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Carisoprodol, Meprobamate, and Driving Impairment*

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ABSTRACT: This paper considers the pharmacology of the centrally acting muscle relaxant carisoprodol, and its metabolite meprobamate, which is also administered as an anxiolytic in its own right. Literature implicating these drugs in impaired driving is also reviewed. A series of 104 incidents in which these drugs were detected in the blood of drivers involved in accidents or arrested for impaired driving was considered, with respect to the analytical toxicology results, patterns of drug use in these subjects, the driving behaviors exhibited, and the symptoms observed in the drivers. Symptomatology and driving impairment were consistent with other CNS depressants, most notably alcohol. Reported driving behaviors included erratic lane travel, weaving, driving slowly, swerving, stopping in traffic, and hitting parked cars and other stationary objects. Drivers on contact by the police displayed poor balance and coordination, horizontal gaze nystagmus, bloodshot eyes, unsteadiness, slurred speech, slow responses, tendency to doze off or fall asleep, difficulty standing, walking or exiting their vehicles, and disorientation. Many of these cases had alcohol or other centrally acting drugs present also, making difficult the attribution of the documented impairment specifically to carisoprodol and meprobamate. In 21 cases, however, no other drugs were detected, and similar symptoms were present. Impairment appeared to be possible at any concentration of these two drugs; however, the most severe driving impairment and most overt symptoms of intoxication were noted when the combined concentration exceeded 10 mg/L, a level still within the normal therapeutic range.

KEYWORDS: forensic science, forensic toxicology, carisoprodol, meprobamate, driving impairment

Muscle relaxants such as carisoprodol, and central nervous system (CNS) depressants such as meprobamate, are among the many drug classes that can adversely affect driving skills. The drugs are considered together here because of their similar chemical properties, and the fact that the meprobamate is a metabolite of carisoprodol.

Carisoprodol is a dicarbamate, centrally acting, oral skeletal muscle relaxant whose chief application is in the treatment of acute muscular spasm associated with craniomandibular disorder, lumbago, sciatica, and other lower back syndromes (1,2). It is prescribed on its own, or in combination products containing phenacetin, caffeine, and codeine (3,4). Typical dosage is 350 mg, three times a day and at bedtime (1500 mg/day). Other muscle relaxing drugs used in the treatment of this condition include cyclobenzaprine, chlorzoxazone, diazepam, methocarbamol, and orphenadrine (2).

Carisoprodol is extensively metabolized to meprobamate, a central nervous system depressant with sedative hypnotic properties, indicated for the treatment of anxiety, and given in daily divided doses of up to 2400 mg (4).

The exact mechanism of action of carisoprodol is not known, but it is central in nature and there appears to be cross-tolerance to the drug in animals dependent on barbiturates. There is also evidence that meprobamate has barbiturate-like activating activity at $GABA_A$ receptors (5).

There are many reports of the development of abuse and dependence involving carisoprodol and meprobamate (6–12). Most abusers of the drug are introduced to it for legitimate therapeutic reasons, but then become habituated to the perceived pleasurable effects, including sedation, relaxation, euphoria, and mood alteration, and continue to use it after the pain has abated, or increase their dose beyond that required for pain control. Frequently, for therapeutic reasons, the drug is used in combination with other central analgesic drugs such as the opiates, propoxyphene, tramadol, barbiturates, benzodiazepines, and other muscle relaxants (13). Side effects associated with the therapeutic use of carisoprodol and meprobamate include agitation, depression, dizziness, drowsiness, facial flushing, fainting, headache, hiccups, sleep disturbance, irritability, light-headedness upon standing up, loss of coordination, nausea, rapid heart rate, stomach upset, tremors, vertigo, and vomiting. In abuse or overdose, subjects are consistently sedated and obtunded, frequently becoming comatose.

