



Pain Therapeutics, Inc.

REMOXY™, A NOVEL DRUG CANDIDATE, DETERS OXYCODONE ABUSE IN HUMANS

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ABSTRACT

Aim:

Abuse and diversion of sustained-release oxycodone is of great concern to health officials. Abusers can easily extract the full dose of oxycodone from sustained-release preparations, resulting in an immediate, large spike in oxycodone blood levels and a powerful morphine-like high. Recreational use of oxycodone can lead to respiratory depression, death, or opiate addiction. In the U.S., oxycodone abuse resulted in over 20,000 ER visits and hundreds of deaths in 2002. Remoxy is a novel drug formulation designed to deter oxycodone abuse. Remoxy's gel-cap formulation provides a long-acting dose of oxycodone, yet cannot be abused by crushing, freezing and crushing, or by dissolving in water, alcohol or other common beverages. This study compared the pharmacokinetics of Remoxy vs. commercially available controlled-release (CR) oxycodone following typical methods of abuse.

METHODS:

Remoxy 10 mg and commercially available CR oxycodone 10 mg were submitted to a series of physical challenges designed to mimic common methods of drug abuse. Both drugs were crushed, chewed or dissolved in alcohol then ingested by human volunteers. Plasma oxycodone levels were monitored for 48 hours and also compared to an immediate release commercial oxycodone formulation.

RESULTS:

Attempts to abuse Remoxy produced significantly lower AUCs of plasma oxycodone at early time-points compared to the commercial formulation. Results were statistically significant and were reproduced across several common methods of oxycodone abuse.

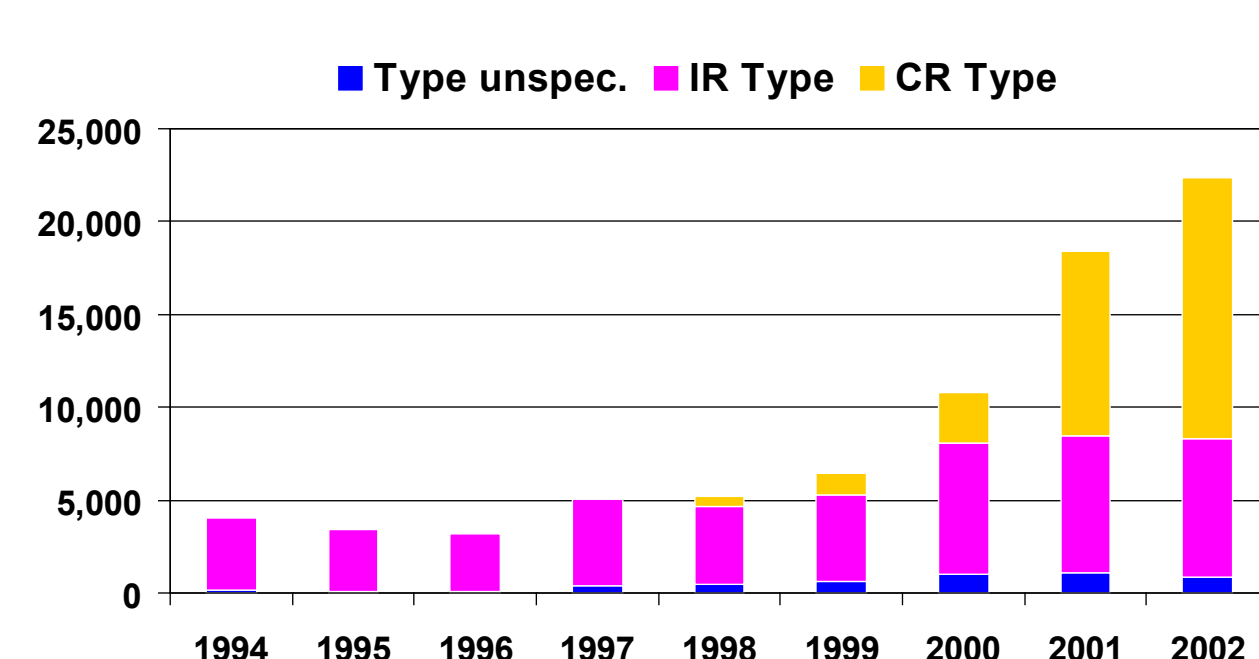
CONCLUSIONS:

These results demonstrate Remoxy is a safer alternative to commercially available CR oxycodone. The expected benefits of Remoxy include less illicit use, less oxycodone diversion and fewer oxycodone-related fatalities.

