

Case of inappropriate ADH syndrome: Hyponatremia due to polyethylene glycol bowel preparation

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Abstract

Colonoscopic screening has been reported to reduce deaths from colorectal cancer. Adequate bowel preparation is essential for this and safety is an important issue in choosing the methods. Polyethylene glycol (PEG) is regarded as a safe method for cleansing, especially compared with oral sodium phosphate. Here, we present a case of hyponatremia caused by the syndrome of inappropriate antidiuretic hormone (ADH) syndrome after PEG precolonoscopic cleansing resulting in generalized tonic-clonic seizures. A 62-year-old women had ingested PEG for precolonoscopic bowel cleansing. While waiting for the colonoscopy, she developed a stuporous mentality and generalized tonic-clonic seizures, which did not correlate with brain magnetic resonance imaging. Her serum sodium level was 113 mEq per liter and laboratory analyses were consistent with inappropriate ADH syndrome. Her thyroid and adrenal functions were normal. There were no malignancies, infections, respiratory disorders or central nervous disorders and

she had no history of taking either diuretics or other medications, which might have caused inappropriate ADH syndrome. She was treated with 3% hypertonic saline and showed a complete neurological recovery as her sodium levels recovered. Follow-up visits showed the patient to have a normal sodium level without neurologic deficits. This case shows that inappropriate ADH syndrome can be caused by PEG preparation, which implies that physicians have to be aware of the possible side effects of this colonic cleansing approach and mindful of the possible ensuing symptoms.

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Key words: Inappropriate antidiuretic hormone syndrome; Colonoscopy; Polyethylene glycol; Hyponatremia; Seizure

Core tip: We report a case of hyponatremia resulting in seizures after precolonoscopic polyethylene glycol cleansing due to inappropriate antidiuretic hormone (ADH) syndrome. Though inappropriate ADH syndrome has been suspected in the few reports of hyponatremia after polyethylene glycol (PEG) preparation, this is the first case to have confirmed an association between the two. Guidelines recommend that colonoscopic screening be done in patients from age 50 with PEG the first choice for bowel cleansing. As colonoscopic screening increases, hyponatremia due to inappropriate ADH syndrome will most likely increase as well. As we show, PEG induced inappropriate ADH syndrome may have severe side effects. However, if recognized and treated, it should have no long-lasting sequelae.

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INTRODUCTION

Endoscopic surveillance for colorectal cancer has been reported to decrease its mortality. The guidelines recommend that colon examinations including colonoscopy be done at regular intervals in individuals over 50 years of age^[1]. Colonoscopy requires an adequate level of cleansing for effective evaluation of the colonic mucosa^[2]. The main types of laxatives used for bowel cleansing are oral sodium phosphate (OSP) and polyethylene glycol (PEG). Safety is also very important, as in the case of sodium phosphate, which was rejected by the United States Food and Drug Administration despite its convenience because it gives an increased risk of phosphate nephropathy. Because of such safety concerns, current guidelines suggest use of PEG over OSP^[2,3]. PEG is a biologically inactive substance that does not bear an electrical charge and therefore cannot influence the movement of other solutes^[4]. It is a water-soluble, nontoxic polymer that is minimally absorbed in the gastrointestinal tract^[5].

Although PEG is generally considered to be safe for colonic cleansing, it can occasionally induce adverse events such as renal failure, hyponatremia, upper gastrointestinal bleeding or aspiration caused by vomiting, and even death^[3,6,7]. Here, we report a case of hyponatremia in the inappropriate antidiuretic hormone (ADH, arginine vasopressin) syndrome resulting in generalized tonic-clonic seizures after PEG precolonoscopic cleansing. As far as we know, there have been no prior reports describing an association between inappropriate ADH syndrome and PEG use for colonic cleansing.

CASE REPORT

A 69-year-old woman weighing 48 kg visited our gastrointestinal clinic for routine colonoscopic checkup. She had a history of diabetes and dyslipidemia, was well-nourished and did not have any history of alcoholism. Her medication history included glimepiride, sitagliptin, metformin and atorvastatin but no history of thiazide diuretics or selective serotonin reuptake inhibitors. She had taken the medicines up to the day before colonoscopy but not on the procedure day. For precolonoscopic bowel preparation, the patient ingested 4 L of a standard bowel preparation solution containing an isosmotic solution of PEG without any further fluid consumption. While the patient was waiting for colonoscopic examination, she began complaining of nausea, headache, generalized weakness and sweating. She developed a stuporous mentality and generalized tonic-clonic seizures. Her vital signs showed a blood pressure of 143/74 mmHg and a pulse of 76 beats per minute. A physical examination did not show any signs of distended jugular veins, pedal edema, ascites, decreased skin turgor or dry mucous membrane, indicating an euvoletic state. No specific neurologic signs were evident.

