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CASE REPORT

Loperamide-induced hypopituitarism

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SUMMARY

Loperamide is the most commonly used antidiarrhoeal medication in the UK. We report a serious and hitherto undocumented adverse effect of chronic use in a 45-year-old man with inflammatory bowel disease. He presented to the endocrine clinic with fatigue and low libido; biochemical assessment revealed hypogonadism and adrenal insufficiency without any elevated adrenocorticotropic hormone. When symptoms allowed, loperamide was reduced and a short synacthen test (SST) showed a 'clear pass' with a normal peak cortisol of 833 nmol/L. Later, worsening diarrhoea necessitated an escalation in loperamide use again. While taking a daily dose of 15–20 mg (recommended daily maximum 16 mg) reassessment revealed a fall in peak cortisol on SST to 483 nmol/L, a subnormal response. Clinicians should exercise caution when relying on loperamide to manage their patients' chronic diarrhoea and remain mindful of the possibility of drug-induced life-threatening adrenal insufficiency.

BACKGROUND

Loperamide, a phenylpiperidine derivative and a potent opioid μ-receptor agonist, is the most commonly used antidiarrhoeal medication in the UK. About 1.79 million prescriptions were issued in 2014[1] and it is also freely available 'over the counter'. Its popularity persists due to a combination of favourable efficacy and a reasonably limited side effect profile; predictable gastrointestinal side effects do occur, but it is widely considered to be a very safe and well-tolerated medication.

Loperamide is directly absorbed into the gut wall, exerting its effect on the myenteric plexus to reduce propulsive activity and increase intestinal transit time. Although gastrointestinal tract absorption is favourable, it is rapidly extracted by hepatic cytochrome P450 metabolism resulting in low levels in the systemic circulation (bioavailability<2%).[2] While extensively used in acute diarrhoea, a significant proportion of patients with chronic gastrointestinal disease take loperamide on a daily basis, often at relatively high doses. Prior studies have paid scant attention to the potential adverse effects of longer term ingestion.

We report a serious and hitherto undocumented adverse effect of chronic loperamide use following presentation to the endocrine clinic.

CASE PRESENTATION

A 45-year-old man presented with profound fatigue and loss of libido. A total colectomy with rectal pouch formation had been performed 2 years previously for ulcerative colitis. For a minimum of 6 months, the patient had been managing his chronic diarrhoea by taking loperamide in doses totalling 40–50 mg daily (recommended maximum dose 16 mg/day). No steroids had been used in the management of his inflammatory bowel disease for at least 2 years and there was no clinical concern that he was otherwise ingesting any corticosteroid. His only other medication was fluoxetine 20 mg and nefopam 60 mg three times a day.

INVESTIGATIONS

On initial assessment, biochemical testing revealed hypogonadism with a morning serum testosterone of 2.9 nmol/L (reference range 9–25). Profound fatigue prompted assessment of his hypothalamic–pituitary–adrenal (HPA) axis; following administration of 250 μg of synacthen (tetracosactide; adrenocorticotropic hormone (ACTH1–24)) his peak serum cortisol was subnormal at 243 nmol/L (table 1). In the context of his gonadal failure and adrenal insufficiency, plasma ACTH and gonadotropins were measured and found to be inappropriately within the normal range (ACTH 20 ng/L, luteinising hormone 3.1 U/L, follicle-stimulating hormone 2.0 IU/L), indicating pituitary dysfunction. Serum-free thyroxine, thyroid-stimulating hormone and prolactin were within reference range. A pituitary MRI revealed no structural abnormality which could account for this secondary adrenal failure and hypogonadism. He started hydrocortisone and testosterone replacement with rapid improvement in his symptoms.