INTRODUCTION

Oxycodone is a strong opiate with an abuse liability similar to morphine. Abuse of CR formulations of oxycodone and other prescription opioids is a large, fast-growing problem in the US¹. Simply crushing and dissolving these formulations can yield the full 12-hr dose to produce an immediate, large spike in opiate blood levels and a powerful morphine-like high, as well as the potential for respiratory depression and death. This problem and associated addictions have attracted a substantial amount of media attention in recent years²⁻⁶. In the U.S., oxycodone abuse resulted in over 20,000 Emergency Room (ER) visits, according to the Drug Abuse Warning Network (DAWN), a division of the Substance Abuse and Mental Health Services Administration. Abuse of oxycodone comprised nearly 20% of all ER visits involving abuse of narcotic analgesics in 2002. The majority of oxycodone abuse resulting in ER visits involves CR formulations, and ER visits related to oxycodone abuse rose markedly since the 1996 introduction and marketing of CR oxycodone (Fig. 1).

Fig. 1. Emergency Room Visits Involving Oxycodone Abuse, 2002



Remoxy is a novel long-acting oxycodone formulation designed to deter oxycodone abuse. When taken whole as directed, Remoxy and a commercial CR oxycodone formulation have a similar C_{max} and AUC (See poster # 21)⁷. *In vitro* tests of abuse deterrence show that Remoxy cannot be fragmented by forceful crushing, even after freezing at -80°C , and that its long-acting properties are preserved after crushing or attempts to extract in alcohol. The abuse deterrent properties of Remoxy are demonstrated here in clinical pharmacokinetic studies. Healthy male volunteers ingested Remoxy or a commercial CR formulation subjected to common methods of abuse: chewing, crushing, or extraction in alcohol.

METHODS

These studies received Institutional Review Board approval, and all subjects gave their written informed consent. Subjects were 18- to 45-year-old healthy male volunteers. Two separate studies were conducted comparing 10 mg Remoxy to a commercial 10 mg CR oxycodone formulation. In the second study, a 10 mg immediate-release (IR) formulation was included as a comparator. In each study, blood samples were taken prior to dosing and at specified intervals for 48 hrs post-dosing to determine oxycodone plasma concentrations. In all cases, doses were separated by a washout period of 2-3 days.

STUDY 1:

Two groups of 5 subjects were randomly assigned to receive either Remoxy or a commercial CR oxycodone formulation in a 3-way crossover of:

- 1) Swallowing whole with water.
- 2) Chewing for 5 minutes followed by drinking water.
- 3) Probing/stirring in 1 oz. of 40 proof alcohol for 10 minutes and drinking the mixture.

STUDY 2:

Two groups of 5 subjects were randomly assigned to receive either Remoxy or a commercial CR oxycodone formulation as well as an IR formulation for comparison in a 4-way crossover of:

