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Subjective and Psychomotor Effects of Carisoprodol in Combination With Oxycodone in Healthy Volunteers

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Abstract

BACKGROUND—Some chronic pain patients on long-term opioid therapy also take centrally-active skeletal muscle relaxants. One of those muscle relaxants is carisoprodol, a drug that is abused and capable of producing impairment. It would be of relevance to characterize the effects of an opioid and carisoprodol when taken together to determine if abuse liability-related measures and psychomotor impairment are increased compared to when the drugs are taken alone.

METHODS—As part of a larger crossover, randomized, double-blind study, we examined the subjective and psychomotor responses of 15 healthy volunteers to four experimental conditions: placebo, 350 mg carisoprodol, 10 mg oxycodone, and 350 mg carisoprodol followed 60 min later by 10 mg oxycodone (intended to test the interaction of the two drugs when they were producing their maximal effects).

RESULTS—Preliminary data analyses indicated that some of carisoprodol's effects were declining when we tested for drug interactions. Despite this, on some outcome measures in which the drugs alone did not differ from placebo, when tested together subjective effects were increased, including those that were abuse liability-related, and psychomotor performance decreased, relative to placebo.

CONCLUSIONS—This is the first study that we are aware of that has shown that carisoprodol and oxycodone, two drugs that are sometimes co-prescribed for relief of pain, produce effects when administered “together” (i.e., separated by 60 min) that are of greater magnitude than when they are administered alone. Some of the effects were not benign, and are of concern from both abuse liability and public safety standpoints.

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Contributors

Dr. Zacny designed the study, had primary responsibility for data analysis, and wrote the first draft of the manuscript. Drs. Paice and Coalson advised on dose selections and changes in study design as the study progressed. Dr. Coalson supervised the anesthesiology residents and certified registered nurse anesthetists who provided medical coverage during experimental sessions. Drs. Paice and Coalson contributed to and have approved the final manuscript.

Conflict of interest

Drs. Zacny, Paice, and Coalson have no conflicts of interest to report.

Keywords

carisoprodol; musculoskeletal relaxant; prescription opioid; oxycodone; subjective effects; abuse liability; psychomotor performance; healthy volunteer

1. Introduction

It is estimated that approximately one-third of US adults (over 25 million people) suffer from chronic pain, some of whom are on long-term opioid therapy for their pain disorder (Johannes et al., 2010). Some chronic pain patients on such therapy take other psychoactive medications, either for pain amelioration or for treatment of a comorbid condition (e.g., anxiety disorder). One class of medications that some chronic pain patients on long-term opioid therapy use are centrally-acting skeletal muscle relaxants (Fillingim et al., 2003; Dillon et al., 2004). One drug within this class, carisoprodol (SOMA®), is known to be abused and also is associated with driving-under-the-influence violations and auto accidents (Bramness et al., 2004, 2007; Reeves and Burke, 2010). The drug is a controlled substance in at least 18 states in the US and is currently under consideration for controlled substance status by the Federal Drug Enforcement Administration (Fass, 2010). Although the mechanism of action by which carisoprodol has therapeutic efficacy is not fully understood, it is known that the drug modulates and directly activates $GABA_A$ receptors (Gonzalez et al., 2009). We thought it important to examine the interaction of carisoprodol with opioids to determine if the two drugs in combination produce a greater magnitude of abuse liability-related subjective effects and/or impairment than either drug alone. There is a case report in the literature in which people reported using tramadol and carisoprodol together because the drugs combined produced feelings of euphoria and relaxation (Reeves and Liberto, 2001). We also included a negative control drug, metaxalone, a muscle relaxant with no apparent history of abuse into the study design. In this way, if we indeed found that carisoprodol and oxycodone generated a profile indicative of increased propensity to abuse or produced greater impairment, and the other muscle relaxant in combination with the opioid did not, this might inform medical caregivers as to which muscle relaxant might be safer to prescribe.