Her laboratory results (Tables 1 and 2) showed a serum sodium level of 113 mEq/L, a decreased total serum osmolality of 233 mOsm/kg (< 275 mOsm/kg) and

Table 1 Patient's serum laboratory data and mental state

Mental state	Reference range	Drowsy to stuporous	Stuporous	Stuporous to verbal response	Complete recovery
		Day 1	Day 2	Day 3	Day 4
Sodium (mEq/L)	136-146	113	117	125	135
Potassium (mEq/L)	3.5-5.1	3.4	3.5	3.1	3.5
Chloride (mEq/L)	98-106	80	84	93	98
Urea nitrogen (mg/dL)	7-20	6.2	9	12.3	6.4
Creatinine (mg/dL)	0.6-1.2	0.51	0.61	0.56	0.45
Glucose (mg/dL)	50-100	125			
Osmolality (mOsm/kg)	275-300	233	-	-	278
Free T4 (ng/dL)	0.85-1.86	1.51			
TSH (mIU/L)	0.17-4.05	1.77			
Cortisol (mg/dL)	9.41-26.06	32.47			
ADH (pg/mL)	0.0-6.7	49.87			
Spot urinary analysis			-	-	
Sodium (mEq/L)		122	-	-	48
Potassium (mEq/L)		28.5	-	-	8
Chloride (mEq/L)		107	-	-	47
Urea nitrogen (mg/dL)		248.2	-	-	222.6
Creatinine (mg/dL)		16	-	-	6.4
Osmolality (mOsm/kg)		344	-	--	249
FENa (%)		3.4			2.5
FEUrea (%)		0.13			0.24

ADH: Antidiuretic hormone; FENa: Fractional excretion of sodium; FEUrea: Fractional excretion of urea.

an increased urine osmolality of 344 mOsm/kg (> 100 mOsm/kg). Her serum creatinine level was 0.51 mg/dL, blood urea nitrogen 6.2 mg/dL (< 10 mg/dL), plasma uric acid 3.1 mg/dL (< 4 mg/dL), and she had a normal acid/base and potassium balance. Thyroid function tests were within normal range and the basal cortisol level was increased, which was consistent with hyponatremia. An antidiuretic hormone study was done, which revealed an ADH level of 49.87 pg/mL (normal range 0.0-6.7 pg/mL). Diffusion-weighted magnetic brain imaging was done, which revealed mild small vessel disease and a tiny restriction focus in the right temporal lobe. An electroencephalogram taken 4 h after the onset of seizures showed waves suggestive of diffuse cerebral dysfunction.

She was diagnosed with inappropriate antidiuretic hormone syndrome resulting in hyponatremic seizures, and treatment was started with 3% intravenous saline with infusion rates based on electrolytes checked every 2-4 h. Symptomatic treatment of the seizures involved

Table 2 Clinical findings of patients with polyethylene glycol related hyponatremia

	Patient 1 ^[20]	Patient 2 ^[20]	Patient 3 ^[6]	Patient 4 ^[6]	Patient 5 ^[19]	Patient 6 ^[10]
Age, yr	51	62	70	65	59	73
Gender	M	F	F	F	F	F
Past history				Breast Cancer, Total thyroidectomy and RAIT	Hysterectomy with oophorectomy	
Underlying disease	Diabetes, ESRD	HTN, Hyperlipidemia	HTN, Osteoporosis,			Hypothyroidism, Depression
Prescription drugs	Amlodipine, Atenolol, Furosemide, Phoslo, Prilosec	Thiazide	Amlodipine, Ibandronic acid, clopidogrel	Levothyroxine	Estradiol, Aspirin	Levothyroxine, citalopram
Preparation methods	N/A	4L PEG	4L PEG + 3 L clear water	4L PEG	3L PEG + 4L weak tea	255g PEG + 64 ounces Gatorade
Sodium (mmol/L)						
Baseline	138	138	140	144	N/A	N/A
Lowest	122	116	110	127	120	117
Post-treatment	N/A	130	138	141	138	131
Potassium (mmol/L)	5.1	3.9	3.4	4.3	4.6	3.3
Chloride (mmol/L)	94	79	72	104	N/A	79
Bicarbonate (mmol/L)	20	26	17.3	17.3	17.2	21
Urea Nitrogen (mg/dL)	24.3	2.5	11.8	14.6	N/A	6
Creatinine (mg/dL)	7.7	0.6	0.67	0.71	0.9	0.6
Glucose (mg/dL)	95.5	N/A	148	235	93	N/A
Clinical Presentation	Emesis, IVR, cardiac arrest	Seizure	Seizure	Seizure	Confused mentality	Seizure
Blood pressure (mmHg)	167/78	130/90	190/100	156/85	110/70	Within normal
Pulse (/min)	103	90	84	86	60	Within normal
Brain CT/MRI	Not done	Cerebral edema	No abnormalities	No abnormalities	No abnormalities	Not done
Treatment	None	IV 3% Saline	IV 3% Saline	IV Normal Saline	IV Normal saline	IV 2% Saline, followed by NaCl tablets and water restriction
Outcome	Death	Complete recovery	Complete recovery	Complete recovery	Complete recovery	Complete recovery

