

มะเฟือง; เหตุแห่งการสะอึกและภาวะเลือดเป็นกรด ในผู้ป่วยโรคไตวายเรื้อรังระยะสุดท้าย

พรชนก ศิริสันติสัมฤทธิ์, ฐปนวงศ์ มิตสูงเนิน, แพรว โคตรจีน และธนัท ทั้งไพศาล*
สาขาเวชศาสตร์ฉุกเฉิน คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

*ผู้ประพันธ์บรรณกิจ

ธนัท ทั้งไพศาล

สาขาวิชาเวชศาสตร์ฉุกเฉิน คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

123 หมู่ 16 ถ.มิตรภาพ ต.ในเมือง อ.เมือง จ.ขอนแก่น 40002

อีเมล: thantan@kku.ac.th

โทรศัพท์ที่ทำงาน: 043-366869

โทรศัพท์มือถือ: 089-6199907


DOI: 10.14456/tjem.2023.9

บทคัดย่อ

ผู้ป่วยชายโรคไตวายเรื้อรังระยะสุดท้าย (end-stage renal disease, ESRD) อายุ 70 ปี มาโรงพยาบาลด้วยอาการสะอึก อาการสะอึกไม่ตอบสนองต่อยามาตรฐานต่าง ๆ ได้แก่ metoclopramide, chlorpromazine, baclofen และ phenytoin

7 ชั่วโมงหลังจากที่ผู้ป่วยมาโรงพยาบาล ผู้ป่วยมีอาการหายใจหอบเหนื่อยมากขึ้นและตรวจพบว่ามีกรดแลคติกในเลือดสูง (lactic acidosis) หลังการพยายามค้นหาสาเหตุอาการสะอึกเพิ่มเติม พบว่า 4 ชั่วโมงก่อนมาโรงพยาบาลผู้ป่วยได้รับประทานมะเฟือง 4 ผล แพทย์พิษวิทยาจึงสันนิษฐานว่ามะเฟืองเป็นสาเหตุให้เกิดอาการสะอึกและภาวะกรดแลคติกในเลือดสูง

คำสำคัญ: มะเฟือง, ไตวายเรื้อรังระยะสุดท้าย, สะอึก



Star Fruits (*Averrhoa carambola*); Persistent Hiccups and Severe Metabolic Acidosis in An End-Stage Renal Disease Patient

Pornchanok Sirisantisamrid, Thapanawong Mitsungrern, Praew Kotruchin and
Thanat Tangpaisarn*
Department of Emergency Medicine, Faculty of Medicine, Khon Kaen University

*corresponding author

Thanat Tangpaisarn, M.D.

Department of Emergency Medicine, Faculty of Medicine, Khon Kaen University
123 Moo 16 Mittraphap Rd., Nai-Muang, Muang District, Khon Kaen 40002, Thailand

Email: thantan@kku.ac.th

Tel: 043-366869

Mobile: 089-6199907

DOI: 10.14456/tjem.2023.9

Abstract

We encountered a man in his 70's with end-stage renal disease (ESRD) who experienced a persistent hiccup. The hiccup was unresponsive to various standard medications, including metoclopramide, chlorpromazine, baclofen, and phenytoin. The patient developed dyspnea due to severe lactic acidosis 7 hours later. After ruling out possible causes of the persistent hiccups and lactic acidosis, a toxicologist discovered that the patient had taken four star fruits 4 hours before the onset of the symptoms.

Key word: Star Fruits, End-Stage Renal Disease Patient, Persistent Hiccups

Introduction

It has long been known that star fruit (*Averrhoa carambola*) causes neurological symptoms ranging from insomnia to hiccups and psychomotor agitation.¹ Death was also reported in chronic kidney disease (CKD) patients due to inappropriate dialysis.¹

Caramboxin, a phenylalanine-like molecule that causes intoxication, was discovered in 2013 by Garcia-Cairasco N et al.² Another active compound found in star fruit is oxalic acid, known to be renal toxic. It has been linked to the previously unknown mechanism of lactic acidosis as.³ In this case report, we would like to present a rare case of an end stage renal disease (ESRD) patient who consumed star fruits, which resulted in persistent hiccups and severe lactic acidosis, causing him to be hospitalized for 17 days.

