Published in final edited form as:

Addict Biol. 2016 January ; 21(1): 146–158. doi:10.1111/adb.12173.

Pharmacodynamic effects of oral oxymorphone: Abuse liability, analgesic profile and direct physiological effects in humans

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Abstract

Oxymorphone is a semisynthetic μ -opioid agonist, marketed as a prescription analgesic purported to be twice as potent as oxycodone for pain relief. Oral formulations of oxymorphone were re-introduced in the United States in 2006 and reports of abuse ensued; however, there are limited data available on its pharmacodynamic effects. The current study aimed to examine the direct physiological effects, relative abuse liability, analgesic profile, and overall pharmacodynamic potency of oxymorphone in comparison to identical doses of oxycodone. Healthy, non-dependent opioid abusers ($n=9$) were enrolled in this within-subject, double-blind, placebo-controlled, 3-week inpatient study. Seven experimental sessions (6.5 hr) were conducted, during which an oral dose of immediate-release formulations of oxymorphone (10, 20, 40 mg), oxycodone (10, 20, 40 mg) or placebo was administered. An array of physiological, abuse liability and experimental pain measures was collected. At identical doses, oxymorphone produced approximately two-fold less potent effects on miosis, compared to oxycodone. Oxymorphone also produced lesser magnitude effects on measures of respiratory depression, two experimental pain models, and observer-rated agonist effects. However, 40 mg of oxymorphone was similar to 40 mg of oxycodone on several abuse-related subjective ratings. Formal relative potency analyses were largely invalid due to the substantially greater effects of oxycodone. Overall, oxymorphone is less potent on most pharmacodynamic measures, although at higher doses, its abuse liability is similar to oxycodone. These data suggest that the published clinical equianalgesic estimates may not be consistent with the observed direct physiological effects of opioids, results of experimental pain models or abuse liability measures, as assessed in the human laboratory.

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Author Contributions

Shanna Babalonis, Michelle Lofwall and Sharon Walsh were responsible for the study concept and design. Shanna Babalonis directly supervised the conduct of the study, interviewed and consented the participants, directed the statistical analyses and wrote the manuscript. Michelle Lofwall conducted medical interviews and physical examinations, reviewed laboratory results, provided medical coverage and edited the manuscript. Paul Nuzzo trained the staff, provided technical support services, supervised daily operations and conducted the statistical analyses. Sharon Walsh supervised the conduct of the study, statistical analyses and interpretation of the data. Sharon Walsh, Michelle Lofwall and Paul Nuzzo provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

Keywords

abuse liability; cold pressor; experimental pain models; oxycodone; oxymorphone; pressure algometer

INTRODUCTION

Oxymorphone (14-hydroxydihydromorphinone) is a semisynthetic μ -opioid agonist, structurally similar to oxycodone and hydromorphone, which displays a very high degree of μ -opioid receptor specificity and intrinsic activity (Metzger et al., 2001; Volpe et al., 2011; Carliss et al., 2009). Oxymorphone is currently marketed in the United States (U.S.) as a prescription analgesic for the treatment of moderate-to-severe pain. Oxymorphone has a long history as an effective analgesic for anesthesia preparations and for the treatment of cancer-related pain (Beaver et al., 1977a, 1977b; Ciliberti and Eddy, 1961; Coblenz and Bierman, 1956; Eddy, et al., 1959). Oxymorphone was first approved by the U.S. Food and Drug Administration in 1959, with oral, rectal and parenteral formulations marketed under the trade name Numorphan®. However, in the late 1970s, the drug manufacturer, Endo Pharmaceuticals, voluntarily removed the oral product from the market citing commercial reasons (FDA, Center for Drug Evaluation and Research, 2006), although there were indications that it was being readily abused, particularly via IV injection, prior to its removal (Watkins & Chambers, 1972). After many years of absence from the U.S. market, the manufacturer reintroduced the oral formulation in 2006 as both immediate- and extended-release products under a new trade name (Opana®, Opana ER®).

In the years surrounding this reintroduction, several clinical trials, supported by the pharmaceutical sponsor, were conducted to assess the analgesic efficacy of the newly formulated oral products for cancer-related and non-cancer pain (i.e., chronic lower back pain, osteoarthritis, postoperative pain) (Aqua et al., 2007; Gabrail et al., 2004; Gimbel et al., 2004; 2005; Hale et al., 2005; 2007; Rauck et al., 2008; Sloan et al., 2005). These studies concluded that oral oxymorphone was safe and effective in the management of acute and chronic pain and oxymorphone-induced analgesia was comparable to standard therapeutic doses of oxycodone. Several of these studies, along with proprietary information held by the drug company, also helped establish the published relative analgesic potency and equianalgesic conversion ratios of oral oxymorphone, which state that oral oxymorphone is twice as potent as oral oxycodone and three times as potent as oral morphine for the treatment of pain (Gabrail et al., 2004; Hale et al., 2005; Endo Pharmaceuticals, 2010).

Although the analgesic effects of oxymorphone are well established, the abuse liability of oxymorphone has not been extensively examined. Schoedel and colleagues (2010, 2011) compared the behavioral effects of controlled-release formulations of oral oxymorphone (15, 30 mg ER) to oral oxycodone (30, 60 mg CR) in a single human laboratory study. This study, also industry-sponsored, reported that oxymorphone produced less cognitive and psychomotor impairment, decreased reports of sedation, as well as lower ratings of abuse-related subjective effects (e.g., drug liking, high and street value) and fewer aversive effects (e.g., ratings of bad drug effects, nausea and dysphoria) relative to the comparator doses of

oxycodone. Importantly, the oxycodone comparator doses were two-fold higher than doses of oxymorphone, selected based on the analgesic equivalency tables; however, examination of several outcome measures clearly indicate that equipotent doses of oxymorphone and oxycodone were not compared. For example, oxycodone doses produced greater pupil constriction (a measure particularly sensitive to μ -opioid receptor activation) than any test dose of oxymorphone, suggesting that oxycodone was substantially more potent than the oxymorphone, thereby limiting the conclusions drawn regarding the relative abuse liability of oxymorphone.