The study was designed to test two doses of carisoprodol (350 mg that is a therapeutic dose and 700 mg that is supratherapeutic) alone and in combination with oxycodone (10 mg); one dose of metaxalone (1600 mg, a supratherapeutic dose serving as the negative control) alone and in combination with oxycodone; and oxycodone by itself and placebo. It should be noted that drugs were administered at different times based on the different t_{max}'s of the drugs (we wanted to study the effects of combining a muscle relaxant with oxycodone when they were both approaching peak effects). Metaxalone with an estimated t_{max} of 3 h (Physicians' Desk Reference, 2007) was administered 2 h before oxycodone with an estimated t_{max} of 1 h (Poyhia et al., 1992), and carisoprodol with an estimated t_{max} of 1.7 h (Bramness et al., 2005; SOMA package insert: http://www.soma250.com/pdf/full_prescribing_info.pdf, accessed June 30, 2011) was administered 1 h before oxycodone.

After six subjects completed the 8-session study, the condition in which 700 mg of carisoprodol and oxycodone were administered in the same session was eliminated from the study because of safety concerns relating to excessive sedation noted with some subjects. Preliminary data analyses after study completion revealed that: 1) metaxalone at a supratherapeutic dose (800 mg is the prescribed dose) administered by itself had no effects whatsoever and did not alter any effects of oxycodone, and 2) some effects of 350 mg of carisoprodol were already on the decline at the first time point at which the effects of it

combined with oxycodone were examined. The first time point we could test for drug interactions was 30 min after oxycodone was administered (i.e., 90 min after carisoprodol was administered), but carisoprodol was exerting greater psychomotor impairment prior to this. On the Digit Symbol Substitution Test (to be described in the Methods section), performance in the 350 mg carisoprodol condition was significantly different from placebo (i.e., impaired performance) 30 and 60 min after capsule ingestion, but not at the 90 min time point. Given these circumstances, we made the decision to present the results of this study in two separate reports. The present paper will report on the effects of the lower dose of carisoprodol and oxycodone alone and when presented in the same session. The second report has been submitted elsewhere and describes the effects of carisoprodol (0, 350, 700 mg) alone, including all time points during which effects were tested after its administration. A concern regarding this current paper is that effects of the two drugs together when carisoprodol's effects are already decreasing might be different qualitatively or quantitatively from the effects of these two drugs if they were peaking simultaneously. We feel, however, that the results are important to document because with a number of different outcome measures, oxycodone and carisoprodol, when tested within the same session, had larger effects than that of placebo, whereas the two drugs when tested alone (in separate sessions) did not.

2. Methods

2.1. Subjects

Requirements for participation in this IRB-approved study included age between 21–39 years, a high school diploma or the equivalent, verbal fluency in English, and some current level of alcohol use. Exclusion criteria included total abstention from drugs, a history of psychiatric or substance use disorders as determined from a structured interview using DSM-IV diagnostic criteria (American Psychiatric Association, 2000), or any significant medical conditions. Qualifying subjects provided written informed consent. The subject population consisted of 8 males and 7 females, with a mean age (±SD) of 27.0 (5.0) years. In the last 30 days all subjects reported drinking alcohol (average of 2.8 (1.9) drinks per week); 3 of the 15 smoked tobacco cigarettes, although none of these smoked more than 1 cigarette a day; and 5 of the 15 used marijuana (average of 1.4 (1.3) joints per week).

2.2. Experimental design and procedures

The study was a double-blind, randomized, placebo-controlled, triple-dummy, crossover trial consisting of seven or eight sessions (at least one week apart) that took place in a departmental laboratory from 0800-1545 hours. Upon arrival, breath alcohol, urine toxicology, and pregnancy (for females) tests were given. After baseline measures were collected, subjects ingested capsules containing metaxalone or placebo. Sixty minutes later, subjects ingested capsules containing carisoprodol or placebo, and 60 minutes after that ingested capsules containing oxycodone or placebo. The focus of this report will be on the four sessions in which subjects received placebo only, 350 mg of carisoprodol only, 10 mg of oxycodone only, and 350 mg of carisoprodol followed 60 min later by oxycodone.