Case presentation

We encountered a man in his 70s with known ESRD. His last hemodialysis (HD) session was two days prior to his arrival. His baseline blood urea nitrogen (BUN) after HD session was 28.2 mg/dL. He usually restricted his oral fluid intake (600 milliliters/day). He also had hypertension, type 2 diabetes mellitus, dyslipidemia, benign prostatic hyperplasia, and gout. His current medication includes allopurinol, clopidogrel, atorvastatin, ferrous fumarate,

folic acid, sodium bicarbonate, simethicone, a supplement of amino acids (Amiyu granule), omeprazole, and gemigliptin.

He came to our emergency department (ED) with persistent hiccups, which continued for 4 hours. He also had an episode of vomiting, but no diarrhea, no fever, and no other abnormal symptoms. At the ED, we sequentially treated the hiccups by administering; 1) Metoclopramide 10 mg intravenously (IV), 2) Baclofen (10) 1 tab per oral (PO), 3) Ondansetron 8 mg IV, 4) Chlorpromazine (25) 1 tab PO, 5) Diazepam 2.5 mg IV, 6) Sugar 1 tablespoon PO, 6) Retain nasogastric tube, 7) Carotid massage, and 8) Phenytoin 1000 mg IV in 30 minutes. (Table 1)

Despite various managements, the hiccup had been persisted, and 3 hours after the phenytoin administration, the patient developed dyspnea. He breathed deeply and rapidly. His respiratory rate was 32 times per minute. The pulse oximetry was 100%.

Investigation

His complete blood count revealed leukocytosis, with white blood cell counts of 18,080 cells/mm³ (Neutrophil, 87.5%; Lymphocyte, 7.1%). Point of care arterial blood gas (ABG) analysis on room air revealed a pH of 7.13; PaCO₂, 36 mmHg; PaO₂, 60 mmHg; HCO₃, 12 mmol/L; Glucose,

Table 1 Timelines of the event and initial treatment

Time	Drugs and Dosage
4.00 pm.	Take 4 star fruits
8.00 pm.	Hiccup starts
1.05 am.	Metoclopramide 5 mg IV
1.45 am.	Omeprazole 40 mg IV
2.15 am.	Baclofen 10 mg PO
3.25 am.	Chlorpromazine (25) 1 tab PO
4.00 am.	Ondansetron 8 mg IV
7.15 am.	Diazepam 2.5 mg IV
7.30 am.	Sugar 1 tablespoon PO
7.45 am.	Retain nasogastric tube
8.00 am.	Carotid massage
8.15 am.	Phenytoin 1000 mg + 0.9%NaCl 100 ml IV in 30 minutes
11.00 am.	Patient developed dyspnea with metabolic acidosis

178 mg/dL; and lactate level of 127.7 mg/dL. Blood urea nitrogen (BUN), 36.5 mg/dL; creatinine, 7.53 mg/dL; Na, 142 mEq/L; K, 5.1 mEq/L; HCO_3^- , 11 mEq/L Cl, 94.0 mEq/L. His chest X-ray was unremarkable, and the abdomen film revealed no signs of bowel obstruction. His initial electrocardiogram revealed a normal sinus rhythm with a rate of 93 beats per minute, a normal axis, and no sign of cardiac ischemia.

Treatment

After seeing the ABG results, we intubated the patient for ventilatory support (ventilator setting was pressure control ventilation mode, inspiration pressure 16 cmH_2O , PEEP 5 cmH_2O , FiO_2 0.4, respiratory rate 16 breaths per minute, inspiratory time 1.2 seconds). However, the patient developed even more dyspnea. Emergency physicians tried to differentiate the causes of the wide anion-gap metabolic acidosis. However, there were no explainable causes, e.g., infection, history of drug or alcohol overdose, severe hypoxemia, severe anemia, or hypotension/shock. In the absence of a specific cause of lactic acidosis, we sought advice from a toxicologist to determine whether the multiple drugs we had administered could be a cause of lactic acidosis. The toxicologist eventually discovered that the patient had been taking 4 star fruits (Figure 1) 4 hours before the onset of the symptoms. Therefore, toxins from star fruits were the most likely cause of both persistent hiccups (caramboxin) and lactic acidosis (oxalate).

