Revisiting Oxycodone Analgesia
A Review and Hypothesis

Xiulu Ruan, MD*, Ken F. Mancuso, MD, Alan David Kaye, MD, PhD

INTRODUCTION

Oxycodone, a semisynthetic opioid analgesic, is widely used in clinical practice. Oxycodone was first synthesized from thebaine in Germany in 1917.¹ For decades, researchers have been challenged by results of a plethora of research studies in different animal models and in humans, related to oxycodone analgesia.² Oxycodone and morphine seem to be equally effective and equipotent when postoperatively administered intravenously via patient-controlled analgesia and in cancer pain. However, data have provided conflicting results.³,⁴ This article aims to provide an updated review on the basic pharmacology of oxycodone with a special focus on pharmacokinetic/pharmacodynamics properties.³ The controversy regarding oxycodone-mediated effects for visceral pain via agonism and the possible role of peripheral opioid analgesia are discussed to propose a plausible explanation to the perplexing question of oxycodone analgesia.
Oxycodone has been shown to be 2 to 4 times as potent as morphine. Thus, it remains largely unclear as to how these data have provided such conflicting results.

This article provides an updated review on the basic pharmacology of oxycodone with a special focus on pharmacokinetic/pharmacodynamics properties. Additionally, a review is provided on the controversy regarding oxycodone-mediated or -modulated effects for visceral pain via \( \kappa \) agonism and the possible role or roles of peripheral opioid analgesia are discussed in the present investigation in an attempt to determine a plausible explanation to the perplexing question of oxycodone analgesia.

**BASIC PHARMACOKINETICS**

Oxycodone is relatively well-absorbed after oral administration. Approximately 40% of oxycodone is bound to plasma proteins in vitro, which is similar to the binding of morphine. The distribution volume at steady state is 2 to 5 L/kg in adults, which is comparable with that of morphine. Passive diffusion, a process whereby drugs or endogenous substances move across the blood–brain barrier (BBB), depends on the physicochemical properties of the drug and concentration gradient from blood to brain. Low-molecular-weight, lipid-soluble, and neutral agents may cross the BBB via passive diffusion. The lipid solubility of oxycodone has been found to be similar to that of morphine. In sheep and rats, after intravenous administration, the unbound concentration of oxycodone has been found to be 2.5 and 6 times higher in the brain than in the blood, suggesting an active transport of oxycodone across the BBB. Okura and colleagues postulated that oxycodone was transported into the central nervous system by an organic cation transporter in vitro and in vivo. However, how significant a role these transporters may play in human BBB (assuming they exist) is largely unknown.

The cerebral endothelium at the BBB has ATP-dependent efflux pumps, efflux transporters, which prevent brain penetration, as well as intracellular and extracellular distribution of a variety of endogenous and exogenous compounds. Morphine has been identified as a substrate of P-glycoprotein; however, there have been conflicting studies regarding whether oxycodone is a substrate of P-glycoprotein. An early study in rats by Boström and colleagues has suggested that oxycodone is not a substrate of P-glycoprotein, unlike morphine. In contrast, these results were subsequently questioned by Hassan and colleagues, who reported that oxycodone was a P-glycoprotein substrate in various in vitro and in vivo models. Further, Hassan and colleagues also demonstrated that chronic administration of oxycodone induced overexpression of P-glycoprotein. In this regard, there is no information on the possible role of P-glycoprotein in regulating BBB transport of oxycodone in humans.

**PHARMACOGENETIC VARIATION OR METABOLITE CONTRIBUTION**

The pharmacogenetic and pharmacodynamic properties of oxycodone and its metabolites have been reviewed extensively by Olkkola and colleagues. The \( \mu \)-opioid receptor binding affinity of nororoxycodone, the primary metabolite of oxycodone, is 4 times lower than that of oxycodone, and it produces 4 to 6 times lower G protein activation measured in a GTP\( \gamma \) binding assay. The other primary oxidative metabolite, oxymorphone, has about a 50-fold higher affinity for the \( \mu \)-opioid receptor and can produce 8- to 30-fold higher G protein activation than oxycodone. The reduction products of oxymorphone, \( \alpha \)- and \( \beta \)-oxymorphol, have been shown to be 2 to 3 times more potent than oxycodone; however, after oral administration of oxycodone in humans, the plasma concentrations of \( \alpha \)- and \( \beta \)-oxymorphol are low.
The most important secondary metabolite of oxycodone, noroxymorphone, has a 2- to 3-fold higher affinity for the \( \mu \)-opioid receptor compared with oxycodone.\(^7,17\) The potency of noroxymorphone for \( \mu \)-opioid receptor-mediated \( G \) protein activation has been shown to be 3- to 7-fold higher than that of oxycodone.\(^17,18\)