2.3 Dependent measures

Five forms were used to assess subjective effects: the short form of the Addiction Research Center Inventory (ARCI) (Martin et al., 1971); an adjective rating scale (ARS) derived from two questionnaires sensitive to the somatic and mood-altering effects of opioids (Fraser et al., 1961; Preston et al., 1989); a locally developed visual analog scale (VAS), consisting of 28 100-mm lines, each labeled with an adjective (e.g., lightheaded); a locally developed Drug Effect/Drug Liking/Take Again questionnaire (DEL/TA); and a locally developed Post-Session Sequelae questionnaire that assessed residual side effects of the drugs (subjects

were asked to fill out this form 24 h after the session). The ARCI and ARS were filled out at hourly intervals and the VAS and DEL/TA were filled out every 30 minutes after first capsule administration. Psychomotor and cognitive performance were measured with five tests: the Digit Symbol Substitution Test (DSST) (Wechsler, 1958); a logical reasoning test (LRT) (Baddeley, 1968), an auditory reaction time (ART) test (Nuotto and Kortilla, 1991); an eye-hand coordination (EHC) test (Nuotto and Kortilla, 1991); and a free recall memory test. The DSST was completed every 30 min, the LRT, ART and EHC tests were completed at hourly intervals, and the memory test was completed two times in the session. Six physiological measures were assessed at hourly intervals: blood pressure, heart rate, arterial oxygen saturation, respiration rate, exophoria, and pupil size.

2.4. Data analysis

Repeated-measures analysis of variance was used for statistical treatment of the data. The analysis compared peak (highest value obtained) or trough (lowest value obtained) effects of placebo, 350 mg carisoprodol, 10 mg oxycodone, and both drugs given in the same session. In the analyses, only values collected between 30 min after the third capsule ingestion period (i.e., earliest time point that drug interaction effects could be tested) and through to the end of the session were included (300 min after the third capsule ingestion period), and values were determined for each subject independent of time point. Mean effect analyses were done on measures from the post-session questionnaire. F values were considered significant for $p \leq 0.05$. When significance was achieved, the Holm-Sidak method for pairwise multiple comparison tests was done.

3. Results

Table 1 summarizes mean peak, mean trough, or mean values (±SEM) of subjective effects, psychomotor performance, and physiological measures that were sensitive to one or more of the three active drug conditions (relative to placebo).

3.1. Subjective effects

Oxycodone by itself produced several subjective effects including increased scores on the PCAG scale of the ARCI, increased ratings of “skin itchy” on the ARS, and increased VAS ratings of “coasting (spaced out),” “high,” and “lightheaded.” Ten mg of oxycodone increased ratings of drug liking or “take again,” but the increases were not statistically significant. The 350 mg dose of carisoprodol had no subjective effects different from placebo. We should note that measures collected 30 and 60 min after carisoprodol had been ingested were not included in the analysis, but in the report referred to in the Introduction, when these time points were included in the analysis, similar results were obtained (i.e., minimal subjective effects). There were ten within-session subjective effects not significantly affected by oxycodone or by carisoprodol alone that were significantly increased when the two were administered in the same session. It is interesting to note that with seven of those ten subjective effects, carisoprodol alone looked no different from placebo (e.g., “coasting,” “dreamy,” drug liking). We should also point out that three of the ten subjective effects were abuse liability-related – “pleasant bodily sensations,” drug liking, “take again.”

3.2. Psychomotor measures

Ten mg of oxycodone and 350 mg of carisoprodol when tested alone did not impair psychomotor performance. However, when examining the data in Table 1, one can detect trends towards decreased performance with both drugs relative to placebo, and when the two drugs were tested within the same session, significant impairment was obtained on ART, the DSST, and the LRT. Psychomotor performance measured 30 and 60 min after carisoprodol

had been ingested were not included in the present analysis - in the other report when these time points were included in the analysis, 350 mg of carisoprodol by itself significantly decreased DSST performance. Thus, the impairment obtained in the present analysis which excluded those time points is likely an underestimate of the maximal degree of impairment that these two drugs would produce if their peak effects occurred at the same time.

