SEVERE ELECTROLYTE DISORDERS AFTER OVERDOSING OF FUROSEMIDE, SPIRONOLACTONE AND CAPTOPRIL IN INFANTS WITH CONGENITAL HEART DEFECTS: A CASE SERIES

Dang Thi Hai Van[1,2] and Bui Thi Khanh Ngoc[2,✉]

[1]Ha Noi Medical University
[2]Vietnam National Children's Hospital.

Six cases of severe electrolyte disorders with acute kidney failure after overdosing on furosemide, spironolactone and captopril were reported. All of them were less than six months of age with congenital heart defects and were treated by cardiologists with a dosage of less than 2mg/kg of furosemide, spironolactone, and captopril per day. However, their parents gave them the wrong dose, as a result, all children received higher doses of both furosemide (8.8 – 13.3mg/kg/day), spironolactone and captopril (5.5 – 8.3mg/kg/day). This led to severe hyponatremia, hyperkalemia, and acute kidney injury. All six patients were treated and eventually recovered without any complication.

Keywords: Acute kidney injury, congenital heart defects, furosemide, spironolactone, captopril, hyperkalemia, hyponatremia.

I. INTRODUCTION

Congenital heart defects are common congenital defects and they are major causes of death in those with congenital malformation.[1,2] Heart failure is a common complication thus all medical treatment should aim for pre-operative and post-operative patient stabilization, improvement of symptoms, as well as slowing progression to heart failure.

Angiotensin converting enzyme inhibitors, such as captopril, and diuretics, such as furosemide and spironolactone, are the two drug groups that are widely used to treat heart failure in adult and children.[3,4] However, the most common side effect of all three drugs is electrolyte disturbance: furosemide may cause hyponatremia and hypokalemia, while spironolactone and captopril may cause hyperkalemia. Studies on adults show that furosemide and spironolactone are generally safe and may cause only mild serum sodium and potassium disturbances, but there are reported cases of moderate and severe disturbances.[5–8]

There is a lack of evidence for the maximum dose of furosemide, spironolactone, and captopril on pediatric patients. Most guidelines recommend 1 – 6 mg/kg/day as a safe dose for furosemide and spironolactone.[9–12]comprehensive, authoritative and, updated survey on the metabolism, pharmacokinetics, pharmacodynamics and side-effects of furosemide in neonates. The bibliographic search was performed using PubMed and EMBASE databases as search engines; January 2013 was the cutoff point. Furosemide half-life (t1/2 Captopril is approved for used in children at the 17th Expert Committee on the Selection and Use of Essential Medicines on March 2009, with a maximum dose for term infant of 2mg/kg/day, 4mg/kg/day for 1-month-old to 1-year-old children, 6mg/kg/day for 1-year-old to 12-year-

Corresponding author: Bui Thi Khanh Ngoc
Hanoi Medical University
Email: khanhngochmu@gmail.com
Received: 06/09/2022
Accepted: 04/10/2022

old children.[13] These drugs are recommended to be used in low dosage, under close observation and their dosage should be gradually increased until reaching therapeutic effect.

We report six cases with congenital heart defects who were treated with furosemide, spironolactone, and captopril at home, however, because of overdosing, and all patients were admitted with severe sodium and potassium disturbances, as well as acute kidney failure.

II. CASE SERIES

All six reported patients, including both males and females, aged 1 to 4 months, were diagnosed with congenital heart defects at Cardiology Center, National Children's Hospital. They were monitored and managed by pediatric cardiologists with furosemide, spironolactone, and captopril at home at safe dosage (0.8 – 1.8mg/kg/day for furosemide, 1 – 2mg/kg/day for spironolactone and 1 – 2 mg/kg/day for captopril). However, it was discovered that their parents had accidentally given them much higher doses compared to their prescription: furosemide (8.8-13.3mg/kg/day); spironolactone and captopril (5.5-8.3 mg/kg/day) in the previous 8 to 20 days. It was unable to determine the exact onset time of electrolyte disturbances, since at admission most patients were in moderate to severe condition. Detailed patient information and drug dosage is presented in Table 1.

