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Carisoprodol tolerance and precipitated withdrawal

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ABSTRACT

Aims: Carisoprodol is a muscle relaxant that acts at the $GABA_A$ receptor. Concerns about the abuse liability of carisoprodol are increasing, but evidence that carisoprodol produces tolerance and a significant withdrawal syndrome has yet to be established. The purpose of the current study was to determine if repeated administration of carisoprodol produces tolerance and withdrawal signs in a mouse model.
Methods: Carisoprodol (0, 100, 200, 300, or 500 mg/kg bid, i.p.) was administered to Swiss-Webster mice for 4 days and loss-of-righting reflex was measured 20–30 min following each administration. On the fourth day, bemegride (20 mg/kg), flumazenil (20 mg/kg), or vehicle was administered following carisoprodol and withdrawal signs were measured. Separate groups of mice receiving the same treatment regimen and dose range were tested for spontaneous withdrawal at 6, 12 and 24 h after the last dose of carisoprodol.
Results: The righting reflex was dose-dependently impaired following the first administration of carisoprodol. A 75–100% decrease in the magnitude of the impairment occurred over the four days of exposure, indicating the development of tolerance to the carisoprodol-elicited loss-of-righting reflex. Withdrawal signs were not observed within 24 h following spontaneous withdrawal; however, bemegride and flumazenil each precipitated withdrawal within 15–30 min of administration.
Conclusions: Carisoprodol treatment resulted in tolerance and antagonist-precipitated withdrawal, suggesting it may have an addiction potential similar to that of other long-acting benzodiazepine or barbiturate compounds.

1. Introduction

Concerns about the abuse of carisoprodol (N-isopropylmeprobamate, Soma), a frequently prescribed muscle relaxant (Fass, 2010; Luo et al., 2004), have increased steadily within the past decade. In the year 2000, the Drug Abuse Warning Network (Substance Abuse and Mental Health Services Administration, 2001) ranked carisoprodol as the 20th most abused drug, and its nonmedical use more than doubled between 2004 and 2008 (Substance Abuse and Mental Health Services Administration, 2011). The abuse potential of carisoprodol in humans has been outlined in several reviews over the past decade (Bailey and Briggs, 2002; Hoiseth et al., 2009; Reeves and Burke, 2010).

These concerns are not surprising, given that the molecular and behavioral effects of carisoprodol are similar to those of barbiturate compounds (Gonzalez et al., 2009), which are well-known for their abuse potential. In that study, carisoprodol was found to allosterically activate and directly gate $GABA_A$ receptor chloride channels in a manner similar to the barbiturates. These effects were blocked by bemegride, a barbiturate antagonist, but not flumazenil, a benzodiazepine antagonist. Although earlier consensus was that the effects of carisoprodol were mediated by its conversion to the anti-anxiety drug meprobamate (Bramness et al., 2004), these data indicate that carisoprodol acts directly at $GABA_A$ receptors.

In addition, carisoprodol has been trained as a discriminative stimulus (Gonzalez et al., 2009). Pentobarbital (a barbiturate), chlordiazepoxide (a benzodiazepine) and meprobamate each fully substituted for the discriminative stimulus effects of carisoprodol. Further, bemegride fully blocked the discriminative stimulus effects of carisoprodol, whereas flumazenil produced partial and non-dose dependent reductions in carisoprodol-appropriate responding (Gonzalez et al., 2009). Taken together, these findings suggested that both electrophysiological and behavioral effects of carisoprodol are mediated by a barbiturate-like mechanism.

Unlike for the barbiturates and benzodiazepines, there has been little basic research on the ability of carisoprodol to produce tolerance and dependence. An early study reported that carisoprodol did not produce dependence or withdrawal signs in humans (Eddy, 1969; Fraser et al., 1961), whereas a number of more recent case reports have presented anecdotal evidence for tolerance and dependence (Eleid et al., 2010; Heacock and Bauer, 2004; Morse and Chua, 1978; Reeves et al., 2004; Rohatgi et al., 2005). However, these individuals were either taking doses many times larger than

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prescribed doses or were taking several other psychoactive compounds, so strong conclusions about the ability of carisoprodol to produce dependence in patients taking clinically appropriate doses cannot be made. In the first case, the adverse effects noted could have been toxicities induced by the high doses rather than withdrawal effects and, in the second case, the adverse effects noted could have been withdrawal signs from one or more of the other psychoactive compounds.

There is evidence that dependence and withdrawal from GABAergic compounds are difficult to observe in rodents. Meprobamate produces robust withdrawal signs in primates, but withdrawal signs are difficult to detect in rodents (Nakamura and Shimizu, 1983). Similarly, it is difficult to detect physiological withdrawal signs in rodents with the long-acting barbiturates and benzodiazepines (Emmett-Oglesby et al., 1988; Woods et al., 1992). There have been suggestions that precipitated withdrawal from long-acting benzodiazepines was much easier to detect in rats than spontaneous withdrawal (e.g., Emmett-Oglesby et al., 1988). These findings suggest that whereas signs of spontaneous withdrawal from carisoprodol may be difficult to detect, the ability to elicit antagonist-precipitated withdrawal would be sufficient to establish a barbiturate-/benzodiazepine-like dependence liability.

