Can high dose loperamide be used to reduce stoma output?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

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Background

Some patients with a stoma resulting from an ileostomy, jejunostomy or a colostomy, can experience high-volume liquid stoma output. This can be problematic for a variety of reasons (e.g. leakage or metabolic disturbances may occur) (1). Several pharmacological and non-pharmacological methods have been employed to alleviate these problems.

Loperamide is a synthetic opioid agonist, which exerts its antimotility effects partly by stimulating μ (mu) opioid receptors on the circular and longitudinal muscle in the small intestine (2). Loperamide has been used in the management of colostomies or ileostomies, to reduce the volume of discharge and is preferred to opiate drugs (for example, codeine phosphate) as it is not sedative, addictive, and does not cause fat malabsorption (3,4). The results of a small study in 10 patients with ileostomy diarrhoea suggest that loperamide may be more effective than codeine phosphate and may be associated with fewer side effects (1). It has been suggested that the effect of both drug treatments may be additive (4).

The use of loperamide for this indication and at doses exceeding the maximum stipulated in the Summary of Product Characteristics (12mg-16mg per 24 hours) would be off-licence (5-7).

However, anecdotal reports suggest that loperamide in high doses may be beneficial for patients with, for example, short bowel syndrome.

Answer

Efficacy/Dosing

Published information regarding the use of high dose loperamide for this indication is limited, with a lack of recent (or randomised controlled) trials in this area. Therefore treatment of patients remains largely empiric, i.e. based on observation and experiment rather than evidence (2). A systematic review of pharmacotherapy for high output stomas or fistulas identified 5 controlled studies in a total of 69 patients, all showing significant effect of loperamide on output reduction (8). However the maximum dose in these studies was 16mg daily.

Loperamide passes through the enterohepatic circulation, which is severely disrupted in patients with a short bowel, so small bowel transit may be very rapid. Thus British Society of Gastroenterology guidelines on the management of patients with a high output jejunostomy or ileostomy suggest that high doses of loperamide e.g. 12 - 24mg at a time may be needed (4). Since these doses may be repeated up to four times a day, this would equate to a maximum daily dose of 96mg. A dose of loperamide of 16mg - 64mg daily has been suggested as part of an antisecretory drug regimen for patients with short bowel syndrome (9). The authors of the systematic review described above recommend doses up to 32mg daily (8mg four times daily) based on their expert opinion (8). Administration of loperamide 30 to 60 minutes before food slows gastrointestinal transit and allows more time for absorption of nutrients and water from food (10,11).

Dosing information in this Medicines Q&A is largely based on practical experience from centres specialising in this area. High doses of loperamide are used to reduce high-volume stoma output at these centres. For reduction of motility in adult patients with short bowel syndrome, loperamide may be started at a dose of 2mg four times a day, typically 30 minutes before meals, and slowly titrated up to a maximum dose of 64mg daily (12,13). The dose required will depend on the volume of stomal loss and should be increased by 2mg until the desired consistency of the stomal loss is reached (13).

At one of these specialist centres loperamide dosing would typically start at 2mg - 4mg four times daily but, since patients usually require high doses, would regularly increase to doses of 16mg - 20mg four times daily, occasionally higher (11). Another centre advocates a starting dose of 2mg - 4mg four

times daily depending on the volume of output, titrating to a maximum dose of 24mg four times daily, but advises that doses above 12mg - 16mg four times daily are rarely required (14).

Higher doses have also been reported in the literature. Two patients outside of the UK were stabilised on total daily doses of 300mg and 400mg and were followed up at 7 months and 2 years respectively after titration (15). At the time of publication neither patient had reported any adverse effects from these doses.

Formulation

There is some debate among experts as to the preferred formulation for high dose loperamide. Although one centre suggests loperamide orodispersible tablets, may be better absorbed (12), the specialist gastrointestinal hospital in London (St Mark's) uses capsules mainly due to their lower cost (11). If required the capsules can be opened and the contents mixed with water, jam or yoghurt, or tablets can be crushed and mixed with water or soft food (off licence) (4,11,14). This is also suggested if undigested capsules or tablets are seen in the stools or stoma.
Although some experts also recommend loperamide liquid formulations, it should be noted that the volumes required to achieve high doses may be problematic for patients with high stoma output (8,11). In addition, Imodium® oral solution contains glycerol and artificial sweeteners which, in high amounts, may cause gastrointestinal side effects, including diarrhoea (5).

