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ORIGINAL RESEARCH ARTICLE

Enzalutamide Reduces Oxycodone Exposure in Men with Prostate Cancer

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Abstract

Background and objective Up to 90% of patients with castration-resistant prostate cancer (CRPC) will develop symptomatic bone metastases requiring pain medication, with opioids being the mainstay of therapy in treating moderate and severe pain. Enzalutamide is an androgen receptor antagonist for the treatment of CRPC and a strong inducer of cytochrome P450 (CYP)3A4. Hereby, enzalutamide potentially reduces the exposure of oxycodone, an opioid metabolized by CYP3A4 and CYP2D6. Our objective was to evaluate the potential drug–drug interaction of enzalutamide and oxycodone.

Methods A prospective, nonrandomized, open-label, two-arm parallel study was performed. All patients received a single dose of 15 mg normal-release oxycodone. Patients in the enzalutamide arm (ENZ-arm) received enzalutamide 160 mg once daily. Plasma concentrations of oxycodone and its metabolites were quantified using a validated liquid chromatography with tandem mass spectrometry (LC–MS/MS) method.

Results Twenty-six patients (13 ENZ-arm; 13 control arm) were enrolled in the study. Enzalutamide decreased the mean $AUC_{0-8\,h}$ and C_{max} of oxycodone with, respectively, 44.7% ($p<0.001$) and 35.5% ($p=0.004$) compared with the control arm. The $AUC_{0-8\,h}$ and C_{max} of the active metabolite oxymorphone were 74.2% ($p<0.001$) and 56.0% ($p=0.001$) lower in the ENZ-arm compared with the control arm. In contrast, $AUC_{0-8\,h}$ and C_{max} of the inactive metabolites noroxycodone and noroxymorphone were significantly increased by enzalutamide.

Conclusion Co-administration of enzalutamide significantly reduced exposure to oxycodone and its active metabolite oxymorphone in men with prostate cancer. This should be taken into account when prescribing enzalutamide combined with oxycodone.

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Key Points

A clinical relevant drug interaction was found when enzalutamide was co-administered with oxycodone; AUC and C_{max} were decreased by 44.7% and 35.5%, respectively.

Inadequate pain control and risk of overdose should be taken into consideration when prescribing oxycodone to patients using enzalutamide and vice versa.

1 Introduction

With an incidence of 63.4 per 100,000 men, prostate cancer is the most common type of cancer among men worldwide [1]. Approximately 90% of the patients with metastatic prostate carcinoma will develop bone metastases, which can cause severe pain [2]. Adequate pain management, for instance with opioids, is required to maintain a good quality of life [3, 4]. Oxycodone is a frequently used opioid receptor agonist for the treatment of cancer related pain. It is mainly metabolized by cytochrome P450 (CYP)3A4 into noroxycodone and by CYP2D6 into oxymorphone. The metabolite noroxymorphone is formed from noroxycodone through CYP2D6 and to a lesser extent from oxymorphone through CYP3A4 metabolism [5]. Oxycodone is mainly responsible for the analgesic effect [6]. Despite oxymorphones' 10–60 times higher affinity for the μ-receptor, the analgesic effect is inferior to oxycodone due to significantly lower plasma concentrations. The remaining metabolites have a minor contribution in the analgesic effect, either due to low μ-receptor affinity or poor distribution through the blood–brain barrier [6, 7].

Enzalutamide is a potent inhibitor of androgen receptor signaling. It is registered for the treatment of metastatic, hormone sensitive, and (non)metastatic castration-resistant prostate carcinoma [8]. Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C19 and CYP2C9 [9]. CYP3A4 is an important enzyme involved in the metabolism of opioids, such as buprenorphine, fentanyl, and oxycodone [7, 10, 11]. Therefore, concomitant use with opioids metabolized by CYP3A4 may lead to relevant drug–drug interactions. For instance, concomitant use of enzalutamide and fentanyl, a substrate of CYP3A4, resulted in undetectable plasma concentrations of fentanyl [12]. In addition, another strong CYP3A4 inductor, rifampicin, strongly decreased the exposure to oxycodone [13]. Furthermore, in a case report, oxycodone rotation to morphine after failure of pain management resulted in the desired analgesic effect when concomitantly used with enzalutamide [14]. Morphine is metabolized by phase 2 glucuronidation, thus making it less susceptible for drug–drug interactions [10, 15]. To date, the effect of enzalutamide on the pharmacokinetics of oxycodone has not been studied.