Demonstrating the abuse liability of a compound involves testing several aspects of the compound including tests of self-administration, drug discrimination, tolerance and cross-tolerance and dependence (Balster, 1991). For carisoprodol, there is substantial evidence of abuse in humans (Bailey and Briggs, 2002; Hoiseth et al., 2009; Reeves and Burke, 2010); as well as confirmation that it is self-administered in monkeys (France et al., 1999). The discriminative stimulus effects of carisoprodol are similar to known GABAergic drugs of abuse (Gonzalez et al., 2009). However, there has not been convincing evidence that carisoprodol produces tolerance and/or dependence. Therefore, the purpose of this study was to assess the ability of carisoprodol to elicit tolerance and to test whether antagonists could precipitate withdrawal from carisoprodol. If carisoprodol produces effects mediated by the barbiturate- or benzodiazepine-sites on the $GABA_A$ receptor, as suggested by our earlier research (Gonzalez et al., 2009), there should be a development of tolerance during repeated administration. It should also be possible to precipitate withdrawal following the benzodiazepine-site antagonist flumazenil, or the barbiturate-site antagonist, bemegride, in the carisoprodol-tolerant subjects. These antagonist compounds have been useful in dissociating the effects of benzodiazepines and barbiturates in drug discrimination testing (De Vry and Slangen, 1986; Herling and Shannon, 1982; Schechter, 1984). In these studies, bemegride blocked the discriminative stimulus effects of pentobarbital but not benzodiazepines, whereas flumazenil blocked the discriminative stimulus effects of benzodiazepines but not pentobarbital. Further, the antagonists also blocked cross-substitution, for example, bemegride blocked both the discriminative stimulus effects of pentobarbital and the ability of pentobarbital to substitute for chlordiazepoxide (Schechter, 1984). Further, bemegride fully blocked the discriminative stimulus effects of carisoprodol, and flumazenil produced a non-dose dependent partial antagonism (Gonzalez et al., 2009), which suggests at least one of these two compounds could potentially precipitate withdrawal from carisoprodol.

2. Methods

2.1. Animals

Male Swiss-Webster mice were obtained from Harlan Laboratories at approximately 8 weeks of age and tested at approximately 10 weeks of age. Mice were group-housed on a 12-h/12-h light/dark cycle and were allowed free access to food and water. All testing of mice was done during the light portion of the cycle. All housing and procedures were in accordance with the guidelines of the *Guide for Care and Use of Laboratory Animals* (Institute of Laboratory Animal Resources, 1996) and were approved by the University of North Texas Health Science Center Animal Care and Use Committee.

Table 1
Experimental conditions.

Antagonist dose	Carisoprodol dose[a]			
	Vehicle (methylcellulose)	100 mg/kg	300 mg/kg	500 mg/kg
Vehicle (saline)	$n=6$	$n=6$	$n=6$	$n=5$
Bemegride, 20 mg/kg	$n=4$	$n=6$	$n=6$	$n=5$
Vehicle (methylcellulose)	$n=6$	$n=6$	$n=6$	$n=5$
Flumazenil, 20 mg/kg	$n=6$	$n=6$	$n=6$	$n=6$

[a] A 200 mg/kg dose of carisoprodol was tested in the tolerance experiments ($n=12$) but not evaluated for bemegride- or flumazenil-precipitated withdrawal.

2.2. Experimental design

For the tolerance and precipitated-withdrawal experiments, five groups of 24 mice were administered carisoprodol or vehicle twice daily for three days and on the morning of day 4. The mice were injected at 7:00 AM and 7:00 PM with vehicle (2% methylcellulose), 100, 200, 300 or 500 mg/kg carisoprodol. Loss-of-righting scores were determined 20 min after administration of carisoprodol. Loss-of-righting was scored as follows: 0, normal lands/rights cleanly onto four feet; 1, slight change; 2, faltering on landing/righting, slight over-compensation; 3, failure of animal to right itself within 15 s (Colpaert, 1986; Gatch et al., 2000). On the morning of day 4, 30 min after the final carisoprodol administration, mice from the vehicle, 100, 300, or 500 mg/kg groups were administered either an antagonist (bemegride (20 mg/kg) or flumazenil (20 mg/kg)) or the appropriate vehicle. The doses of the antagonists selected were those having maximal effect in earlier experiments (Gonzalez et al., 2009). The experimental design and the number of mice in each condition are shown in Table 1. Withdrawal signs were rated at 15 and 30 min after administration of the antagonist. The rating scale (Table 2) was adapted from a barbiturate withdrawal rating scale (Yutrzenka, 1989; Yutrzenka et al., 1996) and an alcohol withdrawal rating scale (Goldstein, 1972). Maximum score on the scale was 14. The observers were blind to the experimental conditions. The 200 mg/kg group was not tested for withdrawal.

For the spontaneous-withdrawal experiment, 4 groups of mice were administered vehicle ($n=8$), 100 ($n=14$), 300 ($n=7$), or 500 ($n=8$) mg/kg carisoprodol twice

Table 2
Carisoprodol Withdrawal Rating Scale.

Withdrawal signs	PT
1. Response to air puff 0 = No response, 1 = Jumps, 2 = Jumps and vocalizes.	0–2
2. Response to being picked up and held 0 = No response, 1 = Struggles or vocalizes, 2 = Struggles and vocalizes, 3 = Struggles, vocalizes, scratches, bites.	0–3
3. Caudal posture 0 = limp or normal tail, 1 = stiff, curls around finger, 2 = stiff, curls around finger, stays elevated after released, 3 = spontaneous abnormal posture of tail such as severe deviation or lift above back, stiff, curls around finger, and stays elevated after released.	0–3
4. Tremor 0 = no tremor, 1 = mild tremor in one portion of body, 2 = occasional generalized tremor, 3 = constant generalized tremor.	0–3
5. Startle 0 = none, 1 = twitch, 2 = jump or freeze, 3 = exaggerated jump or freeze.	0–3