Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Analgesic efficacy, adverse effects, and safety of oxycodone administered as continuous intravenous infusion in patients after total hip arthroplasty

This article was published in the following Dove Press journal:
Journal of Pain Research
4 May 2017
Number of times this article has been viewed

Bogumił Olczak[1]
Grzegorz Kowalski[1,2]
Wojciech Leppert[2]
Iwona Zaporowska-Stachowiak[3]
Katarzyna Wieczorowska-Tobis[2]

[1]Department of Anesthesiology, Józef Struś Multiprofile Municipal Hospital, [2]Department of Palliative Medicine, Poznan University of Medical Sciences, [3]Department of Pharmacology, Poznan University of Medical Sciences, Poland

Background: Total hip arthroplasty (THA) causes extensive tissue damage and severe pain. This study aimed to assess the analgesic efficacy, adverse effects (AEs), and safety of continuous intravenous (iv) oxycodone infusion with ketoprofen (injected into the iv line) in patients after THA, and to assay serum oxycodone levels.

Patients and methods: Fourteen patients, aged 59–82 years with American Society of Anesthesiologists (ASA) classification I or III, underwent THA with intrathecal analgesia and sedation induced by iv propofol. After the surgery, oxycodone (continuous iv infusion) at a dose of 1 mg/h (five patients) or 2 mg/h (nine patients) with 100 mg ketoprofen (injected into the iv line) was administered to each patient every 12 h. Pain was assessed using a numerical rating scale (NRS: 0 – no pain, 10 – the most severe pain) at rest and during movement. AEs, including hemodynamic unsteadiness, nausea, vomiting, pruritus, cognitive impairment, and respiratory depression, were registered during the first 24 h after surgery.

Results: Oxycodone (continuous iv infusion) at a dose of 2 mg/h with ketoprofen (100 mg) administered every 12 h provided satisfactory analgesia in all nine patients without the need of rescue analgesics within the first 24 h after THA. In three out of five patients, oxycodone at 1 mg/h was effective. Oxycodone did not induce drowsiness, vomiting, pruritus, respiratory depression, or changes in blood pressure. Bradycardia appeared in two patients, and nausea was observed in one patient.

Conclusion: Oxycodone infusion with ketoprofen administered by iv is effective in patients after THA. Intravenous infusion of oxycodone is a predictable, stable, and safe method of drug administration.

Keywords: adverse effects, analgesia, opioid, oxycodone, pain.

Introduction

Approximately 47,000 total hip arthroplasty (THA) surgical procedures are done annually in Poland.[1] This is one of the most frequent and also one of the most burdensome orthopedic procedures in terms of extent and number of complications. The main indication for THA is advanced coxarthrosis, which affects both older men and women with similar frequencies, occurs most frequently between ages 60 and 90 years, and is a cause of severe chronic pain. Those patients often suffer from other advanced comorbid diseases, the most frequent being hypertension, heart failure, diabetes, and chronic obstructive pulmonary disease; therefore, the surgical procedure and period of rehabilitation present significant burdens for patients. An effective perioperative analgesia prevents serious cardiovascular complications, decreases the number of infections, and shortens the hospitalization period. It is also a prerequisite for early

Correspondence: Wojciech Leppert
Department of Palliative Medicine, Poznan University of Medical Sciences, Osiedle Rusa 55, 61–245, Poland
Tel +48 61 738 000
Email wojciechleppert@wp.pl

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/JPR.S125449

introduction of effective physiotherapy. In some THA studies, the advantages of regional over general anesthesia have been demonstrated.[2,3] However, a systematic review published in 2016 demonstrated a lack of sufficient evidence for regional anesthesia advantages, although a shorter hospitalization period was used.[4]

In the postoperative period, continuous epidural analgesia plays an important role. For patients with contraindications or those who give no consent to this type of analgesia, an intravenous (iv) route of analgesic administration is the main method of pain treatment, especially during the first 24 h after the surgery. Extensive orthopedic surgery (such as knee or hip arthroplasty) involves extensive tissue damage, especially of bone tissue, which in turn is associated with severe pain; therefore, opioid administration is required in this patient group. For many years, morphine has been the gold standard of treatment for moderate-to-severe pain, although recently, an interest in oxycodone for the treatment of postoperative pain has been observed. Oxycodone is used more frequently by physicians as it displays a beneficial pharmacological profile and lower percentage of adverse effects (AEs) in comparison to morphine. The studies published to date confirm oxycodone's safety and high analgesic efficacy in pain treatment although most of the studies refer to the oral route of administration.[5–7]

