Adjunctive acetazolamide therapy for treatment of Bartter syndrome

MOJGAN MAZAHERI.MD

Pediatric Nephrologist

Semnan University of Medical Science

Background

- Bartter syndrome is a rare hereditary salt-loosing tubulopathy caused by mutations of several genes encoding the Na-K-Cl co-transport in the TAL of Henle
- Increased Na delivery to the collecting duct increases Na and H excretion and increased prostaglandin release and RAAS activation

- Bartter FC, et al. Am J Med 1962; 33:811-28
- Cunha TDS, et al. Int J Nephrol Renovasc Dis. 2018;11:291-301
- Komhoff M, et al. Curr Opin Nephrol Hypertens. 2017;419-25

Background (cont'd)

- The disease is characterized by polyuria, hypokalemic metabolic alkalosis, growth retardation, and normal BP
- NSAIDs, ACE-inhibitors, and K-sparing diuretics along with water, Na and K supplement are currently used to treat electrolytes derangement, but with poor response and overwhelming side effects

- Gasongo G et al. Pediatr Nephrol 2019;34:679-84
- Reinalter SC, et al.Kidney Int. 2002;62:253-60
- Nascimento CLP, etal. J Pediatr. 2014;90:512-7
- White WB, et al. Am J Cardiol. 2007:;99:91-8

Objective

- Acetazolamide (AZM), a carbonic anhydrase inhibitor, is generally safe and effective agent in reducing serum bicarbonate level
- We hypothesized AZM in combination with standard therapy (NSAIDs, ACE-inhibitors, and K-sparing diuretics) may be more effective in treatment in comparison with the use of standard therapy alone in children with Bartter syndrome

METHODS

- This is a multicenter, randomized open label, crossover trial conducted at 3 academic medical centers between June 2018 and July 2019
- Enrolled patients had Bartter syndrome
- The diagnosis of Bartter syndrome was based on the clinical and laboratory manifestations including hypokalemia, metabolic alkalosis, normal BP, polyuria, polydipsia, FTT, elevated PRA, serum aldosterone level, high urinary Na^+, K^+ and CL^- excretion despite low serum levels

Methods (Cont'd)

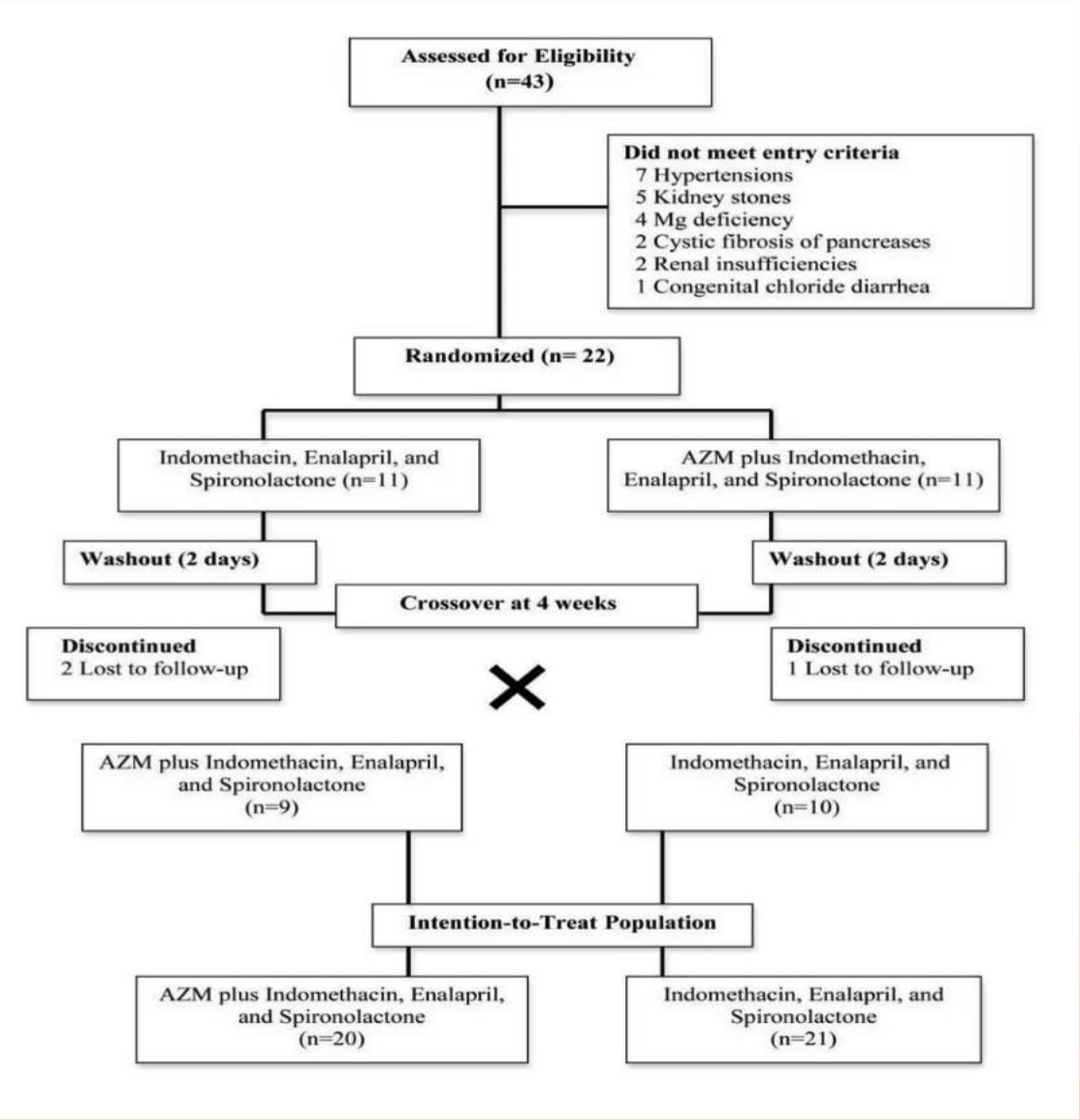
- The clinical diagnosis of Bartter syndrome was confirmed by genetic analysis
- Participant were excluded if had history of CFP, vomiting, diarrhea, hypertension, kidney stone, renal insufficiency, liver disease, diuretics, laxative or licorice use during the last three months, or had history of hypersensitivity to sulfonamide drugs .