Both drugs carry warnings specifically regarding their potential effects on complex tasks such as driving, or operating hazardous machinery (4). In addition, there have been several reports from police officers of motorists who appear highly intoxicated, and subsequently test positive for carisoprodol and meprobamate (3,14,15). These prior reports, however, have consisted of relatively small numbers of cases, have been confounded by the presence of multiple drugs, or have not had access to descriptions of the symptomatology or driving. We report here the toxicological findings, including blood concentrations of meprobamate and carisoprodol, in a series of subjects arrested for impaired driving who subsequently tested positive for one or both of these drugs. In addition, we review the reasons for arrest, patterns of driving behavior, and symptomatology reported by the arresting officer.

Methods

Blood specimens drawn from drivers suspected of driving under the influence of drugs are submitted to the Washington State

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Toxicology Laboratory and are routinely analyzed for a wide variety of centrally acting drugs. Normal procedures include volatiles analysis by headspace gas chromatography, and immunochemical analysis by enzyme immunoassay (EMIT, Syva/Dade Behring) for amphetamines, barbiturates, methadone, benzodiazepines, propoxyphene, phencyclidine, opiates, benzoylecgonine, and marijuana metabolites. The sample preparation procedure for this analysis is as follows. To 1 mL of blood, add 1 mL methanol and 6 mL acetonitrile. Vortex 30 s and centrifuge at 2500 rpm for 5 min. Pour off the supernatant and dry down under air to approximately 50 μL. Reconstitute to 300 μL with Emit Drug Assay Buffer:MeoH (1:1) and analyze on COBAS MIRA-S analyzer according to the manufacturer's protocol. Samples are further subjected to extraction with *n*-butyl chloride (16), for basic and alkaloidal drugs followed by gas chromatography (GC), and gas chromatography/mass spectrometry (GC/MS). Samples are also screened for the presence of weakly acidic and neutral drugs using the following procedure.

One hundred μL of internal standard solution (cyclopentobarbital, 5 mg/L), blood (1 mL) and deionized water (1 mL) are mixed in a 15 mL disposable glass tube. XAD resin (source) is thoroughly prewashed with ethyl acetate, and approximately 1 g is added to the tube, which is vortex mixed for 30 s, and then centrifuged. The supernatant is discarded and ethyl acetate (5 mL) is added. The tube is vortex mixed for 30 s then allowed to sit (<1 min) until the layers separate. The ethyl acetate is transferred to a 10 mL conical centrifuge tube and evaporated to dryness at 60°C under air. The residue is reconstituted in ethyl acetate (100 μL) and transferred to an autosampler vial for analysis by GC with flame ionization detection (FID) and GC/MS. Gas chromatography was performed on a Hewlett Packard 5890 GC with flame ionization detection. Separation was achieved using helium as carrier gas on a 5% phenylmethyl silicone column (Alltech, Econocap EC-5), 30 m × 0.25 mm inside diameter, with 0.25 μm film thickness. Initial temperature was 175°C for 30 s, programmed to 220°C at 10°/min, then to 260°C at 20°/min, with a final hold time of 6 min. Controls of 5 and 15 mg/L for carisoprodol and 10 and 25 mg/L for meprobamate were analyzed with each batch. Presumptive identifications based on retention time using this method are then confirmed by gas chromatography/mass spectrometry.

The GC method was calibrated by peak area and average response factor, using a four-point standard curve (0, 5, 10, and 20 mg/L) run with each assay. Absolute recoveries were 44% for meprobamate and 56% for carisoprodol. The analytical method is linear in the range 0.5 to 150 mg/L for both drugs, and has a CV (between day) of 9.4% for carisoprodol and 12.5% for meprobamate. The method is also suitable for the analysis of other weakly acidic and neutral drugs such as barbiturates, phenytoin, carbamazepine, acetaminophen, and ibuprofen, and has been described with modifications elsewhere for the analysis of the nonsteroidal anti-inflammatory, ketorolac (17). There are no known interferences with carisoprodol or meprobamate. Note that there are currently no commercially available immunoassays for meprobamate and carisoprodol, and unless an appropriate extraction and gas chromatographic assay is performed they will not be detected. Other GC procedures have been described (14,18–20). HPLC with UV detection is not practical because of the lack of a suitable chromophore.

