

Ibuprofen use for the treatment of pediatric patients with polyuria and dysnatremia. A case series report

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ABSTRACT

Children with sellar and/or suprasellar lesions may develop central diabetes insipidus with subsequent inappropriate antidiuretic hormone secretion. An increased incidence of polyuria, natriuresis, and hyponatremia has been reported in some cases, which make up the diagnostic triad of cerebral salt wasting syndrome.

Here we report the clinical course of 7 patients with a history of acute central nervous system injury and central diabetes insipidus followed by cerebral salt wasting syndrome.

Treatment included the sequential use of parenteral saline solution, oral sodium chloride, desmopressin, mineralocorticoids, and even thiazides. Due to persistent polyuria and hyponatremia, ibuprofen was added.

As a result of this sequential therapeutic regimen, daily urine output reduced significantly from 10 mL/kg/h to 2 mL/kg/h over an average period of 5 days, together with a normalization of natremia (from 161 mEq/L to 143 mEq/L) over an average period of 9 days. No treatment-related adverse effects were observed in any case.

Keywords: *ibuprofen; polyuria; electrolyte imbalance; cerebral salt wasting syndrome; diabetes insipidus.*

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INTRODUCTION

Dysnatremia accounts for 25-30% of electrolyte disorders in hospitalized pediatric patients.¹ In addition to the established association between brain lesions and central diabetes insipidus (CDI)² or syndrome of inappropriate antidiuretic hormone secretion (SIADH),³ the presence of neurosurgical conditions accompanied by dysnatremia with polyuria and increased urinary sodium loss may correspond to a rare clinical condition not easily differentiated from CDI and SIADH, called cerebral salt wasting syndrome (CSWS),⁴ whose pathophysiology has not yet been fully established.

We know that increased natriuresis in CSWS by osmotic diuresis causes polyuria and hypovolemia, and leads to body sodium depletion with clinical signs of hypovolemia (acute reduction in body weight, arterial hypotension, tachycardia, dry mucous membranes) and biochemical evidence of dehydration, such as increased hematocrit and uremia. In this context, ibuprofen—an inhibitor of cyclooxygenase (COX)⁵ and prostaglandin E2 (PGE2)—^{6,7} has been used previously to reduce polyuria⁸ and, although it is not standard practice in our hospital, we have used it in specific situations of polyuria and dysnatremia (CDI + CSWS) of very complex management. Therefore, the use of ibuprofen for the treatment of polyuria in patients with hyponatremia is emerging as a promising therapeutic option.

Here we report our experience with a series of 7 cases.

OBJECTIVES

To describe the variations caused by ibuprofen in the internal milieu and kidney function of children with polyuria and underlying central nervous system (CNS) conditions associated with CDI and CSWS in a case series.

To assess the occurrence of clinical adverse events associated with the use of ibuprofen.

MATERIALS AND METHODS

Here we describe a case series of patients with CNS disease seen at Hospital General de Niños Ricardo Gutiérrez (Buenos Aires, Argentina) between January and December 2021.

All patients had a known history of neurosurgical conditions and presented sequentially with CDI (defined by polyuria, hyposthenuria with urinary density < 1005, and hyponatremia > 150 mEq/L,² and positive

response to desmopressin administration) and CSWS (diagnosed in the presence of osmotic polyuria > 3 mL/kg/h or 90 mL/m²/h or 2 L/day, serum sodium < 130 mmol/L, urinary sodium > 20 mmol/L, plasma osmolality < 280 mOsm/L, and lower than urinary osmolality).¹

All patients included had a glomerular filtration rate greater than 60 mL/min/1.73 m², mean systolic blood pressure lower than the 95th percentile, and normal magnesium, calcium, phosphorus, and uric acid serum levels.

Patients with a history of tubulointerstitial kidney disease, renal tubular acidosis, complex tubulopathies (Bartter syndrome, Gittelman syndrome, etc.), SIADH,³ blood dyscrasias (thrombocytopenia, thrombasthenia, absolute or functional deficiency of coagulation factors), chronic gastritis, gastrointestinal bleeding, and heart failure were excluded.