Safety

The risk of adverse effects or toxicity will be increased in patients taking high doses and these are detailed in the Summaries of Product Characteristics and Patient Information Leaflets (refer to sections on 'undesirable effects' and 'overdose'). In particular concerns have been raised over serious cardiac adverse effects with the use of high doses of loperamide, with published case reports of life-threatening cardiac arrhythmias when loperamide has been abused or misused (16-23). In response to these reports and reviews of adverse event reporting systems, the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA) have respectively published safety alerts regarding the misuse or abuse of high doses (24,25). In the majority of published cases patients have taken much higher doses than would normally be recommended for reducing stoma output, often over a prolonged period of time, and the contribution of concomitant drugs of abuse cannot be ruled out. Nonetheless, one case involved a daily dose between 40mg and 160mg and another case involved a daily dose of 144mg with no other substance abuse (16,18). The FDA database reported 11 patients who experienced cardiac events with therapeutic doses of loperamide, however 2 of these patients were children younger than two years and clinical particulars are not given for the other 9 (24). The MHRA Yellow Card database reported 16 cases of cardiac-related adverse events associated with loperamide (25). Of these, 4 reported doses within the licensed range, 2 reported doses above the licensed daily limit, and the remaining 10 did not record the dose.

Cardiac adverse effects have not been reported in patients with high output stomas, although occasional case reports have been published in patients taking high doses for chronic diarrhoea due to other causes (3). Nonetheless, patients with high output stomas may have other electrolyte disturbances (e.g. hypomagnesaemia, hypokalaemia) which could confer additional risk for the development of cardiac rhythm alterations, in particular QT interval prolongation (17). It is not clear how much risk higher doses represent in this subset of patients, particularly when the disruption in enterohepatic recycling (in which loperamide circulates) and reduced surface area are likely to reduce absorption (7,14,26).

Following the MHRA alert, the British Intestinal Failure Alliance issued a statement outlining evidence for the alert and providing guidance for the use of high dose loperamide in patients with intestinal failure (26). This recommends continuing use of high dose loperamide (>16mg daily) since "the risks of not treating the high output stoma/fistula are greater than that of the risks of loperamide in causing cardiac arrhythmias", but suggests the total daily dose should be below 80mg. Recommendations are also made for ECG monitoring (doses >16mg in 24 hours) and measurement of serum loperamide levels* (doses >80mg in 24 hours), as well as actions to be taken if there are cardiac concerns or symptoms of loperamide toxicity – refer to the full document for further details.
*Note: the document highlights that "at present there is limited availability to measure serum loperamide levels in the United Kingdom"

Summary

- The use of high doses of loperamide may be warranted in patients who require pharmacological intervention to reduce high volume stoma output.
- Depending on baseline volume of stoma output, a starting dose of 2mg - 10mg four times a day of loperamide may be prescribed and titrated according to individual response.
- Specialist centres in the UK typically use a maximum total daily dose of 64mg, although this may occasionally be exceeded in resistant cases, possibly up to a total of 96mg daily.
- There are published case reports from outside the UK where higher doses were used, up to a maximum dose of 400mg daily.
- This information is however based on practical experience and does not conform to the maximum dose stipulated in the loperamide Summaries of Product Characteristics (SPCs) . The use of high dose loperamide (>16mg daily) would therefore be off-licence.
- The US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA) have issued safety alerts over the use of high doses with case reports of cardiac arrhythmias when loperamide has been abused or misused.
- Although not usually reported in patients taking high doses for reducing stoma output, caution is advised, particularly as patients may be at increased risk if they have electrolyte disturbances.
- A statement following the MHRA safety alert has been issued by the British Intestinal Failure Alliance advocating continuing use of high dose loperamide in high output stoma patients but to limit the total daily dose to below 80mg. The statement recommends ECG monitoring if doses exceed 16mg daily and serum loperamide levels if doses exceed 80mg daily, although notes the limited availability to measure serum levels in the UK at present.

Limitations

- There is a lack of published information on the use of high dose loperamide for reducing volume of stoma output.
- Further research is required to determine suitable dose ranges for this indication.
- Further research is required to study the cardiac risks of higher doses of loperamide
- Doses suggested in this Q&A are for adults (aged 18 years and over) only.

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Search strategy

- Embase Search:
  - (exp loperamide/ AND exp drug megadose/) AND (exp short bowel syndrome/ OR exp stoma/ OR exp ileostomy/ OR exp colostomy/ OR exp enterostomy/).
  - [exp loperamide/ AND (high AND dose).af] AND (exp short bowel syndrome/ OR exp stoma/ OR exp ileostomy/ OR exp colostomy/ OR exp enterostomy/).
  - [exp loperamide/ AND (high ADJ dose).af] AND (exp short bowel syndrome/ OR exp stoma/ OR exp ileostomy/ OR exp colostomy/ OR exp enterostomy/).
  - exp loperamide/ AND Heart muscle conduction disturbance
- Medline Search:
  - [exp loperamide/ AND (high AND dose).af] Limits LG=EN and H=Y.
  - [exp loperamide/ AND (exp peritoneal stomata/ OR exp ileostomy/ OR exp colostomy/))]. Limits LG=EN and H=Y.
  - exp loperamide/ AND (exp surgical stomas/ OR exp enterostomy/ OR exp short bowel syndrome/). Limits LG=EN and H=Y.
  - [exp loperamide/ AND (high ADJ dose).af]. Limits LG=EN and H=Y.
  - exp loperamide/ AND exp Arrhythmias, Cardiac/
- British Nursing Index (BNI) Search:
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