

restraints in these patients, particularly in obtunded patients who cannot interact with their environment.

Although there is increasing awareness of the need to provide compassionate end-of-life care to incarcerated persons, as highlighted by the development of prison hospice units, this case highlights some of the ongoing challenges and the work that still needs to be done in delivering this essential and humane medical care to inmates.

Zachary Klock, MD  
Department of Family & Community Medicine  
Thomas Jefferson University  
Philadelphia, Pennsylvania, USA  
E-mail: [zachary.klock@jefferson.edu](mailto:zachary.klock@jefferson.edu)

John Liantonio, MD  
Inpatient Palliative Care Service  
Hospice and Palliative Medicine  
Department of Family & Community Medicine  
Thomas Jefferson University  
Philadelphia, Pennsylvania, USA

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## Difficulties in Pain Management Using Oxycodone and Fentanyl in Enzalutamide-Treated Patients With Advanced Prostate Cancer



To the Editor:

Pain treatment in patients with bone-metastasized advanced prostate cancer is often challenging. A range of treatment modalities are available to control prostate cancer-specific pain, such as androgen deprivation therapies, taxane-based chemotherapy, radionuclide therapy with radium-223, or palliative radiotherapy. In addition, analgesics are commonly used for direct symptom management.

We describe three cases which show difficulties of pain management in enzalutamide-treated patients with metastatic bone disease due to castration-resistant prostate cancer (CRPC). The potential illustrations of drug-drug interactions noted in these cases are of important clinical relevance.

Patient A is a 70-year-old CRPC patient with progressive bone disease despite second-generation androgen deprivation therapy with enzalutamide (160 mg per day). The urologist started fixed-dose paracetamol and oxycodone 5 mg immediate release if needed and referred the patient to the radiotherapist for palliative radiotherapy with single-dose treatment of 8 Gy for painful iliac bone metastases. The analgesic treatment was insufficient, and the patient was referred to our outpatient clinic. We added a low dose of controlled-release oxycodone. This was also ineffective and we therefore increased the dose to twice-daily 20 mg plus escape medication for breakthrough pain. Unfortunately, these interventions did not result in any clinical benefit, even after addition of dexamethasone. Enzalutamide is known to be a strong inducer of hepatic drug metabolism via induction of the cytochrome P450 (CYP) enzyme group, so to optimize analgesia, we initiated opioid rotation, specifically morphine sulfate 30 mg twice daily because of non-CYP-mediated drug metabolism.

Within 24 hours, the patient experienced complete pain relief without the use of any escape medication.

Patient B (aged 72) also suffers from bone-metastasized CRPC. After progressive disease on first-generation androgen deprivation therapy (bicalutamide and nilutamide), the treating urologist initiated enzalutamide 160 mg per day. After four months, the patient experienced painful bone metastases on the spine and pelvis. The patient did not respond to paracetamol, diclofenac, and controlled-release oxycodone combined with immediate-release oxycodone. Rotation to low-dose morphine sulfate 10 mg twice a day resulted in successful pain management within 48 hours.

Patient C (aged 62 years) has progressive bone- and liver-metastasized CRPC. During enzalutamide treatment, the patient was hospitalized because of severe pain resulting from bone metastases of the cervical spine, which led to multiple pathological fractures of C5-Th3 with spinal cord compression and extraosseous extension. The patient was treated with high-dose dexamethasone (16 mg per day), a single-dose of 8 Gy palliative radiotherapy, transdermal and oromucosal fentanyl, pregabalin, and amitriptyline. Even after increasing the dose of transdermal fentanyl to 75 µg per hour, these interventions were unsuccessful. After four weeks, the treating urologist and palliative care physician stopped the enzalutamide therapy and discharged the patient eight weeks later; the patient's cervical neuropathic pain was better under control compared to the in-hospital setting.

Enzalutamide is an androgen receptor antagonist interfering with the androgen receptor signal transduction. Compared with first-generation antiandrogens, such as bicalutamide, flutamide, or nilutamide, it more strongly inhibits the binding of androgens to androgen receptors. Bicalutamide is a weak CYP3A4 inhibitor, and there is no clinically relevant inhibition of CYP-mediated drug metabolism expected. Flutamide and nilutamide have no effect on CYP3A4 activity. Moreover, enzalutamide inhibits the nuclear translocation of activated receptors and DNA transcription<sup>1</sup> and is a strong inducer of CYP enzymes CYP3A4, CYP2C9, and CYP2C19.<sup>2</sup> In the clinical setting of pain management, we have focused on enzalutamide-induced CYP3A4 effects. Other effects caused by CYP2C9 and CYP2C19 induction that influence the pharmacokinetics of CYP2C9 and CYP2C19 substrates are beyond the scope of this article.<sup>3</sup>

