Medicines Adverse Reactions Committee

Meeting date	14/03/2024	Agenda item	3.2.1
Title	**Ibuprofen and renal tubular acidosis**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient Ibuprofen Ibuprofen + codeine Ibuprofen + paracetamol	**Product name** **Sponsor** Refer to section 2.3 Only products with published data sheets are listed.		
PHARMAC funding	Yes. Certain immediate release tablets, long-acting tablets and oral liquids are funded.		
International action	EU – updates to ibuprofen with codeine combination products, when taken at higher than the recommended daily dose UK – updates to all systemic ibuprofen products, in overdose and therapeutic doses		
Classification	Ranges from General Sales to Prescription medicine		
Usage data	Refer to section 2.4.		

Advice sought	**The Committee is asked to advise whether:**
	• The data sheets for *all ibuprofen containing products* taken systemically should carry warnings on renal tubular acidosis and hypokalaemia
	  o when taken at *higher than the recommended daily dose/overdose*?
	  o when taken *over long periods within the recommended daily dose*?
	• Further communication is required other than in MARC's remarks?		

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1 PURPOSE

In 2022, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (EMA's PRAC) requested that the product information for all ibuprofen with codeine combination products be updated with warnings that renal tubular acidosis (RTA) and severe hypokalaemia can occur. It was considered that the risk was higher with prolonged use of ibuprofen at higher than recommended doses and particularly in combination with codeine as patients may become dependent on the codeine component.

In the United Kingdom, the product information has been updated with similar warnings, however this warning has been extended to all systemic ibuprofen products (regardless of whether the product contains codeine). In contrast to the EMA request to warn of RTA and hypokalaemia when ibuprofen is taken over prolonged periods at higher than recommended doses, the UK product information has been updated to say the risk may occur following acute overdose and in patients taking ibuprofen products over long periods at high doses, including doses exceeding the recommended daily dose.

In New Zealand, there is one approved product containing ibuprofen with codeine. This data sheet has been updated with warnings that RTA and hypokalaemia have been reported when taking ibuprofen with codeine at higher than recommended doses. The Committee is asked to consider whether the data sheets for all systemic ibuprofen products should include a warning on RTA and hypokalaemia, and if this risk can also occur in patients taking ibuprofen over long periods within the recommended daily dose.

2 BACKGROUND

2.1 Ibuprofen

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID), having anti-inflammatory, analgesic and antipyretic properties. These properties provide symptomatic relief of pain and inflammation [1]. The therapeutic effects of ibuprofen are thought to result from its inhibitory effect on the enzyme cyclooxygenase which results in a marked reduction in prostaglandin synthesis [2].

Ibuprofen is used in conditions associated with pain, inflammation and fever. Such conditions include rheumatoid arthritis, osteoarthritis, back pain, post-operative pain relief, dysmenorrhoea and fever [1].

Ibuprofen has the following classification in New Zealand (Table 1).

Table 1: Classification of ibuprofen in New Zealand

Ingredient	Conditions (if any)	Classification
Ibuprofen	**except** when specified elsewhere in this schedule	Prescription
Ibuprofen	for oral use in tablets or capsules containing up to 400 milligrams per dose form and in packs containing not more than 50 dose units and that have received the consent of the Minister or the Director-General to their distribution as restricted medicines and that are sold in the manufacturer's original pack labelled for use by adults and children over 12 years of age; for oral use in powder form containing 300 milligrams per dose with a recommended daily dose of not more than 1.2 grams and sold in the manufacturers original packs containing not more than 12 dose units, and labelled for use in adults and children over 12 years of age.	Restricted
Ibuprofen	for oral use in liquid form with a recommended daily dose of not more than 1.2 grams for the relief of pain and reduction of fever or inflammation when sold in the manufacturer's original pack containing not more than 8 grams; for oral use in solid dose form containing not more than 200 milligrams per dose form and with a recommended daily dose of not more than 1.2 grams when sold in the manufacturer's original pack containing not more than 100 dose units; **except** in divided solid dosage forms for oral use containing 200 milligrams or less per dose form with a recommended daily dose of not more than 1.2 grams and when sold in the manufacturer's original pack containing not more than 25 dose units	Pharmacy Only
Ibuprofen	for external use; in divided solid dosage forms for oral use containing 200 milligrams or less per dose form with a recommended daily dose of not more than 1.2 grams and when sold in the manufacturer's original pack containing not more than 25 dose units per pack	General Sale

Source: Medsafe classification database https://www.medsafe.govt.nz/profs/class/classintro.asp (accessed 19 February 2024).

Comments:

Systemic ibuprofen sold over-the-counter (ie, general sale, pharmacy medicine and restricted medicine) can only recommend a maximum daily dose of 1.2 grams. Daily doses above this can only be supplied on a prescription.

In adults, the daily dose of systemic immediate release ibuprofen can range from 1200 mg to 1800 mg in divided doses, although some patients can be maintained on lower doses. In severe or acute conditions, the dose may be increased up to 2400 mg [2].

In general, patients with rheumatoid arthritis and osteoarthritis tend to require higher doses than patients with other conditions [2].

Systemic ibuprofen also comes as a 800 mg slow-release formulation. The recommended daily dose is 1600 mg per day, but in severe or acute conditions, it may be increased to 2400 mg per day [3].

Comments:

In general, the maximum oral daily dose of ibuprofen is 2400 mg. Other reference sources state a maximum daily dose of 3200 mg.

Some literature expresses the maximum dose by body weight as 30 mg/kg/day.

To reflect the approved maximum dose in the local data sheets, this report will consider a daily dose of oral ibuprofen >2400 mg to be above the daily therapeutic dose.

2.2 Acid-base regulation and renal tubular acidosis

The lungs and kidneys are responsible for maintaining acid-base balance in the body [4]. The kidney specifically[5]

- Reabsorbs bicarbonate that is filtered by the glomeruli. The majority of the filtered load is reclaimed in the proximal tubule of the nephron. Under normal conditions, when a typical Western diet is ingested (typically acid generating), there is virtually no bicarbonate in the final urine.
- Excrete acid in the form of hydrogen ions. This is done primarily in the distal tubule.

Renal disorders due to the removal of bicarbonate or acid handling in the presence of relatively preserved glomerular filtration are collectively referred to RTA. RTA is characterised by a hyperchloremic (normal anion gap) metabolic acidosis. RTA is uncommon and the condition is in most cases undiagnosed [4].

RTA can be inherited (eg, genetics) or acquired (eg, from tubulointerstitial diseases, autoimmune diseases, medicines and idiopathic causes), with the former being much rarer [4]. RTA can be broadly grouped into four subtypes. Type 1, 2 and 3 RTA correlate with the three mechanisms that facilitates renal acid-base handling (Table 2 and Figure 1). Type 3 RTA is a mix of type 1 and 2 RTA. Type 4 RTA differs from the former RTAs, where the underlying defect is due to aldosterone deficiency [4].