It is known that enzalutamide strongly induces the CYP3A4-mediated metabolism, which may lead to lower oxycodone and oxymorphone concentrations and thereby potentially reduce the analgesic effects of oxycodone, hampering the pain management in patients. However, there is a lack of clinical studies investigating this in patients. In this study, the effect of enzalutamide on the pharmacokinetics (PK) of oxycodone in men with prostate cancer was investigated.

2 Methods

A prospective, nonrandomized, open-label, parallel study has been performed in men ≥ 18 years with prostate cancer that were treated with enzalutamide (ENZ-arm) or not (control arm) in the Deventer Teaching Hospital, the Netherlands. This study was conducted between June 2021 and September 2022. All patients diagnosed with prostate cancer and under treatment of an urologist or oncologist were eligible for inclusion. Patients treated with 160 mg enzalutamide daily for at least 40 days were possible subjects for the ENZ-arm. All other men with any stage of prostate cancer were possible subjects for the control arm, if enzalutamide and/or other interacting drugs were not prescribed. After selection, the participants were screened on the basis of the exclusion criteria. Patients who used normal-release oxycodone within 48 h or controlled-release oxycodone within 4 days prior to oxycodone intake were excluded. CYP3A4 and CYP2D6 ultrarapid or poor metabolizers were excluded. In addition, patients were excluded in case of: a body mass index (BMI) outside the range of 18–30 kg/m^2; liver metastasis; Child–Pugh classification B or C; estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2; gastrointestinal diseases; previous gastric bypass or gastric band surgery; allergy or intolerance to oxycodone or a history of drug abuse. Finally, patients were excluded if they used co-medication possibly affecting the pharmacokinetics of oxycodone or enzalutamide (Table 1).

The sample size was calculated using a previously studied mean maximum plasma concentration (C_{max}) of 26.1 ng/ml after a single oral dose of oxycodone 15 mg and an average total coefficient of variation of 30% (7.83 ng/ml) in four studies with oxycodone [13, 16–18]. On the basis of the results of a study with midazolam and enzalutamide (77% reduction), we expect a 40% decrease (10.44 ng/ml) in C_{max} when taken with enzalutamide 160 mg once daily as co-medication [9]. Midazolam is metabolized only by CYP3A4, while oxycodone is metabolized by both CYP2D6 and CYP3A4 [9, 15]. Hence, we expect less reduction in C_{max} for oxycodone compared with midazolam. To demonstrate this 40% difference at a level of significance $p = 0.05$ and a power of 80%, ten subjects are required for each arm. Thirteen participants were included per arm, taking potential discontinuation into account. It is expected that enzyme induction of enzalutamide will mainly affect the elimination phase of the curve [9]. Therefore, the effect on C_{max} is considered less than the effect on the area under the concentration–time curve from dosing to time t (AUC_t). Thus, it is expected that the sample size calculation with the effect on C_{max} is also sufficient for the effect on AUC_t. This study was approved by the Medical Ethics Committee Isala (Zwolle, the Netherlands). All patients gave written informed consent.

Table 1 Co-medications that can affect the pharmacokinetics of oxycodone and enzalutamide

