General Discussion

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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]. Opioid Induced Constipation (OIC) is the most common symptom of OIBD[2-7] and in contrast to other side effects of opioid treatment patients do not develop a tolerance to constipation[2-7]. 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].

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]. 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)[8,9]. A regime that is comparable with the Belgian laxative regime (source: www.bcfi.be). 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[10,11]. Furthermore, literature describes that laxatives are ineffective to treat OIC[1,2]. Moreover, treatment with laxatives causes side effects and complications[3,12].

Over the years opioid receptor antagonists like methylnaltrexone, naloxegol and naloxone are increasingly being used for the pathophysiological treatment of OIC[13-15]. Peripherally-acting opioid receptor antagonists (PAMORA's) and prolonged release oxycodone/naloxone (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].

In the work presented in this thesis the efficacy of treatments for OIC were studies. In a pilot study the efficacy of a Dutch laxative regime was studied. The efficacy of PAMORA's and PR OXN were analyzed in a systematic review and meta-analysis. And the treatment of OIC with PR OXN has been examined in real-life with a focus on the laxative refractory population, to gain more insight in the efficacy of PR OXN in patients with laxative-refractory OIC in daily practice.

Although literature on treatment of OIC at time of Dutch guideline development was sparse and non-conclusive, based on expert opinion was assumed that the Dutch laxative regime would be a suitable regime to prevent and treat OIC. To gain more insight in the efficacy of a Dutch laxative regimen in daily clinical practice as well as to obtain insights for future randomized controlled trials, the laxative regime has been examined in a pilot study. Our pilot study indicated that this laxative regime, might not be effective and feasible for the prevention and treatment of OIC. Moreover, the results show that a larger clinical study is warranted investigating the efficacy and tolerability of the laxative regime for the prevention and treatment of OIC.

A particular challenge for the study is patient recruitment. In our pilot study it already became apparent that the majority of physicians expected that an "as needed" laxative regime would be more appropriate for the treatment and prevention of OIC. This is also reflected by a project started by de Graeff et al.. In this project the aim was to assess the efficacy of two laxatives (polyethylene glycol (PEG) with electrolytes versus magnesium(hydr)oxide) on the prevention of OIC. This project was terminated early due to insufficient patient recruitment (5 patients in 1.5 years) (source: http://www.zonmw.nl/nl/projecten/project-detail/preventie-van-obstipatie-bij-gebruik-van-opioiden-magnesiumhydroxide-versus-macrogolelektrolyte/voortgang/).

Given the unique etiology of OIC and the effects of opioids on neural activity, motility and secretion throughout the entire gastrointestinal tract[1,2], it is unsurprising that laxatives frequently fail to counteract the symptoms of OIC[11,13,16]. Instead, treatment of OIC should target the etiology of this condition via a μ-opioid receptor mediated approach such as that of the PAMORA's and naloxone (a non-selective opioid antagonist), rather than just focus on symptomatic management[2,14].

To gain insight on the efficacy on OIC between the PAMORA's and PR OXN a systematic review and meta-analysis was performed. A systematic review and consensus article by Gaertner et al.[17] has suggested that when measuring OIC a combination of outcomes should be measured. Therefore the measures evaluated consisted of objective outcome measures, patient reported outcome measures and patient-reported global burden measures of OIC. Despite significant heterogeneity between studies all identified randomized controlled trials showed that the efficacy of opioid antagonist treatment was superior to control treatment with respect to the proportion of patients achieving normal bowel function, the proportion of patients needing additional laxatives as well as the PAC-SYM total score. The Number Needed to Treat (NNT) to obtain normal bowel function was ~5 (~3.5-7; the reciproke of the anticipated absolute risk difference with opioid antagonist treatments), which is comparable to the meta-analysis by Nee et al.[18]. Also variables that were not studied for all agents, like (change in) Bowel Function Index (BFI) and (change in) number of bowel movements, showed that opioid antagonist treatments were superior to control treatment.

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With respect to pain relief the RCTs showed that treatment with opioid antagonists did not significantly interfere with pain relief. The quality of the evidence using the GRADE-systematic was rated low for alvimopan, moderate for PR OXN, MNTX and naldemedine and high for naloxegol.