Case information was reviewed, and salient information regarding driver statements about drug use was abstracted as well as appearance, performance in field sobriety tests, observed driving, and other relevant information.

Results and Discussion

Between January 1996 and July 1998, 104 impaired driving cases submitted to the Washington State Toxicology Laboratory tested positive for meprobamate and/or carisoprodol. All 104 cases were a result of the drivers being involved in an accident or committing moving violations. Overall, 58% of these cases resulted from accidents. The mean subject age was 39 (range 22 to 64), 43% were women and 57% men. The median carisoprodol concentration was 4.30 mg/L (range 0 to 25.1 mg/L), and for meprobamate, 11.65 mg/L (range 1 to 77.6 mg/L). Three drivers were each arrested twice in this series of cases. Three illustrative cases in which meprobamate and carisoprodol alone were present, and one where other drugs were present, are presented below.

Subject 1

A 56-year-old male was driving 10 mph (16 km/h), with very poor lane travel on a major urban freeway at 10:15 a.m. On contact by police he took several minutes to stop, continuing to weave and ignoring flashing lights and emergency equipment. Once stopped, he was shaking violently. He took about six minutes to retrieve his wallet from his pocket and his license from his wallet. He had very slurred, incoherent thick-tongued speech. He could not stand or walk without help. He stated he had taken two of his wife's Soma approximately an hour before being stopped "because of depression." He stated "I shouldn't have been driving." His breath alcohol was negative.

He was evaluated by a drug recognition officer, who noted the following: Eyes: clear, not bloodshot; nystagmus present at rest, with lack of smooth pursuit and jerkiness at maximum deviation in both eyes. No lack of convergence, no hippus or rebound dilation. Pupil size normal, but sluggish to change. Pulse: elevated ~110. Blood pressure: elevated. Temperature: normal. Muscle tone: normal/flaccid.

He made multiple errors in field sobriety tests, swaying and stumbling while standing or balancing, repeatedly using his arms to balance, stepping off the line multiple times, and stopping during the walk-and-turn test, and repeatedly swaying, hopping, using his arms to balance and putting his foot down during the one-leg stand. He was unable to complete either test.

His toxicology results indicated a blood carisoprodol concentration of 9.5 mg/L and meprobamate of 32.9 mg/L. This is well in excess of what would have been expected from a 700 mg dose of carisoprodol. No alcohol or other drugs were detected.

Subject 2

A 22-year-old male was caught shoplifting. He appeared intoxicated to employees. He fled the store getting into his vehicle and driving off. Police observed him weaving and making a very wide turn, causing other vehicles to take evasive action. He had very slurred speech, bloodshot eyes and droopy eyelids, swayed while standing, and repeatedly nodded off. He stated he was taking Soma for a shoulder problem, and he felt he shouldn't have been driving. His breath alcohol was negative.

He performed standardized field sobriety tests, showing lack of smooth pursuit, jerkiness at maximum deviation and onset of nystagmus prior to 45° in both eyes. He made multiple errors in the walk-and-turn test, stopping eight times for balance, using his arms for balance and not following instructions. In the one-leg-stand test, he used his arms for balance, put his foot down several times and was unable to complete the test.

His toxicology results indicated a blood carisoprodol concentra-

tion of 11.6 mg/L, and a meprobamate concentration of 21.8 mg/L. No alcohol or other drugs were detected.

Subject 3

A 38-year-old male, hit two parked cars and a motorcycle, and had apparently been involved in another crash earlier that day. The subject appeared dazed, but his speech was described as fair. He had problems with coordination and balance.

He was not offered field sobriety tests due to his obvious balance problems. His eyes were checked and he exhibited lack of smooth pursuit, jerkiness at maximum deviation and onset of nystagmus prior to 45° in both eyes. He also displayed vertical nystagmus and a lack of convergence. His pupils were of normal size but responded sluggishly to changes in light.

