

ABSTRACT

Abuse of controlled-release oxycodone is a serious health concern. Abusers can defeat the controlled-release mechanism by dissolving oxycodone tablets in alcohol. Ingesting a dissolved tablet results in 'dose-dumping', which produces a quick, powerful euphoric high that can be fatal or lead to opioid addiction. Thus, the development of abuse-resistant opioid medications remains a major, but elusive, public health goal. A study was conducted in healthy volunteers to demonstrate the effects of alcohol on Remoxy™, a unique controlled-release liquid formulation of oxycodone in a capsule, specifically designed to resist common methods of abuse, such as dissolution in alcohol. This single-center, randomized, four-way crossover study was designed to evaluate the effect of ethanol on the rate and extent of absorption of oxycodone from Remoxy. The study recruited 37 healthy volunteers who were 'regular drinkers', i.e., male and female participants consuming 7 to 21 and 4 to 14 alcoholic drinks, respectively, in an average week. After signing informed consent, subjects were fed and pre-treated with the opioid antagonist naltrexone (to minimize opioid-related adverse events). Each subject ingested a single capsule of Remoxy 40 mg during each of four treatment sequences: with 240 mL of water alone; with 240 mL of 4% ethanol; with 240 mL of 20% ethanol; and with 240 mL of 40% ethanol. These ethanol quantities were designed to simulate the amount of alcohol consumed in a 'binge drinking' session. Each sequence was separated by a 96-hour washout period. Blood samples were obtained over 96 hours post drug administration. Patients were monitored for adverse events. Oxycodone C_{max} after Remoxy was 45.3 ng/mL with water alone, versus 45.0 ng/mL with 4% ethanol, 39.0 ng/mL with 20% ethanol and 49.7 ng/mL with 40% ethanol. The shape of the plasma concentration time curve was not affected by ethanol. There was no effect on total exposure; the ratio for AUC_{inf} of water co-ingestion to ethanol co-ingestion was 1.00, 1.06, and 1.14, respectively. No unexpected adverse events were noted. Remoxy is highly resistant to dissolution in alcohol. Consuming Remoxy with up to 40% ethanol did not defeat its unique, controlled-release formulation. The lack of a 'dose-dumping' effect presumably prevents the quick, powerful euphoric high sought by recreational drug abusers. These data suggest Remoxy represents a safer alternative to controlled-release oxycodone.

INTRODUCTION

Abuse of controlled-release oxycodone is a serious health concern. The misuse, abuse, and diversion of prescription pain relievers are a serious problem in the US. An estimated 7.0 million persons ≥ 12 years of age in the US used a prescription-type psychotherapeutic drug for non-medical reasons in the month before the Substance Abuse and Mental Health Services Administration (SAMHSA) survey in 2006.¹ Of these persons, 5.2 million used pain relievers. Thus, the development of abuse-resistant opioid medications remains a major, but elusive, public health goal.

Abusers can defeat the controlled-release mechanism of currently marketed controlled-release formulations by dissolving oxycodone tablets in alcohol. Ingesting a dissolved tablet results in 'dose-dumping', indicating the rapid release of the active ingredient from an extended release product into the blood stream. This produces a quick, powerful euphoric high that can be fatal or lead to opioid addiction. In previous clinical studies, preliminary formulations of Remoxy, a unique controlled-release liquid formulation of oxycodone in a capsule,

specifically designed to resist abuse, were shown to be highly resistant to common methods of abuse, including crushing and dissolving in alcohol.² The current robust clinical Phase I study in healthy volunteers assessed the effects of co-ingestion of alcohol on Remoxy.

METHODS

This was a single-center, randomized, four-way crossover study, designed to evaluate the effects of ethanol on the rate and extent of absorption of oxycodone from Remoxy. Each subject ingested a single capsule of Remoxy 40 mg during each of four treatment sequences (Table 1) that were separated by a 96-hour washout period.

