Abstract

Oxycodone hydrochloride is a semisynthetic opioid which extracted from the baine plant, with a similar analgesic potency compared with morphine. Although oxycodone was introduced in 1917, the global use of oxycodone in acute postoperative management became popular in the past decades. Oxycodone has a bioavailability up to twice from the bioavailability of morphine in the enteral route and shows more potency in visceral pain. Furthermore, oxycodone has better pharmacokinetics in the central nervous system than morphine and has less adverse effects. In this case series, we report the effects of analgesia, inflammatory markers, and adverse effects of continued intravenous oxycodone as acute pain management in patients who underwent a modified radical mastectomy.

Keywords: Intravenous continue, modified radical mastectomy, oxycodone, postoperative analgesia

Introduction

Postoperative acute pain management is essential in the recovery of the patient. Inadequate acute pain management may lead to many complications, such as pneumonia, deep-vein thrombosis, delayed wound healing, depression, and a possibility of developing chronic pain. Opioids including oxycodone have been used widely for acute pain management because they can provide adequate analgesia for moderate to severe pain.[1]

Oxycodone (6-deoxy-7,8-dihydro-14-hydroxy-3-o-methyl-6-oxomorphine) is a semisynthetic opioid with a molecular structure that consists of two planar rings, two aliphatic rings, and four chiral atomic centers. It has a hygrophylic characteristic and can be given through many routes: oral, intranasal, intramuscular, subcutaneous, intravenous (IV), rectal, and via epidural.[2]

The pharmacological effects of oxycodone have started with the ligand to the opioid receptors in presynaptic nervous membrane cells in the central nervous system. The opioid receptors are μ receptor, δ receptor, and κ receptor, but oxycodone interacts mainly with μ-receptor. On IV route, the volume distribution is 2–3 L/kg, with a clearance (CL) of 0.7–0.8 L/min and elimination half-life (t ½) of 2–3 h after the given dose. The efficacy of IV oxycodone is similar to morphine for somatic and visceral pain. The fast onset and high bioavailability in the enteral formulation make oxycodone formula that can be easily adjusted in pain management course.[3]

Case Report

Six adult patients in the age group of 41–62 years, with the American Society of Anesthesiology physical Status I–III, were scheduled for elective modified radical mastectomy (MRM), using general anesthesia at our hospital. They received premedication with IV 10 mg dexamethasone, 10 mg diphenhydramine, and 2 mg midazolam. A blood sample was drawn to check the baseline complete blood count (CBC), blood sugar, and C-reactive protein (CRP).

In the operating room, induction was given by fentanyl 2–3 mcg/kg, propofol 2–3 mg/kg, and atracurium 0.5 mg/kg.

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Anesthesia was maintained using sevoflurane and oxygen-air mixture. After the surgery, the patient was treated with oxycodone 20 mg/24 h using a syringe pump for pain management, combined with 500 mg paracetamol postoperative after the patient can tolerate oral intake. The pain intensity was evaluated using the Visual Analog Scale score at 0, 1, 4, 8, 16, and 24 h until the oxycodone was stopped. The VAS characteristic is shown in Figure 1. Side effects such as nausea, vomiting, urine retention, pruritus, sedation, constipation, hypertension, bradycardia, and diarrhea were noted during the oxycodone use [Table 1].

At 24 h after the surgery, another blood sample was drawn to examine the postoperative CBC, blood sugar, and CRP [Table 2].

**Table 1: Postoperative adverse effects**

| Postoperative adverse events | Patient I | Patient II | Patient III | Patient IV | Patient V | Patient VI |
|-----------------------------|-----------|------------|-------------|------------|-----------|------------|
| Nausea                      | −         | +          | −           | −          | −         | −          |
| Vomiting                    | −         | −          | −           | −          | −         | −          |
| Urine retention             | −         | −          | −           | −          | −         | −          |
| Pruritus                    | −         | −          | −           | −          | −         | −          |
| Sedation                    | −         | −          | −           | −          | −         | −          |
| Constipation                | −         | −          | −           | −          | −         | −          |
| Hypertension                | −         | −          | −           | −          | −         | −          |
| Bradycardia                 | −         | −          | −           | −          | −         | −          |
| Diarrhea                    | −         | −          | −           | −          | −         | −          |

−: Absent, +: Present

**Table 2: Neutrophil, blood sugar, and C-reactive protein preoperative and postoperative**

|                   | Patient I Pre | 24 h | Patient II Pre | 24 h | Patient III Pre | 24 h | Patient IV Pre | 24 h | Patient V Pre | 24 h | Patient VI Pre | 24 h |
|-------------------|--------------|------|---------------|------|----------------|------|----------------|------|---------------|------|----------------|------|
| Neutrophil        | 3.46         | 10.3 | 4.73          | 8.7  | 5.2            | 9.5  | 1.31           | 3.5  | 1.8           | 2.8  | 6.7           | 16.8 |
| Blood sugar       | 81           | 118  | 96            | 113  | 149            | 167  | 93             | 122  | 102           | 103  | 90            | 124  |
| CRP               | 1.05         | 1.4  | 9.4           | 20.9 | 1.0            | 13   | 2.0            | 29   | 1.4           | 5.1  | 1.1           | 53.5 |

