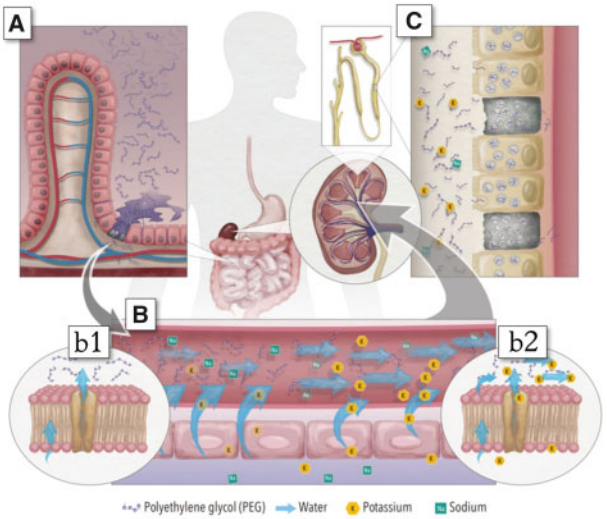

FIGURE 2: Mechanism of iso-osmolar hyponatremia from oral intake of PEG 3350. (**A**) PEG administered in the setting of an ileus and many other risk factors for tight junction dysfunction resulted in a higher risk of PEG permeability. With >24 h exposure, enterocyte death can occur, further increasing PEG absorption. (**B**) Once in the blood, PEG has similar actions as it would have in the intestinal lumen. (**b1**) The most prominent biochemical change is from the large volume of water movement due to the higher serum osmolality. Water will move from a low osmolality environment to a higher osmolality environment, diluting the sodium and resulting in hyperosmolar/iso-osmolar hyponatremia. (**b2**) This large amount of water movement can also influence the movement of other ions, most notably here, potassium. This effect, referred to as solvent drag, is when the movement of fluid (or solvent) 'drags' potassium from a high intracellular concentration, down its concentration gradient to a lower potassium concentration extracellularly. (**C**) This large osmotic load in the systemic circulation will be filtered by the kidney. The proximal tubule has a limited capacity to reabsorb macromolecules in the proximal tubule. This usually includes proteins that once reabsorbed are degraded into amino acids through lysozyme vesicles. Synthetic substances are typically not amenable to degradation, but proximal tubular reabsorption will occur, and this process can be more active if a prerenal state is present as in our patient, due to effective intravascular volume depletion. The inability to break down these macromolecules will cause proximal tubular renal cells to increase in size eventually resulting in their dysfunction (osmotic injury), sluffing and excretion in the urine. If enough of these cells are injured, then an increased serum creatinine is seen, resulting in osmotic nephropathy, which is presumed to be present here based on many factors discussed in the manuscript.

The effectiveness of PEG as a laxative is dependent on its ability to pull water into the lumen of the colon [5]. If absorbed systemically in significant amounts, its strong osmotic pressure will persist as PEG enters the intravascular compartment [6–9]. Based on our patient's clinical presentation of hyponatremia and an osmolar gap, a dilutional hyponatremia was present, and in the absence of hyperglycemia and other potential causes of an osmotic gap, such as mannitol, radiological contrast agents or alcohols, we reasoned that PEG was the cause of the hyponatremia and now speculate on the pathophysiological events occurring in our patient (Figure 2).

Enteral PEG absorption commonly occurs, although the small fraction of the ingested dose that is absorbed is not characteristically clinically significant. Most of the PEG absorption occurs in the jejunum and ileum, where molecules ranging from 60 to 40 000 Da show an inverse correlation between their size and degree of absorption [10–12]. The degree of absorption or intestinal permeability depends on many variables; including

