LOPERAMIDE

Introduction

The most commonly used antimotility drugs to treat diarrhoea are the opioid derivatives, which rely on their constipating side effects, as a therapeutic action.

Most commonly used are codeine, diphenoxylate and **loperamide.**

Codeine containing compounds should be avoided because of the risk of developing dependence on these drugs.

Diphenoxylate is chemically related to pethidine. Diphenoxylate partially crosses the blood–brain barrier and can cause central nervous system adverse effects similar to those of other opioids, including dependence. It is often combined with atropine which can result in significant anticholinergic effect side effects, particularly in elderly people.

Loperamide, is therefore the preferred opioid agent for use in diarrhea, when indicated.

History

It was developed by Janssen Pharmaceutica in 1969.

Preparation

Loperamide hydrochloride as:

Tablets: 2 mg.

Capsules: 2 mg.

Mechanism of Action

Activate opioid receptors in the gut wall:

- Decreasing bowel motility:
  - ♥ Inhibits peristaltic activity by a direct effect on the circular and longitudinal muscles of the intestinal wall.
- Increasing fluid absorption.

Pharmacodynamics

Loperamide on a mg to mg basis is about three times more potent than diphenoxylate hydrochloride and 25 times more potent than codeine phosphate.

Clinical improvement occurs within 1 -3 hours following a 4 mg dose of loperamide.

Loperamide is not associated with significant central opioid actions in normal therapeutic doses in patients with normal hepatic function.

Pharmacokinetics

Absorption:

- Loperamide is given orally.

It undergoes considerable first-pass metabolism in the liver and bioavailability is < 1 %.

Distribution:

- Protein binding is about 97 %.
- Loperamide does not readily cross the blood - brain barrier.

Metabolism and excretion:

- Loperamide is metabolized in the levier and excreted in the bile and urine.
- The is some enterohepatic recirculation.
- The elimination half-life is reported to be about ten hours.

Indications

Indications include:

1. Diarrhoea:
    - Usually *short-term* treatment in adults
    - Note that this is *symptomatic* treatment only.
2. Intestinal stoma:
    - To reduce frequency and fluidity of motions.

Contra-indications/precautions

These include:

1. Contraindicated in patients with severe or bloody diarrhoea i.e **dysentery** where there is a possibility of **invasive** organisms.

2. Contraindicated in patients with severe inflammatory bowel disease because of the risk of the development toxic megacolon.

3. Antimotility drugs are never indicated for managing acute diarrhoea in **infants** and **children** (< 12 years).

    - Risk of paralytic ileus

4. Intestinal obstruction

5. Loperamide is contraindicated in pseudomembranous colitis associated with broad spectrum antibiotics.

6. Loperamide therapy should be discontinued promptly if abdominal distention, constipation, or ileus occurs.

7. Should not be used for > 48 hours.

8. Caution should be used in patients with advanced liver disease; e.g. cirrhosis, on the basis of possible enterohepatic pathway and secondary accumulation

    - In patients with severe hepatic impairment, loperamide may cause CNS depression (i.e precipitate hepatic encephalopathy)

9. Caution in patients with advanced renal disease

Pregnancy

Loperamide is a category B3 drug with respect to pregnancy.

Category B3 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Breast feeding:

Safe in breast feeding.

Adverse Effects

These can include:

1. Allergic reactions
2. Constipation/ ileus, especially in children
3. Toxic megacolon in patients with severe inflammatory bowel disease
4. Hepatic encephalopathy in patients with severe liver disease.

Dosing

Give:

- **Loperamide 4 mg orally, for the first dose, then 2 mg orally, after each unformed stool, up to a maximum of 16 mg per day**

References

1 eTG - March 2015

- Gastrointestinal Therapeutic Guidelines 5th ed 2011.

2. Loperamide in Australian Medicines Handbook, Accessed May 2015
3. Loperamide in MIMs 1 January 2014.

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