Obstipation and diarrhoea in palliative care—a pharmacist’s view

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Summary This article is a brief overview of drugs, which are of use in the treatment of constipation and diarrhoea in palliative care. Whereas most of the drugs mentioned are widely used and known, the aspect of gastrointestinal symptoms as side effect of pharmacological treatments is often underestimated. Therefore, the article highlights the approach of deprescribing, as a tool to reduce both, pill burden and symptoms.

Keywords Laxatives · Medication management · Inappropriate medication · Deprescribing · Symptomatic treatment

Gastrointestinal symptoms at the end of life may have different causes and are stressful for patients. Although causal therapy is rarely possible, symptom relief can be achieved with medication management.

Adding drugs to bring relief to patients in a palliative care setting often seems to be an intuitive approach, but it should not be overlooked that de-escalating or discontinuing of inadequate medication can be a more appropriate strategy, especially when controlling gastrointestinal side effects.

Constipation

Constipation, defined as the slow movement of faeces through the large intestine, resulting in infrequent bowel movements and the passage of dry, hard stools [1], is a very common symptom in patients receiving palliative care. The reported prevalence is up to 90%, depending on the definition for constipation and the exact population taken into account, e.g. patients with malignant primary illness vs. non-malignant, opioid-treated patients [2].

The possible causes for constipation are multiple: primary illness, immobility, dietary, pharmacological, e.g. opioids, 5HT3-antagonists, anticholinergic drugs.

For those patients where nonpharmacological approaches, such as increased mobility, abdominal massage and other lifestyle factors, do not provide sufficient relief, a combination of oral osmotic and stimulating laxatives is recommended. The use of enemas can be useful, although having some limitations, e.g. patient’s acceptance, contraindications. Bulk forming laxatives should not be used in palliative patients due to the risk of bowel obstruction with insufficient fluid intake [3].

Patients receiving opioids may, in addition, need peripheral acting μ-opioid receptor antagonists (PAMORAs) such as methylnaltrexone or naloxegol [4, 5]. Respecting the contraindications when using PAMORAs, namely bowel obstruction and personal increased risk of bowel perforation, is crucial.

Whereas opioids are necessary and valuable agents in palliative patients, a large number of constipation-inducing drugs are considered potentially inappropriate and should be discontinued.

Drugs are considered as potentially inappropriate medications (PIMs) when lacking evidence-based indications, the individual risks of the treatment outweighs the benefits, the medication is associated with adverse drug reactions or when there may be a potential interaction with other medications or diseases [6].

Deprescribing is defined as a systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individ-
ual patient’s care goals [7]. There are encouraging evidence supporting deprescribing in palliative patients [8], as well as in the general geriatric population [9]. The existing criteria to define PIMs for the elderly are the Beer's criteria [10] and the Screening Tool for Older People's Prescriptions (STOPP) [11]. These criteria do not necessarily meet the special needs of palliative patients [12]. OncPal deprescribing guideline is a tool which focuses on de-escalating of inappropriate medications in palliative cancer patients [13].

In the context of gastrointestinal symptoms, the following agents which fulfil the criteria for deprescribing according to the Beer's list, should be used with caution if at all necessary in palliative care, a discontinuation of those drugs might be preferable:

- **5HT3-Antagonists:** consider other antiemetics, preferably those with prokinetic qualities, e.g. metoclopramide.
- **Anticholinergic, antihistaminic, serotonergic drugs:** if necessary, use one single agent. Combining two or more agents of these classes may lead to severe constipation but also to central nervous system (CNS) toxicity.
- **Antacids:** due to the high intake of calcium and/or aluminium ions, antacids favour constipation, as well as iron.
- **Nonsteroidal anti-inflammatory drugs (NSAIDs):** the use of other nonopioid analgesics, such as paracetamol or metamizole is recommended in palliative patients to avoid gastrointestinal, renal and cardiovascular toxicities, with the understanding that patients with an advanced stage of illness carry a higher toxicity risk [14]. Of note, if a NSAID is needed naproxen is the drug with the lowest cardiovascular risk [15], whereas celecoxib has the best gastrointestinal safety profile [16].
- **Oral antidiabetics:** may cause diarrhoea and/or electrolyte disorders and are of low benefit for patients in an advanced stage of incurable illness.