Table 1. Study Design

Treatment 1:	Remoxy 40 mg capsule + water
Treatment 2:	Remoxy 40 mg capsule + 4% Ethanol ("Low Proof")
Treatment 3:	Remoxy 40 mg capsule + 20% Ethanol ("Medium Proof")
Treatment 4:	Remoxy 40 mg capsule + 40% Ethanol ("High Proof")

All treatments were followed by one cup (240 mL) of water.

Ethanol quantities simulated the amount of alcohol consumed in a 'binge drinking' session. The study recruited 37 (26 males and 11 females) healthy volunteers who were 'regular drinkers', i.e., male and female participants consuming 7 to 21 and 4 to 14 alcoholic drinks, respectively, in an average week. Subjects were fed a standard breakfast and pre-treated with the opioid antagonist naltrexone to minimize opioid-related adverse events (AEs). Patients were monitored for AEs.

Blood samples for determination of oxycodone, noroxycodone, and oxymorphone were obtained over 96 hours post drug administration. All subjects who completed the Remoxy + water only and at least one of the alcohol study periods were included in the pharmacokinetic analyses. Subjects who experienced emesis during a study period were excluded from the analysis for that period. PK parameters were calculated using non-compartmental analysis. Analysis of variance (ANOVA) and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log transformed PK exposure parameters. The 90% confidence intervals for the ratio of the geometric means of Test (Remoxy + ethanol) vs. Reference (Remoxy + water) were calculated.

RESULTS

Thirty-seven (37) subjects were enrolled. The mean age was 30.2 years (range, 21-43 years), mean height was 171 cm (range, 155-186 cm), and mean weight was 75.5 kg (range, 53-100 kg). Fig. 1 shows the disposition of subjects and Table 2 the number of subjects included in the PK analysis for each treatment.

A total of 36 subjects received three of the four treatment regimens and 28 completed all four treatment regimens. Nine subjects prematurely withdrew from the study, one due to an AE of hyporeflexia and eight subjects (seven females and one male) due to sponsor request. The sponsor requested premature withdrawal of subjects scheduled to receive 40% ethanol during Treatment Periods 3 and 4 because numerous subjects receiving the 40% ethanol experienced severe intoxication during Treatment Periods 1 and 2.

