REVIEW

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Oxycodone/naloxone prolonged-release tablets in patients with moderate-to-severe, chronic cancer pain: Challenges in the context of hepatic impairment

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Abstract

Opioids such as oxycodone are recommended in the management of moderate-to-severe, chronic cancer pain. All opioids can potentially cause constipation, which may be a significant barrier to their use. Multiple randomised clinical trials have shown that the use of naloxone as a peripherally acting mu-opioid receptor antagonist, in combination with oxycodone can prevent or reduce opioid-induced constipation while having equivalent analgesic efficacy to oxycodone alone. However, clinical experience has shown that unexpected events may occur in some patients when unrecognized liver impairment is present. We describe the underlying biological reasons and propose simple, but effective steps to avoid this unusual but potentially serious occurrence. In healthy individuals, naloxone undergoes extensive hepatic first pass metabolism resulting in low systemic bioavailability. However, in patients with hepatic impairment, porto-systemic shunting can increase systemic bioavailability of naloxone, potentially compromising the analgesic efficacy of oral naloxone–oxycodone combinations. This reduced first pass effect can occur in a range of settings that may not always be apparent to the treating clinician, including silent cirrhosis, non-cirrhotic portal hypertension and disruption of liver internal vasculature by metastases. Hepatic function test results correlate poorly with presence and extent of liver disease, and are not indicative of porto-systemic shunting. Presence of hepatic impairment should thus be considered when medication-related outcomes with oxycodone–naloxone combination are not as expected, even if liver function test results are normal.

KEYWORDS
cancer, chronic pain, hepatic impairment, opioid-induced constipation, oxycodone naloxone prolonged release tablet

1 | INTRODUCTION

Most patients with advanced-stage cancer experience disease-related pain,[1] and strong opioids are the mainstay of moderate-to-severe, chronic cancer pain management.[2,3] However, the actions of opioids on mu-opioid receptors in the intestinal wall causes a reduction in gut peristalsis and fluid secretion, and an increase in fluid reabsorption and sphincter tone, which can lead to opioid-induced symptoms of constipation.[4] Peripherally acting mu-opioid receptor antagonists such as naloxone are able to reduce opioid-induced constipation. In

patients requiring opioids for moderate-to-severe chronic pain, the use of naloxone in combination with oxycodone in a prolonged release tablet (PR OXY/N) can prevent development of opioid-induced constipation or reduce existing opioid-induced constipation.[5]

It has long been known that hepatic impairment, especially in the setting of portal hypertension, increases systemic bioavailability of naloxone,[6–12] potentially compromising the analgesic efficacy of PR OXY/N. For this reason, the manufacturer's recommendation is to avoid PR OXY/N in patients with known severe liver disease. Nevertheless, several case reports have been published describing acute opioid sedation/toxicity or inadequate analgesic efficacy in patients with hepatic impairment when switching between PR OXY/N tablets and oxycodone for cancer-related pain.[7–12]

This article discusses potential treatment challenges with prolonged release oxycodone alone (PR OXY), including opioid toxicity and impaired analgesic efficacy when switching to or from oxycodone alone, in patients with advanced malignancies suffering chronic moderate-to-severe cancer pain, especially in the context of known or unrecognized impaired hepatic function.

1.1 | Pain and constipation in patients with cancer

Strong opioids, which are used to manage moderate-to-severe, chronic cancer pain, can lead to opioid-induced constipation.[4] Pivotal, randomized, controlled trials and open-label extensions have shown improved bowel function and comparatively lower rates of constipation and laxative use with PR OXY/N tablets compared with PR OXY in patients with moderate-to-severe cancer pain, at equivalent analgesic efficacy.[5,13–15] Real-world data from observational studies in patients with cancer-related pain support the efficacy outcomes of pivotal trials.[16–21]

It should be acknowledged that ongoing treatment with laxatives remains important because a number of non-opioid related factors also contribute to constipation in this population, such as concomitant serotonin [5-HT] receptor antagonists and anticholinergic medications as well as dietary and environmental factors[22–26] (see Box 1). Therefore, it has been recommended that a multidisciplinary approach may help clinicians manage constipation better in patients treated with opioids.[27]

