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Combined Dextromethorphan and Chlorpheniramine Intoxication in Impaired Drivers

ABSTRACT: Dextromethorphan is a nonprescription antitussive which has been gaining in popularity as an abused drug, because of the hallucinogenic, dissociative, and intoxicating effects it produces at high doses. This report describes a series of eight drivers arrested for driving under the influence of the combined effects of dextromethorphan and chlorpheniramine, and a further four drivers under the influence of dextromethorphan alone. In the combined dextromethorphan/chlorpheniramine cases, blood dextromethorphan concentrations ranged from 150 to 1220 ng/mL (n = 8; mean 676 ng/mL, median 670 ng/mL), and chlorpheniramine concentrations ranged from 70 to 270 ng/mL (n = 8; mean 200 ng/mL, median 180 ng/mL). The four cases without chlorpheniramine present had blood dextromethorphan concentrations between 190 and 1000 ng/mL (mean 570 ng/mL, median 545 ng/mL). Some drivers had therapeutic concentrations of other drugs present. Drivers generally displayed symptoms of central nervous system (CNS) depressant intoxication, and there was gross evidence of impairment in their driving, including weaving, leaving the lane of travel, failing to obey traffic signals, and involvement in collisions. Drug Recognition Expert opinions confirmed that the subjects were under the influence of a drug in the CNS-depressant category.

KEYWORDS: forensic science, dextromethorphan, chlorpheniramine, Coricidin, driving impairment, toxicology

Dextromethorphan is an over-the-counter cough suppressant/antitussive, present in numerous cough, cold, and flu formulations. It is frequently taken in combination with analgesics (acetaminophen and aspirin), decongestants (phenylephrine, pseudoephedrine), and antihistamines (chlorpheniramine, brompheniramine) and a mucolytic (guaifenesin) for the symptomatic treatment of coughs, colds, and flu. Dextromethorphan is also abused for the intoxicating, hallucinogenic, and dissociative effects it produces when taken in high doses (1,2). Emergency room admission data from the Drug Abuse Warning Network (DAWN) indicate that of *c*. 2 million drug-related emergency room visits in 2006, about half a million involved nonmedical use of pharmaceuticals, of which 12,584 (0.7%) involved dextromethorphan (3). Dextromethorphan-related emergency room visits involved nonmedical use 43% of the time, and adverse reactions 33% of the time. Patients aged 12–20 accounted for 48% of visits due to nonmedical use of dextromethorphan (4). Recently, we reported a series of five deaths in teenagers resulting from dextromethorphan abuse (5).

A report from Wisconsin has documented patterns of dextromethorphan-positive cases in that state's driving under the influence (DUI) population (6). Many of these drivers (25%) were positive for chlorpheniramine also. We report eight cases of intoxication in individuals ingesting the dextromethorphan and chlorpheniramine combination common in some over-the-counter cough and cold remedies such as Coricidin Cough and Cold, Robitussin, and Equate (Wal-Mart) brands, for recreational purposes. The cases include available information on the subject's driving behavior, appearance, Drug Recognition Expert (DRE) evaluation, field sobriety tests, observed symptoms, and toxicology results. These are compared to four dextromethorphan cases in which chlorpheniramine was not present. We also report the patterns of use and dosage admitted to by some of the subjects.

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Methods

Drivers were contacted by police for the investigation of impaired driving in the course of regular traffic law enforcement. Subjects determined by the arresting officer to be under the influence of alcohol and or drugs were typically screened for alcohol by a breath test, and in cases where the circumstances suggested drug use, or the subject's apparent level of intoxication could not be accounted for by their breath alcohol concentration, a further evaluation was carried out (7). The evaluation included an assessment of pulse, blood pressure, muscle tone, and eye indicators, including horizontal and vertical nystagmus, convergence, hippus, and pupil size. It also included psychomotor tests for impairment including a walk and turn test, one leg stand, a Romberg balance test, and a finger-to-nose test. Drivers were either assessed through the administration of standardized field sobriety tests (SFSTs) (horizontal gaze nystagmus [HGN], one leg stand, walk, and turn), or the full DRE protocol (7).