Fig. 1. Disposition of Subjects

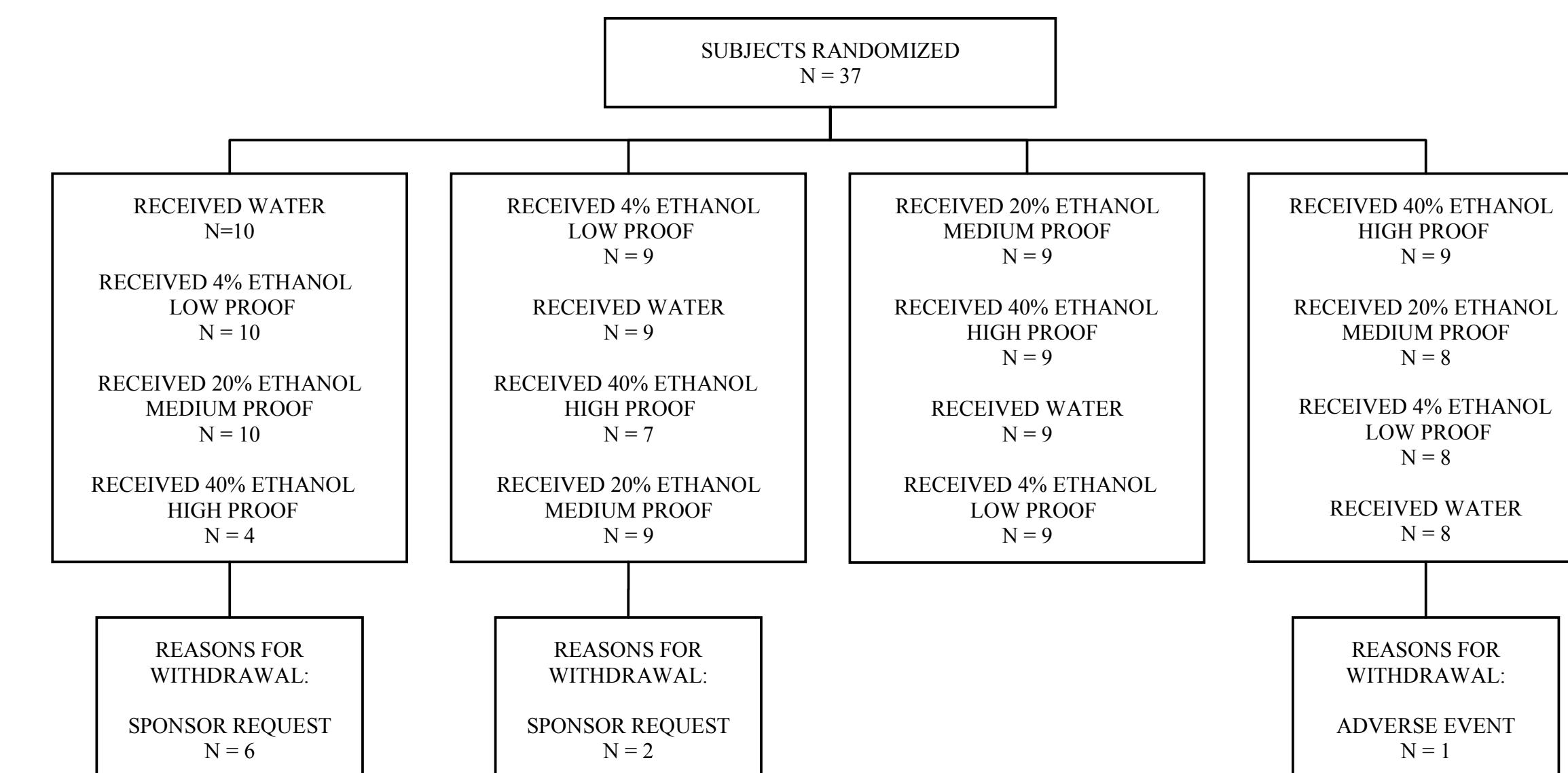
