Naloxegol: First oral peripherally acting mu opioid receptor antagonists for opioid-induced constipation

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ABSTRACT

Opioid-induced constipation (OIC) is one of the most troublesome and the most common effects of opioid use leading to deterioration in quality of life of the patients and also has potentially deleterious repercussions on adherence and compliance to opioid therapy. With the current guidelines advocating liberal use of opioids by physicians even for non-cancer chronic pain, the situation is further complicated as these individuals are not undergoing palliative care and hence there cannot be any justification to subject these patients to the severe constipation brought on by opioid therapy which is no less debilitating than the chronic pain. The aim in these patients is to prevent the opioid-induced constipation but at the same time allow the analgesic activity of opioids. Many drugs have been used with limited success but the most specific among them were the peripherally acting mu opioid receptor antagonists (PAMORA). Methylnaltrexone and alvimopan were the early drugs in this group but were not approved for oral use in OIC. However naloxegol, the latest PAMORA has been very recently approved as the first oral drug for OIC. This article gives an overview of OIC, its current management and more specifically the development and approval of naloxegol, including pharmacokinetics, details of various clinical trials, adverse effects and its current status for the management of OIC.

Key words: Naloxegol, opioid-induced constipation, peripherally acting mu opioid receptor antagonists

INTRODUCTION

Opioids are the potent analgesics which remain the mainstay of treating moderate to severe cancer pain as suggested by World Health Organisation (WHO) in its step ladder approach for choosing analgesics in cancer pain.[1] There is an emerging trend of using opioids even for non-cancer pain and incidence has almost doubled over the past 15–20 years. It has been estimated that more than 3% of adult population receive long-term opioids for chronic non-cancer pain.[2] The prevalence of chronic pain in adult population is expected to be around 2–40%. The condition causing chronic pain may be diverse but the ultimate treatment goal remains pain relief and improvement in functioning of the individual, guiding many physicians to use not only mild opioids but also potent agents like morphine to provide pain relief.[3]

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Opioid Induced Constipation (OIC) is one of the most troublesome and the common side-effects of using opioids for a prolonged duration. It was observed that on using opioids for 8 weeks an average 4% of patients developed OIC.[3] Various studies report constipation as a side effect in up to 40–95% of patients using opioids, which is potentially iatrogenic. It has

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been defined as "a condition in which a person has fewer than three spontaneous bowel movements in a week or has bowel movements with hard, dry, and small stools that are painful/difficult to pass." The major reason for OIC becoming a clinical deadlock in the use of opioids is the pattern of tolerance developed for opioid-induced adverse effects, wherein with the chronic use of opioids an individual develops tolerance to most of the adverse effects except constipation. OIC is known to have a significant impact on quality of life and interferes with day to day activities of the patients. It is also known to affect the adherence and compliance to opioid therapy and many patients may even prefer their chronic pain over the pain induced by severe constipation.[4,5]

Patho-physiology of OIC

Opioid receptors mu, kappa and delta, belonging to the class of G-protein coupled receptors are expressed widely on GIT with mu receptors seen over intestinal submucosa and ileal mucosa where as kappa and delta receptors predominate in stomach and proximal colon. The predominant actions of opioids on gastrointestinal tract are mediated by mu receptors located prejunctional modulating the release of acetylcholine and on postjunctional receptors decrease the release of neurotransmitters and inhibit calcium channels. The above-mentioned mechanisms delay intestinal transit leading to a decrease in peristalsis, inhibit gastric emptying and also reduce mucosal secretions. The ultimate effects are complicated wherein opioids also stimulate non-propulsive motility and increase the tone of anal sphincters and segmentation in intestines, facilitating fluid absorption from intestines. The final outcome of all these mechanism is constipation, to which there is no development of tolerance even on chronic use.[5,6]

CURRENT MANAGEMENT OF OPIOID INDUCED CONSTIPATION

Various non-pharmacological measures like increased consumption of fluids, dietary fibers and increase in physical exercises are initial measures, recommended along with the use of opioids. Pharmacotherapy may be nonspecific like use of laxatives, although effective it does not provide complete symptomatic relief as it is not targeting underlying pathophysiology.[3,7]

