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Case Report

Hypophosphatemia in Users of Cannabis

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As cannabis use has legalized for medical and recreational use in several states, the medical community has become more aware of the drug's potential toxicities. First described in 2004, cannabinoid hyperemesis syndrome is increasingly recognized as a cause of hospitalization among drug users. However, little information is available in the medical literature regarding electrolyte abnormalities in this syndrome. Between 2011 and 2014, six men were treated for cannabinoid hyperemesis syndrome at the Veterans Affairs Medical Center in San Diego, CA, and found to have significant hypophosphatemia (phosphate range, <1-1.3 mg/dL). The 6 cases are presented here and possible causes of hypophosphatemia are discussed. In 3 patients, serum phosphate levels normalized spontaneously within hours, suggesting redistribution of phosphate as a potential mechanism. Hyperventilation, which can lead to phosphate redistribution, was observed in 4 of the 6 individuals and may have contributed. Hypophosphatemia is a presenting feature of cannabinoid hyperemesis syndrome in some patients.

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In 2004, Allen et al[1] described 8 cannabis users who developed intractable vomiting that subsided only through abstinence. The phenomenon was later named cannabinoid hyperemesis syndrome and has since been recognized worldwide.[2-5] Simonetto et al[4] have proposed a set of clinical criteria for the syndrome, including weekly cannabis use, abdominal pain, cyclic vomiting, the resolution of symptoms with abstinence, and a curious amelioration of symptoms with hot baths or showers. Symptoms of cannabinoid hyperemesis syndrome typically resolve soon after cannabis use ceases, often within 24 hours,[3] but quickly recur if the individual returns to using the drug. The underlying cause of the syndrome is unknown. Although cannabinoid hyperemesis syndrome has been described in detail and is known to cause acute kidney injury,[6] little has been written regarding associated electrolyte abnormalities.

From January 1, 2011, through December 31, 2014, six men were treated for cannabinoid hyperemesis syndrome at the San Diego Veterans Affairs Medical Center and found to have significant hypophosphatemia. Details of these cases were examined retrospectively, and an attempt was made to determine whether each patient's hypophosphatemia was acute or chronic. To that end, all serum phosphate levels obtained from the men during the calendar year in which they were treated for the index cannabinoid hyperemesis syndrome event were also reviewed. The study was approved by the institutional review boards of the Veterans Affairs San Diego Healthcare System and the University of California, San Diego (project identification number 1180650) and was conducted in accordance with the Declaration of Helsinki.

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Clinical and historical data for the 6 patients are shown in Table 1. All patients were actively vomiting on arrival at the emergency department, and all met the diagnostic criteria for cannabinoid hyperemesis syndrome as proposed by Simonetto et al.[4] All were alert and appeared well nourished. The duration of patients' symptoms prior to arrival varied (range, 7 hours to 3 days). Four patients had documented weight loss (range, 3-13.9 kg) during the months prior, but for patient 1 this was intentional. None of the men was using calcium carbonate or other agents known to cause hypophosphatemia. Initial blood tests were obtained when these men were unable to ingest food. None of the patients received intravenous (IV) dextrose or other feeding prior to blood being drawn, and none was administered insulin. All patients received IV antiemetics (metoclopramide or ondansetron) and IV normal saline solution in the emergency department. In the case of patients 3 and 4, IV alprazolam, 1 mg, was also given. Measurement of serum phosphate was repeated eventually in all patients, although the timing varied (range, 3-25 hours later). Levels improved in 3 men (patients 1, 2, and 6) after electrolyte replacement had been given (potassium phosphate, given as either 500-1,500 mg orally or 6.8 mmol IV). However, in the other 3 (patients 3, 4, and 5), phosphate levels normalized without supplementation.

