Review

Does the pharmacology of oxycodone justify its increasing use as an analgesic?

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Oxycodone is a semisynthetic opioid analgesic that is increasingly used for the treatment of acute, cancer, and chronic non-malignant pain. Oxycodone was synthesized in 1917 but its pharmacological properties were not thoroughly studied until recently. Oxycodone is a fairly selective μ-opioid receptor agonist, but there is a striking discrepancy between the relatively low binding potential and G protein activation by oxycodone and its analgesic efficacy. It has been claimed that this is because of active metabolites and enhanced passage to the central nervous system by active transport. We critically review studies on the basic pharmacology of oxycodone and on its pharmacokinetics and pharmacodynamics in humans. In particular, the role of pharmacogenomics and population pharmacokinetics in understanding the properties of oxycodone is discussed in detail. We compare oxycodone with morphine, the standard opioid in clinical use.

Origin of oxycodone

The clinical use of opioids and oxycodone in particular has significantly increased over the past few years [1]. Oxycodone and morphine have a very similar clinical profile regarding indications and available formulations. Morphine is an old and cheap drug that is considered the gold standard in the pharmacological management of moderate to severe pain. This review compares these two opioids and discusses their similarities and differences and how relevant these are in the clinical use.

Oxycodone is manufactured from thebaine, which is a minor constituent of opium. Thebaine itself may cause convulsions at high doses [2] and it cannot be used therapeutically. However, it can be converted into a variety of opioid compounds, such as oxycodone, oxymorphone, naloxone, and buprenorphine. The oxycodone (6-deoxy-7,8-dihydro-14-hydroxy-3-*O*-methyl-6-oxomorphine) molecule consists of two planar and two aliphatic rings and it contains four chiral centers; the maximum number of possible stereoisomers is 16.

Basic pharmacology of oxycodone

Receptor binding and activation of oxycodone and its metabolites

Like other clinically used opioids, such as morphine and fentanyl, oxycodone is a relatively selective μ-opioid receptor agonist (Table 1). However, depending on the assay properties, the affinity of oxycodone for the μ-opioid receptor is five to 40 times lower compared with morphine [3–5]. Because the binding affinity of oxycodone to δ- and κ-opioid receptors is also lower, the μ-opioid receptor selectivity is of the same order as for other clinically used opioids [3–5]. The potency of oxycodone in the μ-opioid-receptor-mediated activation of intracellular G proteins measured in the GTPγ[^{35}S] binding assay is four- to eightfold lower than the activity of morphine [3,4,6].

The μ-opioid receptor binding affinity of the primary metabolite of oxycodone, noroxycodone (Figure 1), is four times lower than that of oxycodone, and it produces four to six times lower G protein activation [3,6]. The other primary oxidative metabolite, oxymorphone, has an almost fiftyfold higher affinity for the μ-opioid receptor and can produce eight- to thirtyfold higher G protein activation than oxycodone [3,4,6]. The reduction products of oxymorphone, α- and β-oxymorphol, are two to three times more potent than oxycodone [3], but after oral administration of oxycodone in humans, plasma concentrations of α- and β-oxymorphol are low [3].

The stereoisomers of the primary reductive metabolite, α- and β-oxycodol, have significantly lower binding affinity for the μ-opioid receptor and very low potency [3]. Little is known about the activity of the stereoisomers of the reductive metabolite of noroxycodone, noroxycodol (α- and β-noroxycodol), which are found in significant amounts in humans after administration of oxycodone [3].

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Table 1. Binding (mean±SD) of oxycodone to μ-, δ-, and κ-opioid receptors

Tissue	K_i (nM)			Refs
	μ	δ	κ	
Rat brain membrane	18.0±4.2	958±499	677±326	[68]
Mouse brain membrane	17.8±1.4	1721±143	3490±1654	[69]

The most important secondary metabolite of oxycodone, noroxymorphone, has two- to threefold higher affinity for the μ-opioid receptor compared with oxycodone [3,5]. The potency of noroxymorphone for μ-opioid-receptor-mediated G protein activation is three- to sevenfold higher than that of oxycodone [3,6].

Some studies have suggested that the antinociceptive effect of oxycodone in rat or mouse is mediated via activation of κ-opioid receptors [5,7–10]. However, in most experimental settings, the antinociceptive effect of oxycodone can be reversed with selective μ-opioid receptor antagonists, such as β-funaltrexamine, but not by selective κ-opioid antagonists [11–13].