The specific treatment of OIC began with the use of opioid antagonist naloxone, but it could easily cross the blood–brain barrier and was found to reverse the analgesia induced by opioids; this problem was addressed by combining prolonged release oxycodone/naloxone (OXN) approved in Germany and currently reviewed by FDA. Another drug that was developed is Lubiprostone, which is a derivative of PGE1, and a selective activator of chloride channels. Lubiprostone acts locally in the intestine by increasing secretions and gut motility and although FDA approved currently there are no guidelines recommending its use in OIC.[7]

Peripheral Acting Mu Opioid Receptor Antagonists (PAMORAs)

The management of OIC got a shot in the arm with the development of quarternary opioid antagonists acting only in periphery (PAMORAs). They have been found to selectively antagonize the μ-opioid receptors within the gastrointestinal (GI) tract and have very limited ability to block the opioid receptors in the central nervous system and thus these drugs reverse the OIC without any effect on the analgesic actions of the opioids.[7,8]

Methylnaltrexone a derivative of opioid antagonist naltrexone was approved by US-FDA in April 2008 as alternative day subcutaneous injection for OIC and is regarded as a first-line drug in patients of advanced illness undergoing palliative care suffering from OIC. Being a methyl derivative which is charged, it has limited access across the blood–brain barrier and effectively countered OIC without affecting analgesic actions of opioids. Injected at a dose of 8 mg for patients weighing 38–62 kg and 12 mg for patients weighing 62–114 kg and all others receive dose at 0.15 mg/kg. After injections it produced bowel evacuation within 4 hours in half of the patients. There were many inherent drawbacks with its use, as it has to be given parenterally and is expensive. The application of methylnaltrexone for OIC in non-cancer pain has not been approved.[8]

Alvimopan, another PAMORA approved in May 2008, had relatively higher affinity (approximately 200 times) for peripheral mu opioid receptors compared to methylnaltrexone, but was approved only for postoperative ileus. It was noted in GSK14 studies that alvimopan after long-term use (1-4 months) produced an increase in cardiovascular mortality especially myocardial infarction and further advanced studies were demanded by FDA. Hence, it received approval only for acute short-term treatment of postoperative ileus (POI) as 6 and 12 mg twice a day dose preoperatively and postoperatively for a maximum duration of 7 days. Although alvimopan has shown some efficacy in recent trials, it is not approved at present for OIC in non-cancer pain. The latest PAMORAs at various stages of development for OIC are ADL5945, ALKS37, S-297995 and TD-1211. The other drugs used for constipation, which can also be considered for treating OIC, are lubiprostone (FDA approved for all types of constipation except OIC), prucalopride, linaclotide and plecanatide (guanylate-cyclase C receptor agonists).[4,7]

DEVELOPMENT AND APPROVAL OF NALOXEGOL

The latest drug in this group to be developed is naloxegol (NKTR-118) which is a novel PEGylated form of naloxol,

a naloxone analog. Naloxegol has shown strong selectivity (more than 6000 folds) toward peripheral mu receptors and has been approved as first oral PAMORA for OIC due to use of opioids for non-cancer pain. PEGylation greatly restricts the activity of naloxegol to periphery. Naloxegol has been developed by Nektar Therapeutics and is marketed by AstraZeneca under the brand name *MOVANTIK* and received US-FDA approval on 16 Aug 2014.[7,9]

PHARMACOKINETICS

Naloxegol undergoes rapid absorption after oral administration, with peak plasma concentration (Cmax) achieved in less than 2 hours.[10] Being a PEGylated analog, naloxegol stays for longer time in circulation, metabolized predominantly in liver by CYP3A4 enzymes and is also a substrate of p-glycoprotein transporter. It has shown significant interaction with drugs altering CYP3A4/P-glycoprotein transporter, hence avoided with drugs which are strong CYP3A4 inhibitors. The effect of mild–moderate renal/hepatic failure is found to be nonsignificant and there is no need for dose reduction, but those patients with creatinine clearance less than 60 ml/min are started off with a low dose and if well tolerated they can be switched over to normal dose. The metabolites (six in number) are predominantly excreted in feces (67%) and rest in urine. These pharmacokinetic parameters have been confirmed in 14_C studies in humans. It has been assigned Category C status for use in pregnancy.[11] Pharmacokinetics of existing PAMORAs has been compared [Table 1].