Methods (Cont'd)

- Patients previous medications were stopped 24-hour before starting the trial
- Patients were allowed to have free access to water and salt intake during the study

Methods (cont'd)

- The study consisted of two intervention periods of 4 weeks separated by a washout period of 2 days
- Patients were randomized in a 1:1 ratio to either receive standard (SD) treatment (indomethacin 2 mg/kg, enalepril 0.1 mg/kg, and spironolactone 1 mg/kg) or SD treatment plus AZM 5 mg/kg (SD/AZM) once daily for 4 weeks
- After 2 days washout, patients crossed over to receive the alternative intervention for 4 weeks


Assessed for Eligibility
(n=43)
Did not meet entry criteria
7 Hypertensions
5 Kidney stones
4 Mg deficiency
2 Cystic fibrosis of pancreases
2 Renal insufficiencies
1 Congenital chloride diarrhea
Randomized (n= 22)
Indomethacin, Enalapril, and Spironolactone (n=11)
AZM plus Indomethacin, Enalapril, and Spironolactone (n=11)
Washout (2 days)
Washout (2 days)
Crossover at 4 weeks
Discontinued
2 Lost to follow-up
Discontinued
1 Lost to follow-up
AZM plus Indomethacin, Enalapril, and Spironolactone
(n=9)
Indomethacin, Enalapril, and Spironolactone
(n=10)
Intention-to-Treat Population
AZM plus Indomethacin, Enalapril, and Spironolactone
(n=20)
Indomethacin, Enalapril, and Spironolactone
(n=21)

Objectives

- The study primary endpoint was a decrease in median serum bicarbonate level after 4 weeks
- The secondary endpoint was response rate, defined as achieving mean serum $HCO3^-$ level<26 mEq/L at 4 weeks

- Preisig PA, et al. Renal Physiol. 1987;10:136-59

Results:

- Of the 43 patients screened for eligibility, 22 (47%), between the ages 3 weeks and 6 years, were randomized to intervention.
- Baseline characteristics were similar between the two groups.
- Addition of AZM for a period of 4 weeks significantly reduced serum bicarbonate and increased serum potassium levels, parallel with a reduction in serum aldosterone and plasma renin concentration
- The 24-h urine volume, Na^+, K^+, and Cl^- decreased significantly

Table 1. Baseline demographic characteristics of all study participants¶

Characteristic	All Study Participants (n=22)
Age at treatment initiation (months)	24 [6-42]
Weight (Kg)§	9 [2.8-15.1]
Gender, Male/Female (%)	9/13 (41/59)
Prior medications*, n (%)	
NSAIDs	22 (100)
ACE-inhibitor	10 (45)
K^+-sparing diuretics	18 (82)
KCL supplements	22 (100)
Blood pressure (mmHg)	
Systolic	89 [73-105]
Diastolic	53 [41-66]
eGFR (ml/min/1.73m^2)	95 [91-99]
Serum electrolytes (mmol/L)	
Sodium	131 [126-137]
Potassium	3.0 [2.4-3.6]
Chloride	85 [74-95]
Bicarbonate	35 [31-38]
Urine electrolytes (mmol/L)	
Sodium	75 [58-92]
Potassium	52 [38-67]
Chloride	68 [49-88]
Ca/Cr ratio (mg/mmol)	2.0 [1.7-2.3]
Plasma active renin (µU/mL)	298 [192-405]
Serum aldosterone (pg/mL)	324 [226-422]
Genetic defect	
SLC12A1	4
KCNJ1	3
CLCNKB	13
CLCNKA-CLCNKB	2
Family history of consanguinity, n (%	16/22 (73)