His toxicology results indicated a blood carisoprodol concentration of 4.8 mg/L and a meprobamate concentration of 35.6 mg/L. No alcohol or other drugs were detected.

Subject 4

A 35-year-old female was observed weaving severely, crossing the centerline and driving on the curb. She drove on for several blocks after the police emergency lights were activated. She stared blankly, appeared dazed, and was unresponsive to the officer's requests to roll down her window, or turn off the engine. She had one child unrestrained in the car, and was on her way to pick up her other child, but could not remember his name or where he went to school. She was unsteady on her feet and repeatedly fell down when standing up. She could not perform any field sobriety tests, nor perform finger dexterity tests or recite the alphabet.

Her toxicology results indicated a blood carisoprodol concentration of 14.8 mg/L and a meprobamate concentration of 28.1 mg/L. No alcohol was present, but propoxyphene 0.42 mg/L, norpropoxyphene 0.10 mg/L, butalbital 3.61 mg/L, and acetaminophen 19.5 mg/L were all detected.

In 83 cases (80%), alcohol and/or other drugs besides meprobamate and carisoprodol were present. Narcotic analgesics (morphine, hydrocodone, codeine, meperidine, pentazocine, tramadol, and propoxyphene) were present in 41 cases, benzodiazepines (diazepam, clonazepam, nordiazepam, lorazepam, temazepam, flurazepam) in 45 cases, barbiturates (butalbital) in 12 cases, and cannabinoids in 13 cases. Two or more of these categories (in addition to the carisoprodol or meprobamate) were present in 33 cases. In addition, one case each was positive for benzoylecgonine, methamphetamine, dextromethorphan, diphenhydramine, mirtazepine, amitriptyline, and zolpidem. Only 9 cases were positive for alcohol, and the median blood alcohol level was 0.05 g/100 mL.

For this group, the median carisoprodol and meprobamate concentrations were 2.41 mg/L and 12.00 mg/L, respectively. The combined concentration of carisoprodol and meprobamate exceeded 10 mg/L for 74% of all cases. Driving behaviors reported in this group included erratic lane travel, weaving, driving slowly, swerving, stopping in traffic, and hitting parked cars and other stationary objects. Drivers on contact by the police displayed poor balance and coordination, gaze nystagmus, unsteadiness, slurred speech, slow responses to questions, tendency to doze off or fall asleep, difficulty standing, walking or exiting their vehicles, and disorientation. Other workers have reported anecdotally that carisoprodol may also cause pupillary dilation (21); however, this sign may be unreliable given the presence of opiates in many of these cases.

Trying to identify the effects of carisoprodol or meprobamate in polydrug cases is fraught with difficulty. These drivers were heavily medicated with CNS depressant and narcotic drugs usually for the control of chronic pain, and the effects undoubtedly result from the combined effects of the drugs. Nonetheless, these data show that significant psychomotor impairment, resulting either in DUI arrests or accidents, is a real risk factor for this heavily medicated, chronic pain population.

Twenty-one cases, however, were positive for meprobamate and/or carisoprodol alone, and this group is therefore of more interest in isolating the effects of this medication. The data from these cases are listed in Table 1, and four were presented in detail above. Of these, all were positive for meprobamate, while 16 were posi-

TABLE 1—*Blood concentrations, demographic data, and driver behavior in carisoprodol/meprobamate-only cases. Blood alcohol was negative in all cases. Driver was the causing in all accidents.*

