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Advances in the clinical application of oxycodone in the perioperative period

Hong-Yang Chen, Zi-Ning Wang, Wei-Yi Zhang, Tao Zhu

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Abstract

To review the research progress of pure opioid receptor agonist oxycodone. The research progress of oxycodone in terms of pharmacokinetics, pharmacodynamics, adverse reactions, clinical application, combined medication and new progress in clinical application was summarized by referring to the literature. Oxycodone is a semi-synthetic thebaine derivative of opioid alkaloids, and is a pure opioid μ and κ receptor agonist. The main action sites are the central nervous system and visceral smooth muscle. Due to its advantages of low adverse reactions, good analgesic effects, and a wide range of safe doses, the drug has been widely used in the control of acute and chronic postoperative pain, as well as malignant and non-malignant pain. Since the end of the 20th century, researchers have begun to formulate antipyretic analgesics, opioid receptor agonists, opioid receptor antagonists, dopamine receptor antagonists and other drugs with oxycodone in different proportions to enhance the analgesic effect. At the same time, it can reduce the dosage of oxycodone and reduce its adverse reactions, so as to achieve the purpose of limiting opioid abuse. With the continuous research on the efficacy and safety of oxycodone in the perioperative period at home and abroad, oxycodone has become the only dual-opioid potent analgesic that can be used in clinical work.

Key Words: Oxycodone; Anesthesia; Acute pain; Clinical application; Pharmacodynamics

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Core Tip: Oxycodone is a semi-synthetic opioid extracted from a plant derivative of tiabaine and gradually applied in clinical practice. It is an opioid μ and κ receptor agonist, a class of potent opioid analgesics. It mainly acts on smooth muscle by agonizing κ receptors to relieve visceral neuralgia; on the other hand, it can act on the central nervous system by agonizing μ receptors to produce analgesic effects.

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INTRODUCTION

Pain is defined by the medical community as the fifth vital sign after respiration, pulse, temperature and blood pressure. It is an unpleasant emotional experience and is accompanied by tissue damage as a reflex mechanism for self-protection, and is also a common reaction after surgery. Postoperative pain is mostly a strong acute pain, which not only causes physical discomfort and psychological trauma to patients, but also leads to changes in their endocrine system, causing pulmonary and other complications, thus affecting incision healing and postoperative recovery, and prolonging hospitalization. If this acute pain is poorly controlled, it is often transformed into chronic pain due to psychospiritual changes, peripheral and central sensitization of the patient.

Therefore, to reduce postoperative pain, postoperative complications and the incidence of postoperative stress, adequate postoperative analgesia is required to shorten the recovery period and observation period of patients after surgery and to facilitate early discharge[1]. A wide range of analgesic drugs are currently used in clinical practice, including pure opioid agonists such as morphine, fentanyl, and remifentanyl, partial opioid agonist antagonists such as bupropion and dizocine, weak opioid agonists such as tramadol, and non-opioid drugs such as non-steroidal anti-inflammatory drugs, acetaminophen, local anesthetics, glucocorticoids, NMDA receptor antagonists, α_2 agonists, *etc.* As a potent opioid, oxycodone is a drug with good analgesic effects and is mainly used not only for the treatment of cancer pain and acute and chronic non-cancer pain, but also for the treatment of moderate to severe acute pain, including moderate to severe pain caused by post-surgery. It has replaced morphine as the first-line postoperative analgesic drug in many countries because of its advantages such as low adverse effects, good analgesic effects and a wide range of safe doses[2].

Oxycodone is a semi-synthetic opioid extracted from a plant derivative of tiabaine and gradually applied in clinical practice. It is an opioid μ and κ receptor agonist, which is a class of potent opioid analgesics. It mainly acts on smooth muscle by agonizing κ receptors to relieve visceral neuralgia; on the other hand, it can act on the central nervous system by agonizing μ receptors to produce analgesic effects.