In a recent review, Klimas and colleagues\(^20\) demonstrated that oxycodone itself was responsible for the analgesic effect, despite its active metabolites, oxymorphone and noroxymorphone, possessing much higher \( \mu \)-receptor affinity than oxycodone, because the metabolites concentrations at the site of action, for example, the central nervous system, were too low. Andreassen and colleagues\(^21\) have reported in a cross-sectional study of 450 cancer patients genotyped for CYP2D6, which revealed 27 poor metabolizer, 413 extensive metabolizer, and 10 ultra-rapid metabolizer, oxycodone and noroxymorphone plasma concentrations did not differ between these phenotypes. In addition, the daily intake of oxycodone did not differ among patients, whether they were poor metabolizer, extensive metabolizer, or ultra-rapid metabolizer (70–80 mg/d). Further, Andreassen and colleagues\(^22\) also reported the finding, after a multicenter cross-sectional study of 456 cancer patients, that no relationships were demonstrated between oxycodone or noroxymorphone concentrations and pain intensity, tiredness, nausea, or cognitive function. Oxycodone is primarily metabolized via CYP3A4/3A5 and to a lesser extent via CYP2D6.\(^23\) It is believed that CYP2D6 genotypes cause significant differences in pharmacokinetics without producing major pharmacodynamic consequences or clinical implications.\(^23,24\)

**PHARMACODYNAMIC DILEMMA**

Oxycodone has been shown to be relatively selective at the \( \mu \)-opioid receptor.\(^2\) Depending on the assay properties, the affinity of oxycodone for the \( \mu \)-opioid receptor is 5 to 40 times lower compared with morphine.\(^7,17,19\) The potency of oxycodone in the \( \mu \)-opioid receptor-mediated activation of intracellular \( G \) proteins measured in the GTP\(\gamma\)S binding assay is 4- to 8-fold lower than the activity of morphine.\(^17,19\)

In a radioligand displacement study, Lalovic and colleagues\(^17\) have shown that the \( \mu \)-receptor affinity of oxycodone is only one-fifth that of morphine, whereas its potency in activating GTP\(\gamma\)S binding to the \( \mu \)-receptor is about one-third that of morphine. However, other observations have shown conflicting findings, for example, the antinociceptive potency of oxycodone in rodents is equal to that of morphine\(^6\); oxycodone and morphine seem to be equally effective and equipotent when given intravenously for postoperative patient-controlled analgesia and in patients with cancer pain.\(^3,4\) In rats, with intrathecal administration, morphine has been shown to be 14 times more potent than oxycodone, whereas with subcutaneous and intraperitoneal administration, oxycodone has been demonstrated to be 2 to 4 times as potent as morphine.\(^5\)

In a critical review on oxycodone pharmacology, Olkkola and colleagues\(^2\) opined, “We have still no explanation for the cerebral accumulation of oxycodone. Whether an active influx transporter explains the discrepancy between poor opioid receptor binding and analgesic efficacy remains to be elucidated. More research is also needed to understand why oxycodone is less effective after spinal than after intravenous administration.” Thus, using current opioid analgesic models, none of the hypotheses is able to provide a clear explanation for the conflicting findings in basic research and clinical practice. The apparent differences were hypothesized to be the result of either the involvement of active metabolites\(^3,25\) or the combined actions of oxycodone at the \( \mu \)- and \( \kappa \)-opioid receptors.\(^26,27\)
Regardless of the underlying mechanism, it might be reasonable to consider, therefore, that there is a peripheral contribution from oxycodone and/or its active metabolites, in part, might be responsible for the observed pharmacologic differences.