Medication that is expected to affect oxycodone metabolism includes clinically relevant CYP3A4 inducers and inhibitors and CYP2D6 inhibitors[a]	
CYP3A4 inducers	Apalutamide, bosentan, carbamazepine, dabrafenib, darolutamide, dexamethasone, efavirenz, griseofulvin, hydrocortisone, lorlatinib, methadone, mitotane, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, primidon, rifabutin, rifampicin, St. John's Wort
CYP3A4 inhibitors	Amiodarone, aprepitant, atazanavir, bicalutamide, cimetidine, clarithromycin, cobicistat, crizotinib, diltiazem, erythromycin, fluconazole, fluvoxamin, fosaprepitant, grapefruit juice, idelalsib, imatinib, indinavir, isavuconazole, itraconazole, ketoconazole, nefazodone, nilfinavir, netupitant, nilotinib, palbociclib, posaconazole, ribociclib, ritonavir, roxitromycin, saquinavir, tipranavir, verapamil, voriconazole
CYP2D6 inhibitors	Abiraterone, buproprion, cimetidine, cinacalcet, duloxetine, fluoxetine, mirabegron, paroxetine, propafenon, quinidine, ritonavir, rolapitant, terbinafine
Medication that is expected to affect enzalutamide metabolism includes clinically relevant CYP3A4 and CYP2C8 inducers and inhibitors (ENZ-arm)[a]	
CYP3A4 inducers	Apalutamide, bosentan, carbamazepine, dabrafenib, darolutamide, dexamethasone, efavirenz, griseofulvin, hydrocortisone, lorlatinib, methadone, mitotane, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, primidon, rifabutin, rifampicin, St. John's Wort
CYP3A4 inhibitors	Amiodarone, aprepitant, atazanavir, bicalutamide, cimetidine, clarithromycin, cobicistat, crizotinib, diltiazem, erythromycin, fluconazole, fluvoxamin, fosaprepitant, grapefruit juice, idelalsib, imatinib, indinavir, isavuconazole, itraconazole, ketoconazole, nefazodone, nilfinavir, netupitant, nilotinib, palbociclib, posaconazole, ribociclib, ritonavir, roxitromycin, saquinavir, tipranavir, verapamil, voriconazole
CYP2C8 inducers	Rifampicin
CYP2C8 inhibitors	Gemfibrozil

[a]This list is inexhaustible

The participants visited the hospital once. They received a standardized snack, followed by a single dose of 15 mg normal-release oxycodone tablet in a sitting position. Plasma samples were taken at 0.5, 1, 1.5, 2, 3, 5, and 8 h, respectively, after oral administration of oxycodone. In addition, blood samples were collected to determine levels of creatinine, albumin, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), gamma-glutamyltransferase (GGT), and bilirubin. Blood samples were screened for CYP3A4 genotypes *2, *3, *6, *12, *17, *18, *20, and *22 and CYP2D6 genotypes *2 t/m *10, *12, *14, *17, *29, *41, and gene amplification and hybrids (*13, Hyb-A, Hyb-B). Oxycodone, oxymorphone, noroxycodone, and noroxymorphone plasma concentrations were quantified with a validated LC–MS/MS method. Genomic DNA was analyzed in ErasmusMC using polymerase chain reaction-restriction fragment length polymorphism.

Primary endpoints were $AUC_{0-8\ h}$ and C_{max} of oxycodone. Secondary endpoints were the terminal half-life of oxycodone ($t_{1/2}$) and the $AUC_{0-8\ h}$ and C_{max} of oxymorphone, noroxycodone and noroxymorphone. All plasma concentrations were log transformed. C_{max} was observed directly from the data. The $AUC_{0-8\ h}$ and $t_{1/2}$ were calculated using Phoenix 64 WinNonlin version 8.3. The geometric mean of the $AUC_{0-8\ h}$, C_{max} and $t_{1/2}$ of the two arms were analyzed with an unpaired *t*-test. A p value of <0.05 was considered statistically significant. Analysis on genotype subgroups (CYP3A4 and CYP2D6) was performed if feasible. The statistical analysis was performed with IBM SPSS Statistics 26.

3 Results

In total, 27 patients were eligible for inclusion. Of these patients, one was excluded due to a CYP2D6 poor metabolizer (PM) phenotype. Patient characteristics are summarized in Table 2. Except for a significantly lower ALAT in ENZ-arm, none of the patient characteristics was significantly different.

The geometric means and geometric mean ratios (GMR) of the $AUC_{0-8\ h}$ and C_{max} of oxycodone and its metabolites and the geometric mean and GMR of the $t_{1/2}$ of oxycodone in the ENZ-arm and in the control arm are shown in Fig. 1.

