Accidental overdose of proprietary branded, combination analgesics available over the counter

Introduction

This article presents two cases of accidental overdose involving proprietary branded over the counter combination analgesic medication, where both patients were unaware of potential side effects of the compounds. In the first case the patient presented with an acute confusional state associated with profound metabolic acidosis related to excessive intake of a combination analgesic for poorly controlled back pain. In the second, the patient presented with profound gastrointestinal upset related to use of the same drug, in this case after excessive ingestion related to opiate addiction. These cases demonstrate the potential hidden dangers of combination analgesic abuse and are a reminder that medical staff should always be mindful of unintentional overdose in patients presenting acutely with unexplained symptoms.

Discussion

Non-steroidal anti-inflammatory drug overdose is most typically asymptomatic or associated with mild gastrointestinal symptoms, such as nausea, vomiting and diarrhoea. Massive acute overdose classically presents with a severe metabolic acidosis, which can proceed to muscle weakness with respiratory depression, renal failure and coma (Wood et al, 2006; Hunter et al, 2011). Gastrointestional ulceration and haemorrhage are less common in acute over-dosage compared to chronic abuse, as in these cases.

Fatalities following ibuprofen self-poisoning are rare. Nine cases have been reported, eight with alternate or contributing causes of death, including co-ingestion of other toxins, sepsis and refusal of treatment for renal failure. The single death attributed solely to ibuprofen comprised intake of 100 g of sustained release ibuprofen with severe metabolic acidosis and haemodynamic compromise on presentation (Wood et al, 2006).

Non-steroidal anti-inflammatory drugs act predominantly via cyclooxygenase inhibition, preventing prostaglandin synthesis. Prostaglandins regulate inflammatory mediators, nociception and temperature control, accounting for the therapeutic effect of non-steroidal anti-inflammatory drugs, but are also vital in maintaining gastrointestinal mucosal integrity and renal blood flow, with resultant risk of gastrointestinal haemorrhage and renal failure. The toxic effects of non-steroidal anti-inflammatory drugs in overdose are mediated in part by COX inhibition resulting in renal arteriole vasoconstriction and renal hypoperfusion (Hunter et al, 2011; Ng et al, 2011).

Acidic metabolites cause the profound high anion gap metabolic acidosis seen particularly in massive overdose and often associated with significant CNS toxicity. An alternative mechanism of kidney injury and acidosis is by non-steroidal anti-inflammatory drug-induced renal tubule acidosis. Both type I (distal) and type II (proximal) are described, with a postulated mechanism of carbonic anhydrase inhibition preventing conversion of CO_2 to HCO_3 and therefore acid–base homeostasis. A renal tubule acidosis injury is

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Case Report 1

A 63-year-old woman presented acutely with an episode of confusion. Three months previously she had presented with a similar episode that had resolved spontaneously without a diagnosis being made. Investigations including a computed tomography scan of the head and lumbar puncture were normal. Her past medical history included depression and chronic back pain. She was prescribed duloxetine 30 mg once daily and omeprazole 20 mg twice daily. There was documentation of her having four diagnostic gastroscopies in the preceding 18 months demonstrating a non-healing pre-pyloric ulcer. Histology reported 'chronic inflammation most consistent with reflux or chemical type gastritis' and asked if there was a history of non-steroidal anti-inflammatory drug use. Advice to stop smoking and a prescribed medication history was documented at clinic review, but there was no mention of specific questioning regarding over the counter analgesic use.

On admission she was confused and disorientated. Clinical examination revealed global weakness with predominantly right-sided dystonia. She demonstrated a resting tremor, brisk reflexes and clonus. Biochemistry revealed deranged renal function with hypokalaemia of 2.8 mmol/litre and a raised C-reactive protein level at 150 mg/litre (*Table 1*). The international normalized ratio was raised at 1.6, albumin was 16 g/dl suggestive of impaired hepatic synthetic function and arterial blood gas revealed a profound metabolic acidosis (pH 7.17, HCO_3 11 mmol/litre). Anion gap was calculated at 10 (within normal range). Microbiology blood and urine samples revealed no evidence of infection. Abdominal computed tomography and magnetic resonance imaging brain scans were also normal.

