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ARTICLE

Once-Daily Oxycodone Prolonged-Release Tablets Are Resistant to Alcohol-Induced Dose Dumping: Results From a Randomized Trial in Healthy Volunteers

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The objective of this study was to determine the effect of concomitant alcohol intake on the bioavailability of oxycodone from an oxycodone once-daily (OOD) formulation and an oxycodone twice-daily (OTD) formulation. A phase I, open-label, randomized, crossover alcohol interaction study in 20 healthy volunteers under fasting conditions was conducted. Participants received five treatments, OOD with 240 mL of 0%, 20%, or 40% alcohol; and OTD with 240 mL of 0% or 40% alcohol. Pharmacokinetic parameters did not differ between participants taking OOD with water or with 240 mL of 20% alcohol. There was a slight increase in overall oxycodone absorption from OOD with 40% alcohol but no increase in peak absorption. Oxycodone absorption from OTD showed peak and overall increases with 40% alcohol but maintained a prolonged-release profile. Although it is recommended that alcohol be avoided while taking opioids, there was no evidence of alcohol-induced dose dumping in these oxycodone formulations.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Prolonged-release opioid medicines enable a reduced dosage frequency but increase the risk of harm if the formulation fails and the full dose is released immediately. Given the potential interaction between opioids and alcohol, any new prolonged-release formulation needs to be resistant.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This phase I study tested the effect of concomitant alcohol intake on the bioavailability of oxycodone from an oxycodone once-daily (OOD) formulation and an oxycodone twice-daily formulation.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ This study used pharmacokinetic parameters to show that the prolonged-release characteristics of a OOD formulation remain stable when ingested with alcohol.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Prolonged-release opioid formulations can be used safely when formulated appropriately.

Safe and effective opioid medicines have been used to treat moderate to severe chronic pain for many years. Advances in product design have led to the production of prolonged-release opioids for sustained pain relief. Rather than providing immediate, short-term pain relief, prolonged-release formulations allow less frequent dosing schedules, which are preferred by patients,[1] increase compliance,[2] and could, therefore, improve treatment outcomes. However, because once-daily formulations are designed to provide enough medicine to last for 24 hours, if the mechanism controlling the rate of release is compromised then a large dose will be absorbed too quickly.

Alcohol-induced dose dumping occurs when an interaction between alcohol and a medicine's excipients leads to uncontrolled immediate release of the full dose potentially causing significant harm or death.[3] Despite being a labeled contraindication for opioid medicines, it must be accepted that alcohol remains one of the most widely consumed drugs worldwide,[4] and that dual use of opioids and alcohol is prevalent.[5–7]

In a confirmed case of alcohol-induced dose dumping in a marketed opioid, a hydromorphone hydrochloride preparation (Palladone; Purdue Pharma L.P., Stamford, CT) was withdrawn from the market after a pharmacokinetic study showed that when these prolonged-release capsules were given with 240 mL of 40% alcohol under fasting conditions the maximum concentration of hydromorphone was, on average, six times higher than when taken with water.[8]

As a result, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommend all prolonged-release opioids be tested for alcohol-induced dose dumping. The Committee for Medicinal Products for Human Use (CHMP) was commissioned by the European Commission to assess the interaction between modified-release opioid medication and alcohol.[9] They reviewed 13 modified-release opioid formulations, including

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four oxycodone medicines finding that while half of the formulations were somewhat effected by alcohol *in vitro*, only one formulation (of morphine once-daily capsules) was subject to alcohol-induced dose dumping.[9] The polymethacrylate-triethylcitrate coating used to control release of the morphine in the problematic capsules reacted with alcohol, which led to immediate release of the medicine.[10]

Several prolonged or modified release products have also been tested for effects of concomitant alcohol and opioid use *in vivo*. Oxycodone is the most used opioid treatment for severe pain[11] and is available in i.v., immediate-release solutions, capsules, and twice-daily prolonged-release tablets. In a study of a twice-daily formulation of oxycodone, 37 healthy regular drinkers received a controlled-release oxycodone capsule with 240 mL of water and 240 mL of 4%, 20%, or 40% alcohol with a 4-day washout between treatments.[12] Despite increases in some pharmacokinetic parameters when the capsule was taken with 40% alcohol, there was no evidence that the controlled release formulation was compromised to the extent that dose dumping could occur.[12]

Methodologically similar studies of controlled release formulations of opioid medicines, such as hydromorphone,[13] hydrocodone,[14] and oxymorphone,[15] have likewise reported increases in pharmacokinetic parameters without evidence of dose dumping. Nevertheless, prolonged-release formulations can be at risk of alcohol-induced dose dumping and there are different successful approaches to prevention so it is important to test each category of formulation thoroughly.