Reassessment of HPA axis functioning was limited by his reliance on loperamide for symptom control and steroid replacement for adrenal failure. More than 2 years later, pouch inflammation was treated with antibiotics and an improvement in diarrhoeal symptoms facilitated a temporary reduction in loperamide to 4–6 mg daily for a 48-hour period. On this dose of loperamide, a repeat synacthen test showed a 'clear pass' with a normal peak cortisol of 833 nmol/L. Over subsequent months, worsening diarrhoea necessitated an escalation in loperamide use again. While taking a daily dose of 15–20 mg, biochemical reassessment revealed a fall in peak cortisol following synacthen to 483 nmol/L, a subnormal response. Assessment of HPA functioning at the time of increased symptom severity, but before escalation of loperamide, would have provided useful insights into whether or not his deteriorating physical health contributed to HPA axis suppression. Unfortunately, the severity of his symptoms meant this was not clinically feasible.

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Table 1 The dose–response relationship: stimulated cortisol results on variable doses of loperamide

	October 2012	February 2015	May 2015
Daily loperamide dose	50 mg	6 mg	20 mg
Response to synacthen	Serum cortisol (nmol/L)*		
Baseline	135	604	186
30 min	191	766	385
60 min	243	833	483
	Plasma ACTH (ng/L)†		
Baseline	20	64	13

The synacthen (tetracosactide) tests performed in 2015 were carried out 30 hours after the previous dose of hydrocortisone had been taken.
*Normal peak cortisol response to synacthen (tetracosactide) is 550 nmol/L or more.
†Reference range for plasma ACTH is 10–55 ng/L.
ACTH, adrenocorticotropic hormone.

OUTCOME AND FOLLOW-UP

This symptomatic deterioration has resulted in sustained use of high-dose daily loperamide. The patient continues on steroid replacement and testosterone replacement.

DISCUSSION

It is well recognised that potent opioids, used either as analgesic medications or for illicit recreation, may produce dose-related hypopituitarism, including clinically significant hypoadrenalism and male hypogonadism.[3 4] For illustration, 74% of community dwelling men taking strong opioids (≥20 mg morphine daily or equivalent) had a total serum testosterone concentration below the reference range in a previous study.[5] Similarly, secondary adrenal failure has been frequently reported during both short-term and chronic opioid administration.[6–8] Opioids act centrally to suppress the hypothalamic release of the hormones corticotropin-releasing hormone (CRH) and gonadotropin-releasing hormone, leading to the downstream effects of hypoadrenalism and hypogonadism.

Although clinically manifest hypopituitarism in the setting of loperamide use has not been previously described, the effects of this drug on human HPA physiology were first reported in 1986 when it was found to inhibit plasma ACTH levels in a small number of patients with Addison's disease. 16 mg of oral loperamide induced a marked fall in ACTH levels that was detectable 1-hour postdose and persisted for several hours after administration, with a nadir at 300 min.[9] Similar reductions in basal and CRH-stimulated ACTH have also been demonstrated in normal persons.[10] Plasma levels of ACTH were markedly suppressed 3 hours after oral ingestion of 16 mg of loperamide, with both studies supporting a hypothalamic–pituitary mechanism for the effects observed in our patient.

While adrenal failure in the context of loperamide has not previously been reported, the overlapping chemical structure of this drug with opioids supports the mechanism of secondary adrenal failure seen here with high-dose loperamide.

Learning points

- Adrenal failure secondary to hypopituitarism is a serious and hitherto unrecognised side effect of this very commonly used medication.
- Critically, it was demonstrable in this patient while taking a quantity of loperamide just marginally higher than the maximum recommended dose.
- Failure to recognise adrenal failure in this setting, where warning symptoms and signs (eg, hyponatraemia, hypotension) may overlap with either acute or chronic gastrointestinal disease, could have a disastrous impact.
- Opioids, used more commonly at higher doses with significant systemic absorption than loperamide, can cause dose-related hypopituitarism and clinically significant adrenal failure.
- It is imperative that clinicians exercise caution when relying on loperamide to manage their patients' chronic diarrhoea; we should be mindful of the possibility of drug-induced life-threatening adrenal insufficiency.

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Competing interests None declared.

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