Table 2 Patient characteristics of the participants

	ENZ-arm ($n = 13$)	Control arm ($n = 13$)	p value
Age (years)	72.6 (7.3)	71.5 (9.2)	0.727
Body weight (kg)	83.3 (2.0)	83.1 (2.8)	0.880
BMI (kg/m^2)	26.5 (2.3)	25.6 (2.5)	0.395
eGFR (ml/min)	84 [18]	89 [30]	0.915
Albumin (g/l)	35.7 [3.0]	36.0 [2.8]	0.259
ASAT (µ/l)	27 [7]	27 [12]	0.959
ALAT (µ/l)	15.5 (5.4)	22.9 (10.6)	0.033
GGT (µ/l)	25.5 (10.9)	22.9 (8.3)	0.511
Bilirubin (µmol/l)	6 [5]	5 [4]	0.897
CYP3A4			0.480
NM	13 (100%)	11 (85%)	
IM	0 (0%)	2 (15%)	
CYP2D6			0.073
NM	7 (54%)	12 (92%)	
IM	6 (46%)	1 (8%)	
Cancer stage			0.783
T1	1 (8%)	1 (8%)	
T2	5 (38%)	5 (38%)	
T3	7 (54%)	6 (46%)	
T4	0 (0%)	1 (8%)	
Metastasis			0.118
None	2 (15.4%)	8 (61.5%)	
Bones	7 (53.8%)	3 (23.1%)	
Lymph node	2 (15.4%)	1 (7.7%)	
Bones and lymph node	2 (15.4%)	1 (7.7%)	

Data are presented as mean (± standard deviation) for continuous normally distributed data, median [IQR] for skewed continuous variables and n (%) for categorical data. Differences were tested with an independent samples t-test, a Mann–Whitney U test, and a Fisher's exact test or chi-squared test for these data types, respectively

BMI body mass index, *eGFR* estimated glomerular filtration rate, *ASAT* aspartate aminotransferase, *ALAT* alanine aminotransferase, *GGT* gamma-glutamyl transferase, *CYP* cytochrome P450, *NM* normal metabolizer, *IM* intermediate metabolizer

Oxycodone. The geometric mean $AUC_{0-8\,h}$ of oxycodone was 44.7% ($p < 0.001$) lower and C_{max} was 35.5% ($p = 0.004$) lower when used concomitantly with enzalutamide. The $t_{1/2}$ of oxycodone was significantly shortened from 5.1 to 2.8 h ($p < 0.001$).

Oxymorphone. Enzalutamide significantly decreased the $AUC_{0-8\,h}$ and C_{max} of the active CYP2D6-dependent metabolite oxymorphone with 74.2% ($p < 0.001$) and 56.0% ($p = 0.001$), respectively.

Noroxycodone. Enzalutamide significantly increased the $AUC_{0-8\,h}$ and C_{max} of the inactive CYP3A4-dependent metabolite noroxycodone with 61.2% ($p = 0.001$) and 78.2% ($p = 0.001$), respectively.

Noroxymorphone. Enzalutamide significantly increased the $AUC_{0-8\,h}$ and C_{max} of the inactive metabolite noroxymorphone with 45.0% ($p = 0.032$) and 59.8% ($p = 0.027$), respectively.

Plasma concentration curves of oxycodone and its metabolites in patients treated with (ENZ-arm) or without (control arm) enzalutamide are shown in Fig. 2. Overall, plasma concentrations of oxycodone and oxymorphone were lower in patients in the ENZ-arm, whereas plasma concentrations of noroxycodone and noroxymorphone were higher in this group, compared with the control group. The terminal half-life of the metabolites could not be determined due to the limited sampling time.