An oxycodone once-daily (OOD) formulation, which received marketing approval in 2013, was designed by Develco Pharma Schweiz AG (Oxycodon-HCl beta 20 mg Prolonged-release tablets; Betapharm Arzneimittel GmbH, Augsburg, Germany). This OOD is a prolonged-release multi-pellet formulation intended for administration every 24 hours and was specifically designed to have abuse-deterrent and alcohol-resistant properties.

Its bioavailability has already been assessed in comparison to an established oxycodone twice-daily (OTD) formulation (Oxygesic 10 mg Prolonged-release tablets; Mundipharma GmbH, Frankfurt a.M., Germany) and found to be comparable in both fed and fasted states.[16] However, data on its relative stability when taken with alcohol have not yet been published.

The aim of this study was to compare the bioavailability of oxycodone when OOD and the comparator OTD prolonged-release products were taken with water or alcohol.

METHODS

This was a phase I, single-dose, randomized, open-label, five period, five-sequence, five-treatment, single-center, crossover, comparative bioavailability study of OOD (Oxycodon-HCl beta 20 mg Prolonged-release tablets; Betapharm Arzneimittel GmbH) and OTD (Oxygesic 10 mg Prolonged-release tablets; Mundipharma GmbH).

The study protocol was approved by the Institutional Review Board (Optimum Clinical Research) in Oshawa, Ontario, Canada, and the study was conducted in accordance with Canadian Food and Drug Regulations, FDA guidance documents,[17] and Good Clinical Practice, as established by the International Conference on Harmonization (ICH-GCP). Written informed consent was obtained from all participants before study participation.

Participants

Healthy men and women aged 18–55 who were moderate drinkers (7–21 units of alcohol per week for at least 6 months before first drug administration), had consumed five or more standard drinks on at least one occasion in the preceding month, had a body mass index of 18.5 to 30 kg/m^2 and a body weight of at least 70 kg for men and 60 kg for women were recruited. Participants were nonsmokers (for at least the preceding 6 months), and healthy according to medical history, electrocardiogram, laboratory results, and physical examination. Women were required to be neither pregnant nor lactating and to use appropriate contraception if they were not surgically sterile or postmenopausal.

Participants were excluded if they tested positive to HIV, hepatitis B or C, drugs of abuse, alcohol, or cotinine, or had any clinically significant history or current medical condition that could interact with the research drugs. Participants with a history of substance or alcohol dependence except to nicotine or caffeine in the past 2 years or who had ever been in substance or alcohol treatment were excluded along with those who had a sensitivity or idiosyncratic response to the medicines, food, or alcohol to be administered during the study. Likewise, participation was prevented from those with difficulty with blood sampling, abnormal diet patterns, recent blood donation or clinical trial participation, or diagnoses of conditions where alcohol consumption is contraindicated. Other exclusion criteria included consumption of caffeine, poppy, or alcohol within 48 hours, or grapefruit or pomelo within 10 days; use of any prescription or over-the-counter medications within 14 days, or any enzyme-modifying drugs, central nervous system depressants, or oral or transdermal contraceptives in the past 30 days. Having used an internal hormonal contraceptive or undergone major surgery in the past 6 months, or had a tattoo or piercing in the past 30 days resulted in exclusion, as did difficulty swallowing tablets.

Study design

There were five different treatments with participants randomized by a computer-generated randomization list to one of five treatment-order sequences. Each treatment involved taking one dose medicine with 240 mL of chilled water containing 0, 20, or 40% alcohol. The treatments were:

- Treatment A: OOD (20 mg) with 240 mL water
- Treatment B: OOD (20 mg) with 240 mL of 20% alcohol (v/v)
- Treatment C: OOD (20 mg) with 240 mL of 40% alcohol (v/v)
- Treatment D: OTD (10 mg) with 240 mL water
- Treatment E: OTD (10 mg) with 240 of 40% alcohol (v/v)

The treatment sequences (**Figure 1**) determined the order in which each participant received treatments. If a participant was unable to complete a treatment, they