Preclinical and clinical trials

Pre-clinical studies

The *in vitro* assays using Chinese Hamster Ovary (CHO) cells with cloned human opioid receptors and membrane preparations of cells expressing opioid receptors clearly demonstrated the antagonism of naloxegol at μ and δ opioid receptors, partial agonism at κ opioid receptors. *In vivo* Rat model of reversal of morphine-induced opioid effects demonstrated the peripheral action of naloxegol, compared to naloxone effectively inhibiting the effects of morphine both in central nervous system and in periphery. The conventional safety pharmacological studies, repeated dose toxicity, genotoxicity and fertility studies have revealed no special hazard for humans. Carcinogenicity studies performed demonstrate an increase in leydig cell adenomas and interstitial cell hyperplasia but at a dose in excess of human dose. The studies in suckling rats demonstrated the secretion of naloxegol in milk.[12]

Clinical trials

A phase I open label multicenter study (NCT02099591) to assess the pharmacokinetics and safety of naloxegol in paediatric ages ≥6 months to ≤18 months receiving opioid treatment is currently under trial.

A phase 2, double-blind, randomized, placebo-controlled, dose escalation study conducted in patients on stable regimen of 30–1000 mg/day of morphine for non-cancer pain with less than three spontaneous bowel movements (SBMs) per week. After a week of placebo, individuals were randomized into either placebo or naloxegol (5, 25 or 50 mg) groups. The

Table 1: Approved PAMORAs: Comparison of pharmacokinetic parameters[10-14]

Pharmacokinetic parameter	Methylnaltrexone	Alvimopan	Naloxegol
Absorption: Bioavailability	-	6% (1-19%)	Not determined in humans
C_{max}	32.7 ng/ml (0.15 mg/kg dose) 35.6 ng/ml (0.30 mg/kg dose)	10.98 ng/ml	-
T_{max}	20-30 minutes	2 hours (after single dose) 34 hours (active metabolite)	2 hours (after single dose)
Distribution: Volume of distribution	1.1 L	11-98 L	160
Plasma protein binding	11-16%	70-80%	4.2%
Metabolism: Site	Hepatic: Produces six metabolites (none constituting >6% to be of significance) Conversion to methyl-6-naltrexol (5%) Methyl Naltrexone sulphate (1.3%)	Gut microflora mediated hydrolysis producing active amide metabolite	Hepatic: Six metabolites (none producing significant effects) Substrate of Cytochrome 3A4 enzyme Limited Glucuronidation
Half-life	8 hours	14 hours (4-17 hours)	10 hours
Excretion: Route	Urine: In an unchanged form (54%) Feces (18%)	Biliary (65%) Renal (35%) Unabsorbed excreted in feces and urine (after metabolism in gut)	Feces (67%) Urine (33%)

primary endpoint was a change in baseline SBMs after 1 week of drug administration. The results demonstrated a statistically significant change in SBMs in 25 and 50 mg naloxegol group compared to placebo.[10]

The predominant studies on which naloxegol got its FDA approval are KODIAC-04 (NCT01309841) and KODIAC-05 (NCT01323790): Two identical Phase III, multicenter, randomized, double-blind, placebo-controlled trials conducted in 652 and 700 patients, respectively. Selected patients were on stable regimen of 30–1000 mg/day of morphine for non-cancer pain with less than three SBMs and patients were randomly assigned to naloxegol 12.5, 25 mg or placebo once a day for 12 weeks. The primary endpoint considered was ≥3 SBMs per week or an increase of ≥1 SBMs from baseline for ≥9 of 12 weeks and an increase of ≥3 for final 4 weeks. KODIAC-04 showed significant improvement with naloxegol compared to placebo at both the doses, but in KODIAC-05 trial only 25 mg of naloxegol produced statistically significant results.[13]

