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-

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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 focusses 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 antidiarrheal 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, antisecretory 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 discomforting 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 μ g 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—*opii 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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References

- Doyle D, Hanks GWC, Cherny N, Calman K. Constipation and Diarrhoea. In: Oxford textbook of palliative medicine. Oxford: Oxford University Press; 2004. pp. 483–96.
- Candy B, Jones L, Larkin P, et al. Laxatives for the management of constipation in people receiving palliative care. *Cochrane Database Syst Rev*. 2015; <https://doi.org/10.1002/14651858.CD003448.pub4>.
- Larkin P, Cherny N, La Carpia D, et al. Diagnosis, assessment and management of constipation in advanced cancer: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2018;29:iv111–iv25.
- Rauck RL. Treatment of Opioid-induced constipation: focus on the peripheral μ -Opioid receptor antagonist Methylnaltrexone. *Drugs*. 2013;73(12):1297–306.
- Candy B, Jones L, Vickerstaff V. Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care. *Cochrane Database Syst Rev*. 2018; <https://doi.org/10.1002/14651858.CD006332.pub3>.
- Dimitrow M, Airaksinen M, Kivelä S, et al. Comparison of prescribing criteria to evaluate the appropriateness of drug treatment in individuals aged 65 and older: a systematic review. *J Am Geriatr Soc*. 2011;59(8):1521–30. <https://doi.org/10.1111/j.1532-5415.2011.03497.x>
- Scott I, Hilmer S, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med*. 2015;175:827–34.
- Thompson J. Deprescribing in palliative care. *Clin Med*. 2019;19(4):311–4.
- Lindsay J, Dooley M, Martin J, et al. Reducing potentially inappropriate medications in palliative cancer patients: evidence to support deprescribing approaches. *Support Care Cancer*. 2014;22:1113–9.
- By the 2019 American Geriatrics Society Beers Criteria Update Expert Panel. American geriatrics society 2019 updated AGS beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674–94. <https://doi.org/10.1111/jgs.15767>
- O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing*. 2015;44(2):2013–8. <https://doi.org/10.1093/ageing/afu145>
- Sharma M, Loh K, Nightingale G. Polypharmacy and potentially inappropriate medication use in geriatric oncology. *J Geriatr Oncol*. 2016;7:346–53.
- Lindsay J, et al. The development and evaluation of an oncological palliative care deprescribing guideline: the 'OncPal deprescribing guideline'. *Support Care Cancer*. 2015;23(1):71–8. <https://doi.org/10.1007/s00520-014-2322-0>.
- Wood H, Dickmann A, Boland JW. Updates in palliative care—overview and recent advancements in the pharmacological management of cancer pain. *Clin Med*. 2018;18(1):17–22.
- Collaboration, Coxib and traditional NSAID Trialists' (CNT). Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet*. 2013;382(9894):769–79.
- Chan FKL, Ching JYL, Tse YK, et al. Gastrointestinal safety of celecoxib versus naproxen in patients with cardiovascular diseases and arthritis after upper gastrointestinal bleeding (CONCERN): an industry-independent, double-blind, double-dummy, randomised trial. *Lancet*. 2017;389(10087):2375–82. [https://doi.org/10.1016/S0140-6736\(17\)30981-9](https://doi.org/10.1016/S0140-6736(17)30981-9).
- World Health Organization. Diarrhoeal disease fact sheet nr.330. 2017. Accessed 06 Jan 2020.
- Bossi P, Antonuzzo A, Cherny N. Diarrhoea in adult cancer patients: ESMO clinical practice guidelines. *Ann Oncol*. 2018;29:iv126–iv42.
- Rémi C, Bausewein C, Twycross R, Wilcock A, Howard P. Arzneimitteltherapie in der Palliativmedizin. 2015.
- Currow D, Clark K, Cartmill J. A multi-site, fixed dose, parallel arm, double-blind, placebo controlled, block randomised trial of the addition of infusional octreotide or placebo to regular ranitidine and dexamethasone for the evaluation of vomiting associated with bowel obstruction a. ASCO Annual Meeting; American Society for Clinical Oncology. 2012. p. TPS9153.
- Lunetta M, De Mauro M, Le Moli R. Effect of octreotide on blood glucose and counterregulatory hormones in insulin-dependent diabetic patients: the role of dose and route of administration. *Eur J Clin Pharmacol*. 1996;51:139–44.
- European directorate for the quality of medicines medicines, Pharmacopoea europaea 9.8, 2019
- Fachinformation, editor. Dropizol 10 mg/ml. 2020. <https://www.fachinfo.de/suche/fi/022209>. Accessed 22 Feb 2020.
- Eberlin M, Mück T, Michel M. A comprehensive review of the pharmacodynamics, pharmacokinetics, and clinical effects of the neutral endopeptidase inhibitor racecadotril.

Front Pharmacol. 2012; <https://doi.org/10.3389/fphar.2012.00093>.

25. Gallelli L, Colosimo M, Tolotta G, et al. Prospective randomized double-blind trial of racecadotril compared with loperamide in elderly people with gastroenteritis living in nursing homes. Eur J Clin Pharmacol. 2010; <https://doi.org/10.1007/s00228-009-0751-3>.

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