¶Values are median (range); §weight below the 3rd percentile; * Participants were on various combination of medications. eGFR, estimated glomerular filtration rate; Ca/Cr, calcium/creatinine ratio.

Table 2. Changes from baseline between the two treatment groups at 4 weeks

Variable	Indomethacin, Enalapril, and Spirinolactone (n=21)	AZM plus Indomethacin, Enalapril, and Spirionlactone (n=20)	***P* Value**
eGFR (mL/min/1.73 m^2)			
Baseline	94 [91; 96]	95 [93; 96]	
Change at 4 weeks	-3 [-1; -5]	-4 [-2; -6]	0.11
Serum Sodium (mmol/L)			
Baseline	130 [128; 132]	133 [127; 137]	
Change at 4 weeks	0.5 [0.2; 0.8]	-0.4 [-0.2; -0.06]	0.06
Serum Potassium (mmol/L)			
Baseline	2.8 [2.5; 3.0]	3.0 [2.6; 3.4]	
Changes at 4 weeks	**0.2 [0.1; 0.3]**	**0.8 [0.3; 1.2]**	**0.03**
Serum Chloride (mmol/L)			
Baseline	85 [76; 94]	86 [79; 93]	
Change at 4 weeks	**6 [4; 7]**	**9 [3; 15]**	**0.04**
Serum Bicarbonate (mmol/L)			
Baseline	35 [32; 37]	35 [31-38]	
Change at 4 weeks	**-2 [-1; -5]**	**-11 [-5; -12]**	**0.01**
Urine output/day (mL)			
Baseline	1184 (459; 1910)	1147 (412; 1882)	
Change at 4 weeks	**-436 (-312: -561)**	**-532 (-246; -819)**	**0.02**
Urine Sodium (mmol/L)			
Baseline	75 [59; 91]	78 [61; 95]	
Change at 4 weeks	**2.8 [1.5; 4.2]**	**3.6 [2.8; 4.5]**	**0.07**
Urine Potassium (mmol/L)			
Baseline	53 [41; 66]	57 [51; 64]	
Change at 4 weeks	**-3 [-2; -5]**	**-5 [-2; -9]**	**0.05**
Urine chloride (mmol/L)			
Baseline	71 [56; 85]	71 [54; 87]	
Change at 4 weeks	**-11 [-6; -17]**	**-20 [-11; -29]**	**0.04**
Urine Ca/Cr ratio (mg/mmol)			
Baseline	2.0 [1.8; 2.3]	2.1 [1.9; 2.3]	
Change at 4 weeks	**-0.6 [-0.5; -0.8]**	**-1.3 [-1.2; -1.4]**	**0.04**
Plasma active renin (mlU/L)			
Baseline	314 [197; 432]	313 [213; 413]	
Change at 4 weeks	**-112 [-41; -182]**	**-204 [-86; -254]**	**0.03**
Serum aldosterone (pg/mL)			
Baseline	326 [238; 415]	332 [217; 448]	
Change at 4 weeks	**-203 [-96; -201]**	**-151 [-114; -187]**	**0.04**

Table 3. All partic4pants with adverse events during the 4 weeks on both intervention¶

Adverse Event	SD Therapy (n=21)	SD/AZM Therapy (n=20)
Hypotension	1	1
Gastrointestinal disorders		
Nausea	7	9
Vomiting	2	2
Diarrhea	3	1
Nervous system disorders		
Headache	5	6
Dizziness	8	6

¶All participant could have experienced the same adverse events m ore than once during 4 weeks monitoring.

Conclusions

- AZM significantly enhances the renal response to indomethacin, enalapril, and spironolactone in children with BS
- The study suggests AZM may be considered as an adjunctive agent for the treatment of Bartter syndrome
- The long term efficacy and safety of AZM therapy requires further well-defined controlled trial to determine the reproducibility of the benefits associated with AZM in BS

Collaborative investigators

- Farahnak Assadi, M.D.Distinguished Professor, Emeritus, Pediatric Nephrology division ,Rush University,The designer & leader of study
- Mojgan Mazaheri,M.D., Semnan University of Medical Science
- Simin Sadeghi-Bojd,M.D., Zahedan University of Medical Sciences