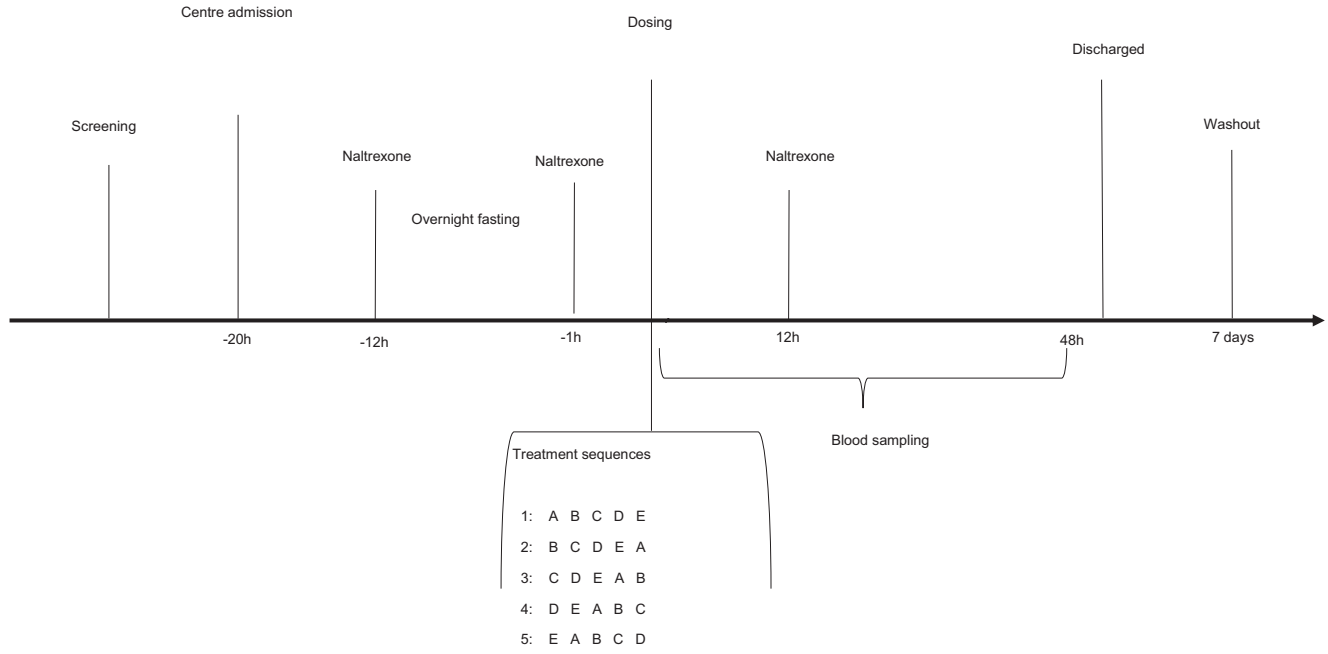

Figure 1 Study design. One treatment period was from center admission to discharge.

were allowed to return for subsequent treatments in their sequence.

Participants arrived at the clinic at least 20 hours before dosing and underwent assessment of vital signs and testing of breath alcohol. They received meals 16 and 12.5 hours before getting the study drug. Naltrexone 50 mg (Revia; Duramed Pharmaceuticals, Pomona, NY) was given twice before study drug administration. Naltrexone is an opioid antagonist and was provided to reduce the risk of any opioid-related adverse events.

Participants fasted for 10 hours and refrained from drinking anything for 1 hour before taking the study medication. Treatment involved taking one dose of the assigned study drug with water or alcohol solution as assigned in that treatment period. Participants drank the water and alcohol in four 60 mL shots no more than 5 minutes apart.

Participants refrained from drinking anything for an hour after taking the study drug and fasted for 4 hours. The meals were given 4.5, 9.5, 24, 28.5, 33.5, and 37 hours after study drug administration. Another dose of 50 mg naltrexone was administered after 12 hours. Participants were confined to the clinic for at least 48 hours post dose and breathalyzed for alcohol to determine whether they could be released.

A washout period of at least 7 days separated each treatment period. Participants were dismissed from the treatment period if they failed the alcohol breath test before drug administration or vomited during alcohol intake.

Sample collection and sample analysis

Blood samples were collected by direct venipuncture or by indwelling catheter into prechilled 4 mL tubes at predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 36, and 48 hours postdose. Samples were centrifuged within 30 minutes from the time of collection at 3,000 revolutions per minute for 10 minutes under refrigerated conditions.

After centrifugation, the plasma was aspirated and aliquoted into two clear polypropylene tubes. A minimum of 1.0 mL plasma was transferred to the first tube, and any remaining plasma was aliquoted into a second tube. Polypropylene tubes were prechilled and labeled. Throughout sample collection and following centrifugation, the samples were maintained in an ice-bath until stored in a freezer. Quality assurance audits were performed throughout the study.

Pharmacokinetic parameters

The relative bioavailability of oxycodone was estimated for each treatment based on plasma concentrations of oxycodone. The measures presented were maximum plasma drug concentration (C_{max}), time to C_{max} (T_{max}), area under the plasma drug concentration-vs.-time curve (AUC) from time zero to the last measurable concentration (C_{last}), or last sampling time t (AUC_t), and from time zero to infinity (AUC_{inf}) calculated as $AUC_t + C_{last}$/lambda.

Statistical methods

Descriptive statistics of pharmacokinetic parameters were calculated for oxycodone for the five treatments and the AUCs were calculated using the linear trapezoidal method.

Analyses of variance (ANOVA) were performed on ln-transformed AUC and C_{max} data in SAS version 9.4. These ANOVA included sequence, participants nested within sequence, period, and treatment.

The 90% confidence intervals (CIs) of the test/reference ratios of geometric means for AUC_t, AUC_{inf}, and C_{max} were

calculated based on the least squares means and estimate of the ANOVA and presented as a percentage relative to the reference.

For comparisons between treatments with different oxycodone formulations, the results were dose normalized to account for the different strengths (10 mg for OTD and 20 mg for OOD).

