Five Deaths Resulting from Abuse of Dextromethorphan Sold Over the Internet

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Abstract

Dextromethorphan is a widely available over-the-counter antitussive that produces intoxicating, hallucinogenic, and dissociative effects at doses significantly exceeding the therapeutic range. We report the deaths of five teenage males in three incidents in three states (WA, FL, and VA) who purposefully ingested large doses of dextromethorphan for recreational purposes and died as a result of the direct toxic effects of the drug. The dextromethorphan was obtained from the same internet supplier in each case. Postmortem blood dextromethorphan concentrations ranged from 950 to 3230 ng/mL (median 1890 ng/mL). Three subjects had diphenhydramine present, one had a trace of alprazolam, and two were positive for cannabinoids. In each case, the death was attributed to dextromethorphan toxicity or toxicity from dextromethorphan and other drugs. The article discusses the metabolism, pharmacology, and potential for drug interactions for dextromethorphan and the likely mechanisms for toxicity. The dextromethorphan concentrations in all five subjects significantly exceeded the therapeutic range and are consistent with concentrations reported in other cases of dextromethorphan abuse and toxicity. The deaths resulted in the prosecution of three individuals involved in sale or distribution of the drug.

Introduction

Dextromethorphan (slang terms: DXM, Dex, Skittles, Robo, Triple-c) is a widely available over-the-counter antitussive. The drug has a complex effect profile, with markedly different effects at different doses. With normal therapeutic use, it is an effective, non-opiate, cough suppressant with minimal side effects; however, at very high doses, its effects on NMDA and serotonin transmission, its potential for interaction with other serotonergic drugs, and pharmacogentically determined differences in its metabolism, can combine to cause a very different effect profile (1,2). Hyperdosing with the drug produces intoxicating, hallucinogenic, and dissociative effects which have become the subject of much internet lore, contributing to its growing popularity (3,4). We report the deaths of five teenagers who purposefully ingested large doses of dextromethorphan obtained over the internet for recreational purposes and died as a result of the direct toxic effects of the drug. Investigation of the deaths led to a federal prosecution (5).

Case Histories

Incident 1—Bellingham, WA

Two Caucasian males, aged 17 and 19 years, obtained dextromethorphan over the internet for recreational use. They were discovered dead in the bedroom of the 17-year-old following a sleepover. There was no external evidence of trauma to either victim. A clear Ziploc bag of white powdered material labeled "dextromethorphan Hbr 100 grams, not for human use" was discovered in proximity to the bodies (approximately 47/100 g residual), in addition to several empty cans of taurine-containing sports drinks. No additional drugs or drug paraphernalia were recovered. Interviews with friends and family of the 17-year-old reported that the drug was obtained over the internet from a company identified as "Omega Fine Chemicals, Chemical API" and that the decedents had previously experimented with dextromethorphan for recreational purposes on multiple occasions. Their use began with consumption of over-

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the-counter cold medications, and escalated over time to the bulk powder formulation. The purchase was made by a third party teen with payment by credit card in the amount of $205. Law enforcement investigation suggested that the decedents had obtained a large quantity of drug for potential distribution at the local high school which the boys attended. They reportedly repackaged the powder into gelatin capsules obtained at a local health food store. At least three additional non-fatal overdoses, two of which resulted in documented emergency room treatment, were linked to the repackaged product.

Complete forensic autopsies were conducted on both subjects. The autopsy results revealed two healthy individuals with non-specific but common findings associated with an opiate-type overdose: pulmonary edema, cerebral edema, presence of frothy foam in oropharynx and major airways, and no signs of trauma or antecedent natural disease. Heart blood was obtained due to extensive intravascular postmortem coagulation. No residual capsules or pill fragments were present in gastric contents. No identifiable powder was present in the nose to suggest insufflation, and no intravenous puncture sites were identified. The dextromethorphan is presumed to have been ingested orally. The cause of death was established for the subjects based upon scene investigation, complete forensic autopsies, and corroborating postmortem toxicology performed on central whole blood. Toxicology revealed a heart blood dextromethorphan concentration of 3230 µg/L in the 17-year-old. The 19-year-old had heart blood concentrations of 1890 µg/L dextromethorphan and 20 µg/L diphenhydramine. Both individuals tested positive for the presence of cannabinoids by immunoassay. The cause of death in both cases was determined to be acute dextromethorphan intoxication, and the manner of death was ruled accidental in nature. The absence of other significant drugs in these cases provides a useful index of the potential lethal threshold for dextromethorphan.

