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Eliminating side effects of pain therapies

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ABSTRACT

Pain is a very serious problem associated with many types of health conditions. Unfortunately, patients suffering from intense pain often give up or cut down on taking analgesics because of side effects of such treatment. New generation drugs create an opportunity for supporting therapies effectively. Persistent constipation is one of the more acute side effects of administration of opioids. This article gives an extensive coverage of the PAMORA group of drugs that eliminate opioid-induced constipation. It also proposes future directions for contemporary studies on the subject and other feasible therapeutic applications for this group of medicines. The molecule developed under the POIG.01.04.00-14-213/12 project "New intestinal drug for control of side effects of opioid therapies" is one of the prospects. [The project] researched structures based on opioid peptide analogs behaving like opioid antagonists vs. intestinal μ receptors. In addition, [the structures] feature properties that can be used in oncological therapies because they inhibit growth of malignant cells. The structures are being tested on animal models.

***Keywords*:** pain, opioid, constipation, peptide, PAMORA, cancer, morphine

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1. INTRODUCTION

Medicine is paying more attention to pain management from year to year. Pain is increasingly less frequently considered as a comorbidity associated with diseases or injuries. It has come to being described as a separate and independent phenomenon.

Almost 20% of the European population of adults experience chronic pain. Statistics show that the problem can affect more than one half of the population worldwide. Costs of pain management have increased to approx. EUR 200 billion in Europe alone. Less than 2% of patients get help from specialist clinics. The rest rely mainly on basic health care services. Nearly 2/3^{rds} of people experiencing pain, in some cases persisting for many years, evaluate their therapies as insufficient.

Research on new analgesics, and on means to alleviate side effects of the drugs, continues.

2. OPIOID'S SIDE EFFECTS

Opioid agonists have found a number of therapeutic applications, mainly in controlling acute and chronic pain. These are the main class of medicines in used in managing malignancy-induced pain.[1] But the frequency of prescribing opioids for managing non-malignancy-induced pain is increasing too.[2] The term "opioid" represents both natural opiates (derived from opium) and synthetic and semisynthetic ones, behaving like opiate receptor agonists. We distinguish three types of receptors: δ (delta), κ (kappa) and μ (mu). These receptors occur in many locations in the body. Opioid compounds delivered to the body permeate to the do central nervous system and produce analgesic, euphoric and antitussive effects. Most morphinomimetics used by clinics to control pain are agonists of receptors μ. Apart from the central nervous system, the agonists occur in large numbers in the peripheral system (particularly in lungs, spleen, kidneys, heart, skeletal muscles, synovial membrane, periosteum, tendons, bones, cartilages, liver, thymus, pancreas, adrenal glands, dorsal root ganglia, etc.)[3-5], so acting on these agonists can produce a number of adverse effects. Given that large numbers of receptors μ are located also in the intestinal system, suppression of gastrointestinal peristalsis is a common symptom accompanying morphinomimetic stimulation of the receptors. Other frequent symptoms include suppression of appetite, nausea, vomitus, intensified reflux,[6,7], abdominal pain, flatulence or spasms. Still other effects include development of dependence or tolerance, sedation, hyperalgesia,[8] or respiratory depression.[9] During an extended drug therapy, a patient can develop tolerance of most of these life quality deteriorating effects[14,15] except the insufficiency of gastrointestinal peristalsis leading to acute constipation.[10-13] Problems with defecation are one of the most frequent side effects of taking opioids.[16,17] The incidence of opioid-induced constipation increases with the growth of duration of analgesic therapy.[18] This makes the therapy increasingly arduous and, finally, can even result in laying off the drug.[19]

2. 1. Constipations

According to studies carried out on animal models, concentration of systemically administered morphine is significantly higher in the alimentary tract than in the central nervous system, which is directly related to suppression of intestinal passage. What is more,

studies comparing consequences of systemic and central administration of morphine suggest that opioid receptors present in the central nervous system can also affect intestinal passage.[20] Interactions between opioids and opioid receptors μ in the intestinal nervous system and in the alimentary tract produce various effects including retardation of intestinal passage, which, in combination with the opioid-induced stimulation of mucous sensory receptors, leads to intensified reabsorption of fluids that further promotes constipation.[21,22]