An interesting population with respect to OIC is the laxative refractory population. Therefore we also included analyses for the subgroup of laxative refractory patients. Five RCTs (KODIAC-4, KODIAC-5, OXN2001, OXN3001 and OXN3006) were identified that reported on bowel function efficacy in laxative refractory patients or laxative inadequate responders. For naloxegol the NNT was ~6.7. For PR OXN the change in BFI was less pronounced compared with the total population (MD -8.93 95%CI -16.26 to -1.59; n=75). Within the naloxegol and OXN studies no heterogeneity was detected. However, a difference between both studies was the definition with respect to laxative refractory patients and laxative inadequate responder patients. For PR OXN a patient was considered laxative refractory if the patients still experienced OIC (defined as a BFI>28.8) despite the use of at least 2 laxatives from a different therapeutic class (e.g. macrogol and bisacodyl). For naloxegol a patient was considered a laxative inadequate responder when the patient took medication from one or more laxative classes for a minimum of 4 days within 2 weeks before screening and still experienced moderate, severe, or very severe symptoms in at least one of four stool-symptom domains of a laxative-response questionnaire. There are some limitations to our analyses. Firstly, there is heterogeneity in the analyses of the bowel function outcomes, this heterogeneity might be caused by differences in the trial populations. Detected differences identified were differences with respect to OIC at baseline due to differences in definitions for OIC as well as differences is the underlying pain conditions (e.g. malignant pain and non-malignant pain).

To reduce heterogeneity due to trial populations when studying OIC and the efficacy/effect with respect to OIC, Poulsen et al.[19] have developed a model for OIC in healthy volunteers, in which these population differences can be ruled out. It will be interesting to see whether healthy volunteers can be identified that develop laxative-refractory OIC. For this it might be interesting whether predictive factors can be identified that can be used to select high-risk populations for laxative-refractory OIC. There has been one publication that discussed the elucidation of predictive markers for OIC[20]. Unfortunately, Rosti et al. did not elucidate predictive markers for identification of laxative-refractory OIC. Another interesting approach would be head-to-head comparisons of opioid antagonists in patients with laxative-refractory OIC.

Based on clinical trials of PR OXN and the mechanism of action of PR OXN expectations were that PR OXN is a suitable option for the treatment of OIC in patients refractory to at least 2 different laxatives (ATC level 4 class) with a different mode of action. A post-hoc analysis was performed exploring the efficacy of PR OXN in this patient population. At screening, when patients were receiving opioid analgesia of any type and at least two

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different types of laxatives, patients had a reduced bowel function (BFI>28.8). During treatment with PR OXN, statistically significant and clinically relevant improvements in bowel function were observed in both groups of patients at the end of double-blind treatment with OXN. The positive effect of OXN PR on bowel function is further emphasized by the finding that the proportion of patients who had a normal bowel function increased by over four-fold from screening with a decrease in laxative use. This post-hoc analysis suggested that the effects seen in the randomized controlled clinical trial program are also valid for patients with persisting OIC despite the use of at least two different types of laxatives, and provides further confirmation that naloxone addresses OIC from a pathophysiological point of view rather than merely a symptomatic standpoint.

However, with current guidelines it is likely that patient switched to PR OXN already have been extensively treated with laxatives for a prolonged period. Moreover, patients included in the clinical trials might not represent the patient population in real-life. Therefore, an observational study was performed that followed laxative-refractory patients that were switched to PR OXN in Belgium. The laxative regime in the Benelux is very similar and laxatives prescribed in Belgium are similar to the laxatives prescribed in the Netherlands (source: www.bcfi.be and www.farmacotherapeutischkompas.nl). In Belgium, patients were eligible for reimbursement of PR OXN if they met the following conditions: (1) all patients had to be aged≥18 years, with a documented history of severe pain requiring around-the-clock opioid therapy, treated with prolonged release oxycodone (PR OXY for at least 30 days with insufficient pain relief and/or unacceptable adverse effects; and (2) all patients had to be experiencing OIC (Bowel Function Index [BFI]>28.8) despite the use of at least 2 laxatives with different mechanisms of action (level 4 ATC term) during the previous PR OXY treatment. The study found that PR OXN was superior to PR OXY in terms of pain relief, OIC, and quality of life in patients with chronic pain previously treated with PR OXY and experiencing OIC despite the use of at least 2 different laxatives. This study confirmed that after 4 weeks of treatment with PR OXN, a clinically relevant improvement in OIC was attained in patients experiencing laxative-refractory OIC. The average BFI was ≤28.8 after 6 weeks of PR OXN treatment, indicating that most patients were no longer constipated despite the opioid treatment. Also the number of patients needing additional laxatives declined significantly during the study and the majority of patients using laxatives indicated that the laxative use had decreased. These results support the rationale that PR OXN treatment counteracts OIC through mechanisms other than those of laxatives and that PR OXN addresses the underlying mechanism of OIC. However, an observational study has limitations, one of them being that we could not ensure that all data were documented. This limitation was addressed by marking important parameters (e.g., BFI, pain relief, laxative use yes/no, rescue medication yes/no) as mandatory fields in the electronic case record form; as a result, few data were missing for these fields.