Oxycodone is a semisynthetic, thebaine opioid derivative, which was synthesized for the first time in 1916 and used in 1917.[8] It has been widely used in the treatment of both acute and chronic pain for over 80 years. The mechanism of oxycodone's action is based on the activation of peripheral and central μ and κ opioid receptors. Compared with morphine, oxycodone displays a lower affinity to μ-opioid receptors, but it activates κ opioid receptors to a significantly larger extent than morphine. In addition, its concentration in the brain is approximately six times higher, owing to the active transport through the blood–brain barrier, which significantly increases its analgesic efficacy.[9–12] Moreover, in experimental studies, a beneficial influence of oxycodone as a result of an increased expression of GABA-B receptors in sensory neurons has been found. This increased expression induced hyperalgesia inhibition in a neuropathic pain model induced by the cytostatic drug vincristine.[13]

Forty-five percent of oxycodone binds to serum proteins (slightly more than morphine at 35%), and it is metabolized through cytochrome P-450 liver enzymes to the first-order metabolites, oxymorphone and noroxycodone.[14] Only oxymorphone displays analgesic effects via agonist effects on μ-opioid receptors, which are 14 times stronger compared with oxycodone administered parenterally, although oxymorphone concentration is too low for significant clinical effects.[15–18] Oxycodone's plasma elimination half-life ($T_{1/2}$) is ~4 h, irrespective of the route of administration. Oxycodone is excreted in the urine, mainly in the form of unbound noroxycodone and oxymorphone conjugated with glucuronic acid. Only about 10% of the administered oxycodone is excreted unchanged in the urine.[19–21]

Aim of the study

The primary aim of the study was to assess the analgesic efficacy, AEs, and oxycodone safety administered as a continuous infusion with ketoprofen injected into the iv line to patients after THA. A secondary aim was to assay serum oxycodone levels.

Patients and methods

The study protocol has been approved by the Bioethical Committee of the Poznan University of Medical Sciences. The study was conducted from March to November 2014 in the Józef Struś Multiprofile Municipal Hospital in Poznan.

All patients provided written informed consent for this study. A total of 14 patients who had undergone a total non-cemented hip arthroplasty from a lateral access were recruited for the study. The mean age of patients was 68±8 years. All patients had suffered from coxarthrosis. Several tests were conducted before the surgery: 1) full blood count and 2) determination of plasma concentrations of sodium, potassium, creatinine (for the calculation of the estimated glomerular filtration rate), urea, alanine aminotransferase, asparginate aminotransferase, total protein, and albumin. The perioperative risk was American Society of Anesthesiologists (ASA) II in five patients and ASA III in nine patients. The mean height of patients was 170±6 cm, and the mean body mass was 75±12 kg.

Before surgery, all patients received oral midazolam (Dormicum tablets; Roche) at a dose of 7.5 mg. All patients received analgesia consisting of 15 mg heavy bupivacaine (Marcaine® Spinal 0.5% Heavy; AstraZeneca) via the subarachnoid route at the L3/L4 level. In addition, sedation was induced during anesthesia by propofol injection (propofol 1% MCT/LCT Fresenius) via the iv route at a dose of 1–3 mg/kg of body weight/h with oxygen therapy and maintenance of respiratory tract patency via the oropharyngeal airway or through a laryngeal mask airway, whenever necessary. After surgery, patients were transferred to a postoperative unit. If no pain was present 3 h after spinal anesthesia, continuous infusion of oxycodone chloride (OxyNorm® ampoules;

Mundipharma) via an iv route was started at a dose of 1 mg/h (n=5) or 2 mg/h (n=9). A dose of 1 mg/h was administered to patients with a body mass ≤65 kg (n=5), and a dose of 2 mg/h was given to patients whose body mass was >65 kg (n=9). All patients in the postoperative unit received an iv ketoprofen (100 mg) injection every 12 h. All patients were prescribed a rescue dose (in the case of pain intensity over 4 according to a numerical rating scale [NRS]) of 2 mg of oxycodone administered via the iv route in the nurse-controlled analgesia system, which could be repeated every 10 min.