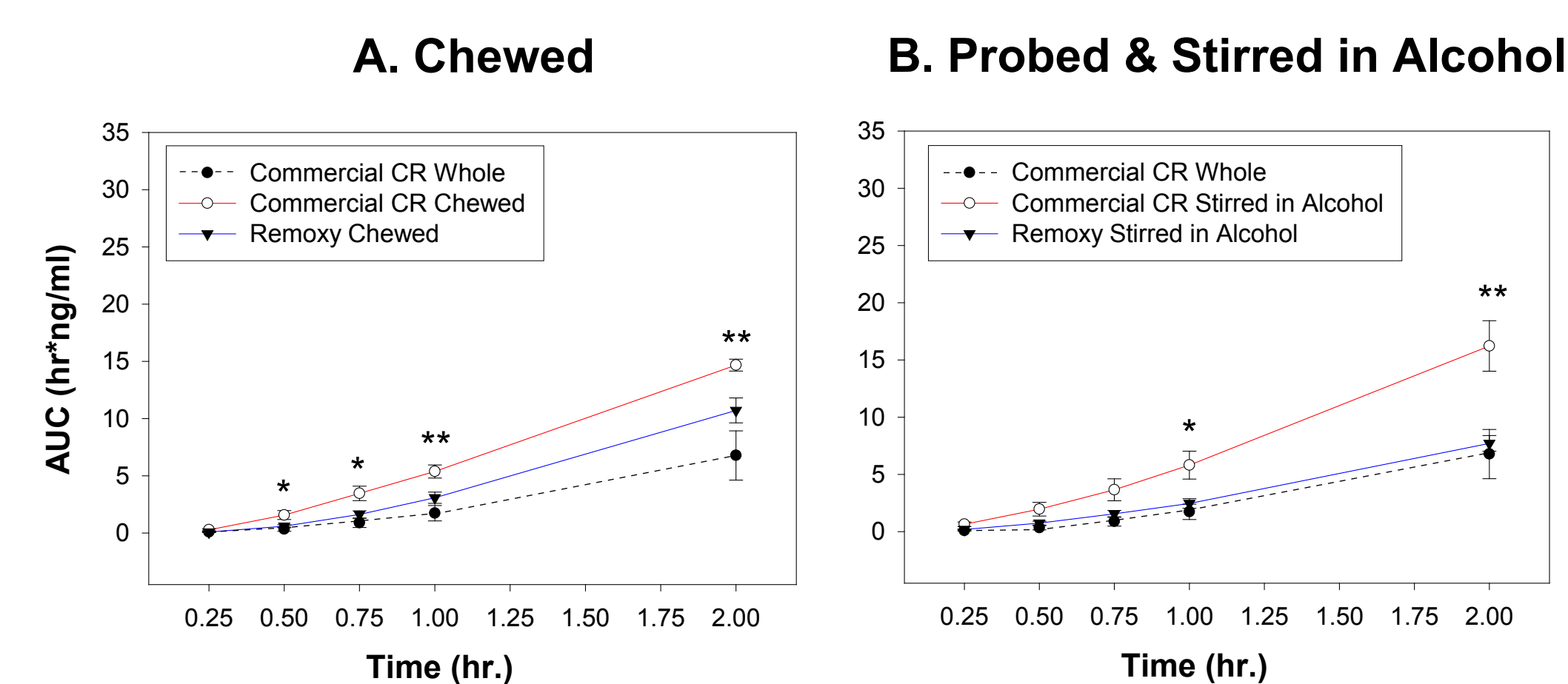
- 1) Swallowing whole with water.
- 2) Swallowing the IR formulation whole with water.
- 3) Crushing and dissolving in water, then drinking the mixture.
- 4) Crushing and dissolving in 1 oz. of 40 proof alcohol, then drinking the mixture.

RESULTS

STUDY 1

The first abuse deterrence study demonstrated that Remoxy resists abuse by chewing or by probing and stirring in alcohol, although neither challenge fully compromised the CR feature of the commercial formulation. After chewing, the oxycodone plasma AUCs were significantly lower for Remoxy than for the commercial CR formulation at all time-points between 30 min. and 2 hrs. ($P=0.06$ at 15 min, $P=0.04$ at 30 min., $P=0.03$ at 45 min, and $P=0.01$ at 1 and 2 hrs; Fig. 2A). After stirring and probing in alcohol, Remoxy produced significantly lower oxycodone AUCs than the commercial CR formulation at 1 and 2 hrs, with a trend toward significance at earlier time-points ($P=0.06$ at 15 min, $P=0.09$ at 30 min., $P=0.07$ at 45 min., $P=0.03$ at 1 hr, and $P=0.006$ at 2 hrs; Fig. 2B).