The following pairs of the bioavailability comparison were conducted on the least squares means of the ln-transformed AUC and C_{max} for the following comparisons.

Comparisons within OOD treatments:

- Treatment B: (20% alcohol)/ Treatment A: (0% alcohol)
- Treatment C: (40% alcohol)/ Treatment A: (0% alcohol)

Comparisons within OTD treatments:

- Treatment E: (40% alcohol)/ Treatment D: (0% alcohol)

Dose normalized bioavailability comparisons between OOD and OTD treatments:

- Treatment A: (0% alcohol)/ Treatment D: (0% alcohol)
- Treatment C: (40% alcohol)/ Treatment E: (40% alcohol)

Safety

Several measures ensured participant safety. Administration of the opioid antagonist naltrexone reduced the risk of opioid-related adverse events. Two sentinel participants were dosed 24 hours before the remainder to check for any unexpected safety issues, while naloxone (i.v.), antiemetics (i.v. and oral), and intubation kits were available.

Prior to drug administration the participants were screened for acceptable ranges of systolic blood pressure (100–140 mmHg), diastolic blood pressure (60–90 mmHg), heart rate (50–100 bpm), respiration rate (12–20 breaths per minute), and oximetry (95–100%).

Participant wellbeing was also assessed throughout the study. Vital signs (blood pressure, heart rate, respiratory rate, and oximetry) were measured before the first dose of naltrexone in each study period and at 1, 2, 4, 8, 12, 14, 16, 24, and 48 hours postdose in each study period.

All adverse events were recorded and assessed as mild, moderate, or severe. A breath alcohol test was performed at clinic exit for each study period. In the event of a positive result, the participant was required to remain in the clinic until deemed safe to leave.

RESULTS

Participants

The study was completed in June 2015. Twenty participants (5 women and 15 men) with an average age of 40 years (SD = 10 years) were dosed in their first treatment period and the participant disposition is shown in **Figure 2**.

Three participants were dismissed but returned to complete subsequent periods. These dismissals were due to a positive breath alcohol test at check-in (n = 2), or because of vomiting after dosing (n = 1). A further five participants were dismissed (vomiting, n = 2) or withdrew (personal reasons n = 3) and did not return.

There were 17 participants dosed in treatments A and C, 18 in treatments B and E, and 19 in treatment D. Twelve participants completed all five study periods.

Data were not included in the pharmacokinetic analyses for periods in which participants were not dosed, or if they vomited after dosing. Two participants had no data included, 10 had data included for some periods, and 8 had data included from all study periods. One participant received the incorrect dose in treatments B and D so their data from those treatments were excluded. The final data analysis set by treatment

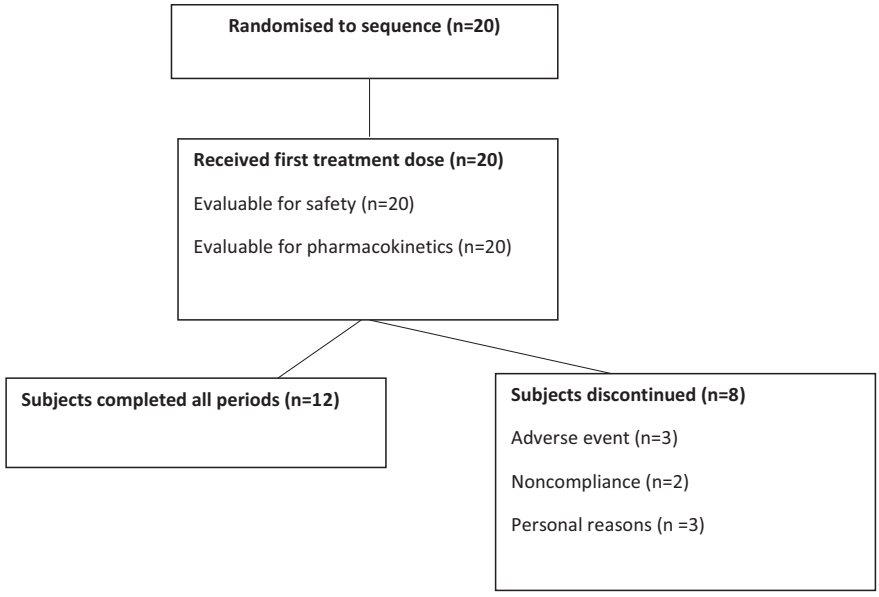

Figure 2 Subject disposition.

group was: treatment A (n = 16), treatment B (n = 14), treatment C (n = 12), treatment D (n = 17), and treatment E (n = 14).

Pharmacokinetics

Pharmacokinetic parameters for each treatment are shown in **Table 1**. Using dose normalized parameters, the AUCs were generally higher in the OOD treatments, whereas maximum oxycodone concentration C_{max} was higher in the OTD treatments. The arithmetic means were similar between alcohol amounts within OOD treatments. The maximum concentration of oxycodone and the overall exposure seemed to be higher for OTD when it was taken with 40% alcohol (treatment E). As expected, the time to maximum concentration was much shorter for the faster acting twice-daily formulation.