Regional differences in oxycodone-induced G protein activation

Activation of opioid receptors by their agonists can vary in different regions of the central nervous system (CNS). Oxycodone, like other μ-opioid receptor agonists, is most effective in the thalamus compared with the cortex and spinal cord (Table 2). Interestingly, opioid-induced G protein activation can change in disease states, and there may be important differences between opioids. In a mouse model of bone cancer pain, G protein activation induced by a μ-opioid receptor agonist was significantly reduced in different CNS regions relevant for pain processing [14]. Oxycodone-induced G protein activation was attenuated significantly less (9–26%) than the effect of morphine (46–65%) in the periaqueductal grey matter and the region ventral to it, and in mediodorsal thalamus. In the ventral thalamus, there was no decrease in G protein activation for either opioid, whereas in the ipsilateral spinal cord oxycodone-induced G protein activation was attenuated from 47% to 32%. The corresponding reduction for morphine was from 85% to 39%. These differences could be important in explaining variations in the efficacy of different opioids in pain states with different pathogenesis. Unfortunately, at present there are too few clinical or even experimental studies that systematically compare effects of different opioids in different pain models to draw conclusions on this issue.

Efficacy of oxycodone and its metabolites after different routes of administration

In models of acute nociception, the administration route for oxycodone is important. After systemic administration in

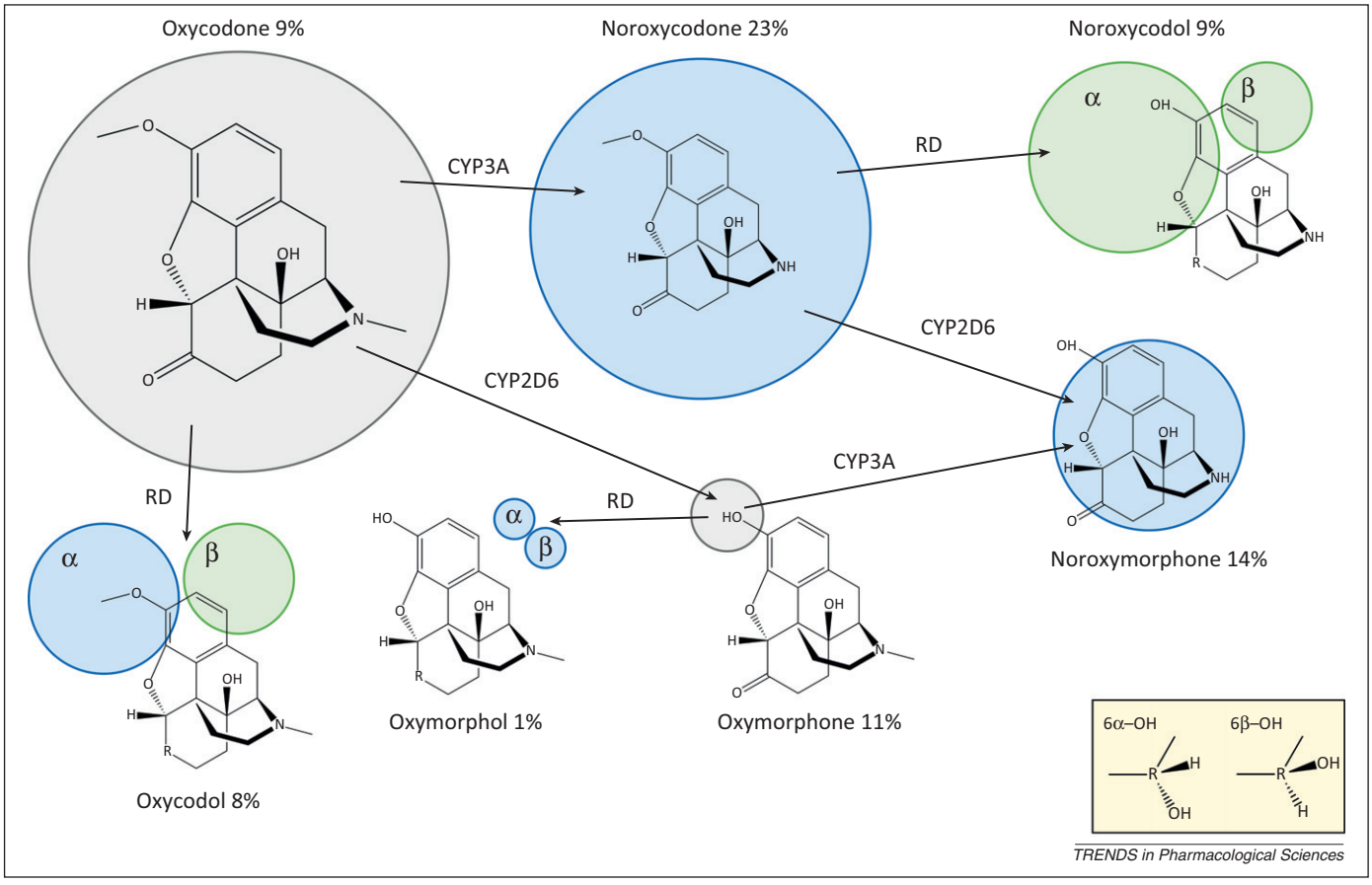

Figure 1. Metabolism of oral oxycodone. The size of the circles illustrates the maximum concentration (C_{max}) of each metabolite and their color represents the timing of the peak (t_{max}: gray, <1.5 h; blue, 1.5–2.5 h; green, >2.5 h). Ketone reduction of oxycodone (RD) produces two metabolites that are stereoisomers (6α - and 6β-epimers; see yellow box). The letter R shows the location of the 6′ carbon in the formulas. The epimers of the reduced metabolites are indicated by α and β. The percentage values after the names of the molecules indicate the amount of metabolites excreted to urine as a percentage of the oxycodone dose. Data are based on the pharmacokinetic values reported by Lalovic *et al.* [3].

