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Naloxegol

A Review of Clinical Trials and Applications to Practice

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Opioid-induced constipation is a known side effect of long-term opioid therapy and may contribute to increased healthcare utilization. Common laxatives such as polyethylene glycol and bisacodyl are often selected as first-line agents. However, refractory constipation may persist despite the addition of a second agent. In such situations, alternate agents may be considered. The peripherally acting mu-opioid receptor antagonist naloxegol was approved in 2014 for management of opioid-induced constipation in adult patients with chronic noncancer pain. This agent is similar to the mu-opioid antagonist naloxone but selectively blocks opioid receptors in the periphery, thereby preventing constipation while avoiding any worsening of pain scores. Given that the medication undergoes hepatic metabolism, it is important to monitor liver function prior to initiation and assess for other medications, which may increase or decrease the levels of naloxegol, to determine whether adjustment in therapy may be required.

Introduction and FDA Approval

Opioid-induced constipation is a common complaint, occurring in 41% of patients in one systematic review and often within weeks of initiating treatment (Kalso, Edwards, Moore, & McQuay, 2004). A recent study of Medicaid patients found that approximately 10% of patients on opioid therapy greater than 1 year experienced constipation (Olufade et al., 2017). Healthcare utilization was higher compared with those without constipation, with a median increase of $4166 per person. Traditional laxatives such as polyethylene glycol or bisacodyl are considered first-line agents for initial management (Crockett et al., 2019). However, up to 94% of patients may have inadequate response on a single agent, whereas 27% in one study reported inadequate response to two more agents from separate classes (Coyne et al., 2014). For these treatment-refractory individuals, alternate agents may be considered (Crockett et al., 2019). Naloxegol (Movantic) is a peripherally acting μ (mu)-opioid receptor antagonist (PAMORA) FDA approved in 2014 for the treatment of opioid-induced constipation in adult patients with chronic noncancer pain (AstraZeneca Pharmaceuticals LP, 2014). Structurally, naloxegol is a PEGylated formulation of naloxone (Webster et al., 2014). This occurs by adding a polyethylene glycol (PEG) chain to the molecule naloxol (Floettmann, Bui, Sostek, Payza, & Eldon, 2017). In addition, it is a substrate for the P-glycoprotein transporter, which functions to limit systemic absorption of medications (Horn & Hansten, 2008). As a result, there is decreased permeability across the blood–brain barrier, simultaneously increasing oral bioavailability and limiting the agent to peripheral antagonism of μ-opioid receptors as its mechanism of action.

Pharmacokinetic Profile and Initial Dosing

Naloxegol is rapidly absorbed from the gastrointestinal tract during oral administration, with a half-life of 14–20 hours (Al-Huniti et al., 2017). A phase 2, double-blind, placebo-controlled randomized study looked to evaluate the efficacy, safety, and tolerability of naloxegol in patients with opioid-induced constipation (Webster et al., 2013). Participants 18 years and older were included in the study if they were experiencing opioid-induced constipation attributed to comorbid chronic noncancer pain and receiving a stable oral opioid regimen of 30–1000 mg/day of morphine-equivalent doses, with no anticipated change through the duration of the study. Patients were randomized to one of four groups: placebo, 5 mg, 25 mg, or 50 mg of naloxegol once daily for 4 weeks. The primary endpoint of the study was to assess a change from baseline in spontaneous bowel movements per week after the first week of administration. There was a statistically significant difference in the 25- and 50-mg cohorts when compared with placebo (2.9 vs. 1.0, $p = .0020$, and 3.3 vs. 0.5, $p = .0001$, respectively). The most frequent adverse events were abdominal pain, diarrhea, and nausea. The 5-mg dose was found to be no different from placebo in terms of increase in spontaneous bowl movements, whereas the 50-mg dose resulted in increased side effects. Therefore,

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The authors have no conflicts of interest including, but not limited to, consulting fees, paid expert testimony, employment, grants, honoraria, patents, royalties, stocks, or other financial or material gain that may involve the subject matter of the article.

DOI: 10.1097/NOR.0000000000000558

future studies did not include the 5- or 50-mg doses (Al-Huniti et al., 2017).

In a phase 3, double-blind, placebo-controlled study, patients with noncancer pain and opioid-induced constipation were randomized to receive either naloxegol 12.5 or 25 mg or placebo and followed up for 12 weeks (Chey et al., 2014). Response rate was defined as three or more spontaneous bowel movements per week and an increase from baseline of one or more spontaneous bowel movements for 9 or more of 12 weeks and for 3 or more of the final 4 weeks. Results showed a significantly higher response rate in the group using 25 mg when compared with placebo (44.4% vs. 29.4%, $p = .001$). There was a shorter time to first postdose spontaneous bowel movement observed in the 25-mg group when compared with placebo ($p = .001$) as well. Adverse events were highest in the 25 mg and were primarily gastrointestinal in nature.

Naloxegol was also studied within populations of laxative-inadequate responders, defined as persons using laxatives for a minimum of 4 days in a 2-week period who continued to experience constipation as defined as moderate, severe, or very severe scores on the Stool Symptom Screener (Tack, Lappalainen, Diva, Tummala, & Sostek, 2015). In a pooled analysis of data from two separate 12-week studies, 44% of individuals receiving the 25-mg dose of naloxegol noted response (defined as three or more spontaneous bowel movements per week with one or more spontaneous bowel movement increase over baseline for 9 or more weeks), compared with 35% receiving the 12.5-mg dose and 25.1% of those prescribed placebo.