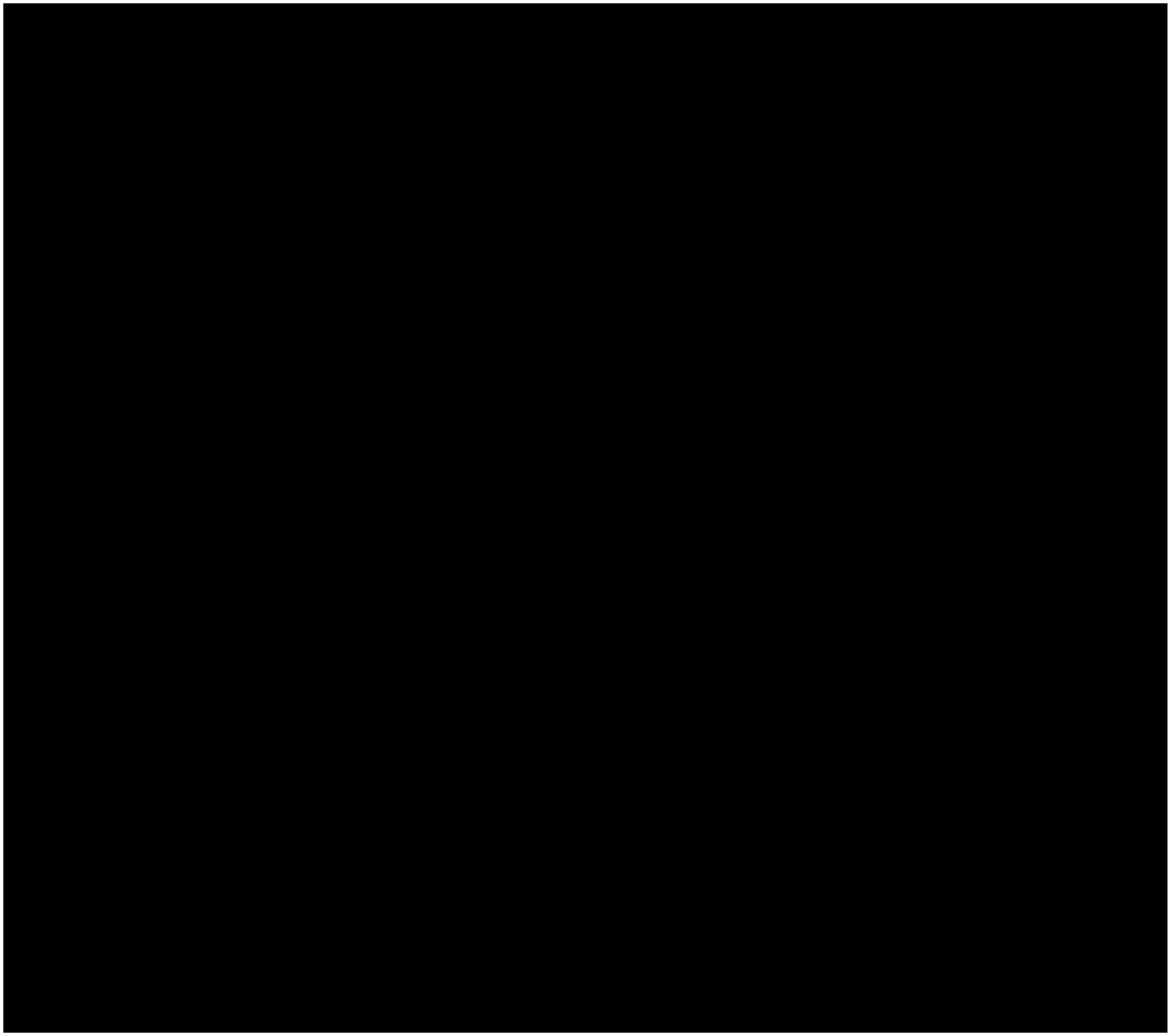
Alteration in potassium secretion is common in RTA, and depending on the site of defect, can result in hypokalaemia (in the case of type 1 and 2 RTA) or hyperkalaemia (in the case of type 4 RTA) [5] .

Table 2: Characteristics of type 1, 2 and 4 renal tubular acidosis [6]

Type	Distal (type 1) RTA	Proximal (type 2) RTA	Hyperkalaemic/hypoaldosteronism (type 4) RTA
Primary defect	Deceased distal acid excretion (through decreased net activity of H^+-ATPase or H^+/K^+-ATPase, or increased H^+ membrane permeability	Decreased proximal reabsorption of filtered bicarbonate	Decreased aldosterone secretion or effect. Reduced excretion of acid and K^+ in the collecting duct
Symptoms	Polydipsia, polyuria, muscle weakness, nephrolithiasis, nephrocalcinosis, growth retardation or failure to thrive, rickets	Muscle weakness or paralysis (if severely hypokalaemia), growth retardation in early childhood	Often asymptomatic, occasional muscle weakness of cardiac arrythmia
Urine pH	>5.3 (alkaline)	<5.5 (acidic)	
Serum bicarbonate	10-20 mmol/L	16-20 mmol/L	16-22 mmol/L
Serum chloride	High		
Serum potassium	Low (< 3.5 mmol/L)		High (5.5-5.6 mmol/L)
Serum anion gap	Normal		
Urine potassium	Potassium wasting	Potassium wasting	-
Diagnostic tests	Positive urinary anion gap after $NH4^+$ loading test	Fractional excretion of $HCO3^-$ > 15% or urine pH > 7.5 after HCO3-loading test. Glucosuria, hypophosphatemia, and hypouricemia indicates Fanconi syndrome.	Urinary K^+ < 40 mmol/L, or fractional K^+ excretion < 20%, abnormal serum aldosterone, with near-normal renal function.

Note: Table adapted from Palmer et al.

Figure 1: A schematic diagram illustrating the underlying kidney tubule defects causing the different types of renal tubular acidosis and location within the nephron [6]



The treatment for drug-induced type 1 and 2 RTA involves withdrawing the offending medicine, if possible [7]. Alkali therapy (usually with sodium bicarbonate or potassium citrate) is needed to correct the metabolic acidosis [4]. Potassium supplements may be required if there is hypokalaemia [4].

2.3 Review of New Zealand data sheets

The data sheets for all systemic ibuprofen containing products were reviewed for warnings on RTA, hypokalaemia and acidosis (Table 3). Note that not all registered products in New Zealand containing systemic ibuprofen have a data sheet due to its classification.

Table 3: Review of New Zealand data sheets for products containing ibuprofen used systemically as at 14 February 2024

Ibuprofen				
Product (sponsor)	**RTA**	**Hypokalaemia**	**Acidosis**	**Data sheet wording**
Nurofen 12 Hour (Reckitt Benckiser)	×	×	✓	Metabolic acidosis in overdose (section 4.9)
Nurofen 400 Double Strength (Reckitt Benckiser)	×	×	✓	Metabolic acidosis in overdose (section 4.9)
Brufen (Viatris)	×	×	✓	Metabolic acidosis in overdose (section 4.9)
Brufen SR (Viatris)	×	×	✓	Metabolic acidosis in overdose (section 4.9)
Ibugesic (Rex Medical Ltd)	×	×	✓	'Acidosis' listed as an ADR in section 4.8. Note: metabolic acidosis not listed in section 4.9
Ibuprofen (Viatris)	×	×	✓	Metabolic acidosis in overdose (section 4.9)
Ibuprofen (Neo Pharma Limited)	×	×	✓	Metabolic acidosis in overdose (section 4.9)
Ibuprofen SR BNM (BNM Group)	×	×	✓	Metabolic acidosis in overdose (section 4.9)
Ibuprofen Ethics oral liquid (Multichem NZ Ltd)	×	×	✓	Metabolic acidosis in overdose (section 4.9)
Fenpaed oral suspension (AFT Pharmaceuticals Ltd)	×	×	✓	Metabolic acidosis in overdose (section 4.9)
Ibuprofen with paracetamol				
Product (sponsor)	**RTA**	**Hypokalaemia**	**Acidosis**	**Data sheet wording**
Brufen Extra (Viatris)	×	×	✓	Acidosis listed as an ADR in section 4.8 Metabolic acidosis in overdose for the paracetamol component only (section 4.9)
Maxigesic IV (AFT Pharmaceuticals Ltd)	×	×	✓	Acidosis listed as an ADR in section 4.8 Metabolic acidosis in overdose for the paracetamol component only (section 4.9)
Maxigesic tablet (AFT Pharmaceuticals Ltd)	×	×	✓	Acidosis listed as an ADR in section 4.8 Metabolic acidosis in overdose for the paracetamol component only (section 4.9)
Mersynofen (Sanofi-aventis)	✓	✓	✓	Note: this data sheet is not yet published. **Section 4.4:** *Renal disorders* Renal tubular acidosis and hypokalemia may occur following ibuprofen overdose with/without a prolonged treatment period. Presenting signs and symptoms include reduced level of consciousness and generalized weakness. Ibuprofen induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis. **Section 4.8:**