**Diarrhoea**

Diarrhoea is a symptom with several potential causes that has a high impact on wellbeing of patients. It is objectively defined by the passage of more than three unformed stools in 24 h [17], but the patient’s definition may be different and therefore needs clarification and assessment by medical staff.

The symptomatic pharmacological management, after ruling out treatable causes, e.g. infection, consists in substitution of fluids and electrolytes and administration of antidiarrehan agents [18].

Loperamide is a µ-opioid receptor agonist which binds in the intestinal wall. Different oral formulations are available, alcohol-containing solutions should be avoided for patients with injured oral mucosa. The onset of the antidiarrheal effect is relatively fast within 1 h after intake, with a maximum effect after 16–24 h. For patients with a short episode of diarrhoea, this may lead to unintentional overdosing and in consequence a subsequent need for laxatives. Loperamide is extensively metabolized in the liver. The systemic bioavailability is only 0.3% and it does not pass the blood–brain barrier [19].

For those patients, where loperamide is not sufficient, an intensification of the therapy can be made by adding octreotide. This synthetic peptide hormone has analogue effects than somatostatin but with a longer duration [18]. The inhibiting, antiserotonin and absorption increasing effects can, beside multiple other indications, be useful in the treatment of loperamide-refractory diarrhoea.

Due to the reduced secretion of multiple hormones and neurotransmitters, serotonin amongst others, an additional antiemetic effect can be observed [20]. This can be useful in some patients, but on the other hand, this may also lead to a feeling of dry mouth, which is disconcerting for most palliative patients.

Additional caution should be taken for patients with insulin-dependent diabetes, as even a single dose of octreotide can lower the blood glucose level. The risk of unintended overdose of insulin and thereafter hypoglycaemia is high in such patients [21].

For the treatment of diarrhoea doses of 250–500 µg per day are recommended (usually applied in 3 single doses). The preferred administration route is a subcutaneous injection. To prevent pain at injection site, it is helpful to warm the solution before application. The onset of effect is 30 min after application and lasts for 8 h [19].

Tincture of opium is another opioid which can be used as alternative to loperamide. The commonly used preparation—opi tinctura normata according to the Pharmacopoea europaea (PhEu)—is a standardized alcoholic solution containing 1% (10 mg/ml) of morphine, which is beside codeine the effective component [22]. In some countries the solution is available under the trade name Dropizol® [23]. The recommended dose is 10–15 drops every 3–4 h [18]. Caution should be taken to avoid confusion with solutions of different concentrations.

A different mechanism of action is the inhibition of enkephalinase, which reduces the intestinal secretion without affecting the motility of the gut [24]. Racecadotril is the only available drug of this class. No systematic data are available for the use in the palliative population, but, having a favourable safety profile [25]—especially the lack of inhibiting effects on the motility—and a rapid onset of effectiveness (30 min), this seems to be a drug which should be taken into consideration. Further studies in palliative patients should be encouraged.

Anticholinergic drugs such as atropine or glycopyrrolate have antidiarrheal effects and may be considered, but with awareness of unwanted side effects (e.g. dry mouth, dry skin, flush).
Additionally all patients suffering from diarrhoea should be provided with skin barrier ointments to protect the perianal skin, especially those who are immobile.

In summary it can be said that the management of patients in a palliative setting suffering from constipation and/or diarrhoea is always a balancing act, whereby the personal preferences and needs of the patient should be focused on.

Take home message

Consider deprescribing as a tool to reduce both, pill burden and gastrointestinal symptoms.

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