ESRD: End stage renal disease; HTN: Hypertension; IVR: Idioventricular rhythm; IV: Intravenous; N/A: Not available; PEG: Polyethylene glycol; RAIT: Radioiodine therapy.

the administration of 1500 mg of the anticonvulsant valproic acid daily for 3 d. After 72 h of treatment with 10-40 mL/h of 3% intravenous saline, she began to respond to vocal stimulation. The patient had recovered to a normal state by day 4 with no residual neurological abnormalities. There were no signs of malignancies during a detailed physical examination and her chest X-rays were negative. Serum tumor markers such as carcinoembryonic antigen, alpha-fetoprotein, CA-125 and CA 19-9 were all within normal range. Electrolyte levels continued to be normal until her discharge and subsequent outpatient follow-up. This case report was approved by the institutional review board of the Seoul St. Mary's hospital (KC13ZISE0724).

DISCUSSION

We demonstrate here for the first time that preparation with PEG for colonoscopy might be associated with hyponatremia caused by newly developed inappropriate antidiuretic hormone syndrome. The main symptoms of hyponatremia are nausea, vomiting, headache, confusion, lethargy, fatigue, restlessness and irritability, weakness, seizures, decreased consciousness and coma^[8].

Hyponatremia can be caused by salt loss secondary to excessive volume loss, renal disease, adrenal insufficiency and hypothyroidism, but is often caused by inappropriate antidiuretic hormone syndrome. In this syndrome, hyponatremia results from ADH-induced retention of ingested or infused water. Although water excretion is impaired, sodium handling is intact, because there are no abnormalities in volume-regulating mechanisms such as the renin-angiotensin-aldosterone system or atrial natriuretic peptide^[9]. Inappropriate ADH syndrome has many different causes, including ectopic production of arginine vasopressin (AVP) by neoplasms, acute infections, pulmonary diseases and central nervous disorders. Common medications such as thiazide diuretics, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors and opiate derivatives can also raise ADH levels. Treatment with desmopressin, oxytocin or vasopressin might stimulate release of AVP or enhance its action. Antidepressants from the selective serotonin reuptake inhibitor family are also known to cause hyponatremia via inappropriate ADH syndrome^[8,10]. Nausea, anxiety, stress, pain or manipulation of gastrointestinal organs can also induce ADH release independent of osmotic stimuli^[11]. Advanced age can also be a contributing factor^[12].

Increased free tissue water does not cause hyponatremia in patients with normal renal function and a normal solute load^[8]. For hyponatremia to develop, free water clearance, which is regulated by ADH, must be impaired. Increased ADH has been reported during colonoscopy^[13,14]. This might be caused by increased nonosmotic ADH stimuli such as nausea, vomiting, stress, pain, intestinal hyperactivity or abdominal manipulation. However, most colonoscopic procedures do not result in hyponatremia, even among elderly patients. While some studies have reported absorption of water during PEG preparation^[15,16], the amount has been reported to be small and not enough to cause symptomatic hyponatremia^[17].

In our patient, although inappropriate ADH syndrome caused by an undiscovered malignancy could not be ruled out completely, this was thought to be unlikely as she had no subjective symptoms, a comprehensive physical examination was normal, chest X-rays showed no evidence of lung masses and her serum tumor markers were within normal range. Electroencephalography showed waves suggestive of diffuse cerebral dysfunction, representative of her stuporous state. Although her brain diffusion magnetic resonance imaging showed mild small vessel disease and a tiny restriction focus in the right temporal lobe, this did not correlate clinically with her neurologic symptoms and seizure type. Other factors were excluded because our patient had a normal thyroid function and basal cortisol hormone test, and was not taking any medication known to cause hyponatremia or inappropriate ADH syndrome. She did not show any signs of recurrent hyponatremia after discontinuation of treatment, which was confirmed during outpatient follow-up. We conclude that hyponatremia in our patient was probably caused by inappropriate ADH syndrome associated with nonosmotic stimuli due to PEG preparation.