As oral oxymorphone prescribing and availability has increased over the past several years, rates of diversion, abuse, and overdose deaths involving oxymorphone have also increased (Butler et al., 2013; Crum et al., 2013; Garside et al., 2009; McIntyre et al., 2009). Given these public health harms and the relative dearth of controlled studies on the abuse-related effects of oxymorphone, further evaluation of oxymorphone is warranted. Thus, the objectives of this study were 1) to examine the relative abuse liability and potency of oxymorphone compared to oxycodone employing a broad array of pharmacodynamic outcomes and 2) to determine simultaneously the analgesic response to both drugs using two experimental pain models in a population of prescription opioid abusers.

METHODS

Participants

Participants were healthy, adult prescription opioid abusers who were not physically dependent on opioids. All participants completed in-person screening evaluations that included substance use and psychiatric assessments, medical history and physical exam, blood chemistry, urinalysis, and ECG. Participants were required to be literate, English-speaking adults ages 18–50 with current non-medical opioid use (confirmed by an opioid-positive observed urine sample and self-report of recreational opioid use on average of 1–2 times per week). Participants were required to provide an opioid-negative observed urine sample in the absence of opioid withdrawal symptoms in order to exclude those with physiological opioid dependence. Other exclusion criteria included desire for treatment, successfully maintaining abstinence, current physiological drug dependence requiring medical intervention, pregnancy, significant medical or psychiatric problems (e.g., seizure disorder, chronic pain, suicidality) and insensitivity or inability to tolerate the experimental pain procedures. All participants provided sober, written informed consent prior to participation and were paid for their participation. The study was approved by the University of Kentucky Institutional Review Board and was conducted in accordance with the Helsinki guidelines for ethical research. A Certificate of Confidentiality was obtained from the National Institute on Drug Abuse.

Drugs

This study was conducted under an investigator-initiated Investigational New Drug Application from the Food and Drug Administration (#69,214). Drugs were stored and prepared by the University of Kentucky (UK) Investigational Pharmacy. Doses of oxymorphone hydrochloride (Roxane Laboratories, Inc., Columbus, OH) and oxycodone

hydrochloride (KVK Tech, Inc., Newtown, PA) were obtained in commercially available immediate-release 10 mg tablets. One, two or four tablets were over-encapsulated across two uniform size 00 gelatin capsules (Health Care Logistics, Circleville, OH) to create the active doses (10, 20, 40 mg). Lactose monohydrate powder (Medisca Pharmaceuticals, Plattsburgh, NY) was used for the placebo condition and as filler in the active dose capsules.

Dose Selection Rationale

There was very little information available regarding the acute physiological effects of oxymorphone. To guide dosing selection, the published analgesic tables were reviewed – these tables suggested that oral oxymorphone was twice as potent as oxycodone. However, one published study (Schoedel et al., 2011) presented miosis data indicating that oxymorphone was not twice as potent as oxycodone (rather it appeared *less* potent on this measure), although the relative potency ratio was not provided and could not be easily calculated. Thus, equal doses of each drug (10, 20, 40 mg) were selected and the current study was initiated with oxymorphone doses administered in ascending order (imposed on a randomized order for all other conditions) for the first three participants to assess dose safety. Those data ($n=3$) indicated that the lower doses of oxymorphone (10, 20 mg) were less potent than equal doses of oxycodone on miosis; however, the high dose produced miotic and subjective effects equal to those of 40 mg oxycodone. These preliminary data that indicated that testing a higher dose range of oxymorphone (e.g., doses that would produce effects greater than 40 mg of a dose of oxycodone) was not reasonably safe for a non-physically dependent population and a comparatively lower dose range would not produce effects that were comparable to oxycodone. Thus, the remaining six participants completed the study under fully randomized dose conditions with equal doses of oxycodone and oxymorphone (10, 20, 40 mg).

Study Design

This study utilized a within-subject crossover, randomized, double-blind placebo controlled design and examined oral oxymorphone (10, 20, 40 mg), oxycodone (10, 20, 40 mg), and placebo. Participants resided at the UK Center for Clinical and Translational Science Inpatient Unit for approximately 2.5 weeks and completed a total of 7 experimental sessions that were each 6.5 hours in duration. Sessions were separated by at least 48 hours.

General Methods

Participants were maintained on a caffeine-free diet and were provided a light, standardized breakfast 2 hrs prior to experimental sessions. Smoking was permitted up to 30 minutes prior to the start of session; *ad lib* smoking was allowed under supervision after session completion and on non-session days. Urine samples were collected each morning and were tested for drugs of abuse. Female participants were tested for pregnancy daily. Breath samples were obtained prior to each session and were tested for the presence of alcohol.

Physiological Measures

Heart rate, blood pressure and oxygen saturation (Dinamap Non-Invasive Patient Monitor, GE Medical Systems, Tampa, FL) were collected every minute for 30 min prior to and 6 hr

after drug administration (with the exception of brief, scheduled intervals when the blood pressure cuff was removed during the cold pressor trials; O₂ saturation sensor was removed during algometer pressure testing). Respiration rate, expired end-tidal carbon dioxide (N-85 Capnograph, Nellcor, Boulder, CO) and pupil diameter measurements (PLR-200, NeurOptics, Irvine, CA) were collected at baseline, in 15 min intervals for the first 2.5 hr and in 30 min intervals for the remaining 3.5 hr.

Pain Assessments

Each pain procedure was conducted once during study screening to acclimate participants to the tests and to determine sensitivity to and tolerability of the procedures. During inpatient sessions, each pain procedure was conducted prior to and 60, 120 and 180 minutes after drug administration. Primary outcome measures included pain threshold: point at which pain was initially detected, and pain tolerance: the point at which pain was no longer tolerable, which signaled termination of the pain trial.

