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British Intestinal Failure Alliance (BIFA) Position Statement

The use of high dose loperamide in patients with intestinal failure

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On 26 September 2017 the Medicines and Healthcare products Regulatory Agency (MHRA) issued an alert about 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). This alert is 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 evidence for the alert and suggests guidance when using high doses of loperamide.

Introduction

Patients with intestinal failure often have a high output stoma/fistula which can cause dehydration, chronic renal failure, hypomagnesaemia and osteopenia. High doses of loperamide may be given to patients with a short bowel (jejunostomy) or post vagotomy diarrhoea (2, 3). 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 (2). 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 (4). 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 no reports of cardiac toxicity in patients with gastrointestinal illnesses. There are difficulties in practically taking high doses of loperamide (2 mg capsules) as handfuls of capsules need to be swallowed. There is also a question about preparations of loperamide designed for oral/rapid absorption which may have a greater risk of causing toxicity in these patients.

Background of toxicity reports

There has been increasing usage of high doses of oral loperamide to achieve a “high” (The poor man’s methadone) or to overcome the symptoms of opiate withdrawal. There have been reports of it, in high dose, causing bradycardia, prolonged QT (and indeed QRS complex), ventricular tachycardia and Torsade’s de Pointes (table 1 - duplicate case reports have been omitted). There are also 3 reports of sudden death (3 men aged 19, 24 and 39) in which high serum loperamide

levels were subsequently found. The cases reported have a fully functional gut and no previous small bowel resections.

Ventricular tachycardia or Torsades de Pointes with loperamide (5-18)

Age (sex)	*Loperamide mg/24 hr*	*Reason for taking*
48 F	80-160	opiate abuser
28 M	134	opiate withdrawal
54 F	144	cholecystectomy diarrhoea
26 M	192	opiate abuser
34 F	192	cholecystectomy diarrhoea
43 F	288	opiate withdrawal
43 F	300	opiate abuser
30 M	<400	opiate abuser
24 M	<400	opiate abuser
30 M	400	opiate abuser
28 F	400-600	opiate withdrawal
28 M	80-792	opiate abuser (pain)

A **European review** of worldwide spontaneous reports identified 19 cases suggestive of cardiac rhythm disorders associated with loperamide abuse and misuse. In all cases, there was evidence of intentional high doses being taken for unapproved indications. In 13 of the 19 reports, QT prolongation or torsades de pointes were recorded with daily dosages ranging from 40-80 up to 800 mg (the licenced maximum daily dose is 16 mg).

Of the other 6 reports, one described syncope and irregular heart beat (daily dose 400–600 mg), one described cardiac arrest with a rhythm of pulseless electrical activity (daily dose 400–800 mg), one described ventricular dysrhythmia (daily dose 400 mg), and one described asystole and death (chronic massive overdose). Two reports did not provide specific information on cardiac rhythm disorders or dose, with one describing syncope and death and one loss of consciousness.

UK data

There have been 16 UK Yellow Card reports of cardiac-related adverse events associated with loperamide; however, most of these cases date back to the 1970s and 1980s and provide few details. Two of 16 reports list doses higher than the licenced daily limit. Dose was not recorded in 10 of the 16 cases. Of 4 cases reporting doses within the licensed range, only one report was not associated with anaphylaxis or underlying cardiac disease. Of the 16 cardiac-related adverse events described by Yellow Cards, 5 were fatal. One death was suspected to be due to a large overdose of loperamide, whereas 4 deaths were associated with underlying cardiac disease or anaphylaxis.

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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. It is metabolized and conjugated in the liver before being excreted via the bile. It acts on the μ receptors in the myenteric plexus. Loperamide inhibits gut motility by binding to opiate receptors in the gut wall and may also reduce gastrointestinal secretions, resulting in improvement in diarrhoea symptoms. 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 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 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 have been asked to update their product information to include warnings of cardiac events associated with high doses. The patient leaflet will also be 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 of than adults. If a child takes too much or shows any of the above symptoms, call a doctor immediately.”

BIFA reasons for recommending the continuing use of high doses loperamide therapy in patients with 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 renal failure that can become irreversible. The measures to maintain fluid balance (restricting oral hypotonic fluid, giving a glucose saline 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% (19-21). As there are no reports of loperamide toxicity in patients with gastrointestinal diseases and as loperamide absorption

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is likely to be much reduced in short bowel patients, we believe that high dose loperamide therapy (greater than 16 mg daily) 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 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 and documented. The ECG should be repeated after starting the high dose and then every 3 years if the patient remains on high dose loperamide therapy.

2. If the QT interval is prolonged cardiac co-morbidities are considered, drugs known to prolong the QT interval are rationalised and metabolic causes (e.g. hypomagnesaemia) are treated. A cardiological opinion may be sought.