Table 1. Cases of PEG causing hyponatremia published in the literature

Author, location, year	Case description	Sodium nadir (mmol/L)/ serum osmolality (mOsm/kg H_2O)	Etiology of hyponatremia as determined by authors
Nagler *et al.*, USA, 2006 [16]	73-year-old female ingested PEG (225 g) in Gatorade for a screening colonoscopy	117/225	SIADH
Baeg *et al.*, South Korea, 2013 [17]	70-year-old female admitted for seizure after ingesting PEG for colonoscopy prep	110/–	None given
	65-year-old female admitted with a seizure after ingesting PEG for colonoscopy prep	127/–	None given
Ayus *et al.*, USA, 2003 [18]	62-year-old female with ESRD on HD presents with seizures after PEG for colonoscopy prep	116/–	None given
	51-year-old male with ESRD on HD p/w emesis, arrhythmia, cardiac arrest after prep	134/–	None given
Ko *et al.*, South Korea, 2014 [19]	69-year-old female ingested PEG for colonoscopy and p/w nausea, headache, weakness and seizure	113/233	SIADH
Samad and Fraser, Australia, 2017 [20]	68-year-old female admitted to the ICU for seizures after bowel prep	106/224	Hypovolemic hyponatremia
Schroppel *et al.*, Germany, 2001 [21]	59-year-old with rectal bleeding, underwent colonoscopy with 4 L tea and 3 L PEG. Postprocedure had confusion, unsteady gait, slurred speech	120/264 (Na 126 when osmolality obtained)	Water intoxication
Tucker *et al.*, USA, 2020 (current case)	69-year-old male with sarcoidosis hospitalized for pneumonia, complicated with an ileus, received high PEG doses without bowel movements	122/277	Iso-osmolar hyponatremia from enteral PEG absorption

SIADH, syndrome of inappropriate antidiuretic hormone secretion; ICU, intensive care unit; AMS, altered mental status; p/w; presents with; Na, sodium; ESRD, end-stage renal disease; HD, hemodialysis.

transit time, mucosal surface area, contact time and transfer, mesenteric blood/lymphatic flow and kidney function. The major factors increasing intestinal permeability in our patient include ileus and sarcoidosis (interferon-γ and tumor necrosis factor-α) [13, 14]. The absence of intestinal motility results in the progressive accumulation of intraluminal PEG, and in the face of an inflammatory (and infectious) state augmenting intestinal permeability, produce a favorable environment for the absorption of PEG (Figure 2A).

Upon entering the blood, most of PEG's clearance occurs within 24 h via renal filtration [15]. As an effective osmole, PEG can shift water into the vascular space, diluting the serum sodium concentration, resulting in hyponatremia [Figure 2B(b1)].

Several reports of PEG administration and hyponatremia have been published, as presented in Table 1. The prevalence of hyponatremia is reported at 7% in bowel prep patients [22]. The underlying mechanism of hyponatremia is commonly confined to the hypo-osmolar subtype and no previously reported case presenting with an osmolar gap exists in the literature (Table 1).

Large amounts of water movement can move potassium down its concentration gradient (intracellular to extracellular) resulting in hyperkalemia, a process known as solvent drag. In this case, occurrences of hyperkalemia mirrored those of hyponatremia [Figure 2B(b2)], or in other words, each time that potassium moved down its concentration gradient into the vascular space, it was associated with water movement in the same direction. Based on this association and the clinical context, we speculate that solvent drag was the mechanism for this patient's hyperkalemia.

As stated before, most of PEG's clearance is via renal filtration. We speculate, based on the patient findings and renal physiology, that a mild osmotic nephropathy may have been present (Figure 2C). Once filtered, the proximal tubule cells reabsorb a portion of the filtered PEG and due to the inability to properly metabolize the PEG molecule, large and vacuolated renal tubular cells result [23]. Similar cells were visualized in the urine sediment in our patient (Figure 1B) and have been demonstrated in many other studies when PEG is administered [24–26]. The time- and dose-dependent changes in serum creatinine, albeit mild, along with the presence of large vacuolated renal tubular epithelial cells in the urine sediment support the diagnosis of a mild acute tubulopathy secondary to PEG.

The series of physiological events discussed in this case are not unique to PEG. Iso-osmolar/hyperosmolar hyponatremia resulting in hyperkalemia from solvent drag ultimately leading to osmotic nephropathy can be seen with all the etiologies of hyperosmolar hyponatremia as well [27–31]. Differentials include irrigation solutions (sorbitol, mannitol, glycine-glycerol, maltose and sucrose), intravenous administered substances (radiocontrast agents, intravenous immunoglobulin, hydroxyethyl starch, mannitol, histidine–tryptophan–ketoglutarate and lorazepam drip) and now orally administered PEG.

Ultimately, after improvement of hyponatremia and hyperkalemia, the patient's sarcoidosis was too advanced, and he chose to pursue hospice care after a month in the hospital. He died a few days later.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

CONFLICT OF INTEREST STATEMENT

None declared.

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