Cold Pressor Test

During the cold pressor test, participants immersed their non-dominant forearm in a room-temperature circulating bath for a total of 2 minutes and then placed his/her forearm in a cold water bath ($1.0^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$) without touching the side or bottom of the water bath container. Maximum cold water immersion time was 5 minutes (pre-determined cut-off to avoid tissue damage). Participants verbally indicated pain threshold and removed their arm from the cold water to indicate pain tolerance; these outcomes (threshold and tolerance) were recorded as seconds (e.g., time elapsed since cold water immersion). This procedure was adapted and modified from Compton et al., 2010.

Pressure Algometer Test

The pressure algometer test was conducted using a computerized algometer system (Medoc AlgoMed, U.S.A, Durham, N.C.). Pressure was applied with the algometer device to the palmar surface of the thenar eminence of the dominant hand at the rate of 40 kilopascals (kPa)/second. The maximum pressure applied on any given trial was 1500 kPa (predetermined safety cut-off). During each administration, two trials were conducted, with 5 minutes separating each pressure application. Participants indicated pain threshold and tolerance via a button press on a response apparatus connected to the AlgoMed system; these outcome measures are reported in kPa.

Subjective Ratings of Pain

Immediately upon completion of each pain trial, participants answered two visual analog scale (VAS) questions, “How intense was the pain you just experienced?” and “How unpleasant was the pain you just experienced?”. The 100 mm VAS line was anchored with the terms “not at all” and “extremely.”

Subjective and Observer-Rated Measures

Subjective effects measurements included a six-item Visual Analog Scale (VAS) (Walsh et al., 2008), collected at baseline and at 15-min intervals for the first 2.5 hr, then every 30 min

for the remaining 3.5 hr; a drug street value measure, presented in 30-min intervals after drug administration; the Participant-Rated Opioid Adjective Scale (Fraser et. al., 1961), presented at baseline and at 30-min intervals post-dose; and the Pharmacological Class Questionnaire (Jasinski et al., 1977) collected once, 6 hrs post-dose. Trained research assistants rated signs of opioid agonist effects on the Observer-Rated Opioid Adjective Scale (Fraser et. al., 1961) at baseline and at 30-min intervals after drug administration.

Cognitive Performance Measure

A 90-second computerized version of the DSST (adopted from McLeod et al., 1982) was collected at baseline and at 30-min intervals after drug administration.

Statistical Analyses

All measures were initially analyzed as raw time course data using a two-factor repeated measures model (drug condition, time) with an AR(1) covariance structure. Physiological measures, collected minute-by-minute, were initially averaged across 15–30 min intervals corresponding to the subjective reporting intervals. Peak/trough scores were analyzed using a one-factor model (drug condition). Time-to-peak effect (e.g., $T_{\min}$ or $T_{\max}$) was calculated for individual participants and dose conditions and was analyzed in a one-factor model (drug condition). Tukey's post-hoc tests were performed to examine the time course of the drug effects, the effects of individual doses (as compared to placebo) and differences between active comparator dose conditions. All models were conducted with Proc Mixed in SAS 9.3 (Cary, NC) with significance at $p < 0.05$.

A sensitivity analysis (Thebane et al., 2013; Holbrook et al., 2012) was conducted using study group ($n=3$ vs. $n=6$) as a covariate to assess the impact of the non-randomized, ascending-order oxymorphone doses (implemented with the first three participants to ensure safety) in comparison to the fully randomized dose conditions (employed for the last 6 participants).

For select measures in which significant peak effects were observed, the Finney parallel lines bioassay (Finney, 1964) was employed to assess the relative potency of both drugs, with oxycodone serving as the comparator drug. This assay utilizes a six-point method (3 active doses of each drug) and valid analyses are obtained if the dose response curves are linear, parallel, have slopes that are significantly different from zero and have comparable magnitude effects (e.g., preparation model).

RESULTS

Participants

A total of 29 participants signed consent for the screening process; 14 of these individuals went on to sign main study consent. Of these 14 participants, two were excluded because they did not meet drug use criteria. A total of 12 participants met qualification criteria and were enrolled. Three of those enrolled did not complete the study; one left due to a family emergency and two were discharged due to behavioral problems - data from these individuals were not included in analyses. Thus, 9 participants (2 Caucasian women, 1

African American male, 6 Caucasian males) completed the study. They were 30.5 (± 1.6) years old and reported current illicit use of short-acting opioids on 8.0 (± 0.8) days out of the past 30 days prior to enrollment; oxycodone and hydrocodone were most commonly used, with infrequent reports of methadone and codeine use. Primary routes of administration included oral ($n=3$), intranasal ($n=5$), and intravenous ($n=1$). Participants reported a history of 6.6 (± 1.7) years of non-medical (i.e., recreational) opioid use and 5 individuals reported a lifetime history of physical dependence. Seven participants were daily cigarette smokers (16.3 [± 1.3] cigarettes per day), and two were non-smokers. Other past-month drug use included benzodiazepines on 1.0 (± 1.5) days ($n=4$); alcohol on 2.4 (± 1.8) days ($n=3$); and marijuana on 9.8 (± 5.2) days ($n=4$).

Time Course and Peak Effect Outcomes

Physiological Outcomes—The time course profile and mean trough effects of oxycodone and oxymorphone on pupil diameter are displayed in Figure 1. Both drugs decreased pupil diameter in a dose-related manner; time course analyses indicated a dose by time interaction (see figure legend for statistical detail) and mean trough pupil diameter was different from placebo under each active dose condition (Figure 1, Table 1). However, the magnitude of these miotic effects differed substantially across the drugs and doses ($p < .05$, Table 1). At identical doses, oxycodone produced effects that were approximately two-fold greater than those produced by oxymorphone. For example, 20 mg oxycodone produced miosis that was similar to that produced by 40 mg oxymorphone (Figure 1, Table 1). There were no significant differences between the drugs in time-to-pupil nadir (calculated $t_{\min}$), as trough effects occurred at similar times (between 1.5 – 2.0 hours post dose). The duration of effects was also comparable, as the higher doses of both drugs (20, 40 mg) produced miosis that persisted through the end of data collection (6-h post dose).