Age	Sex	Carisoprodol (mg/L)	Meprobamate (mg/L)	Combined (C+M) (mg/L)	Accident	Circumstances
31	f	0.00	1.00	1.00	y	hit-and-run collision
28	m	0.00	1.60	1.60	n	arrested for DUI
47	m	0.00	1.90	1.90	y	driver causing 4-car fatality collision
62	f	0.00	2.10	2.10	y	arrested for DUI
29	f	0.00	5.30	5.30	y	drifted off roadway and struck a tree
39	m	4.10	6.40	10.50	y	driver collided with semi truck
64	f	3.40	9.50	12.90	y	extreme lane travel, rear-ending another vehicle
29	f	4.90	8.60	13.50	n	stopped for extreme lane travel
40	m	5.80	9.10	14.90	y	causing driver in accident with obvious impairment
42	m	3.60	11.30	14.90	y	erratic lane travel, hit a large truck.
29	f	4.40	11.00	15.40	y	wrong way on freeway, hit oncoming traffic
40	f	4.40	11.00	15.40	n	arrested for DUI
37	f	5.50	13.10	18.60	y	hit-and-run collision
37	m	9.20	12.10	21.30	n	stopped for poor driving, excessive weaving
39	m	15.20	15.60	30.80	n	erratic driving, weaving, very groggy
35	m	2.60	29.00	31.60	n	weaving, highly impaired
46	f	0.00	33.00	33.00	y	arrested for DUI
22	m	11.60	21.80	33.40	n	erratic lane travel, nearly hit another vehicle
38	m	4.80	35.60	40.40	y	hit multiple parked cars, did not stop
42	m	8.60	32.30	40.90	n	arrested for DUI
56	m	9.50	32.90	42.40	n	driving 10 mph on freeway, erratic lane travel

tive for carisoprodol also. Carisoprodol concentrations were in the range 2.60 mg/L to 15.2 mg/L (median 4.85 mg/L), and meprobamate concentrations were in the range 1.00 to 35.6 mg/L (median 11 mg/L).

For comparison, following acute administration of 350 mg of carisoprodol, peak concentrations of 2.1 mg/L were reached in 1 h, and declined to 0.24 mg/L by 6 h (20). In another study, subjects taking 700 mg of carisoprodol reached peak plasma concentrations of carisoprodol of 3.5 ± 0.94 mg/L in 45 min, and for meprobamate of 4.01 ± 0.59 mg/L in 220 min, respectively (22). The half-life of carisoprodol was 99 ± 46 min. In another experiment under identical dosing conditions, the same workers reported peak plasma concentrations of carisoprodol of 3.1 ± 1.0 mg/L in 96 min, and for meprobamate of 4.8 ± 0.44 mg/L in 336 min, respectively (23). The half-life of carisoprodol is 102 min. In the group of drivers in Table 1, with only carisoprodol or meprobamate present, the concentrations for carisoprodol were elevated over the peak concentrations resulting from single-dose therapeutic use for muscle pain in 66% of the cases. While this most likely results from very recent use or overuse of the drug, it may also result from chronic administration, particularly if the subject has impaired metabolism. We could find no literature indicating a range for likely steady-state concentrations of carisoprodol resulting from chronic administration. The relatively short half-life, however, makes the accumulation of concentrations.

Meprobamate concentrations following the administration of that drug are generally higher than those arising during therapy with carisoprodol. The half-life for meprobamate is also much longer than for carisoprodol, and is reported as being between 6 and 17 h (24). Finkle (14) reported peak meprobamate concentrations of 15.6 mg/L at 120 min following the administration of 1200 mg of meprobamate over 4 h, and noted that the subject felt only mild drowsiness at the maximum plasma concentration. Meprobamate concentrations in the treatment of anxiety have been reported in the range 3 to 26 mg/L (24). Meprobamate concentrations in the drivers in Table 1 were generally within this range.

The isoenzyme cytochrome P4502C19 is responsible for the conversion of carisoprodol to meprobamate, and a polymorphism of this isoenzyme exists that is characterized by poor metabolism of mephenytoin. In these subjects, metabolism of carisoprodol is impaired, with a half-life of 376 min (22) or 216 min (23), approximately 2 to 3 times longer than normal. The fact that drowsiness as a side effect was reported equally by extensive and poor metabolizers of the drug, however, suggests that sedation and CNS depression associated with the use of the carisoprodol are properties of the parent drug also, and not just of the meprobamate metabolite. In fact, the authors note that poor metabolizers will be more susceptible to accumulation of carisoprodol, and the corresponding concentration-dependent side effects discussed above.