PHARMACODYNAMICS

Pöyhiä *et al*[3] compared the analgesic effects of different routes of administration of oxycodone and morphine by the heat radiation tail-shaking method and the hot plate method in rats. Subcutaneous (5 mg/kg) and intraperitoneal (2.5 mg/kg) administration of oxycodone was two to four times more potent than morphine. The onset of analgesia of subcutaneous and intraperitoneal (2.5-5 mg/kg) oxycodone is faster (15-30 min) than that of subcutaneous and intraperitoneal (5-10 mg/kg) morphine, the onset of action is the same at high doses (15 min), and the duration of analgesia of subcutaneous oxycodone and morphine is similar, with no significant difference. Staahl *et al*[4] compared the analgesic effects of oxycodone and morphine on pain produced by mechanical, thermal and electrical stimuli in healthy subjects. Subjects were given morphine (30 mg), oxycodone (15 mg), and placebo, and the analgesic effects of morphine versus oxycodone were examined by mechanical, thermal, and electrical stimulation of pain after 30 min of oral administration. The results showed that morphine and oxycodone had analgesic effects on pain produced by the three types of stimuli, but the analgesic effects of oxycodone on pain produced by mechanical and thermal stimuli were better than those of morphine.

PHARMACOKINETICS

Oxycodone is a weak base with a drug dissociation constant of 8.5. Its lipid solubility is mainly bound to serum proteins, similar to morphine, but both have lower lipid solubility than fentanyl[5]. Oxycodone is

currently available as controlled and sustained-release tablets, injectables, and suppositories, and is administered orally, subcutaneously and intravenously, as well as rectally, epidurally, and intranasally [6]. Oxycodone is well absorbed orally and is 3-4 times more bioavailable than morphine [7]. Olkkola *et al* [7] found that intravenous oxycodone has a rapid onset of action and can rapidly achieve blood-brain homeostasis. Clinical data show that when oxycodone is administered intravenously, its analgesic effect is comparable to or 1.5 times greater than that of morphine [8].

Oxycodone is mainly metabolized by the liver in the body, and its metabolic pathway is mainly through O-position demethylation catalyzed by CYP2D6 subtypes to form active oxymorphone, and then through CYP3A4N demethylation to inactive norethindrone; another pathway is N-position demethylation catalyzed by CYP3A4 and CYP3A5 subtypes of hepatic P450 to inactive norethindrone. The other pathway is that the N position demethylation is catalyzed by two subtypes of hepatic P450, CYP3A4 and CYP3A5, to the inactive noroxycodone, which is then metabolized by CYP2D6 to the inactive hydromorphone. The concentrations of noroxycodone in plasma and urine were significantly higher after oral administration than after intramuscular injection, suggesting that oxycodone is metabolized mainly by demethylation in the first-pass effect. The oxycodone metabolite oxymorphone is mainly excreted in the bound state, norethindrone is mainly excreted in the free form, and some free oxycodone is excreted in the urine [9].

ADVERSE REACTIONS

Oxycodone, one of the opioid analgesics, has adverse effects common to other opioids, such as dry mouth, constipation, nausea, vomiting, pruritus, dizziness, drowsiness, and confusion [10]. The literature reports that oxycodone has the risk of causing dependence and drug abuse, and its psychiatric dependence is associated with increased release of striatal dopamine, but the risk is much less than other μ opioid agonists and does not cause side effects such as psychotic euphoria and respiratory depression [11]. Strong opioids such as morphine and fentanyl reduce T cells and have immunosuppressive effects, but oxycodone has weaker immunosuppressive effects than morphine.

Oxycodone overdose can lead to drowsiness, coma, pupil constriction, muscle relaxation, seizures, bradycardia, respiratory depression, and hypotonia [12]. Detoxification should be performed with intravenous naloxone, repeated intravenous pushes or continuous intravenous drips to prevent fatal poisoning [13]. Cardiopulmonary resuscitation should be given immediately in the presence of cardiogenic shock due to severe oxycodone overdose [14-17]. The studies by Warner *et al* and Ahmedzai *et al* [18] showed that Oxycodone reduced opioid-induced constipation in chronic pain management, which not only prevented gastrointestinal adverse effects, but also had little effect on analgesic efficacy [19].

