Introduction

Diabetes is associated with significant gastrointestinal symptoms including constipation, diarrhoea and faecal incontinence. Advanced glycation end products, as a consequence of poor glycaemic control, lead to damage to cellular DNA and tissues in the myenteric nerve plexus causing autonomic neuropathy. This affects gut motility leading to constipation or diarrhoea. The diarrhoea experienced can be acute, intermittent, or chronic, and have a significant impact on drug absorption, nutrition, glycaemic control and quality of life. Identifying and treating this is likely to have a positive effect on the general well-being of individuals living with diabetes.

Loperamide is an antidiarrhoeal agent that has been widely used for 40 years, and may be useful in the management of diarrhoea in diabetics. It has a good efficacy and safety profile and in 1988 the Food and Drug Administration approved loperamide for over the counter use.

Pharmacology

Figure 1 illustrates the pharmacological action of loperamide.

Loperamide is a potent opioid μ-receptor agonist. These receptors are highly expressed in the myenteric and submucosal plexus stimulating secretion of inhibitory neurotransmitters which increase non-propulsive contractions in the intestine and so decrease peristalsis, allowing increased contact time for absorption.
Onset of action occurs around 1 hour post ingestion. It reaches peak plasma concentration between 2.5 and 5 hours with a plasma half-life of 11 hours. Maximum therapeutic effect may not occur until between 16 and 24 hours.

It should be used in caution in severe hepatic impairment as this has the potential for increased plasma concentration. Drug interactions are mainly as a result of metabolism by the cytochrome P450 system, therefore drugs which are enzyme inhibitors can increase plasma concentration. Drugs which also reduce gastrointestinal motility should be avoided. Adverse effects mainly affect the gastrointestinal system. Reus, faecal impaction, abdominal cramping and bloating have all been reported.

Loperamide is not recommended in pregnancy due to lack of evidence, but no major teratogenicity has been reported. When considering breast feeding, it is thought that the amount secreted into breast milk is probably too small to be harmful.

**Trials of safety and efficacy**

Trials have assessed efficacy and safety in both acute and chronic diarrhoea with a review of the evidence supporting the conclusion that it is efficacious and safe.

Specifically, a multicentre, double-blind, placebo-controlled trial undertaken in 1975 involving 213 patients compared loperamide with two other antidiarrhoeal agents plus placebo in acute diarrhoea. As an indicator for efficacy it measured duration to next unformed stool post medication administration. This revealed that duration to next unformed stool was significantly longer with loperamide when compared with the other groups, in keeping with a longer duration of action. Forty percent of the patients in the loperamide cohort had no further unformed stools after a single dose of loperamide. Another multicentre, double-blind, placebo-controlled trial was carried out in 1976 involving 141 patients. This time, patients with both acute and acutely relapsing chronic diarrhoea were included and loperamide was compared with placebo only. This study showed that diarrhoea was controlled within 24 hours in 60% of patients in the loperamide cohort as opposed to 31% of patients in the placebo cohort.

As well as non-specific acute or chronic diarrhoea, trials have also assessed and demonstrated the safety and efficacy of loperamide in diarrhoea secondary to irritable bowel syndrome, high output ileostomy and non-dysenteric travellers’ diarrhoea.

The published trials also reveal a good safety profile. The main adverse effects were related to the gastrointestinal system and were generally minor. However, it is worthwhile noting that some of these gastrointestinal side effects experienced could also be attributed to the underlying diarrhoea.

One more serious adverse reaction reported was in a patient being treated for ulcerative colitis who developed a toxic megacolon. In addition to loperamide, the patient was taking clozapine which is also known to reduce gastrointestinal motility. However, during widespread clinical use for 40 years there have been no new reports of unusual side effects such as this.

The trials have also shown that as an opioid µ-receptor agonist there is no centrally acting narcotic effect and no potential for abuse. There have been no trials undertaken specifically to assess the use of loperamide for the treatment of diarrhoea in individuals with diabetes.

**Discussion**

There are some limitations in the trials assessing safety and efficacy of loperamide. Most involve patients with acute diarrhoea and data are relatively lacking on chronic diarrhoea. Often the cause of the diarrhoea is unknown. It is also difficult to define acute diarrhoea with clinical trials using different definitions. However, the heterogeneous nature of those in the clinical studies and positive safety signals suggest that loperamide has a place in the treatment of both acute and chronic diarrhoea. In those with diabetes, diarrhoea can be multifactorial. As well as autonomic neuropathy, other important causes must be considered. Drugs such as metformin, GLP-1 receptor agonists, overflow from constipation, pancreatic insufficiency, small bowel bacterial overgrowth, coeliac disease, bile salt malabsorption and steatorrhoea must all be considered before treatment is commenced. Therefore a careful history, examination and investigation are key before commencing loperamide treatment.

Loperamide has been shown to be superior to other antidiarrhoeal agents and shown to be safe. It is more potent and longer acting when compared with codeine, with a superior side effect profile. It is generally well tolerated as it acts peripherally on the gut which limits systemic side effects. Unlike other opioids it has no analgesic effect and there is less potential for abuse. Given the good efficacy and safety data, there is a role for use of loperamide in individuals with diabetes complaining of diarrhoea.

**Key points**

- Diarrhoea in individuals with diabetes can be multifactorial and a careful history is required to establish the likely cause.
- Loperamide is a peripherally active opioid µ-receptor agonist used to slow intestinal motility, with evidence of safety and efficacy.
- Loperamide is a safe and efficacious option when treating diarrhoea caused by diabetic autonomic neuropathy.

**References**