				Renal and urinary disorders: Unknown: hypokalaemia and renal tubular acidosis (typically following prolonged use of ibuprofen at higher than recommended doses). **Section 4.9:** Metabolic acidosis in overdose for the paracetamol component only (section 4.9). Renal tubular acidosis and hypokalemia with/without prolonged treatment period. Symptoms may include reduced level of consciousness and generalised weakness.
Ibuprofen with codeine				
Product (sponsor)	**RTA**	**Hypokalaemia**	**Acidosis**	**Data sheet wording**
Nurofen Plus (Reckitt Benckiser)	✓	✓	✓	**Section 4.4:** Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of ibuprofen/codeine at higher than recommended doses, due to the development of codeine dependency. Symptoms may include reduced level of consciousness and generalised weakness. **Section 4.8:** Renal tubular acidosis* with an ADR frequency 'Not known' Hypokalaemia* with an ADR frequency 'Not known' *Renal tubular acidosis and hypokalaemia have been reported following chronic overdose of the ibuprofen component, due to dependence on the codeine component. **Section 4.9:** Metabolic acidosis in overdose (in section 4.9). Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

Comment:

The Nurofen Plus and Mersynofen data sheets have warnings on RTA and hypokalaemia, but in higher than the recommended dose (ie, using the EMA's wording).

Most data sheets have information on 'acidosis' or 'metabolic acidosis' in overdose in section 4.9 but does not mention RTA and hypokalaemia.

2.4 Usage

Information on the number of people dispensed a community-funded ibuprofen product is outlined in Table 4. This data represents only ibuprofen taken orally as these are the only funded products. This data does not include ibuprofen purchased over-the-counter.

Table 4: Number of people dispensed a community-funded ibuprofen product in 2018-2022

Year	Number of people dispensed*
2018	778,726
2019	825,265
2020	685,868
2021	730,112
2022	865,885

*Number of people who received a dispensing of a pharmaceutical product as a named person from a pharmacy at lease once during the year (includes people who only received a repeat dispensing during the year).

Source: Pharmaceutical Data web tool: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (date accessed 26 February 2024).

3 SCIENTIFIC INFORMATION

3.1 Published literature

A literature search found one recent systematic review and limited case reports/series. This section summarises the systematic review by Man et al (2022), and case reports identified in the literature. Table 7 summarises the case reports where ibuprofen with codeine was implicated, while Table 8 summarises case reports where ibuprofen without codeine was implicated. Highlighted in yellow are cases where ibuprofen was taken within therapeutic doses.

3.1.1 Systematic review

3.1.1.1 Man et al (2022) – Ibuprofen-associated hypokalaemia and metabolic acidosis: systematic literature review [8]

Background: A few published case reports describe subjects with hypokalaemia, metabolic acidosis or both after the ingestion of ibuprofen, however this association has never been systematically studied. The aim of the paper was to review the literature on this issue and to address the underlying pathophysiology through a systematic review.

Methods: A search of case reports were conducted in various databases. Cases were included if reported in humans on ibuprofen treatment, with otherwise unexplained hypokalaemia (< 3.5 mmol/L), metabolic acidosis (pH < 7.38 and bicarbonate < 20 mmol/L), or both.

Cases of hypokalaemia, acidosis or both observed after ingestion of ibuprofen > 40 mg/kg body weight were classified as intentional, accidental or dosage mistake.

Cases occurring after ingestion of ibuprofen for >1 week were considered chronic ingestions.

Results: Forty-one articles were identified, describing 50 cases (14 in children and 36 in adults).

A summary of the clinical and laboratory data from these patients is outlined in Table 5, categorised broadly as acute, chronic and all ingestions.

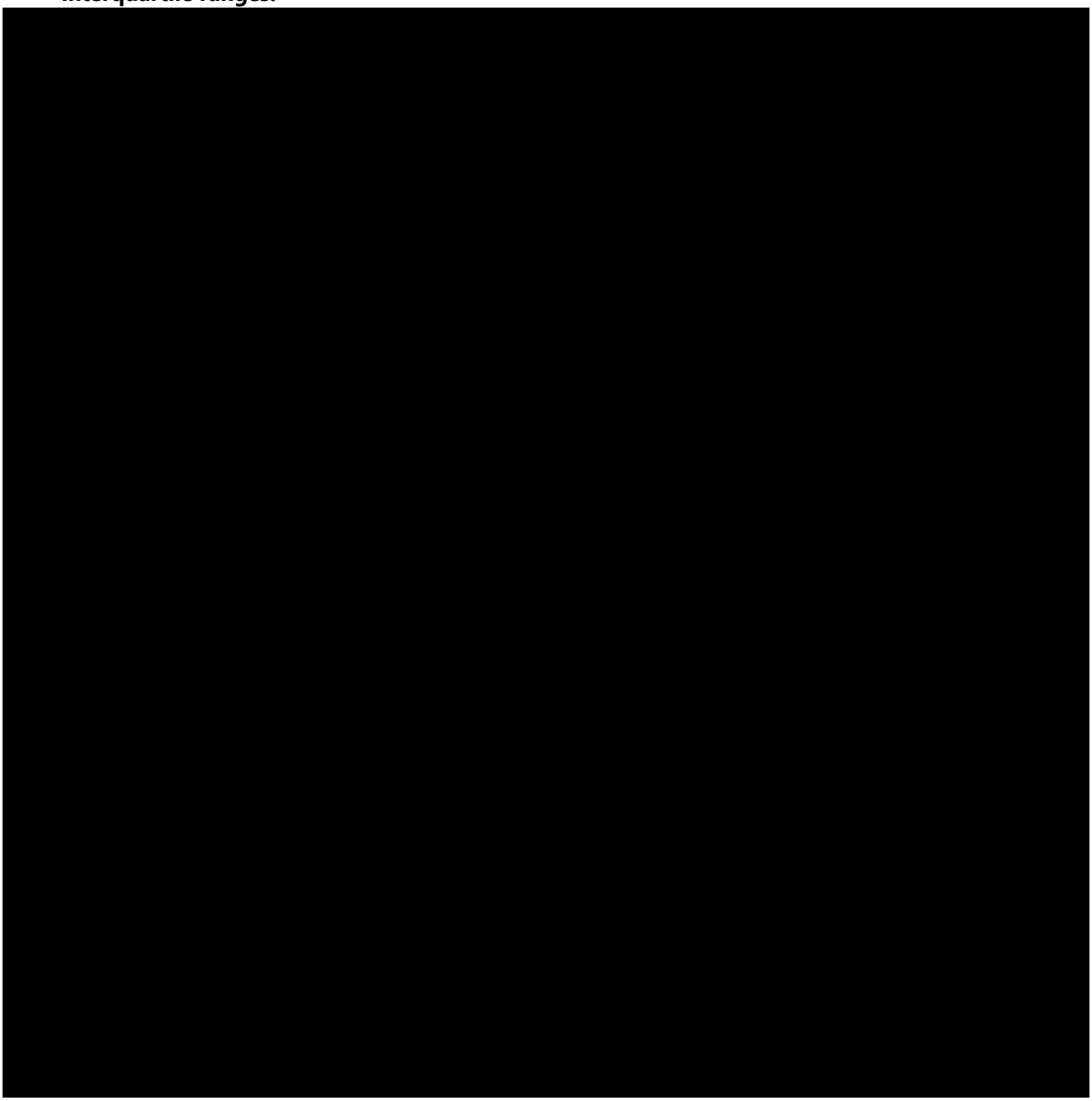
Hypokalaemia or acidosis were observed in 44 (88%) of patients who ingested an excessive amount of ibuprofen (> 40m/kg body weight/day). Six patients (12%) ingested a normal amount.