For a long time we lacked a consensus on the definition of opioid-induced constipation.[23] The definition was proposed quite recently by the Roman Criteria of the 4th revision:[18] the condition was described as "the occurrence of new, or aggravation of existing, symptoms of constipation on the start, change or intensification of opioid pain therapy", provided that the patient experiences at least 2 of the following 6 symptoms: strong tenesmus, hard stool, sense of incomplete evacuation, sense of obstruction, patient's own "maneuvers" for facilitation of evacuation, less than 3 spontaneous intestinal movements per week, and provided that loose stools without use of laxatives occur rarely.[24] Also, attempts were made to distinguish between opioid-induced and opioid-exacerbated constipation. Finally, it was decided that the former condition was fully blamable to medication while the latter consisted of an aggravation of existing symptoms.

A sensation of pain is referred to as "chronic" where it persists at all times for more than 3 months.[26] It is estimated that up to 10-15 percent of population can experience this type of pain.[27] Patients taking morphinomimetics to get relief from pain need to consider a high risk of occurrence of side effects. Approximately 90% of patients experiencing moderate or strong pain take opioids.[28] Regarding non-malignant patients, opioid-induced constipation can be experienced by 41-81 percent of this population.[12,14] This percentage can be higher in the malignant population due to higher frequencies and doses of medication: 23-90 percent,[29,30] up to 94% according to some sources.[12]

The patophysiology of opioid-induced constipation involves the action of opioids on receptors located in the alimentary tract. The analgesic effect is produced mainly by the action of opioids on receptors in the central nervous system, mostly those of type μ.[25] The same receptors occur in intestinal mucous membrane and in the myalgic-submucosal plexus of the alimentary tract. Activation of the plexus leads to increased absorption of water and reduced excretion of fluids and electrolytes, which promotes constipation. What is more, opioids increase tension of the sphincter and impair anus relaxation with ectasia, which can cause problems with coordination of pelvic floor during defecation.[30]

Administration of laxatives is the first therapy of choice in managing opioid-induced constipation due to medication safety, low cost and over-the-counter availability.[18,24] Note, however, that no randomized controlled studies have been completed yet to evaluate the effect of such medication on opioid-induced constipation[31] and there is no firm scientific evidence to explicitly propose an optimal laxative.[32] Knowledge on the subject is still very limited.[6] What is more, experimental results show that efficacy of conventional laxatives is very low in patients taking the strongest analgesics:[16,17,19] in a group of 322 patients receiving morphinomimetics and laxatives 81% reported constipation and 58% complained about significant problems with defecation.[14] A study carried out on malignant patients showed that 85.7% of them experienced constipation although 84.7% of the patients received laxatives.[7] In addition, other studies involving patients with chronic pain demonstrated that 63.5% of patients taking strong opioids experienced medication-induced intestinal disorders although 89.5% of them took laxatives.[33] A number of similar studies provided similar

results, without any solid proof for efficacy of laxatives, so further efforts to develop more effective solutions were taken in the following years. Attempts to substitute laxatives with opioid antagonists to block receptors μ in the alimentary tract failed to provide the desirable results.

2. 2. The PAMORA group of drugs

The many years of research developed a new group of medicines: *Peripheral Acting Mu-Opioid Receptor Antagonists* (PAMORA). In contrast to conventional medicines, those belonging to the PAMORA group were aimed at direct interaction with opioid receptors in the alimentary tract, by which they were supposed to reverse side effect of application of exogenous opioids without affecting the central analgesic effect. The inability to penetrate the blood-brain barrier is the major feature of the PAMORA group of drugs. In practice, no clinically significant symptoms of laying off opioids were found in studies on PAMORA drugs intended for controlling opioid-induced constipation.[34-36] What is more, it is possible that, in addition to alleviation of constipation, these compounds can lower the frequency of occurrence of opioid-related adverse effects in other tissues including heart by blocking opioid receptors.

