Case Report

Refractory hyperkalemia related to heparin abuse

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Abstract

Hyperkalemia is a potentially life-threatening condition, which may occur in many clinical settings. Heparin-induced hyperkalemia is less well-recognized than other side effects of heparin therapy. Even lesser known is heparin abuse amongst drug addicts. We report a case of fatal hyperkalemia related to long-term heparin abuse, which was refractory to anti-hyperkalemia therapy including hemodialysis. The objective is to alert the clinicians to possible abuse of heparin in drug addicts, which can be a cause for refractory hyperkalemia. We also briefly review the available literature on heparin-induced hyperkalemia.

Keywords: Hemodialysis, heparin abuse, hyperkalemia

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Introduction

Hyperkalemia may occur in many clinical settings and lead to serious events.[1] Heparin-induced hyperkalemia is presumably less well-recognized than other untoward effects of heparin treatment and more frequent than commonly perceived. There have been case reports of heparin induced hyperkalemia during heparin therapy but heparin abuse has not been widely reported in literature. We present a case of multi-substance abuse including heparin leading to refractory hyperkalemia.

Case Report

A 26-year-old male patient was admitted in the emergency department with the complaint of weakness of all four limbs since 1 day prior to admission, which was rapidly progressive. He was a pharmacist at a private nursing home addicted to multiple medicines including tramadol, diclofenac, pheniramine, and dexamethasone along with heparin to maintain the venous patency since several years. He was a known case of bronchial asthma and was on and off steroids for the past several years.

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On admission, patient was conscious and oriented, hemodynamically stable with a heart rate of 112 beats/min, non-invasive blood pressure of 130/80 mmHg, respiratory rate of 24/min and a temperature of 99°F. There was no pallor. No signs of clubbing or lymphadenopathy were there. Oral thrush was present. Chest, cardiovascular system and per abdomen examination were grossly normal. On central nervous system examination, power was grade 3/5 in upper limbs and 1/5 in lower limbs. Generalized areflexia was present. Planters were bilateral flexors. Sensory examination was normal. Laboratory investigations are tabulated in Table 1. Arterial blood gas (ABG) at admission showed a normal pH (7.437) with hyperkalemia (K^+ = 6.01). Although the first lab sample did not show hyperkalaemia, all repeat values did. Also the hyperkalemia was subsequently treated after 6 hours or so when repeat samples confirmed hyperkalemia. Patient was admitted to intensive care unit for monitoring and within an hour of admission, he got tachypnoeic with respiratory rate of 36-40/min and was put on non-invasive ventilation. Heart rate went up to 130 beats/min, regular but pulses got feeble. His blood pressure dropped down to 100/56 mmHg. At this time, invasive lines were put in, in the form of central venous cannulation and arterial line. Central venous pressure was 6 cm H_2O and mean arterial pressure (MAP) was 55 mmHg. Patient was resuscitated with a fluid bolus of 1 litre normal saline. His blood pressure improved with MAP going up to 64 mmHg. He was further