Colonoscopic screening and adenoma removal have been reported to reduce deaths from colorectal cancer^[1,18]. Proper bowel preparation is needed for adequate visualization of colon mucosa^[2]. Issues about the safety of OSP have been raised, with guidelines recommending the use of PEG^[2,3]. Using PEG for precolonoscopic bowel cleansing has been reported not to cause any electrolyte disturbances^[13]. However, as our case shows, the use of PEG for this purpose can also result in serious adverse events.

There have been six reports of hyponatremia associated with PEG intake that have resulted in encephalopathy or fatalities^[6,10,13,19]. All of the patients were over 50 years old, with four of them over 60 years of age. One patient had preexisting end-stage renal disease, which most likely would have impaired free water excretion^[20]. A second patient was taking thiazide diuretics, which would have impaired their ability to excrete water^[20]. Another had been taking serotonin reuptake inhibitors, had inadequate thyroid replacement and was over 70 years old, which might have further aggravated her hyponatremia^[10]. Two patients were similar in that they showed normal renal, thyroid and adrenal function but had ingested 3 L of flu-

ids in addition to the 4 L of PEG^[6,19]. Nonosmotic ADH stimuli combined with old age and a large volume of fluid most likely caused their hyponatremia. The authors of these case reports hypothesized that PEG-related hyponatremia was probably caused by an increase in ADH resulting from bowel manipulation that occurred during colonoscopy preparation. However, these reports did not confirm inappropriate ADH syndrome as the cause of hyponatremia, and failed to prove an actual increase in ADH^[6,19]. Further laboratory and clinical data regarding these patients can be found in Table 2. Our case is interesting in that hyponatremic seizures developed despite the patient having normal renal function and no other risk factors except PEG preparation.

Current guidelines recommend that colonoscopic screening be done regularly in patients from age 50 years onwards, which would place many elderly patients at risk of hyponatremia-related inappropriate ADH syndrome. We conclude that physicians should be thoroughly familiar with a patient's medical history before prescribing PEG, and that all patients should be well hydrated with electrolyte-containing solutions both during and after PEG ingestion. Also, serum electrolytes should be promptly checked and treatment begun in patients showing symptoms suggesting their imbalance.

COMMENTS

Case characteristics

A 62-year-old woman was admitted with generalized tonic-clonic seizures and in a semi-comatose state.

Clinical diagnosis

The woman was diagnosed with hyponatremia due to bowel cleansing from polyethylene glycol (PEG).

Differential diagnosis

Excess fluid, salt loss secondary to excessive volume loss, inappropriate antidiuretic hormone (ADH) syndrome, brain damage.

Laboratory diagnosis

Serum Na 113 mEq/L, serum osmolality of 233 mOsm/kg, serum antidiuretic hormone 49.87 pg/mL, urine osmolality of 344 mOsm/kg, urine sodium 122 mEq/L.

Imaging diagnosis

Her brain magnetic resonance imaging showed mild small vessel disease and a restriction focus in the right temporal lobe which could not be correlated with her neurologic symptoms.

Treatment

She was treated for 72 h with 3% intravenous saline and her mental state and symptoms returned to normal after normalization of her serum sodium levels.

Term explanation

Inappropriate ADH syndrome: A syndrome where hyponatremia results from antidiuretic hormone-induced retention of ingested or infused water. Although water excretion is impaired, sodium handling is intact, because there are no abnormalities in volume-regulating mechanisms such as the renin-angiotensin-aldosterone system or atrial natriuretic peptide. Inappropriate ADH syndrome has many different causes, including ectopic production of arginine vasopressin by neoplasms, acute infections, pulmonary diseases and central nervous disorders. Common medications such as thiazide diuretics, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors and opiate derivatives can also raise antidiuretic hormone levels.

Experiences and lessons

Inappropriate ADH syndrome has been rarely reported as a result of PEG bowel cleansing. However, as the symptoms are severe and potentially fatal, medical

personnel must be aware of such side effects and treatment methods.

Peer review

The authors present a case report of a patient with a complication related to the colon cleansing preparation for colonoscopy. The patient was admitted to the hospital after PEG colon cleansing preparation for colonoscopy because of an acute reaction leading to stupor requiring intensive care admission and was finally diagnosed with a syndrome of inappropriate secretion of antidiuretic hormone. PEG colon cleansing is considered safe and this is a rare condition induced by PEG colon cleansing for colonoscopy in a middle aged patient needing intensive care. The description of this exceptional complication is interesting and it is convenient to have knowledge in this regard. The presentation, the diagnostic work-up and the Discussion are adequate and supported by updated bibliographic data.

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