There was no discernible relationship between the amount of alcohol taken and oxycodone absorption from OOD in the curves of the plasma concentration-vs.-time graph. However, an apparent peak increase in absorption of oxycodone when the OTD was taken with alcohol is seen in **Figure 3**.

Table 2 shows the results of between-treatment comparisons of the geometric means of AUC and C_{max} controlled for randomization sequence, participants within sequence, period, and treatment.

When OOD was taken with 240 mL of 20% alcohol (treatment B) compared with water the ratio of the relevant pharmacokinetic parameters remained between 95 and 105, and the CIs fell between 85% and 115% (**Table 2**).

The AUC ratios comparing 40% alcohol and 0% alcohol with OOD were ~ 116 and the upper CI bounds approached 130%, suggesting that there could have been greater oxycodone absorption when it was taken with the highest amount of alcohol. However, ingesting 40% alcohol did not increase the maximum concentration of oxycodone.

Compared with OTD taken with water, when taken with 40% alcohol the pharmacokinetic parameter ratios of AUC_t, AUC_{inf}, and C_{max} were about 25% higher and the upper limits of the ratios' CIs approached 140% (**Table 2**).

The results of the C_{max} comparisons within each treatment can be seen in **Figure 4**. There was no difference in maximum plasma concentration of oxycodone when OOD was taken with alcohol but taking OTD with 40% alcohol resulted in an ~ 30% higher peak concentration.

The comparative bioavailability of oxycodone between OOD and OTD when they were administered with either water or 40% alcohol was assessed with dose-normalized data (**Table 2**). When both formulations were taken with water, OOD had 1015% greater overall absorption than that obtained from OTD but an ~ 16% lower peak absorption compared with OTD tablets.

When both formulations were administered with 40% alcohol, OOD had similar overall absorption as obtained from

Table 1 Pharmacokinetic measures for OOD and OTD taken with various concentrations of alcohol

	Treatment A OOD with water n = 16	Treatment B OOD with 20% alcohol n = 14	Treatment C OOD with 40% alcohol n = 12	Treatment Dc OTD with water n = 17	Treatment Ec OTD with 40% alcohol n = 14
AUC_t[a]	256.6 (29.2)	240.5 (27.1)	256.5 (24.1)	213.7 (28.5)	246.3 (23.8)
AUC_{inf}[a]	261.1 (28.9)	244.5 (26.3)	261.7 (22.4)	226.0 (26.1)	256.5 (22.1)
C_{max}[a]	18.1 (26.0)	16.3 (23.9)	17.0 (22.7)	20.8 (18.3)	25.4 (15.5)
T_{max}[b]	10.0 (5.5–10.1)	10.0 (8.0–12.0)	10.0 (8.0–12.0)	1.0 (0.8–5.5)	2.0 (0.8–8.0)

AUC_{inf}, area under the plasma drug concentration-vs.-time curve from time zero to infinity; AUC_t, area under the plasma drug concentration-vs.-time curve from time zero to last sampling time; C_{max}, maximum plasma drug concentration; OOD, oxycodone once-daily; OTD, oxycodone twice-daily; T_{max}, time to maximum plasma drug concentration.
[a]ng.hour/mL, arithmetic mean (percentage of coefficient of variation).
[b]Hour, median (range).
[c]Dose normalized.