On the third day of admission the patient regained lucidity and revealed that she had been taking over the counter medication for poorly controlled back pain. She had found relief from her back pain from large doses of codeine, and aware of the risks of paracetamol overdose, had been consciously avoiding paracetamol-based combination analgesics. As an alternative she had been taking Nurofen Plus (ibuprofen 200 mg, codeine phosphate 12.8 mg) in quantities of up to 34 tablets a day, resulting in a daily intake of 6.8 g of ibuprofen and 435 mg of codeine.

A diagnosis of overdose of non-steroidal anti-inflammatory medication was made. Her acidosis resolved with intravenous bicarbonate and she recovered with supportive treatment and cessation of the combination analgesic.

Table 1. Patients' admission biochemistry

Blood levels	Case 1	Case 2
pH	7.17	7.39
pCO_2 (kPa)	2.8	3.6
pO_2 (kPa)	25.7	26.1
Base excess	-17	-2.5
HCO_3 (mmol/litre)	11	21.9
Anion gap	10	Not applicable
Na (mmol/litre)	140	131
K (mmol/litre)	2.8	2.4
Urea (mmol/litre)	8.0	13.2
Creatinine (umol/litre)	124	75

typified by hypokalaemia, normal anion gap acidosis and non-acidified urine, with profound hypokalaemia being a predominant feature in ibuprofen overdose (Chetty et al, 2003; Dyer et al, 2004; Lambert and Close, 2005; Ernest et al, 2010).

There is increasing awareness of the risks associated with overdose of paracetamol but overdose, particularly in combination preparations, is still the commonest cause of acute liver failure in the United States and UK (Larson et al, 2005). Confusion regarding which drugs are being taken in what quantity can occur with over the counter medication, particularly in those using proprietary branding, and in particular with combination preparations where packaging does not always make it immediately obvious how much and which drugs are contained within (Fosnocht et al, 2008).

In the UK, restrictions have applied to the amount of paracetamol and salicylates that can be purchased over the counter at any one time since 16 September 1998. This has had the intended effect of reducing the number of both deliberate and accidental overdoses with consequent reductions in morbidity and mortality (Hawton et al, 2004; Craig et al, 2011). Branded compound preparations are widely available over the counter but many people, including many doctors, have a poor understanding of what is contained in each product. This can lead to accidental overdoses in the public and a failure to realise and diagnose the overdose by the admitting medical team.

Conclusions

There is a need for better understanding of the risks of over the counter combination analgesics both in the general public and within the medical profession. Clearer labelling of the different constituents of these preparations and appropriate warnings on packaging could reduce the risk of their accidental overdose and misuse. An increased awareness by medical staff of the complications relating to the misuse of these compounds could lead to prompt diagnosis and appropriate management of these often acutely ill patients. BJHM

Case Report 2

The second patient was a 41-year-old woman admitted from an inpatient drug detoxification centre, where she had been treated for 5 days for chronic codeine dependence. She presented with worsening abdominal pain, diarrhoea, hyponatraemia, hypokalaemia and microcytic anaemia. She had been using large doses of over the counter Nurofen Plus as part of her dependence on codeine and was ingesting a daily dose of over 500 mg of codeine with 8 g of ibuprofen.

On admission she complained of malaise and diarrhoea with blood gases showing a compensated metabolic acidosis (*Table 1*). Abdominal computed tomography revealed oedema surrounding the gastric antrum and pericolonic oedema. She went on to have a gastroscopy which revealed multiple giant gastric ulcers and a limited flexible sigmoidoscopy with poor views but an apparently normal rectosigmoid mucosa.

A diagnosis of non-steroidal anti-inflammatory drug-induced peptic ulceration and colitis was made. This patient also settled with conservative management and cessation of the non-steroidal anti-inflammatory drug. A follow-up gastroscopy confirmed healing of the gastric ulcers. Owing to persistence of diarrhoea a colonoscopy was carried out, terminating at the splenic flexure because of the presence of severely active colitis with rectosigmoid sparing. Histology was consistent with Crohn's disease. A clinical diagnosis of de novo inflammatory bowel disease precipitated by non-steroidal anti-inflammatory drug use was made and she is currently being treated with steroids and an aminosalicylate preparation.

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LEARNING POINTS

- Covert non-steroidal anti-inflammatory drug excess should always be considered when patients present with unexplained metabolic acidosis or recurrent gastric ulcer.
- Doctors should be aware of the ingredients contained in common over the counter combination analgesics and their potential consequences, particularly in patients with analgesic dependence.
- A thorough medication history includes a routine enquiry about over the counter, supplement or alternative medicine products.