The working of the PAMORA molecules is based on antagonistic blocking of addition of opioids to peripheral opioid receptors μ. This can result in recovery of normal functioning of the intestinal nervous system and, thereby, assurance of adequate mobility and contractibility of tissues in this area. The history of research on the PAMORA compounds is related to studies on the possibility of using naloxon (antagonist of opioid receptors μ) in the management of opioid-induced constipation.[37,38] In studies on malignant patients taking morphine and experiencing related constipation, naloxon produced clinically significant evacuative effect in 9 out of 12 persons but 2 patients showed symptoms of drug withdrawal and 1 patient experienced recurrence of pain.[38] In a subsequent pilot study in which patients were administered small oral doses of naloxon, the peristalsis rate increased in all patients with opioid-induced constipation but the analgesic effect was reversed in one half of them.[37] This ambiguity of results compelled researchers to continue their work with an aim to reduce the ability of the compound to pass the blood-brain barrier. This has lead to development of the first PAMORA molecule.

Methylnaltrexone bromide was the first FDA-approved molecule of this group designed for constipation management. Then naloxegol was approved and naldemedin followed a few years later. The former was available starting from 2008 in the subcutaneous form intended for patients in advanced disease phases covered by palliative care, in whom application of traditional evacuative medication was unsuccessful. The scope of application of the drug was modified in 2014. From that time, it could be administered to non-malignant patients experiencing opioid-induced constipation. The oral form of the medicine was launched in 2016.[25] Methylnaltrexone in the forms of tablets and injection is marketed under the name of "Relistor". Also naloxegol debuted in 2014 under the commercial name of "Movantik".

This PEGylated derivative of naloxon (antagonist of opioid receptors μ) was approved by FDA as another preparation for managing opioid-induced constipation.[36] Naldemedin, the third PAMORA compound, was approved by FDA in March 2017. The chemical structure of this substance is similar to that of naltrexon[39] because contains a molecule of naltrexon with an added side chain increasing the molecular mass and polar surface of the molecule for inhibition of its passage through the blood-brain barrier.

Like the 2 former molecules, naldemedin, marketed as "Symproic", was designed to control opioid-induced constipation in non-malignant patients. In addition to the above mentioned substances, the PAMORA group of drugs includes alvimopan launched under the name of "Entereg". The molecule was approved by FDA in 2008 but it was not dedicated to opioid-induced constipation management: it was intended for use after resection of a part of the small or large intestine.[40]

2. 3. Compounds at the research phase

TD-1211, more commonly known as axelopran, is one of the PAMORA compounds that is still being studied. Pre-clinical experiments showed that the preparation could reverse loperamid-induced suppression of the alimentary tract without producing the drug withdrawal effect and without disturbing the analgesic effect.[41] According to the ClinicalTrials.gov service, clinical studies on this substance (phase 1 or 2) started in 2010 and the last of them were finalized in 2013. However, no results have been published. This research has apparently been abandoned.

Two cycles of research (clinical studies of phase 2) on bevenopran (ADL5945) were launched in 2010 and in 2011.[60,61] The molecule was checked for usability in managing opioid-induced constipation in adult non-malignant patients. The both studies demonstrated that the preparation had beneficial effect on intestines: the frequency of spontaneous peristalsis increased by up to 2 times vs. the placebo group of patients

Further, 3 clinical studies on the ALKS 37 molecule (also known as RDC-1036) were undertaken in 2010-2011.[62-64] In addition to safety, the research evaluated the ability of the drug to suppress morphinomimetic-induced constipation. The frequency of spontaneous peristalsis during administration of the largest drug dose (100 mg) increased by 6 times vs. the placebo group. No significant side effects were noted (other than diarrhea) and there was no suppression of efficacy of the analgesic opioid.[42]

TD-8954 is another recently tested member of the PAMORA group of drugs. The first research cycle was started in 2012 but in the very same year it was abandoned due to business considerations.[65] Another clinical study cycle (phases 1 and 2) was launched in 2014. Its results were published in 2017. TD-8954 is a highly selective agonist of receptors 5-HT_4 (like prucalopride that is used in controlling idiopathic constipation). Its oral form has an attractive pharmacokinetic profile. The substance features a significant potential for application in peristalsis disorder therapies.[43] The clinical study compared the substance to vomitus-suppressing and peristalsis-stimulating metoclopramide. Results of the study on stomach evacuation using the breathing test were similar for the both drugs, which demonstrates that TD-8954 can be useful in gastric disorder therapies.[59]

Studies on 6β-naltrexol and 6β-naltrexamin have reached an early phase. The former is the main metabolite of naltrexon. It inhibits activation of receptors but fails to suppress basic signaling, which makes it a neutral antagonist of opioid receptors. While administered intravenously, the substance antagonized retardation of functions of the alimentary tract induced with hydrocodone in mice[44] and induced with morphine in healthy humans.[45] The latter molecule, a derivative of naltrexamin, is a substrate of glycoprotein P. In studies on murine models, the substance increased peristaltic rate after subcutaneous administration.[46] The both molecules seem to act as neutral antagonists in various test conditions, so they have potential for application in larger doses for efficient suppression of the constipating effect of

opioids without inducing significant symptoms of analgesic withdrawal. However, further studies are required.