2 | HOW THE HEALTHY LIVER PROCESSES OXY/N

Oxycodone passes from the gastrointestinal tract through the healthy liver mostly unchanged, resulting in a high bioavailability of up to 87%.[28] Following systemic exposure, the majority of opioids, including oxycodone, are then broken down in the liver and excreted.[29] Opioid metabolism may vary considerably between different people due to inter-individual variability in pharmacokinetics (e.g. differences in drug metabolism and elimination) and pharmacodynamics (e.g. differences in opioid receptor structure and function).[30]

When taken orally by individuals with healthy liver function, naloxone is active in the gastrointestinal tract and – in contrast to

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> **BOX 1. Non-opioid factors related to constipation in patients with cancer**
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> - Medications (e.g. serotonin [5-HT] receptor antagonists, anticholinergics, antacids, diuretics, iron supplements)
> - Dietary factors (e.g. poor hydration, inadequate food intake, low fiber intake)
> - Health-related factors (e.g. reduced mobility, reduced urge to defaecate, abdominal tumors creating blockage or nerve damage, neurological/neuromuscular comorbidities)
> - Environmental factors (e.g. inactivity, reduced mobility, lack of privacy or requiring assistance when needing to use the toilet)

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oxycodone – undergoes extensive hepatic first pass metabolism, resulting in it being destroyed in the liver and not entering the systemic circulation (Figure 1a).[31] The systemic bioavailability of naloxone is low, ranging from 0.9% to 2.0% when it is given orally at doses between 5 and 120 mg.[31] Systemic bioavailability of naloxone in healthy individuals is too low to affect the analgesic efficacy of oxycodone,[31] which is why several clinical trials have shown that PR OXY/N tablets have equivalent analgesic efficacy to PR OXY alone.[5,13–15]

3 | HEPATIC IMPAIRMENT IN ADVANCED MALIGNANCIES

Patients with advanced cancer, who may be approaching end of life, not only have more pain than at earlier disease stages, but also are more prone to multiorgan dysfunction, including hepatic impairment.[3,32–34] This makes the management of pain in patients with advanced cancer more challenging than in earlier stage disease, especially when patients transition from one setting to another, such as from oncology to palliative care, where the burden of polypharmacy can be particularly high.[35]

Poor liver function in patients with advanced malignancies may be due to primary liver cancer, secondary metastases or to a noncancer-related comorbidity. Liver function test results correlate poorly with presence and extent of liver disease and can be within the normal range in individuals, even when severe fibrosis is seen on liver histology.[36,37] In individuals with liver disease, hepatic function and capability for drug metabolism are increasingly impaired with disease progression.[29] Hepatic blood flow is reduced, hepatocyte numbers and function are decreased and, most importantly, there is shunting of blood past or through the liver due to porto-systemic shunting.[29] Reduced drug–protein binding, caused by low serum albumin (a serum marker of liver failure, malnutrition or protein losing enteropathy), can further increase the systemic drug bioavailability.[29]
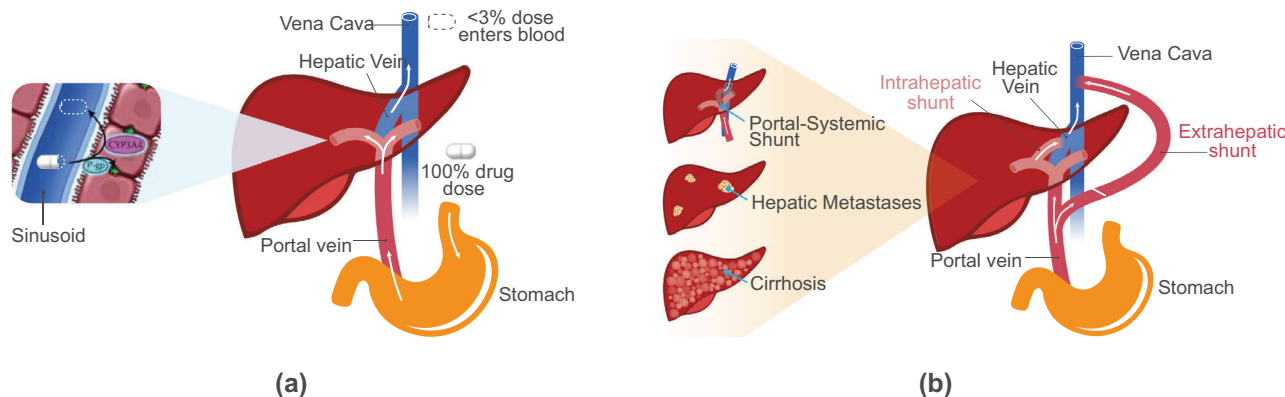
FIGURE 1 (a) Normal first pass metabolism by liver sinusoids of the naloxone component of prolonged release oxycodone/naloxone tablet. (b) Intra- and extrahepatic shunting due to cirrhosis, portal hypertension or portal-systemic shunts [Colour figure can be viewed at wileyonlinelibrary.com]