Blood samples were taken for oxycodone concentration assays in blood serum (a free fraction and protein-bound) after 30, 120, and 240 min after starting the drug infusion. At the moment of blood sampling, patients were asked about pain intensity according to NRS (0–10) at rest and during movement. An NRS ≤3 at rest and an NRS ≤4 during movement (hip flexion) were considered satisfactory. In the postoperative unit, blood pressure, heart rate, blood oxygen saturation, and electrocardiogram were continuously monitored in all patients. The number of oxycodone rescue doses was recorded, and patients were also observed for the appearance of drug-related AEs such as nausea, vomiting, pruritus, cognitive impairment (recognizing time, place, and appropriate responses to questions posed), and respiratory depression defined as <8 breaths/min with a decrease in oxygen blood saturation <90%.

Results

Patients' basic demographic and clinical data are shown in Table 1. Mean values of the laboratory parameters from analyzed patients are demonstrated in Table 2. In all patients, laboratory parameters were within normal range. No factors influencing metabolism and excretion of the selected drugs were found (Table 2). The surgery time was 90±15 min, and the length of patients' stay in the operation theater was 150±15 min.

Table 1 Mean values and standard deviation of Patients' basic demographic and clinical data (n=14)

Age (years)	Body weight (kg)	Height (cm)	ASA II/III	Surgery duration (min)
68±8	75±12	170±6	5/9	90±15

Abbreviation: ASA, American Society of Anesthesiologists.

From the group of patients treated with oxycodone infusion at a dose of 1 mg/h, two patients required a single bolus of 2 mg oxycodone (NRS 5/6 at rest at the time of oxycodone bolus administration), and the oxycodone dose in the infusion was increased to 2 mg/h. Oxycodone concentration was not assayed in these patients, and additional rescue doses of oxycodone were not required.

In the rest of the analyzed group of patients, there was no need for rescue doses of oxycodone during the postoperative period, both at rest and during movement. In the analyzed patients, oxycodone AEs such as vomiting, pruritus, cognitive impairment, respiratory depression, and blood pressure changes were not observed. Bradycardia was observed in two patients, and one patient experienced nausea.

Mean total and protein-bound oxycodone serum concentrations in three out of five patients receiving oxycodone at a dose of 1 mg/h and mean pain intensity (NRS) at rest and during movement (n=3) are shown in Table 3. Mean total and protein-bound oxycodone concentrations in the blood serum in nine patients treated with oxycodone at a dose of 2 mg/h, and mean pain intensity (NRS) at rest and during movement are shown in Table 4.

Discussion

In this study, oxycodone, administered in a continuous infusion for postoperative pain treatment in THA patients, was coadministered with ketoprofen injected into the iv line every 12 h. Oxycodone was used at 1 and 2 mg/h depending on patient's body weight. In both patient groups, in consecutive observations, pain intensity was mild and did not exceed

Table 3 Mean total and protein-bound serum oxycodone concentrations (±SD) in patients who were treated with a dose of 1 mg/h and mean pain intensity in NRS (±SD) at rest and during movement (n=3)

Time (min) of oxycodone infusion	Total oxycodone (ng/mL)	Bound oxycodone (ng/mL)	NRS at rest	NRS on movement
30	0.49±0.20	0.18±0.06	0.3±0.6	1.7±0.6
120	6.04±2.64	5.73±0.39	2.3±0.6	3.7±0.6
240	24.37±2.86	17.32±1.14	2.3±0.6	3.3±0.6

Abbreviations: NRS, numerical rating scale; SD, standard deviation.

Table 2 Mean values and standard deviation of laboratory tests in the analyzed patients (n=14)

WBC (10^3/μL)	Hb (mmol/L)	Hct (%)	PLT (10^3/μL)	Albumin (G/L)	Protein (G/L)	Na (mmol/L)	K (mmol/L)	Creatinine (μmol/L)	Urea (mmol/L)	ALT (U/L)	AST (U/L)
7.06±2.13	7.55±0.93	35.8±4.6	211±83	25.1±2.7	47.5±6.1	138.7±4.2	4.28±0.47	70.9±26.4	6.81±2.87	11±7	15±11

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; Hct, hematocryte; Hb, hemoglobin; PLT, platelets; WBC, white blood cells.