The 7 patients received a sequential therapeutic regimen with fluids corresponding to the sum of 75% of their concurrent urinary losses (diuresis greater than 2 mL/kg/h) plus insensible fluid losses; enteral sodium chloride supplementation, starting with 6 mEq/kg/day fractionated and increasing the dose as per the patient's requirements until normalization of natremia (daily increases greater than 12 mEq/L/day were avoided); desmopressin as per requirements prior to the start of CSWS (0.05–0.2 mg/day); hydrocortisone (10–40 mg/m²/day) or fludrocortisone (0.2 mg/day); thiazides (1–2 mg/kg/day), and ibuprofen (10–30 mg/kg/day) (Figure 1).

Clinical, biochemical, and imaging monitoring

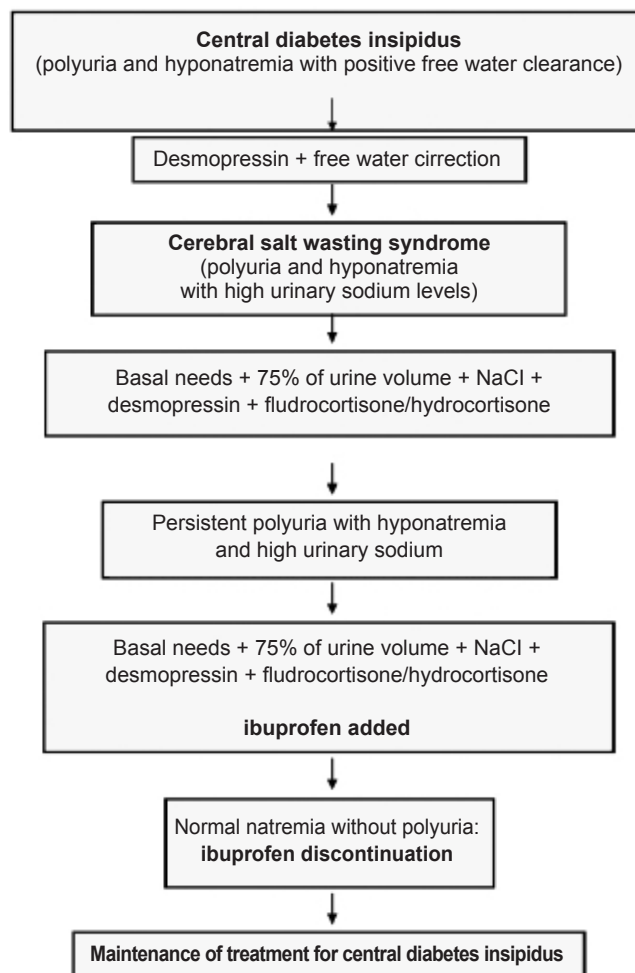
Clinical controls. Weight (kg), blood pressure (mmHg), electrolyte balance of intake and output with urine output (mL/kg/hour).

Lab controls. Blood: blood count, creatinine, urea, ionogram, gases, estimated serum osmolality, uric acid, calcium, magnesium, phosphate. Urine (single collection or 24-hour collection): ionogram, estimated osmolality, density, uric acid, creatinine, urea.

X-ray and ultrasound controls. Chest teleradiograph (normal cardiothoracic ratio: 0.4), kidney ultrasound, and vena cava Doppler ultrasound (normal collapsibility index: 8–11.5 mm/m²).

Study variables

For analysis, independent variables were

FIGURE 1. Flow chart of treatment based on diagnosis and clinical course

regulated electrolyte intake and ibuprofen dose; and dependent variables were urine output, electrolyte imbalance, plasma and urinary osmolarities, and variation in glomerular filtration rate.

Statistical analysis

A one-way analysis of variance (one-factor between-group ANOVA) was used as a statistical formula to compare variances and infer the potential presence of statistically significant differences between the means of each continuous dependent variable analyzed (urinary and plasma sodium, plasma osmolarity, and urine output) at their different levels with the qualitative variable or independent factor (ibuprofen) among our 3 study groups. The GRAPHPAD PRISM 8.0 statistical software was used.

Results were described as mean \pm SD.

Ethical considerations

All patients and their parents signed the informed consent and assent (when applicable) for the implementation of the treatments described, as well as to report clinical data related to what was done in the study.