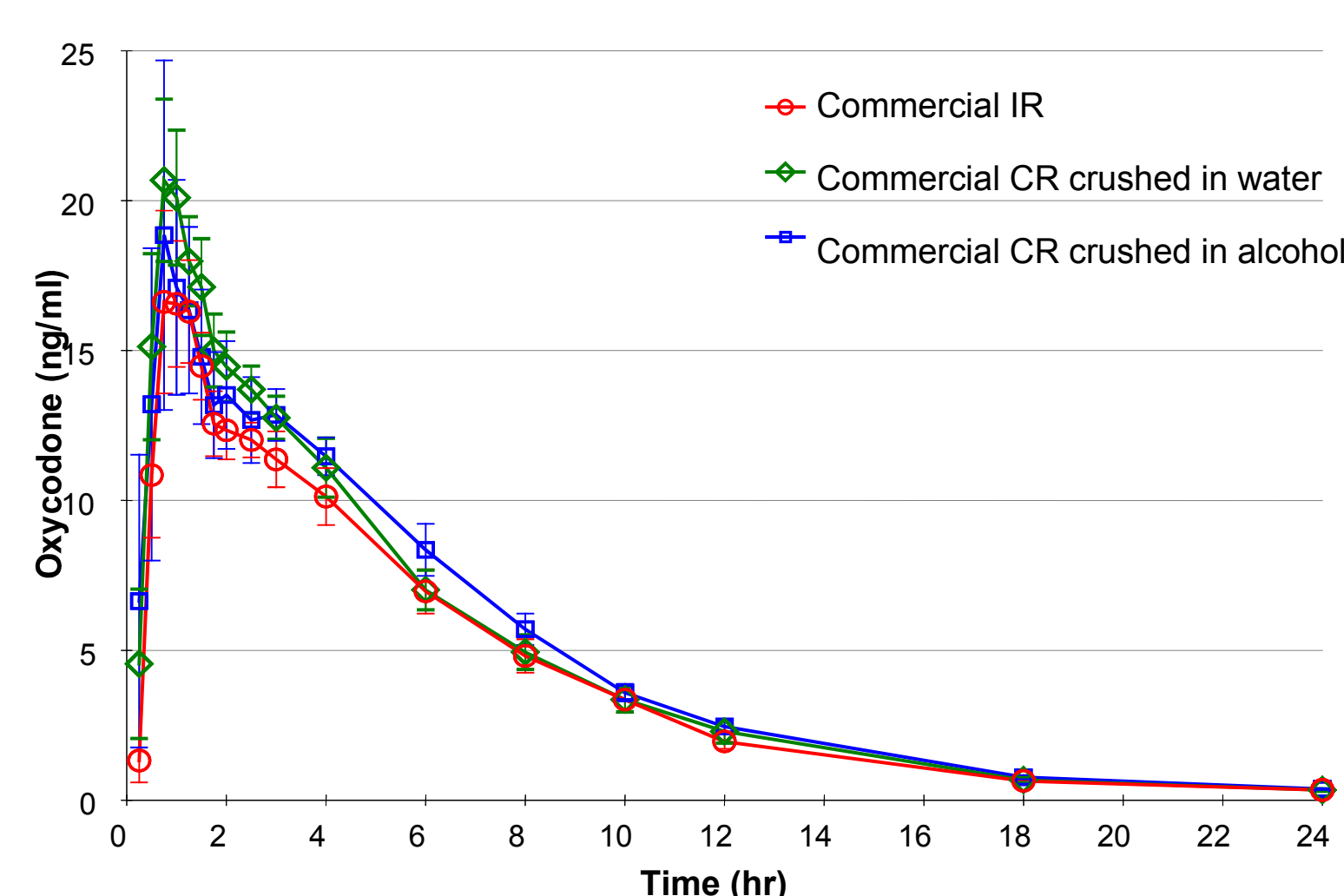
Fig. 2



STUDY 2

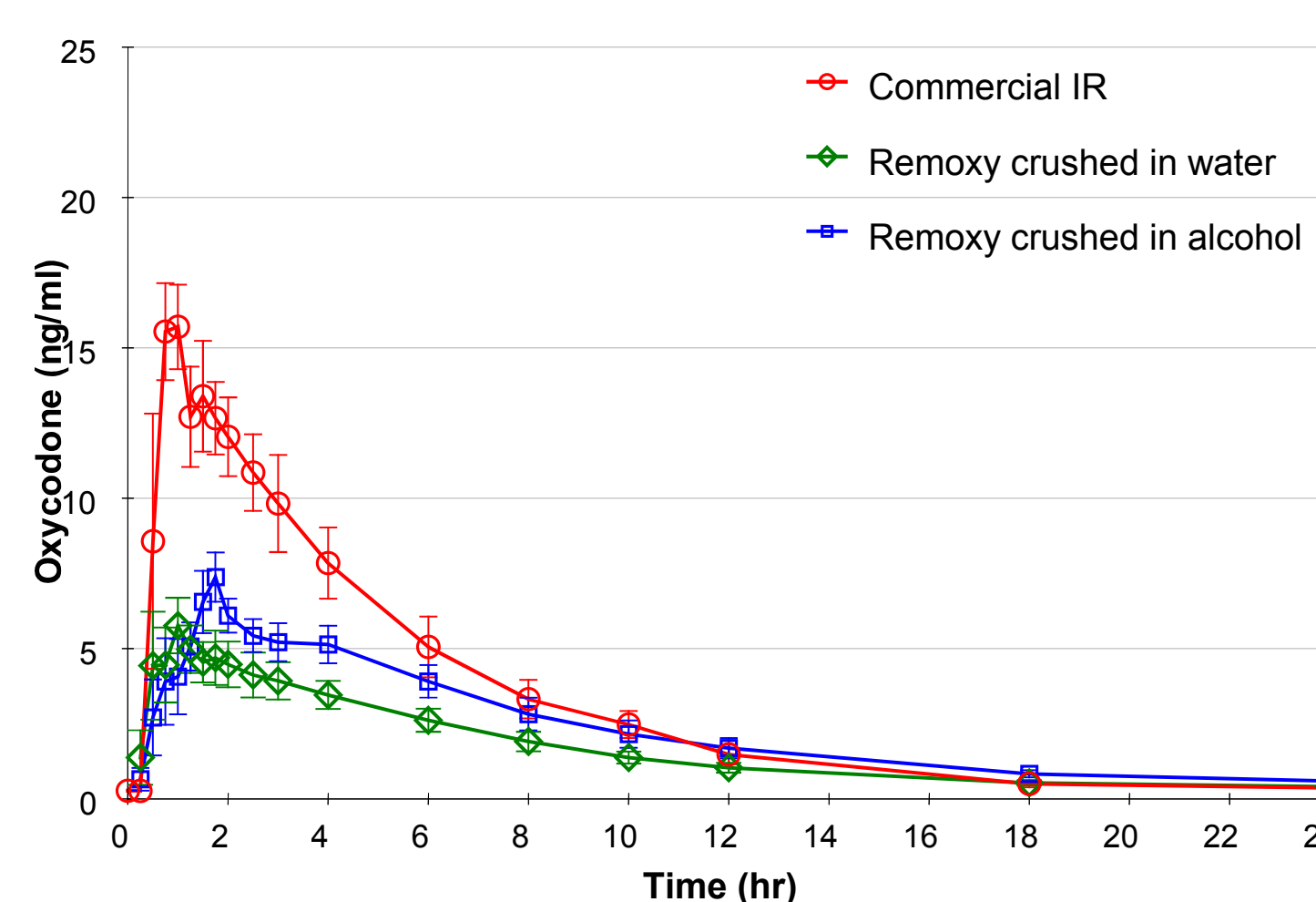
Study 1 assessed abuse potential by *partial destruction* of the formulation via chewing or dissolution in alcohol. In contrast, Study 2 assessed abuse potential by *complete destruction* of the formulation by crushing and dissolution in water or alcohol. For comparison, subjects in Study 2 also took a commercial IR oxycodone formulation of the same dose strength. When crushed and taken with water or alcohol, the commercial CR formulation produced plasma oxycodone levels very similar to the commercial IR formulation. In fact, the C_{max} values resulting from crushing the commercial CR formulation in water (21.8 ng/ml) or in alcohol (21.0 ng/ml) were slightly higher than the C_{max} of the commercial IR formulation (18.9 ng/ml) (Fig. 3).