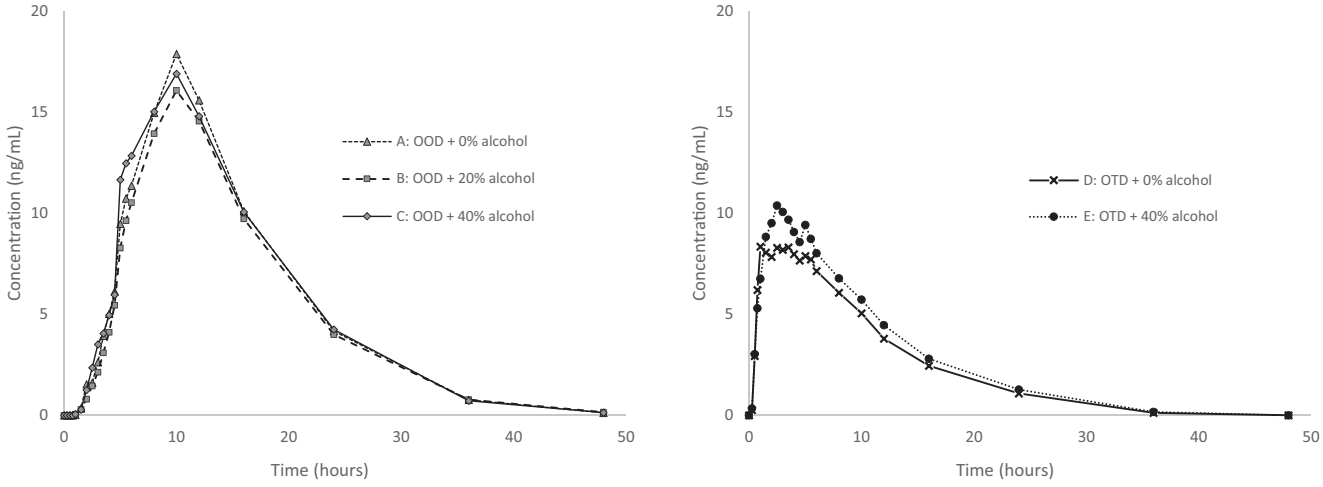

Figure 3 Mean (arithmetic) plasma oxycodone concentration against time for oxycodone once-daily (OOD) and oxycodone twice-daily (OTD) treatments.

OTD (AUC_{inf} of 261.1 and 256.5, respectively) but showed ~ 33% lower peak absorption.

Safety

Adverse events are displayed in **Table 3**. As expected, given the aforementioned preventative methods, there were no serious adverse events. The adverse events were mild (87%) or moderate (13%) and the most common of these are shown by treatment in **Table 3**.

Table 2 Analysis of variance ratios of geometric means of pharmacokinetic parameters from between treatment comparisons

Comparisons within OOD treatments		
	Treatment B/A (90% CI)	**Treatment C/A (90% CI)**
AUC_t	103.8 (94.3–114.3)	116.7 (105.3–129.4)
AUC_{inf}	103.8 (94.6–113.8)	116.5 (105.6–128.6)
C_{max}	96.0 (88.4–104.3)	102.6 (93.9–112.1)
Comparisons within OTD treatments		
		Treatment E/D (90% CI)
AUC_t		125.0 (113.9–137.2)
AUC_{inf}		122.8 (112.4–134.3)
C_{max}		129.1 (119.1–139.8)
Dose normalized bioavailability comparisons between OOD and OTD treatments		
	Treatment A/D (90% CI)	**Treatment C/E (90% CI)**
AUC_t	115.6 (105.8–126.3)	108.0 (97.1–120.1)
AUC_{inf}	110.9 (102.0–120.7)	105.2 (95.0–116.5)
C_{max}	84.3 (78.1–90.9)	67.0 (61.2–73.4)

AUC_{inf}, area under the plasma drug concentration-vs.-time curve from time zero to infinity; AUC_t, area under the plasma drug concentration-vs.-time curve from time zero to last sampling time; CI, confidence interval; C_{max}, maximum plasma drug concentration; OOD, oxycodone once-daily; OTD, oxycodone twice-daily.
Treatment A: OOD with water (n = 16); treatment B: OOD with 20% alcohol (n = 14); treatment C: OOD with 40% alcohol (n = 12); treatment D: OTD with water (n = 17); and treatment E:, OTD with 40% alcohol (n = 14).

DISCUSSION

This study examined the bioavailability of oxycodone when prolonged-release formulations were administered with various amounts of alcohol under fasting conditions. Comparisons between means of the pharmacokinetic parameters of AUC and C_{max} taking OOD with 240 mL of 20% alcohol did not increase the rate or extent of exposure to oxycodone. Taking OOD with 40% alcohol slightly increased the extent of oxycodone absorption but not the peak concentration. When OTD was administered with 40% alcohol the peak absorption of oxycodone increased by almost 30%.

These data suggest the physical properties of both prolonged-release formulations were not impaired. Because alcohol-induced dose dumping describes a situation where the formulation is compromised to the extent that the full dose of the medicine is released immediately,[3] it can be concluded that both the OTD and OOD formulations were not at risk. Even if someone took the OOD formulation with, for example, a full cup of vodka after fasting for 10 hours they would not be exposed to dangerous amounts of oxycodone.

The OOD tested here is the only marketed formulation of oxycodone that is designed to be taken once-daily.[18] This benefits patients with moderate-to-severe chronic pain by simplifying their dosage schedule and providing consistent pain relief. However, the longer the prolongation of a dosage formulation the higher the strength of each dose. This necessitates greater care ensuring its resistance to alcohol-induced dose dumping. If the prolonged-release function of a once-daily formulation were to fail, thus immediately releasing the full day's dose, then serious harm could occur.