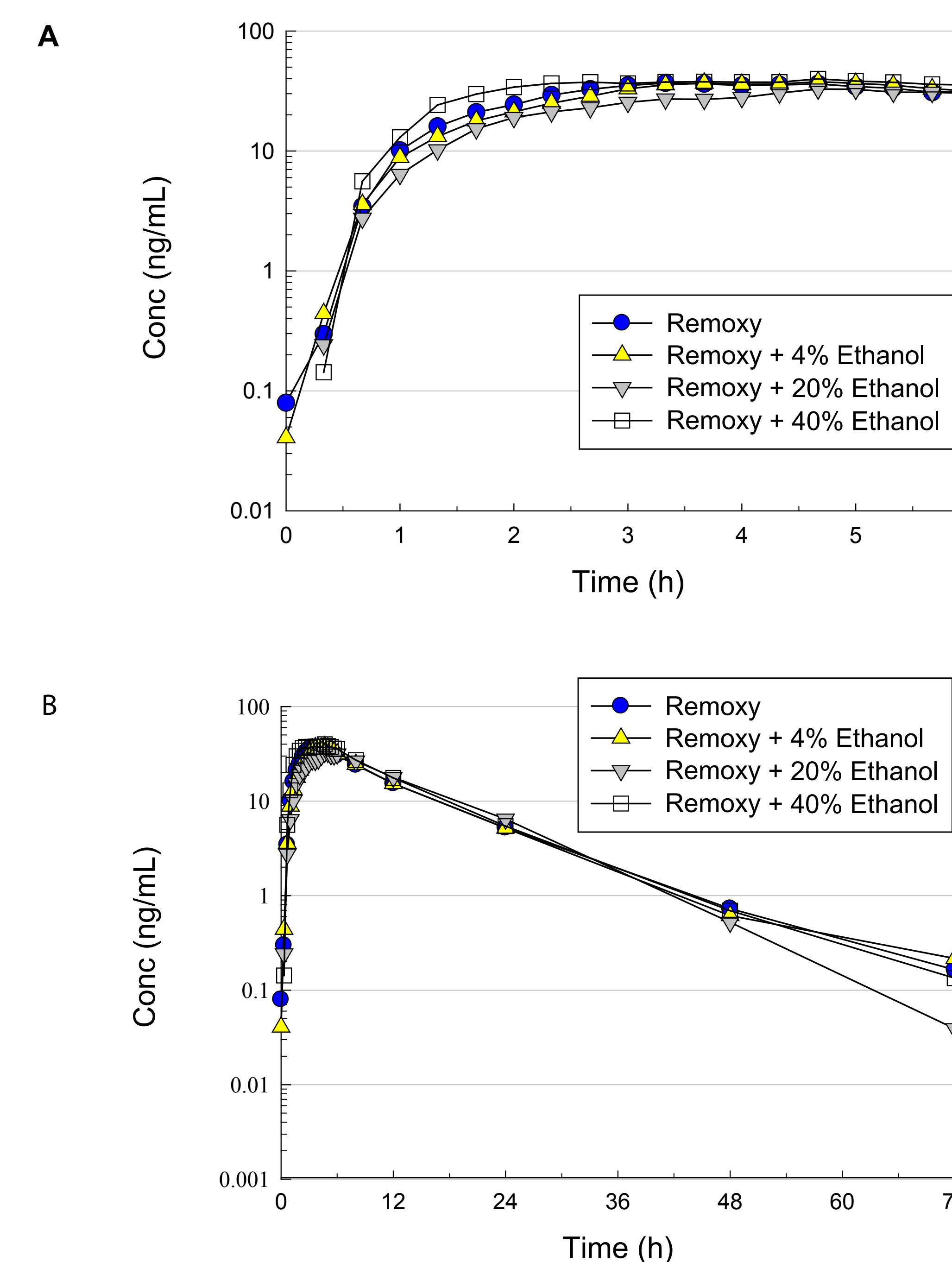