THE ROLE OF PERIPHERAL OPIOID RECEPTORS IN PERIPHERAL OXYCODONE ANALGESIA

Opioid receptors exist not only in the nervous system, but also in peripheral organs, such as the heart, lungs, liver, and gastrointestinal and reproductive tracts. However, the expression and distribution of these receptors vary significantly among different organs as well as among different animal species. Peripheral opioid receptors in the periphery can be a site for mediating analgesia. Peripheral analgesic effects of opioids are enhanced under inflammatory conditions and hyperalgesia. Inflammation increases the peripherally directed axonal transport of opioid receptors, which leads to upregulation of opioid receptors on peripheral nerve terminals, in particular, \( \kappa \)-opioid receptors. In addition, the number of primary afferent neuron terminals is increased in inflamed tissues.

Opioid receptors are classified into 3 major groups: \( \mu \)-opioid receptors, \( \delta \)-opioid receptors, and \( \kappa \)-opioid receptors. Pharmacologically, the 3 classes of opioid receptors have been subdivided into 3 subtypes of \( \mu \)-opioid receptors, 2 subtypes of \( \delta \)-opioid receptors, and at least 3 subtypes of \( \kappa \)-opioid receptors. All the receptor subtypes for \( \mu \), \( \delta \), and \( \kappa \)-receptors have been proposed based on pharmacologic data; to date, there is only 1 known gene product for each subtype, which results in the expression of the functional receptor. It has also been demonstrated that characteristics of peripheral opioid receptors are very similar to those in the brain. Both \( \mu \)-opioid and \( \kappa \)-opioid receptors have been found to be expressed in the stomach, duodenum, jejunum, and ileum as well as the proximal and distal colon, where their function is thought to include control of visceral pain, regulation of transit time of luminal contents, and mucosal transport of fluids and electrolytes.

In contrast with \( \mu \)-opioid receptor and \( \delta \)-opioid receptor agonists, \( \kappa \)-receptor agonists have long been recognized to be analgesics with no addiction and tolerance liability. However, almost all \( \kappa \)-receptor agonists cause dysphoria, anhedonia, and hallucinations. Multiple lines of evidences suggest that the \( \kappa \)-receptor modulates overlapping neurocircuits, connecting brainstem monoaminergic nuclei with forebrain limbic structures and thereby regulating the neurobiological effects of stress and psychostimulants. The emerging concept of “biased agonism” (also known as functional selectivity) for G-protein–coupled receptor ligands have provided new insights into overall response generated by a ligand. According to this concept, every ligand possesses the unique ability (coded in its structure) that dictates a distinct signaling pattern, and consequently beneficial or adverse response. Thus, the predominant signaling pattern of a G-protein–coupled receptor may differ from cell to cell in various tissues and organs. Finally, the promise of “biased agonism” lies in its ability to produce therapeutically beneficial signals while minimizing adverse effects.

Peripheral \( \kappa \)-opioid receptors in the gut have been suggested as an important feature of the visceral pain system. The \( \kappa \)-receptors are more abundant in peripheral nerves than in central nerves. There are 3 subtypes of \( \kappa \)-receptors that inhibit afferent firing and visceromotor responses to noxious colorectal distention in animal models.

Analgesic development programs in the pharmaceutical industry for \( \kappa_1 \)-opioid receptor selective ligands produced highly potent alternative analgesics to morphine in the late 1980s; however, they failed in the clinical setting related to
psychotomimetic side effects. The $\kappa_2$-opioid receptors are described as binding sites typically labeled by the nonselective benzomorphan ligand $[^{3}\text{H}]\text{bremazocine}$ in the presence of $\mu$-, $\delta$-, and $\kappa_1$-opioid receptor blocking ligands.\(^{50}\) Simonin and colleagues\(^{50}\) investigated the genetic origin of $\kappa_2$-opioid receptors, using homogenate binding experiments with $[^{3}\text{H}]\text{bremazocine}$ in brains of single, double, triple knockout mice. They found that no additional gene is required to explain the total population of $[^{3}\text{H}]\text{bremazocine}$ binding sites. Altogether the data demonstrate that the putative $\kappa_2$-opioid receptors are in fact a mixed population of receptor proteins produced by the 3 known opioid receptor genes.\(^{50}\)