Incident 2—Danville, VA

A third dextromethorphan death occurred in Danville, VA and was linked to the same internet supplier of dextromethorphan. This 19-year-old male was known to be up late "doing drugs". He was known to be asleep at 4:00 a.m., and at 11:00 a.m. he was heard snoring loudly. He was found on the floor unresponsive at 2:45 p.m. An emergency 911 call was made, and he was pronounced dead at 3:33 p.m. The only significant pathology finding in this otherwise healthy teenager was pulmonary edema. He had dextromethorphan concentrations of 1300 µg/L in iliac blood, 700 µg/L in vitreous humor, 19,000 µg/kg in liver, and > 20,000 µg/L in urine. The blood also tested positive for alprazolam (< 10 µg/L) and qualitatively positive for dextrorphan. The cause of death was drug toxicity, dextromethorphan, and the manner of death was accidental.

Incident 3—Cape Coral, FL

Two 19-year old-males were found dead in Cape Coral, FL. They had iliac blood dextromethorphan concentrations of 950 and 3080 µg/L. In addition, these males combined the dextromethorphan purchased over the internet from the same supplier as incidents 1 and 2, with the over-the-counter medications Benadryl (diphenhydramine) and Robitussin HL. The postmortem iliac blood diphenhydramine concentrations were 264 and 238 µg/L (normal therapeutic range of 30–50 µg/L). These individuals also had complete forensic autopsies, and postmortem studies revealed no underlying natural disease processes. Both individuals had heavy, wet, congested lungs. The cause of death for both individuals was determined to be drug intoxication by ingestion of dextromethorphan and diphenhydramine.

One additional teenage male in Cape Coral, FL survived the hyperdosing of dextromethorphan and diphenhydramine. He informed the police that he became ill soon after ingesting the medications and subsequently vomited. In addition, he was an estimated 70 pounds heavier than his 2 friends who died. The surviving teenager told police that he had purchased the powdered dextromethorphan on an internet website on multiple occasions and had abused the same amount of medication in the past without ill side effects.

All three incidents and all five deaths were linked to the same internet supplier of dextromethorphan, "Chemical API", a chemical resale company in Indianapolis, IN. The two men from Indianapolis who operated the website bought the drug in bulk from India, repacked it, and sold it over the internet. They later plead guilty to 3 counts of introduction of misbranded drugs into interstate commerce and were sentenced to 77 months imprisonment (5). The individual in VA who ordered the drug and provided it to the teenager who died was convicted of involuntary manslaughter (6).

Discussion

Clinical signs and symptoms of dextromethorphan intoxication are reported by users after having ingested doses of 100–400 mg and include euphoria, laughing, stupor, and hyperexcitability. In mild to moderate intoxication, mydriasis, nystagmus, diaphoresis, nausea, and vomiting are documented. With increasing dosage, intoxication becomes more severe and is associated with hallucinations, delusions, a plodding ataxic gait (described by users as "zombie-like walking"), agitation, and extreme somnolence. With more intensive usage (~600–1500 mg), abusers may experience a dissociative psychotic state with hallucinations, delusions, paranoia, coma, and death. Toxic effects from supratherapeutic dosing include a racing, irregular heartbeat; seizures; serotonin syndrome; hyperthermia; and rhabdomyolysis (1–4,7–9).

Dextromethorphan is a non-controlled drug, structurally related to the opiate codeine, with which it shares its antitussive properties. But, unlike codeine, it has no opiate-like analgesic activity. It is the principal active ingredient in many multi-symptom cough and cold preparations, many of which additionally contain an analgesic (acetaminophen, aspirin), decongestant (phenylephrine, pseudoephedrine), antihistamine (chlorpheniramine, brompheniramine, pheniramine), and/or the expectorant/mucolytic agent guafenesin. Some the many popular brand name product families of which dextromethorphan is a constituent are Robitussin, Coricidin, Alkaseltzer, Benylin, Dimetapp, Triaminic, and Theraflu. It is also periodi-

cally available over the internet via chemical resellers. Drug culture websites promoting dextromethorphan awareness are careful to point out the dangers of using formulations compounded with other sedatives, most notably chlorpheniramine, which contribute to its toxicity (3,4,10). Dextromethorphan is the d-isomer of 3-methoxy-N-methyl-methorphinan. The l-isomer, levomethorphan, is a prodrug for the potent analgesic levorphanol (the l-analogue of the dextromethorphan metabolite dextrorphan). When the stereochemical identity of the drug is in question, a chiral analysis should be considered. Separation of the enantiomers has been demonsrated by capillary electrophoresis on cyclodextrin phases (11,12).