Table 4 Mean total and protein-bound serum oxycodone concentrations (±SD) in patients who were treated with a dose of 2 mg/h and mean pain intensity in NRS (±SD) at rest and during movement (n=9)

Time (min) of oxycodone infusion	Total oxycodone ng/mL	Bound oxycodone ng/mL	NRS at rest	NRS on movement
30	0.85±0.30	0.60±0.14	0.6±0.7	1.0±1.0
120	22.68±5.90	10.00±5.69	1.1±0.9	2.7±1.0
240	42.32±8.32	25.33±11.00	1.5±1.0	2.9±1.0

Abbreviations: NRS, numerical rating scale; SD, standard deviation.

3 (according to NRS) at rest and 4 during movement. In the group of patients treated with oxycodone at 1 mg/h, some patients did not require a dose increase to 2 mg/h. An oxycodone dose of 2 mg/h provided all nine treated patients with satisfactory analgesic effects, which is substantiated by the fact that no patient required administration of additional doses of analgesics. The mean oxycodone concentration in this patient group did not exceed 43 ng/mL of the total and 26 ng/mL of protein-bound oxycodone, whereas pain intensity did not exceed 3 (according to NRS).

An oxycodone dose of 1 mg/h provided effective analgesia in three out of five treated patients with mean oxycodone concentration in the three-patient group did not exceed 25 ng/mL of the total and 18 ng/mL of protein-bound oxycodone. In three analyzed patients, pain intensity did not exceed 4 (according to NRS). Two patients required administration of rescue doses of 2 mg oxycodone (NRS 5/6 at the moment of the drug administration) and a dose increase to 2 mg/h. Oxycodone concentrations in these patients were not measured. In the patient group with body weights ≤65 kg, an oxycodone dose of 1 mg/h was effective only in some patients. A dose increase to 2 mg/h was used in cases of severe pain intensity associated with extensive surgery and the fact that bone pain usually displays severe intensity associated with mixed receptor and neuropathic components.[12]

Nausea, vomiting, bradycardia, and hypotension are opioid-induced AEs. Oxycodone AEs such as vomiting, pruritus, cognitive impairment, respiratory depression, and blood pressure changes were not observed. One patient experienced nausea, which disappeared after iv administration of ondansetron at a dose of 4 mg. Bradycardia was observed in two patients (heart rate <45), and it also disappeared after iv atropine administration at a dose of 0.5 mg.

In both patient groups in the study period, serum oxycodone steady state was not achieved. Four hours after starting oxycodone infusion, total and protein-bound drug concentrations were still increasing. To establish the time necessary to achieve a serum drug steady state when administering oxycodone as continuous iv infusion, another study with a longer assay period and more time points should be done.

Analgesia may be associated with serum opioid concentrations. In a study conducted by Kokki et al, patients undergoing laparoscopic cholecystectomy had oxycodone concentrations equaling 20–50 ng/mL.[22] In another study performed among patients after cardiac surgery, oxycodone concentrations were in the range of 6–25 ng/mL.[23] These observations demonstrate that oxycodone concentrations may vary significantly depending on the doses used, time of blood sampling, and type of surgery. To the best of our knowledge, no such data exist for orthopedic surgery. The data obtained in our study indicate that oxycodone concentrations in patients after THA may be in the range of 24–42 ng/mL. However, a full pharmacokinetic/pharmacodynamic analysis of oxycodone administered after THA surgery should be done.

The number of THA surgeries rises steadily. Patients undergoing this procedure are most frequently aged >60 years and apart from arthrosis, suffer from other advanced chronic comorbidities, which require constant drug administration. These comorbidities should thus be considered when choosing pre- and postsurgical analgesia methods, which would enable patients' rapid return to normal functioning.

