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Brief report

Non-steroidal anti-inflammatory drug-associated nephrotoxicity in Bartter syndrome

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Abstract. We have followed four patients with Bartter syndrome for a mean of 25.4 years (range 21.5–28.8 years) after diagnosis. All patients received non-steroidal anti-inflammatory drugs (NSAID). In all patients, various degrees of renal dysfunction were noted to be temporally associated with NSAID therapy. In two patients, renal dysfunction resolved after discontinuing NSAID therapy, while maintaining other chronic medications such as potassium-sparing diuretics. Renal dysfunction persisted after NSAID withdrawal in two patients. We report these cases as a warning that NSAID should be considered an important cause of either reversible or irreversible renal dysfunction in Bartter syndrome.

Key words: Bartter syndrome – Nephrotoxicity – Non-steroidal anti-inflammatory drugs – Creatinine clearance

Introduction

Bartter syndrome (BS) is a group of renal tubular disorders which is classified into at least two sub-syndromes based on clinical presentation and, more recently, genetic analysis. Antenatal BS (ABS) is caused by mutations in the bumetanide-sensitive Na-K-2Cl cotransporter (NKCC2) in the medullary thick ascending limb of the loop of Henle [1]. Mutations in the potassium channel ROMK, the channel which is involved in regulating luminal potassium concentration critical to adequate functioning of NKCC2, also causes ABS, establishing the genetic heterogeneity of these disorders [2]. A mutation in the renal chloride channel, CLCNKB, has been found in patients with BS in the absence of nephrocalcinosis [3]. The precise molecular defect in classic BS (CBS) is as yet undetermined.

Treatment of these syndromes has consisted mainly of potassium and/or magnesium supplements, potassium-sparing diuretics (PSD), and non-steroidal anti-inflammatory drugs (NSAID) [4, 5]. Over the past 25 years we followed four patients at our hospital who were diagnosed with ABS or CBS based on clinical presentation and laboratory parameters [6]. Four patients developed renal dysfunction [decreased creatinine clearance (C_{Cr}) or proteinuria] that was temporally associated with NSAID therapy. Renal dysfunction resolved following withdrawal of NSAID therapy in two cases, but persisted in two patients. The purpose of this report is to stress the importance of recognizing potentially reversible NSAID-induced nephrotoxicity in the differential diagnosis of renal dysfunction in this group of patients.

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Patients and methods

Patient information was obtained from hospital records, office records, and by telephone contact with the patient's most-current physician. Information collected included physical growth parameters, medications, serum electrolyte values, renal function tests, and urinalyses. Classification of patients as either ABS or CBS was based on initial clinical and biochemical characteristics at presentation, and clinical course, as definitive genetic tests were not yet widely available.

C_{Cr} was calculated from a formula using the patient's height and concurrent serum creatinine level [7]. Each patient's pre-NSAID C_{Cr}, lowest calculated C_{Cr} while on NSAID therapy (C_{Cr}-trough), and most-recent calculated C_{Cr} of NSAID therapy (C_{Cr}-final) were determined. All patients received NSAID prior to measurement of C_{Cr}-trough and no patients were receiving NSAID at the time of C_{Cr}-final.

Results

Three patients were female. Patients' ages at diagnosis ranged from 0.25 to 3.5 years and at follow-up ranged from 23 to 29 years. Follow-up periods ranged from 22 to 29 years. Based on age at presentation and clinical and laboratory parameters, patients were given a diagnosis of ABS (n=2) or CBS (n=2) (Table 1).

Table 1. Creatinine clearance (C_{Cr}), C_{Cr}-trough, and C_{Cr}-final in antenatal (ABS) and classic Bartter syndrome (CBS) patients[a]

Patient diagnosis	Sex	Age at onset (years)	Presentation	NSAID (duration)	C_{Cr} pre NSAID; serum Cr; age (years)	C_{Cr}-trough on NSAID; serum Cr; age (years)	C_{Cr}-final off NSAID; serum Cr; age (years)
1 ABS	Female	0.25	Hypokalemia metabolic alkalosis	Ibuprofen (>5 years)	No data	45.8; 173; 18	43.1; 167; 27
2 ABS	Female	0.25	Polyhydramnios hypokalemia metabolic alkalosis failure to thrive	Ibuprofen (3 years)	74.5; 79.8; 11	18.1; 349; 21	9.0; 800; 26 (pre transplant)
3 CBS	Male	1.0	Polydipsia/polyuria hypokalemia metabolic alkalosis Ca:Cr ratio 0.6	Ibuprofen (>5 years)	94.2; 53.2; 9	94.8; 107; 16 proteinuria (1.2–3.4 g/24 h) interstitial nephritis	89.9; 117; 23 urine protein negative (dipstick)
4 CBS	Female	3.5	Hypokalemia metabolic alkalosis hyponatremia	Ibuprofen (one dose)	87.1; 53.2; 4	39; 141; 8	147.8; 50; 28

NSAID, Non-steroidal anti-inflammatory drugs; Ca, calcium
[a] C_{Cr} expressed as ml/min per 1.73 m^2; serum Cr is expressed as μmol/l

Three patients (nos. 2, 3, and 4) had normal calculated C_{Cr} prior to NSAID therapy. Pre-NSAID creatinine measurements were not available for patient no. 1. All four patients received NSAID therapy in the form of ibuprofen (ABS=2, CBS=2) at doses in the range of 2.3–2.8 mg/kg per day, divided into two to four equal doses. Three patients (nos. 1, 2, and 4) demonstrated decreased calculated C_{Cr} after initiation of NSAID therapy. One patient (no. 3) maintained a normal C_{Cr} and had no proteinuria prior to NSAID therapy, but developed persistent proteinuria (1.2–3.4 g/24 h) and biopsy-proven interstitial nephritis while receiving NSAID. All other patients maintained normal urinalyses.