Table 2. Subject Inclusion by Analyses

	Water	Low Proof	Medium Proof	High Proof
Pharmacokinetic N	36	36	27	18

The shape of the plasma concentration time curve was not affected by the co-ingestion of Remoxy with ethanol and showed a typical controlled-release profile for all treatments (Fig. 2). Oxycodone C_{max} after Remoxy was 45.3 ng/mL with water alone, versus 45.0 ng/mL with 4% ethanol, 39.0 ng/mL with 20% ethanol, and 49.7 ng/mL with 40% ethanol.

Fig. 2. Mean Plasma Oxycodone Concentrations through 6 hr Post-Dose (A) and 72 hr Post-Dose (B)



Mean plasma concentrations of oxycodone were comparable across treatments as were mean values of C_{max} and AUC_{inf} (Table 3). The time to reach peak exposure was not affected by co-ingestion with 4% or 40% ethanol, while the Remoxy + 20% ethanol group exhibited a slight increase relative to Remoxy + water. The mean elimination half-lives ($T_{1/2}$) for the four treatments ranged from 7.57 hours to 10.37 hours.

Table 3. Summary of Oxycodone PK Parameters

Parameter	Remoxy + Water	Remoxy + 4% Ethanol	Remoxy + 20% Ethanol	Remoxy + 40% Ethanol
C_{max} (ng/mL)	45.3 (23.1)	45.0 (20.6)	39.0 (16.1)	49.7 (27.2)
AUC_{0-4} (hr*ng/mL)	471.3 (154.6)	471.8 (147.5)	496.3 (153.6)	537.7 (191.5)
AUC_{inf} (hr*ng/mL)	513.8 (156.5)	516.0 (144.1)	542.5 (144.6)	585.3 (184.3)
$T_{1/2}$ (hr)	10.37 (3.78)	8.84 (3.84)	7.57 (2.49)	9.10 (4.36)

There was no effect of co-ingestion with ethanol on C_{max} , AUC_{0-4} , and AUC_{inf} after Remoxy + water and Remoxy + 4% ethanol (Table 4). After Remoxy with 20% ethanol, there was a decrease in C_{max} relative to Remoxy with water, but no significant change in AUC_{0-4} or AUC_{inf} . Administration with 40% ethanol resulted in an approximately 10% increase in C_{max} and confidence intervals for total exposure (AUC_{0-4} or AUC_{inf}) that were slightly above the generally accepted 80% to 125% limits.

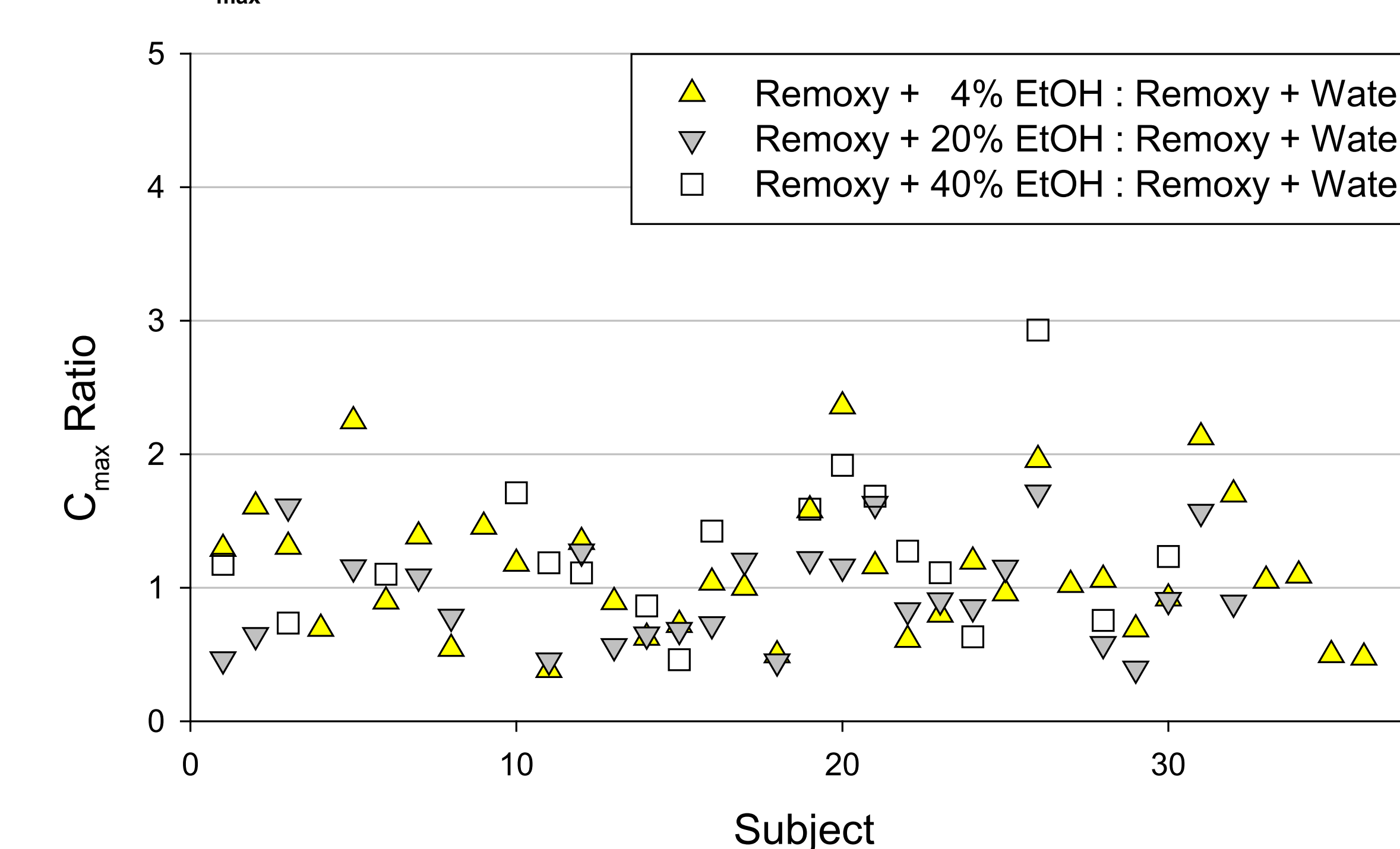
Table 4. ANOVA Ratios of Least-Squares Means (LSM)