Portal blood flows from the intestines through the hepatic sinusoids, before it rejoins the systemic circulation via the hepatic vein. When the flow of portal blood through the liver is diverted, such as occurs in portal hypertension, drugs such as naloxone that normally experience extensive first pass metabolism will bypass the liver and reach the systemic circulation in increasing amounts by using intra- and extra-hepatic shunts. First pass metabolism by the liver may be variably affected by processes that reduce the flow of portal blood from the intestines, and among the most well-known causes of reduced portal blood flow are established cirrhosis and portal hypertension.[38] Due to the resultant increased hepatic pressure, significant proportions of portal blood are diverted away from the liver into collaterals (also called varices), which enter the systemic circulation directly via the splenorenal and gastro-esophageal veins (Figure 1b). In the case of PR OXY/N tablets, this diversion would allow un-metabolized naloxone to enter the systemic circulation and impair the analgesic effect of oxycodone.

Reduced first pass effect occurs in a number of settings that may not always be apparent to the treating clinician. Cirrhosis may be "silent," meaning it is not recognized on routine liver biochemistry or imaging, or suspected on history and examination. Portal hypertension can also occur in the absence of cirrhosis, known as non-cirrhotic portal hypertension.[39,40] Liver internal vasculature may be disrupted by metastases, or altered by the presence of internal portal-systemic shunts that may occur as a normal variant on a small scale but are more likely to be due to interventional radiology procedures, surgery or disease.[41–46]

Clinicians should be aware of the importance of this phenomenon with many drugs. For example, another drug for which first pass metabolism reduces systemic side effects is oral budesonide, used in Crohn's disease and autoimmune hepatitis. The effect of reduced first pass metabolism on budesonide has been studied in patients with cirrhosis, portal hypertension and idiopathic shunting past the hepatic sinusoids, showing often severe systemic effects of the steroid in these individuals.[47,48]

3.1 | Identifying reduced hepatic first pass metabolism

There is no simple clinical method to test for a reduced hepatic first pass effect in patients with or without cirrhosis. The Child-Pugh classification, which is widely used to categorize the severity of liver cirrhosis and prognosis[49] may not be predictive of reduced first pass metabolism. A reduced serum platelet count may be a useful sign of undiagnosed portal hypertension.[50] It may be assumed that any evidence of portal hypertension seen on imaging (e.g. enlarged portal vein, presence of intra-abdominal varices, splenomegaly), or suspected in the setting of a low platelet count, indicates a high possibility of reduced first pass metabolism. In the absence of direct or easy assessment methods, it falls to the clinician to consider this possibility if a drug that normally undergoes extensive hepatic first pass metabolism is not having the expected outcome.

4 | TREATMENT ISSUES IN THE CONTEXT OF HEPATIC IMPAIRMENT

4.1 | Overview

Plasma concentrations of both oxycodone and naloxone are elevated following oral intake of PR OXY/N in patients with hepatic impairment, compared with healthy volunteers, with naloxone being affected to a far greater extent than oxycodone.[6] Although the plasma accumulation of oxycodone in severe liver failure is caused by a decrease in hepatic drug metabolism, the elevation in systemic naloxone concentrations is caused by a reduced hepatic first pass effect, as discussed above. Increased concentrations of oxycodone, used alone, in this scenario can lead to symptoms of opioid toxicity which clinicians should normally be aware of. However, when systemic concentrations of naloxone are also increased, this may antagonize the effects of the opioids, leading unexpectedly to reduced analgesia and, in extreme cases, to opioid

withdrawal symptoms. Although results from a small observational study suggest that PR OXY/N tablets can be a safe and effective option in cirrhotic patients with cancer pain,[21] for this reason PR OXY/N tablets have always been contraindicated in patients with moderate-to-severe hepatic impairment.[6]