CLINICAL APPLICATIONS

Prophylactic analgesia is a form of analgesia that blocks the transmission, conduction, and establishment of peripheral injurious impulses to the center and reduces the peripheral and central sensitization caused by noxious stimulus afferents [20]. As a long-acting, non-accumulative opioid, oxycodone can provide suitable prophylactic analgesia. As the only dual agonist of μ and κ receptors in clinical practice, oxycodone has been occupying an extremely important position in postoperative analgesia and cancer pain control [21].

ACUTE PAIN

Studies have shown that oxycodone reaches stable concentrations in the brain more quickly than morphine, making it superior to morphine for rapid analgesia. The release of histamine in the body is significantly less with oxycodone analgesia than with morphine. In a review of oral oxycodone analgesia, it was demonstrated that oral oxycodone was effective for acute postoperative pain control and that the analgesic strength of oxycodone was two to three times that of codeine; in addition, the analgesic effect of oxycodone was enhanced by combining it with acetaminophen [22]. Subsequently, the authors reviewed single-dose oral oxycodone in combination with ibuprofen and came to a similar conclusion: The combination of oxycodone prolongs the duration of analgesia and reduces the incidence of adverse effects [23].

Oxycodone is used for postoperative analgesia and has a lower incidence of nausea and easier termination of analgesia when given orally compared to intravenous self-administered pumps [24]. Evidence suggests that epidural administration of oxycodone is not superior to intravenous administration [25], and the dosage of oxycodone is approximately 10 times that of morphine for the same analgesic effect, consistent with preclinical studies [25,26]. In a randomized controlled study comparing

the analgesic effect of oral oxycodone with intrathecal morphine after cesarean delivery, the analgesic effect was similar and the incidence of pruritus was lower in the oxycodone group[27]. In acute pain control, the analgesic effect of oxycodone may be related to the route of administration.

CHRONIC PAIN

Although opioids are spreading rapidly in the management of chronic non-cancer pain. However, it is not the first-line treatment for chronic noncancer pain, nor is it recommended to treat chronic noncancer pain with opioids alone. Although some chronic pain can be relieved with strong opioid therapy, such as osteoarthritic pain, intervertebral disc disease, diabetic polyneuropathy, and postherpetic neuralgia. However, the need for continued use of opioids for non-cancer pain needs to be evaluated periodically. Therefore, when patients no longer require treatment with oxycodone, the dose of the drug should be gradually reduced to prevent withdrawal symptoms[28,29].

VISCERAL NEURALGIA PAIN

Visceral pain is caused by mechanical stretching, spasm, inflammation, and surgical stimulation and is the result of sensory afferent nerve stimulation of visceral organ activity, and receptors on the walls of cavernous organs are sensitive to stretching and distending stimuli. Oxycodone can agonize κ -opioid receptors, which are involved in the modulation of visceral pain; therefore, oxycodone is more effective in visceral pain[30]. One study again compared the analgesic effect of oxycodone with morphine by inducing nociceptive sensitization in humans, and the analgesia was superior to morphine in different experimental pain models[31]. Although the effect of oxycodone on visceral pain is controversial, Lenz *et al*[32] compared the analgesic effect of oxycodone and morphine when used in patients with self-administered pumps and showed that the total consumption of oxycodone was less than morphine and that the analgesic effect was superior to morphine in the first postoperative hour.

CANCER PAIN

The quality of life of cancer patients in the late stage of cancer often depends on the degree of cancer pain, and the quality of life of patients with cancer pain is very poor. Oxycodone also has a good effect in controlling cancer pain. Compared to morphine, oxycodone may have a lower incidence of nausea and hallucinations. Oral morphine, oxycodone, and hydromorphone have been reported to produce similar efficacy as well as toxic effects in patients with cancer pain[33]. Constipation is the most common and difficult to control adverse effects when using opioids to control cancer pain[18,34]. Combination with naloxone may improve this condition. Therefore, for the treatment of advanced cancer, the best drug choice is currently oxycodone to improve the quality of survival and reduce patients' pain.