The study adhered to the ethical and regulatory guidelines established in the Declaration of Helsinki and was approved by the hospital's Ethics Committee for publication as an observational case series study. The authors state that they have no conflicts of interest to disclose.

The mean study period since its initiation until the last clinical control was 6 months.

RESULTS

We studied a case series of 7 patients (5 girls); their median age was 6.2 years (r: 5 to 19 years); all had polyuria, dysnatremia, and history of

neurosurgical conditions (*Table 1*).

The mean time between CDI and CSWS diagnosis was 7 days (SD: 2). The mean length of hospitalization was 20 days (SD: 5); then patients continued with outpatient controls until completing 6 months.

Mean urine output values in patients with CDI were 7.2 mL/kg/h (SD: 4.2); CDI + CSWS, 10 mL/kg/h (SD: 3.3); and CDI + CSWS post-ibuprofen, 2 mL/kg/h (SD: 0.3) (*Figure 2*).

Mean plasma sodium values in patients with CDI were 161 mEq/L (SD: 18); CDI + CSWS, 119 mEq/L (SD: 6.5); and CDI + CSWS post-ibuprofen, 143 mEq/L (SD: 2.9) (*Figure 3a*).

Mean urinary sodium values in patients with

CDI were 25 mEq/L (SD: 2.7); CDI + CSWS, 308 mEq/L (SD: 3.3); and CDI + CSWS post-ibuprofen, 64 mEq/L (SD: 2.8) (*Figure 3b*).

Lastly, mean plasma osmolarity in patients with CDI was 300 mOsm/L (SD: 4.7); CDI + CSWS, 257 mOsm/L (SD: 14); and CDI + CSWS post-ibuprofen, 290 mOsm/L (SD: 10) (*Figure 4*).

In relation to urine output, a 42% increase was observed between CDI and CDI + CSWS, while an 80% reduction was noted between CDI + CSWS pre- and post-ibuprofen (ANOVA, $F: 9153$, $p: 0.018$, $R^2: 0.504$). In relation to plasma sodium, a 26% reduction was observed between CDI and CDI + CSWS, while a 20% increase was noted between CDI + CSWS pre- and post-

TABLE 1. Description of the study population

Sex	Age (years)	GFR (ml/min/ 1.73 m ²)		Mean values during the study			Brain injury	Ca/P/Mg		Albuminuria (ucg/min)		Fractional excretion of uric acid (%)(1)
		ibuprofen pre-	ibuprofen post-	WBC (cel/mm ³)	Hct (%)	Platelets (mil/mm ³)		ibuprofen pre-	ibuprofen post-	ibuprofen pre-	ibuprofen post-	
F	7	101	99	9900	38	170	Craniopharyngioma	8/4.1/1.7	8/3.9/1.8	18	14	14
F	6	99	101	11 100	35	220	Astrocytoma	9/5.5/1.9	8.1/4/1.7	11	8	13
M	19	112	110	10 830	40	312	Rathke cleft cyst	8.8/4/1.8	8.6/3.9/2.1	5.5	6.3	15
F	4	104	105	7560	29	360	Craniopharyngioma	10/4/1.8	9.3/4.9/1.7	14	12.5	13
F	8	107	102	5690	33	228	Glioma	8.7/6/1.8	10/5.5/2.1	3.5	7.4	16
M	6	112	107	6280	28	190	Pituitary adenoma	10.2/5.5/2	9.6/5.3/1.8	11	9	14
F	5	106	105	7792	37	322	Glioma	9/6.1/1.9	8.5/4.6/1.7	9.2	11.5	13

F: female; M: male.

Ca: calcium; P: phosphorus, Mg: magnesium.

