Pediatric Nephrology (2021) 36:3621–3626
https://doi.org/10.1007/s00467-021-05213-6

MANAGEMENT DILEMMA

Management of severe polyuria in idiopathic Fanconi syndrome

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Received: 21 May 2021 / Revised: 23 June 2021 / Accepted: 24 June 2021 / Published online: 24 August 2021

Abstract

Background Polyuria is a common problem in patients with tubular diseases, especially for those with CKD and high-output Fanconi syndrome. There are currently no guidelines on how to treat debilitating polyuria, in children or adults, and vasopressin is usually not effective.

Case-diagnosis/treatment A 13-year-old female with idiopathic Fanconi syndrome and an eGFR of 69 mL/min/1.73 m^2 was severely affected by polyuria of 5 L per day (voiding at least 11 times during the day and up to 8 times at night), impacting her mood (measured by the RCADS-child) and academic performance at school. In the absence of guidelines and with literature discouraging the use of indomethacin in this condition, we attempted indomethacin treatment at a dose of 2 mg/kg divided in two doses with substantial success. Urine output dropped to 2.5L and this was accompanied by a substantial decrease of her sodium wasting from 24.6 to 7.7 mmol/kg/day. Over the course of 18 months, the patient's eGFR dropped temporarily to 60 mL/min/1.73 m^2 and was 68 mL/min/1.73 m^2 at last follow-up. However, a sodium-23 (^{23}Na) MRI of her thigh revealed ongoing moderate sodium decrease in her skin and substantial Na^+ decrease in her muscle when compared to age-matched peers with normal kidney function.

Conclusions Indomethacin may be a safe and effective treatment option for polyuria in idiopathic Fanconi syndrome.

Keywords Fanconi syndrome; Indomethacin · Polyuria · Tubular defect; Reduction of free water clearance · Sodium-23 (^{23}Na) MRI · Academic performance · Mood and quality of life

Key points **What is known about this subject** Polyuria is a common problem in patients with tubular disorders and nocturia is highly disruptive, leading to a poor quality of life and negative mood outcomes. The mechanism of polyuria in Fanconi syndrome is thought to be caused by solute and water wasting in the tubules, especially sodium (Na^+). Indomethacin therapy is an option for treatment of polyuria in children with infantile cystinosis, as it reduces polyuria by decreasing urinary solute delivery (especially Na+). In the past, this therapy was not recommended for the much rarer idiopathic Fanconi syndrome.

What this study adds We report the successful use of indomethacin in an adolescent female with idiopathic Fanconi syndrome associated with the loss of 0.385 Mb in chromosome region 3p12.2 (unknown significance). This patient had chronic kidney disease (CKD) stage II, debilitating nocturia and the need to void 11 times during the day and 8 times at night. The treatment was safe, did not lead to accelerated deterioration of kidney function, and resulted in a significant improvement in urinary frequency/volume, self-reported mood symptomatology (per the RCADS-Child survey), and academic performance. We also demonstrated a substantial reduction of Na^+ wasting with indomethacin while the patient's muscle Na^+ concentration remained substantially depleted, suggesting no further role with Na^+intake reduction.

Extended author information available on the last page of the article

Introduction

Fanconi syndrome is a rare disorder of proximal tubular function that results in excess amounts of glucose, bicarbonate, phosphates, uric acid, potassium, and certain amino acids being excreted in the urine. While it is most commonly encountered in patients with infantile cystinosis [1, 2], Fanconi syndrome can also be seen as a consequence of other disorders such as fructose intolerance, Wilson's disease, galactosemia, glycogen storage disease, Dent's disease, Lowe's syndrome, mitochondrial cytopathies, and arthrogryposis-kidney dysfunction cholestasis syndrome. There are also acquired forms of this condition related to drugs like ifosfamide or heavy metals. Cases are defined as idiopathic Fanconi syndrome if no other associated condition can be identified [2].