Outcome and follow-up

The patient was admitted to the intensive care unit (ICU) and was treated with continuous renal replacement therapy (CRRT) for eliminating caramboxin and



Figure 1 Star fruits

oxalate,^{4,5} and for lactic clearance.^{6,7} The patient's lactic acidosis was resolved within the first 24 hours after CRRT. However, the hiccups were over 48 hours later. Overall, the CRRT was continued for 72 hours. The laboratory trends are shown (Table 2). However, following the intubation, he developed ventilator-associated pneumonia four days later. Unfortunately, he had difficulty weaning from the ventilator due to a lack of coughing effort and excessive secretions. He was admitted to the hospital

Table 2 Comparison of laboratory parameters at baseline vs. when the patient was having worsening dyspnea and when the patient was recovered from hiccups and lactic acidosis

Lab	Baseline (at ED) 1.00 am.	Clinical worsening 11.00 am.	After CRRT (72 hours later)
BS (mg/dL)	158	273	198
BUN (mg/dL)	30.2	36.5	51.2
Creatinine (mg/dL)	7.03	7.53	3.77
Bicarbonate (mEq/L)	23.1	11.0	23.3
Serum ketone (mmol/L)	-	0.37	-
Anion gap (mEq/L)	23	37	14.7
Measured serum osmole (mmol/L)	-	318	-
Calculated serum osmole (mmol/L)	$2(140) + 30.2/2.8 + 158/18 = 300$	$2(142) + 36.5/2.8 + 273/18 = 312$	$2(139) + 51.2/2.8 + 198/18 = 307$
Osmolar gap (mmol/L)	NA	6	NA
Lactate (mg/dL)	-	127.7	15.1

for a total of 17 days before being discharged home safely. Health education on foods and nutrition was intensively given to him and his caregiver.

Discussion

This was a report of a 74-year-old man with ESRD who experienced persistent hiccups after taking 4 star fruits. During his ED treatment, he became dyspnea due to severe lactic acidosis.

Several cases of star fruit ingestion from prior literature addressed its neurotoxin and nephrotoxin.⁸ The two main substances that cause the symptoms are caramboxin and oxalate. Caramboxin is a nonpeptide amino acid, phenylalanine-like molecule that affects the GABAergic system through a glutamatergic ionotropic molecular action.⁹ It is usually cleared via renal excretion. Therefore, patients with renal failure may develop seizures, hiccups, confusion, coma, and even death due to inadequate clearance of the toxin.¹⁰

Star fruit is also a source of high-level oxalate, explaining the gastrointestinal symptoms that patients usually complain about. The described mechanism was a direct corrosive injury of oxalate, which was accumulated in the digestive tracts. Furthermore, a nephropathy caused by oxalate occurs a few hours later.¹¹ The mechanism by which tubular damage

occurs, is the obstruction of renal tubules by crystals of oxalate, as well as an apoptosis of renal tubular epithelial cells.¹²

In this case report, not only did the patient have neurotoxic symptoms, but they also presented with severe lactic acidosis. Lactic acidosis was reported in a case of oxalic acid ingestion.³ Thus, it may cause lactic acidosis in our patient.³ Even though the patient had a prior regular hemodialysis session, after the star fruit ingestion, he became unwell and did not go for the hemodialysis. However, without a clear pathophysiology of lactic acidosis from star fruits, the other possible cause was propylene glycol toxicity. Since it was the solvent of phenytoin that was given to the patient to treat his persistent hiccups. There was a case report which showed that even a regular dose of phenytoin can cause lactic acidosis in a patient with ESRD.¹³ However, the onset of severe lactic acidosis in our patient was quite early compared with the other case report of lactic acidosis from propylene glycol, which was 12-24 hours after the infusion.^{14,15}

In conclusion, persistent hiccups in this patient were caused by a neurotoxin in star fruits; however, for lactic acidosis, differential causes might be either star fruits (oxalate) or propylene glycol, a solvent of phenytoin. Physicians should keep in mind that when treating a patient who has star

fruit toxicity, any drugs with propylene glycol should be avoided if possible.

Learning point/Take home message

- Star fruit should be strictly avoided in CKD patients.
- Star fruit can cause severe neurotoxicity and nephrotoxicity in CKD patients.
- Star fruit may cause severe lactic acidosis in CKD patients.