The peak effects on end tidal CO₂ (EtCO₂) concentrations are displayed in Figure 2. Oxycodone (20, 40 mg) increased peak EtCO₂ concentrations relative to placebo (Table 1). Only the high dose of oxymorphone produced a significant increase relative to placebo; however, an equal dose of oxycodone (40 mg) produced effects of greater magnitude (Table 1). The time course profile of EtCO₂ effects did not differ between drugs, with peak effects (calculated $t_{\max}$) occurring 1.25 – 1.78 hours post dose across all doses.

Similarly, trough analyses indicated that both 20 and 40 mg of oxycodone decreased respiration rate, while only the high dose of oxymorphone produced decreases relative to placebo (Table 1); time course analyses did not detect a main effect of dose on respiration rate. For trough oxygen saturation, only the high dose of oxycodone decreased concentrations, and this was greater than the effect produced by same dose of oxymorphone (Table 1); time course analyses indicated a main effect of dose ($F(6,48)=5.7$, $p < .001$). A main effect of dose was also detected on trough heart rate ($F(6,48)=2.3$, $p < .05$) (active doses produced mean decreases of 1–4 beats per minute relative to placebo); however, post-hoc tests and time course analyses did not detect a significant effect of dose. No significant changes for systolic or diastolic blood pressure were detected after administration of either opioid.

Measures of Analgesia

The peak dose effects on pain threshold and tolerance on the cold pressor test are presented in the top row of Figure 3. Oxycodone produced analgesia as measured by cold pain threshold, with the high dose producing greater analgesia than the same dose of oxymorphone (Table 2). Oxymorphone did not affect cold pressor threshold, displaying a relatively flat function with no differences from placebo. Both drugs, at the 40 mg doses, increased peak cold pain tolerance. Time to peak effect did not significantly differ between the drugs (estimated ranges: threshold $t_{\max} = 1.67 - 2.12$ hrs; tolerance $t_{\max} = 1.45 - 2.12$ hrs).

The pattern of effects on the pressure algometer test (averaged across both trials) was similar to that on the cold pressor task (bottom row of Figure 3), as oxycodone significantly increased mean pressure pain threshold and tolerance compared to placebo. However, oxymorphone did not produce analgesia on either outcome; a significant difference was detected between the drugs at high dose condition on pressure tolerance (Table 2).

Differences between the two algometer trials were also detected, with time course analyses indicating a main effect of trial ($F(1,8)=11.1, p=.01$). Upon inspection of the data, there were no consistent trends of either pain sensitization or tolerance from Trial 1 to Trial 2; however, peak effect analyses detected significant effects of dose on Trial 1 threshold and tolerance and Trial 2 tolerance ($F(6,48)= 3.6 - 4.3, p<.05$), while no dose effects were detected on Trial 2 threshold ($F(6,48)= 2.0, p=.09$).

Peak effect analyses of subjective VAS ratings of pain intensity and unpleasantness indicated a main effect of dose on ratings cold pressor pain intensity and ratings (mean of Trial 1 and 2 ratings) of pressure pain unpleasantness (Table 2); however, the post hoc tests did not indicate an effect of any specific dose (as compared to placebo) on either measure. Time course analyses did not reveal any significant effects of dose.

Subject- and Observer-Rated Effects

Figure 4 displays the time course and peak effects for the representative subject-rated visual analog question, “How much do you like the drug?”. Oxycodone produced dose-dependent increases on this measure, with time course and peak effect analyses indicating increases in ratings at 20 mg and 40 mg oxycodone (Table 1; see legend for time course statistics). The lower doses of oxymorphone (10, 20 mg) produced minimal effects, while the high dose produced significant ratings, comparable in magnitude to the high dose of oxycodone (Figure 4, Table 1). The time course of ratings of drug liking and time-to-peak effects was similar across drugs (1.1 – 1.6 hours post dose). Similar dose-related effects and time-action profiles were observed on other VAS items, including Drug Effect, High, and Good Drug Effect (Table 1), with peak effects ($t_{\max}$) occurring from 0.97 – 1.7 hrs post dose. No significant effects of dose were detected on time course or peak effect analyses for Bad Drug Effect or Desire for Opiates.

Figure 5 displays peak effects of subject-rated street value estimates (left panel), agonist sub-scale of the participant-rated (middle panel) and observer-rated adjectives (right panel). Overall, ratings of street value were dose-dependent, with oxycodone producing peak ratings

of approximately \$1 per milligram (range: \$0.86–\$1.40/mg oxycodone); oxymorphone was rated as having less value (range: \$0.60–\$0.70/mg oxymorphone) and only the high dose of oxymorphone produced a significant peak increase relative to placebo (Table 1). Similar to the other subjective effects, participant-rated agonist-like effects ratings occurred at both 20 and 40 mg oxycodone, while only the high dose of oxymorphone increased ratings (Table 1). In comparison, trained observers rated the high doses of each drug as agonist-like, with ratings of oxycodone effects significantly greater than those produced by oxymorphone (Table 1).

Cognitive Performance Measure

No effects of dose were detected in DSST trial rate or accuracy.

Drug Identification

All participants identified each of the active doses of oxycodone as an opioid agonist on the Drug Identification Questionnaire. Participants identified oxymorphone as an opioid agonist less consistently, sometimes rating it as placebo-like (10 mg: $n=4$, 20 mg: $n=2$, 40 mg: $n=1$); one participant identified the 20 mg oxymorphone dose as “other” on the list of 9 common drug categories (e.g., an active drug that could not be identified as fitting into the predetermined categories). Placebo was identified correctly by 6 subjects, but was identified as opioid-like by 3.