Table 2. Maximal (10 μM) opioid agonist-stimulated GTPγ[^{35}S] binding in dog membrane homogenates

	Stimulation of binding over baseline (%)[a]		
	Cortex	Thalamus	Spinal cord
DAMGO	28.5±2.3	66.3±6.3	26.7±3.9
Morphine	23.0±3.7	36.5±1.5	10.3±1.5
Oxycodone	2±0.7	13±1.3	7±1.6
Oxymorphone	13.4±1.2	33.8±1.3	11.3±2.5

[a]Values are mean±SD. Modified from [70].

rodent models of acute nociception, oxycodone is two- to fourfold more potent or at least equipotent to morphine [4,5,11]. After central (intrathecal or intracerebroventricular) administration, oxycodone is significantly less potent compared with morphine [5,15].

Noroxycodone has a poor antinociceptive effect compared with oxycodone after oral, subcutaneous, and intracerebroventricular administration in mice and rats [5]. Oxymorphone-induced antinociceptive effects have been well characterized in mice and rats [5,16], and oxymorphone is used in veterinary medicine. Oxymorphone has also shown significant analgesia in humans [5] and it has been available for clinical use in the USA since the 1950s. Noroxymorphone produces long-lasting antinociceptive effects after intrathecal administration in rats, whereas it has no antinociceptive effect after subcutaneous administration [17]. The lack of systemic efficacy may indicate low penetration of noroxymorphone to the CNS through the blood–brain barrier (BBB) because of its low lipophilicity.

Oxycodone in different animal models of nociception

In the rat carrageenan model of acute inflammatory pain, oxycodone has a potent antihyperalgesic effect [17]. In the formalin-induced inflammation model in rats, oxycodone is more potent than morphine [18]. In a model of arthritis induced by Freund's complete adjuvant, the potency of oxycodone was increased compared to the non-inflamed state in male but not female rats [19]. Noroxymorphone was ineffective in the carrageenan model after subcutaneous administration in rats. In mice and rats with neuropathic pain in a streptozocin-induced diabetes model and a sciatic nerve ligation model, oxycodone has a more effective antihyperalgesic or antiallodynic effect than morphine [8–10,13,15,20]. There was no difference in the G protein activation induced by oxycodone and morphine, measured as GTPγ[^{35}S] binding, between mice with sciatic nerve ligation in a model of neuropathic pain and control animals [13].

On the basis of studies in opioid receptor knockout mice [21] and comparison of the effects of κ-opioid receptor agonist with μ- and δ-opioid receptor agonists in visceral pain models [21–23], it is assumed that κ-opioid receptors are important in visceral pain. In a mouse model of bone cancer pain, intracerebroventricular oxycodone inhibited pain-related behaviors, whereas comparable doses of morphine had only a partial analgesic effect [14]. The seemingly increased efficacy of oxycodone compared to morphine in models of inflammatory and neuropathic pain could be because of changes in the transport of oxycodone to the CNS.

Pharmacokinetics

Oxycodone is relatively well absorbed after oral administration, and modern commercially available formulations have a bioavailability of 60–80%, which clearly exceeds the bioavailability of morphine (Table 3). The sublingual bioavailability of oxycodone is less than 20% at normal pH [24]. The mean bioavailability of intranasal oxycodone is 46% but there is wide interindividual variability from 16% to 100% [25].

Approximately 40% of oxycodone is bound to plasma proteins *in vitro*, which is similar to the binding of morphine [5]. The distribution volume at steady state is 2–5 l/kg in adults, which is comparable to that of morphine. Approximately 99% of oxycodone is located outside the plasma compartment. Total plasma clearance of oxycodone in adults is 0.7–1 l/min, which is consistent with intermediate hepatic extraction and a moderate first-pass effect. The elimination half-life of oxycodone is typically 3–6 h [26,27].

There is no information on the distribution of oxycodone in the human brain, but in sheep, oxycodone has a sevenfold higher permeability across the BBB than morphine, as well as a higher cerebral distribution volume. The equilibration half-time for brain/blood was 7.2 min, which is considerably longer than that observed for alfentanil (0.8 min) but shorter than for morphine (10.3 min) [28]. In rats, the brain/plasma ratio is 2.1, which is consistent with the cerebral accumulation of oxycodone [3]. P-Glycoprotein is a transmembrane efflux transporter that limits the absorption of its substrates through the BBB. Opioids such as morphine and methadone have been identified as substrates of P-glycoprotein [29,30] but the role of P-glycoprotein in the cerebral distribution of oxycodone is highly controversial. Boström *et al.* suggested that P-glycoprotein has no role in the regulation of the BBB permeability of oxycodone in rats [31]. However, it was later demonstrated that oxycodone is a substrate for P-glycoprotein in rats, but there is no information on its possible role in humans [32]. It has been suggested that the cerebral accumulation of oxycodone is due to an active influx transporter [33]. In rats, BBB transport of oxycodone is at least partly mediated by a common transporter with pyrilamine, a putative organic cation transporter [34]. This organic cation transporter can be inhibited *in vitro* by many antidepressants, such as amitriptyline, imipramine, and fluvoxamine, as well as an intravenous anesthetic, ketamine. However, the inhibition does not occur at pharmacologically relevant concentrations *in vivo* [35].