COMBINATION MEDICATION

Oxycodone grouped with antipyretic and analgesic

Pain is mostly caused by the release of a large number of inflammatory mediators from the damaged area stimulating nerve endings to form excitatory transmission, which is integrated *via* the spinal reticular upward transmission system to the central brain to produce a nociceptive response.

Antipyretic and analgesic drugs are mainly used in the periphery to inhibit cyclooxygenase activity, reduce prostaglandin production and release of inflammatory substances (*e.g.* cytokines interleukin 1 (IL-1), IL-6 and IL-8, substance P, bradykinin, nerve growth factor, *etc.*) to produce anti-inflammatory and analgesic effects. Oxycodone is a central analgesic, that mainly inhibits the transmission and integration of nociceptive information to achieve analgesic effects. The combination of antipyretic and analgesic drugs with oxycodone not only complements the mechanism of action and improves analgesic efficacy, but also reduces the dose of oxycodone alone and reduces adverse effects such as oxycodone tolerance and addiction. Several clinical studies have confirmed that this compound has been widely used for clinical analgesia, including rheumatoid arthritis, osteoarthritis pain in elderly women, chronic non-cancer pain, cancer pain, post-surgical pain, chronic skeletal muscle sarcoid pain and neuropathic pain of various moderate to severe pain, all of which have shown good analgesic effects[22,35,36].

In addition, it also has clear analgesic effects in postoperative pain such as orthopedic surgery, dental surgery, and abdominal or pelvic surgery. The analgesic strength is better than that of each single drug (such as Aspirin, Acetaminophen, Indomethacin, Meloxicam, Ibuprofen and Diclofenac), the onset of action is faster (15 min after administration), and the effective duration of analgesia is significantly

longer than that of any of the single drugs.

Oxycodone grouped with opioid receptor antagonists

Because oxycodone is an opioid agonist, it has the same adverse effects as other opioids, the most common of which are effects on bowel function. Opioids increase intestinal smooth muscle tone and decrease its propulsion, increase fluid absorption and inhibit its secretion, thus inducing intestinal dysfunction, leading to gas, difficult bowel movements and constipation (called opioid-induced constipation (OIC))[37,38].

More seriously, long-term use of opioid agonists can induce nociceptive hypersensitivity and drug dependence, severely limiting the scope of use of this class of drugs. In recent years, it has been found that chronic opioid treatment induces a shift from Gi/Gs to Gs in μ -opioid receptor (MOR)-coupled G proteins, and thus the effect of opioid agonists changes from initial inhibition to excitation, causing enhanced excitatory synaptic transmission in the spinal cord, a change that can lead to nociceptive hypersensitivity, while this response is also involved in opioid-induced tolerance and dependence. This change leads to the development of nociceptive hyperalgesia, and this response is also involved in the development of opioid-induced tolerance and dependence[39]. Concomitant administration of an ultra-low dose of an opioid receptor antagonist (naloxone or naltrexone) with opioids not only reduces the shift from inhibition to excitation induced by chronic agonist processing, but also reduces the formation of dependence.

Therefore, therapeutic doses of oxycodone have been made into oral tablets with ultra-low doses of antagonists in an attempt to reduce their adverse effects without compromising their analgesic effects [40]. Several clinical studies have shown that compounding has the same analgesic effect compared to oxycodone alone, but significantly improves OIC, with other adverse effects less than or comparable to those of the single agent. After 4 weeks of compounding in patients with chronic neuropathic pain, 1488 patients showed a significant reduction in pain intensity, a return to normal bowel function, and a significant improvement in quality of life (47%)[41,42].