The results of this study are only pertinent to the medicines tested and are not generalizable to other formulations

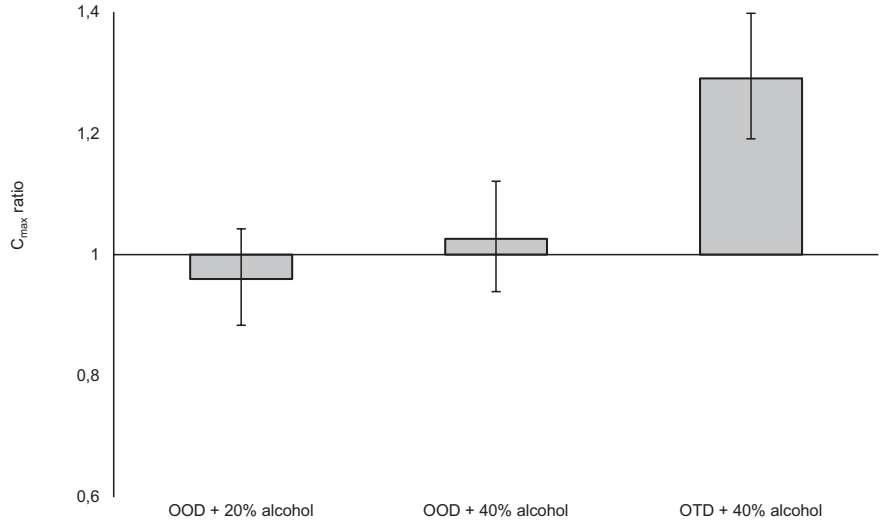

Figure 4 Maximum plasma drug concentration (C_{max}) ratio between alcohol treatments and water treatments with 90% confidence intervals. The reference treatment is that drug's water condition. OOD, oxycodone once-daily; OTD, oxycodone twice-daily.

Table 3 Commonly reported adverse events

	Number (%) of participants who experienced adverse events				
	Treatment A OOD with water (*n* = 17)	**Treatment B OOD with 20% alcohol (*n* = 18)**	**Treatment C OOD with 40% alcohol (*n* = 17)**	**Treatment D OTD with water (*n* = 19)**	**Treatment E OTD with 40% alcohol (*n* = 18)**
Any adverse event	10 (59)	17 (94)	17 (100)	9 (47)	18 (100)
Feeling drunk	0 (0)	10 (56)	11 (65)	1 (5)	12 (67)
Nausea	1 (6)	7 (39)	6 (35)	0 (0)	5 (28)
Vomiting	2 (12)	4 (22)	8 (47)	1 (5)	6 (33)
Dizziness	1 (6)	1 (6)	4 (24)	0 (0)	4 (22)
Headache	1 (6)	1 (6)	4 (24)	0 (0)	3 (17)
Somnolence	7 (41)	12 (67)	10 (59)	4 (21)	12 (67)

OOD, oxycodone once-daily; OTD, oxycodone twice-daily.
All participants who were dosed in the respective treatments were included in adverse event counts. Adverse events are listed if they occurred in more than two participants in a single treatment. Data are presented as absolute numbers and percentages.

of modified release opioids. However, similar *in vivo* findings have been reported for various modified release opioid formulations in which concomitant alcohol ingestion produced small changes in pharmacokinetic parameters without causing alcohol-induced dose dumping.[19]

Despite existing marketed products being resistant to alcohol-induced dose dumping, simultaneous use of alcohol and prolonged-release opioid medications remains contraindicated and a category-wide warning about the risk of alcohol for modified release products exists because of the significant past failings of previously marketed opioids.[8,10] Whether an effect that is unique to specific ingredients should result in all products of the same category being considered risky is beyond the scope of this study.

Nevertheless, it is clear that alcohol-induced dose dumping can be avoided through adequate formulation development. The OOD formulation tested here has proven this to be the case with alcohol, as well as in both fed and fasted states.[16]

This study did not attempt to assess the results of deliberate tampering before taking with alcohol but the abuse-deterrent properties of the formulation minimize any risk. There was also no scope to assess effects of alcohol or combined effect of alcohol and opioid medication on pain relief or on the behavioral effects of alcohol consumption, such as incorrect dosage due to drunkenness.

In conclusion, due to a history of inadequate formulations being susceptible to alcohol-induced dose dumping, it is understandable that blanket warnings about concomitant alcohol use remain. However, pharmacokinetic results showed that Develco Pharma Schweiz AG's once-daily formulation does not interact with alcohol, which, in addition to its proven efficacy and resistance to potential food-induced interactions, show it as safe and effective regardless of the context in which it is taken. This also lends confidence to other medicines that use the same prolonged-release technology.

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Conflict of Interest. All authors were employed by Develco Pharma Schweiz AG or BioPharma Services Inc. at the time of writing this paper and declared no competing interests for this work.

Author Contributions. D.F., N.B., and M.A.M. wrote the manuscript. N.B. and M.A.M. designed the research. J.F. performed the research. D.F. and J.F. analyzed the data. H.R. contributed new reagents/analytical tools.