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As the reimbursement guidelines for laxative-refractory OIC were very strict, also an observational study was performed in which patients were followed after switching from WHO-step 1, WHO-step 2 or WHO-step 3 medication to PR OXN treatment. Patients had been switched to PR OXN because of insufficient pain relief and/or unacceptable side effects on their previous medication and the presence of OIC was not an inclusion parameter. The present study showed that the majority of patients in the total population and in all WHO-step groups experienced symptoms of constipation as defined by a BFI≥28.8. It was shown that significantly more patients with symptoms of constipation at study entry were older and of female gender, both factors that are known to be associated with constipation and patients with pain are less mobile which could also have contributed to constipation. Moreover, it is possible that there is a bias in the percentage of constipated patients in this observation as in Belgium PR OXN was marketed especially for patients with a BFI above 30. Already after 2 weeks of PR OXN treatment a clinically relevant improvement of bowel function (defined by a reduction in BFI of 12 points or more) was observed in the overall population and in the WHO-step 2 and WHO-step 3 groups. Mean BFI dropped below 28.8 after 6 weeks of PR OXN treatment for the overall population and the WHO-step 1 and WHO-step 2 groups. In the WHO-step 3 group mean BFI reached 28.8 after 11 weeks of PR OXN treatment. The reduction in BFI is in line with reduction of BFI reported in previous observational studies with PR OXN for patients with neuropathic pain28, constipated patients with non-malignant pain29 and patients with severe pain30. When looking more closely at constipated patients at study entry (irrespective of previous analgesic treatment), it was shown that treatment with PR OXN led to a clinically relevant improved bowel function already in the first two weeks of PR OXN treatment and the improvement was maintained over time. After 17 weeks, BFI was close to the threshold of 28.8 showing that bowel function was almost restored to normal values despite the treatment with the opioid PR OXN. Interestingly, for patients not constipated at study entry the BFI remained below 28.8 even during PR OXN treatment up to 17 weeks. This indicates that treating pain adequately with strong opioids in non-constipated patients normal bowel function is maintained despite the initiation of the opioid PR OXN, even in patients stepping-up from non-opioid treatment. This study adds to the evidence found in previous studies with PR OXN which have also shown that switching non-constipated patients to PR OXN maintained their bowel function in a more controlled study setting (one clinical trial and one prospective open-label study with a blinded endpoint)[21-23].

To evaluate whether PR OXN is a cost-effective option for the treatment of patients with laxative-refractory OIC a cost-utility analysis was performed. This analysis demonstrated cost-effectiveness of PR OXN for opioid-treated patients with non-malignant pain suffering from laxative-refractory OIC with an incremental cost-effectiveness ratio (ICER) of € 6,924 per quality adjusted life year (QALY)gained. The model did not

include other peripheral opioid antagonists as comparator. However, medication costs of PR OXN are the lowest with current list-prices of these medications; subcutaneous (sc) methylnaltrexone approximately €178,- per week (assuming 4 flacons with 0.6 ml 20mg/ml per week), naloxegol approximately €36,75 per week (assuming 1 tablet of 25 mg per day) and PR OXN approximately €16,13 per week (assuming 14 tablets of 10 mg per week) and assuming a comparable clinical benefit of PR OXN, sc methylnaltrexone and naloxegol on OIC, (source: www.medicijnkosten.nl; last accessed: April 29th 2018). However, until now there are no data available that compare the clinical benefit between the different peripherally acting μ-opioid receptor antagonists (PAMORA's) and the comparability found in the systematic reviews still needs to be confirmed. Moreover, also side effects and ease of administration should be taken into account in establishing the clinical benefit from a societal perspective.