Findings in rodent experiments suggest that oxycodone is a partial $\kappa$-opioid receptor agonist.\(^{26,51-54}\) Nielsen and colleagues\(^{26}\) proposed that oxycodone is a putative $\kappa_{2\text{b}}$ agonist. In their study, rats pretreated with intracerebroventricular (ICV) nor-binaltorphimine ($\kappa$-antagonist) prevented ICV oxycodone but not morphine antinociception. The opposite was shown with naloxonazine (putative $\mu_1$ antagonist), suggesting an oxycodone analgesic effect mediated or modulated through $\kappa$-opioid receptor binding.\(^{26}\) Further, Nielsen and colleagues\(^{26}\) demonstrated that, in animals tolerant to intravenous morphine, there is an absence of antinociceptive cross-tolerance to ICV oxycodone. These investigators summarized that their findings provide support to the concept that oxycodone and morphine produce antinociception through distinctly different opioid receptor populations, that is, oxycodone seems to act as a $\kappa_{2\text{b}}$ opioid agonist with a relatively low affinity for the $\mu$-opioid receptor.

However, Nozaki and Kamei\(^{55}\) showed that the antinociceptive effect of subcutaneous oxycodone was completely antagonized by pretreatment with naloxonazine in both nondiabetic and diabetic mice. The selective $\kappa$-opioid receptor antagonist nor-binaltorphimine also antagonized oxycodone-induced antinociception in diabetic mice, but only had a partial effect in nondiabetic mice. Nozaki and Kamei\(^{55}\) allude that their findings suggest that, although oxycodone primarily interacts with $\mu_1$-opioid receptor, $\kappa$-opioid receptors are also strongly involved in oxycodone-induced antinociception.\(^{55}\) These studies imply a marked difference in the distribution of the putative $\kappa_2$ receptor subtypes and possibly an interaction with $\mu$ receptors at different sites.\(^{56}\)

In a recent review article by Gaveriaux-Ruff,\(^{57}\) entitled, “Opiate-induced analgesia: contributions from $\mu$-, $\delta$-, and $\kappa$-opioid receptors mouse mutants,” the author summarized the findings regarding $\kappa$-opioid receptor knockout mice, “Altogether, these findings indicate that $\mu$- and $\delta$-receptor proteins are necessary for the activity of $\kappa$-2 opioid agonists, substantiating the idea that $\kappa$-$\delta$ heterodimers may mediate $\kappa$-2 antinociceptive effects.”

The regulation of opioid receptor system function in peripheral sensory neurons is still not well-understood. Opioid agonist efficacy to inhibit nociceptor function and promote antinociception is generally weak under basal conditions and frequently no response occurs.\(^{58}\) However, after injury or inflammation, the functional competence of $\mu$-, $\delta$-, and $\kappa$-opioid receptor agonists to elicit antinociception via peripheral opioid receptors is increased markedly.\(^{39,59-62}\)

Reichert and colleagues\(^{63}\) found that the intraperitoneal application of low doses of opioids produced antinociception in the writhing model via peripheral mechanisms. The $\kappa$-opioids in animal models have been shown to reduce inflammation (colitis) nociceptive responses.\(^{36,64}\) The $\kappa$-receptor gene “knocked-out” mice display increasing writhes to acetic acid peritonitis compared with wild-type mice.\(^{65}\) The $\kappa$-opioid receptor agonists are particularly effective analgesics in experimental models of visceral pain.\(^{47}\) Their analgesic effects are mediated in the periphery.

Smith and colleagues\(^{66}\) investigated the analgesic efficacy and systemic exposure of oxycodone administered topically in a novel tocopheryl phosphate mixture gel.
formulation to the inflamed hindpaws in a rat model of inflammatory pain. Topical application of oxycodone in a novel tocopheryl phosphate mixture gel formulation to the inflamed hindpaws of Freund’s complete adjuvant rats produced marked antihyperalgesia at a dose that produced insignificant systemic exposure to oxycodone or its major metabolite, noroxycodone. Smith and colleagues believe their findings suggest that topically applied oxycodone interacts with upregulated opioid receptors expressed on peripheral nerve terminals in inflamed tissue, to produce localized pain relief.

Olesen and colleagues investigated the pharmacokinetic and pharmacodynamic profiles of oxycodone in a human experimental pain model of hyperalgesia. Twenty-four healthy subjects received oral oxycodone (15 mg) or placebo. Pharmacodynamics were assessed using a multimodal, multitissue paradigm where pain was assessed from skin (heat), muscle (pressure), and viscera (heat and electricity) where the induction of generalized hyperalgesia evoked by perfusion of acid and capsaicin in the esophagus. They found that there was a measurable effect of oxycodone, compared with placebo, on all pain measures, and a linear concentration–effect relationship without an effect delay was demonstrated. Olesen and colleagues concluded their findings indicate an initial peripheral analgesic effect of oxycodone on cutaneous, muscular, and visceral pain after the induction of hyperalgesia.