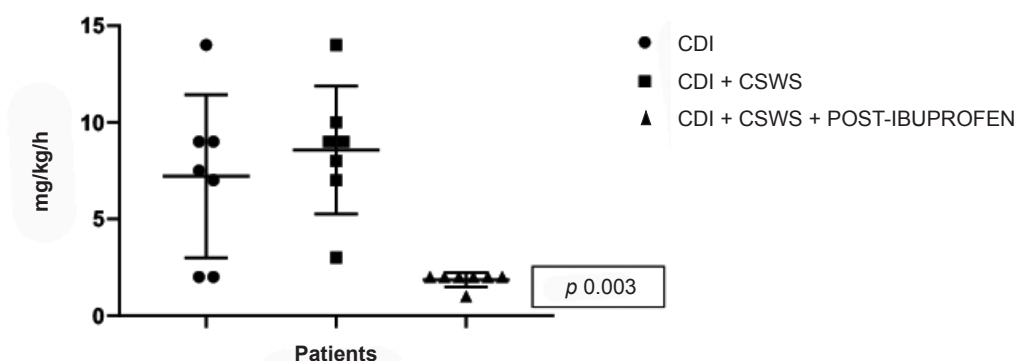
GFR: glomerular filtration rate.

WBC: white blood cells.

Hct: hematocrit.

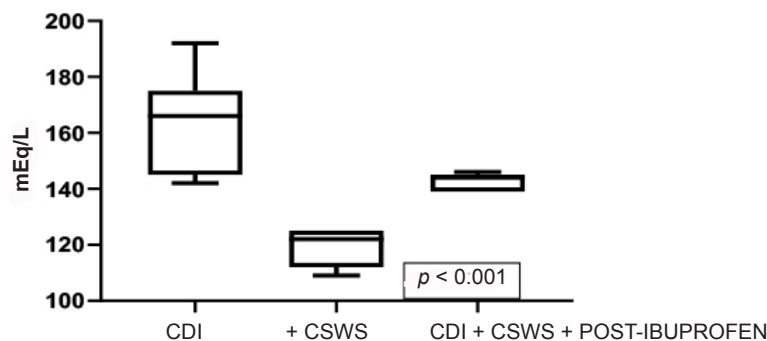
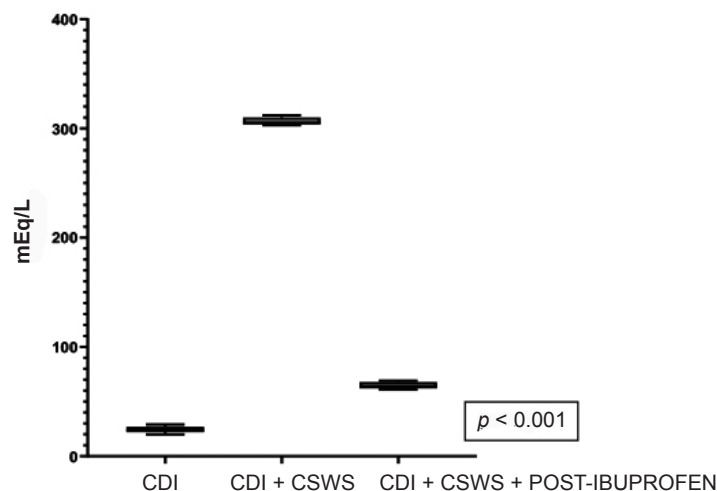
(1): the fractional extraction of uric acid in the 7 patients was higher than 11% during the entire study, before and after the therapeutic intervention.

FIGURE 2. Variations in urine output during the three clinical stages of the study



CDI: central diabetes insipidus.

CSWS: cerebral salt wasting syndrome.

FIGURE 3a. Variation in plasma sodium**FIGURE 3b. Variation in urinary sodium**

Given the minimum variation in values, a cluster of patients is observed in each group.

CDI: central diabetes insipidus.

CSWS: cerebral salt wasting syndrome.

ibuprofen (ANOVA, $F: 23.7$, $p: 0.0001$, $R^2: 0.72$). In addition, urinary sodium increased by 52% in average between CDI and CDI + CSWS, while it was reduced by 77% in average between CDI + CSWS pre- and post-ibuprofen (ANOVA, $F: 161$, $p: < 0.0001$, $R^2: 0.99$). In average, a 14% reduction was observed between CDI and CDI + CSWS, while a 13% increase was noted between CDI + CSWS pre- and post-ibuprofen (ANOVA, $F: 28.8$, $p: < 0.0001$, $R^2: 0.76$). The differences among the average values across the 3 clinical stages (CDI, CDI + CSWS, and CDI + CSWS post-ibuprofen) and their percent variations mentioned above were statistically significant.