Carisoprodol and meprobamate are classical central nervous system depressants, and like alcohol, will generally produce dose-dependent effects. Ellinwood and Nikaido (25) have described the general trend towards concentration-dependent effects for increasing and then decreasing blood concentrations of depressants. Several authors have attempted to correlate blood concentrations of meprobamate or carisoprodol to effects. Maddock and Bloomer (26) reported that patients with plasma meprobamate concentrations of greater than 100 mg/L were associated with deep coma, light coma between 60 and 120 mg/L, and that patients with levels below 50 mg/L were invariably conscious. Bailey and Shaw (27) also found a statistically significant relationship between plasma levels and consciousness of patients. Factors such as tolerance to the effects of these drugs, cross tolerance to other CNS depressants such as the barbiturates (5), fatigue, other drug or alcohol use, and set and setting will all, however, contribute to substantial variation in response between individuals. In the cases listed in Table 1, although symptomatology was reported in some cases with marginal or therapeutic concentrations, (as low as 1 mg/L), specific evidence of psychomotor impairment was invariably noted at combined meprobamate/carisoprodol concentrations of greater than 10 mg/L. Likewise, other literature supports the onset of unconsciousness between 10 and 50 mg/L, a range which overlaps with the effective therapeutic range. Finkle (14) reported a series of 11 drivers with meprobamate in their blood, although most had alcohol or other drugs present. Symptomatology was generally that of erratic driving and gross symptoms of intoxication. Meprobamate concentrations were of the order of 30 mg/L and above. Marinetti-Scheff (15) reported a high incidence of DUI cases in the Detroit/Flint area of Michigan involving carisoprodol and meprobamate, but did not include specific details of symptomatology, driving behaviors or quantitative blood toxicology.

Twelve (57%) of the meprobamate/carisoprodol-only driving cases reviewed involved accidents, and the driver was deemed to be the causing driver in each case. As with the polydrug cases, driving behaviors observed when meprobamate and carisoprodol were present alone included extreme lane travel and weaving, striking other vehicles and fixed objects, slow speed, hit-and-run accidents where the subject appeared to be unaware he or she had hit another vehicle, and driving in the wrong direction on a freeway. In reviewing the symptomatology reported by the arresting officer, there was an apparent progression of effects from depressed reflexes, slowed movements, confusion, impairment in balance and coordination, disorientated to time and place, slurred or thick speech, and dazed or groggy appearance. Subjects were generally cooperative, compliant and lethargic, and none were combative. In some cases they were somnolent, and apparently unable to understand instructions or communicate. Subjects also invariably displayed horizontal gaze nystagmus.

Conclusions

The constellation of symptoms associated with use of carisoprodol or meprobamate in these drivers is characteristic of CNS depression, and the associated effects on complex tasks will resemble those of alcohol. As with other more common CNS depressants, divided attention, coordination, reaction time, judgment and decision making, and other skills essential to safe driving can all be affected. Some of these subjects were profoundly impaired, bordering on unconsciousness. Since these drugs are often present together with other CNS depressants or narcotics, it is likely that the combined effects will be more pronounced, and may differ slightly from those of the drug on its own. Many laboratories investigating DUI cases and traffic deaths do not test for either of these drugs; however, these data support the results of other workers who concluded that carisoprodol and meprobamate are important contributors to both DUI and traffic crashes, and should be more routinely tested for. Blood drug concentrations cannot predict with any definitive reliability the specific effects and the degree to which they will be present in any individual; however, the literature discussed and the cases presented here show the potential for significant psychomotor impairment following either therapeutic use or abuse of these drugs, whether taken alone or with other drugs. Physicians should exercise great care in the prescription of this medication, and carefully warn patients about the potential for these drugs to significantly impair their ability to drive.

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