Therefore, dosing is initiated at 25 mg daily, with a recommendation to discontinue use of other maintenance laxative regimens (AstraZeneca Pharmaceuticals LP, 2014). These may be restarted if necessary 3 days after initiation of naloxegol. Because meals high in fat content increase drug absorption, it is recommended to take the medication either on an empty stomach 1 hour prior to the first meal of the day or 2 hours afterward. If the 25-mg dose is poorly tolerated, then it may be decreased to 12.5 mg daily.

Dose Adjustments

Naloxegol is primarily metabolized hepatically and eliminated within the feces, although there is still some elimination via the urine (Bui, She, & Sostek, 2014a). Studies of use in patients with moderate or severe renal function impairment demonstrate increases in area under the curve (AUC) of 1.7- and 1.8-fold, respectively. As a result of this, it is recommended that the starting dose is reduced to 12.5 mg once daily in persons with creatinine clearance less than 60 mL/min (AstraZeneca Pharmaceuticals LP, 2014). The dose may then be titrated upward as tolerated to 25 mg.

Given that naloxegol undergoes extensive hepatic metabolism, specifically via cytochrome P450 (CYP) enzymes 3A4/3A5, studies were performed to assess pharmacokinetic impact of adding strong and moderate inhibitors ketoconazole and diltiazem, respectively (Bui, Zhou, Sostek, She, & Al-Huniti, 2016). It was noted that these inhibitors resulted in an AUC increase of 12.9-fold and 3.4-fold, respectively; in the presence of the strong CYP3A4 inducer rifampin, drug exposure decreased by 90%.

Area under the curve was also noted to be decreased by approximately 17% in the presence of mild to moderate hepatic impairment (Bui, She, & Sostek, 2014b). It is believed that this may be due to enterohepatic recycling, wherein active drug and metabolites circulate through the bile and may be eliminated using this pathway instead. Dose adjustments are not required for mild or moderate hepatic impairment (AstraZeneca Pharmaceuticals LP, 2014). There is no data regarding the effects of severe hepatic impairment; use in this population is not recommended. Studies were also performed to determine whether P-glycoprotein inhibition would increase systemic exposure to naloxegol (Bui, She, Zhou, Butler, Al-Huniti, & Sostek, 2016). No interaction was found, and therefore no dose adjustments are recommended in the presence of other medications which inhibit P-glycoprotein.

Contraindications

Based on these interactions, naloxegol is contraindicated in patients concomitantly prescribed strong CYP3A4 inducers, given concern for precipitation of opioid withdrawal symptoms such as chills, diarrhea, abdominal pain, irritability, and yawning (AstraZeneca Pharmaceuticals LP, 2014). It is recommended that use with moderate inhibitors be avoided; if required, recommendation is to decrease naloxegol dose to 12.5 mg daily and monitor for increase in adverse effects. Use with strong inducers is also not recommended, nor is consumption of grapefruit or grapefruit juice. Lastly, the medication should not be used in cases of intestinal obstruction or risk of obstruction.

Adverse Effects and Clinical Counseling Points

Abdominal pain was the most common adverse effect noted in both 12-week (12.5-mg dose, 7.6%; 25 -mg dose, 15.8%) and 52-week (25 mg, 17.8%) studies (Tack et al., 2015; Webster et al., 2014). Other adverse effects occurring in greater than 5% of patients on naloxegol in any study included diarrhea, nausea, back pain, headache, flatulence, arthralgia, nasopharyngitis, upper respiratory tract infection, bronchitis, vomiting, and upper abdominal pain.

Due to concern for withdrawal effects from use of opioid receptor antagonists, cardiovascular data across four phase 3 studies was evaluated (White, Kowey, Diva, Sostek, & Tummala, 2018). Note that patients at risk for ventricular arrhythmias were excluded from enrollment in these trials. However, the majority of patients enrolled did have at least one cardiovascular risk factor or disease (27.3% with one risk factor, 40.9% with a history of cardiovascular disease, diabetes, or two or more cardiovascular risk factors). Pooled analysis of safety data was performed. Changes in blood pressure and heart rate were similar between treatment and placebo groups. Similarly, there were no clinically meaningful differences in electrocardiogram parameters. There were four major adverse cardiac events in the placebo/usual care group, compared with five in the naloxegol group.

Because naloxegol is structurally similar to naloxone, there is in theory also a concern for diminishing of the analgesic effect of opioids. However, when data from the initial 12-week clinical studies were analyzed, there were no statistically significant changes from baseline in terms of average or worst pain scores (Webster, Diva, Tummala, & Sostek, 2018). Therefore, the authors concluded that naloxegol does not have a clinically relevant effect on patient-reported pain levels for patients with noncancer pain and comorbid opioid-induced constipation.

Given that the medication works to counter the effects of opioid-induced constipation, it is recommended to stop taking naloxegol when opioid therapy is discontinued (AstraZeneca Pharmaceuticals LP, 2014).

Summary

For patients with opioid-induced constipation which fails to respond to traditional stimulant and osmotic laxatives, it may be worthwhile to consider agents with differing mechanisms of action such as the peripherally acting mu-opioid receptor antagonist naloxegol. Despite concern for precipitation of withdrawal from systemic absorption, the medication is tolerated well overall and side effects are generally gastrointestinal in nature. Pain scores and cardiovascular parameters do not appear to be affected by naloxegol. Important considerations before starting this medication include a review of potential drug interactions via the CYP3A4 enzymatic pathway as well as calculation of renal function. Patients should be reminded to take the medication apart from meals to avoid increases in drug concentration.

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