given 500 mL of normal saline in the subsequent hour and was started on normal saline 100 mL/h infusion. Subsequently, a MAP of >65 mmHg was targeted. Urine output was >0.5 mL/kg at all times. His chest X-ray showed a patch of consolidation on the right middle and lower zones. Echocardiography showed global hypokinesia with severe left ventricular dysfunction with ejection fraction of 30%. Repeat ABG after 6 h showed metabolic acidosis with lactic acidosis and hyperkalemia (pH = 7.257, pCO_2 = 27.2, pO_2 = 98.6, HCO_3^- =13.8, Lactate = 7.1, K^+ = 7.0). Lab values of S. K^+ were 6.7 mEq/L and anti-hyperkalemia treatment was started in the form of calcium gluconate, dextrose-insulin, and salbutamol nebulization. With nephrologist's opinion, patient was urgently taken up for slow low-efficiency dialysis (SLED) of 8 h. Within 20 min of starting dialysis, patient had an episode of pulseless ventricular tachycardia. Patient was defibrillated and cardiopulmonary resuscitation (CPR) was done. Anti-hyperkalemia regimen was repeated. Urgent serum K^+ levels done at the time of event were 9.1 mEq/L. After 40 min of CPR, patient was revived with normal sinus rhythm, was intubated and put on invasive ventilatory support. He was started on inotropes and vasopressors. Subsequent ABG done before the end of planned duration of SLED still showed persistent hyperkalemia (K^+ = 7.1), with slight improvement in pH values. On discussion with the nephrologist, we planned to extend the ongoing SLED. After another 4 h of extended SLED, blood gas still showed raised potassium values (K^+ = 7.2) with constant pH. For persistent hyperkalemia, SLED was further extended making a total duration of 20 h. Post dialysis, patient still had lab serum K^+ level of 7.6 mEq/L. Next morning, patient developed blisters all over the body. He had coagulopathy and thrombocytopenia (PT/INR increased from 1.21 to 6.8 and platelets dropped down to 33,000 from 1.55 lacs/mm^3), which was thought to be related to sepsis. On admission, patient was started empirically on ceftriaxone but in view of deteriorating clinical condition, he was shifted to meropenem, teicoplanin and ampicillin. It was an emperical selection of broad spectrum antibiotics keeping in mind MRSA and ampicillin for coverage for leptospira, with plans to de-escalate after obtaining culture reports. With deterioration in blood gas showing acidosis and again rise in potassium levels, patient was taken up for SLED again. He was dialyzed for more than 32 h, out of his 40 h hospital stay but his hyperkalemia remained refractory to antihyperkalemic agents and dialysis. Serial blood gases done showed that patient continued to have high anion gap acidosis and hyperkalemia at all times during his hospital stay [Table 2]. This refractory hyperkalemia made us think over its cause. After ruling out all possible causes, it was considered to be related to heparin abuse.

Table 1: Investigations

Day of admission	Day 1	Day 2
Investigations		
Hb (g/dL)	13.2	10.1
TLC (/cu.mm)	2400	12300
Platlets (Lac/cu.mm)	1.55	0.33/0.21
PT/INR	1.21	6.80/4.07/2.54
PTTK	T-90 s, C-27 s	T-67 s, C-27 s
B urea (mg/dL)	101	49
S creatinine (mg/dL)	1.45	1.66
S Na (mEq/L)	136	145
S K (mEq/L)	5.1/6.7/9.1	8.1/7.6/7.2/6.5
S calcium (g/dL)	7.6	8.6
S Mg (mg/L)		2.6
S albumin (g/dL)	1.9	
SGOT/SGPT (U/L)	439/153	
S LDH (U/L)	1609	
S CPK (IU/L)	19, 525	
Troponin I (μg/L)	0.18	
Urine for myoglobins	Negative	

Hb: Hemoglobin; TLC: Total leukocyte count; PT: Prothrombin time; INR: International normalized ratio; PTTK: Partial thromboplastin time activated with Kaolin; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; LDH: Lactate dehydrogenase; CPK: Creatinine phosphokinase

Table 2: Arterial blood gases

ABG	Day 1	Day 2					Day 3	
Hours after admission	0	6	8	14	18	24	30	36
pH	7.437	7.257	7.284	7.312	7.301	7.320	7.154	7.194
pCO_2	24	27.2	31.2	28.1	39.2	34.0	47.0	37.9
pO_2	65	98.6	203	87.6	76.5	71.0	62.8	61.2
K^+	6.1	7.0	7.1	7.1	7.2	5.7	6.3	6.6
Lactate	1.7	7.1	6.4	2.7	13.0	14.9	12.5	13.6
HCO_3	19.2	13.8	15.9	16.1	18.9	18.0	14.8	13.7
BE	−7.4	−14.0	−11.0	−11.2	−6.5	−7.9	−11.3	−12.5

ABG: Arterial blood gas

Following this, fludrocortisone in the dose of 100 μg/day was also added on morning of day 2. Correlating thrombocytopenia and coagulopathy also with heparin, activated clotting time was monitored and protamine sulphate was also given. On the 3rd day morning, patient had an episode of upper gastrointestinal bleed, following which he went into asystole. CPR was done according to protocol but patient could not be revived and was declared dead. Blood cultures obtained after 72 h showed methicilin-resistant staphylococci.