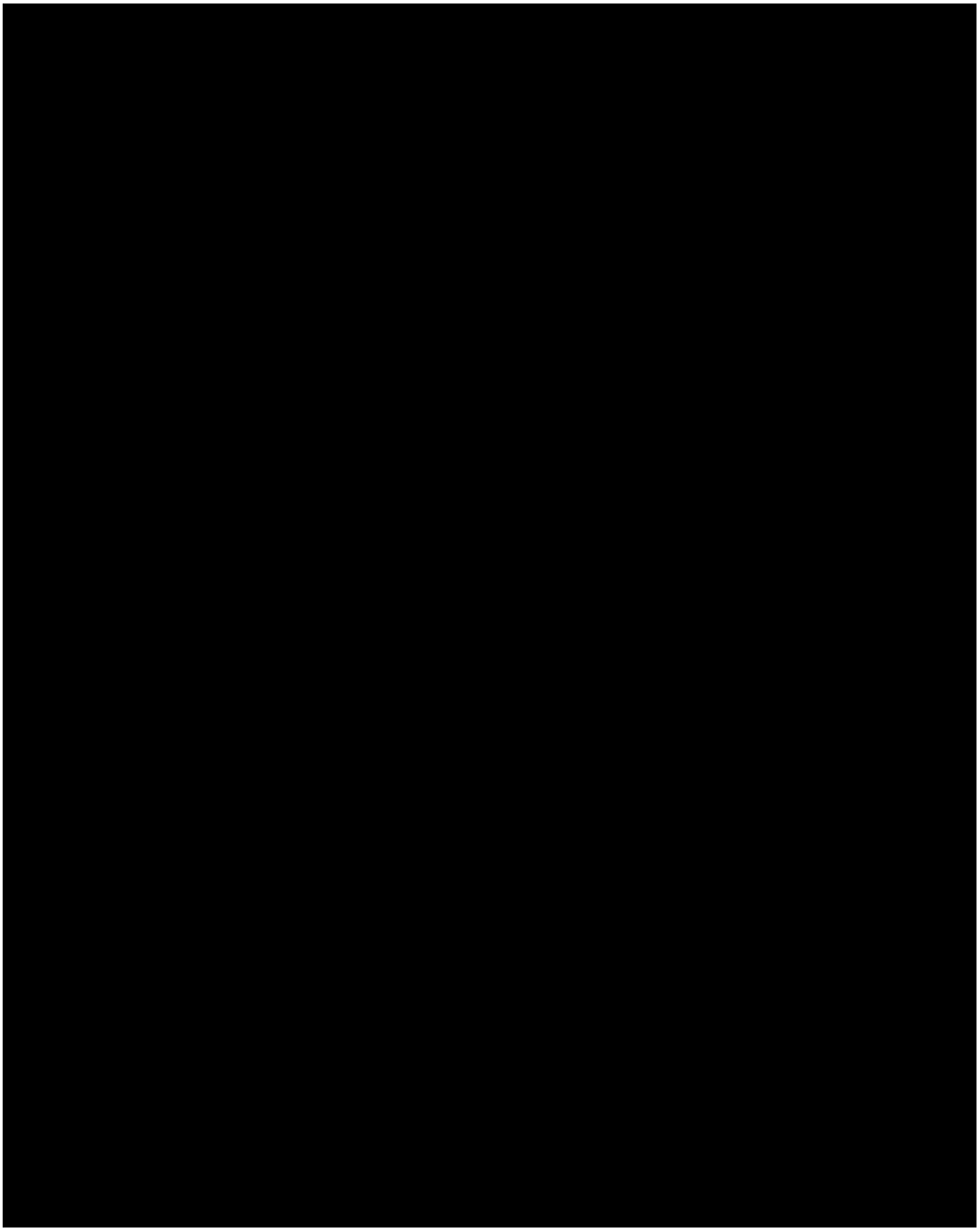
Twenty-four were observed after a single dose of ibuprofen: 96 mg/kg in one case, 101-500 mg/kg in five cases, 501-1000 mg/kg in nine cases, >1000 mg/kg in eight cases (this information was not provided in one case). Two ingested ibuprofen 28 mg/kg body weight daily, respectively 67 mg/kg body weight daily for three days or less.

The remaining twenty-four cases were considered chronic.

Twenty-two of the patients with chronic treatment were observed after ingestion of ibuprofen 40 mg/kg body weight or less daily (n=5), 41-100 mg/kg body weight daily (n=6), or >100 mg/kg body weight daily (n=11). The duration of ingestion was two weeks (n=1), 1-3 months (n=8), 4-12 months (n=7), more than 12 months (n=3) and unspecified (but more than two weeks) in three cases. The remaining two cases received an unknown amount of ibuprofen for more than 12 months.

Table 5: Clinical and laboratory data in patients with both metabolic acidosis and/or hypokalaemia associated with acute and chronic ibuprofen ingestion. Continuous data are shown as median and interquartile ranges.





The renal tubular handling of potassium or acid-base balance was investigated in 19 cases. Urinary findings consistent with an altered renal tubular function were noted in 14 of them (Table 6).

Table 6: Urinary investigations indicative of a disturbed renal tubular function in patients with acute and chronic ibuprofen ingestion. Continuous data are shown as median and interquartile ranges.

Discussion:

The severity of acidosis was similar in acute and chronic cases. In contrast, hypokalaemia was more common and severe in chronic cases. The blood anion gap, which is usually normal in the context of hypokalaemia and acidosis of renal origin, was higher in acute as compared with chronic cases. This observation suggests that further factors may have contributed to the development of metabolic acidosis in many cases, including accumulation of lactic acid or fasting ketosis.

The authors note that overdose symptoms in general does not typically present at doses ≤ 100 mg/kg/day. In addition, serious symptoms are not expected until doses ≥ 200 mg/kg/day are ingested. This analysis showed that hypokalaemia and acidosis may occur also in patients ingesting a normal amount of this agent (< 40 mg/kg body weight daily) and in cases ingesting a 'non-toxic' amount ranging from 40 to 100 mg/kg body weight daily.

Author's conclusion: Acute and chronic ingestion of ibuprofen can induce profound hypokalaemia and acidosis of renal origin. These derangements occur not only after ingestion of very high doses, but also after ingestion of moderately high or even normal doses of ibuprofen.

Comment:

In summary, this systematic review identified 50 case reports of metabolic acidosis, hypokalaemia, or both following ibuprofen use. Whilst the majority of the cases (n=44, 88%) were found to be taken more than recommended dose (defined as > 40 mg/kg of body weight per day), 6 patients (12%) were taking normal therapeutic doses of ibuprofen.

48% of cases (n=22) occurred following chronic ingestion of ibuprofen, of which five cases were observed following ingestion of ibuprofen within the recommended doses.

32% (n=16) cases involved concomitant use of codeine, although the review did not distinguish whether these were combination products.

Please note that since this systematic review is quite recent, there is the possibility that case reports in Tables 7 an 8 below may already be included in this review and may not necessarily represent more cases.