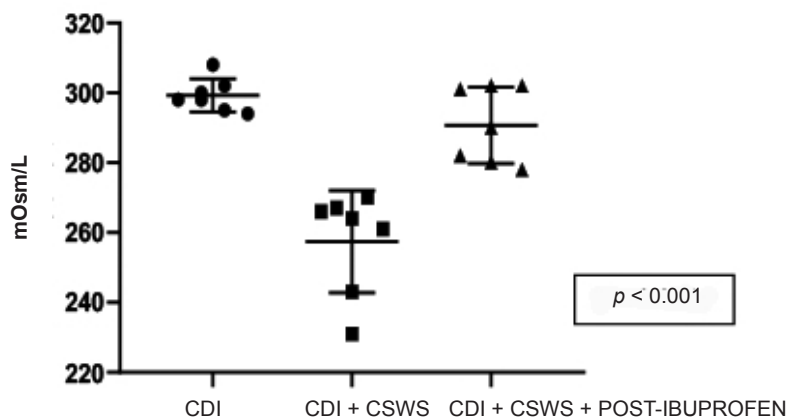
The mean desmopressin dose was 0.2 mg/day (SD: 0.1) and the mean sodium chloride dose was 4.5 mEq/kg/day (SD: 0.7). The average

hydrocortisone dose was 1.5 mg/kg (SD: 0.5), and the mean fludrocortisone dose in the 4 patients who received it was 0.2 mg/day (SD: 0.1).

Lastly, the mean ibuprofen dose was 10.7 mg/kg/dose (SD: 1.8), and the mean period of ibuprofen use was 55 days ($r: 15$ –60 days). In the polyuria phases, the mean fluid intake corresponded to 80% ($r: 77$ –85%) of basal needs + urine output.

Patients had normal chest teleradiographs with no signs of hyperflow, with mean cardiothoracic ratios of 40% (SD: 5%). Kidney ultrasounds showed that all patients had normal kidney size, with preserved kidney location and echotexture. A Doppler ultrasound of the vena cava was done in 4 patients with a mean collapsibility index of 8 mm/m² (SD: 1).

The mean glomerular filtration rate was 92 mL/

FIGURE 4. Variations in plasma osmolarity during the three clinical stages of the study

CDI: central diabetes insipidus.
CSWS: cerebral salt wasting syndrome.

min/1.73 m² before ibuprofen administration and 90 mL/min/1.73 m² after it (p : 0.7). Mean albuminuria was 11 μ cg/min (SD: 5) throughout the study period.

No permanent changes in serum levels or urinary electrolyte excretions other than sodium were observed in any patient (Table 1). There were also no clinical manifestations compatible with gastritis, cardiovascular and/or hematological alterations in the laboratory controls and we did not observe the development of microscopic or macroscopic hematuria.

DISCUSSION

Our 7 patients with CDI and CSWS were treated with the sequential therapeutic regimen; their urine output reduced and dysnatremia was corrected. It is known that there is a brain injury association among CDI, CSWS⁷ (characterized by polyuria and hyponatremia due to urinary leakage secondary to circulating natriuretic factors),^{8,9} and SIADH.¹⁰

Firstly, we established the differential diagnosis between CDI and CSWS on the basis of hypernatremia followed by hyponatremia.¹¹ Secondly, to establish the difference between SIADH and CSWS, we focused comparisons on urine output and the estimation of blood volume¹² inferred from indirect measurements of hydration status (clinical assessment, chest teleradiography, Doppler ultrasound of the vena cava, blood pressure recording). For operational reasons, we did not use other more sensitive and specific parameters to record blood volume, such as central venous pressure or impedance cardiography.