Sensitivity Analysis

A sensitivity analysis was conducted to determine if there were differences in the subjective data as a function of the ascending oxymorphone dose regimen imposed on the first 3 participants, compared to the fully randomized dose order employed for the last 6 participants. No significant differences were detected ($F(1,7)$ values = 0.0 – 3.3, $p > 0.05$).

Potency Analyses

Relative potency analyses were conducted on outcome measures of interest for which a significant effect of dose was obtained (i.e., pupil diameter, EtCO₂ concentration, threshold and tolerance on both analgesic measures, opioid VAS items, observer-rated composite agonist scale), using oxycodone as the reference drug. However, the majority of these analyses yielded invalid results due to violation of the “preparation” criteria (e.g., preparation was significantly different between the two drugs). Preparation assesses the range of scores for the comparator dose response curves; for a valid comparison, the numeric ranges for responses need to overlap considerably between the two dose response curves. Because oxymorphone was far less potent than expected, there were a limited number of valid assays obtained; compared to oxycodone, the relative potency estimates for oxymorphone were calculated as follows: Threshold on the Pressure Algometer = 0.48; VAS items of Like Drug, Drug Effect, Good Effects and High = range 0.84–0.85.

DISCUSSION

This study examined the relative abuse liability, analgesic profile and pharmacodynamic potency of oral oxymorphone, compared to an identical range of doses of oral oxycodone in

a sample of non-physically dependent opioid abusers. All of the doses tested were well tolerated and both drugs produced effects typical of μ -opioid agonists, including miosis, respiratory depression, positive/euphoric subjective effects and observer-rated agonist effects. However, substantial qualitative and quantitative differences were detected between the two drugs on each of the measures collected.

All of the active doses produced pupillary constriction with similar time action curves (e.g., similar $t_{\min} = 1.5 - 2\text{h}$); however, the degree of miosis differed considerably between the drugs and doses. At identical doses, oxycodone produced miotic effects that were approximately two-fold greater than those produced by oxymorphone. For example, both 10 mg oxycodone and 20 mg oxymorphone produced a mean trough pupil diameter of 4.1 mm, while trough measurements were 3.1 mm under both 20 mg oxycodone and 40 mg oxymorphone conditions (Figure 1, Table 1). Formal potency analyses were conducted, but because oxymorphone was far less potent than anticipated, the miosis analyses were not valid due to a violation of the preparation model (Finney, 1964). The only other available data on the miotic effects of oxymorphone (Schoedel et al., 2011) reported similar findings and indicated that 30 mg controlled-release oxycodone produced significantly greater pupillary miosis than an identical dose of extended release oxymorphone. Thus, if miosis is used as a physiological index of intrinsic opioid activity (Fraser et al., 1954; Martin, 1983), the data from the current study indicate that oral oxycodone is twice as potent as oral oxymorphone, placing these results in direct contrast to the published analgesic potency estimates and results from several clinical trials (Gabrail et al., 2004; Hale et al., 2005), which suggest that oxymorphone is two-fold more potent than oxycodone for clinical pain relief. It is possible that the clinical analgesic effects of μ -opioid agonists do not directly correspond with their direct physiological effects (e.g., miosis, respiratory depression). It is also possible that these trials were not sufficiently sensitive to estimate relative analgesic potency accurately (e.g., reliance on an open-label testing to guide dosing for double-blind phases).

Similarly, oxycodone (20, 40 mg) significantly increased EtCO_2 concentrations (indicating respiratory depression), but only the high dose of oxymorphone produced this prototypic μ -agonist-like effect; however, oxycodone produced a much greater effect than oxymorphone at 40 mg (Figure 2). Previous research has indicated that a dose range of intramuscular (7, 14, 28 $\mu\text{g/kg}$) oxymorphone produced naloxone-attenuated decreases in respiration rate and EtCO_2 concentrations, relative to placebo (a positive control was not included) (Kallós et al., 1972). These data, along with the miosis data, indicate that when administered orally, oxycodone is more potent than oxymorphone on physiological indices of μ -opioid effects.

Oxycodone (20, 40 mg) produced significant increases in subjective measures typically associated with abuse liability (e.g., ratings of drug liking, high, street value estimates). In comparison, 20 mg of oxymorphone was placebo-like on these measures, while 40 mg produced peak ratings and a time-active profile comparable to 40 mg oxycodone on a subset of subjective measures including ratings of drug liking, good drug effect, high and overall drug effect. This profile of subjective effects is potentially indicative of a comparatively narrow safety index, which could be dangerous for those using/abusing oxymorphone via the oral route. Schoedel and colleagues (2011) examined the subjective

effects of oxymorphone (15 mg and 30 mg ER), as compared to oxycodone (30 mg and 60 mg CR) in non-dependent opioid abusers. The authors reported that the low dose of oxymorphone (15 mg ER) was placebo-like, while the high dose (30 mg ER) produced opioid-like subjective effects; however, this 30 mg oxymorphone dose produced ratings that were lesser in magnitude than those of an identical dose of oxycodone (30 mg CR) on 7 out of 8 positive/euphorogenic subjective measures (e.g., “high”, “good drug effects”) where direct comparisons between the two doses were reported. Although different dose ranges were tested in the former and current study, the Schoedel (2011) data generally align with the present data; however, the conclusions drawn from the data are much different. Even though equipotent doses of the two drugs were not examined, Schoedel et al. (2011) concluded that oxymorphone produced substantially less abuse-related subjective effects than oxycodone; however, the current data suggest that at physiologically equipotent doses (i.e., 20 mg oxycodone and 40 mg oxymorphone), oxymorphone exhibits greater abuse liability than oxycodone.