The most common clinical features of Fanconi syndrome are polydipsia and polyuria [1]. The mechanism of polyuria is related to excessive urinary solute wasting with associated loss of water [3], negatively impacting mood and quality of

life [3]. Nocturia, especially when causing sleep deprivation, is the most bothersome of all urinary symptoms [4]. Treatment options of polyuria in children with Fanconi syndrome are limited, as these patients are characteristically not responsive to vasopressin [5]. The non-steroidal anti-inflammatory drug indomethacin, at a dose of 1–3 mg/kg/day, has been proposed as a potential treatment to relieve polyuria without accelerating the decline of kidney function [1]. Indomethacin decreases urinary volume, fractional sodium excretion, fractional excretion of potassium, and the osmolar and free water clearance in healthy subjects and patients with polyuria [6]. Seyberth described the mechanism and effect of indomethacin among patients with tubulopathies [7]. Indomethacin inhibits prostaglandin synthetase—which consistently reduces kidney blood flow and glomerular filtration rate (GFR)—while enhancing tubular Na + reabsorption [1]. Indomethacin showed positive effects in children with infantile cystinosis, but was ineffective in patients with idiopathic Fanconi syndrome. As a consequence, its use in that specific indication was discouraged by Parchoux et al. [8].

We describe the successful and safe use of indomethacin (at a dose of 2 mg/kg) and its impact on self-reported mood, self-reported quality of life, and academic performance [9] in an adolescent female with severe polyuria requiring 4.5–5 L of water intake per day to compensate the losses.

Case report

History and initial presentation/management

A 4-year-old female of unrelated parents was admitted to the hospital with failure to thrive, signs of rickets, weight loss, polyuria, polydipsia, and dehydration. Height and weight were at the 17th percentile based on WHO criteria. She had a mixed proximal and distal acidosis (arterial gas pH 7.23 on admission [normal 7.35–7.45], bicarbonate 6 mmol/L [normal 21–28], potassium 3.4 mmol/L [normal 3.5–5.0], Na^+ 138 mmol/L [normal 135–145], anion gap + 19 mmol/L [normal 3–13], low molecular weight proteinuria measured as beta-2-microglobulin/creatinine ratio at 1358 mg/mmol [normal 0–29], hypophosphatemia at 0.67 mmol/L [normal 1.10–1.90], and generalized hyperaminoaciduria, in the absence of hypercalciuria or glucosuria). The initial urine pH was 5.5 and urine anion gap was + 40 to + 63 mmol/L. The initial serum osmolality was 307 mOsm/kg [normal 275–295]. Her initial cystatin C estimated GFR (C eGFR) was 130 mL/min/1.73 m^2 [10]. Both kidney and muscle biopsy were obtained to search for an underlying cause to her Fanconi syndrome, which unfortunately did not yield a definitive diagnosis. Electron microscopy from the kidney biopsy showed patchy podocyte effacement with variable thickness, and abnormal irregularly enlarged mitochondria, with atypical, circular, or aberrant cristae. The muscle biopsy showed mild increase of lipid deposit in muscle fibers. The description of her abnormal mitochondria abnormalities is of uncertain significance, but no features of mitochondrial cytopathy were detected on her muscle biopsy. Testing for infantile cystinosis, mitochondrial cytopathy, and other known metabolic or inherited causes of Fanconi syndrome was negative. The genetic workup revealed the loss of 0.385 Mb in chromosome region 3p12.2 of unknown significance. This deletion was not found in the mother and unfortunately, the father was unavailable for genetic testing. Though this genetic defect has been reported to be associated with autism, our patient did not present or subsequently develop autistic features. She was initially treated with oral phosphate supplements [58 mg/kg/day], Na^+ bicarbonate [320 mg/kg/day], potassium citrate [0.7 mmol/kg/day], and active vitamin D (0.17 ug/kg/day, initial vitamin D level 72 nmol/L [normal range 75–225 nmol/L]). Doses needed to be increased proportionally as she grew. She subsequently developed glucosuria at the age of 5 years.