Finally, we assessed acquired renal tubulopathies as a differential diagnosis in the presence of polyuria with hyponatremic dehydration; however, exclusive natriuresis without loss of other electrolytes (phosphorus, potassium, calcium, magnesium) or blood gas alterations ruled out tubular injury as the main pathophysiological event.¹³

Next, and for treatment selection, it was important to know the intrarenal hemodynamic physiological pattern, where COX-1 acts mainly on the control of glomerular filtration, while COX-2 plays a role in the excretion of sodium and water. Both enzymes stimulate the synthesis of PGI₂; PGE₂ and cause vasodilatation and improved oxygenation in the renal medulla.^{5,14}

In addition, PGE₂ increases urine output and sodium excretion by activating tubular receptors, blocking sodium and chloride transport in the ascending loop of Henle and collecting ducts, where it also antagonizes the effects on AQP2 trafficking through the EP3 receptor.¹⁵

In the presence of both CDI and CSWS, we administered a sequential treatment aimed at managing symptoms and restoring the electrolyte balance, considering that prolonged polyuria, in CDI and CSWS, may “wash” the medullary interstitial tubular gradient^{16,17} and even promote the onset of a type of secondary nephrogenic diabetes insipidus not associated with aquaporin production and/or expression.¹⁸ To counteract this pathophysiological sequence, progressive reductions in fluid intake were indicated to restore the kidney’s osmotic gradient and reestablish vasopressin effectiveness.¹⁹ However, when polyuria and severe dysnatremia persisted,

ibuprofen was added;²⁰ this non-steroidal anti-inflammatory drug nonspecifically inhibits COX-1 and COX-2 and prevents the conversion of arachidonic acid into PGE₂, prostacyclins, and thromboxane E₂. In addition, as part of its antinatriuretic effect, it positively regulates the Na-K-2Cl cotransporter in the ascending limb of the loop of Henle.²¹

According to the bibliography, other selective COX-2 inhibitors have been used, such as rofecoxib and celecoxib,^{5,22} as well as non-selective inhibitors, such as indomethacin, especially in Bartter syndrome and congenital nephrotic syndrome.²³ However, we opted for ibuprofen for reasons of operational availability and because, although both drugs affect the glomerular filtration rate, in general the recovery of glomerular filtration rate is slower in patients treated with indomethacin.^{24,25}

In our patients, the non-steroidal anti-inflammatory drug (NSAID) ibuprofen reduced polyuria and total urinary sodium excretion, without evidence of effects on cardiovascular function or glomerular filtration rate. This potential benefit on urine output may cause sodium retention and the development of edema, arterial hypertension, and even SIADH;²⁶ however, in our experience, none of these events was observed.

Another form of NSAID-induced kidney injury is acute interstitial nephritis and, although its diagnosis is usually based on histology,²⁷ we do not think performing a kidney biopsy is sufficiently justified in the absence of significant changes in glomerular filtration rate and in the absence of persistent pathological hematuria and/or albuminuria after starting ibuprofen. Moreover, the long-term effects of ibuprofen on the development of chronic kidney disease occur with daily use for more than 1 year and with doses greater than 100 mg/kg/day.^{28,29}

At the extrarenal level, ibuprofen inhibits PGE₂ production, thus blocking several actions, such as gastrointestinal mucosal protection (gastric perforation and ulceration), platelet activation (thrombotic events), liver function (cirrhosis), etc.³⁰ None of these alterations was detected in our group.

The novelty of this study lies in the effective use of ibuprofen, with the antipyretic and analgesic dosage routinely administered, to control an electrolyte disorder refractory to the treatment generally used. However, this study has some marked weaknesses. Since this is a case series, the observations so far are a preliminary

report and future randomized clinical studies will be required that will make it possible to significantly establish the safety and effectiveness of the treatment. In addition, another limitation of this study is its retrospective design, the low number of patients included (for this reason we only refer to the study as a case series), and the limited follow-up time of 6 months, which, although it could be considered suitable for assessing the acute effects of NSAIDs on kidney function, especially glomerular filtration rate and tubular alterations, does not seem sufficient to assess tissue lesions at the kidney level, especially interstitial lesions. However, to reduce the risk of this event, the fact that we used a reduced dose for a short period of time is in our favor.

CONCLUSIONS

The use of ibuprofen in therapeutic doses and for limited periods of time helped to reduce polyuria and correct dysnatremia in pediatric patients with electrolyte alterations of neurological origin without affecting the glomerular filtration rate in this group of children.

No relevant treatment-associated adverse effects were observed.

The conduct of randomized clinical trials may allow to reach significant conclusions on the clinical management of both diseases. ■

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