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British Intestinal Failure Alliance (BIFA) Position Statement

# The use of high dose loperamide in patients with short bowel associated intestinal failure.

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## Summary

There are reports of serious cardiovascular events (QT prolongation, torsades de pointes, and cardiac arrest/deaths) associated with high or very high doses of loperamide when used as a drug of abuse or for self-treatment of opioid withdrawal (1-21). Reference 2-21 were used by the Medicines and Healthcare products Regulatory Agency (MHRA) to support their 2017 medication safety alert (1). These reports are extremely important to those healthcare workers who manage patients with a short length of bowel (often having a stoma or enterocutaneous fistula) and taking higher than the recommended doses of loperamide. This document outlines the problems reported and suggests guidance when using high doses of loperamide in patients with a short bowel.

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## Introduction

Patients with intestinal failure often have a high output stoma/fistula which can cause dehydration, acute kidney injury leading to chronic kidney disease, hypomagnesaemia and osteopenia. High doses of loperamide may be given to patients with a short bowel (jejunostomy) or post vagotomy diarrhoea (22,23). The licensed maximum dose of loperamide for all licensed indications is 16mg / 24 hours in the UK. Loperamide is not licensed for the management of high output stoma/fistula in the UK. As patients with a short bowel are likely to have a malabsorption problem, it has been common to prescribe loperamide 2-24 mg four times a day half an hour before food as recommended in the BSG guidelines of 2006 (22). However, a report of 3 patients from Australia suggested even higher doses (40 mg five times a day, 30 mg three times a day and 100 mg four times a day) were effective in reducing losses (24). While most clinicians report increasing doses of loperamide to be beneficial in treating a high output stoma/fistula there are no formal balance studies to support this practice. At present there are few reports of cardiac events relating to loperamide in patients with gastrointestinal illnesses, though a prolongation of the QT interval was observed in 27% of patients with a high output stoma (HOS) or fistula taking over 40 mg /24 hours. (25) There are difficulties in practically taking high doses of loperamide (2 mg dose in a capsule) as handfuls of capsules need to be swallowed. It is not clear if oral dispersible tablets of loperamide (designed for early liberation of the drug and rapid absorption) have a greater risk of causing toxicity.

## Background of toxicity reports

In people with a fully functional gut and no previous small bowel resections, there has been an increasing usage of high doses of oral loperamide to achieve a "high" or to overcome the symptoms of opiate withdrawal. In a high dose it may cause syncope or sudden death due to bradycardia, prolonged QT (and indeed the whole QRS complex), ventricular tachycardia and Torsade's de Pointes (1-21).

Much of the data comes from the United States of America (USA) where the number of reports of loperamide toxicity are increasing (16-19). The World Health Organisation (WHO) sited 792 of 12845 (6.2%) reports of adverse reactions to loperamide to be cardiovascular (mainly in men) and of these 18% were fatal. (21) The doses of loperamide were generally over 200 mg/24 hours (70-1600 mg/ 24 hours).

## UK Data

Between 01 January 2017 and 31 December 2023, the MHRA received 16 UK adverse drug reactions reports, via the yellow card reporting scheme, concerning loperamide and cardiac adverse events. The nature of the cardiac events was not stated for any of the sixteen reports. Two of the reports state the indication for the loperamide treatment was "gastrointestinal stoma complication". However, they did not state a clear dose and frequency or a list of other medications. Of the remaining fourteen reports, the stated indications included: euphoric mood, intentional product misuse, drug withdrawal maintenance therapy, diarrhoea, irritable bowel syndrome (IBS) and depression. Four doses were listed, the highest dose was 100mg / 24 hours (for drug withdrawal maintenance therapy), then 48mg / 24 hours (for diarrhoea) and 80mg / 24 hours (unstated indication) and lowest dose was 2mg / 24 hours (for IBS).

In a UK audit 4 of 15 patients with a high output stoma/fistula and taking 49-104 mg loperamide / 24 hours had a prolonged QT interval. (25)

## Pharmacokinetics of loperamide

Loperamide has been on the market since the 1970s and is a synthetic piperidine opioid with peak plasma level 4-5 hours after being taken orally, its half-life is 7-19 hours. However, it has a poor oral bioavailability (amount reaching the circulation after being taken orally) of 0.3%. This is due to poor absorption (30-40% is excreted in faeces), rapid first pass metabolism with conjugation in the liver and subsequent excretion in bile, and recycling into the enterohepatic circulation.

It is an agonist on the μ opiate receptors in the myenteric plexus. Loperamide inhibits gut motility and may also reduce gastrointestinal secretions, resulting in an improvement in diarrhoea symptoms. It has been specifically shown to reduce trypsin and bilirubin secretion from the liver and pancreas in patients with a short bowel. (26). Loperamide also increases the tone of the anal sphincter.

In the UK, loperamide is available on general sale for the symptomatic treatment of acute diarrhoea adults and children 12 years and over (maximum daily dose 12 mg and maximum 6 capsules per box) and from pharmacies (maximum daily dose 16 mg and maximum 12 capsules per box). Taking 100 – 400 mg will cause a euphoric high.