Blood was collected subsequent to the arrest and assessment. Toxicological analysis was performed at the Washington State Toxicology Laboratory, Seattle, WA. Blood samples were screened using Enzyme Multiplied Immunoassay Technique (EMIT®) for cocaine metabolite, opiates, benzodiazepines, barbiturates, cannabinoids, amphetamines, phencyclidine, propoxyphene, methadone, and tricyclic antidepressants. Blood was extracted for basic and weakly acidic drug fractions, using liquid–liquid, and liquid–solid extraction procedures described elsewhere (8). Extracts were analyzed by gas chromatography, with flame ionization, nitrogen phosphorus, and mass selective detection. Screening and confirmation thresholds generally met or exceeded those described in Farrell et al. (9).

Results

Table 1 lists all 12 cases reported here. Ten subjects were male and two female. The average age of the subjects was 26.4 (15–51). Seven cases (1,3–8) had admissions or recent medical histories of

TABLE 1—*Selected symptoms, behaviors and toxicology in dextromethorphan-related impaired driving arrests.*

Gender	Age	Driving Behavior	General Appearance	Eyes	SFSTs	Admissions to Drug Ingestion	DRE Opinion	Dextromethorphan Concentration (ng/mL)	Chlorpheniramine Concentration (ng/mL)	Other Drugs Detected
M	20	Driving slowly, crossing center line and weaving	Slurred speech, cooperative, polite, poor coordination, face flushed	Watery, bloodshot, pupils dilated, HGN present	Circular sway 4–5 inches, poor balance, could not complete the SFSTs	Coricidin. States he had taken 16 pills in the prior 15 h	No DRE examination	150	140	ND
M	26	Tail light out. Weaving within lane (center line to fog line)	Cooperative, hands/arms shaking, speech thick and slow/normal	Bloodshot watery eyes, six clues HGN, immediate onset, VGN present, dilated pupils	Stepped off the line, swayed 2 inches, could not keep balance, put foot down, wrong # steps	Just released from hospital for Coricidin overdose (48 pills); Takes Olanzapine	Hallucinogen	470	180	ND
M	20	Weaving between lanes; "All over the road"	Cooperative, mood swings, argumentative; slurred speech	HGN present with onset prior to 45 degrees. Pupils dilated	Lost balance, put foot down, swayed, missed heel to toe	History of Coricidin overdoses on three prior occasions, latest was day before arrest. Took 16 Coricidin pills on that occasion	No DRE examination	670	230	ND
M	20	Zig-zagging within lane, struck curb, driving down center of road, made sharp turn without signalling	Cooperative, poor coordination and balance, obviously intoxicated, speech slow and slurred, face flushed, moved in slow motion, slow deliberate steps, stumbled, eyelid tremors	Droopy, watery eyes; HGN present with onset prior to 45 degrees, VGN present, pupils 7.0 mm, no hippus, no rebound dilation, unable to converge eyes, eyelid tremors present	Very slow on walk and turn, missed heel to toe, fast at end, used arms to balance	Took 3 sheets of Coricidin (24 pills) 5 h earlier; Recent/daily marijuana use; Takes Prozac	Cannabinoids and CNS depressant	670	180	THC-COOH 47 ng/mL, Fluoxetine <0.10 mg/L
M	19	Speeding	Cooperative, flushed, slow and deliberate in movements, slurred speech	Droopy, red eyes, 7 mm pupils, resting nystagmus, VGN present, no hippus, rebound dilation present	Lost balance, missed heel to toes, leg tremors, circular sway	Admitted to taking 24 Coricidin pills 2 h earlier to get high. Has taken 24–32 pills at a time	CNS depressant	740	130	ND
M	21	Drove off roadway, struck parked car	Cooperative, easily distracted; Worried, compliant; Slow movements, staggered, "not all there," poor coordination, sleepy, accelerated heart rate	Droopy eyes; No nystagmus present	Extreme impairment, barely able to stand, easily distracted, unable to stand or do SFSTs	Drank 2 bottles of Robitussin, and took 5 trays (~40 pills) of Coricidin	No DRE examination	1220	270	Dextrorphan
M	22	Weaving badly within lane, crossed fog line and center line	Cooperative, watery bloodshot eyes, constricted pupils, slurred speech, movements slow and unsteady, lost balance on exiting vehicle	Resting nystagmus, VGN present, droopy eyelids, lack of convergence, pupils dilated, rebound dilation, no hippus	Eylid and leg tremors, poor balance, slow to respond, balance problems, could not complete SFSTs	Two 8 ounce bottles of Equate, 20 Robitussin pills 9 h prior, Marijuana 3 days ago	CNS depressant	1000	ND	Guaifenesin pos., Dextrorphan pos., THC-COOH 17 ng/mL

