CASE REPORT

Phentermine induced acute interstitial nephritis

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SUMMARY

Acute interstitial nephritis (AIN) has a number of medication-related aetiologies. Antibiotics, proton pump inhibitors and non-steroidal anti-inflammatory drugs are common causes; however, any medication has the potential to cause drug-induced AIN. We report the first case of phentermine-induced AIN. A Caucasian woman aged 43 years presented with a 5-week history of lethargy, left-sided lower abdominal pain, nausea and vomiting. She had been taking phentermine for weight loss for 9 months and had recently ceased the medication. The patient underwent a renal biopsy that showed a predominantly lymphohistiocytic interstitial infiltrate with a moderate number of eosinophils consistent with AIN. Phentermine is increasingly used for weight loss in obese patients. This is the first case implicating phentermine as the causative agent for drug-induced AIN. While rare, phentermine-induced AIN is a possible adverse reaction of phentermine. Physicians and patients need to be aware of this risk.

BACKGROUND

Acute interstitial nephritis (AIN) is an immune-mediated condition characterised by an inflammatory infiltrate in the kidney interstitium. The incidence of AIN is increasing worldwide due to rising rates of drug-induced AIN.^{1–3} Antibiotics (particularly penicillins), proton pump inhibitors and non-steroidal anti-inflammatory drugs are the most common causes of drug-induced AIN; however, virtually, any medication has the potential to precipitate AIN.

In Australia, rates of obesity are increasing with over 60% of adults and 25% of children estimated to be overweight or obese. Increasingly, medications are being prescribed as short-term adjuncts to aid in weight loss. Phentermine (Duromine) is a sympathomimetic amine (substituted amphetamine) that is licensed for short-term use (a maximum of 3 months) to aid in weight loss as part of a medically managed comprehensive weight loss programme and is one of the most commonly prescribed weight loss medications.⁴

CASE PRESENTATION

A Caucasian woman aged 43 years presented to hospital with a 5-week history of lethargy, nausea, vomiting and left-sided lower abdominal pain. These symptoms had been associated with a progressive polydipsia and polyuria. She had started phentermine 9 months ago to aid in weight loss. This had initially been successful with a reported weight loss of 13 kg. She had ceased the medication 5 weeks preceding her admission due to the development of symptoms and plateauing weight.

The patient had a medical history significant for depression for which she was taking long-term citalopram, Paget's disease of the breast requiring a bilateral mastectomy and obesity with a body mass index of 32.9 on admission. She was not on any other medication including over-the-counter or herbal medications and had not previously used recreational drugs. She was an ex-smoker having quit 4 years ago and did not drink alcohol. She had no previous or family history of renal or autoimmune disease. Her baseline renal function before starting phentermine was normal with an estimated glomerular filtration rate (eGFR) of >90 mL/min/1.73 m² (reference range >90 mL/min/1.73 m²) and serum creatinine 69 µmol/L (reference range 45–90 µmol/L).

On examination, she was euvolaemic with a blood pressure of 115/70 mm Hg and a pulse of 90. She was afebrile and remained so during the admission. Her examination was otherwise unremarkable with no rash or uveitis.

INVESTIGATIONS

Standard blood testing on admission showed a markedly raised serum creatinine of 629 µmol/L, a urea of 23.8 mmol/L (reference range 2.1–7.1 mmol/L) and an eGFR of 6 mL/min/1.73 m². The full blood count showed a normocytic anaemia with a haemoglobin count of 82 g/L (reference range 115–160 g/L) and a leucocytosis of 11.4×10⁹/L without eosinophilia. Inflammatory markers were elevated with a CRP of 92 mg/L (reference range <5 mg/L) and ESR of 140 mm/hour (reference range <12 mm/hour).

Urine microscopy showed a sterile pyuria with 100×10⁶/L leucocytes (<5/hpf) and 30×10⁶/L erythrocytes. Protein creatinine ratio was elevated at 165 g/mol/creatinine that was confirmed with a 24-hour urine protein measuring 1.8 g. No urinary casts or eosinophils were seen.

A CT kidney, ureter and bladder were unremarkable with kidneys of normal size and normal cortical thickness. There was no hydronephrosis.

With the exception of a mildly positive ANA (1:40 titre; reference range <40) and a elevated C3 (2.15; reference range 0.90–1.80), the glomerulonephritis screen, including ANCA, ENA, dsDNA, ASOT, anti-DNAse, HIV, hepatitis B, hepatitis C and serum and urine electrophoresis, was negative. Creatine kinase was normal.