An additional study for efficacy KODIAC-8 (NCT01336205): A 52 week, multicenter, open-label study included 804 patients out of these 84 patients were taken as roll over from previous KODIAC-4 trial. All were on 30–1000 mg/day morphine for more than 4 weeks for non-cancer pain with less than three SBMs. The subjects were randomly assigned into 25 mg/day of naloxegol or usual palliative care. The results demonstrated that 25 mg/day of naloxegol for up to 52 weeks is safe and usually well tolerated.[14] There was no reversal of analgesic effect of opioids used in these studies as measured by the pain rating scale and need of opioid.[13,14]

To rule out any adverse cardiac events noted with its precursor alvimopan, an additional trial was conducted (NCT01325415). A randomized, placebo-controlled crossover thorough the QT/QT_C study with therapeutic (25 mg) and supratherapeutic (150 mg) of naloxegol or moxifloxacin 400 mg or placebo in health volunteers demonstrated no significant cardiovascular changes.[15]

Table 2: Therapeutic selection of PAMORAs using step criteria[10,11,13]

Drug	Safety	Tolerability	Effectiveness	Price
Methylnaltrexone	Usually well tolerated <1% report with severe diarrhea (leads to discontinuation of use) C/I: GI dysfunction Pregnancy category B Excretion in breast milk: Not determined Approved for use <4 months (as no study beyond 4 months of use) No significant drug interactions	Various reported adverse effects: (in various clinical trials) Abdominal pain (17-30%) Flatulence (8-13%) Nausea (11-21%)	Effectively induces bowel movements in <4 hours Yuan *et al*.: Demonstrated in healthy volunteers the delay in oro-caecal transit time using Lactulose hydrogen breath test and thereby establishing the peripheral actions of methylnaltrexone MNTX 301: Compared 0.15 mg/kg or 0.30 mg/kg SC versus placebo over 04 weeks >60% had bowel movements in 4 hours 0.30 mg/kg was associated with more gastrointestinal side effects MNTX 302: Compared 0.15 mg/kg to 0.30 mg/kg or placebo for 2 weeks 0.15 mg/kg group showed bowel movements in <4 hrs in 48% patients	12 mg/0.6 ml (SC kit) $63.88 per unit (or approx Rs. 3,974.61)
Alvimopan	Long-term use lead to ↑ incidence of myocardial infarction Safe for use lasting ≤7 days In severe hepatic impairment raised plasma levels C/I: Use of opioid analgesic ≥7 days Pregnancy category B Safety not established in breast feeding mothers	Various adverse effects reported in <3% individuals Anemia Back pain Dyspepsia Hypokalemia Urinary retention	Effective only in short-term use: It reduces GI recovery time and helps in early hospital discharge Phase III trials 14CL302, 14CL308, 14CL313: Conducted in US, with pre-operative dose given 2-5 hours prior and twice a day for 7 days compared to placebo 14CL314: Alvimopan pre-operative dose 3-90 minutes prior, rest remains same	$62.50 per 12 mg capsule (or approx Rs 3,888.75)
Naloxegol	Pregnancy category C Relatively well tolerated	Common adverse effects noted Diarrhea; nausea; headache; flatulence Very rare adverse effects Abdominal distension; hyperhydrosis	Phase III trials KODIAC-04 (NCT01309841) and KODIAC-05 (NCT01323790) Inclusion criteria: Patients on stable morphine regimen of 30-1000 mg/day Naloxegol 12.5, 25 mg once a day compared to placebo for 12 weeks Statistically significant spontaneous bowel movements	-

PAMORAs=Peripherally acting mu opioid receptor antagonists, GI=Gastrointestinal

ADVERSE EFFECTS

The most common adverse effect that forced the patients to leave the trial was abdominal pain. The other adverse effects noted were diarrhea, nausea, headache, and flatulence. The very rare adverse effects were abdominal distension, hyperhydrosis, fatigue, sinusitis, nasopharyngitis and dizziness. KODIAC-04 and 05 studies reported death of seven patients, two were on naloxegol 25 mg and three patients were on 12.5 mg dose and were due to cardiovascular cause as assessed by cardiovascular event adjudication committee. To ensure safety the QT/QTc study was undertaken which showed no ECG/other significant changes from baseline.[13,14]