However, Lalovic and colleagues previously studied the pupil diameter and found delay for the measure of central analgesia. Staahl and colleagues demonstrated that visceral analgesia of oxycodone was more directly correlated with plasma concentrations than somatic analgesia. Olesen and colleagues hypothesized that the peripherally located opioid receptor is the κ-opioid receptor (assuming that oxycodone may interact with the κ-opioid receptor, as shown in animal studies). Although results from in vitro opioid receptor-binding studies have raised questions about the κ-opioid receptor-binding affinity of oxycodone, it has been shown that oxycodone interacts, at least in part, with a different population of opioid receptors or modulates μ-opioid receptor signaling in inflammation in a way that is subtly different from that of other opioids.

More recently, Olesen and colleagues conducted an investigation to compare the pharmacokinetic and pharmacodynamic profile of a novel peripherally selective κ-opioid agonist, CR665, with oxycodone in a randomized, placebo-controlled, double-blind, 3-way crossover study in healthy volunteers. They found that the oxycodone kinetics were best described by a 1-compartment model with transit compartment absorption feeding directly into the central compartment. For both drugs, the plasma concentration effects on visceral pain tolerance threshold were best fit by a direct linear model, that is, without the concentration–analgesia delay characteristic of brain-penetrant opioids. Olesen and colleagues conclude that their results are consistent with the peripheral selectivity of CR665, as well as the possibility that peripheral actions of oxycodone contribute to its visceral analgesic efficacy.

Lalovic and colleagues have demonstrated that the time course of central opioid effects of oxycodone can be explained by the pharmacokinetics–pharmacodynamics of the parent drug alone, not its metabolites. Klimas and colleagues have also demonstrated that oxycodone itself is responsible for the analgesic effect, despite its active metabolites oxymorphone and noroxymorphone having much higher μ-receptor affinity than oxycodone. The concentrations of the metabolites at the site of action (central nervous system) are too low.

**OXYCODONE AND ITS ACTIVE METABOLITES BINDING SITES**

Lalovic and colleagues have concluded that significant κ-receptor activity is unlikely based on the substantially lower affinity of oxycodone and other metabolites...
to κ-receptor in comparison with the μ-receptor.\textsuperscript{17} Their data clearly demonstrate the μ-receptor selectivity of oxycodone and all of its metabolites, as indicated by their nanomolar \(K_i\) values for the μ-receptor compared with that for the κ- and δ-opioid receptors, for example, the affinity of noroxymorphone and oxymorphone toward κ- and δ-receptors was more than 15-fold lower than that at the μ-opioid receptor.\textsuperscript{17} Kalso\textsuperscript{71} has concluded that oxycodone is a much weaker μ-receptor agonist (μ-receptor affinity 20 times less and the [35S]GTP\(\gamma\)S activity 3–8 times weaker, comparing to that of morphine) and has summarized that oxycodone binding to κ-receptor is unsubstantiated. He attributes the observed discrepancy of potency/efficacy of oxycodone versus morphine when given epidurally or spinally versus systemically to the production of active oxycodone metabolites, for example, oxymorphone.\textsuperscript{71}

Khotib and colleagues\textsuperscript{72} demonstrated that repeated stimulation of κ-opioid receptor markedly increased the functional μ- and δ-opioid receptors, whereas repeated stimulation of either the μ- or δ-opioid receptor had no direct effect on κ-opioidergic function in mice. It is unclear if, in humans, such unique synergy between different types opioid receptor exists to mediate or modulate biologic functions. If so, it may partially explain the need for stimulation of κ-receptor not only for κ-receptor activation itself, but also for enhanced response of μ- and δ-receptors, therefore enhancing analgesia. Finally, it seems that the κ-receptor activation is unique with oxycodone. Some research work with κ-receptor knockout mice has ruled out the participation of κ-receptors for analgesia induced by morphine\textsuperscript{65} and fentanyl.\textsuperscript{73} A study of human volunteers found that oxycodone significantly blocked visceral pain better than morphine, which has little kappa receptor activity.\textsuperscript{48}