The duration of NSAID therapy was at least 3 years in patients 1, 2, and 3. One patient (no. 4) received a single trial dose of NSAID therapy. All four patients received PSD therapy concurrently with NSAID therapy. No patients were receiving NSAID therapy at the time of measurement of C_{Cr}-trough. Patients 1, 2, and 4 were maintained on PSD therapy after discontinuing NSAID. The time between measurement of C_{Cr}-trough and C_{Cr}-final ranged from 1.2 years to 19.3 years (mean 8.8 years).

Both patients in the ABS group had subnormal C_{Cr}-trough and C_{Cr}-final (patient 1 and 2). One ABS patient (no. 2) ultimately underwent renal transplantation, with normal allograft function 4 years posttransplantation. Proteinuria ultimately resolved in patient no. 3 following discontinuation of NSAID and initiation of angiotensin converting enzyme inhibitor therapy. Patient no. 4 experienced a transiently decreased serum creatinine following a single trial dose of ibuprofen. Her serum creatinine subsequently returned to the normal range.

None of the patients had evidence of persistent hematuria, hypertension, or a systemic disease such as vasculitis or diabetes. None had received any other potentially nephrotoxic medications on a regular basis. None of the patients ever had evidence of nephrocalcinosis on ultrasound examination.

Discussion

The observation of prostaglandinuria in BS led to the therapeutic use of prostaglandin synthase-inhibiting NSAID, with beneficial effects in terms of alleviation of symptoms, partial or complete resolution of hypokalemia, and better growth [4, 5]. In 1979, we described nine patients with BS [6]. We now report degrees of NSAID-associated renal dysfunction in four of these patients.

Previous reports on renal failure in BS [8–14] focus mainly on the development of renal dysfunction as part of the natural history of BS, rather than in association with NSAID therapy. One of the earliest described BS patients in the literature was lost to follow-up for several years until she presented with hypertension, uremia, and normal serum potassium levels [8, 9]. Trygstad et al. [10] reported three siblings with CBS each having subnormal C_{Cr} in the absence of chronic NSAID therapy. Arant et al. [11] described two siblings with ABS who developed renal failure in the absence of NSAID therapy. Dillon et al. [12] followed ten patients for up to 15 years. Six patients were treated with NSAID therapy with only one recorded complication (duodenal ulcer). However, the maximum reported duration of NSAID therapy was only 24 months. Rudin [13] followed 28 patients with BS for 10 years. Of these, 3.6% (1/28) developed terminal renal failure. However this study did not look for an association between renal failure in BS and specific treatment modalities. Takahashi et al. [14] reported a living-related kidney transplant in a patient with CBS who presented with azotemia and was therefore never treated with NSAID.

NSAID are believed to cause renal damage both by direct cytotoxic effects, as well as by causing renal ischemia due to inhibition of vasodilating autoregulatory prostaglandins, resulting in papillary necrosis and interstitial scarring [15]. Kidneys with pre-existing dysfunction and vascular compromise appear to be more suscep-

tible to these effects [15]. These detrimental effects are generally reversible upon NSAID withdrawal, and improvement in this setting confirms that NSAID toxicity was evident.

It is emphasized that the purpose of this report is a cautionary note about possible NSAID toxicity in BS. Our subject group is small in number, and many of our data are retrospective, limiting our ability to fully assess confounding variables and other possible causes of renal dysfunction. However, the temporal association of renal failure with NSAID therapy, as well as resolution of nephrotoxicity upon NSAID withdrawal in two of the four cases, suggest a causal effect. The use of a calculated C_{Cr} may be less accurate in this group of patients given their typically short stature. We attempted to minimize this limitation by comparing serial calculated C_{Cr} for each patient over a significantly long period to time (several years). Although syndrome classification in this report has been based on clinical findings and laboratory parameters, correlating genetic studies with clinical diagnoses will be interesting when these tests become more widely available.

Both patients with persistent renal dysfunction were diagnosed with ABS, while patients who improved following NSAID withdrawal belonged to the CBS group. Reversibility of nephrotoxicity following NSAID withdrawal may be more feasible in CBS than the clinically more-severe ABS variant.

In conclusion, NSAID-induced nephrotoxicity in BS should be suspected as an important cause of renal dysfunction, particularly in patients with the more-severe ABS variant. An attempt to discontinue NSAID therapy may be warranted when irreversible nephrotoxicity is evident.

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Literature abstract

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Cerebral defects and nephrogenic diabetes insipidus with the ARC syndrome – additional findings or a new syndrome (ARCC-NDI)

R. A. Coleman, J. L. K. Vanhove, C. R. Morris, J. M. Rhoads, and M. L. Summar

We report on 4 children from 2 unrelated families who appear to have the lethal ARC syndrome (arthrogryposis, renal tubular dysfunction, and cholestasis) together with the additional findings of nephrogenic diabetes insipidus and cerebral anomalies, including deafness. With increased survival time in our patients, paucity of the intrahepatic bile ductules and cholestasis progressed to cirrhosis, growth was severely impaired, and severe mental retardation became apparent. No evidence was found for peroxisomal chromosomal, or mitochondrial disorders. We propose to amend the ARC mnemonic to ARCC-NDI (A-Arthrogryposis, R-renal Fanconi, C-cerebral, C-cholestasis, NDI-nephrogenic diabetes insipidus) to name the major manifestations of this syndrome, several of which have not been appreciated.