CURRENT STATUS OF NALOXEGOL

Naloxegol is the first oral PAMORA for OIC in adults with chronic non-cancer pain, with approval from US-FDA and European Union. It is administered at a dose of 25 mg twice daily in empty stomach or 2 hours after the meal. The starting dose is 12.5 mg twice daily for individuals with creatinine clearance less than 60 ml/min and increased up to 25 mg twice daily if well tolerated. The exact cost of the product is not yet known. The STEP criterion for selection of PAMORAs in OIC has been tabulated [Table 2].

CONCLUSION

Opioid-induced constipation is a particularly burdensome problem causing considerable misery and morbidity in patients on opioid therapy. Drugs like methylnaltrexone and alvimopan although were intended to be used for OIC had many drawbacks and currently methylnaltrexone given parenterally is restricted for use in only patients on palliative care and alvimopan restricted for short-term use in post operative ileus. Against this backdrop, the approval of naloxegol as first oral PAMORA has opened up new horizons for treating opioid-induced constipation. Naloxegol's approval comes as a great relief to many patients in need of opioids and will provide more freedom to physicians to use opioids in patients who need them without subjecting them to the agony of constipation. However, it must be used with caution and judiciously as it could be potentially misused.

REFERENCES

1. Gehdoo RP. Cancer pain management. Indian J Anaesth 2006;50:375-90.
2. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Mernil JO, Sullivan MD, *et al*. Opioid prescription for chronic pain and overdose: A cohort study. Ann Intern Med 2010;152:85-92.
3. Camilleri M. Opioid-induced constipation: Challenges and therapeutic opportunities. Am J Gastroenterol 2011;106:835-42; quiz 843.
4. Kumar L, Barker C, Emmanuel A. Opioid-induced constipation: Pathophysiology, clinical consequences, and management. Gastroenterol Res Pract 2014;2014:141737.
5. Holzer P. Opioid receptors in the gastrointestinal tract. Regul Pept 2009;155:11-7.
6. Chung HH. The novel role of opioid -receptors in gastroenterology. J Gastroenterol Hepatol Res 2013;2:614-7.
7. Aurilio C, Pace MC, Pota V, Sansone P. Opioid induced constipation. In: Smith AC, editor. Constipation-Causes, Diagnosis and Treatment. Croatia: InTech; 2012. p. 81-8.
8. Clemens KE, Klaschik E. Managing opioid-induced constipation in advanced illness: Focus on methylnaltrexone bromide. Ther Clin Risk Manag 2010;6:77-82.
9. FDA Okays Naloxegol (Movantik) in Opioid-Induced Constipation. Available from: http://www.medscape.com/viewarticle/831780. [Last accessed on 2014 Sep 24].
10. Webster L, Dhar S, Eldon M, Masuoka L, Lappalainen J, Sostek M. A phase 2, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the efficacy, safety, and tolerability of Naloxegol in patients with opioid-induced constipation. Pain 2013;154:1542-50.
11. Bui K, She F, Sostek M. The effects of renal impairment on the pharmacokinetics, safety, and tolerability of Naloxegol. J Clin Pharmacol 2014;54:1375-82.
12. Poulsen JL, Brock C, Olesen AE, Nilsson M, Drewes AM. Clinical potential of naloxegol in the management of opioid-induced bowel dysfunction. Clin Exp Gastroenterol 2014;7:345-58.
13. Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with non-cancer pain. N Engl J Med 2014;370:2387-96.
14. Webster L, Chey WD, Tack J, Lappalainen J, Diva U, Sostek M. Randomised clinical trial: The long-term safety and tolerability of Naloxegol in patients with pain and opioid-induced constipation. Aliment Pharmacol Ther 2014;40:771-9.
15. Gottfridsson C, Carlson G, Lappalainen J, Sostek M. Evaluation of the effect of naloxegol on cardiac repolarization: A randomized, placebo- and positive-controlled crossover thorough QT/QTc study in healthy volunteers. Clin Ther 2013;35:1876-83.

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