Over the years a lot of evidence has been generated that unravels that effect and efficacy of PR OXN treatment. In this thesis also the efficacy of PR OXN treatment in laxative-refractory patients has been evaluated. Unfortunately, as of today PR OXN is still not reimbursed in the Netherlands, caused by uncertainty of the effect due to low patient numbers suffering from laxative-refractory OIC within the clinical studies and in the observational studies, as well as the bias introduced by the study designs in this specific population and uncertainty on the appropriateness of the comparator.

In order to know when sufficient patient numbers have been studied the prevalence of laxative-refractory OIC needs to be elucidated in daily practice. However, in literature already two definitions are being used for the term laxative-refractory. One definition is derived from laxative inadequate responder (defined as a patient that took medication from one or more laxative classes for a minimum of 4 days within 2 weeks before screening and still experienced moderate, severe, or very severe symptoms in at least one of four stool-symptom domains of a laxative-response questionnaire).The other was derived from treatment guidance for OIC (a patient is laxative-refractory if the patient still experienced OIC (defined as a BFI>28.8) despite the use of at least 2 laxatives from a different therapeutic class (e.g. macrogol and bisacodyl)). This would most likely result in differences in prevalence. Prevalence could also be estimated from insurance data, but as laxatives are commonly used for other conditions and a number of laxatives are available as over the counter medications this is not very promising. Looking at the number of users of a peripheral opioid antagonist in the Drug Information System of the National Health Care Institute probably underestimates the total number of laxative-refractory patients, as only 436 users were registered using in 2016 (source: www.gipdatbank. nl). Elucidating the prevalence of laxative-refractory OIC in daily practice would be an important first step.

To address study design issues a randomized controlled double-blind trial would be the gold standard. However, this would most probably result in ethical issues as

comparing PR OXN to PR OXY with a standardized laxative regimen (e.g. macrogol plus electrolytes and bisacodyl as needed) as is usual in Dutch practice would be the appropriate comparison. This would result in patients that are refractory to laxatives having to continue the ineffective treatment with the addition of frequent use of enema's and an increased risk of developing haemorrhoids and anal fissures[6]. Another option would be to perform a prospective open-label blinded-endpoint (PROBE) study in patients with laxative-refractory OIC[21,23]. A similar study was already performed to compare the efficacy of PR OXN with PR OXY and PR morphine. Patients could use unblinded laxative-treatment as in daily practice and results showed that under the conditions of the PROBE design, PR OXN was associated with a significantly better tolerability, a lower risk of OIC and a significantly better analgesic efficacy than PR OXY and PR Morphine[21,23].

In the past years the debate on opioid use is increasing, especially when used chronically and for patients with non-malignant pain. Of course stopping opioid use would result in improvement of OIC and this can be seen as an easy option for the treatment of OIC. However, we should be careful that we don't withhold opioid treatment for those patients who do benefit from opioid treatment on specific indication, like severe pain during short-lived painful events and at the end of life. Opioid treatment should also be available for carefully selected patients with chronic pain who can be managed in a monitored setting. Within this monitored setting precautions can be taken to avoid misuse and diversion and closely monitor adverse events (https://www.iasp-pain.org/Advocacy/OpioidPositionStatement?navItemNumber=7225).

This monitored opioid prescribing should in our opinion be accompanied by adequate pain education for all health-care professionals in the (chronic) pain patient pathway as well as pain education for patients and their caregivers. Moreover, monitored opioid prescribing is an opportunity to closely monitor OIC, an adverse event that still results in unnecessary hospital admissions (https://www.nivel.nl/sites/default/files/bestanden/Vervolgonderzoek_Medicatieveiligheid_Eindrapport.pdf).

In contrast to guidelines in the Netherlands several European guidance and guidelines have already included opioid antagonists (including PR OXN) in the treatment algorithms of OIC[1,2,14,15,24]. Unfortunately, despite the wealth of available data from RCTs and observational studies, the national healthcare institute did not grant reimbursement for PR OXN in the Netherlands and it is unlikely that PR OXN will be reimbursed in the near future with the current assessment framework for reimbursement.

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