No significant pharmacokinetic difference was found between CYP2D6 NM and CYP2D6 IM within the ENZ-arm (Table 3). In addition, CYP2D6 NM of the ENZ-arm and control arm showed similar pharmacokinetic outcomes compared with the data of all included patients (Fig. 3). Due

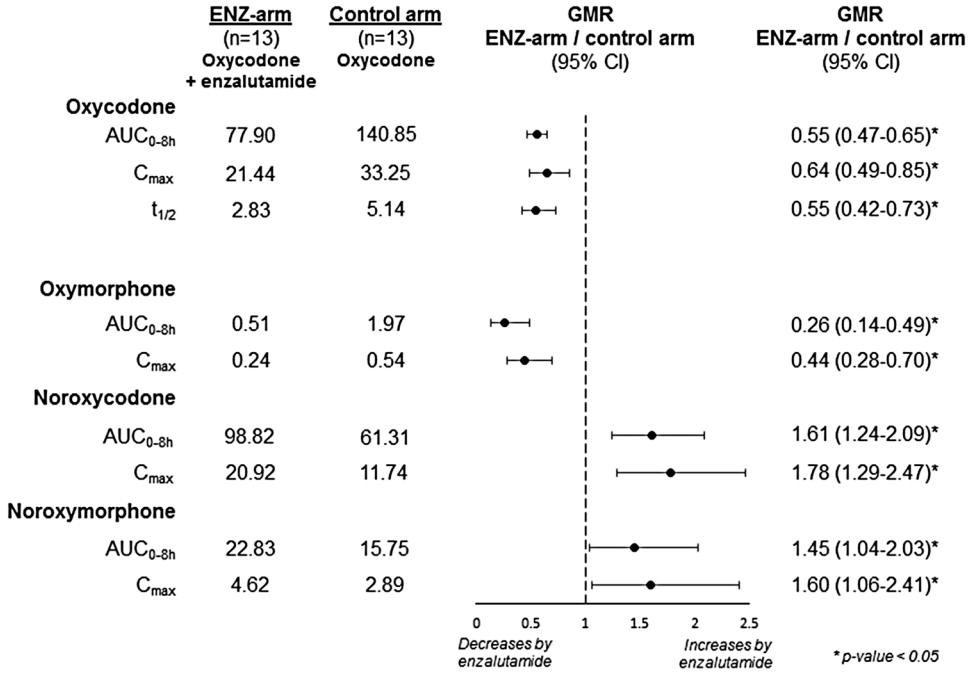

Fig. 1. The area under the curve from 0 to 8 h in µg*h/l ($AUC_{0-8\,h}$), maximum plasma concentration in µg/l (C_{max}) and terminal half-life in hours ($t_{1/2}$) of oxycodone and the $AUC_{0-8\,h}$ and C_{max} of its metabolites in patients treated with (ENZ-arm) or without (control arm) enzalutamide. Results are represented as geometric mean. Dots represent the geometric mean ratio (GMR) (95% CI). Significance was determined with an independent samples *t*-test