Pre: Baseline preoperative results, 24 h: Results at 24 h postsurgery, CRP: C-reactive protein

**Discussion**

Oxycodone and its active metabolites, oxymorphone, act on the opioid receptor in the cerebral and dorsal horn of the medulla spinalis. Despite its low lipophilic characteristic, researches on rats and sheep show that oxycocdone can pass through the blood–brain barrier without needing any active transporter-like p-glycoproteins.[2]

In cerebral tissue, oxycodone binds to µ-opioid receptor with relatively high affinity. Oxycodone also binds minimally with delta receptor and kappa receptor. The active metabolite, oxymorphone, has a higher affinity to µ receptor compared to oxycodone, while noroxycodone and other reduced metabolites, α- and β-oxycodol, have a lower affinity to mu receptor than oxycodone.[2]

The equilibrium of blood–brain concentration occurs faster compared to morphine, which explains why oxycodone provides better analgesia than morphine when given intravenously.[4] A study on patients who received either 0.015 mg opioid/kg, oxycodone, or morphine postlaparoscopic hysterectomy found that the VAS was significantly lower in the 1st postoperatively in the oxycodone group.[5]

In our serial case, all patients experienced very minimal postoperative pain during the treatment with oxycodone, with VAS <4 in 24 h. In our patients, all oxycodone stopped after 24 h since the patients had only mild pain on the 2nd day. Using only paracetamol tablet for analgesia, all our patients were able to go home on the 3rd day. None of them required additional/rescue dose of oxycodone during hospital stays.

The pharmacokinetics of oxycodone and its active metabolite in healthy controls are different according to the route of which the oxycodone is given. In IV route, the median steady-state volume of distribution is 2.6 L/kg (1.8–9.7), total plasma CL is 0.82 L/min (0.4–1.3), elimination half-life (t ½) is 3.0 h (1.8–9.7), and noroxycodone: oxycodone ratio for area under the concentration–time curve is 0.3 (0.06–0.83).[3]

Oxycodone is extensively metabolized in the liver by hepatic cytochrome, about 45% was mediated by the cytochrome p-450 3A through N-demethylation.[4,6] Lalovic et al. reported about the metabolism of oral oxycodone in healthy controls. They measured the concentration of oxycodone, noroxycodone, oxymorphone, noroxymorphone, α- and β-oxycodol, β noroxycodol, and α- and β-oxymorphol in plasma and urine. The reductive metabolite in urine was found around 18% of the given doses, while the oxidative metabolite...
was about 47%. About 18% is excreted in the form of pure oxycodone, mostly in unconjugated.[6]

As oxycodone is primarily eliminated in the liver, the liver dysfunction will attenuate the drug elimination. In patients with severe liver dysfunction, the plasma CL of oxycodone decreased to 75%, and the volume distribution increased to 50%, with a prolonged half-life (3–14 h). Even when only 10% of oxycodone will be excreted through the urine in pure form, but the decreasing of renal function will also prolong the elimination of oxycodone due to the increase of volume distributions. Evaluation of the effects of decreasing renal function in the pharmacokinetics of oxycodone is almost impossible to be done since the patient with this disease also has other comorbid diseases, which using medications that affect the metabolism of oxycodone.[4]

Opioid also interact with opioid receptors in the immune cell membrane, thus interrupting the production of cytokine and inducing the inflammation. An increased CRP can be used as a clinical marker to identify an increase in pro-inflammatory opioid-induced conditions. CRP is a protein that is produced in the liver and it is increased as a response to inflammation. CRP concentration increases in opioid-induced inflammation. A cohort study also reports that compared to the nonopioid-user patient, the plasma CRP was found to be lower than the concentration in patients with opioid therapy. The total CRP level also associated with the total consumption of postoperative opioids and the pain intensity postoperatively.[7]

In our case series, all six of our patients also show a significant increase in inflammation markers (neutrophil, blood sugar, and CRP).

Besides the analgesic effect, oxycodone also has adverse effects, including a decrease of alert, nausea, vomiting, mood changes, pruritus, and pupil constriction.[9] Oxycodone, as with other opioids, has an antitussive effect and can cause respiratory depression.[9] Another study also found the adverse effects of oxycodone, such as constipation, urine retention, and sweating.[9] Nausea and vomiting are the most often found adverse effects in the use of opioids.

Opioid stimulated the chemoreceptor trigger area in the medulla spinalis and caused the effect of nausea and vomiting, which overall decreases the patient’s comfort and even increasing the pain scale postoperatively. Kwon et al.[10] found that oxycodone rarely causing complaints of nausea and vomiting, almost similar to alfentanil, especially when given in boluses. Oxycodone was reported to cause dizziness, which is identical to alfentanil. Another adverse effect is respiratory depressions, urine retention, and abdominal discomfort.[10] In our case series, we found only one of six patients complaining of nausea during the use of oxycodone and no other adverse effects.

Our case series shows that oxycodone IV is effective in acute pain management post-MRM surgery as it offers potent analgesia and minimum adverse effects.

**Conclusions**

Oxycodone can be considered an alternative in acute pain management postoperatively due to its superior characteristics and minimum adverse effects.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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