Reference

1. Neto MM, da Costa JAC, Garcia-Cairasco N, Netto JC, Nakagawa B, Dantas M. Intoxication by star fruit (*Averrhoa carambola*) in 32 uraemic patients: treatment and outcome. *Nephrol Dial Transplant*. 2003;18(1):120-125. doi:10.1093/ndt/18.1.120
2. Garcia-Cairasco N, Moyses-Neto M, Del Vecchio F, et al. Elucidating the Neurotoxicity of the Star Fruit. *Angewandte Chemie International Edition*. 2013;52(49):13067-13070. doi:10.1002/anie.201305382
3. Yamamoto R, Morita S, Aoki H, Nakagawa Y, Yamamoto I, Inokuchi S. Acute renal failure and metabolic acidosis due to oxalic acid intoxication: a case report. *Tokai J Exp Clin Med*. 2011;36(4):116-119.
4. Wijayaratne DR, Bavanthan V, de Silva MVC, Nazar ALM, Wijewickrama ES. Star fruit nephrotoxicity: a case series and literature review. *BMC Nephrol*. 2018;19(1):288. doi:10.1186/s12882-018-1084-1
5. Chua CB, Sun CK, Tsui HW, et al. Association of renal function and symptoms with mortality in star fruit (*Averrhoa carambola*) intoxication. *Clin Toxicol (Phila)*. 2017;55(7):624-628. doi:10.1080/15563650.2017.1314490
6. Cheungpasitporn W, Zand L, Dillon JJ, Qian Q, Leung N. Lactate clearance and metabolic aspects of continuous high-volume hemofiltration. *Clin Kidney J*. 2015;8(4):374-377. doi:10.1093/ckj/sfv045
7. Cruz MD, Ershad M, Mostafa A. Metabolic Acidosis and Hyperlactatemia Requiring Continuous Venovenous Hemofiltration after Intentional Ingestion of Metformin. *Indian J Nephrol*. 2021;31(1):77-78. doi:10.4103/ijn.IJN_117_19
8. Aranguren C, Vergara C, Rosselli D. Toxicity of star fruit (*Averrhoa carambola*) in renal patients: A systematic review of the literature. *Saudi J Kidney Dis Transpl*. 2017;28(4):709-715.
9. Fernandez-Prado R, Esteras R, Perez-Gomez MV, et al. Nutrients Turned into Toxins: Microbiota Modulation of Nutrient Properties in Chronic Kidney Disease. *Nutrients*. 2017;9(5):E489. doi:10.3390/nu9050489
10. Stumpf MAM, Schuinski AFM, Baroni G, Ramthun M. Acute Kidney Injury with Neurological Features: Beware of the Star Fruit and its Caramboxin. *Indian J Nephrol*. 2020;30(1):42-46. doi:10.4103/ijn.IJN_53_19
11. Barman AK, Goel R, Sharma M, Mahanta PJ. Acute kidney injury associated with ingestion of star fruit: Acute oxalate nephropathy. *Indian J Nephrol*. 2016;26(6):446-448. doi:10.4103/0971-4065.175978
12. Jonassen JA, Cao LC, Honeyman T, Scheid CR. Mechanisms mediating oxalate-induced alterations in renal cell functions. *Crit Rev*

- Eukaryot Gene Expr. 2003;13(1):55-72.
doi:10.1615/critreveukaryotgeneexpr.v13.i1.50
13. Pillai U, Hothi JC, Bhat ZY. Severe propylene glycol toxicity secondary to use of anti-epileptics. Am J Ther. 2014;21(4):e106-109. doi:10.1097/MJT.0b013e31824c407d
 14. Miller MA, Forni A, Yogaratnam D. Propylene glycol-induced lactic acidosis in a patient receiving continuous infusion pentobarbital. Ann Pharmacother. 2008;42(10):1502-1506. doi:10.1345/aph.1L186
 15. Golden TR, Solnick V, Wadea R, Ghazala S. Pentobarbital-induced lactic acidosis following status epilepticus barbiturate coma. BMJ Case Rep. 2018;2018:bcr-2017-223482. doi:10.1136/bcr-2017-223482