SFSTs, Standardized Field Sobriety Tests; ND, not detected.

excessive dextromethorphan ingestion with or without chlorpheniramine. Eight cases were positive for dextromethorphan and chlorpheniramine (cases 1–8), while in four cases chlorpheniramine was not present (cases 9–12). In the combined dextromethorphan/chlorpheniramine cases, dextromethorphan concentrations ranged from 150–1220 ng/mL (n = 8; mean 676 ng/mL, median 670 ng/mL), and chlorpheniramine concentrations ranged from 70 to 270 ng/mL (n = 8; mean 200 ng/mL, median 180 ng/mL). The unconjugated metabolite dextrorphan was noted as an incidental finding in two cases, but was not quantitated, nor was it distinguished from its enantiomer levorphanol. Most cases had no other drugs present; however, one case had temazepam, lorazepam, oxazepam, clonazepam, trazodone, venlafaxine, and bupropion present at therapeutic or sub therapeutic concentrations, which may have contributed to this individual's condition. A second case had carboxy-THC and fluoxetine present. All of these cases were negative for alcohol. The four cases without chlorpheniramine present had dextromethorphan concentrations between 190 and 1000 ng/mL (mean 570 ng/mL, median 545 ng/mL). One of these cases had alcohol present at 0.02 g/100 mL, and a second had guaifenesin and carboxy-THC present. Narrative information abstracted from the arrest reports, including statements made by the subject about their pattern of ingestion, or other history related to ingestion, are included in Table 1. This table also shows the whole blood drug toxicology results.

In the subjects evaluated here, there were no major distinguishing features between those cases testing positive for dextromethorphan alone and those with the combination of dextromethorphan and chlorpheniramine. The intoxication syndrome for dextromethorphan with or without chlorpheniramine was characterized by central nervous system (CNS) depressant-like intoxication, inattention, and poorly controlled vehicle positioning with weaving, zig-zagging, or crossing the center line. Both speeding and slow driving were noted in one case each. The subjects were generally cooperative but displayed gross evidence of impairment with gait ataxia, stumbling, poor balance, deliberate slow or slurred speech, and slow and deliberate movements in general. The subject's eyes were usually described as red, or watery and bloodshot, with a pupil size of 5–7 mm (slightly dilated). The subject's eyes were checked for HGN, which was present, with four or more clues in nine of the 11 cases in which it was assessed. Vertical gaze nystagmus, diagnostic of severe intoxication, and associated with the use of hallucinogens and dissociative drugs was present in eight of 10 cases in which it was evaluated. Surprisingly, no nystagmus was noted by the officer assessing the subject with the highest concentrations of dextromethorphan (1220 ng/mL). Other clues such as the presence or absence of hippus, rebound dilation, and lack of convergence were inconsistent indicators, as was body temperature. On the standardized divided attention SFSTs, the subjects performed very poorly demonstrating significant sway (2–5′ from the vertical), poor balance, using arms for balance, inability to step down a straight line, and inability to follow directions. Subjects also performed poorly on the finger-to-nose test of coordination. DRE evaluations were conducted in three of the four dextromethorphan-only cases, and five of the eight dextromethorphan/chlorpheniramine cases. Pulse and blood pressure were typically elevated in the cases of combined dextromethorphan and chlorpheniramine use (n = 5; mean blood pressure 153/107, mean pulse 103). In cases where chlorpheniramine was not present, pulse and blood pressure were similarly elevated (n = 3; mean blood pressure 134/100, mean pulse 104). These findings suggest that dextromethorphan produces tachycardia and hypertension independent of the known tendency of chlorpheniramine to do so in overdose.

Seven subjects either made admissions to their ingestion pattern, or additional information was available. This is shown together with selected observations and toxicology data in Table 1. Most admissions are couched in terms of numbers of pills or "trays" (8-pill blister packs), and bottles of cough syrup (8–12 oz). No specific timeframes are given so the dose is difficult to estimate with any accuracy in a given case. However, using typical doses of 15 mg of dextromethorphan and 4 mg of chlorpheniramine in a pill, and similar dosage per 5 mL measure of syrup, the doses in these subjects could be in the range 240–2500 mg for dextromethorphan, and 64–160 mg for chlorpheniramine. Of the 12 cases reported here, DRE officers assessed eight of the subjects. In two cases, they gave the opinion that the subjects were under the influence of CNS depressant and cannabinoids, in four cases they indicated a CNS depressant alone, and in one case each, an hallucinogen and a stimulant.