3.1.2 Case reports of renal tubular acidosis from ibuprofen with codeine

Table 7: Case reports in the literature of renal tubular acidosis from ibuprofen with codeine exposure

Author and (year), reference number	Presenting signs/symptoms	Investigations and diagnosis	Exposure	Comments (author's comments are not italicised)
Blackstock et al (2012), [9]	38-year old female with a two day history of confusion, agitation and 'restless, swollen legs'.	CT brain and lumbar puncture normal. Potassium 1.9 mmol/L Sodium 146 mmol/L Phosphate 0.57 mmol/L Chloride 122 mmol/L Renal function normal. Arterial blood gas showed compensated metabolic acidosis. ECG showed ST segment depression and U-waves. No ectopic beats or arrythmias. Serum anion gap of 9 mmol/L, urinary anion gap of 20 mmol/L Transtubular potassium gradient of 11.37 Diagnosis: RTA	20-40 Nurofen Plus tablets (200mg ibuprofen with 12.8mg codeine) per day during the preceding weeks.	The authors commented that the prolonged and excessive intake of Nurofen Plus was likely due to the codeine component, resulting in opiate dependence.
Chetty et al (2002), [10]	28-year old female with a two day history of generalised weakness but no neurological deficits. She was unable to stand up or hold her neck straight.	Potassium 1.4 mmol/L Sodium 141 mmol/L Creatinine 65 µmol/L Calcium 2.54 mmol/L Phosphate 0.43 mmol/L Bicarbonate 14.7 mmol/L Chloride 112 mmol/L Anion gap 15.7 mmol/L Urine potassium 26.6 mmol/L ECG showed prolonged QT interval and inverted T waves. Diagnosis: RTA type 2 (proximal)	40-60 tablets of Nurofen Plus per day, and on and off over the last 2-4 years.	

Dang et al (2016), [11]	34-year old male with a four day history of evolving generalised weakness and myalgia. Further investigation also confirmed a diagnosis of rhabdomyolysis.	Potassium 2.0 mmol/L Bicarbonate 19 mmol/L Anion gap 12 mmol/L Venous blood gas revealed a mild metabolic acidosis with pH 7.37. Urine potassium 31 mmol/L ECG showed widespread ST depression, T wave inversion and prominent U waves and SR elevation, consistent with hypokalaemia. Diagnosis: RTA	Taking over the counter ibuprofen and codeine containing products for the past 14 years, with a daily dose of 60 tablets (12 grams of ibuprofen).	This case illustrates a rare occurrence of rhabdomyolysis in a patient presenting with ibuprofen-induced RTA and hypokalaemia.
Ernest et al (2010), [12]	39-year old with a three day history of right leg weakness progressing to profound weakness of all limbs but with preserved reflexes. No sensory disturbances noted, muscle tenderness or clinical features suggestive of either spinal or intracranial pathology.	Hypokalaemia 1.8 mmol/L Hypophosphatemia 0.63 mmol/L Serum creatinine kinase 9,394 IU/L raised suggesting rhabdomyolysis Normal serum magnesium, urea and creatinine Urinary sodium 104 mmol/L Urinary potassium 22 mmol/L ECG showed sinus rhythm with U waves	Admitted that three days prior, 6L of Red Bull energy drink, 1875mL of a homeopathic preparation and 72 tablets of Nurofen Plus (total 14,400mg ibuprofen and 922 mg of codeine) were ingested.	The authors commented that the patient's hypokalaemia was most probably attributable to the significant ingestion of Nurofen Plus. However, it is difficult to determine the single cause because of the unusually high doses of multiple substances ingested. *Comment: The diagnosis of RTA was not mentioned in this case report, so unsure if this is a case of hypokalaemia secondary to RTA.*
Li et al (2019), [13]	33-year old female with reduced but fluctuating conscious state following a few days of confusion with constipation and vomiting. History of several weeks of general malaise and severe fatigue.	ECG showed sinus rhythm with prolonged QTc and inferolateral ST depression. Venous blood glass showed hyperchloremic metabolic acidosis with a normal anion gap (12.1 mmol/L) and elevated lactate (3.2 mmol/L). Laboratory test showed neutrophilia (26.74 x10^9/L), profound hypokalaemia (1.4 mmol/L), hypernatremia (151 mmol/L), hypophosphatemia (0.4 mmol/L), and hypercalcaemia (2.7 mmol/L). Blood evaluation showed mild rhabdomyolysis with a creatinine kinase level of 3,002 IU/L. CT brain and lumbar puncture were unremarkable. Possible sepsis of uncertain source. Diagnosis: RTA without an unconfirmed aetiology. The urine pH consistently above 6 supported a Type 1 (distal) renal tubular acidosis, but	Had been taking Nurofen Plus for at least the last 2 months and sometimes up to 32 tablets a day.	

		without urine electrolytes, this could not be confirmed. Pneumonia. The fluctuating conscious state was consistent with either an infective or non-infective encephalopathy.		
Mallet et al (2011), [14]	34-year old female with nausea, emesis, and diarrhoea at 36 weeks gestation.	Serum: creatinine 144 umol/L, urea 4.0 mmol/L, eGFR 36 mL/min, potassium 2.4 mmol/L, bicarbonate 11 mmol/L, chloride 111 mmol/L Acute renal dysfunction, hypokalaemic hyperchloremic metabolic acidosis and normal serum anion gap. Hyperchloremic metabolic acidosis in this patient may have been present since at least 16 weeks gestation. Glycosuria (a potential marker of proximal tubular function) was absent throughout. Distal tubular function was impaired as shown by the consistent urinary pH of 5.5 and a positive urinary anion gap (6 mmol/L). Diagnosis: Type 1 RTA (distal).	The patient had been consuming between 30 and 90 tablets of ibuprofen 200 mg/codeine phosphate 12.8 mg per day for the previous six years. Other substances detected: benzodiazepines, cannabis metabolites, amphetamine-like substances, methadone and opiates.	*Comments: this case is complicated by pregnancy and that several substances detected upon drug screening. However, the authors state that none of these substances have reported a significant association with RTA.*
Ng et al (2011), [15]	Case 1: 32-year old female with a two day history of evolving paralysis, epigastric pain without diarrhoea or vomiting. There was general flaccid weakness with normal sensation.	Serum potassium: 1 mmol/L, pH 7.26, bicarbonate 10 mmol/L, chloride 122 mmol/L, anion gap 10 mmol/L Urine pH: 6.5, sodium 63 mmol/L, potassium 25 mmol/L, chloride 85 mmol/L, anion gap 3 mmol/L ECG: widespread ST-segment depression and U waves. Diagnosis: distal RTA.	Had been consuming ibuprofen with codeine over a prolonged period – ibuprofen component 0.6-4.0 grams per day.	
Ng et al (2011), [15]	Case 2: 37-year old male presented with three days of progressive muscle weakness with hyporeflexia and muscle tenderness.	Serum: potassium 2 mmol/L, bicarbonate 14 mmol/L, chloride: 120 mmol/L, anion gap 8 mmol/L Urine: potassium 25 mmol/L, pH 6.5, sodium 49 mmol/L, chloride 69 mmol/L, anion gap 5 mmol/L Diagnosis: distal RTA.	Had been consuming ibuprofen with codeine for several years (4.8 grams of ibuprofen per day)	
Thammineni et al (2019), [16]	Case 1: A 52-year old male was referred to the ED for severe hypokalaemia. He had chronic right shoulder	Serum: potassium 1.9 mmol/L, bicarbonate 17 mmol/L, sodium 139 mmol/L, chloride 106 mmol/L, anion gap of -16 mmol/L ECG showed mild QT prolongation Diagnosis: Ibuprofen-induced hypokalaemia and proximal RTA	Had taken ibuprofen for the past three months. He started with five tablets/day and increased to 35 tablets/day to achieve	

