Title: Treatment of paediatric renal tubular acidosis with a prolonged-release alkali supplementation

Authors:

Hai Liang Tan[1], Matko Marlais[1], Faidra Veligratli[1] , Sarit Shah[2], Wesley Hayes[1], Detlef Bockenhauer[1,3]

Affiliations

1. Paediatric Nephrology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK.
2. Pharmacy, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK.
3. Department of Paediatric Nephrology, UZ Leuven and Cellular and Molecular Physiology, KUL, Leuven, Belgium

Corresponding author:

Detlef Bockenhauer

Department of Paediatric Nephrology

UZ Leuven

Heerestrat 49

Leuven, Belgium

Email: detlef.bockenhauer@uzleuven.be

Renal tubular acidosis (RTA) refers to a group of diseases characterised by impaired acid-base homeostasis. Complications of chronic acidosis include rickets or osteomalacia, hypercalciuria with nephrocalcinosis and/or nephrolithiasis, faltering growth and chronic kidney disease, which can be ameliorated or prevented by sufficient alkali supplementation. Adequate metabolic control is defined as normalization of blood bicarbonate and urinary calcium excretion.[1] Numerous different alkali supplements are used with more than 30 different formulations reported.[2] Most of these consist of immediate release products of bicarbonate or citrate with rapid absorption and peak alkali load. Gastrointestinal discomfort and poor palatability are commonly reported side effects which, together with frequent dosing may contribute to the finding that only about half of patients with dRTA achieve adequate metabolic control.[2] In October 2022, Sibnayal®, a tasteless, prolonged release alkali formulation became available at Great Ormond Street Hospital (GOSH) and we here describe our experience with this formulation in the real-world setting. A total of 20 children were prescribed Sibnayal® with pertinent clinical and demographic details shown in table 1. Six of the 20 patients (30%) preferred standard treatment and returned to it. Three of these were below the age of 4 years and refused to swallow the granules. Of the others, one patient had autistic spectrum disorder and did not like the texture of granules, one had Lowe syndrome with associated developmental delay and would not swallow the granules and one adolescent did not like the granules as “they stick to the roof of the mouth”. Sibnayal® was well-tolerated and preferred by the remaining 14 patients and ascertained outcome parameters for these are detailed in table 1.

Our results overall show equivalent efficacy of standard and Sibnayal® treatment, with all patients maintaining normal bicarbonate levels. Our cohort is in this regard different to the international dRTA cohort study, where only 57% patients had a normal plasma bicarbonate level at last follow-up.[2] This may reflect that treatment occurred in a dedicated clinic for tubular diseases in a large tertiary centre, which is not fully representative for RTA patients in general. In a previous study of Sibnayal®, a significant rise in the plasma bicarbonate levels and decrease in calcium/creatinine ratio was seen after switching to Sibnayal® and subsequent data also showed improvement in height Z-score.[3,4] Given the

already excellent metabolic control and growth on standard treatment, such treatment effect of Sibnayal® was not apparent in our cohort.

Sibnayal® is approved for the treatment of patients from the age of 1 years, yet, in our experience, many of the younger children or those with developmental delay had difficulties with the granular formulation and its texture. Still, 70% of patients preferred Sibnayal® to standard treatment, suggesting that this is an attractive treatment option, especially for school-aged children, as it obviates the need for medication intake during school hours.

Declaration of competing interests: DB has received lecture honoraria from Advicenne

References

1. Trepiccione F, Walsh SB, Ariceta G, et al. Distal renal tubular acidosis: ERKNet/ESPN clinical practice points. Nephrol Dial Transplant 2021;36:1585-96.
2. Lopez-Garcia SC, Emma F, Walsh SB, et al. Treatment and long-term outcome in primary distal renal tubular acidosis. Nephrol Dial Transplant 2019.
3. Bertholet-Thomas A, Guittet C, Manso-Silvan MA, et al. Efficacy and safety of an innovative prolonged-release combination drug in patients with distal renal tubular acidosis: an open-label comparative trial versus standard of care treatments. Pediatr Nephrol 2021;36:83-91.
4. Bertholet-Thomas A, Manso-Silvan MA, Navas-Serrano V, et al. Bone mineral density and growth changes in patients with distal renal tubular acidosis after two-years treatment with a new alkalizing drug (ADV7103). Nefrologia (Engl Ed) 2023;43:458-66.

Table 1

Baseline characteristics (n=20)	**Reverted to Standard (n=6)**	**Remained on Sibnayal® (n=14)**	**HCO_3^-**			**K^+**			**nCa/Crea**			**Height SDS**			**AMC**		
Diagnosis n (%)			Std	Sib	p	Std	Sib	p	Std	Sib	p	Std	Sib	p	Std	Sib	p
dRTA	3 (50.0%)	10 (71.4%)	25.5	25	0.9	3.7	3.8	0.1	0.5	0.6	0.5	-0.3	-0.2	0.4	77.8	88.9	0.5
Cystinosis	1 (16.7%)	3 (21.4%)	24	24.5	0.3	3.5	3.3	0.3	1.36	4.4	0.7	-2.2	-2.2	1.0	n/a	n/a	n/a
Acquired Renal Fanconi Syndrome		1 (7.25%)															
Lowe syndrome	1 (16.7%)																
Osteopetrosis with RTA (CA2 deficiency)	1 (16.7%)																
Age, initial presentation, months (median, IQR)	1.9 (1.5, 16.4)	4.2 (2.4, 16.5)															
Gender male	3 (50.0%)	8 (57.1%)															
female	3 (50.0%)	6 (42.9%)															
Age at start of Sibnayal®, years (median, IQR)	5.8 (1.3, 15)	9.6 (5.8, 13.7)															

Table 1: Baseline characteristics of the patients and outcomes

In the first 3 columns are shown baseline demographic and clinical data of the 20 patients. The columns to the right detail the ascertained outcomes. The median prescribed daily alkali dose was similar with 2.17 (1.94 to 3.59) vs 2.63 (1.71 to 3.69) mEq/kg/d for standard and Sibnayal® treatment, respectively.

CA2: Carbanhydrase 2; HCO3-: median plasma bicarbonate concentration [mmol/l]; K+: median plasma potassium concentration [mmol/l]; nCa/Crea: median urinary calcium/creatinine ratio normalized to the age-specific upper limit of normal (i.e. a value >1 indicates hypercalciuria); Height SD: End of treatment height standard deviation score; N: number of patients; Std: standard treatment; Sib: Sibnayal® treatment; AMC: adequate metabolic control [%]; p: P-value (paired t-test); n/a: not applicable