Management of emerging complications and introduction of indomethacin

Unfortunately, the patient's eGFR dropped continuously, by 4 mL/min/1.73 m^2 per year. At age 12 years, she required 290 mg/kg/day of Na^+ bicarbonate to maintain a bicarbonate concentration > 18 mmol/L. Her eGFR [10] dropped to 69 mL/min/1.73 m^2 from age 4 to 13. Metabolic bone disease, metabolic acidosis, hypokalemia, and metabolic acidosis all remained well-controlled over that time. Polyuria persisted with 10–11 voids per day, causing her to drink 4.5–5 L/day to prevent dehydration. Nocturia increased to cause voiding in the toilet 8 times per night (as she never wet the bed), and her chronic sleep deprivation affected school performance, self-reported mood (Fig. 1) [9], quality of life, and treatment adherence. She was a struggling student with grades at the low 60% level but was not eligible for informal or formal support. At baseline, her self-reported mood symptomatology per the RCADS-Child survey [9] revealed separation anxiety with a *T*-score > 80 and a total anxiety and depression score of 48 (Fig. 1).

Before the treatment trial, she demonstrated substantial Na^+ wasting, losing 24.6 mmol/kg/day. We started indomethacin at a dose of 2 mg/kg, resulting in a dramatic improvement of her polyuria. Within a week of the indomethacin therapy, her required fluid intake dropped by 50% to 2.5 L/day and nocturia dropped to one void per night. The indomethacin response was maintained 18 months after starting the medication. Her cystatin C eGFR dropped temporarily to 60 mL/min/1.73 m^2, while she also progressed to Tanner stage 3 of puberty. Six months after starting her indomethacin, the C eGFR recovered back to 69 mL/min/1.73

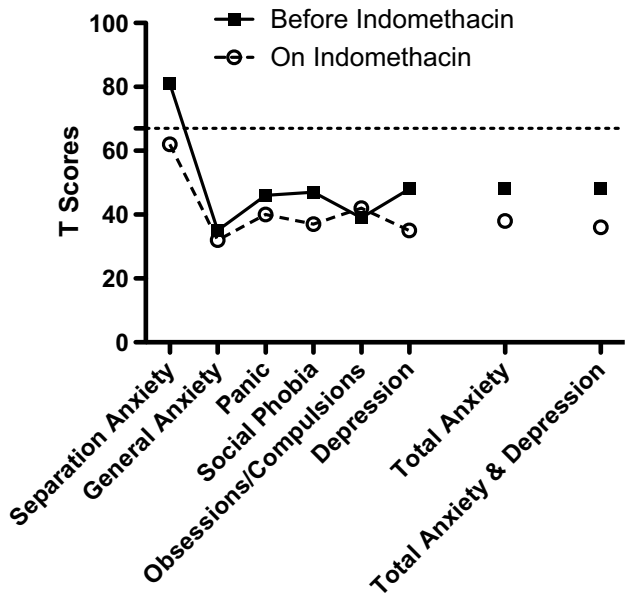

Fig. 1 Self-reported mood-related scores using RCADS-C [9] before and 1 year into indomethacin therapy in a 14-year-old female with idiopathic Fanconi syndrome. The score improved significantly ($p = 0.0078$, paired t-test). Points above the dotted line indicate significantly abnormal values

m^2 and her most recent C eGFR 18 months after starting the indomethacin was 68 mL/min/1.73 m^2. No medication side effects were reported but there was no improvement regarding the control of other features of her Fanconi syndrome as potassium and phosphate values remained unchanged.

Her follow-up RCADS-Child scores improved in most areas, with an improved separation anxiety T-score of 62 and an overall anxiety and depression score of 36 (Fig. 1). A normal overall anxiety and depression score for her grade would be 21.89 ± 14.39 and as such, her total score is at plus one standard deviation [9]. Her general anxiety and obsessive/compulsive scores did not change. Since RCADS was administered again at age 14, there is likelihood for regression to the mean given that the prevalence of separation anxiety continues to decrease with increased age into adolescence, so this improvement may not have been related to indomethacin. However, her academic performance markedly improved with grades increasing to the 75–80% range.

