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Reduced Oxycodone Efficacy Associated With Carbamazepine Use in a Patient With Advanced Cholangiocarcinoma

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Abstract

Drug-drug interactions are a frequently under-recognised cause of suboptimal symptom control in palliative care. We describe a case of a 72-year-old woman with advanced cholangiocarcinoma who developed escalating abdominal pain despite increasing doses of oxycodone, including patient-controlled analgesia. Alternative explanations were considered, including disease progression, visceral pain, and psychological distress. Following opioid rotation to morphine, there was rapid improvement in analgesia, followed by features of opioid-induced neurotoxicity at moderate doses. A potentially clinically significant interaction between carbamazepine and oxycodone was subsequently identified. This case highlights the importance of recognising enzyme-inducing medications as a potential cause of reduced opioid efficacy and demonstrates the clinical value of opioid rotation in complex cases.

Categories: Pain Management, Palliative Care, Pharmacology
Keywords: carbamazapine, cytochrome p-450 cyp3a4, drug interaction, oxycodone, palliative care and palliative medicine, treatment failure

Introduction

In palliative care, opioids remain the cornerstone of analgesic therapy for cancer-related pain and play a fundamental role in improving patients' quality of life [1]. Polypharmacy is common among patients with advanced malignancy, who frequently receive multiple concomitant medications, increasing the risk of pharmacokinetic interactions that may significantly alter opioid efficacy [2]. In contrast to morphine, which is metabolised primarily through glucuronidation, oxycodone is metabolised predominantly by cytochrome P450 3A4 (CYP3A4) and is therefore susceptible to increased clearance and reduced analgesic efficacy with enzyme-inducing medications such as carbamazepine [3]. Although this interaction is recognised in pharmacological references [4], reports of clinically significant reductions in efficacy of oxycodone in palliative care remain limited [5]. We describe a case of reduced oxycodone efficacy potentially associated with concurrent carbamazepine therapy in a patient with advanced cholangiocarcinoma, highlighting the importance of careful medication review and consideration of opioid metabolism when evaluating refractory pain.

Case Presentation

A 72-year-old woman with cholangiocarcinoma was admitted to hospital following clinical deterioration during neoadjuvant chemotherapy. Initially, the disease was considered borderline resectable; however, interval imaging during an admission for acute cholecystitis in December 2025 demonstrated circumferential involvement of the superior mesenteric vein, rendering the tumour unresectable. She subsequently underwent laparoscopic cholecystectomy, and management of her malignancy was changed to palliative intent.

Her past medical history included epilepsy, which was well controlled on carbamazepine 200 mg twice daily for many years. She had recently moved into a new apartment with her husband shortly prior to admission and expressed significant concerns about coping at home. Psychological assessment identified multiple stressors, including her cancer diagnosis and significant family illness.

During the first month of admission, she developed worsening central abdominal pain associated with nausea in early January 2026. The pain was diffuse, difficult to characterise, and was sometimes exacerbated by oral intake. The patient's clinical course is summarised in Table *1*.

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Time Point	Clinical Event
3 months before admission	Cholangiocarcinoma was diagnosed following investigation of abdominal pain and jaundice. Neoadjuvant FOLFIRINOX chemotherapy commenced. Carbamazepine 200 mg twice daily for epilepsy continued throughout treatment.
Day 1 (Admission)	Admitted following clinical deterioration during neoadjuvant chemotherapy. Imaging on admission demonstrated acute cholecystitis and disease progression with circumferential involvement of the superior mesenteric vein, rendering the tumour unresectable. Management was changed to palliative intent.
Early admission	A laparoscopic cholecystectomy was performed during the admission. The patient was subsequently transferred to her local hospital for ongoing care and discharge planning. Initially, pain and nausea were well controlled.
First month of admission	Progressive diffuse abdominal pain and nausea developed. Oral morphine was commenced and titrated to long-acting morphine 30 mg twice daily with short-acting oral morphine use reaching 80 mg/day; analgesia remained suboptimal.
Day 38	Severe uncontrolled pain prompted review by the Acute Pain Service. IV oxycodone patient-controlled analgesia (PCA), 1 mg bolus dose with a 5-minute lockout, was commenced without basal infusion. Long-acting oral morphine reduced to 20 mg twice daily and then stopped. Oral celecoxib 100 mg twice daily commenced.
Days 39-41	Pain remained poorly controlled despite progressive PCA bolus dose escalation to 1.5 mg with a 5-minute lockout. On Day 41, 96 mg of oxycodone was delivered over 24 hours with 168 PCA attempts.
Day 44	Referral to the Palliative Care Team for ongoing pain and symptom management.
Day 47	Oxycodone PCA was converted to oral long-acting oxycodone 10 mg twice daily, following a period of relative stability.
Days 47-55	Long-acting oxycodone was escalated to 40 mg twice daily, with short-acting oral oxycodone use reaching 90 mg/day. Pain remained difficult to control, and breakthrough requirements suggested possible end-of-dose failure. Alternative explanations including disease progression, visceral pain, constipation and psychological distress were considered. Celecoxib 100 mg twice daily was discontinued due to lack of effect; however, paracetamol 1 g four times daily continued until discharge.
Day 55	Persistent poor response to oxycodone prompted opioid rotation. During multidisciplinary review, a potential interaction between carbamazepine and oxycodone was identified. Long-acting oxycodone 40 mg twice daily was converted to long-acting morphine 60 mg twice daily. The conversion used a 1:1.5 oxycodone-to-morphine ratio; breakthrough oxycodone use was not included in the calculation.
Days 56-57	Analgesia improved rapidly and substantially. Within 24 hours, the patient developed opioid-induced neurotoxicity characterised by drowsiness, confusion and vivid dreams.
Days 57-60	Stepwise reduction in morphine dose resulted in complete resolution of neurotoxicity while maintaining satisfactory analgesia.
Day 68 (Discharge)	Stable symptom control on long-acting morphine 20 mg twice daily with 20-30 mg/day short-acting oral morphine use. Carbamazepine 200 mg twice daily remained unchanged throughout the admission.

