Life-threatening hypokalaemia associated with ibuprofen-induced renal tubular acidosis

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Renal tubular acidosis is an underreported complication of ibuprofen misuse, and can result in life-threatening hypokalaemia. We describe four patients who presented with profound hypokalaemia and muscle weakness associated with excessive ibuprofen ingestion. Ibuprofen cessation and supportive management resulted in complete biochemical resolution within a few days. These cases remind practitioners about potential complications of unmonitored use of over-the-counter analgesics, including those with potential for misuse due to their codeine content. **(MJA 2011; 194: 313-316)**

Clinical records

Patient 1

A 32-year-old woman presented to the emergency department with a 2-day history of evolving paralysis associated with profound hypokalaemia (potassium, 1 mmol/L; reference range [RR], 3–5 mmol/L). She also had epigastric pain without diarrhoea or vomiting and a past medical history of depression, iron deficiency anaemia, chronic constipation, migraines, cigarette smoking and previous intravenous drug use. Family history was unremarkable. Her only medications were citalopram 20 mg daily and a combination of ibuprofen (200 mg) and codeine phosphate (12.8 mg) for migraines. She denied taking laxatives, diuretics, alcohol or illicit drugs.

On examination, the patient weighed 38 kg (body mass index, 14 kg/m^2), her blood pressure was 90/55 mmHg, and other vital signs were normal. There was generalised flaccid weakness (graded 3/5) with normal sensation. She also had epigastric tenderness.

Results of initial laboratory investigations (Box 1) were consistent with distal renal tubular acidosis (dRTA). An electrocardiogram (ECG) demonstrated features of hypokalaemia, including widespread ST-segment depression and U waves. Endoscopy revealed oesophageal erosions and a benign gastric ulcer. An abdominal computed tomography scan demonstrated enlarged, oedematous kidneys without nephrocalcinosis.

The patient's husband revealed she had been consuming the combination ibuprofen–codeine over a prolonged period — at least 25 tablets (5.0 g of ibuprofen) per week and up to 20 tablets in 1 day. Ibuprofen toxicity explained both the gastrointestinal symptoms and the biochemical manifestations of dRTA. No alternate explanation for dRTA was found.

The ibuprofen–codeine combination was ceased, and intravenous potassium chloride (KCl) was administered (610 mmol at 5–10 mmol/h over 5 days), with concurrent oral replacement of 64 mmol potassium/day. No signs of opioid withdrawal were detected. Within 5 days, her serum potassium level stabilised at 4 mmol/L and bicarbonate levels normalised without bicarbonate supplementation. She was discharged 3 weeks later on a regimen of 16 mmol of potassium daily; her serum potassium level at discharge was 5 mmol/L.

Patient 2

A 37-year-old man presented with 3 days of progressive muscle weakness. He had been taking ibuprofen–codeine for several years, with a daily dose of 24 tablets (4.8 g ibuprofen). He was a smoker and denied taking any other medications. There was no history of diarrhoea or vomiting, and family history was unremarkable. He had proximal muscle weakness (graded 3/5) with hyporeflexia and muscle tenderness, but sensation was preserved. Initial investigation revealed a very low serum potassium level (2 mmol/L) and biochemical features consistent with dRTA (Box 1).

The ibuprofen–codeine was ceased, and intravenous KCl was administered for 4 days (10–30 mmol/h) with 112 mmol of oral potassium/day. The weakness resolved after 2 days. Oral sodium bicarbonate supplementation (2520 mg/day for 9 days) contributed to normalisation of serum bicarbonate levels. Symptoms of overt opioid withdrawal developed on Day 3 and buprenorphine treatment was commenced. He was discharged on Day 9 after cessation of potassium and bicarbonate supplements, with a serum potassium level of 4 mmol/L.

Patient 3

A 45-year-old woman, with a remote history of intravenous drug use, presented after 7 days of lethargy and anorexia. She had multiple dental caries, and for several months had ingested 9.6–14.4 g/day of ibuprofen (about 50 tablets per day). She took no other medications and had an unremarkable family history and physical examination.

Initial investigations revealed hypokalaemia (potassium, 2 mmol/L) with acute kidney injury, renal potassium wasting and biochemistry consistent with dRTA (Box 1). Gastroscopic investigation of microcytic anaemia found gastric antral ulceration with a peptic oesophageal stricture. No cause for RTA other than ibuprofen overdose was found.

Ibuprofen was ceased, and intravenous sodium bicarbonate and KCl (220 mmol over 3 days at a maximum rate of 10 mmol/h) were administered. Concurrent oral potassium replacement occurred at 60 mmol/day. On discharge, 5 days later, renal function was normal and the serum potassium level was 3 mmol/L.

Patient 4

A 40-year-old man presented with a 2-day history of profound generalised weakness associated with hypokalaemia (potassium, 1 mmol/L). He had consumed 1.4–2.0 g/day of ibuprofen for 3 months for degenerative back pain. There was no history of diarrhoea or vomiting, he took no other medications and had no significant family history, and he was a smoker.

