Introduction

Binding of opioids to μ-receptors within the gastrointestinal (GI) tract can lead to impairment of motility and secretion and induce a variety of symptoms, including nausea, gastro-paresis, secondary pseudo-obstruction and constipation[1]. This complex of impairment and symptoms is called Opioid Induced Bowel Dysfunction (OIBD)[1-3]. OIC is the most common symptom of OIBD[2-7].

In 2014 a consensus definition for OIC was agreed upon and by consensus, OIC is defined as follows: "A change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency"[1]. Other associated symptoms of OIC are: bloating, acid reflux, rectal pain and nausea[8,9]. OIC is a common side effect of opioid treatment and in contrast to other side effects of opioid treatment patients do not develop a tolerance to constipation[2-7]. In literature the incidence of OIC varies between 15-90% of patients on opioid treatment[3,10-13]. Besides opioid use also other factors can contribute to the development of constipation in patients on opioid treatment. Factors that have been identified are disease progression, dehydration, other medications (like chemotherapeutic agents), immobility and age[10,14,15].

Pathophysiology

The effects that opioids have on the physiological function of the GI tract have been extensively studied in animal models and humans[1,2,8-10]. OIC develops predominantly as a result of activation of enteric μ-opioid receptors which are distributed throughout the GI tract[1,2]. They mediate a number of effects that influence the function of the GI-tract when activated by opioids[1,2].

Activation of the enteric μ-opioid receptors by opioids for example: causes non-peristaltic contractions, decreases gastric motility and emptying, increases pyloric sphincter tone; decreases GI, biliary, and pancreatic secretions; inhibits peristalsis in the small and large intestines; increases the amplitude of non-propulsive segmental contractions in the small intestine; increases water absorption from bowel contents; increases anal sphincter tone; and constricts the sphincter of Oddi [2,16].

The combined action of opioids on inhibition of GI emptying, GI motility, GI transit, intestinal fluid secretion and the enhancement of absorption contribute to the constipating effect of opioids; as these effects are localized to the GI tract, it is called peripheral action[2].

Besides the physical burden of OIC and OIC associated symptoms, OIC has a major impact on patient's quality of life (QoL)[10,12,17-19]. Significant differences are detected in QoL between patients depending on the presence and severity of OIC[17,20]. Besides a direct

impact of OIC and associated symptoms on QoL, OIC also has an impact on the treatment of pain. Literature has described that OIC can be intolerable to patients. Nearly 2/3 of patients changed the opioid dose; either lowering the dose (10.2%) or skipping doses and/or irregular use (7.5%) or discontinued opioid treatment (5.4%) all at the expense of analgesic efficacy[2,12,18,20]. The interference of OIC with pain management also results in a decrease of QoL[20].

Pharmacological treatment of OIC

In current practice the advice for treatment and prevention of OIC is to treat patients on opioid analgesics prophylactically with a laxative regime in addition to lifestyle modifications, such as increased exercise, greater fluid intake, and dietary changes[1,2]. The pharmacological component of the laxative regimen may include stool softeners, bulking agents, osmotic agents, and stimulant-type laxatives[1,3,21]. In some cases, two or more laxatives with complementary mechanisms of action may be prescribed, such as a stool softener plus a stimulant. Rectal laxatives, including stimulant suppositories such as bisacodyl, lubricants such as glycerin, and enemas are sometimes used, although care should be taken with enemas to preserve the patient's electrolyte balance[1,3,21].

Despite this laxative regimen, literature describes that some patients still experience OIC and/or do not tolerate the adverse events of the laxative regime; i.e. patients with laxative-refractory OIC[12,19]. Also literature describes that laxatives are ineffective to treat OIC[1,2]. Moreover, treatment with laxatives causes side effects and complications[3,14].

In Dutch clinical practice a prophylactic laxative regime is advised consisting of treatment with at least one laxative in an adequate dosage (e.g. macrogol plus electrolytes or lactulose) and if needed addition of a second laxative of a different therapeutic class (e.g. bisacodyl)[22,23]. As the efficacy of this laxative regime for the treatment and prevention of OIC has not been established yet, a pilot study was conducted to explore the efficacy of the current Dutch prophylactic laxative regime under conditions of daily practice.

Over the last decade opioid receptor antagonists like methylnaltrexone, naloxegol and naloxone are increasingly being used for the pathophysiological treatment of OIC[24-26]. Currently described peripherally-acting μ-opioid receptor antagonists (PAMORA's) in literature are methylnaltrexone (MNTX), naloxegol, alvimopan and naldemedine[1,2]. Another agent described in literature is prolonged release combination of oxycodone and naloxone (PR OXN), although it acts on peripheral opioid receptors it is sometimes considered to be another agent as it relies on the drug combination[2]. PAMORA's and PR OXN block opioid actions at peripheral opioid receptors that mediate decreased intestinal secretion and propulsive colonic motility[1,2]. By blocking μ-opioid receptors in the

gut, there is restoration of the function of the enteric nervous system, and propulsive motility and secretory functions can be generated by local enteric neural circuits in response to physiologic stimuli such as meal ingestion, or sensation of a bolus to evoke normal peristalsis[1,2].

As the number of PAMORAs increase it is important to explore their efficacy not only in randomized controlled trials but also in real-life settings and when possible explore their efficacy in comparison to each other. A systematic review and meta-analysis was performed to obtain more insights in the efficacy of these opioid receptor antagonist for the treatment of OIC.

The aim of this thesis was to further elucidate the efficacy of PR OXN, specifically for patients with laxative-refractory OIC. PR OXN combines the opioid receptor agonist oxycodone and the opioid receptor antagonist naloxone. When administered orally, a reduction of constipation can be achieved due to a local action of naloxone in the gut without affecting pain relief by oxycodone[27-29]. PR OXN has proven equivalent analgesic efficacy to prolonged release oxycodone (PR OXY) with significant improvements in bowel function in chronic non-malignant pain[30-35] as well as in moderate/severe malignant pain[36-38].

In order to gain more insights in the efficacy of PR OXN in patients with laxative-refractory OIC a post-hoc analysis was designed to explore the efficacy of PR OXN in this specific population. Moreover, two additional observational studies were designed in which patients (with and without laxative-refractory OIC) were treated as in daily practice in Belgium with PR OXN, investigating the efficacy of treatment in a real-life situation.

As treatment with PR OXN is more expensive than treatment with PR OXY, it was also important to assess cost utility of PR OXN treatment for laxative-refractory patients, therefore also a cost-utility analysis was performed.

The results of the studies in this thesis add to the current knowledge of opioid antagonist treatments, especially PR OXN treatment, specifically in patients with laxative-refractory OIC. Moreover, the results may, hopefully, improve treatment of OIC in this specific patient population.

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