3.3. Physiological measures

Oxycodone, but not carisoprodol, induced miosis. When combined, the maximum degree of pupil constriction was significantly increased relative to 10 mg of oxycodone alone (this phenomenon was observed in 8 of the 15 subjects).

4. Discussion

In the Introduction, we discussed how this study originated and discussed problems associated with it. One caveat is that when measuring the interactive effects of carisoprodol and oxycodone, some of the former drug's effects (psychomotor impairment) were subsiding. Despite this, in the present study 350 mg of carisoprodol still had effects as evidenced by it and oxycodone producing significant effects that were not present when the drugs were tested alone. This applied not only to psychomotor impairment but to subjective effects, including those that could be considered to be abuse liability-related. A systematic replication is needed in which the interval between carisoprodol and oxycodone administration is modified so as to capture the impact of the two drugs when they are both close to their peak pharmacodynamic effects.

The results from our report are significant, because it is the first study that we are aware of that has shown that carisoprodol and oxycodone, two drugs that are sometimes co-prescribed for relief of pain, produce effects when administered "together" (i.e., an hour apart) that are of greater magnitude than when they are administered alone. Some of the effects were not benign, and are of concern from both abuse liability and public safety standpoints (Bramness et al., 2004, 2007; Reeves and Burke, 2010). It is important to point out the effects we obtained were with therapeutic doses of the two drugs. Consuming supratherapeutic doses of either of the two drugs when taken in combination would increase the risk of a serious adverse event, and indeed there is at least one case report in the literature documenting this (Reeves and Mack, 2003).

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Table 1

Mean peak, trough, or average scores/ratings (±SEM) of subjective, psychomotor, and physiological effects significantly affected by one or more of the active drug conditions.

	P value	Placebo	CARIS 350	OXY 10	CARIS 350/OXY 10
Subjective effects measures					
ARCI					
BG[a,b] (range: 0–13)	<0.001	4.5 (0.6)	3.5 (0.5)	2.6 (0.5)*	2.0 (0.6)*
LSD[b] (range: 0–14)	<0.001	4.2 (0.6)	4.2 (0.5)	6.4 (0.8)*	5.8 (0.7)*
PCAG[b] (range: 0–15)	<0.001	5.8 (0.9)	7.1 (0.9)	9.3 (0.8)*	9.4 (0.7)*
Adjective rating scale (range: 0–4)					
Dry mouth	0.003	0.4 (0.2)	0.4 (0.2)	1.3 (0.3)*	0.9 (0.3)
Flushing	0.002	0.1 (0.1)	0.1 (0.1)	0.9 (0.3)*	0.5 (0.2)
Nodding	0.005	0.1 (0.1)	0.9 (0.3)	1.2 (0.4)	1.7 (0.4)*
Numb	0.004	0.2 (0.1)	0.1 (0.1)	0.5 (0.2)	0.9 (0.3)*
Skin itchy	<0.001	0 (0)	0.1 (0.1)	0.8 (0.2)*	1.3 (0.3)*
VAS (range: 0–100)					
Coasting (‘spaced out’)	<0.001	15.3 (7.4)	13.3 (5.9)	28.5 (8.6)	43.7 (9.8)*
Difficulty concentrating	0.003	19.2 (7.7)	26.5 (8.4)	39.3 (10.5)	48.5 (10.2)*
Dizzy	0.01	7.3 (5.8)	7.5 (6.1)	22.6 (9.1)*	18.7 (7.1)
Dreamy	<0.001	16.7 (7.9)	16.0 (6.8)	25.0 (7.8)	43.9 (9.9)*
Floating	<0.001	7.4 (5.4)	2.3 (1.1)	19.3 (7.8)	34.5 (9.2)*
Heavy, sluggish feeling	0.009	19.5 (9.2)	26.5 (8.4)	37.7 (10.1)	48.5 (10.3)*
High (drug ‘high’)	<0.001	4.7 (4.0)	8.5 (6.1)	25.2 (8.1)*	36.9 (10.2)*
Lightheaded	0.004	4.3 (1.9)	2.3 (1.0)	26.1 (8.5)*	25.7 (8.4)*
Pleasant bodily sensations	0.004	6.8 (4.5)	6.7 (4.9)	18.1 (5.7)	23.7 (8.4)*
Pleasant thoughts	0.009	20.1 (7.8)	25.1 (6.8)	48.5 (10.6)*	30.9 (7.7)
Sedated (calm, tranquil)	0.007	14.8 (6.3)	21.9 (6.2)	35.1 (7.6)*	33.9 (8.0)*
Unpleasant bodily sensations	0.01	10.0 (6.4)	9.9 (6.8)	22.5 (8.9)*	16.7 (8.0)

