Treatment With Prolonged-Release Oxycodone/Naloxone Improves Pain Relief and Opioid-Induced Constipation Compared With Prolonged-Release Oxycodone in Patients With Chronic Severe Pain and Laxative-Refractory Constipation

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ABSTRACT

Purpose: Laxative-refractory opioid-induced constipation (OIC) is defined as OIC despite using 2 laxatives with a different mechanism of action (based on the Anatomical Therapeutic Chemical Classification System level 4 term [contact laxatives, osmotically acting laxatives, softeners/emollients, enemas, and others]). OIC has a significant impact on the treatment and quality of life of patients with severe chronic pain. This noninterventional, observational, real-life study in Belgium investigated the efficacy of prolonged-release oxycodone/naloxone combination (PR OXN) treatment regarding pain relief and OIC compared with previous prolonged-release oxycodone (PR OXY) treatment for laxative-refractory OIC in daily clinical practice.

Methods: Laxative-refractory OIC patients with severe chronic pain were treated with PR OXN for 12 weeks (3 visits). Pain relief (assessed on a numerical rating scale) and OIC (assessed by using the Bowel Function Index [BFI]) were evaluated at each visit. A responder was defined as a patient who had: (1) no worsening of pain at the last visit compared with visit 1 or a numerical rating scale ≤ 4 at visit 3/last visit; and (2) a reduction in BFI ≥ 12 units at visit 3/last visit compared with visit 1; or (3) a BFI ≤ 28.8 at visit 3/last visit.

Findings: Sixty-eight laxative-refractory OIC patients with severe chronic pain (mean (sd) age 59.8 (13.3) years, 67.6% female and 91.2% nonmalignant pain) were treated for 91 days with PR OXN (median daily dose, 20 mg). Treatment with PR OXN resulted in a significant and clinically relevant decrease of pain of 2.1 units ($P < 0.001$; 95% CI, 1.66–2.54) and of BFI by 48.5 units ($P < 0.001$; 95% CI, 44.4–52.7) compared with PR OXY treatment; use of laxatives was also significantly reduced ($P < 0.001$). Approximately 95% of patients were responders, and quality of life (as measured by using the EQ-5D) improved significantly. Adverse events were opioid related, and PR OXN treatment was well tolerated.

Implications: Treatment with PR OXN resulted in a significant and clinically relevant reduction in OIC compared with previous PR OXY treatment for these patients with severe chronic pain and laxative-refractory OIC. Treatment with PR OXN also resulted in a significant improvement in pain relief and quality of life. ClinicalTrials.gov identifier: NCT01710917. (*Clin Ther*. 2015;37:784–792) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

Key words: laxative refractory, laxatives, opioid-induced constipation, pain, quality of life.

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INTRODUCTION

Opioids are widely used for the treatment of patients with severe chronic pain. However, adverse drug reactions associated with the use of opioids, particularly opioid-induced bowel dysfunction, can be problematic and severely affect quality of life.[1] Opioid-induced constipation (OIC) is the most distressing symptom of opioid-induced bowel dysfunction and occurs in ~40% of opioid-treated patients.[2,3] In contrast to opioid-related adverse effects mediated through the central opioid receptors, which occur at the start of treatment and usually rapidly lessen, OIC is mediated through intestinal opioid receptors and often persists throughout opioid treatment with no decline in intensity.[4] OIC is the most troublesome opioid-related adverse effect reported by patients, resulting in reduction or discontinuation of treatment in one third of opioid-treated patients.[1] Laxatives are the most common drugs used for relieving OIC. However, because laxatives do not address the underlying mechanisms of OIC, they are insufficiently effective in the majority of patients experiencing this condition.[5,6] Moreover, there are no direct comparative data on different laxatives in the prevention or treatment of OIC, resulting in a lack of generally accepted guidelines regarding laxative use for this condition.[6]

One strategy to minimize or prevent OIC while maintaining analgesic efficacy is blocking intestinal opioid receptors while allowing the activation of central opioid receptors.[6] To this end, a prolonged-release tablet consisting of oxycodone and naloxone (PR OXN) in a 2:1 ratio was developed. Oxycodone has been shown to be an effective analgesic in various types of pain.[7] Naloxone is an opioid receptor antagonist with low systemic bioavailability (<3%) primarily used as an injectable solution for the treatment of opioid overdose by its antagonizing effect on central opioid receptors. When administered orally, naloxone antagonizes the opioid receptors in the gut wall, thereby counteracting OIC, while its extensive first-pass hepatic metabolism ensures the lack of antagonist influence on the central analgesic effect of oxycodone.[8]

Several randomized controlled studies have reported on the comparable analgesic efficacy of PR OXN and prolonged-release oxycodone (PR OXY), with a significant and clinically relevant improvement in OIC with PR OXN compared with PR OXY in various types of pain even after long-term treatment.[9–15] The frequency of adverse events was similar between PR OXN and PR OXY treatments. This outcome was confirmed in daily clinical practice in Germany for patients with a variety of pain etiologies.[16]

PR OXN is indicated for the treatment of severe pain that can only be adequately managed with opioid analgesics. In Belgium, reimbursement for PR OXN is strictly limited to patients who have been treated with PR OXY for at least the last 30 days before PR OXN treatment and who are experiencing laxative-refractory OIC; this form is defined as OIC despite the use of at least 2 laxatives with different mechanisms of action (based on the Anatomical Therapeutic Chemical [ATC] Classification System level 4 term [eg, contact laxatives, osmotically acting laxatives, softeners/emollients, enemas, and others) during previous PR OXY treatment.

The present real-life study was requested by the Belgian reimbursement authorities to investigate the efficacy of PR OXN in terms of both pain relief and OIC in chronic pain patients eligible for PR OXN reimbursement in Belgium. In addition to evaluation of efficacy regarding pain relief and OIC use of laxatives and analgesic rescue medication, quality of life and safety during PR OXN treatment compared with the previous PR OXY treatment were evaluated.

PATIENTS AND METHODS

Study Design

This noninterventional, observational, real-life study was designed to evaluate the pain relief and OIC of PR OXN treatment in daily practice in patients with chronic severe pain compared with previous PR OXY treatment. PR OXN treatment was started at visit 1. The study was performed by using electronic case record forms, and all parameters collected at visit 1 reflected the PR OXY treatment. Evaluations were performed during 2 follow-up visits. Visit 2 was scheduled after PR OXN dose titration, and visit 3 was scheduled at least 12 weeks after visit 1.

The study was conducted in accordance with Belgian and European health law and controlled drug regulations.

Patients

Patients enrolled in the present study met the reimbursement conditions for PR OXN in Belgium as well as the summary of product characteristics for