4.2 | Opioid toxicity

The main signs and symptoms of acute opioid toxicity are drowsiness, respiratory depression (rate and depth), reduced level of consciousness and pinpoint pupils. Cases of opioid toxicity have been described in the context of switching patients from PR OXY/N tablets to an equivalent dose of PR OXY in the presence of progressive liver impairment.[7,8] In this scenario, liver injury is likely to have increased the systemic bioavailability of naloxone from PR OXY/N tablets via porto-systemic shunting, leading to reduced efficacy of the oxycodone component. The switch to an equivalent dose of PR OXY alone, without the antagonistic effect of systemically bioavailable naloxone in the presence of impaired liver function, would have increased the number of central opioid receptors available for oxycodone binding, leading to acute opioid toxicity. Acute opioid toxicity is typically treated with parenteral naloxone.

When switching between opioids, a helpful guideline is to use a starting dose for the new opioid that is 25–50% lower than the equi-analgesic dose of the original opioid, to allow for incomplete cross-tolerance and variations in response.[51] This principle is equally valid when switching from PR OXY/N to PR OXY. For safety reasons, a start dose of 50% of the approximate equi-analgesic dose has been suggested when patients with impaired liver function are switched from PR OXY/N tablets to PR OXY alone, with careful monitoring for adverse effects or toxicity.[12] However, real world data to guide switching from PR OXY/N tablets to PR OXY alone in the setting of known or suspected hepatic impairment are lacking.

Opioid toxicity has also been described when PR OXY/N tablets have been discontinued against a background of concomitant methadone treatment in the presence of liver disease.[12] In this case, increased systemic bioavailability of naloxone via porto-systemic shunting is likely to have reduced the effect of methadone, leading to methadone toxicity upon discontinuation of PR OXY/N tablets.

4.3 | Causes of inadequate analgesia

Breakthrough pain can occur even in patients receiving continuous analgesia and is typically treated with supplemental, short-acting and rapid-onset opioids. Worsening pain and poorly controlled background pain may be signs of inadequate analgesia, which may occur for a variety of reasons such as poor medication compliance or issues with metabolism of the chosen analgesic therapy.[3,30] Poor analgesic efficacy and symptoms of opioid withdrawal have been described in patients with liver impairment using PR OXY/N tablets or switch-ing from other opioid treatments to PR OXY/N tablets.[7,9,10,12,52] In this setting, the increased systemic bioavailability of naloxone from PR OXY/N tablets via porto-systemic shunting is likely to have led to analgesic antagonism and reduced pain control. Similarly, severe pain can also develop when switching analgesia from PR morphine to PR OXY/N tablets in the presence of impaired liver function.[7,9,10,12]

If therapy with PR OXY/N tablets is not having the expected analgesic effect, then the presence of reduced hepatic first pass metabolism should be considered. When porto-systemic shunting of naloxone is the suspected reason for inadequate analgesia, switching from PR OXY/N tablets to PR OXY can lead to improved pain control.[12] It is important to avoid continued treatment with PR OXY/N tablets in patients with deteriorating liver function,[12] and to switch early to another opioid. However, the opioid equivalent dose of the new opioid should be lower than the PR OXY/N, because it is likely that sufficient naloxone has been entering the systemic circulation to antagonize some of the oxycodone. A conservative approach is therefore recommended when patients with liver impairment are switched to an opioid-only formulation, starting with a lower equivalent dose (by 25–50%) of the new opioid and monitoring the patient for adverse effects or toxicity as well as adequate pain control.[12]

5 | CONCLUSION

Patients with cancer pain can be managed in most cases successfully and safely with PR OXY/N tablets, which has confirmed equivalent analgesic efficacy to PR OXY and can prevent development of, or reduce existing, opioid-induced constipation or reduce existing opioid-induced constipation, providing the manufacturer's warnings in respect of severe liver disease are observed. Careful patient selection and monitoring are important when using PR OXY/N, as underlined by the case reports described here. Consider the possibility of reduced first pass hepatic metabolism, due to known or unknown liver dysfunction or porto-systemic shunting, in the event of unexpected adverse effects or medication-related outcomes are not as expected, even if liver function test results are within the normal range. Opioid switching from PR OXY/N tablets to PR OXY can lead to improved pain control in this dynamic clinical situation.

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