Importantly, oxymorphone produced comparatively weak analgesic effects on both experimental pain measures. On the cold pressor test, which has demonstrated sensitivity to the dose-related effects of μ -opioid agonists (Ravn et al., 2013; Black et al., 1999; Walker and Zacny, 1998; Cleeland et al., 1996) and provides a model for some aspects of clinical pain (see Chen et al., 1989), oxycodone (40 mg) produced increases in both threshold and tolerance. In contrast, oxymorphone did not produce any significant changes in cold pressor threshold at any dose, but did produce significant increases in tolerance at the high dose only. Previous studies have reported that oxycodone produces robust effects on cold pain tolerance, threshold, and subjective pain ratings (Lofwall et al., 2012; Eisenberg et al., 2010; Grach et al., 2004); however, there are no available data that indicate oxymorphone has been tested in the cold pressor model. Although several classes of drugs produce inconsistent analgesic effects on the cold pressor test (e.g., NSAIDs, tricyclic antidepressants, GABAergic agents), opioids produce rather reliable analgesia on this measure (Andresen et al., 2011; Jones et al., 1988; Jarvik et al., 1981), so it is somewhat surprising that oxymorphone did not produce more robust analgesic effects, even at the therapeutic and supratherapeutic analgesic doses tested here. Further, oxymorphone did not display any readily discernable analgesic effects on the pressure algometer test, as it produced a relatively flat dose response function on both pressure threshold and tolerance. Conversely, oxycodone (40 mg) produced increases on both measures of analgesia in this pain model. A pressure algometer model of pain has not been extensively used to assess the acute effects of opioid medications; however, several studies have reported that oxycodone and other μ -opioid agonists (i.e., morphine) increase both pressure pain threshold and tolerance under various types of pressure application in healthy participants (Arendt-Nielsen et al., 2009; Olesen et al., 2010; Ravn et al., 2013) and pain patients (Staahl et al., 2007; Sorensen et al., 1997). Future studies should examine a higher oral dose range of oxymorphone to determine its efficacy in these experimental pain models.

One possible contributing factor to the overall array of results is the differences in relative bioavailability between the two drugs. The bioavailability of oral oxycodone is estimated between 60–87% (Poyhia et al., 1992; Leow et al., 1992). However, oxymorphone is purported to have 10–11% oral bioavailability (Endo Pharmaceuticals, 2012; Adams &

Ahdieh, 2005), although the data from which this estimate is derived are not publically available for review. One published study examined both oral and intramuscular oxymorphone on measures of cancer pain relief and reported that the oral preparation was 16% as potent for measures of pain intensity (i.e., change from baseline pain ratings) and 7% as potent in terms of peak analgesic effects (i.e., peak pain ratings), as compared to IM oxymorphone (Beaver et al., 1977b). Although these data do not provide an estimate of bioavailability, they suggest that oral oxymorphone is not well absorbed via the oral route and that parental administration may be necessary to produce greater analgesic effects of oxymorphone, as parenteral oxymorphone has been demonstrated to be a potent analgesic (approximately 10-fold more potent than morphine) (Eddy and Lee, 1959). Future studies should examine parenteral doses and higher oral doses of oxymorphone to assess its oral bioavailability and to further examine its pharmacodynamic potency.

Despite its relatively low oral bioavailability, it is not clear why oxymorphone did not produce robust analgesic effects on the experimental pain procedures, when multiple clinical trials have reported acute and clinical pain relief with the dose range currently tested (Aqua et al., 2007; Gimbel et al., 2004; 2005). Although there are notable differences in clinical and experimental pain that have been reviewed elsewhere (see Olesen et al., 2012), it is very common for opioid doses utilized for clinical pain relief to demonstrate pain modulation in experimental pain models (Martin, 1983; Olesen et al., 2012), particularly the measures selected for this study (Andresen et al., 2011; Grach et al., 2004; Jones et al., 1988; Olesen et al., 2010). Thus, if the results from the clinical trials examining oxymorphone for the treatment of acute and chronic pain conditions are assumed to be accurate, it is possible that clinical analgesic effects are not associated with dose-related relative potency for other pharmacodynamic actions, including other measures of intrinsic activity (e.g., pupil diameter, respiratory effects), abuse liability measures and experimental pain measures. If this is the case and the analgesic potency tables are correct, then the dose range of oxymorphone (e.g., half the dose of oxycodone) required for adequate analgesia may be safer and produce less respiratory depression than equianalgesic oxycodone doses. However, if experimentally-induced pain is assumed to be a valid assay for analgesia, then oxymorphone may have greater abuse liability than oxycodone at doses that would produce equianalgesia on experimental pain assays. Future studies that examine clinical pain response to opioids should consider including assays of experimental pain as well as physiological markers of opioid effect. Further, future human laboratory studies should carefully examine the correlation between subjective measures of drug effect and analgesic effects on pain models.

In summary, oxymorphone, relative to equal doses of oxycodone, produced μ -opioid agonist-like effects that were of significantly lower magnitude on physiological indices (i.e., miosis, respiratory function), observer-rated signs, and experimental pain. Because of these differences, relative potency analyses were invalid for the majority of measures; this could not have been predicted by published equianalgesic conversion ratios or from the only other reports describing the acute pharmacodynamic effects of oxymorphone (Schoedel et al., 2010, 2011). These findings highlight a surprising dissociation between the clinically reported relative potency estimates for analgesia versus the observed analgesia in response to experimental pain. In contrast to the apparent lower potency of oxymorphone on

physiological and observer-rated outcomes, the highest dose of oxymorphone produced subjective ratings on several measures related to abuse liability that were comparable to oxycodone, which may suggest that oxymorphone may have greater abuse potential than oxycodone at equipotent doses.

Acknowledgements

Grants from National Institute on Drug Abuse (R01DA016718 [SLW] and T32 DA 007304 [SB]) and the National Center for Research Resources UL1RR033173 (UK CCTS) provided support for this project. These institutes had no role in the study design, collection, analysis or interpretation of the data, writing of the report or in the decision to submit the paper for publication.