For many years, morphine has been the gold standard opioid for the treatment of moderate-to-severe pain. In 2009, oxycodone was registered in Poland, and thus it was possible to also start using oxycodone by the parenteral route, which had been widely used earlier in other countries mainly by the oral route. Oxycodone is an opioid, which thanks to its unique mode of action (affinity of μ and κ receptors, active transport to central nervous system, and activation of the GABA system) provides effective analgesia, also due to a short plasma half-life, easy dose titration, and relatively mild AEs.

Due to its agonist action on κ opioid receptors, oxycodone is often successfully used in visceral pain treatment (such as after extensive abdominal surgery), as these receptors have been shown to be present on nerve endings in the peritoneum and dorsal horns of the spinal cord.[24] The results of this study demonstrated that oxycodone was also effective in postoperative pain treatment after an extensive orthopedic surgery during the first 24 h. The titration of an effective dose of oxycodone administered by iv infusion allows a switch to the oral route of or oxycodone administration that should be effective and safe for each patient.

Analgesia administered via the iv route in the early postoperative period should provide fast pain relief, stable

pharmacokinetics, and convenient dosing. THA is one of most extensive orthopedic surgeries, and it is associated with severe postoperative pain; therefore, apart from central and peripheral blockades, opioids from step 3 of the World Health Organization analgesia classification are most commonly used. To limit oxycodone doses, a nonsteroidal anti-inflammatory drug was added. In this case, ketoprofen that possesses significant analgesic efficacy as far as bone pain is concerned was used. It should be noted that among patients enrolled, no patient had been diagnosed with renal and/or liver diseases or peptic ulcers, which would have been contraindications to ketoprofen administration. Laboratory parameters were within normal range; thus, no factors that would have influenced drug metabolism and excretion were found. In this study, opioid treatment had been started by the time central blockade analgesia subsided, and the patient had already recovered normal cognitive functions after propofol sedation.

Study limitations include lack of a control group, moderate number of enrolled patients, short period of observation (24 h), and limited number of serum oxycodone assays (done only at 4 h), which had not allowed drug steady state to be reached. However, despite the aforementioned limitations, we were able to demonstrate an effective analgesic effect, good profile of AEs, and safety of a combination of oxycodone infusion at a dose of 2 mg/h together with a bolus of 100 mg ketoprofen administered every 12 h for severe pain intensity treatment after THA surgery.