3. Patients already taking high dose loperamide should continue with it and the QT 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 be measured (normal therapeutic range 0.24 – 1.2 mg/ml). *

5. Serum loperamide levels should be measured if there are any cardiac concerns*.

6. Loperamide toxicity should be considered in any patient with fainting episodes not accounted for by dehydration or other drugs. It should also be considered if there is QT prolongation on the ECG or a 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 CNS depression.

8. Report all suspected adverse reactions, including those associated with abuse or misuse, to the Yellow Card Scheme.

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

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References

1. Medicines and Healthcare products Regulatory Agency. Loperamide (Imodium): reports of serious cardiac adverse reactions with high doses of loperamide associated with abuse or misuse. 26 September 2017. www.gov.uk/drug-safety-update/loperamide-imodium-reports-of-serious-cardiac-adverse-reactions-with-high-doses-of-loperamide-associated-with-abuse-or-misuse

2. Nightingale JMD, Woodward J and Small bowel/Nutrition Committee of BSG. Guidelines for the management of patients with a short bowel. *Gut 2006; 55 (suppl IV)*

3. O'Brien JD, Thompson DG, McIntyre A, Burnham WR, Walker ER. Effect of codeine and loperamide on upper intestinal transit and absorption in normal subjects and patients with postvagotomy diarrhoea. *Gut* 1988; 29: 312-318.

4. Mackowski A, Chen HK, Levitt M. Successful management of chronic high-output ileostomy with high dose loperamide. BMJ Case Rep 22 April 2015.

5. Sheyman J, Crake R. Loperamide induced Brugada syndrome. Ohio Valley Medical Center, Wheeling, WV Poster Presentation. February 2014.

6. Mukarram O, Hindi Y, Catalasan G, Ward J. Loperamide induced torsades de pointes: a case report and review of the literature. Case Rep Med 2016;2016:4061980.
7. Emergency Medicine PharmD. Loperamide-induced cardiotoxicity. Published July 21, 2015. Accessed March 30, 2016.

8. Dierksen J, Gonsoulin M, Walterscheid JP. Poor man's methadone: a case report of loperamide toxicity. Am J Forensic Med Pathol 2015;36:268-70.

9. Spinner HL, Lonardo NW, Mulamalla R, Stehlik J. Ventricular tachycardia associated with high-dose chronic loperamide use. Pharmacotherapy 2015;35:234-8.

10. O'Connell CW, Schricker AA, Schneir AB, Metushi IG, Birgersdotter-Green U, Minns AB. High-dose loperamide abuse – associated ventricular arrhythmias. HeartRhythm Case Reports.

11. Lasoff DR, Schneir A. Ventricular dysrhythmias from loperamide misuse. J Emerg Med 2016;50:508-9.

12. Wightman RS, Hoffman RS, Howland MA, Rice B, Biary R, Lugassy D. Not your regular high: cardiac dysrhythmias caused by loperamide. Clin Toxicol (Phila) 2016;54:454-8.

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13. Eggleston W, Clark KH, Marraffa JM. Loperamide abuse associated with cardiac dysrhythmia and death. Ann Emerg Med 2016 Apr 26.

14. Marraffa JM, Holland MG, Sullivan RW, Morgan BW, Oakes JA, Wiegand TJ, Hodgman MJ.. Cardiac conduction disturbance after loperamide abuse. Clin Toxicol (Phila), 2014 Nov; 52(9):952.

15. Eggleston W, Nacca N, Marraffa JM. Buprenorphine induced acute precipitated withdrawal in the setting of loperamide abuse. Clin Toxicol (Phila) 2015; 53(7):662.

16. Enakpene EO, Riaz IB, Shirazi FM, et al. The long QT teaser: Loperamide abuse. Am J Med 2015; 128(10):1083–6.

17. Marraffa JM, Holland MG, Sullivan RW, et al. Syncope and recurrent polymorphic ventricular tachycardia following loperamide misuse. Clin Toxicol (Phila) 2013; 51(7):653 abstr. 174.

18. Hurtado-Torres GF, Sandoval-Munro RL. An Additional Clinical Scenario of Risk for Loperamide Cardiac-Induced Toxicity. Am. J. Med. 2016 129:4

19. Newton C R. Effect of codeine phosphate, Lomotil and Isogel on ileostomy function. *Gut* 1978; 19: 377-383.

20. King RFGJ, Norton T, Hill GL. A double-blind crossover study of the effect of loperamide hydrochloride and codeine phosphate on ileostomy output. *Aust NZ J Surg* 1982; 52: 121-124.

21. Tytgat GN, Huibregtse K. Loperamide and ileostomy output-placebo-controlled double-blind crossover study. *Br Med J* 1975; 2: 667-668.