Parameter	Remoxy + Ethanol	Ratio of LSM, % Remoxy + EtOH/Remoxy + Water	90% CI (lower; upper)
C_{max} (ng/mL)	4%	101.18	89.37; 114.56
	20%	85.42	74.34; 98.15
	40%	113.71	96.68; 133.75
AUC_{0-4} (hr*ng/mL)	4%	100.72	95.66; 106.06
	20%	106.62	100.64; 112.96
	40%	117.80	110.11; 126.01
AUC_{inf} (hr*ng/mL)	4%	100.75	94.39; 107.53
	20%	103.05	96.87; 109.62
	40%	118.57	111.03; 126.62

Individual subjects' C_{max} ratios of Remoxy + ethanol vs. Remoxy + water, based on non-transformed data, were similar between treatments for most subjects (Fig. 3). For co-ingestion of Remoxy with 4% ethanol relative to water, individual C_{max} ratios ranged from 0.38 to 2.36; three subjects showed a ratio greater than 2. Subjects co-ingesting Remoxy with 20% ethanol relative to water had C_{max} ratios ranging from 0.39 to 1.71. For co-ingestion with 40% ethanol relative to water, individual C_{max} ratios ranged from 0.46 to 2.93 with only one subject showing a ratio greater than 2.00. The ratios for the remaining subjects in this group ranged from 0.46 to 1.92.

The metabolism of oxycodone did not appear to be affected by co-administration of alcohol based on the PK profile of the metabolites noroxycodone and oxymorphone. No serious or unexpected adverse events were reported during the study.

Fig. 3. C_{max} Ratio of Remoxy + Ethanol vs. Remoxy + Water for Each Subject



DISCUSSION

The misuse, abuse, and diversion of prescription pain relievers remains a serious problem in the US. Remoxy, a unique controlled-release liquid formulation of oxycodone in a capsule, specifically designed to resist abuse, has been shown to resist common methods of abuse such as crushing and dissolving in alcohol or other solvents as well as using a range of temperatures and pH's. Remoxy is efficacious: in a large phase III clinical study, Remoxy showed analgesic efficacy over a period of 12 weeks.³

Prior clinical studies assessed the pharmacokinetics of preliminary formulations of Remoxy capsules that were ingested after crushing with alcohol or water and compared these to commercially available controlled-release oxycodone.² The current study confirms that Remoxy maintains its controlled-release mechanism when co-administered with up to 40% ethanol. This lack of 'dose-dumping' prevents the rapid rise in oxycodone plasma levels and the resulting euphoric high that is sought by drug abusers.

CONCLUSIONS

- Remoxy is highly resistant to dissolution in alcohol.
- Administration of Remoxy with up to 40% ethanol did not defeat its unique, controlled-release formulation as shown by the plasma concentration profiles.
- The lack of 'dose-dumping' prevents the quick, powerful euphoric high sought by recreational drug abusers. These data suggest Remoxy represents a safer alternative to current formulations of controlled-release oxycodone.

REFERENCES

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