1. Müller-Schwefe, G.H., Wimmer, A.M., Dejonckheere, J., Eggers, A. & Vellucci, R. Patients' and physicians' perspectives on opioid therapy for chronic cancer and musculoskeletal pain in Germany, Italy, and Turkey: PAin RESearch (PARES) survey. *Curr. Med. Res. Opinion* **30**, 339–347 (2014).
2. Cramer, M.P. & Saks, S.R. Translating safety, efficacy and compliance into economic value for controlled release dosage forms. *Pharmacoeconomics* **5**, 482–504 (1994).
3. Meyer, R.J. & Hussain, A.S.Awareness topic: mitigating the risks of ethanol induced dose dumping from oral sustained/controlled release dosage forms. FDA´s ACPS meeting October 2005.
4. World Health Organization. Management of Substance Abuse Unit. Global status report on alcohol and health. <https://www.who.int/substance_abuse/publications/global_alcohol_report/en/> (2018).
5. Saunders, K.W. *et al*. Concurrent use of alcohol and sedatives among persons prescribed chronic opioid therapy: prevalence and risk factors. *J. Pain* **13**, 266–275 (2012).
6. Larance, B. *et al*. Pain, alcohol use disorders and risky patterns of drinking among people with chronic non-cancer pain receiving long-term opioid therapy. *Drug Alcohol Depend.* **162**, 79–87 (2016).
7. Jones, C.M., Paulozzi, L.J. & Mack, K.A. Centers for Disease Control and Prevention (CDC). Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse-related emergency department visits and drug-related deaths-United States, 2010. *MMWR Morb. Mortal. Wkly. Rep.* **63**, 881–885 (2014).
8. US Food and Drug Administration. Information for healthcare professionals: hydromorphone hydrochloride extended-release capsules (marketed as Palladone). <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-healthcare-professionals-hydromorphone-hydrochloride-extended-release-capsules-marketed> (2005).
9. European Medicine Agency (EMA). Assessment report for authorised modified-release oral medicinal products of the WHO level III scale for the management of pain (intense sustained pain resistant to previous medications) (containing morphine, oxycodone, and hydromorphone). EMEA/H/A-31/1232. <https://www.ema.europa.eu/en/documents/referral/assessment-report-authorised-modified-release-oral-medicinal-products-who-level-iii-scale-management_en.pdf> (2011)
10. European Medicines Agency. Questions and answers on Ethirfin and associated names (morphine sulphate, prolonged-release capsules, 20, 60, 120 and 200 mg).

EMA/468843/2010 rev. EMEA/H/A-29/001248. <https://www.ema.europa.eu/en/documents/referral/questions-answers-ethirfin-associated-names-morphine-sulphate-prolonged-release-capsules-20-60-120_en.pdf>. Accessed December 20, 2010.

11. Riley, J., Eisenberg, E., Müller-Schwefe, G., Drewes, A.M. & Arendt-Nielsen, L. Oxycodone: a review of its use in the management of pain. *Curr. Med. Res. Opinion* **24**, 175–192 (2008).
12. de Kater, A., Butera, P., Haux, E., Schoenhard, G. & Friedmann, N.The effects of alcohol on an abuse-resistant formulation of controlled-release oxycodone. International Association for the Study of Pain. Glasgow, UK. August 17, 2008. Pain Therapeutics, Inc., #755 poster presentation.
13. Sathyan, G., Sivakumar, K. & Thipphawong, J. Pharmacokinetic profile of a 24-hour controlled-release OROS formulation of hydromorphone in the presence of alcohol. *Curr. Med. Res. Opinion* **24**, 297–305 (2008).
14. Farr, S.J., Robinson, C.Y. & Rubino, C.M. Effects of food and alcohol on the pharmacokinetics of an oral, extended-release formulation of hydrocodone in healthy volunteers. *Clin. Pharmacol. Adv. Appl.* **7**, 1 (2015).
15. Fiske, W.D., Jobes, J., Xiang, Q., Chang, S.C. & Benedek, I.H. The effects of ethanol on the bioavailability of oxymorphone extended-release tablets and oxymorphone crush-resistant extended-release tablets. *J. Pain* **13**, 90–99 (2012).
16. Scheidel, B. *et al.* Bioavailability of oxycodone after administration of a new prolonged-release once-daily tablet formulation in healthy subjects, in comparison to an established twice-daily tablet. *Int. J. Clin. Pharmacol. Ther.* **55**, 881–890 (2017).
17. Guidance for Industry – Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations. Center for Drug Evaluation and Research (CDER), Food and Drug Administration. <https://www.ipqpubs.com/wp-content/uploads/2014/04/BABEOld.pdf>. (March 2003).
18. Lux, E.A., Janecki, M. & Maritz, M.A. Clinical evaluation of the first oxycodone once daily prolonged release tablet in moderate to severe chronic pain: a randomized, double-blind, multicenter, cross-over, non-inferiority study to investigate efficacy and safety in comparison with an established oxycodone twice daily prolonged release tablet. *Curr. Med. Res. Opinion* **30**, 2365–2375 (2014).
19. D'Souza, S., Mayock, S. & Salt, A. A review of in vivo and in vitro aspects of alcohol-induced dose dumping. *AAPS Open* **3**, 5 (2017).

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