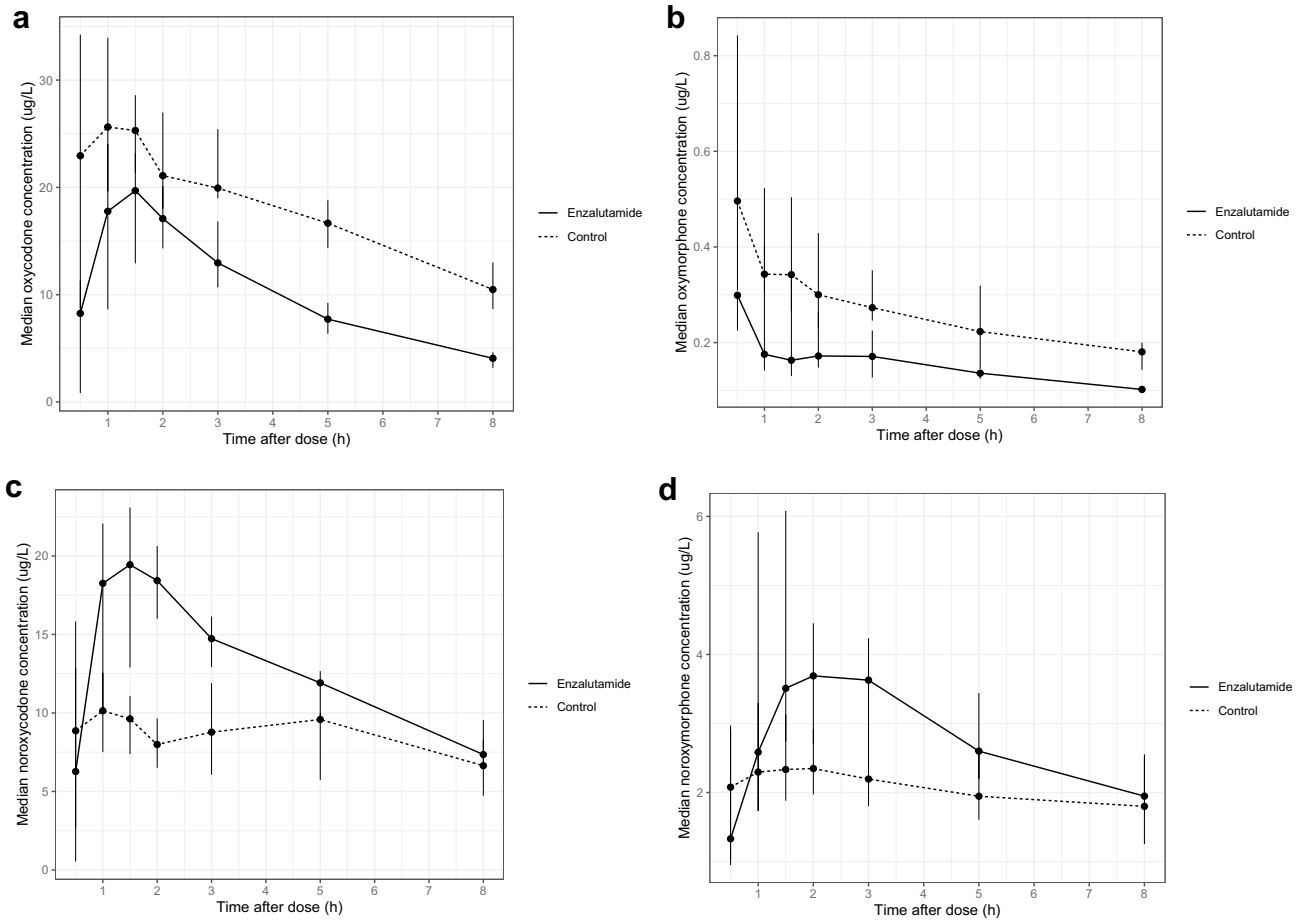

Fig. 2. Median concentrations and corresponding IQR of oxycodone (**a**), oxymorphone (**b**), noroxycodone (**c**), and noroxymorhone (**d**) in µg/l versus time after dose in hours, over a period of 8 h. The uninterrupted line presents concentrations of patients treated with enzalutamide (ENZ-arm), whereas the dotted line presents concentrations of patients without enzalutamide treatment (control arm)

Table 3 Pharmacokinetic parameters of oxycodone and its metabolites in normal metabolizers (NM) and intermediate metabolizers (IM) of CYP2D6 treated with enzalutamide (ENZ-arm)

	CYP2D6 NM ENZ-arm ($n=7$)	CYP2D6 IM ENZ-arm ($n=6$)	p value
Oxycodone			
$AUC_{0-8\,h}$	75.03 (46.18–98.24)	81.40 (70.65–95.99)	0.542
C_{max}	21.83 (10.14–36.32)	20.99 (12.67–37.09)	0.863
$t_{1/2}$	2.72 (1.96–3.92)	2.97	0.544
Oxymorphone			
$AUC_{0-8\,h}$	0.62 (0.12–1.64)	0.40 (0.07–1.01)	0.470
C_{max}	0.29 (0.12–0.76)	0.19 (0.11–0.30)	0.237
Noroxycodone			
$AUC_{0-8\,h}$	89.31 (60.84–109.07)	111.21 (64.55–168.43)	0.185
C_{max}	19.98 (10.93–27.36)	22.08 (11.73–32.33)	0.648
Noroxymorphone			
$AUC_{0-8\,h}$	26.10 (16.26–52.74)	19.53 (15.63–25.86)	0.130
C_{max}	5.48 (3.16–10.47)	3.78 (2.74–5.82)	0.128

Data are presented as the geometric mean. Significance was determined with an independent samples t-test

$AUC_{0-8\,h}$ area under the curve from 0 to 8 h in µg*h/l, C_{max} maximum plasma concentration in µg/l, $t_{1/2}$ terminal half-life in hours

to the limited number of CYP3A4 NM and IM in the control group (Fig. 1), a subanalysis to determine pharmacokinetic differences between these phenotypes was not possible.