Because some of the metabolites of oxycodone are pharmacologically active, detailed information on the human metabolism of oxycodone is important for evaluating the possible role of metabolites in the pharmacological action of oxycodone. Lalovic *et al.* studied the metabolism of oral oxycodone in healthy volunteers and quantified the concentrations of oxycodone and its oxidative (noroxycodone, oxymorphone, and noroxymorphone) and reductive (α- and β-oxycodol, α- and β-noroxycodol, and α- and β-oxymorphol) metabolites in plasma and in urine (Figure 1) [3]. Reduced metabolites account for approximately 18% of the dose in urine, whereas oxidative metabolites account for 47%. Some 9% is excreted as unchanged oxycodone,

Table 3. Pharmacokinetic properties of oxycodone compared to the most commonly clinically used opioid, morphine

	Oxycodone [3,27,39,71–73]	Morphine [74]
Clearance (ml/min/kg)	10–15	15–30
Volume of distribution at steady state (l/kg)	2–4	3–5
Elimination half-life (h)	3–5	2–4
Oral bioavailability (%)	60–80	15–40
Peak concentration time after oral administration (h)	1–2 (capsule) 0.5–1.5 (oral solution)	0.5–1.5 (oral solution)
Plasma/effect site equilibrium half-time, based on pupil size (min)	11	170
Protein binding (%)	45	30–40
Excreted unchanged (%)	<10	<10
Primary metabolic pathways	CYP450 3A4, CYP450 2D6	Conjugation with glucuronic acid

mainly in unconjugated form. Urinary metabolites from cytochrome P450 3A (CYP3A)-mediated *N*-demethylation of oxycodone are responsible for approximately 45% of the dose, whereas the CYP2D6-mediated *O*-demethylation pathway accounts for 11% and 6-keto-reduction to α- and β-oxycodol for 8% of the dose.

Metabolites identified in urine account for some 72% of the oral dose. There is no information on whether the rest of the dose is excreted via unidentified metabolic or excretory pathways or whether the missing 28% is due to incomplete gastrointestinal absorption. It has been suggested that oxycodone *N*-oxide could be one of the unidentified metabolites. However, *N*-oxide metabolites have been identified in overdose and abuse patients in just one study [36], and other research groups have not been able to measure oxycodone *N*-oxides in urine.

Patient-related factors affecting pharmacokinetics

Age

In addition to healthy adults, the pharmacokinetics of oxycodone has been studied in infants, children, and the elderly. Children aged 0.5–8 years appear to have approximately 20–40% higher values for plasma clearance than adults when expressed as milliliters per body weight [5,37–39]. Because the distribution volume is somewhat smaller in children than in adults, it is plausible that the average elimination half-life is also shorter in children. Newborn infants younger than 1 week have significantly lower oxycodone plasma clearance, and they typically also have a marked variation in pharmacokinetics [40]. The metabolism of oxycodone matures early, and oxycodone clearance approaches adult values in many infants within the first months of life when expressed per kilogram body weight. The distribution volume in infants is relatively stable in all age groups and it similar to values observed in older children and adults.

The maternal pharmacokinetics of intravenous oxycodone and neonatal exposure have also been studied recently [41]. Because the distribution volume was lower and the clearance higher than observed earlier in non-pregnant patients, the mean elimination half-life of intravenous oxycodone of 2.6 h in laboring women was shorter than in non-pregnant patients (Table 3). The maternal plasma oxycodone concentration at birth was similar to that in the umbilical venous and arterial plasma, which means that maternal concentrations can be used to estimate fetal exposure. The neonatal outcome was similar in neonates whose mothers had been given oxycodone in early labor and in the control group, which indicates that oxycodone may be used relatively safely in laboring women.

During oral administration of oxycodone, patients aged 70–90 years have, on average, 50–80% greater exposure to oxycodone than patients aged 20–40 years, mainly because of decreased plasma clearance. Changes in oxycodone clearance are also reflected in the elimination half-life, which was prolonged by up to 50% in patients older than 70 years [26]. Differences in oxycodone pharmacokinetics are also obvious following intravenous administration. Because patients aged 60–90 years have, on average, 30–40% lower clearance of oxycodone than young adults, they also have significantly higher exposure to oxycodone [27].