Table 1. Case description and summary

Age	Sex	CHD	Actual Dose			Symptoms		Na	K	Bun/ Cre	eCCL
			Las	Ald	Cap						
2	M	VSD	11	6.9	6.9	Vomiting	Dehydration Fatigue Oliguria	121	6.8	24.8	15.8
4	F	ALCAPA	8.8	5.5	5.5			130.8	7.5	38.9	9.2
1	F	PDA	12	7.5	7.5	Confusion		118	6.1	24.3	4.5
2	F	VSD	13.3	8.3	8.3	Vomiting		121	6.8	41.4	15.8
3	F	VSD/CoA	13.3	8.3	8.3	Hypovole-mic shock		125	8.3	35.3	7
2	M	VSD	13.3	8.3	8.3	Vomiting		120	7	39.1	19.4

Age, month; M, male; F, femle; CHD, congenital heart defect; VSD, ventricular septal defect; ALCAPA, the anomalous origin of the left corronary artery from the pulmonary artery; DPA, patent ductus arteriosus; CoA, aortic coarctation; Las, lasix(mg/kg/day); Ald, spironolactone(mg/kg/day); Cap, captopril(mg/kg/day); Na, serum sodium concentration(mEq/l); K, serum potassium concentration(mg/kg/day); eCCl, estimated creatine clearance(ml/1.73m^2/min); Bun/cre, blood urea nitrogen/creatinin serum

All six patients were admitted for neurological symptoms: agitation, confusion and three patients had vomiting. At admission, it was noted that all had dehydration, oliguria and tachycardia (125 – 170 bpm). However, 12-lead ECG was not performed for all six patients due to their inability to coordinate with the medical staff and the urgency of the situation. One patient had severe dehydration (hypovolemic shock and severe neurological disturbance), requiring invasive ventilation. Six

patients had moderate to severe hyponatremia (118 - 130.8 mEg/l), hyperkalemia (6.1 -8.3 mEq/l), and pre-renal acute kidney injury with a glomerular filtration rate of 4.5-19.4 ml/1.73m^2/min (calculated using Schwartz's formula) and a serum BUN/Creatinin ratio of 24.8 - 41.1

Especially, the fifth patient**,** a 3-month-old female patient was managed at home with 1mg/kg/day of furosemide and spironolactone, and 2mg/kg/day of captopril daily. Her family gave her 13.3 mg/kg/day of furosemide and 8.3mg/kg/day of spironolactone and captopril. After 10 days, she was lethargic, unresponsive, vomitous, and oliguric. She was admitted with hypovolemic shock, acute kidney failure, altered consciousness with moderate hyponatremia (125 mEq/l), severe hyperkalemia (8.2 mEq/l), and an eGFR of 7 ml/1.73m^2/min. She was intubated and given a bolus injection of NaCl 0.9%, after that IV 0.2 mcg/kg/minute of adrenaline infusion. At National Children Hospital, she was treated with ventilation, rehydration therapy and continuous veno-venous hemofiltration because of serious hyperkalemia. After 12 hours, her blood potassium and sodium returned to normal. After 2 days, her kidney function and urine recovered, and hemofiltration was ceased. The remaining five patients were treated with saline infusion for rehydration, NaCl 3% infusion for hyponatremia, sodium bicarbonate 4.2%; calcium gluconate 3%; and aerosolized salbutamol for hyperkalemia. Diuretics and captopril were ceased at admission. Fortunately, all six patients recovered, with kidney function and electrolytes level stabilized and without complication.