4 Discussion

Oxycodone is a widely used opioid for pain management in patients with CRPC. This is the first study to show the clinical relevance of the drug–drug interaction of enzalutamide and oxycodone in men with prostate cancer. This study assessed the potential drug interaction of enzalutamide with oxycodone in men with prostate cancer. We found enzalutamide to decrease the $AUC_{0-8\,h}$ and C_{max} of oxycodone with 45% and 36%, respectively. In addition, the C_{max} of the active metabolite oxymorphone decreased, whereas the C_{max} of noroxycodone and noroxymorphone (inactive metabolites) increased.

Pain management is important in men with prostate cancer. However, treatment with oxycodone was found to be insufficient in patients using enzalutamide [14]. In clinical practice the combination of enzalutamide and oxycodone is used in almost half of enzalutamide patients [19]. Therefore, awareness of this interaction is of utmost importance (Figs.1 and 2).

Previous studies described the effect of CYP inhibitors on the exposure of oxycodone. For instance, Grönlund et al. found a 2.9-fold increase in exposure of oxycodone when used simultaneously with paroxetine and itraconazole, CYP2D6, and CYP3A4 inhibitors, respectively [20]. In addition, voriconazole increased the exposure 3.6-fold [18]. However, little is known about the effect of CYP inductors on the exposure of oxycodone. Nieminen et al. found a 86% and 44% reduction of the area under the curve from dosing time to infinity ($AUC_{0-\infty}$) and C_{max} of oxycodone when used concomitantly with strong CYP3A4-inductor rifampicin [13]. The observed decrease in $AUC_{0-8\,h}$ and C_{max} of oxycodone with simultaneous use of enzalutamide is lower than previous findings with rifampicin. However, their study population consisted of both healthy men and women and an unknown CYP3A4 genotype. In addition, blood samples were collected up to 48 h after ingestion, while we only measured up to 8 h [13]. In another study by Nieminen et al., a 50% decrease in exposure to oxycodone was found when simultaneously used with St John's Wort, also a CYP3A4 inductor, which is in line with our findings [21]. Finally, the terminal half-life of oxycodone in our control group was comparable to a similar patient population, described by Kokki et al. [22].

Enzalutamide significantly decreased the C_{max} of oxycodone and oxymorphone and increased the concentrations of noroxymorphone and noroxycodone in patients with a CYP2D6 NM phenotype (Fig. 3). Poor and ultrarapid metabolizers of CYP2D6 were excluded in order to solely study the pharmacokinetic effect of enzalutamide on oxycodone without interference of pharmacogenetic differences. A subanalysis was conducted on NM and IM to preclude the influence of the IM phenotype on the pharmacokinetics of oxycodone. No difference in pharmacokinetic parameters was found between these groups within the ENZ-arm. In addition, the results of solely NM did not differ from the results including IM and NM. Therefore, including patients