Liver dysfunction

Because oxycodone is eliminated mainly by metabolism, hepatic dysfunction clearly impairs its elimination. Plasma clearance of oxycodone is decreased by 75% and the distribution volume at steady state increased by 50% in patients with severe hepatic dysfunction. These changes increase the mean elimination half-life from 3 to 14 h [5].

Renal dysfunction

Although less than 10% of oxycodone is excreted unchanged in urine, renal failure delays the elimination of oxycodone. Delayed elimination is mainly due to an increase in distribution volume. Following oral administration, exposure to oxycodone may be increased by up to 60% (Oxycontin prescribing information, http://app.purduepharma.com/xmlpublishing/pi.aspx?id=o). Assessment of the effect of pure renal failure on oxycodone pharmacokinetics is difficult because many patients have co-morbidities requiring drug therapy affecting the metabolism of oxycodone.

Effect of *CYP2D6* genotype on oxycodone pharmacokinetics and pharmacodynamics

CYP2D6 is a crucial and highly polymorphic enzyme involved in the biotransformation of numerous clinically important drugs. Inactivating polymorphisms caused by gene mutations and deletion(s) result in a non-functional enzyme, whereas gene duplication(s) cause overexpression of active enzyme. Consequently, poor, intermediate, extensive, and ultrarapid metabolizer phenotypes are observed

in a population when challenged with a probe substrate [42,43]. Interestingly, the clinical significance of CYP2D6 polymorphism on the analgesic efficacy of oxycodone is somewhat controversial. Two experimental pain studies suggest that oxycodone analgesia is dependent on *CYP2D6* genotype and the production of oxymorphone. Zwisler *et al*. studied the effect of CYP2D6 polymorphism on the pharmacokinetics and hypoalgesic effect of oxycodone in 33 healthy volunteers using sural nerve stimulation [44]. Because poor metabolizers with reduced CYP2D6 function experienced a lower analgesic effect than extensive metabolizers in three out of five pain tests, the authors concluded that oxycodone analgesia depends on both oxycodone and its metabolite oxymorphone. These results were supported by another experimental study in 10 volunteers [45]. However, this study was underpowered for detection of differences between *CYP2D6* genotypes, because only one of the volunteers was a poor metabolizer.

By contrast, there is overwhelming evidence demonstrating that *CYP2D6* genotype is of minor if any significance for oxycodone analgesia [46–48], and the parent drug seems to be responsible for the analgesic effects of oxycodone. In experimental studies, oxymorphone concentrations have been low or below the limit of quantification and there has been no association between oxymorphone concentrations and the behavioral, miotic, or hypoalgesic effects observed [3,5,39]. The lack of effect of *CYP2D6* genotype on oxycodone analgesia has also been confirmed in acute postoperative pain and cancer pain. Although *CYP2D6* genotype is associated with the formation of oxymorphone in both postoperative and cancer patients, these pharmacokinetic changes are not associated with differences in pain control or the risk of adverse effects [46–48].

Effect of concomitant drug therapy

The involvement of CYP enzymes in the metabolism of oxycodone makes it prone to drug interactions. Because oxycodone is mainly metabolized via CYP3A enzymes, it is not surprising that inhibitors and inducers of CYP3A enzymes have a major impact on oxycodone elimination. According to studies in healthy volunteers, strong inhibitors of CYP3A enzymes (e.g., ritonavir and voriconazole) are likely to increase exposure to oral oxycodone by 200–300%, as quantified by the area under the oxycodone concentration–time curve [49,50]. An interaction of this magnitude is no doubt of clinical significance and necessitates careful titration of the oxycodone dose. Inhibition of CYP2D6 has a negligible effect on oxycodone pharmacokinetics of, but the effect may be more pronounced when CYP3A is inhibited [45]. Induction of CYP3A by St John's wort [51] or rifampicin [39] reduces exposure to oxycodone by 50% or 85%, respectively (Figure 2).

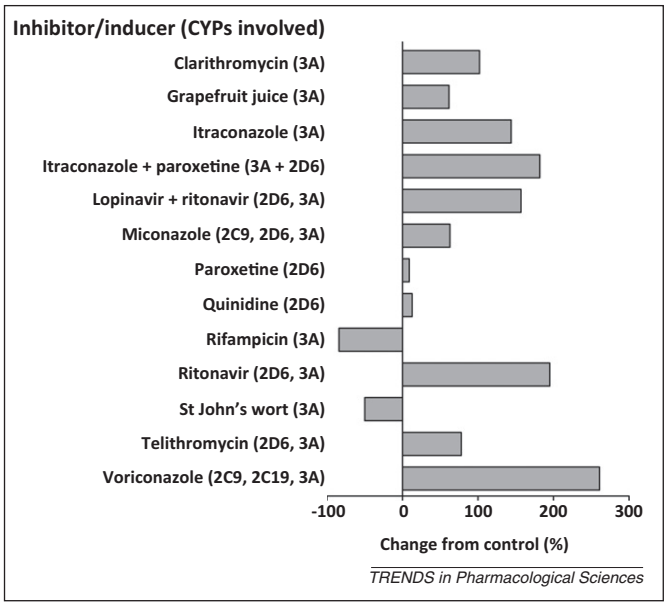

Figure 2. Change in the mean area under the concentration–time curve for oral oxycodone after concomitant administration with clarithromycin [75], grapefruit juice [76], itraconazole [77], itraconazole + paroxetine [78], lopinavir + ritonavir [50], miconazole [79], paroxetine [78], quinidine [80], rifampicin [39], ritonavir [50], St John's wort [51], telithromycin [81], or voriconazole [49]. All studies were performed in healthy volunteers in a crossover manner.