III. DISCUSSION

Furosemide is a diuretic affecting the ascending limb of the loop of Henle, particularly on the Na-K-2Cl cotransporter, which reduces sodium and potassium re-uptake, causing diuretic effects and lower serum potassium and sodium concentration.[9] On the other hand, aldosterone affects the distal convoluted tubule, acting as an antagonist of intracellular receptor of spironolactone, reducing the synthesis of Na-K-ATPase, thus reducing sodium re-uptake and potassium secretion, reducing blood sodium concentration and increasing potassium concentration.[12] Captopril is an angiotensin converting enzyme inhibitor, which affects the renin-angiotensin-aldosterone system, reduces the synthesis of Na-K-ATP channel at the distal convoluted tubule, thus reducing serum sodium concentration and increasing potassium concentration. At therapeutic doses, furosemide and spironolactone are shown to cause mild dysnatremia and dyskalemia.[6–8,14] Clinical guidelines also emphasize on the possible risk of hyperkalemia when combining spironolactone and captopril, and recommend closer monitoring of serum electrolyte for this combination.[15]

In this case series, all patients were treated with furosemide, spironolactone and captopril at home, with a dose of less than 2mg/kg/day. However, all their parents failed to follow the prescription, as the result all of them overdosed, leading to severe dysnatremia, dyskalemia and acute kidney failure. All 6 cases manifested with these following clinical symptoms: agitation, vomiting, oliguria and dehydration. Laboratory tests revealed a moderate to severe hyponatremia (blood sodium level 113 – 130.8 mEq/L); mild to severe hyperkalemia (blood potassium level 6.1 – 8.3 mEq/L) and acute kidney failure, with eGFR of 4.5 to 19ml/1.73m2/min because of dehydration. It was noted that all patients were admitted with dehydration due to oliguria and vomiting, followed by neurological symptoms: agitation and vomiting might be the signs of hyponatremia. Thorough

history-taking, especially for medication history, is crucial to avoid missing this cause and derailing the treatment course. This case report is limited by the lack of confirmatory serum level of furosemide, spironolactone and captopril. However, given their history, in conjunction with the appropriately matched clinical symptoms, is convincing in identifying furosemide, spironolactone and captopril as the causes of the condition.

The cause of hyponatremia in these 6 cases are furosemide and spironolactone overdose. In theory, furosemide causes hypokalemia, however, in all 6 cases it caused hyperkalemia. This is because of the potassium-retentive property of spironolactone and captopril. Furthermore, polyuria and vomiting may cause dehydration and acute kidney failure, reducing eGFR and subsequently, hyperkalemia. As a result, all 6 patients were dehydrated and oligouric with a severe decreased eGFR but recovered quickly after rehydration.

Regrettably, the reason for overdosing in all 6 cases was due to the misread of their parents when following the prescription, thus all patients were admitted late, after 8 to 20 days of overdosing, with clinically marked dyskalemia and dysnatremia. The cause for overdosing in Vietnam is due to two reasons. First, in Vietnam, the minimum dosage on the market for furosemide, captopril and spironolactone are 40mg/tablet, 25mg/tablet and 25mg/tablet, respectively. As the tablets are stored and diluted at home by the parents, it is difficult to divide these tablets correctly, especially in low weight children. Moreover, since some parents were from rural areas, they were unable to follow the doctor instruction correctly, thus causing these mistakes. In all six cases, despite of the clear instructions of the pediatricians, the parents unintentionally made mistakes and gave the patients the full tablets multiple times a day.

IV. CONCLUSION

Furosemide, spironolactone and captopril are used widely to manage heart failure for outpatients. However, their usage at home can be dangerous because the caretakers are unaware of the danger of overdosing, they may not read the instruction carefully or they may not understand how to use the drugs. From these cases, it is important to notice side effects of these drugs, as well as to properly instruct the parents in an easy-to-understand manner. It is recommended for cardiologist to provide training for the parents in preparing the solution, especially in lower weight children, to prevent unnecessary mistakes in the future. Furthermore, clinicians should follow up for patient compliance to discover and adjust mistakes, especially for those with severe adverse effect if being used incorrectly.