Fig. 3 Plasma Oxycodone Levels After Crushing Commercial CR



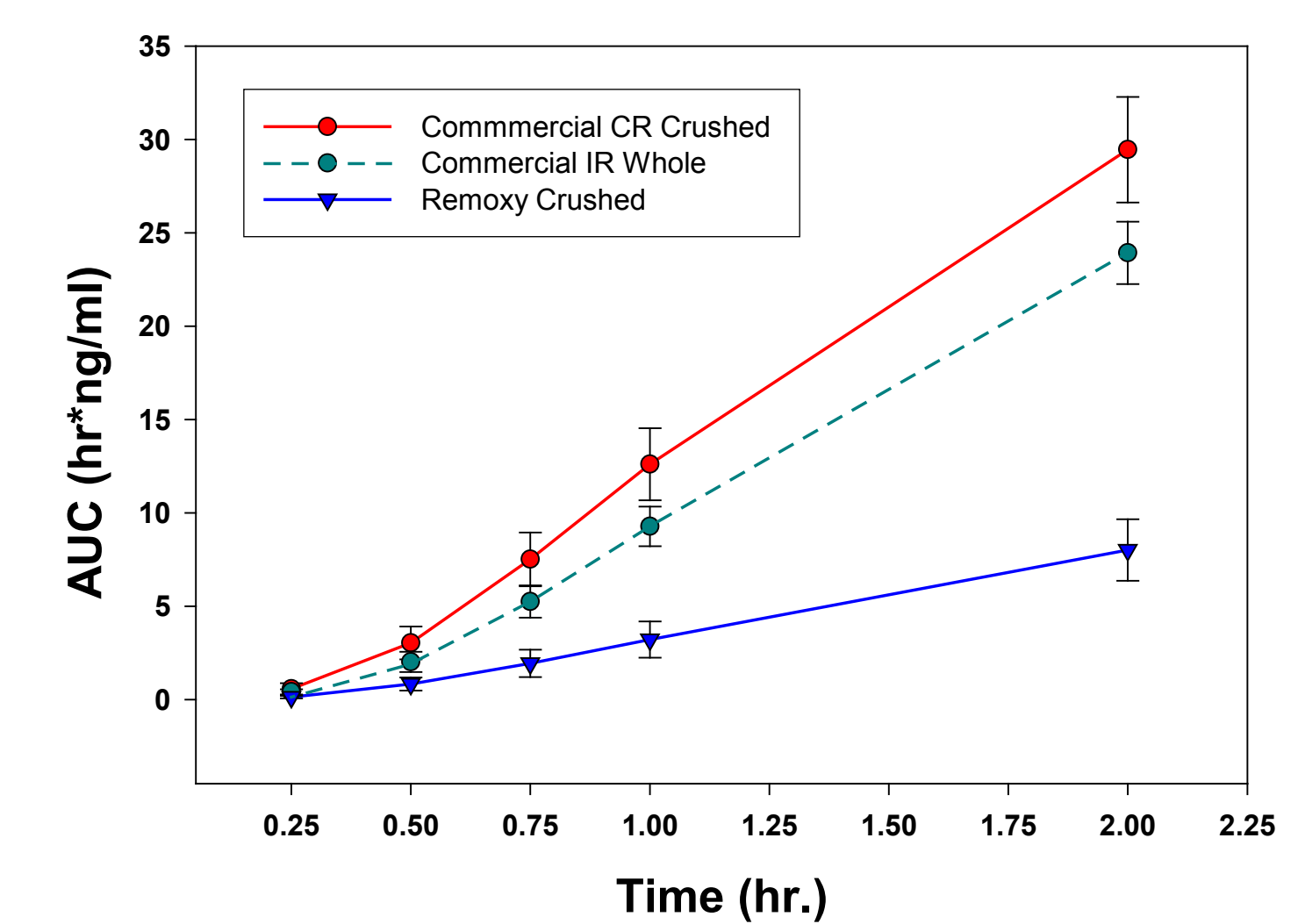
In contrast, the oxycodone C_{max} for Remoxy after crushing and taking with water (6.2 ng/ml) or alcohol (7.7 ng/ml), was significantly lower than the C_{max} produced by the commercial IR formulation (18.2 ng/ml) ($P<0.001$ for Remoxy with water; $P<0.001$ for Remoxy with alcohol; Fig. 4).