Further studies revealed ongoing Na^+ wasting with 475 mmol of Na^+ per day or 7.7 mmol/kg/day, and this was a substantial improvement. Around the 18th month of indomethacin treatment, we performed a sodium-23 (^{23}Na) MRI of her leg (Fig. 2), to obtain an objective measure of her tissue Na^+ status under an ongoing observational study protocol (ClinicalTrials.gov Identifier: NCT03004547), and to gain insight regarding further Na^+ restriction [11, 12]. The skin Na^+ concentration was 10.681 mmol/L which yielded a z-score of -0.82 versus healthy children, and the muscle Na^+ concentration was 14.608 mmol/L (z-score of -2.50 versus healthy children). As such, the patient had low skin Na^+ concentration compared to healthy children despite her CKD and very low muscle Na^+ concentration (indicative of intra-cellular reserves), compared to healthy children (mean age 11.5 ± 3.5 years, females 47%). At her 18-month follow-up, we attempted to wean her indomethacin to once daily, but this resulted in worsening of her polyuria. In view of the maintained cystatin C eGFR, we left her at twice daily dosing.

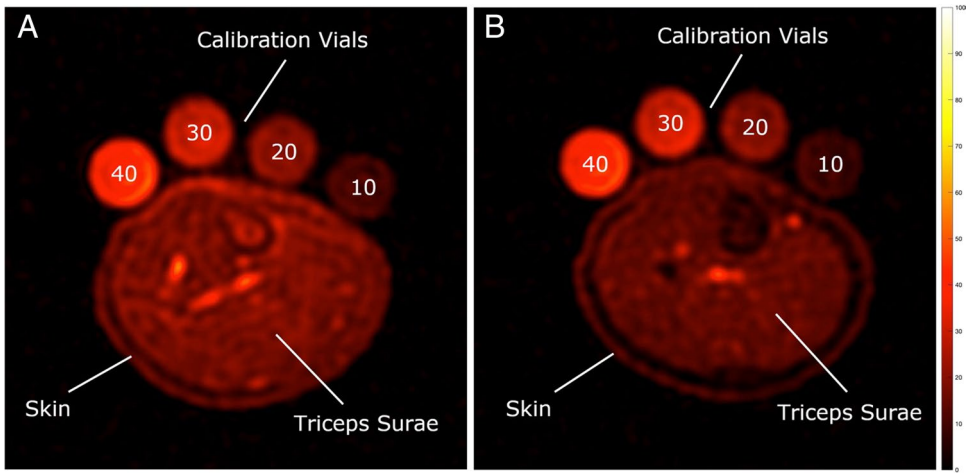

Fig. 2 ^{23}Na MRI of the leg in a 13-year-old healthy female (**A**) and a 13-year-old female patient with Fanconi syndrome on indomethacin (**B**). Images show a substantially reduced skin [Na^+] ((**A**) 15.2 mmol/L vs (**B**) 10.7 mmol/L) and triceps surae muscle [Na^+] ((**A**) 18.6 mmol/L vs (**B**) 14.6 mmol/L) in our case in point, despite decreased kidney sodium wasting. [Na^+] measurement was possible by linear trend analysis as detailed in [11], using four calibration vials containing increasing concentrations of NaCl solution (from left to right: 40, 30, 20, 10 mmol/L). Tissue [Na^+] is displayed as heat map, with greater signal intensity proportional to tissue [Na^+]

Fig. 3 Flowchart summarizing management of polyuria in Fanconi syndrome with indomethacin

Discussion

There are very few guidelines on how to treat polyuria in CKD, and we are unaware of any treatment guidelines for the debilitating polyuria in patients with Fanconi syndrome. Exogenous administration of vasopressin is ineffective [5]. There are only small case series about the use of indomethacin in children with Fanconi syndrome due to cystinosis. Parchoux et al. [8] discouraged the use of indomethacin in children with idiopathic Fanconi syndrome based on the rapid deterioration of the eGFR.