Conclusion

Continuous oxycodone infusion at a dose of 2 mg/h in conjunction with ketoprofen (100 mg) every 12 h, both administered via the iv route, can provide effective analgesia in patients during the first 24 h after THA surgery. Oxycodone at 1 mg/h administered as an iv infusion is effective in some patients after THA. Oxycodone iv infusions at doses of 1 and 2 mg/h do not induce drowsiness, vomiting, pruritus, respiratory depression, or blood pressure changes; however, out of 14 treated patients, bradycardia was observed in two patients and nausea in one. Intravenous infusion of oxycodone chloride in conjunction with iv ketoprofen provides analgesia that is effective and acceptable to patients during the first 24 h after THA. Oxycodone administered as a continuous iv infusion is a safe pain management method in patients after THA.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Central Database of total hip arthroplasty of the National Health Fund in Poland 2015. Available from: http://www.nfz.gov.pl/download/gfx/nfz/pl/defaultstronaopisowa/349/30/1/cbe_za_2015.pdf. Polish. Accessed October 15, 2016
2. Basques BA, Toy JO, Bohl DD, Golinvaux NS, Grauer JN. General compared with spinal anesthesia for total hip arthroplasty. *J Bone Joint Surg Am*. 2015;97(6):455–461.
3. Helwani MA, Avidan MS, Ben Abdallah A, et al. Effects of regional versus general anesthesia on outcomes after total hip arthroplasty: a retrospective propensity-matched cohort study. *J Bone Joint Surg Am*. 2015;97(3):186–193.
4. Johnson RL, Kopp SL, Burkle CM, et al. Neuraxial vs general anaesthesia for total hip and total knee arthroplasty: a systematic review of comparative-effectiveness research. *Br J Anaesth* 2016;116(2):163–176.
5. Pergolizzi JV, Seow-Choen F, Wexner SD, Zampogna G, Raffa RB, Taylor R. Perspectives on intravenous oxycodone for control of postoperative pain. *Pain Pract*. 2016;16(7):924–934.
6. Kokki H, Kokki M, Sjövall S. Oxycodone for the treatment of postoperative pain. *Exp Opin Pharmacother* 2012;13(7):1045–1058.
7. de Beer Jde V, Winemaker MJ, Donnelly GA, et al. Efficacy and safety of controlled-release oxycodone and standard therapies for postoperative pain after knee or hip replacement. *Can J Surg.* 2005;48(4):277–283.
8. Falk E. Eukodal, ein neues Narkotikum. *Munc Med Wochenschr.* 1917;20:381–384.
9. Lugo RA, Kern SE. The pharmacokinetics of oxycodone. *J Pain Palliat Care Pharmacother* 2004;18(4):17–30.
10. Lalovic B, Kharasch E, Hoffer C, Risler L, Liu–Chen LY, Shen DD. Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. *Clin Pharmacol Ther.* 2006;79(5):461–479.
11. Boström E, Hammarlund-Udenaes M, Simonsson U. Blood–brain barrier transport helps to explain discrepancies in vivo potency between oxycodone and morphine. *Anesthesiology.* 2008;108(3):495–505.
12. Sacerdote P, Manfredi B, Mantegazza P, Panerai AE. Antinociceptive and immunosuppressive effects of opiate drugs: a structure-related activity study. *Br J Pharmacol.* 1997; 121(4): 834–838.
13. Thibault K, Calvino B, Rivals I, et al. Molecular mechanisms underlying the enhanced analgesic effect of oxycodone compared to morphine in chemotherapy-induced neuropathic pain. *PLoS One.* 2014;9(3):e91297.
14. Leow KP, Wright AWE, Cramond T, Smith MT. Determination of the serum protein binding of oxycodone and morphine using ultrafiltration. *Ther Drug Monit.* 1993;15(5):440–447.
15. Beaver WT, Wallenstein SL, Rogers A, Houde RW. Analgesic studies of codeine and oxycodone in patients with cancer. II. Comparisons of intramuscular oxycodone with intramuscular morphine and codeine. *J Pharmacol Exp Ther.* 1978;207(1):101–108.
16. Kaiko RF, Benziger DP, Fitzmartin RD, Burke BE, Reder RF, Goldenheim PD. Pharmacokinetic pharmacodynamic relationships of controlled-release oxycodone. *Clin Pharmacol Ther.* 1996;59(1):52–61.
17. Pöyhiä R, Olkkola KT, Seppälä T, Kalso E. The pharmacokinetics of oxycodone after intravenous injection in adults. *Br J Clin Pharmacol.* 1991;32(4):516–518.
18. Lalovic B, Phillips B, Risler LL, Howald W, Shen DD. Quantitative contribution of CYP2D6 and CYP3A to oxycodone metabolism in human liver and intestinal microsomes. *Drug Metab Dispos.* 2004;32(4):447–454.
19. Villesen HH, Banning AM, Petersen RH, et al. Pharmacokinetics of morphine and oxycodone following intravenous administration in elderly patients. *Ther Clin Risk Manag*. 2007;3(5):961–967.
20. Pöyhiä R, Seppälä T. Liposolubility and protein binding of oxycodone in vitro. *Pharmacol Toxicol.* 1994;74(1):23–27.

21. Leow KP, Smith MT, Watt JA, Williams BE, Cramond T. Comparative oxycodone pharmacokinetics in humans after intravenous, oral, and rectal administration. *Ther Drug Monit.* 1992;14(6):479–484.
22. Kokki M, Broms S, Eskelinen M, Rasanen I, Ojanperä I, Kokki H. Analgesic concentrations of oxycodone – a prospective clinical PK/PD study in patients with laparoscopic cholecystectomy. *Basic Clin Pharmacol Toxicol*. 2012;110:469–475.
23. Pesonen A, Suojaranta-Ylinen R, Hammarén E, Tarkkila P, Seppälä T, Rosenberg PH. Comparison of effects and plasma concentrations of opioids between elderly and middle-aged patients after cardiac surgery. Acta Anaesthesiol Scand. 2009;53(1):101–108.
24. Kalso E. Oxycodone. J Pain Symptom Manage 2005;29(5):S47–S56.