TABLE 1: Timeline of the patient's clinical course

Oral morphine was commenced and gradually escalated to long-acting morphine 30 mg twice daily, with short-acting oral morphine use for breakthrough pain reaching 80 mg per day. Despite this, pain control remained suboptimal. She reported that morphine was ineffective and at times expressed concerns it might be worsening her symptoms.

On Day 38, she developed severe uncontrolled pain over a weekend period. The acute pain service was consulted and recommended adjustments to analgesia, including increased use of short-acting morphine, celecoxib 100 mg twice daily, and reduction of long-acting morphine to 20 mg twice daily. Due to ongoing poor pain control and difficulty accessing timely breakthrough medication, she was transitioned to an oxycodone patient-controlled analgesia (PCA) regimen. This was an oxycodone 1 mg IV bolus with a five-minute lockout period. No basal oxycodone infusion was used at any point during the admission.

Despite the dose escalation of the PCA oxycodone to 1.5 mg IV bolus with a five-minute lockout period, her pain remained poorly controlled. On Day 41, she received 96 mg of IV oxycodone with 168 attempts over the 24-hour period, indicating a high level of unmet analgesic need. PCA boluses only provided brief relief. Pain worsened with nausea and vomiting, and CT imaging revealed no new pathology for her symptoms beyond known malignancy.

On Day 47, after a period of relative stability, she was transitioned from PCA to oral long-acting oxycodone 10 mg twice daily. However, pain remained difficult to control despite progressive dose escalation over eight days, reaching long-acting oral oxycodone 40 mg twice daily, with short-acting oral oxycodone use for breakthrough pain reaching 90 mg per day.

Contributing factors such as disease progression, visceral pain, constipation, and psychological distress were considered. Overnight breakthrough dosing suggested possible end-of-dose failure. No other analgesic medication changes or adjuvants were given other than regular paracetamol 1 g four times daily, which continued until discharge, and celecoxib 100 mg twice daily, which was stopped on day 49 due to lack of effect. Opioid rotation was recommended by the palliative care team due to the persistent poor response to oxycodone and the patient's report that morphine had previously provided effective postoperative analgesia.

On Day 55, oxycodone 40 mg twice daily was converted to long-acting morphine 60 mg twice daily using a conservative oxycodone-to-morphine conversion ratio of 1:1.5. This conversion was chosen because of concern regarding incomplete cross-tolerance and the possibility that patient-specific factors were reducing the clinical efficacy of oxycodone. Breakthrough oxycodone use was not included in the conversion calculation. Renal and liver function blood tests were unremarkable. Soon after, multidisciplinary discussion with the palliative care team clinical pharmacist identified a potential interaction between carbamazepine and oxycodone.

Following conversion to morphine, analgesia improved rapidly and substantially. However, within 24 hours, she developed features of opioid-induced neurotoxicity, including drowsiness, confusion, and vivid dreams with stable respiratory parameters. Stepwise reduction of her morphine dose resulted in complete resolution of neurotoxic symptoms without loss of analgesia. By Day 60, pain and nausea were well controlled. For the remainder of her admission, she remained stable on long-acting morphine 20 mg twice daily with 20 to 30 mg short-acting oral morphine use per day for breakthrough pain, representing a markedly lower opioid requirement than predicted from her prior oxycodone use.

Neurology input was sought regarding her long-term carbamazepine therapy, given the potential for further drug interactions. Alternatives were discussed, but she elected to defer changes until after discharge. The patient remained on a stable dose of carbamazepine throughout the entire admission and on discharge.