We thank the staff at the University of Kentucky (UK) Center on Drug and Alcohol Research, particularly Jaclyn O. Miller, Pamela A. Henderson, Rebecca Jude, Anna M. Miracle, Michelle N. Wolff and Victoria A. Vessels for their technical expertise, Drs. Stephen Sitzlar and Jeffery Carrico at the UK Investigational Pharmacy for preparing the study medications, and Dr. Manish Nair and the nursing staff at the UK Center for Clinical and Translational Science (CCTS) for providing patient care.

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Figure 1.

Mean pupil diameter after administration of oxycodone (left panel) and oxymorphone (middle panel) as a function of time following drug administration, from baseline through the end of the 6-hr session ($n=9$; ± 1 SEM). Time course analyses detected a significant effect of dose on pupil diameter ($F(6,48) = 11.25$, $p < .001$). Tukey post-hoc tests indicated that oxycodone (20 mg, 40 mg) and oxymorphone (40 mg) significantly decreased pupil diameter relative to placebo ($p < .01$). Filled symbols indicate means that were significantly different from placebo at that same time point (Tukey post-hoc, $p < .05$). Mean trough pupil diameter is presented in the right panel ($n=9$; ± 1 SEM). Filled symbols indicate significant effect of a dose relative to placebo and the asterisk indicates a significant difference between the drugs at the same dose (Tukey post-hoc, $p < .05$).

END TIDAL CO₂ CONCENTRATION

Figure 2.

Mean peak concentrations of end tidal CO₂ expiration displayed as a function of dose ($n=9$; ± 1 SEM). Time course analyses indicated a main effect of dose ($F(6,48)=3.8$, $p<.05$); Tukey's post-hoc test indicated the high dose of oxycodone increased CO₂ concentrations relative to placebo ($p<.05$). Filled symbols indicate a significant effect of dose relative to placebo and the asterisk indicates a significant difference between drugs at the same dose (Tukey post-hoc, $p<.05$).

Figure 3.

Mean peak effects of oxycodone and oxymorphone on the cold pressor test (top row) and the pressure algometer test (bottom row), displayed as a function of pain threshold (left column), pain tolerance (right column) and dose ($n=9$; ± 1 SEM). Time course analyses detected dose by time interactions for both threshold ($F(18,143)=2.8$, $p<.01$) and tolerance measures ($F(18,144)=3.2$, $p<.01$) on the cold pressor test. Time course analyses indicated a dose by time interaction on pressure pain tolerance ($F(18,143)=1.7$, $p<.05$). Filled symbols indicate significant peak effect of a dose relative to placebo and the asterisk indicates a significant difference between the drugs at the same dose (Tukey post-hoc, $p<.05$).

Figure 4.

Mean VAS ratings of the subjective measure “How much do you like the drug?” after administration of oxycodone (left panel) and oxymorphone (right panel), as a function of time following drug administration, from baseline through the end of the 6 hr session ($n=9$; ± 1 SEM). Time course analysis indicated a main effect of dose ($F(6,48) = 4.95$, $p=.001$) and a dose by time interaction ($F(96,768) = 1.43$, $p<.01$). Tukey post-hoc tests indicated that the high doses (40 mg) of each drug increased ratings relative to placebo ($p<.05$). Filled symbols indicate means that were significantly different from placebo at that same time point (Tukey post-hoc, $p<.05$). Mean peak ratings are presented in the right panel ($n=9$; ± 1 SEM). Filled symbols indicate significant peak effect of a dose relative to placebo (Tukey post-hoc, $p<.05$).

Figure 5.

Mean peak ratings of estimated street value (left panel), participant- (middle panel) and observer-rated (right panel) opioid agonist ratings, presented as a function of dose ($n=9$; ± 1 SEM). Time course analyses indicated a main effect of dose on each of the three measures ($F(6,48) = 2.76-4.72$, $p < .05$). Tukey's post-hoc tests indicated the high dose of oxycodone increased street value ratings and observer-rated agonist ratings relative to placebo ($p < .05$). Filled symbols indicate significant peak effect of a dose relative to placebo and the asterisk indicates a significant difference between the drugs at the same dose (Tukey post-hoc, $p < .05$).