Fig. 4 Plasma Oxycodone Levels After Crushing Remoxy



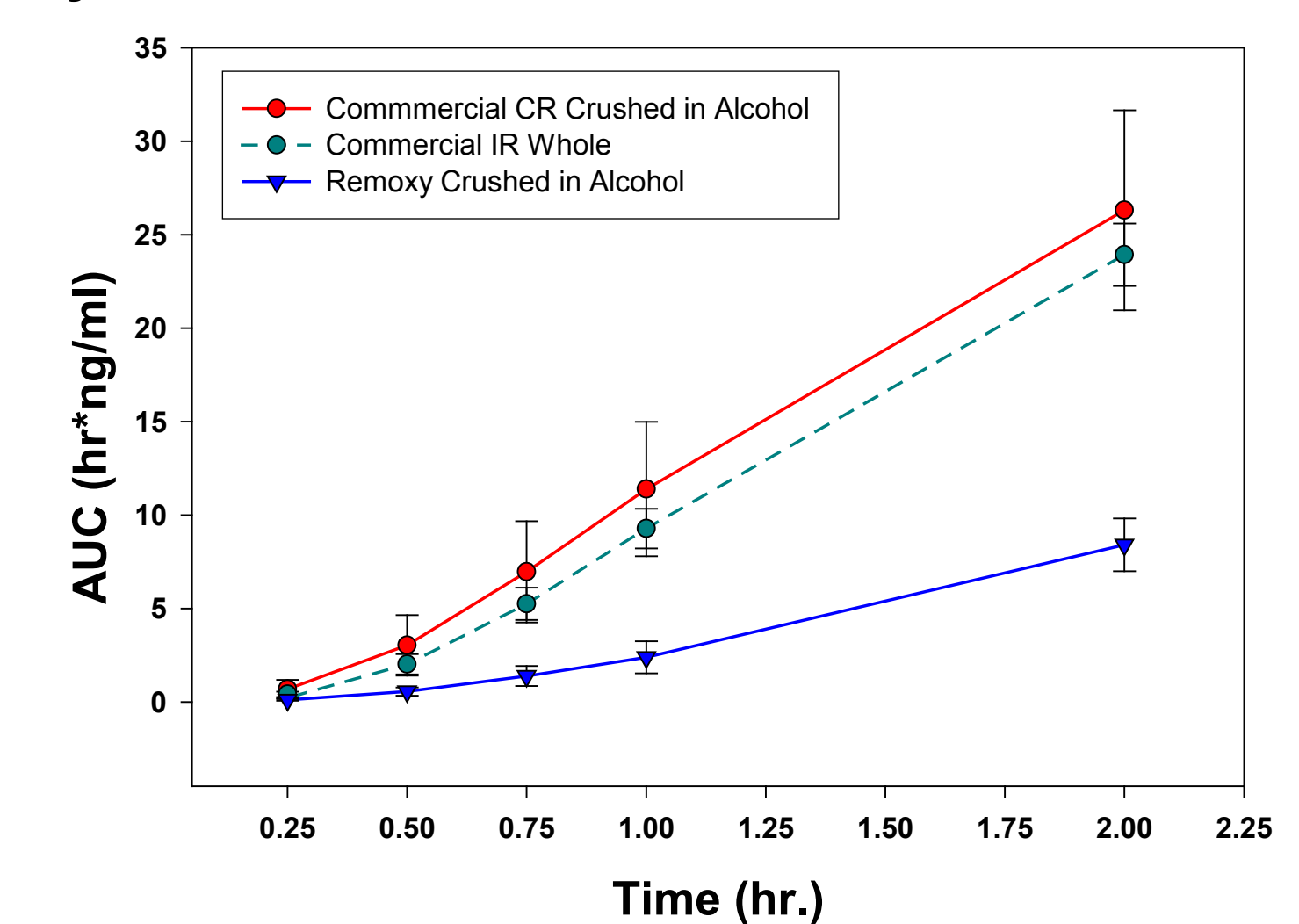
In addition, crushing and ingesting the commercial CR formulation with water resulted in oxycodone AUCs that were slightly higher than AUCs produced by the IR formulation. In contrast, crushing Remoxy and taking it with water produced AUCs that were significantly lower than the commercial IR formulation ($P=0.03$ at 45 min; $P=0.003$ at 1 hr; $P<0.001$ at 2 hr; Fig. 5).