A renal biopsy showed a tubulointerstitium infiltrated by lymphohistiocytic inflammatory cells with moderate numbers of eosinophils, plasma cells and small collections of neutrophils (figure 1). Tubulitis was noted with inflammatory cells focally infiltrating into the tubular basement membrane and tubular

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Figure 1 Kidney biopsy showing oedema with dense inflammatory cell infiltrate. Tubulitis is present with inflammatory cell infiltrate along the tubular basement membrane and into the tubular epithelium. Note normal glomerulus (H&E; original magnification ×200).

epithelium. These features were consistent with a diagnosis of AIN, with the presence of eosinophils supporting a drug-induced aetiology. There were no microabscesses or viral cytopathic changes and immunofluorescence staining was negative for immunoglobulin, complement and light chains. Glomeruli were normal. There was no evidence of chronic renal disease.

TREATMENT

A diagnosis of phentermine-induced AIN was made and the patient was started on a 3-day course of 500 mg intravenous methylprednisone followed by 60 mg oral prednisone for a 16-week weaning regime. The patient was discharged on pantoprazole 20 mg a day and sodium bicarbonate 840 mg two times per day.

OUTCOME AND FOLLOW-UP

The patient's serum creatinine peaked at 629 µmol/L on day 1 of admission. She was discharged on day 7 with a creatinine 449 µmol/L. At clinic review 1 month following discharge, the patient's creatinine measured 129 µmol/L with an eGFR of 44 mL/min/1.73 m².

DISCUSSION

We present the first reported case of drug-induced AIN related to phentermine use. Previously, drug-induced AIN from a combination phentermine and phendimetrazine (also a sympathomimetic amine) use and intermittent amphetamine use resulting in drug-induced AIN have been reported in two case reports.^{5 6} Our case is the first reported instance of isolated phentermine use as a cause of drug-induced AIN. Amphetamines (and their derivatives) can cause acute kidney injury through rhabdomyolysis, hyperpyrexia, cardiovascular shock or necrotising angitis⁷ as well as lead to chronic kidney disease through amphetamine-induced hypertension.⁸ There have also been case reports describing mesangiocapillary glomerulonephritis secondary to amphetamine use.⁸ However, AIN has not previously been described with phentermine use alone and it is unclear from these three cases whether drug-induced AIN is a class effect of amphetamines or limited to these three agents.

AIN has a heterogeneous presentation and the classic presentation of fever, rash and eosinophilia is seen in <10% of patients.⁹ More commonly, patients present with non-specific symptoms such as malaise, nausea and vomiting and in severe cases symptoms of acute renal dysfunction.⁹ In this case, the

development of AIN occurred after significant period of drug exposure. Classically, drug-induced AIN occurs days to weeks after exposure; however, it is increasingly being recognised that AIN can develop months after initiation of a medication.⁹ AIN can also be slowly progressive and as our case demonstrates, it is common for patients to have a delayed presentation to hospital with acute kidney injury.⁹

The mainstay of treatment in drug-induced AIN is the cessation of the offending agent.¹⁰ Corticosteroid therapy is often used; however, evidence for this is mixed.^{2 10 11} As this case demonstrates, the majority of patients with AIN have partial or complete renal recovery even in severe episodes.¹⁰ However, some patients do require long-term renal replacement therapy and this is more common in those with pre-existing chronic kidney disease.¹⁰

With an increasing prevalence of obesity in developed countries, antiobesity medication use is increasing. In 2011, ~2.74 million patients in the USA used antiobesity drugs.⁴ Eighty-nine per cent of these were prescriptions for phentermine and 25% of users took the medication for longer than recommended.⁴

The Therapeutic Goods Administration of Australia and the Food and Drug Administration of the USA have identified adverse reactions of phentermine that include cardiovascular, central nervous system, gastrointestinal, allergic and endocrine events.^{12 13} Primary renal dysfunction is not a known adverse reaction.

Phentermine is an effective weight loss drug and is increasingly being prescribed. We present the first case of phentermine-induced AIN. Physicians and patients should be aware of all the possible adverse events caused by phentermine, including the rare possibility of AIN.

Learning points

- ▶ Phentermine is a rare cause of drug-induced acute interstitial nephritis (AIN).
- ▶ The mainstay of treatment in AIN removal of the offending agent and though evidence is mixed, steroid therapy should also be considered.
- ▶ The majority of patients with AIN have complete or partial renal recovery even when severe.

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Contributors DR conceived the study. EXS wrote the manuscript with significant input and edits from GJW. All authors had final say over the manuscript.

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