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Table 1

Mean peak and trough values of measures for which a significant drug effect was detected							
Outcome Measure	F (6,48)	PLC	OC 10	OC 20	OC 40	OM 10	OM 20
Physiological Effects							
Expired CO ₂	14.3	39.2 (0.7)	40.8 (0.9)	41.8 (0.9)	45.7 (0.9)	41.0 (0.6)	40.9 (0.7)
Pupil Diameter	51.4	5.6 (0.3)	4.1 (0.4)	3.1 (0.2)	2.5 (0.1)	4.9 (0.3)	4.1 (0.2)
Respiration Rate	7.1	14.7 (1.3)	13.1 (1.2)	12.4 (1.3)	11.2 (0.9)	13.7 (1.3)	12.9 (1.2)
Oxygen Saturation	2.7	97.1 (0.4)	96.6 (0.4)	96.2 (0.2)	95.1 (0.3)	97.4 (0.2)	97.0 (0.2)
Subjective Effects							
Visual Analog Scales							
Drug Effect	10.8	5.6 (2.7)	21.3 (4.9)	36.6 (7.1)	46.7 (6.1)	11.0 (5.1)	19.0 (8.8)
High	9.6	5.0 (3.0)	21.4 (4.9)	35.4 (7.3)	47.4 (6.2)	11.8 (5.5)	18.9 (9.3)
Good Drug Effect	9.8	5.1 (2.7)	20.3 (4.7)	35.6 (7.2)	47.6 (6.4)	11.3 (5.2)	18.9 (9.4)
Like Drug Effect	9.5	5.1 (3.4)	20.0 (4.9)	36.3 (7.2)	46.9 (6.7)	11.0 (5.0)	17.2 (9.7)
Street Value Estimate	7.1	3.9 (2.2)	13.9 (4.3)	26.1 (7.0)	34.3 (9.0)	6.0 (2.3)	13.6 (6.9)
Participant Adjectives							
Agonist Sub-Scale	10.1	7.0 (1.3)	9.9 (1.6)	12.1 (2.7)	14.8 (1.9)	7.0 (1.6)	10.6 (2.3)
Itchy Skin	14.1	0.0 (0.0)	0.7 (0.2)	1.1 (0.2)	2.0 (0.3)	0.2 (0.1)	0.4 (0.2)
Nodding	7.2	0.2 (0.1)	0.3 (0.2)	0.9 (0.4)	1.7 (0.4)	0.1 (0.1)	0.3 (0.2)
Relaxed	3.4	1.3 (0.2)	1.4 (0.2)	1.6 (0.2)	1.9 (0.2)	1.1 (0.2)	1.7 (0.2)
Talkative	5.9	0.2 (0.1)	1.1 (0.4)	1.0 (0.5)	1.6 (0.4)	0.4 (0.3)	1.0 (0.4)
Heavy or Sluggish	3.7	0.0 (0.0)	0.4 (0.2)	0.4 (0.2)	0.8 (0.3)	0.0 (0.0)	0.3 (0.2)
Dry Mouth	3.6	0.0 (0.0)	0.4 (0.2)	0.3 (0.2)	0.4 (0.2)	0.1 (0.1)	0.3 (0.2)
Good Mood	2.5	1.7 (0.4)	1.9 (0.4)	2.1 (0.4)	2.3 (0.4)	1.7 (0.4)	2.0 (0.3)
Energetic	2.4	0.1 (0.1)	0.9 (0.3)	1.0 (0.4)	1.0 (0.3)	0.3 (0.2)	0.9 (0.3)
Observer-Rated Effect							
Observer Adjectives							
Agonist Sub-Scale	13.5	6.1 (0.6)	6.9 (0.8)	8.4 (0.9)	12.6 (0.9)	6.3 (0.4)	7.0 (0.8)
Itchy Skin	11.7	0.2 (0.2)	0.2 (0.1)	1.0 (0.3)	2.2 (0.2)	0.1 (0.1)	0.4 (0.2)
Friendly	2.8	1.7 (0.2)	1.7 (0.2)	1.7 (0.2)	2.0 (0.2)	1.7 (0.2)	1.7 (0.2)
Nodding	7.6	0.1 (0.1)	0.3 (0.2)	0.3 (0.2)	1.2 (0.3)	0.0 (0.0)	0.1 (0.1)
Relaxed	2.6	1.3 (0.2)	1.3 (0.2)	1.4 (0.2)	1.8 (0.2)	1.3 (0.2)	1.3 (0.2)
Coasting	5.2	0.0 (0.0)	0.1 (0.1)	0.6 (0.2)	1.0 (0.3)	0.0 (0.0)	0.3 (0.2)
Talkative	4.8	0.9 (0.3)	1.2 (0.2)	1.3 (0.2)	1.8 (0.3)	0.8 (0.3)	1.2 (0.2)
Heavy	2.8	0.1 (0.1)	0.2 (0.1)	0.4 (0.2)	0.6 (0.2)	0.0 (0.0)	0.1 (0.1)
Good Mood	5.3	1.6 (0.2)	1.6 (0.2)	1.7 (0.2)	2.1 (0.2)	1.6 (0.2)	1.6 (0.2)

All measures were analyzed as peak maximum score, with the exception of pupil diameter, respiration rate and oxygen saturation (which are trough or minimum scores). Values are mean peak scores and standard error of the mean for placebo (PLC), oxycodone (OC) and oxymorphone (OM) doses (numbers next to drug abbreviations are doses expressed in mg). Bolded values indicate the mean is significantly different from the corresponding placebo value ($p < 0.05$, Tukey post-hoc); boxed values indicate a significant difference between the two drugs at the same dose ($p < 0.05$, Tukey post-hoc).

Table 2

Mean peak values of experimental pain measures.

Exp. Pain Measures	F (6.48)		PLC		OC 10		OC 20		OC 40		OM 10	
	OM 20		OM 40									
Cold Pressor												
Threshold	4.8	9.2 (1.7)	12.7 (2.4)	14.6 (2.7)	23.1 (5.8)		11.2 (1.8)		9.8 (1.9)		12.8 (2.3)	
Tolerance	6.9	18.0 (2.5)	23.9 (3.6)	28.0 (4.5)	42.7 (7.4)		23.4 (3.6)		22.8 (3.4)		32.8 (5.6)	
VAS - Pain Intensity	2.7	71.4 (6.2)	72.4 (6.4)	67.0 (5.9)	62.4 (6.0)		71.9 (5.9)		71.6 (6.7)		63.1 (7.6)	
Igometer Test												
Mean Threshold	3.7	541.6 (73.1)	663.5 (114.3)	633.6 (86.3)	743.7 (63.9)		557.7 (59.6)		604.1 (65.4)		601.4 (60.7)	
Mean Tolerance	5.5	829.1 (102.5)	934.7 (96.0)	971.6 (129.8)	1151.0 (86.7)		824.2 (74.7)		948.7 (94.9)		890.7 (87.5)	
VAS - Unpleasant	2.4	56.1 (8.6)	58.2 (6.3)	48.8 (8.6)	48.6 (8.7)		54.9 (8.4)		51.7 (8.0)		47.6 (8.5)	

All experimental pain measures were analyzed as peak maximum score. Values are mean peak scores and standard error of the mean (SEM) for placebo (PLC), oxycodone (OC) and oxymorphone (OM) doses (numbers next to drug abbreviations are doses expressed in mg). Bolded *F*-values indicate a significant main effect of dose. Bolded mean values (SEM) indicate a significant difference from the corresponding placebo value ($p < 0.05$, Tukey post-hoc); boxed values indicate a significant difference between the two drugs at the same dose ($p < 0.05$, Tukey post