Discussion

Dextromethorphan is deliberately abused for its intoxicating, hallucinogenic, and dissociative effects. Many of the readily available preparations also contain the antihistamine chlorpheniramine, which most likely adds a sedating/stimulating component to the drug experience. There are relatively few reports of deaths or intoxications attributed specifically to chlorpheniramine alone. The reported adverse effects in an emergency room population following ingestion of Coricidin HBP Cough and Cold (10), typically 8–16 pills (200–400 mg dextromethorphan; 32–64 mg chlorpheniramine), were tachycardia (54%), lethargy (43%), hypertension (31%), ataxia or dizziness (22%), confusion (17%), vomiting (10%), slurred speech (5%), and agitation (5%). Altered mental state was reported by 66% of patients. The doses reported in the subjects in this study, and the patterns of effects, are similar to that emergency room population. Websites frequented by the recreational dextromethorphan-using community report low-level recreational effects including euphoria, mild intoxication, lightheadedness, progressing to mild hallucinations, loss of concentration, slurred speech, memory impairment, delusions and more intense hallucinations, disturbed thought, and mind/body dissociation with increasing doses (2). These symptoms are also consistent with those seen in the subjects we assessed here.

Rates of dextromethorphan metabolism vary as a result of pharmacogenetic factors. Both extensive and poor metabolizers have been identified. Super-extensive metabolizers with multiple copies of the CYP2D6 gene probably also exist (11). Plasma concentrations following therapeutic use (30 mg q.i.d. over 7 days) averaged between 2.4 and 207 ng/L in extensive and poor metabolizers, respectively (12). Steinberg et al. (13) administered dextromethorphan doses of up to 400 mg q.i.d. to neurosurgery patients in an assessment of the neuroprotective effects of the drug. Subjects achieved serum dextromethorphan concentrations of up to 1514 ng/mL and dextrorphan (total) concentrations of 502 ng/mL. They made no differentiation between extensive and poor metabolizers, but there was a 40-fold variation in serum concentrations at the highest doses administered (>5 mg/kg). Up to 64% of patients experienced side effects such as nystagmus, dysarthria (a motor speech disorder resulting from neurological injury), visual disturbances, feeling "drunk," euphoria, visual hallucinations, persecutory delusions, nausea and vomiting, gait ataxia, and dizziness. Inhibition of CYP2D6 metabolism with quinidine, a well-known CYP2D6 inhibitor, produced a significant elevation in dextromethorphan concentration (115 ng/mL vs. 2.9 ng/mL) following the same 30-mg QID dose for 7 days dosage regimen (14). Other

inhibitors of CYP2D6 which may be co-ingested with dextromethorphan and increase its toxicity include fluoxetine, paroxetine, and chlorpheniramine (15). The average whole blood dextromethorphan concentrations in the subjects reported here (676 ng/mL) was 300 times the concentration normally seen in plasma samples following therapeutic use in rapid metabolizers, and three times the concentrations encountered following therapeutic use in poor metabolizers.[1] This indicates that the concentrations reported here likely resulted from massive ingestion, consistent with the histories, rather than from a metabolic insufficiency.

Chlorpheniramine concentrations in man following administration of three 2-mg oral doses, peaked at 10 ng/L (17), and a single 8-mg oral dose produced a mean plasma concentration of 9.9 ng/mL at 3 h (18). The chlorpheniramine concentrations in the subjects reported here were 7–27 times these therapeutic concentrations. The highest chlorpheniramine concentration (270 ng/mL) was recorded in a subject who admitted to drinking 16 ounces of Robitussin, and swallowing ~40 Coricidin pills (Table 1).