Oxycodone and Morphine formulation

The results of numerous studies in animals and humans suggest that when opioids acting on different opioid receptor subtypes are combined, it is possible to enhance their analgesic effects and attenuate adverse effects. The analgesic effect of morphine is mainly mediated by μ 1-receptors, and the analgesic effect of oxycodone is mainly mediated by μ 1 and κ -receptors. In the absence of morphine, oxycodone activates κ receptors to produce analgesic effects; in the presence of morphine, oxycodone activates κ -receptors to produce satisfactory analgesic effects, and at the same time antagonizes morphine μ 2-receptor-like effects, reducing or eliminate side effects such as respiratory depression. Therefore, in recent years, some studies have combined morphine with oxycodone and found that the analgesic effects of the two drugs have a significant synergistic effect in a large number of animal and human studies, and the adverse effects are significantly reduced[43,44].

The analgesic efficacy of morphine/oxycodone combination on postoperative pain was compared in a clinical randomized, double-blind, multicenter, parallel-controlled study abroad. The results showed that the analgesic effect of morphine in combination with an oxycodone controlled-release formulation was also significantly enhanced in patients with cancer pain, and patient subjective satisfaction and quality of life were significantly improved. Adverse effects such as nausea, vomiting, sedation and respiratory depression were significantly reduced compared with the two single-drug groups[45]. Therefore, the morphine/oxycodone combination can be used as the drug of choice for moderate to severe pain.

Oxycodone grouped with dopamine receptor antagonists

ROTUNDINE is a dopamine (DA) 2 receptor antagonist. The involvement of the central DA nervous system in nociceptive modulation has been extensively investigated, focusing on the function and interaction of endogenous opioid peptides and monoamine neurotransmitters in the spinal cord and brainstem nociceptive downstream regulatory systems, and in particular on the important role of the DA nervous system in the formation of opioid-induced psychiatric dependence. Current research suggests that all natural or non-natural rewarding stimuli produce "euphoria" by activating the limbic DA reward system in the midbrain, and that the DA and opioid systems are two important components of the reward mechanism[46,47]. Studies have shown that the combination of oxycodone and rotenone not only significantly increases the analgesic effect of oxycodone, but also decreases the dosage of oxycodone and reduces its tolerance rate and dependence potential.

Oxycodone compounded with other drugs

The prevalence of neuropathic pain is very high both nationally and internationally. Studies have shown that the combination of oxycodone and gabapentin significantly relieved neuropathic pain, and the combination of the two drugs was significantly better than gabapentin alone in terms of pain relief, withdrawal ratio, and improvement in sleep quality, while oxycodone-induced adverse effects were not exacerbated by the combination of the two drugs[48]. Zacny *et al*[49] found that pregabalin was able to

dose-dependently increase certain subjective effects in healthy volunteers that decreased respiratory rate, but did not affect psychomotor behavior in volunteers, nor subjective behaviors related to abuse propensity such as drug addiction and craving behavior; oxycodone alone was able to increase a variety of subjective behaviors, including rates of drug addiction; however, pregabalin did not affect the effects of oxycodone; these results suggest that the combination of pregabalin and oxycodone does not increase the addictive potential of oxycodone. Therefore, it is possible to use the two-drug combination for the treatment of neuropathic pain in the future.

NEW ADVANCES IN CLINICAL APPLICATIONS

Fentanyl is a commonly used opioid with rapid onset, short duration, and relatively stable hemodynamics. Although there may be some adverse effects, such as hypotension, chest wall stiffness, respiratory depression, and postoperative nausea, it is still used clinically for the induction and maintenance of general anesthesia because it can block the afferent impulse from pharyngeal stimulation during intubation and reduce the cardiovascular response during intubation[50]. The induction dose used in non-cardiac surgery is 2-4 µg/kg. Oxycodone is administered intravenously, with an onset of action of 2-3 min and a peak blood concentration of 5 min. And the maintenance time is approximately 4 h[51]. The equivalent dose conversion between fentanyl and oxycodone is 1:100[52], so the choice of oxycodone is 0.2 mg/kg. Some literature reports[53], that fentanyl doses greater than 5 µg/kg to completely block the sympathetic nervous response induced by tracheal intubation.