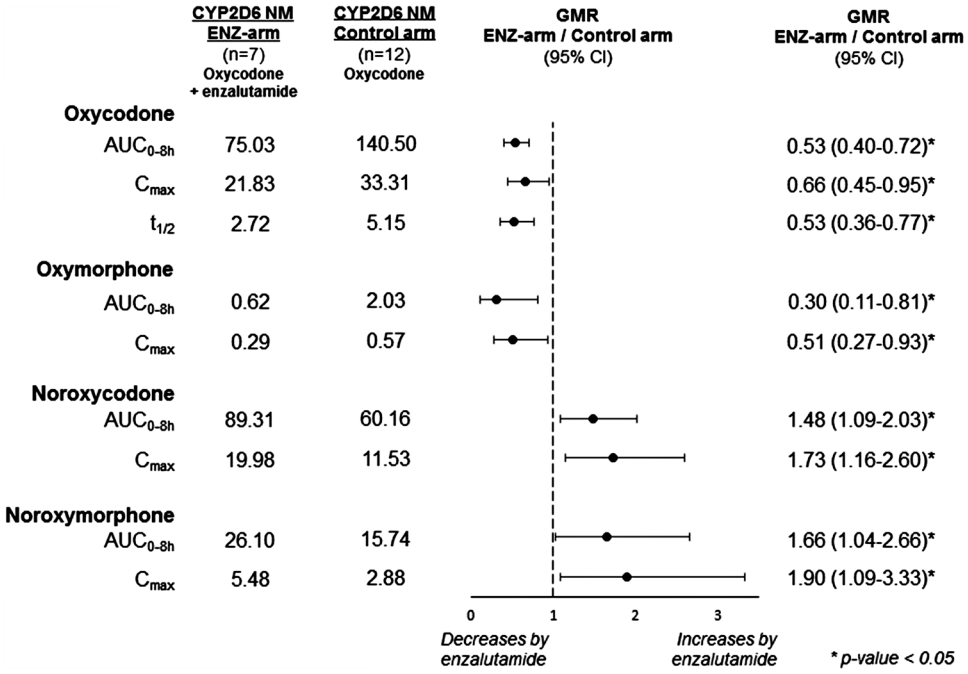

Fig. 3. The area under the curve from 0 to 8 h in µg*h/l ($AUC_{0–8\ h}$), maximum plasma concentration in µg/l (C_{max}) and terminal half-life in hours ($t_{1/2}$) of oxycodone and the $AUC_{0–8\ h}$ and C_{max} of its metabolites in normal metabolizers (NM) of CYP2D6 treated with (ENZ-arm) or without (control arm) enzalutamide. Results are presented as geometric mean. Dots show the geometric mean ratio (GMR) (95% CI). Significance was determined with an independent samples *t*-test

with an intermediate CYP2D6 phenotype did not affect the final conclusion of this study. Given the large amount of CYP3A4 NM in both arms, it was not possible to conduct a subanalysis to determine whether the difference in phenotype affected the outcome. Therefore, the CYP3A4 phenotype is not expected to have significantly affected the outcome.

This study has a few limitations. A crossover study design would have been more powerful but is not feasible in this population of patients with CRPC. Other limitations include the absence of blood sample collection prior to oxycodone ingestion and the limited duration of post-ingestion blood sample collection, which was only conducted up to 8 hours post-ingestion. Hence, reliable $AUC_{0–\infty}$ estimations were not possible. In addition, a noncompartmental analysis was used to obtain the pharmacokinetic data. A POP PK model could have been more informative on the PK of the metabolites. Lastly, the posture of the patients was not controlled after administration. This might have affected the absorption of oxycodone [23]. Strengths of this study include a prospective design and a representative control group since only men with prostate cancer were included. In addition, a current medication overview of all patients was collected to exclude patients using oxycodone or potentially interfering drugs. Furthermore, we performed CYP3A4 and CYP2D6 genotyping. Moreover, food intake during administration was standardized. Therefore, factors potentially affecting our pharmacokinetic data were minimized. Finally, we measured both oxycodone and its metabolites with a sensitive bioanalytical method. As a result, our findings can be translated into the clinical setting in which enzalutamide is indicated for prostate cancer.

In this study, we describe a clinically relevant drug–drug interaction of enzalutamide and oxycodone in men with prostate cancer. Enzalutamide lowers the exposure to oxycodone and its active metabolite oxymorphone. This should be taken into account when prescribing enzalutamide to patients taking oxycodone. There is a risk of inadequate pain control when starting enzalutamide and a risk of overdose upon enzalutamide discontinuation.

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Declarations

Funding Not applicable.

Conflict of interest Not applicable.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Medical Ethics Committee Isala (Zwolle, the Netherlands). All patients gave written informed consent.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to publish Informed consent was obtained from all individual participants included in the study.

Data and/or code availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by S.E.H. Detert Oude Weme and L.M.G. Hulskotte. The first draft of the manuscript was written by S.E.H. Detert Oude Weme and L.M.G. Hulskotte, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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