Has population pharmacokinetics revealed anything new about oxycodone?

Prediction of the time course of drug concentrations and effects in an individual patient is the ultimate goal of clinical pharmacology. Population-based modeling uses nonlinear mixed-effect modeling to identify and model variability in drug concentrations or pharmacological effects between individuals (Figure 3) [52]. Unexplained inter- and intraindividual variability can be modeled even when the data collection design varies considerably between individuals. Parameter estimates can be obtained for individuals for whom there are too few observations to allow parameter estimation by standard methods [52]. The population approach is useful for rationalizing drug development and for developing optimal dosing strategies for specific patient groups that cannot be studied otherwise (e.g., intensive care patients and infants) [53].

El-Tahtawy *et al*. constructed a population model of oxycodone pharmacokinetics after a single dose in children aged 6 months to 7 years undergoing surgery under general anesthesia [54]. The study used pooled data after oral, buccal, intravenous, and intramuscular dosing. Patient weight had a significant influence on both elimination clearance and central distribution volume, and most of the interindividual variance in drug exposure could be explained using allometric scaling. In allometric scaling, the population value of the parameter is described as a function of individual body weight normalized by a reference weight and raised to a power, which can be estimated or fixed to a typical value of 0.75. The median weight of the population is commonly used as the reference weight. A population approach was also recently used to develop a pharmacokinetic model for a single intravenous dose in an adult population of orthopedic surgery patients and healthy volunteers. Some 1272 samples from 77 individuals were analyzed [55]. A two-compartment linear model was used to describe oxycodone pharmacokinetics in the study population. Lean body mass and age were significant covariates for elimination clearance and the central compartment volume. The elimination half-life of oxycodone increased with age and the context-sensitive half-time at