Current medicine development strategies are oriented on improvement of selectivity and affinity of new molecules and on new application methods. Considering that opioid receptors μ show functional selectivity / partial agonist,[47] functionally selective antagonist of substances from the PAMORA group or functionally selective agonists partial to β-arrestine 2[48] can represent prospective directions for development of opioid-induced constipation therapies.

2. 4. Peptide analogs

New peptide analogs have been developed as part of the POIG.01.04.00-14-213/12 project "New intestinal drug for control of side effects of opioid therapies" in collaboration with the Mossakowski Medical Research Centre Polish Academy of Science. The structures tested in the project were based on opioid peptide analogs. Molecules behave like opioid antagonist with μ receptors interaction in the colon and ileum. *In vivo* tests have shown that administration of the substances before application of morphine secured alimentary tract against loss of peristaltic rate almost completely. In addition, investigation into penetration of these molecules through the ileum and colon walls have demonstrated that the penetration of the substances to blood is practically null, which means their activity is contained to the lumen of the alimentary tract. Another very important feature of the compounds is that they reduce proliferation of malignant cells. This effect is not so strong as the action of anticancer drugs but can be sufficient for supporting the oncological therapy proper. Note at this point that analgesic opioids often promote and stimulate proliferation of malignant cells. Therefore, the new molecule can act as the means of suppressing opioid-induced constipation and of supporting oncological constipation management at the same time, for instance, providing a safeguard against intestinal metastasis. Studies on animals aimed to collect inputs for documenting the pre-clinical phase are continued.

3. CONCLUSIONS

The therapeutic potential of the PAMORA compounds can cover a wider range of applications, going beyond opioid-induced constipation management. Apart from alvimopan (used for constipation management in hospitals, after partial intestine resection with shunting), the substances belonging to the PAMORA group can play an important role in oncological constipation management. According to recent studies, these substances can reduce likely effect of morphinomimetics on proliferation of cells and on metastasis. In *in vitro* studies on human lung cancer, the blocking of opioid receptors μ inhibited proliferation and migration of cells stimulated by epidermal growth factor while stimulation of malignant cells with morphine, phentanyl or synthetic peptide derivatives accelerated these processes.[49] These results reveal a relationship between opioid receptors and malignant cell growth. Retrospective evaluations of application of opioids by malignant patients in advanced disease stages have proven existence of dependencies between increased demand for opioids and much smaller general survivorship of prostate tumor patients[50] or non-small cell lung cancer.[51] Recent retrospective *post hoc* tests related to subcutaneous application of methylnaltrexone in malignant patients experiencing opioid-induced constipation have shown

that there can be a relationship between administration of the drug and the significantly higher median of overall survivorship.[52]

Additional non-analgesic effects of application of opioids ensue from the fact that opioid receptors occur in various peripheral tissues including heart muscle cells or heart nervous fibers.[3] Studies on patients taking opioids for suppressing non-malignant pain have shown that cardiac infarction occurred up to 1.4 times more frequently in these patients vs. opioid-naïve ones.[53] Other studies have proven that long-term use of opioids by non-malignant patients involved a 2.7 times higher incidence of cardiac infarction.[54] The risk of occurrence of cardiovascular dysfunction in patients with osteoarthritis or rheumatoid arthritis (cardiac infarction, apoplexy, revascularization, off-hospital sudden cardiac death) related to the use of opioids was 1.8 times higher than in patients using non-steroid anti-inflammatory drugs.[55] Many other studies have shown various adverse effects of opioids on the cardiovascular system.[56,57] Therefore, researchers are strongly interested in the PAMORA group of molecules, perceiving their mechanism of interaction with opioid receptors as a prospective cardioprospective solution.[58]

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