Discussion

Potassium is the most abundant intracellular cation (100-150 mmol/L) and is critical in many physiological functions.[2] Hyperkalemia is a potentially life-threatening condition in which serum potassium exceeds 5.5 mmol/L.[2] Heparin sodium is routinely used in the prophylaxis against deep venous thrombosis in medical and surgical patients.[3] Less commonly known is the surreptitious use of heparin by patients.[4] While most physicians are aware of heparin induced thrombocytopenia

and skin necrosis, the association of heparin and hyperkalemia is less well-recognized.[3] The objective of reporting this case was to highlight the lesser known heparin abuse and association of long-term heparin use with refractory hyperkalemia, which can be fatal.

Our patient was a young polysubstance abuser, probably presented to us with pneumonia and sepsis. Patient was stable at the time of admission but acutely decompensated within few hours and went into severe sepsis. Blood gas which was done after 6 h of admission showed metabolic acidosis with hyperkalemia. This could be attributed to the deteriorating clinical condition of the patient with ongoing sepsis and septic shock. It was observed that in spite of adequate fluid resuscitation, lactic acidosis persisted in our patient. Furthermore, although the patient maintained adequate renal function he continued to have rising potassium levels. On considering the cause of hyperkalemia in our patient, acidosis itself can lead onto rise in potassium levels. However, the blood gas at the time of admission showed hyperkalemia with a normal pH. The renal function parameters were normal at the outset. Subsequently, the patient had gone into metabolic acidosis, probably due to circulatory shock. We had also made a presumptive diagnosis of rhabdomyolysis in the setting of a drug addict presenting with muscle weakness and hyperkalemia. Creatinine phosphokinase (CPK) levels and urine for myoglobin were sent on the day of admission. Although, CPK levels were high in the range of 19,000 units/L, we got a negative report for urine myoglobins. Also, our patient never went into renal shutdown. We could not arrive at the diagnosis of rhabdomyolysis, although even with a proven diagnosis, the treatment modalities, i.e., fluids and hemodialysis would have remained the same.[5] High CPK levels in our patient could be attributed to intramuscular injections, which the patient might have had, myopathy, narcotic addiction, sepsis or myocardial injury.[5] History of Iv drug abuse was conclusive but we also found injection marks over the gluteal and deltoid regions suggestive of intramuscular routes as well..

Long-term heparin abuse in our patient to keep the veins patent might have led to refractory hyperkalemia. Patient had hyperkalemia right from the time of presentation in the emergency room, which was refractory to anti-hyperkalemic treatment including hemodialysis. Protamine was also given in our patient as an antidote to heparin induced coagulopathy but protamine does not have any effect on heparin induced hyperkalemia as suggested by the mechanism of action.[6]

Almost 60 years ago, Donzelot and Kaufman first described the diuretic effect of heparin sodium that is now thought to be the result of decreased aldosterone secretion and a sodium diuresis.[7,8] Since that time, numerous workers have shown that long-term heparin use causes a selective atrophy of the zona glomerulosa of the adrenal cortex and thus, may lead to hypoaldosteronism.[9] Heparin induced hyperkalemia is mediated by an enzymatic block in the synthesis of aldosterone.[10] It has been reported that reduced aldosterone levels may be evident as early as 4th day of initiation of heparin therapy.[1] Although, patients who receive heparin may have reduced aldosterone levels, most are able to compensate through increased renin production. However, patients on prolonged heparin therapy or those unable to adequately increase renin production, e.g. diabetics or with renal insufficiency, may exhibit signs of hypoaldosteronism, such as hyperkalemia.[7,11]

Literature does not recommend any specific treatment modality for heparin induced hyperkalemia. Sherman suggested fludrocortisone as a reasonable alternative therapy for patients with hyperkalemia secondary to heparin therapy.[12] Fludrocortisone has been shown to decrease serum potassium levels in end stage renal disease other than routine therapy.[13,14] Fludrocortisone stimulates the Na^+-K^+ ATPase activity and increase potassium secretion from gastrointestinal tract.[13] Another mechanism suggested has been the intracellular shift of potassium.[13] Several studies have shown potassium lowering effect of fludrocortisone in the dose range of 0.1-0.3 mg/day.[14,15] We also started our patient on fludrocortisone 0.1 mg OD, but could not find any benefit. There might have been some other drug that the patient have been addicted to which could not be elicited on history, since the patient had free access to restricted drugs (pharmacist by profession).

The aim of this case report is to highlight that although heparin abuse is not widely known, there have been rare reports of unwitting heparin abuse in drug addicts, which should always be kept in mind while dealing with refractory hyperkalemia.[4]

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