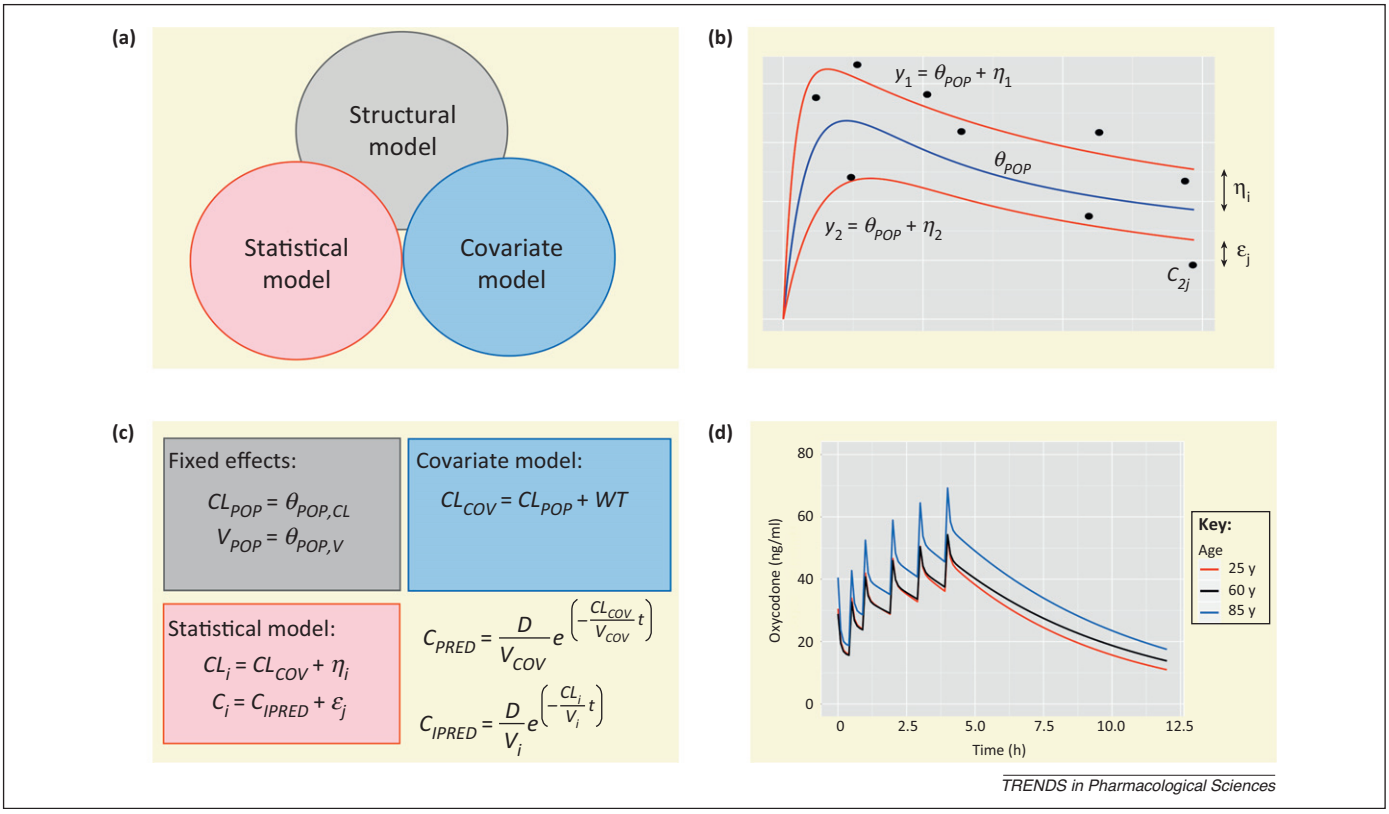

Figure 3. Principles of population modeling. **(a)** Population models have several components: structural models, stochastic models, and covariate models. Structural models consist of functions that describe the time course of a measured response (e.g., concentrations). Stochastic models describe the variability in the observed data, and covariate models the influence of factors such as biometric data or disease on the individual time course of the response. **(b)** Consider a pharmacokinetic study with two subjects (red lines), each of whom is administered a single intravenous dose. Population models usually have fixed and random-effect parameters, and are therefore called mixed-effect models. Structural models (blue line) present fixed effects by parameters (θ_{POP}) that have the same value for every subject. Each subject (i) is described by unique parameter values (y_i). Random effects (η_i) account for the difference between an individual's parameter value and the population value. A residual or unexplained error (ε_{ij}) describes the difference between the observed data for an individual (C_{ij}) and the model prediction for each measurement (j). **(c)** In this population, a one-compartment model is used to describe the pharmacokinetics. The covariate model shows that clearance (CL_{POP}) scales linearly with body weight (WT), which explains the variability in this parameter attributable to body size. The statistical model adds the influence of random effects and residual errors. The model equations are used to calculate the population (C_{PRED}) and individual (C_{IPRED}) predicted concentrations. For further reference, see a recent review by Mould and Upton [52]. **(d)** Population models can be utilized to simulate scenarios after clinically relevant dosing schemes. The figure shows the effect of age on the simulated concentration–time course of oxycodone after intravenous bolus dosing (redrawn from [55]).

steady state increased from 3.8 h at 25 years to 4.6 h at 85 years. Simulations of repetitive bolus dosing showed a 20% increase in oxycodone concentrations in the elderly. Population values for the pharmacokinetic parameters in this study were comparable to the pediatric study [54], with elimination clearance (standardized to a 70-kg person using allometric scaling) values of 51.0 and 55.3 l/h, respectively.

Population pharmacokinetics of oral oxycodone has been evaluated in two studies. The first of these evaluated the pharmacokinetics of immediate-release (IR) and controlled-release (CR) oxycodone after oral dosing in healthy volunteers [56]. The absorption profile for the IR formulation was modeled using a lag time, whereas the profile for CR oxycodone was best described using a bi-exponential absorption model. The elimination pharmacokinetics of oxycodone was further described using a one-compartment model. Staahl *et al*. reported consistent results for IR oxycodone in a volunteer study [57]. The oxycodone pharmacokinetic–pharmacodynamic relationship was investigated in this study using a multimodal pain model. For somatic pain, a linear concentration–effect relationship was found using an effect–compartment link to represent the concentration–analgesia delay, whereas alleviation of visceral pain was well correlated to plasma concentrations of oxycodone [57].

There is no evidence that gender would have any effect on the pharmacokinetics of oxycodone in humans [54,55].

Clinical use of oxycodone

Opioids are used to alleviate both acute and chronic pain. Opioids are considered very effective in acute pain and approximately 85% of cancer patients achieve adequate pain relief with opioids if adverse effects are effectively taken care of. In chronic non-cancer pain, opioids are less efficacious because adverse effects impair both physical and cognitive functioning and prevent dose escalation. The most common adverse effects of opioids in acute pain relief are respiratory depression if dose titration is not appropriately balanced against pain, nausea, constipation, urinary retention, sedation, and itching. In chronic use, constipation is a major problem in approximately 40% of the patients, followed by nausea and somnolence. With the increased use of opioids in chronic pain prescription, opioid abuse, endocrinological adverse effects, and concerns about the immunological effects of opioids have emerged.

Opioids are often used in combination with nonsteroidal anti-inflammatory analgesics in acute and chronic inflammatory pain and sometimes with gabapentinoids in neuropathic pain. Most preclinical studies have been performed with morphine, and it has been assumed that opioids are also comparable in clinical use apart from significant pharmacokinetic differences. Very few clinical studies have compared different opioids in large randomized and controlled trials. We compare oxycodone with morphine, the standard opioid in clinical use.