### Mechanism of adverse reaction

Non-clinical data offer a biologically plausible mechanism for the cardiovascular reaction (QT prolongation and arrhythmias) caused by potassium channel (hERG) inhibition at high doses). At extremely high concentrations, loperamide also has the potential to slow cardiac conduction via inhibition of sodium channels and so produce conduction arrhythmias.

## Actions from these reports

As a result of the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency report all manufacturers of loperamide products were asked to update their product information to include warnings of cardiac events associated with high doses. The patient leaflet has also been updated to warn patients never to take more than the recommended amount.

“If you have taken too many loperamide, immediately contact a doctor or hospital for advice. Symptoms may include increased heart rate, irregular heartbeat, changes to your heartbeat (these symptoms can have potentially serious, life-threatening consequences), muscle stiffness, uncoordinated movements, drowsiness, difficulty urinating, or weak breathing. Children react more strongly to large amounts than adults. If a child takes too much or shows any of the above symptoms, call a doctor immediately.”

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# BIFA reasons for recommending the continuing use of high doses loperamide therapy in patients with short bowel associated intestinal failure

Patients with a short bowel/intestinal failure and high gastrointestinal losses of water and salt may have life threatening metabolic/electrolyte disturbances that result in dehydration with acute kidney injury that can become irreversible and lead to chronic kidney disease. The measures to maintain fluid balance (restricting oral hypotonic fluid, giving a glucose/sodium solution to drink and taking drugs that reduce gut motility and secretions) are a priority. Loperamide and codeine phosphate reduce intestinal motility and thus decrease water and sodium output from an ileostomy by about 20-30% (27-30). As there are few reports of loperamide toxicity in patients with gastrointestinal diseases and as loperamide absorption is likely to be much reduced in patients with short bowel, we believe that high dose loperamide therapy (greater than 16 mg / 24 hours) should continue to be used. The risks of not treating the high output stoma/fistula are greater than that of the risks of loperamide in causing cardiac arrhythmias. The following recommendations should be followed.

## Recommendations

1. Perform an electrocardiograph (ECG) in all patients with a high output stoma/fistula before starting high dose loperamide (more than 4 mg four times a day) and the QT interval should be measured, corrected for heart rate (QTc) and documented. The ECG should be repeated after starting the high dose and then we suggest every 3 years if the patient remains on high dose loperamide therapy. Repeat sooner if the loperamide dose is increased, gastrointestinal absorption increases, new cardiac comorbidities are diagnosed, or after the addition of drugs that may cause QTc interval prolongation (table 1).
2. If the QTc interval is prolonged cardiac co-morbidities are considered, drugs known to prolong the QTc interval are rationalised and metabolic causes (e.g. hypokalaemia or hypomagnesaemia) are treated. A cardiology opinion may be sought.
3. Patients already taking high dose loperamide should continue with it and the QTc interval measured on an ECG. The loperamide should not be stopped.
4. The total daily dose of loperamide should be below 80 mg, however if this is exceeded serum loperamide levels should ideally be measured (normal therapeutic range 0.24 – 1.2 mg/ml). *
5. Serum loperamide levels should ideally be measured if there are any cardiac concerns. *
6. Loperamide toxicity should be considered in any patient with fainting (syncope) episodes not accounted for by dehydration or other drugs. It should also be considered if there is QTc prolongation on the ECG or serious ventricular arrhythmias including torsades de pointes or cardiac arrest occur.
7. If symptoms of toxicity/overdose occur, naloxone can be given as an antidote but as the

duration of action of loperamide is longer than that of naloxone (1–3 hours), repeated treatment with naloxone may be needed and the patient should be monitored closely for at least 48 hours to detect possible central nervous system depression.

8. Report all suspected adverse reactions, including those associated with abuse or misuse, to the Yellow Card Scheme (in UK).
9. All NHS Trusts initiating doses of loperamide above 16mg / 24 hours and or for the management for high output stoma/fistula should have clear governance in place to cover the prescribing of the unlicensed indication and dose.

*: At present there is limited availability to measure serum loperamide levels in the United Kingdom.

## Table 1.

**Commonly prescribed drugs that may cause a prolonged QTc.** (31)

chlorpromazine

citalopram

clarithromycin

erythromycin

escitalopram

fluconazole

haloperidol

levomepromazine

loperamide

methadone

ondansetron

quinine

risperidone

venlafaxine

voriconazole

## Table 2.

**Commonly prescribed drugs that may increase the risk of a prolonged QTc. (31)**

domperidone

granisetron

ivabradine

In general, manufactures advise that the use of two or more drugs that are associated with QTc prolongation should be avoided. Increase in age, female gender, cardiac disease, and some metabolic disturbances (notably hypokalaemia) predispose QTc prolongation. Caution must be given to drugs that cause hypokalaemia. (31)

This is not exhaustive list: please check the British National Formulary (BNF) for drug side effects and drug interactions for all prescribed drugs. (31)

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