ARTICLE INFORMATION

Disclosure. There is no conflict of interest to disclose. The authors had complete access to the patient information in the article. The authors take full responsibility for the accuracy of the article.

Ethics. Given the nature of this study, no review board or ethics committee were required in our institution.

Acknowledgement. Pediatric Cardiology physicians, nurses and pharmacologist at Center of Pediatric Cardiology, National Children Hospital, Hanoi, Vietnam for their assistance.

REFERENCES

1. Wren C, Irving CA, Griffiths JA, et al. Mortality in infants with cardiovascular

malformations. *Eur J Pediatr*. 2012; 171(2): 281-287. doi:10.1007/s00431-011-1525-3.

2. Wik G, Jortveit J, Sitras V, Døhlen G, Rønnestad AE, Holmstrøm H. Severe congenital heart defects: incidence, causes and time trends of preoperative mortality in Norway. *Arch Dis Child*. 2020; 105(8): 738-743. doi:10.1136/archdischild-2019-317581

3. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022; 145(18): e895-e1032. doi:10.1161/CIR.0000000000001063.

4. Kirk R, Dipchand AI, Rosenthal DN, et al. The International Society for Heart and Lung Transplantation Guidelines for the management of pediatric heart failure: Executive summary. *J Heart Lung Transplant*. 2014; 33(9): 888-909. doi:10.1016/j.healun.2014.06.002.

5. Arampatzis S, Funk GC, Leichtle AB, et al. Impact of diuretic therapy-associated electrolyte disorders present on admission to the emergency department: a cross-sectional analysis. *BMC Med*. 2013; 11: 83. doi:10.1186/1741-7015-11-83.

6. Dolovich L, Gavura S, Pottie K. Hyperkalemia associated with spironolactone therapy. *Can Fam Physician*. 2005;51(3):357-360. Accessed September 29, 2022. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1472969/

7. Sonnenblick M, Friedlander Y, Rosin AJ. Diuretic-induced Severe Hyponatremia: Review and Analysis of 129 Reported Patients. *CHEST*. 1993; 103(2): 601-606. doi:10.1378/chest.103.2.601.

8. Knochel JP. Diuretic-induced hypokalemia. *Am J Med*. 1984; 77(5): 18-27. doi:10.1016/S0002-9343(84)80004-2.

9. Pacifici GM. Clinical Pharmacology of Furosemide in Neonates: A Review. *Pharmaceuticals*. 2013; 6(9): 1094-1129. doi:10.3390/ph6091094.

10. Wimmer M, Bachl G, Schlemmer M, Stiskal A. [Experiences with aldactone in pediatric cardiology (author's transl)]. *Padiatr Padol*. 1979; 14(4): 363-372.

11. Buck ML. Clinical Experience with Spironolactone in Pediatrics. *Ann Pharmacother*. 2005; 39(5): 823-828. doi:10.1345/aph.1E618.

12. Ellison DH. Clinical Pharmacology in Diuretic Use | American Society of Nephrology. *Nephropharmacology Clin*. 2019; 14: 1248-1257. doi:10.2215/CJN.09630818.

13. Momma K. ACE Inhibitors in Pediatric Patients with Heart Failure. *Pediatr Drugs*. 2006; 8(1): 55-69. doi:10.2165/00148581-200608010-00005.

14. Ogawa K, Kawachi F, Mori T, Hishitani T, Hoshino K. Electrolyte Imbalance Caused by Diuretic Therapy in Infants with Congenital Heart Diseases. *Pediatr Ther*. 2017; 07(01). doi:10.4172/2161-0665.1000313.

15. Spironolactone and renin-angiotensin system drugs in heart failure: risk of potentially fatal hyperkalaemia-February 2016 article. GOV.UK. Accessed September 29, 2022. https://www.gov.uk/drug-safety-update/spironolactone-and-renin-angiotensin-system-drugs-in-heart-failure-risk-of-potentially-fatal-hyperkalaemia.