Acute pain

Oxycodone has been used for decades in perioperative medicine in some countries (e.g., Finland), whereas its use for acute pain management is currently being introduced worldwide. Compared with morphine (average 35 mg), less intravenous oxycodone (average 22 mg) was needed to achieve similar analgesia during a 2-h titration after abdominal surgery [5]. In addition, satisfactory analgesia was achieved faster and with less sedation with oxycodone compared to morphine. Lenz *et al*. reported similar results for hysterectomies [58]. These clinical trials and the fact that the brain–plasma equilibrium is achieved significantly faster with oxycodone than with morphine indicates that oxycodone is more favorable than morphine in rapid intravenous analgesic titration. Oxycodone also releases significantly less histamine than morphine, whereas fentanyl does not release any histamine [59].

Oxycodone can be administered orally for postoperative analgesia with some benefits over intravenous patient-controlled oxycodone, such as less nausea and faster analgesic discontinuation [60]. The clinical evidence supports the notion that epidural oxycodone is no more effective that intravenous oxycodone [5]. The epidural dose of oxycodone required was approximately ten times higher than that of morphine to achieve the same analgesic effect. These data also agree with results from preclinical studies [5,61].

Cancer pain

Oxycodone was first used for cancer pain management as an oral solution in the late 1980s [5]. Since the introduction of CR oxycodone tablets, the drug has become a major asset in cancer pain management [5]. Small crossover studies suggested that oxycodone might cause less nausea and hallucinations than morphine [62]. Recent systematic reviews, however, suggest that oral morphine, oxycodone, and hydromorphone have similar efficacy and toxicity in cancer patients [63]. Individual differences are probably due to pharmacokinetic factors. The average equianalgesic dose of oral oxycodone is 67% that of morphine.

In addition to oral administration, oxycodone can be administered as a subcutaneous infusion to manage cancer pain and dyspnea.

Visceral pain

It has been suggested that oxycodone is more effective than morphine in visceral pain because κ-opioid receptors are involved in the regulation of visceral pain and oxycodone was erroneously identified as a κ-opioid receptor agonist [5]. Staahl *et al*. performed an interesting study in which they used oral morphine (30 mg) and oxycodone (15 mg) in a human experimental pain model [64]. The two opioids showed similar efficacy in pain modulation when skin and muscles were stimulated, but oxycodone produced somewhat better analgesia when the esophagus was stimulated. However, in a second volunteer study by the same group, there were no differences in the potency of oxycodone and morphine [57]. Oxycodone and morphine provided similar analgesia in pancreatic cancer pain [65].

Chronic non-malignant pain

The use of opioids in chronic non-malignant pain has increased dramatically over the past 20 years, particularly in the USA and Australia. This trend was started by aggressive marketing of CR oxycodone. Ill-considered prescribing of opioids and consequent problems such as opioid intoxication and mortality due to too high doses and diversion of prescription opioids have mainly been observed for oxycodone. It is not clear whether this is entirely due to increased marketing or whether oxycodone is more addictive than morphine based on the pharmacological differences discussed above.

CR oxycodone has been studied in randomized and controlled studies (RCTs) mostly for osteoarthirits-related and neuropathic pain [66,67]. The average effective and tolerated dose in both conditions was 40 mg/day. These trials have been fairly short (4–6 weeks), and the drop-out rate due to adverse effects has been approximately 30%. In long-term follow-up studies, more than half of the patients stop the treatment because of adverse effects or a lack of efficacy. There are no head-to-head comparisons of oxycodone and morphine in either osteoarthritis or neuropathic pain.

Opioids are considered as second-line treatment for neuropathic pain. Most evidence on the efficacy of opioids in neuropathic pain is based on RCTs in diabetic polyneuropathy and postherpetic neuralgia.

Concluding remarks

Our current understanding of the pharmacology of oxycodone does not explain the significant increase in its clinical use. However, it is important to have alternative opioids to improve personalized patient care.

Oxycodone has many similarities to morphine, but it has also properties that set it apart from morphine. It has a faster onset of action, which is likely to be related to its cerebral accumulation and possible active influx transport through the BBB. Unlike morphine, it has good oral bioavailability and a longer duration of action and it may have somewhat less side effects than morphine. Unlike morphine, oxycodone is mainly metabolized by CYP enzymes, so it is more prone to drug interactions compared with morphine. Many problems, such as addiction and increased incidence of fatal intoxication, associated with inappropriate prescribing of opioids have been related to oxycodone. It is not known whether this is because of real pharmacological differences between oxycodone and other opioids.

Although we have learnt a lot about the pharmacology of oxycodone during the past few years, there are still

unanswered questions. 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 or how morphine and oxycodone differ in secondary messenger signaling, glial activation, and immunological effects, and how these differences are affected by diseases causing pain.

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