She was discharged on Day 68 with stable symptom control.

Discussion

This case suggests that a clinically significant drug-drug interaction with carbamazepine was a probable contributor to the observed lack of efficacy of oxycodone. The patient experienced escalating pain despite high-dose oxycodone, followed by rapid improvement and subsequent toxicity after opioid conversion to morphine.

Alternative explanations were considered, including disease progression, visceral pain, constipation, infection, and psychological distress. These factors are common in palliative care and may have contributed to her symptom burden, but they did not adequately explain the marked improvement following opioid rotation. The authors acknowledge the impact of psychological distress as being a potential confounder and note that psychosocial supportive measures were provided throughout the period of analgesic medication titration.

The patient demonstrated clinical features suggestive of altered oxycodone pharmacokinetics, including the requirement for high oxycodone doses, short-lived analgesic effects, and rapid improvement following opioid rotation to morphine. This occurred in the context of consistently clinically unremarkable liver and renal function blood tests. Although oral morphine had been used earlier in the admission without clear benefit, symptom interpretation was complicated by multiple concurrent factors, including nausea, significant psychological distress, and progressive malignancy. The subsequent development of opioid-induced neurotoxicity at moderate morphine doses, together with the marked improvement in analgesia following opioid rotation, suggests that reduced oxycodone exposure due to enzyme induction may have contributed substantially to the inadequate analgesic response rather than this representing intrinsic opioid non-responsiveness.

The marked discrepancy between the patient's high oxycodone requirements and her subsequent low stable morphine dose supports a pharmacokinetic explanation for her reduced analgesic efficacy with oxycodone. However, the absence of oxycodone plasma concentration monitoring limits the strength of this evidence as a definitive causal explanation.

Carbamazepine is a potent inducer of cytochrome P450 enzymes, particularly CYP3A4, which is the major enzyme responsible for oxycodone metabolism. CYP3A4 enzyme induction accelerates oxycodone clearance, resulting in reduced oxycodone plasma concentrations and diminished analgesic effect [4-6]. Although this interaction is recognised as theoretical in prescribing references [4], published case reports describing

clinically significant reductions in oxycodone efficacy remain scarce [5].

Unlike oxycodone, which is extensively metabolised by CYP3A4, morphine undergoes metabolism primarily through glucuronidation and is largely unaffected by CYP450 enzyme induction [7]. In patients receiving enzyme-inducing medications such as carbamazepine, opioids that are less dependent on CYP-mediated metabolism may provide more predictable analgesia. However, opioid selection should be individualised and guided by consideration of potential drug interactions, organ function, prior opioid exposure, clinical response, adverse effects, and patient preferences. In this case, opioid rotation to morphine was associated with improved pain control, supporting the possibility that carbamazepine-mediated enzyme induction contributed to the reduced efficacy of oxycodone.

Although isobologram analysis is a recognised method for assessing synergistic or antagonistic interactions between drug combinations, it was not applicable to this single-patient clinical case. The interaction between carbamazepine and oxycodone was evaluated based on the patient's clinical response and the known pharmacokinetic effect of CYP3A4 enzyme induction by carbamazepine.

This case highlights the importance of careful medication review when evaluating refractory cancer pain. Drug-drug interactions should be considered in patients with unexpectedly high opioid requirements, transient analgesic benefit, or apparent end-of-dose failure. Clinicians should be aware that carbamazepine may substantially reduce oxycodone exposure through CYP3A4 enzyme induction. When opioid failure is suspected, opioid rotation may not only improve symptom control but also provide valuable diagnostic insight into the underlying mechanism of treatment resistance. Limitations of this case include the absence of plasma oxycodone levels and the lack of formal assessment using validated pain scales during medication titration.

Conclusions

This case demonstrates that drug-drug interactions can be an important and potentially overlooked cause of reduced opioid efficacy in palliative care. In this patient with advanced cholangiocarcinoma, concurrent carbamazepine therapy was associated with markedly reduced analgesic response to escalating doses of oxycodone, resulting in persistent pain despite intensive opioid management. Recognition of this potential interaction and subsequent opioid rotation to morphine led to rapid improvement in symptom control. The development of opioid-induced neurotoxicity at comparatively modest morphine doses further supported a possible pharmacokinetic explanation for these clinical observations.

Clinicians should maintain a high index of suspicion for enzyme-inducing medications when evaluating refractory pain or unexpectedly high opioid requirements. Comprehensive medication review, together with consideration of opioid metabolism and alternative explanations for reduced analgesic efficacy, may help identify clinically significant interactions, avoid unnecessary dose escalation, and reduce patient distress. This case highlights the value of opioid rotation as both a therapeutic and diagnostic strategy in complex palliative care settings and underscores the importance of recognising carbamazepine as a potential cause of reduced oxycodone efficacy.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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