Fig. 5. Oxycodone AUCs: Crushed & Taken with Water



Similarly, after crushing the commercial CR formulation in alcohol, oxycodone AUCs did not differ from those produced by an IR formulation. In contrast, taking crushed Remoxy in alcohol produced AUCs significantly lower than the IR formulation ($P=0.01$ at 45 min; $P=0.001$ at 1 hr; $P<0.001$ at 2 hr).

Fig. 6. Oxycodone AUCs: Crushed & Taken with Alcohol



No adverse events were reported after taking either formulation whole with water except one report of dizziness in the Remoxy group. Crushing and taking Remoxy with water resulted in one report of lethargy. In contrast, crushing and taking the commercial CR formulation with water produced dizziness (4 subjects), a feeling of relaxation (3 subjects), a euphoric mood, fatigue and somnolence (2 reports, each) and nausea, decreased blood pressure, bradycardia, both increased and decreased heart rate, both increased and decreased respiration, dyspnea, pruritis, feeling hot, diaphoresis (a single report of each). The decrease in blood pressure in 1 subject was clinically significant, i.e., a drop from 114/66 pre-dosing to 78/39 in one hour, but recovered within 2 hrs. Crushing and taking with alcohol instead of water did not notably change the incidence of reported side effects for either formulation other than an increase in lethargy or somnolence.

DISCUSSION

Remoxy is highly resistant to abuse by crushing and dissolving in water or alcohol, in contrast to the commercial CR oxycodone formulation. Crushing the commercial CR oxycodone formulation and taking it with water or alcohol resulted in oxycodone plasma levels that were similar to those produced by a commercial IR formulation. The crushing challenges to Remoxy resulted in oxycodone plasma levels that were significantly lower than those from the commercial IR or crushed CR formulations. Crushing Remoxy also produced fewer adverse events than crushing the commercial CR formulation, presumably due to lower blood levels of oxycodone.

CONCLUSION

Remoxy is a novel 12-hr oxycodone formulation that is highly resistant to abuse. Crushing Remoxy produced oxycodone plasma concentrations that were significantly lower than both the IR and crushed CR commercial formulations. Preventing high plasma concentrations of oxycodone presumably prevents the euphoria sought by recreational users and may also reduce oxycodone-related ER visits and fatalities. Remoxy therefore represents a safer alternative to currently marketed CR oxycodone formulations.

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