There is no dispute on oxycodone being responsible for its own central opioid effects, not its metabolites. Lalovic and colleagues\textsuperscript{17} have demonstrated that the time course of central opioid effects of oxycodone can be explained by the pharmacokinetics–pharmacodynamics of the parent drug alone. Although it has been shown that the potent active metabolite noroxymorphone is present at relatively high concentrations in circulation, it does not seem to penetrate the BBB to a significant extent. Other metabolites either demonstrate low potency (noroxycodone and β-noroxycodol) or are present in circulation at very low levels (oxymorphone and α- and β-oxycodol). In addition, all metabolites demonstrate restricted brain penetration as compared with the parent drug.\textsuperscript{17} Nevertheless, peripheral opioid receptors are readily accessible. At this point, there seems to be no literature that has clearly defined the role played by the active metabolites of oxycodone via peripheral mechanism.

Recently, in a mouse model of bone cancer pain, Nakamura and colleagues\textsuperscript{74} showed that G protein activation induced by a μ-opioid receptor agonist was attenuated significantly less (9%–26%) than the effect of morphine (46%–65%) in the periaqueductal gray matter and the region ventral to it, and in mediodorsal thalamus. Furthermore, ICV oxycodone at doses of 0.02 to 1.0 mg per mouse clearly inhibited pain-related behaviors, whereas ICV morphine (0.05–2.0 mg per mouse) had only partial or little analgesic effect on pain-related behavior. Nakamura and colleagues suggest that the modulation of μ-opioid receptor function under bone cancer pain seems to be one of the mechanisms underlying the unique analgesic profile of oxycodone, that is, that modification of the μ-opioid receptor is responsible for the distinct analgesic effect of oxycodone and morphine.\textsuperscript{74} Unfortunately, at present, there are too few clinical or even experimental studies that systematically compare the effects of different opioids in different pain models to draw meaningful conclusions on this issue.\textsuperscript{2}

Recent evidence suggests that activation of these peripheral opioid receptors can contribute to analgesia produced by systemic opioid administration.\textsuperscript{75–77} Jagla and
colleagues demonstrated that selective blockade of peripheral opioid receptors by methylnaltrexone significantly increased patients’ demand for morphine (about 40%) after knee replacement surgery, implying peripheral opioid analgesia plays a significant role in postoperative overall opioid analgesia. It seems that some newly formulated oxycodone formulation with added peripheral opioid antagonist such as methylnaltrexone or naloxegol would be less likely to affect oxycodone analgesia comparing to that of morphine because of both NNX and naloxegol have high selectivity for μ-receptor, sparing κ-receptor.78,79 As a matter of fact, both methylnaltrexone and naloxegaol have partial agonist activity at κ-receptors and thus can activate κ-receptors.78,80

Methadone, a potent and efficacious opioid, has been shown to be dependent on peripheral opioid receptors to mediate or to modulate antinociception in both rat and mouse. He and colleagues81 demonstrated that naloxone methiodide, a peripherally restricted opioid antagonist, when administered subcutaneously, blocked the antinociception of systemically and centrally administered methadone, although it had no effect on blocking antinociception to centrally administered morphine. Further, centrally administered naloxone methiodide blocked the antinociception of centrally administered morphine, but not centrally administered methadone. All of these data strongly support that the peripheral opioid receptors play crucial role in methadone antinociception.81

The finding of He and colleagues81 suggest that the dominance of opioid analgesia by centrally located opioid receptors may not be equally shared by all opioids. Thus, in summary, we theorize that the central antinociceptive effect of oxycodone is primarily via its interaction with the μ-opioid receptor, while it engages in peripheral opioid analgesia through the interaction with primarily κ-receptors, but also μ-receptors, and possibly δ-receptors in the peripheral tissue, in a not well-understood interaction. We further hypothesize that the active metabolites of oxycodone, such as oxymorphone and noroxymorphone, may contribute analgesia through interaction with peripheral opioid receptors, primarily κ, but also μ in the peripheral tissues. Finally, we speculate that peripheral contribution of oxycodone and its active metabolites may be responsible for making up the difference of centrally mediated opioid response, observed in preclinical and clinical studies.

REFERENCES