	pain, back pain, loss of weight about 15 pounds in the last two months, loss of appetite, and difficulty with walking up and down the stairs for the past few days before presentation.		adequate pain control. Other medicines included acetaminophen and tramadol.	
Thammineni et al (2019), [16]	Case 2: 63-year old female presented with ED with epigastric pain, nausea and vomiting for ten days.	Serum: potassium 2.0 mmol/L, sodium 139 mmol/L, chloride 106 mmol/L, bicarbonate 17 mmol/L, anon gap 16 mmol/L, BUN 85 mg/dL, and creatinine of 3.9 mg/dL. Urine: pH 6.0, sodium 17 mmol/L, potassium 23.7 mmol/L, chloride 28 mmol/L, anon gap 12.7 mmol/L. EC showed normal sinus rhythm. Hyperaldosteronism was ruled out. Diagnosis: distal RTA.	Reported taking ibuprofen 800 mg on an average of 10-12 tablets/day for the past 10 months. Denied taking any other medicine.	
Lambert et al (2005), [17]	45-year old female was admitted to hospital three times with low serum potassium. Showed drowsiness and generalised weakness in the last two admissions.	First admission: serum potassium 2.6 mmol/L with normal creatinine. On the third admission to hospital: • Arterial pH 7.4, serum HCO3 19 mmol/L, chloride 110 mmol/L, anion gap 18 mmol/L. • Urine: pH 7.0, 24 hour urine potassium 120 mmol Urine drug screen was positive for ibuprofen, paracetamol, opioids and benzodiazepines. She was subsequently readmitted after self-poisoning with Nurofen Plus. Diagnosis: RTA	Regularly consuming 28 grams of ibuprofen per day.	*Comments: Not clear from case narrative if the person was taking 28 grams of just ibuprofen or in combination with codeine.*
Ter et al (2008), [18]	36-year old female presented with a two day history of generalised weakness of limbs. Two days prior she had been exercising vigorously and developed muscle pain.	Serum: potassium 1.7 mmol/L, creatinine 282 mmol/L, urea 12.8 mmol/L, chloride 95 mmol/L, anion gap 25 mmol/L Arterial blood gas showed metabolic acidosis with a pH 7.2. Urine: sodium 42 mmol/L, potassium 12.4 mmol/L, urea 27 mmol/L and osmolality of 134 mOsm/kg. The urine osmolal gap was −1.8. High 24-hour potassium wasting of 175 mmol/24 hours. ECG changes consistent with hypokalaemia. Diagnosis: type 1 RTA.	Had been taking eight tablets of ibuprofen with codeine (200mg + 12.8 mg) every day for three months.	The author also noted that she re-presented to hospital with similar symptoms a month later. On this occasion she had hypokalaemic with hypochloraemic metabolic acidosis, with a normal anion gap. However, the patient denied use of further NSAIDs during this time. A diagnosis of longstanding type 1 RTA was made.

Comments:

Cases were generally quite young. Not surprisingly, cases of RTA from ibuprofen with codeine products occurred in overdoses and not at therapeutic doses.

3.1.3 Case reports of renal tubular acidosis from ibuprofen without codeine

Table 8: Case reports in the literature of renal tubular acidosis from ibuprofen without codeine exposure (cases highlighted in yellow represents ibuprofen exposure within therapeutic dose)

Author and (year), reference number	Presenting signs/symptoms	Investigations and diagnosis	Exposure	Comments (author's comments are not italicised)
Hwij et al (2017), [19]	65-year old with altered mental status	Serum: potassium 2.2, HCO3 9, BUN 18, creatinine 0.69, Urine: potassium 13, sodium 63, chloride 71, anion gap 5, pH 6.5 Venous blood gas: pH 7.179 Diagnosis: RTA type 1.	Ibuprofen was the presumed underlying culprit as she had more than 6 months of daily use of ibuprofen 800 mg twice daily. After ibuprofen was stopped and with supportive management her symptoms as well as her laboratory investigations improved.	
Ghimire et al (2023), [20]	66-year old male presented to hospital with a 1-week history of increasing lethargy and confusion. Otherwise, unremarkable review of other systems.	Investigations showed acute kidney injury, hypokalaemia, hyperchloremia, and non anion gap metabolic acidosis with elevated urinary pH and positive urine anion gap. [redacted] Studies suggested impairment in renal ammonium excretion and renal potassium wasting.	Had been taking tablets containing ibuprofen 200 mg—methocarbamol 500 mg per tablet (*Robax Platinum*) to treat chronic back pain with 80 tablets used the month prior.	The patient was admitted to hospital 5 months prior for persistent diarrhoea where he was found to have mixed anion gap metabolic acidosis and non anion gap metabolic acidosis with decreased level of consciousness requiring intubation and intensive care admission. This was likely due to starvation ketoacidemia with coexisting diarrhoea-associated non-anion metabolic acidosis. Given his hypokalaemia non anion gap metabolic acidosis in the setting of heavy ibuprofen-methocarbamol

		Diagnosis: hypokalaemia RTA		use with no other identifiable causes, the authors felt his NAGMA was most likely secondary to ibuprofen use. *Comment: Although the case states 80 tablets taken in the space of a month, there is no indication on how the ibuprofen was taken and whether this was in normal- or over-dose.*
Ng et al (2011), [15]	Case 3: 45-year old female presented with a seven day history of lethargy and anorexia.	Serum: potassium 2mmol/L, pH 7.16, HCO3 8 mol/L, chloride 112 mmol/L, anion gap 16 mmol/L Urine: potassium 22 mmol/L, pH 6.5, chloride 32 mmol/L, anion gap 22 mmol/L Diagnosis: Distal RTA.	For several months, she had ingested 9.6-14.4 grams of ibuprofen per day.	The patient was not on any other medicines or OTC products when the RTA occurred.
Ng et al (2011), [15]	Case 4: 40-year old male with a two day history of profound generalised weakness but preserved reflexes and sensation.	ECG showed sinus bradycardia with prolonged QT interval and U waves. Serum: potassium 1 mmol/L, pH 7.27, HCO3 11 mmol/L , chloride 116 mmol/L, anion gap 15 mmol/L Urine: potassium 25 mmol/L, pH 6.5, chloride 78 mmol/L, anion gap -11 mmol/L. Diagnosis: proximal RTA	Had been taking 1.4-2.0 grams of ibuprofen per day for three months.	No other medicines or significant family history noted.
Oladele et al (2016), [21]	48-year old male presented with progressive muscle weakness for the past ten days.	Serum: potassium < 1.5 mmol/L, BUN 68 mg/dL, creatinine 3.84 mg/dL, chloride 78 mmol/L, sodium 123 mmol/L, and HCO3 7 mmol/L. Urine: pH 5.5, potassium 118 mmol/L, sodium 80 mmol/L, chloride 56 mmol/L Toxicology screen was negative.	Had been taking 10-12 tablets (600mg/tablet) of ibuprofen every 4-6 hours almost daily for about year	
Ragunanthan et al (2023) (abstract only), [22]	38-year old male presented to ED with new-onset agitation and confusion.	Brain imaging and blood and urine cultures were unremarkable. Laboratory investigations were notable for ammonia 74 umol/L, albumin of 4.4 g/dL (3.2 - 5.2), potassium of 2.8 mmol/L, venous pH of 7.22, venous pCO2 of 36 mmHg, serum bicarbonate of 15 mmol/L, anion gap of 16, creatinine of 0.97 mg/dL (0.80 - 1.50) correlating to eGFR 102 mL/min/1.73m2, and glucose of 58 mg/dL (65 - 199). Diagnosis: Type 1 RTA.	Had been taking ibuprofen 800 mg every 6 to 8 hours and oxycodone.	