In this 13-year-old female with significant polyuria, we found a sustained positive effect of indomethacin therapy with a 50% reduction of her urine output and an 83% reduction of nocturia, but without an accelerated decline of kidney function. We chose indomethacin over ibuprofen or other non-steroidal antiphlogistic drugs because its use for this indication has been documented the most in the medical literature. She tolerated the medication well and no antacid was needed, although prophylactic antacid therapy is recommended for indomethacin treatment [13]. The main reason against prophylactic antacid therapy was the goal to limit her medication burden since the number of medications has a profound impact on quality of life [14]. Our results were similar to those obtained by Haycock et al. in children with infantile cystinosis, placed on indomethacin at 3 mg/kg/day [1]. In Haycock's series, one child was able to sleep through the night, having previously risen up to 6 times nightly to void [1]. Ammenti et al. also described a very positive effect of indomethacin in a 13-month old boy with cystinosis [15]. Similar to the findings of Usberti, indomethacin therapy in our patient did not accelerate the decline of kidney function [16]. However, in a case series of patients with a different tubulopathy for the relief of polyuria, a decline of eGFR was observed in 2/12 children with Bartter syndrome [17]. By contrast, Reinalter et al. reported on 12 patients with salt-losing tubulopathies who did not worsen their eGFR on indomethacin therapy [18]. Usberti reported one boy with Fanconi syndrome in his case series of tubulopathy patients treated with indomethacin, who also demonstrated an increase in phosphate levels. In contrast, our patient's serum phosphate was 1.08 mmol/L [normal 0.80 to 1.33 mmol/L] before the start of indomethacin and remained essentially unchanged at 1.02 mmol/L at last follow-up. Parchoux discouraged the use of indomethacin in idiopathic Fanconi syndrome, although in that case series, one patient with idiopathic Fanconi syndrome exhibited a substantial benefit with this drug [8]. Our case would suggest that indomethacin may be a treatment option in patients with idiopathic Fanconi-associated polyuria, as in this patient it was an effective and safe option to treat debilitating polyuria and its consequences (Fig. 3). While we cannot infer causality, we hypothesize that the improvement of her academic performance is related to the reduction of her nocturia. We also confirmed the substantial impact of indomethacin on urinary Na^+ wasting while failing to normalize the MRI-measured skin and muscle Na^+ concentration over an 18-month treatment. Further studies may confirm our findings.

Key management points

- Polyuria in Fanconi syndrome is due to solute wasting, especially Na^+.
- There are no treatment guidelines for polyuria with CKD.
- Indomethacin reduces polyuria and Na^+ wasting but does not restore tissue Na^+ levels.
- Careful management of kidney function while on indomethacin is essential.

Author contribution Guido Filler conceived this project, wrote the drafts, collated the results, made multiple edits, collated all changes, added intellectual content, and approved the final version.

Rishika Geda conducted the literature review, provided major intellectual input into the design of the study, helped with the interpretation of the results, carefully edited and revised the various versions of the manuscript, and approved the final manuscript.

Fabio Salerno performed the sodium-23 (^{23}Na) MRI study, provided major intellectual input into the analysis of the results, carefully edited and revised various versions of the manuscript, and approved the final manuscript.

Yun Cong Zhang provided major intellectual input into the design of the study, helped with the interpretation of the results, carefully edited and revised various versions of the manuscript, and approved the final manuscript.

Christopher William McIntyre provided major intellectual input into the design of the study, facilitated the sodium-23 (^{23}Na) MRI, helped with the interpretation of the results, carefully edited and revised various versions of the manuscript, and approved the final manuscript.

Maria E Díaz-González de Ferris provided major intellectual input into the design of the study, helped with the interpretation of the results, carefully edited and revised various versions of the manuscript, and approved the final manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declarations

Ethics approval Case reports are ethics-exempt in our institution; however, written informed consent about publication was obtained by the caregivers. The sodium MRI study received full approval from the Research Ethics Board.

Consent to participate The authors declare that they have obtained consent to participate from the caregiver of the study.

Conflict of interest The authors declare no competing interests.

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