Chlorpheniramine is the prototypical first generation alkylamine-type antihistamine, and is among the most potent H_1 receptor antagonists, although it is considered to be less sedating than diphenhydramine. There are very few reports of abuse or intoxication resulting from ingestion of chlorpheniramine on its own.[2] The most common side effect of chlorpheniramine use is sedation (19), and related side effects include dizziness, tinnitus, lassitude, incoordination, fatigue, and blurred vision. Some individuals experience paradoxical CNS stimulating effects from use of this drug, reporting euphoria, nervousness, insomnia, and tremors (19), possibly related to its known serotonin reuptake inhibition and serotonin agonist properties (20), and cocaine-like stimulation of dopamine transmission (21). In overdose or poisoning the most significant effects appear to be the CNS stimulating effects, including hallucinations, excitement, ataxia, incoordination, chorea-like athetosis (hands and/or feet move in a slow continuous twisting, circling motion), and convulsions (19). Chlorpheniramine is extensively metabolized in man, undergoing demethylation through CYP2D6, where it also acts as an inhibitor. A typical 4 mg dose of chlorpheniramine has a 4–6 h duration of action, although the drug has a half life of 12–43 h.

Combining dextromethorphan with chlorpheniramine in overdose creates the potential for increased intoxication, additional risk of hallucinogenic effects, and an additional CNS stimulating component to the intoxication. Other potential interactions between the two drugs include the serotonergic reuptake inhibition shared by both, and the inhibition of CYP2D6 metabolism of dextromethorphan by chlorpheniramine. Other selective serotonin reuptake inhibitors such as fluoxetine, paroxetine, and venlafaxine, will also interact increasing the risk of a serotonergic crisis (22,23).

Cochems et al. (6) have noted in dextromethorphan-impaired drivers in Wisconsin, that their general appearance was consistent with CNS depression, including poor performance on psychophysical tests, poor balance and coordination, presence of horizontal and vertical nystagmus, lethargy, slurred speech, and ataxia. Physiological indicators—dilated pupils and elevated pulse and blood pressure—and the drug categories called by the DRE were consistent with our findings here. The mean dextromethorphan concentration in the Wisconsin cases was 207 ng/mL (range <5 to 1800 ng/mL), substantially less than the subjects reported here (mean 641 ng/mL); however, our cases were selected specifically based on evidence of massive dextromethorphan ingestion (blood concentrations >150 ng/mL), and associated histories. Polydrug use was reported in 96% of the Wisconsin cases. There is little evidence to suggest significant impairment from dextromethorphan alone in therapeutic use.

No controlled on-road driving studies have been performed for dextromethorphan; however, chlorpheniramine has been studied in an actual on-road driving paradigm. Theunissen et al. (24) administered two 6 mg sustained release tablets of chlorpheniramine BID to subjects for 8 days, and found a significant deterioration in driving performance on the first day, but the effects disappeared after 8 days of administration, presumably because of the development of tolerance. Vermeeren et al. (25) administered 8 or 12 mg sustained release doses of chlorpheniramine to 24 subjects at bedtime, followed the next morning by a dose of the nonsedating antihistamine terfenadine. Subjects then completed an on-road driving test consisting of a car following test and a highway driving test. They concluded there was no residual effect of either the 8 or 12 mg sustained release chlorpheniramine preparation.

Conclusions

These cases describe representative dextromethorphan abuse scenarios encountered by law enforcement personnel and presumably emergency medicine staff. The presentation is one of marked CNS depressant intoxication, with no alcohol present. Psychomotor impairment, poor coordination, slurred speech, flushed face, horizontal gaze nystagmus (often at rest), and vertical gaze nystagmus, together with elevated pulse and blood pressure characterize these cases. Hallucinations were rare. Some component of the intoxication is likely a consequence of the co-ingestion of chlorpheniramine, but the combination does not seem to alter the overall constellation of effects. The subject's driving characterized by weaving, drifting out of their lanes, inappropriate speed, inattentive driving and involvement in collisions is consistent with that seen in drivers with CNS depressant intoxication such as with alcohol. Some subjects may accrue elevated blood concentrations of dextromethorphan as a result of metabolic insufficiency or drug interaction, but concentrations in excess of 150 ng/mL achieved by subjects reported here resulted from abuse.

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[1]The whole blood to plasma ratio for dextromethorphan in man has not been established, but has been reported as 1.76:1 in rats (16), so the corresponding plasma concentrations in the subjects reported here may be as little as 0.57 times the reported whole blood concentrations.

[2]For user accounts of intoxication from chlorpheniramine, with and without dextromethorphan, see http://www.erowid.org.

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