	P value	Placebo	CARIS 350	OXY 10	CARIS 350/OXY 10
Drug effect/Drug liking/Take again[c]					
Feel drug effect	<0.001	2.0 (0.2)	2.5 (0.2)	3.7 (0.2)*	3.8 (0.2)*
Like drug	0.02	58.1 (4.0)	58.1 (2.8)	66.4 (6.4)	72.2 (5.4)*
Like drug[a]	0.006	47.2 (0.7)	44.1 (1.5)	34.7 (5.3)*	33.7 (4.6)*
Take drug again	0.03	60.3 (4.3)	61.3 (3.6)	68.0 (6.3)	74.9 (5.4)*
Take drug again[a]	0.01	53.1 (3.0)	45.1 (2.1)	37.1 (6.0)*	36.1 (4.6)*
Post-session Sequelae Questionnaire (Range: 0–4)					
Nausea	0.004	0.1 (0.1)	0 (0)	0.6 (0.3)	0.9 (0.3)*
Psychomotor measures					
ART (msec)[b]	0.01	332 (12)	343 (14)	343 (17)	369 (18)*
DSST (# of symbols completed)[a]	0.02	45.6 (2.0)	41.9 (3.2)	41.3 (2.6)	37.6 (2.3)*
DSST (# of symbols correct)[a]	0.01	45.3 (2.1)	41.1 (3.3)	41.1 (2.6)	37.1 (2.4)*
LRT (# of statements completed)[a,b,d]	0.008	17.8 (1.4)	15.9 (1.2)	15.6 (1.2)	14.4 (1.2)*
LRT (# of statements correct)[a,b,d]	0.009	15.6 (1.9)	13.4 (1.4)	13.2 (1.6)	11.9 (1.5)*
Physiological measures					
Miosis (mm)[a]	<0.001	6.6 (0.3)	6.5 (0.3)	4.9 (0.4)*	4.4 (0.4)*

Abbreviations: CARIS 350, carisoprodol 350 mg; OXY 10, oxycodone 10 mg; CARIS 350/OXY 10, carisoprodol followed 60 min later by 10 mg oxycodone; ARCI, Addiction Research Center Inventory; BG, Benzedrine Group scale; LSD, Lysergic Acid Diethylamide scale; PCAG, Pentobarbital-Chlorpromazine-Alcohol Group scale; ART, auditory reaction time; DSST, Digit Symbol Substitution Test; EHC, eye-hand coordination test; LRT, logical reasoning test

*p<0.05 compared with placebo

[a] trough rating

[b] data based on 14 subjects – one subject's data not included because of missing data due to a file transfer error

[c] Drug effect, range 1–5 in which 1=I feel no effect at all from the drug(s) and 5=I feel a very strong effect; Like drug, range, 0–100, 0=dislike a lot, 50=neutral, 100=like a lot; Take again, 0=definitely would not, 50=neutral (don't care), 100=definitely would. Last measure refers to desire to take drug(s) again on another session if given the opportunity

[d] the LRT is a 1-min computerized test that consists of true-false statements about the juxtaposition of the two letters A and B (e.g., A is preceded by B – true or false)