Studies on exploring the effectiveness and safety of oxycodone for general anesthesia tracheal intubation have shown that oxycodone has less effect on blood pressure and heart rate than fentanyl and has a relatively smooth circulation[52,54-56]. Another issue to consider with oxycodone as an induction drug is its effect on anesthetic awakening and extubation. This study showed no significant difference between oxycodone and fentanyl at the time of awakening and extubation for procedures within 4 h.

In addition, the use of oxycodone for the induction of general anesthesia can also prevent some common adverse complications and improve patient comfort to a large extent while ensuring the safety of anesthesia. (1) Oxycodone can prevent fentanyl-induced cough (FIC), and its mechanism of action is related to the direct action of oxycodone on the cough center of the medulla oblongata. The mechanism of action is related to the direct action of oxycodone on the cough center of the medulla oblongata, which produces cough suppression[52]. In addition, oxycodone can reduce the dosage of fentanyl drugs, thus reducing their blood concentration, which also reduces the occurrence of FIC to a certain extent; (2) Oxycodone can effectively improve the adverse complications of rocuronium bromide and propofol injection pain, and its mechanism of action may be related to the agonization of opioid receptors in the central nervous system, but there is no conclusive evidence yet[57,58]; and (3) some studies have shown that oxycodone given intravenously at 0.1 mg/kg before etomidate induction has a better effect on the prevention of myoclonus and a lower incidence of respiratory depression than fentanyl at 1 µg/kg, and the ED₅₀ (median effective dose) of oxycodone inhibition of etomidate-induced myoclonus is higher in middle-aged patients than in older patients[58,59], but the mechanism of its occurrence needs to be further studied.

Therefore, more refined research and exploration of whether oxycodone can be safely and effectively used for the induction of general anesthesia and whether it can be used to maintain anesthesia in the book remain to be done in the future.

COMMENT

As the only double opioid potent analgesic available in clinical practice, oxycodone has the following advantages: first, the central analgesic effect of the original drug is dominant, the metabolites are almost inactive, only oxymorphone is active, but its content is extremely low. Second, intravenous administration has a rapid onset of action, and it is easy to achieve stable blood concentrations, which can provide rapid pain relief. Third, the bioavailability of different routes of administration is high, which facilitates the transition from intravenous to oral administration in postoperative patients.

However, it must be admitted that it has the common adverse effects of opioids. Although there are some foreign studies on the efficacy and safety of oxycodone in the perioperative period, it is important not to copy foreign experiences due to the differences in ethnicity, medical system and environment. We need to re-evaluate the perioperative safety and efficacy of oxycodone through more clinical studies to explore the effective dose and safe dose, the incidence and severity of related adverse reactions, and the principles of treatment that are suitable for the national population.

CONCLUSION

Oxycodone is a semi-synthetic thebaine derivative of opioid alkaloids, and is a pure opioid μ and κ receptor agonist. The main action sites are the central nervous system and visceral smooth muscle. Due to its advantages of low adverse reactions, good analgesic effects, and a wide range of safe doses, the drug has been widely used in the control of acute and chronic postoperative pain, as well as malignant and non-malignant pain. Since the end of the 20th century, researchers have begun to formulate antipyretic analgesics, opioid receptor agonists, opioid receptor antagonists, dopamine receptor antagonists and other drugs with oxycodone in different proportions to enhance the analgesic effect. At the same time, it can reduce the dosage of oxycodone and reduce its adverse reactions, so as to achieve the purpose of limiting opioid abuse. With the continuous research on the efficacy and safety of oxycodone in the perioperative period at home and abroad, oxycodone has become the only dual-opioid potent analgesic that can be used in clinical work.

FOOTNOTES

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