1 Baseline laboratory investigations and other characteristics of four patients with ibuprofen-induced renal tubular acidosis

	Reference range	Patient 1	Patient 2	Patient 3	Patient 4
Sex, age in years		Female, 32	Male, 37	Female, 45	Male, 40
Ibuprofen dose*		0.6–4.0 g/day	4.8 g/day	9.6–14.4 g/day	1.4–2.0 g/day
Other medications		Citalopram 20 mg/day; no complementary medicines, laxatives, diuretics or illicit drugs	No prescription medicines, laxatives, diuretics or illicit drugs	No other prescribed or over-the-counter medicines	No other prescribed, over-the-counter or complementary medicines, diuretics or laxatives
Serum					
pH	7.32–7.43	7.26	7.28	7.16 (venous)	7.27
P_{CO_2}, mmHg	37–50	21	32	22	27
HCO_3^-, mmol/L	22–32	10	14	8	11
Anion gap	7–17	10	8	16	15
Na^+, mmol/L	134–146	141	140	134	141
Cl^-, mmol/L	98–108	122	120	112	116
Urea, mmol/L	3.8	3.9	5.4	18.0	6.0
Creatinine, µmol/L	60–110	106	83	222	83
K^+, mmol/L at presentation	3–5	1	2	2	1
K^+, mmol/L on discharge	3–5	5	4	3	3
Urine					
pH		6.5	6.9	6.5	6.5
Na^+, mmol/L		63	49	35	42
K^+, mmol/L		25	25	22	25
Cl^-, mmol/L		85	69	32	78
Anion gap		3	5	25	–11

P_{CO_2} = partial pressure of carbon dioxide. HCO_3^- = bicarbonate ion. Na^+ = sodium ion. Cl^- = chloride ion. K^+ = potassium ion. * Maximum recommended: 3.2 g/day. ◆

The patient had normal vital signs apart from bradycardia (50 beats/min), with generalised flaccid weakness (graded 1–2/5) with preserved reflexes and sensation. An ECG demonstrated sinus bradycardia with prolonged QTc interval and U waves.

Initial biochemistry results (Box 1) were consistent with RTA. Although the urine pH of 6.5 was higher than expected for the low serum bicarbonate level (11 mmol/L), proximal RTA (pRTA) was diagnosed in view of the negative urine anion gap and findings suggesting proximal tubular dysfunction. These included hypouricaemia (0.18 mmol/L; RR, 0.20–0.42 mmol/L), hypophosphataemia (0.40 mmol/L; RR, 0.8–1.5 mmol/L) and mild proteinuria.

As there were no features suggesting alternative causes for pRTA, ibuprofen was considered the most likely causative factor, and was discontinued. Intravenous potassium (1010 mmol over 3 days at a maximum rate of 20 mmol/h), bicarbonate (total dose, 500 mmol) and phosphate (total dose, 50 mmol) were administered under electrocardiographic monitoring. The patient's muscle strength improved within 24 hours and he was discharged 4 days later with a serum potassium level of 3 mmol/L. Potassium supplementation was ceased on discharge.

Discussion

Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), is widely used and readily available over the counter (OTC). Excessive ingestion of ibuprofen, in combination with codeine or alone, can result in ibuprofen toxicity, including RTA. In Australia, the maximum quantity of ibuprofen–codeine available OTC has recently been reduced from 72 to 28 tablets due to problems related to codeine misuse.

We have described four patients with profound hypokalaemia due to ibuprofen-induced RTA. This is an underreported complication, which may present with hypokalaemic paralysis. Three of the patients were admitted to the same tertiary care hospital within 3 months of each other. The remaining patient was admitted to a peripheral hospital the previous year. In each case, the differential diagnosis of hypokalaemia initially included transcellular potassium shift, renal potassium wasting and gastrointestinal losses. Medication histories were uniformly negative for drugs known to cause intracellular potassium movement. Thyroid function was normal and there was no family history of hypokalaemic periodic paralysis. Urinary potassium wasting was documented in all cases by excessive urine potassium excretion (> 20 mmol/day or spot urine potassium > 20 mmol/L) in the presence of hypokalaemia.[1] This was not explained by diuretic use or magnesium deficiency. The hyperchloraemic metabolic acidosis and non-acidified urine pH were in keeping with RTA. Gastrointestinal potassium and bicarbonate loss was unlikely in the absence of diarrhoea or laxative use. In two cases, gastric ulceration provided corroborative evidence for ibuprofen toxicity. Investigations found no alternative aetiology for RTA (Box 2). Ibuprofen cessation and supportive therapy allowed complete biochemical resolution within days.