Salter et al (2013), [23]	38-year old female presented with myalgia, evolving paralysis and vomiting for three weeks.	Serum: potassium 2.1 mmol/L, pH 7.25, HCO3 15 mmol/L, sodium 141 mmol/L, chloride 115 mmol/L Mild transaminitis, an inflammatory response with white cell count of $27.1x10^9$/L and procalcitonin 108 U/L with normal C-reactive protein. Normal renal function. Possible myositis with a creatinine kinase level 2,500 U/L, and a creatinine kinase level 85 umol/L. Urine: myoglobin was 266,900 u/L, pH 9, potassium 22 mmol/L, sodium 105 mmol/L. ECG showed mild ST depression without U waves. Diagnosis: Type 1 RTA with rhabdomyolysis, and a possible differential of undifferentiated myositis.	Was taking 1.2–2 g of Nurofen (ibuprofen) and 8 Fiorinal dental capsules (contains paracetamol 500 mg, codeine phosphate 10 mg, and doxylamine succinate 2 mg) daily for the past five weeks.	*Comments: Although the authors attribute RTA from the use of ibuprofen and codeine, it appears that ibuprofen was not in a fixed-dose combination with codeine.*
Wu et al (2015), [24]	45-year old presented to hospital with unexplained generalised weakness and acidaemia.	pH of 6.89 Serum: HCO3 5 mmol/L, potassium 2.5 mmol/L, hyperchloremia (result not stated) Urine: pH 7.0 Toxicology screening negative for alcohol and drugs of abuse. Conclusion: distal RTA secondary to ibuprofen.	Ibuprofen detected in serum and urine.	The patient did not have any underlying co-morbidities and reported only taking pantoprazole. *Comments: Case report did not specify duration and dose of ibuprofen use.*
Gaul et al (1997) (abstract only), [25]	72-year old female presented with acute tetraparesis.	Serum potassium 1.4 mmol/L, metabolic acidosis with a pH 7.29 ECG showed ST-segment depression and U wave.	Was taking ibuprofen up to 4.8 grams per day for six months.	
Patil et al (2018), [26]	48-year old female presented with diffuse myalgias and severe generalised weakness of all extremities and polyuria for a few weeks.	Serum potassium 1.2 mmol/L, sodium 141 mmol/L, chloride 111 mmol/L, CO2 16 mmol/L, creating kinase 28,880 IU/L, venous blood gas pH of 7.27 Urine: pH 6.5, potassium 20.5 mmol/L and a 24-hour potassium of 104mmol/24 hours suggesting potassium wasting, sodium 69 mmol/L, chloride 78 mmol/L. Also noted hypophosphatemia and urinary phosphate wasting, possible due to the patient's underlying vitamin D deficiency. Diagnosis: distal RTA and nontraumatic rhabdomyolysis secondary to severe hypokalaemia, likely due to ibuprofen use.	Had been taking about 20 tablets of ibuprofen tablets daily (~4 grams per day) for the last 3 months.	

Chávez-Iñiguez et al (2018), [27]	42-year old male presented with altered mental and severe respiratory distress. Had difficulty walking and standing for the past two weeks.	Serum: pH 7.06, HCO3 11.3 mmol/L, potassium 0.9 mmol/L, chloride 109 mmol/L, anion gap 16 mmol/L Urine: pH 6, spot urine potassium 7.1 mmol/L, anion gap 16 mmol/L. Unremarkable immunological tests. ECG showed mild ST depression with U wave. Diagnosis: ibuprofen-induced distal RTA.	Was taking ibuprofen 3.2 grams per day for headache over the preceding five months, and increased to 4.8 grams per day because of flu symptoms.	
Mandal et al (2020), [28]	45-year old female was found collapsed and noted to have flaccid quadriparesis. Noted to have an analgesia addiction, and had presented seven times over 12 months with acute paralysis after ibuprofen ingestion.	Hypokalaemia (1.3 mmol/L) Hyperchloremia (120 mmol/L) Normal anion gap 10.7 mmol/L, metabolic acidosis with a pH 7.06. Urine: pH of 6.5, and 24-hour potassium output showed potassium wasting (139 mmol/L). ECG: showed large-amplitude U waves with normal corrected Q-au interval. Diagnosis: Type 1 distal RTA.	Ibuprofen poisoning (daily dose and duration not stated)	

3.1.4 Possible mechanisms and discussion on a drug-class effect

The pathophysiology behind renal tubular acidosis from ibuprofen use is not well understood. However, a consistent mechanism described in the literature is inhibition of carbonic anhydrase II activity. This isoform of the enzyme carbonic anhydrase is predominantly found in both proximal and distal tubules of the nephron, converting carbon dioxide and water into bicarbonate which is then retained in the respective site [11, 20]. Ibuprofen inhibition of carbonic anhydrase II activity is thought to lead to proximal and distal RTA or a combination of both (type III RTA) [20].

In terms of other NSAIDs, aspirin and flurbiprofen have also been shown to have carbonic anhydrase inhibitory effect *in vitro*. The COX-2 inhibitors, celecoxib and valdecoxib have shown to be potent inhibitors of this enzyme in animals [15]. Despite these non-human studies, case reports of RTA in the literature have not been identified for other NSAIDs. [redacted]

4 SPONTANEOUS REPORTS

4.1 New Zealand reports

The reaction terms 'acidosis', 'metabolic acidosis', 'renal tubular disorder', 'renal tubular acidosis' and 'hypokalaemia' were used to interrogate the local database for potential ibuprofen-induced RTA reports.

Up to 31 January 2024, the Centre for Adverse Reactions Monitoring (CARM) had received two reports of acidosis/metabolic acidosis/RTA where ibuprofen was reported as the suspect/co-suspect medicine (Table 9).

Table 9: New Zealand reports of acidosis/RTA where ibuprofen was listed as the suspect/co-suspect medicine

ICSR ID	Age in years	Sex	Medicines (suspect bolded) and dose	Treatment start/stop dates date of reaction Reactions
107512	63	F	**Ibuprofen** [redacted] Candesartan Tramadol	**Start/stop dates, onset date:** [redacted] **Reactions:** Acidosis Pancreatitis
132202	35	F	**Ibuprofen** [redacted] Paracetamol	**Start/stop dates, onset date:** [redacted] **Reactions:** Renal tubular disorder Hypokalaemia Muscular weakness

Comments:

Case# 107512 reported the events of acidosis and pancreatitis, [redacted]

In both cases, the reactions occurred in the context of ibuprofen without codeine, [redacted]

For a relatively small database and rare disorder, it is interesting to see an event of RTA being reported with ibuprofen.