Hyperventilation, a potential cause of hypophosphatemia, was observed in two-thirds of the patients (recorded rates, 22-25

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Table 1. Male Veterans Presenting to the VA San Diego Medical Center in 2011 to 2014 With Cannabinoid Hyperemesis and Hypophosphatemia

Characteristic	Case No.					
	1	2	3	4	5	6
Age, y	33	43	68	27	57	24
BMI, kg/m^2	24.2	20.9	32.8	21.9	29.8	23.8
Symptom duration	2 d	9 h	7 h	3 d	2 d	2 d
Frequency of cannabis use[a]	Daily	Daily	Daily	Weekly	Daily	Daily
Use confirmed by urine toxicology[b]				+		+
Psychiatric diagnosis	SAD	PTSD	PTSD	GAD	MDD	—
Noted to be tachypneic (>20 breaths/min)	Yes	Yes	No	Yes	Yes	No
Documented weight loss, kg/mo	9.5/12	4.7/4	13.9/6	None	3/6	None
Initial serum chemistries						
Sodium (reference, 135-145), mmol/L	137	145	131	136	134	141
Potassium (reference, 3.5-5.0), mmol/L	3.7	3.5	3.6	3.3	3.4	3.1
Chloride (reference, 95-106), mmol/L	97	104	94	94	102	100
Bicarbonate (reference, 24-31), mEq/L	20	19	20	21	19	22
Urea nitrogen (reference, 8-23), mg/dL	18	8	15	23	13	9
Creatinine (reference, 0.6-1.3), mg/dL	0.84	0.96	1.49	1.22	0.82	1.00
eGFR (reference, 94-140), mL/min/1.73 m^2[c]	107	85	47	71	97	88
Albumin (reference, 3.2-4.6), g/dL	4.8	5.4	4.5	7[d]	4.9	4.4
Calcium (reference, 8.5-10.4), mmol/L	10.2	10.5	9.5	11.7	9.7	9.0
Phosphate (reference, 2.5-4.7), mg/dL	<1.0	<1.0	1.0	1.1	1.2	1.3
Received phosphate replacement	Yes	Yes	No	No	No	Yes
Repeat phosphate measurement						
Phosphate, mg/dL	4.5	3.7	3.4	3.2	3.2	4.3
Time after initial measurement, h	10	6	4.5	3	10	12
Individual summary data for 1 y						
Total ED visits	1	6	42	8	7	3
Visits with serum phosphate < 2.5 mg/dL	1	3	15	1	4	2
Admissions for CHS	1	6	22	3	7	1
Average length of stay, d	1	1.2	1.3	1.3	4.1	1

Note: All patients received intravenous normal saline solution in the ED. Conversion factors for units: creatinine in mg/dL to μmol/L, ×88.4; urea nitrogen in mg/dL to mmol/L, ×0.357.

Abbreviations: BMI, body mass index; CHS, cannabinoid hyperemesis syndrome; ED, emergency department; eGFR, estimated glomerular filtration rate; GAD, generalized anxiety disorder; MDD, major depressive disorder; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder; VA, Veterans Affairs.

[a]Reported.

[b]Urine screen for Δ^6-tetrahydrocannabinol at time of admission. All other patients had documented positive screening results during the period 3 months before or after admission.

[c]Calculated using the isotope-dilution mass spectrometry–traceable 4-variable MDRD (Modification of Diet in Renal Disease) Study equation.[7]

[d]Thought to be laboratory error. Repeat measure 3 hours later was 4.3 g/dL.

breaths/min). Four of the 6 men were being treated for anxiety, either in the setting of major depression or in the form of post-traumatic stress, social anxiety, or generalized anxiety disorder. A fifth patient was given a diagnosis of generalized anxiety disorder a month after his hospitalization. All 6 patients reported anxiety as the reason for their cannabis use. Patients 4 and 6 had positive urine toxicology tests for Δ^6-tetrahydrocannabinol (THC) at the time of admission. The other 4 patients had documented positive screening results during the 3 weeks before or after their hospitalization, consistent with their reported drug use.

In order to assess the relative acuity of hypophosphatemia in these cases, each patient's chart was later reviewed for the calendar year in which they presented. Five of the 6 patients presented repeatedly to the hospital with cannabinoid hyperemesis syndrome during the course of a year, 4 with serum phosphate levels < 2.5 mg/dL (Fig 1).

DISCUSSION

These case reports represent the first description of hypophosphatemia in individuals with cannabinoid hyperemesis syndrome. Phosphate nadirs ranged from <1 to 1.3 mg/dL. In half the cases, the serum phosphate level self-corrected within hours. Four of the 6 men presented repeatedly with hypophosphatemia over 1 year. None of the 6 was known to abuse alcohol or displayed signs of malnutrition, although in none of the cases was prealbumin measured. None of the patients was taking phosphate binders orally.

Although phosphate levels < 2.5 mg/dL may be seen in up to 5% of hospitalized patients,[8] hypophosphatemia