2 Causes of renal tubular acidosis (RTA)[1]

Causes of proximal RTA

- Primary
- Secondary
  - With Fanconi syndrome (eg, multiple myeloma, light chain disease)
  - Drugs and toxins (acetazolamide, outdated tetracycline, aminoglycosides, sodium valproate, 6-mercaptopurine, streptozotocin, iphosphamide, lead, cadmium, mercury)
  - Associated with other clinical entities (vitamin D deficiency, hyperparathyroidism, chronic hypocapnia, cyanotic congenital heart disease, medullary cystic kidney disease, Alport syndrome, corticoresistant nephrotic syndrome, renal transplantation, amyloidosis, recurrent nephrolithiasis)

Causes of distal RTA

- Primary
- Secondary
  - Autoimmune diseases (eg, systemic lupus erythematosus, Sjögren syndrome, chronic active hepatitis, primary biliary cirrhosis, thyroiditis, fibrosing alveolitis, rheumatoid arthritis)
  - Drugs and toxins (amphotericin B, lithium, toluene, amiloride, trimethoprim, pentamidine, vanadium)
  - Calcium disorders (eg, primary hyperparathyroidism, vitamin D intoxication, idiopathic hypercalciuria with nephrocalcinosis)
  - Dysproteinemic syndromes (hypergammaglobulinemia, amyloidosis, cryoglobulinemia)
  - Renal diseases (eg, renal transplant rejection, medullary sponge kidney, obstructive and reflux nephropathy)
  - Liver disease (hepatic cirrhosis)
  - Genetic diseases (eg, osteopetrosis, sickle cell disease, Ehlers–Danlos syndrome) ◆

Unfortunately, no follow-up information could be obtained to ascertain whether the RTA was recurrent, or whether a previously unrecognised aetiology for RTA had become apparent.

Characteristics of RTA are summarised in Box 3. Renal acidification is impaired, resulting in a hyperchloraemic metabolic acidosis.[2] Hypokalaemia due to kaluresis is a feature of both proximal and distal RTA. Multiple factors contribute to hypokalaemia. Metabolic acidosis impairs proximal sodium reabsorption, leading to increased distal sodium delivery, secondary hyperaldosteronism and increased potassium secretion.[3] In distal RTA, impaired hydrogen ion excretion promotes potassium loss in exchange for sodium to maintain electroneutrality. Reduced H–K-ATPase pump activity results in reduced distal potassium reabsorption.[4]

Four previously published case reports[5-8] have described similar clinical presentations occurring with ibuprofen use of 4.8 to 28 g per day. However, one of our patients (Patient 4) developed RTA at a dose below the maximum recommended. No other NSAID has yet been implicated with this complication.

The mechanism by which ibuprofen induces RTA is unknown. Other nephrotoxic effects of NSAIDs, including acute and chronic kidney injury, interstitial nephritis and nephrotic syndrome, result from impaired synthesis of cytoprotective prostaglandins, a consequence of cyclo-oxygenase-1 (COX-1) inhibition. It is hypothesised that the pathogenesis of ibuprofen-induced RTA may involve carbonic anhydrase (CA) inhibition. CA catalyses the interconversion between carbon dioxide and bicarbonate and is crucial to renal acid–base regulation. It is present in renal proximal tubules and collecting ducts as well as a variety of other tissues, including bone, brain and gut.[9] Congenital CA deficiency is characterised by proximal and distal RTA, osteopetrosis and cerebral calcification.[10] High titres of an auto-antibody directed against CA II have been noted in some patients with dRTA associated with Sjögren syndrome.[11] Induction of these auto-antibodies has resulted in the development of RTA in a mouse model of Sjögren syndrome.[12] Other NSAIDs including aspirin[13] and flurbiprofen[14] have been shown to have CA-inhibitory activity in vitro. More recently, celecoxib and valdecoxib, which are COX-2 selective NSAIDs, have been demonstrated to be potent inhibitors of CA due to binding of their sulfonamide moiety to its zinc (Zn^{2+}) ion.[15] Although ibuprofen lacks a sulfonamide moiety, it can inhibit human and bovine erythrocyte CA II.[14] CA inhibition would be consistent with our observations of both proximal and distal RTA.

In conclusion, profound hypokalaemia due to RTA is a potentially fatal complication of ibuprofen use. Although it usually occurs with excessive doses, it can occur at doses below the maximum recommended. The pathogenesis is unknown but may involve CA inhibition. Opioid addiction with deliberate misuse of ibuprofen–codeine analgesics is common.[16] Therefore, ibuprofen toxicity should be considered in the differential diagnosis of patients presenting with severe hypokalaemia or hypokalaemic paralysis.

Competing interests

None identified.

3 Characteristics of renal tubular acidosis (RTA)[1]

	Distal RTA (type 1)	Proximal RTA (type 2)	RTA type 4
Primary defect	Impaired distal H^+ excretion	Impaired proximal HCO_3^- reabsorption	Decreased aldosterone secretion or effect
Plasma potassium	Usually reduced (hyperkalaemic forms exist)	Reduced	Increased
Urine pH	> 5.5	Variable: usually > 5.5 if plasma HCO_3^- > 16mmol/L; < 5.5 if plasma HCO_3^- < 16 mmol/L	< 5.5
Urine anion gap	Positive	Negative	Positive
Nephrocalcinosis	Common	Rare	Rare
Other tubular defects	Rare	Common (generalised proximal tubular dysfunction)	Rare

H^+ = hydrogen ion. HCO_3^- = bicarbonate ion. ◆

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