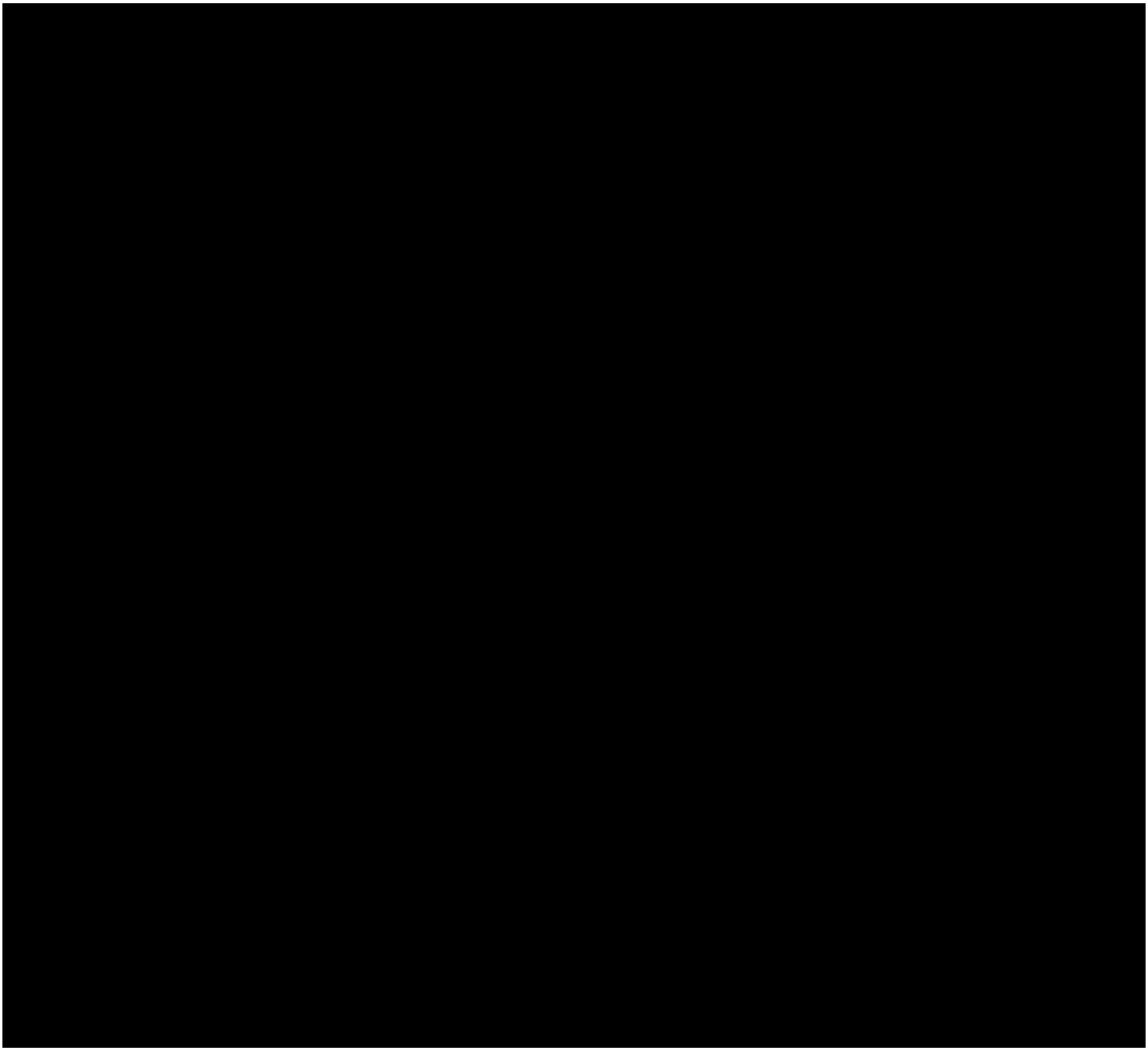
4.2 World Health Organization VigiBase

VigiBase is the World Health Organization's global database containing Individual Case Safety Reports (ICSRs) submitted by over 130 countries. Some participating members may submit ICSRs even when the medicine was not considered the suspect medicine.

[redacted]

Comment:
A positive IC value indicates that a particular drug-reaction pair is reported more often than expected, based on all the reports in the database. Conversely, a negative IC value means that the drug-reaction pair is reported less frequently than expected. A positive IC value does not imply causality and can be influenced by reporting bias, among other factors.
The $IC_{0.25}$ is the lower limit of the 95% credibility interval for the IC. It provides information about the stability of a particular IC, with the narrower the interval, the higher the stability.

[redacted]



5 REVIEW OF INTERNATIONAL DATA SHEETS

A review of international product information is provided for ibuprofen with codeine, ibuprofen, and ibuprofen with paracetamol (Table 11).

Table 11: International data sheet review of ibuprofen containing products as at 14 February 2024.

Australian product information (all data sheets were reviewed)		
	RTA and Hypokalaemia	**Metabolic acidosis**
Ibuprofen	No information	Section 4.9 – listed as a symptom of overdose for ibuprofen
Ibuprofen with codeine	No information	Section 4.9 – listed as a symptom of overdose for ibuprofen
Ibuprofen with paracetamol	No information	Section 4.9 – listed as a symptom of overdose for ibuprofen
UK product information (only the Nurofen data sheets were reviewed)		
	RTA and Hypokalaemia	**Metabolic acidosis**
Ibuprofen (Nurofen) Ibuprofen with codeine (Nurofen Plus) Ibuprofen with paracetamol (Nuromol)	**Section 4.4** *Renal* Renal tubular acidosis and hypokalaemia may occur following acute overdose and in patients taking ibuprofen products over long periods at high doses (typically greater than 4 weeks), including doses exceeding the recommended daily dose. **Section 4.8** Renal tubular acidosis* with an ADR frequency 'Not known' Hypokalaemia* with an ADR frequency 'Not known' *Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component at higher than recommended doses. **Section 4.9** Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).	**Section 4.9** In serious poisoning metabolic acidosis may occur…

EU product information (Nurofen data sheets published by the Irish regulator were reviewed)		
	RTA and Hypokalaemia	**Metabolic acidosis**
Ibuprofen	No information	**Section 4.9** In serious poisoning metabolic acidosis may occur…
Ibuprofen with codeine (Nurofen Plus)	**Section 4.4** *Renal* Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of ibuprofen at higher than recommended doses. This risk is increased with the use of codeine/ibuprofen as patients may become dependent on the codeine component (see warning on Opioid use disorder, section 4.8 and section 4.9). Presenting signs and symptoms included reduced level of consciousness and generalised weakness. Ibuprofen induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis. *Opioid use disorder (abuse and dependence)* Serious clinical outcomes, including fatalities, have been reported in association with abuse and dependence with codeine/ibuprofen combinations, particularly when taken for prolonged periods at higher than recommended doses. These have included reports of… renal tubular acidosis and severe hypokalaemia associated with the ibuprofen component. **Section 4.8** Renal tubular acidosis* with an ADR frequency 'Not known' Hypokalaemia* with an ADR frequency 'Not known' *Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component at higher than recommended doses due to dependence on the codeine component. **Section 4.9** Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).	
Ibuprofen with paracetamol	No data sheet found.	

6 DISCUSSION AND CONCLUSIONS

In 2022, the EMA requested that all sponsors of ibuprofen with codeine combination products update their product information with warnings that RTA and severe hypokalaemia have been reported due to prolonged use of ibuprofen at higher than recommended doses, and that the risk is increased due to dependency of the codeine component. The sponsors of ibuprofen products not containing codeine were not required to update their product information. The UK has applied this warning to all ibuprofen containing products (regardless of whether the product contains codeine) and that RTA and hypokalaemia may occur in long term treatment with doses that are high but within therapeutic limits.

This paper reviews whether the current available information supports these updates and in particular, if the risk of RTA and hypokalaemia can occur in patients taking ibuprofen (regardless of whether it contains codeine or not) within therapeutic doses.

A literature review identified one systematic review and a number of case reports describing RTA and hypokalaemia following ibuprofen use.

The systematic review by Man et al identified 41 published articles containing 50 case reports of profound hypokalaemia, acidosis, or both after ingestion of ibuprofen. This review identified that in most cases the patient had taken more than recommended dose (defined as > 40 mg/kg of body weight per day), however 12% of the cases (n=12) occurred following use of ibuprofen taken at the recommended dose. Of the 50 case reports, 16 patients (32%) were taking codeine concomitantly, although the paper did not distinguish whether this was a combination product.

Individual case reports in the literature describe RTA and hypokalaemia occurring following ibuprofen with and without codeine. Further, there have been reports of these reactions occurring within therapeutic doses, often after prolonged periods of time. Details of these case reports often describe non-specific signs and symptoms of altered mental status and muscle weakness. This highlights the potential need to alert healthcare professionals to consider the possibility of RTA in patients who present with unexplained hypokalaemia and metabolic acidosis.

[redacted]

In New Zealand, there have been two cases of acidosis following ibuprofen use of which one reported RTA. [redacted]

Ibuprofen inhibition of carbonic anhydrase II found in the nephron has been described as the potential mechanism of RTA. Non-human studies have shown that other NSAIDs may also inhibit this enzyme, however there have been no case reports identified in the literature. [redacted]

At the current time, most ibuprofen data sheets in New Zealand list metabolic acidosis as a symptom of overdose. Only the data sheets for Mersynofen (ibuprofen with paracetamol) and Nurofen Plus (ibuprofen with codeine) contain warnings on RTA and hypokalaemia in the context of overdose/when used higher than the recommended dose in sections 4.4, 4.8 and 4.9 of the data sheets.

7 ADVICE SOUGHT

The Committee is asked to advise whether:

- The data sheets for *all ibuprofen containing products* taken systemically should carry warnings on renal tubular acidosis and hypokalaemia
    - when taken at *higher than the recommended daily dose/overdose*?
    - when taken *over long periods within the recommended daily dose*?

- Further communication is required other than in MARC's remarks?

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