Treatment with enzalutamide reduces the exposure to the hallmark CYP3A4 substrate midazolam by between 56% and 86%.<sup>4</sup> Therefore, the area under the curve (AUC) of other CYP3A4 substrates can also be expected to show a significant decrease, which is clinically relevant to the analgesics oxycodone (Patients A

and B), fentanyl (Patient C), and tramadol, methadone, and buprenorphine.<sup>5</sup> This is also true for the CYP3A4 substrate dexamethasone which is often used in treatment of pain in palliative treatment because of its edema-reducing effect. In the cases mentioned previously, the latter is thought to account for Patient C having decreased dexamethasone efficacy on neuropathic pain symptoms due to CYP3A4 enzyme induction.

Another clinically relevant aspect is the length of time needed to achieve steady-state (approximately one month) and enzalutamide's long half-life (5.8 days).<sup>6</sup> Moreover, CYP enzyme induction and enzyme recovery can both take up to two weeks to be established. This implies that the clinical effect on CYP3A4 enzymes may only start gradually (two to six weeks) and that it takes a number of weeks to clear after withdrawing enzalutamide, which may explain why any new agents metabolized by CYP3A4 may only show limited effects. For example, if midazolam is introduced for palliative sedation because of uncontrollable pain, this may be expressed by an unexpectedly laborious sedation induction phase with a need for frequent bolus dosing, and a higher than expected dose of midazolam in continuous infusion. This effect may last for several weeks after withdrawing enzalutamide.

Literature on the clinical implication of the CYP3A pathway on pharmacokinetics of oxycodone and fentanyl in cancer patients is sparse. However, CYP3A4 activities affect oxycodone pharmacokinetics significantly in both patients<sup>7</sup> and healthy volunteers.<sup>8</sup> Coadministration of rifampicin, a strong CYP3A4 inducer, has been associated with a remarkable reduction of 86% in oxycodone exposure in these volunteers.<sup>8</sup> Coadministration of rifampicin led to a 2.6-fold lower AUC compared to fentanyl alone in volunteers using transmucosal fentanyl.<sup>9</sup> The use of carbamazepine and phenobarbital in patients using transdermal fentanyl patches led to a significantly higher fentanyl clearance (more than twice as high).<sup>10</sup> This shows that there is significant potential for interaction of both oxycodone and fentanyl with strong CYP3A4 inducers.

The drug-drug interactions with enzalutamide could therefore possibly be handled by increasing the oxycodone, fentanyl, or dexamethasone dose. Increasing oxycodone is unlikely to be successful for pain management as half of the oxycodone metabolism through the CYP3A pathway results in the active metabolite noroxycodone. However, noroxycodone has a poor penetration across the blood-brain barrier; thus, it is probably ineffective.<sup>7,11</sup> The effects of fentanyl and dexamethasone on the AUC are also uncertain. Therefore, non-CYP3A4-metabolized opioids such as morphine or hydromorphone are

currently preferred over oxycodone, fentanyl, or buprenorphine in patients with advanced prostate cancer in need of treatment with enzalutamide. Caution should be taken when administering combination treatments of enzalutamide and CYP3A4 substrates. Therefore, we recommend that a clinician confronted with patients using enzalutamide with little or no analgesic response should be aware of the clinical value of switching to a non-CYP3A4-metabolized opioid. Nevertheless, pharmacokinetic studies are needed to determine the true impact and confirm our clinical observations.

Harm Westdorp, MD  
Evelien J.M. Kuip, MD  
Department of Anesthesiology  
Pain and Palliative Medicine  
Radboud University Medical Center  
Nijmegen, The Netherlands  
Department of Medical Oncology  
Radboud University Medical Center  
Nijmegen, The Netherlands

Inge M. van Oort, MD, PhD  
Department of Urology  
Radboud University Medical Center  
Nijmegen, The Netherlands

Cornelis Kramers, MD, PhD  
Department of Pharmacology and  
Toxicology  
Radboud University Medical Center  
Nijmegen, The Netherlands

Winald R. Gerritsen, MD, PhD  
Department of Medical Oncology  
Radboud University Medical Center  
Nijmegen, The Netherlands

Kris C.P. Vissers, MD, PhD, FIPP  
Department of Anesthesiology  
Pain and Palliative Medicine  
Radboud University Medical Center  
Nijmegen, The Netherlands  
E-mail: [Kris.Vissers@radboudumc.nl](mailto:Kris.Vissers@radboudumc.nl)

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