Dextromethorphan is metabolized via CYP2D6 to dextrorphan and via CYP3A4/5 to 3-methoxymorphinan, which is further oxidized to 3-OH-morphinan (13). Approximately 20% of the dextrorphan is conjugated as the glucuronide metabolite, and 80% is free. Both dextromethorphan and dextrorphan are NMDA receptor antagonists. Dextrorphan has greater NMDA antagonist activity allowing it to bind more readily to the PCP_1 receptor of the NMDA receptor complex (14). NMDA receptor binding is responsible for the hallucinogenic and dissociative effects of phencyclidine and ketamine and most likely accounts for the hallucinogenic and dissociative effects of dextromethorphan and dextrorphan. Genetic polymorphism of CYP2D6 exists with about 10% of the Caucasian population being poor metabolizers of 2D6 substrates like dextromethorphan (13). Because both dextromethorphan and dextrorphan exhibit PCP_1 binding, both extensive and poor metabolizers of dextromethorphan will likely experience the dissociative and hallucinogenic effects of the drug if the dose is sufficiently high. Inhibitors of CYP2D6 such as amitriptyline may increase blood concentrations of dextromethorphan with corresponding toxicity (15).

Both dextromethorphan and dextrorphan have sigma agonist activity, contributing to the increased muscle tension, tachycardia, tachypnea, and mydriasis often identified in recreational dextromethorphan users. The sigma activity is also linked to motor function (16), and there is speculation that this link may be involved in the peculiar plodding gait ("zombie walking", "sea legs", or "robo shuffle") often reported in dextromethorphan intoxication (7).

Dextromethorphan and dextrorphan also both inhibit reuptake of serotonin, and have competitive $5HT_1$ agonist activity, creating the potential for interaction with selective serotonin reuptake inhibitors such as paroxetine (17) and fluoxetine (18), and the commonly co-ingested antihistamines chlorpheniramine and, to a lesser extent, diphenhydramine (19). Overdosing or co-ingestion of drugs with serotonergic effects can lead to serotonin syndrome, a life-threatening condition diagnosed by the presence of serotonergic agents and the presence of at least three of the following symptoms: mental status change, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever (20). The serotonergic properties of all other co-ingested drugs should be considered when evaluating a potential dextromethorphan death.

Some literature suggests the possibility of bromide toxicity resulting from ingestion of dextromethorphan in its common hydrobromide salt form. However, in one reported overdose case where this was investigated, bromide concentrations were not elevated (21).

Normal antitussive use of dextromethorphan requires doses of 20–30 mg up to four times a day in divided doses, for a total daily dose of 90–120mg, although some users may administer higher doses for cough relief. A single acute oral dose of dextromethorphan (60 mg) resulted in average peak plasma concentrations at 2.1 h of 5.2 µg/L for dextromethorphan and 879 µg/L for conjugated dextrorphan (22). Individuals ingesting 30 mg of dextromethorphan four times daily for seven days achieved peak plasma concentrations of 2.4 µg/L (range 0.5–5.9 µg/L) in rapid metabolizers and 207 µg/L (182–231 µg/L) in poor metabolizers (23). Therapeutic use of dextromethorphan is generally not detected in routine toxicology screening. The drug has very low cross-reactivity on opiate or PCP immunoassays, and an analytical cut-off concentration of 20 µg/L has been recommended for laboratories performing drug impaired driver testing (24). A specific ELISA assay for dextromethorphan is available (25). The presence of dextromethorphan is an incidental finding in many polydrug deaths and is usually within normal therapeutic concentrations.

Drug concentrations in forensic casework are typically reported in whole blood as it was in these cases. The whole blood-to-plasma ratio for dextromethorphan in humans has not been established, but it has been reported as 1.76:1 in rats (26), so the corresponding plasma concentrations in the subjects reported here may be as little as 0.57 times the reported whole blood concentrations.

Median whole blood dextromethorphan concentrations of 51 µg/L (range 5–1800 µg/L) have been reported in impaired drivers in Wisconsin (27). A series of five drivers with documented abuse histories of recreational dextromethorphan abuse in Washington State had a median concentration of 790 µg/L (range 470–1220 µg/L) after consumption of up to 1500 mg of dextromethorphan (28). In many of these cases, other drugs compounded with dextromethorphan in cough and flu preparations were also present, most notably the sedating antihistamine chlorpheniramine.

Only a limited number of deaths have been attributed specifically to dextromethorphan. Kintz and Mangin (29) reported an adult suicidal poisoning with dextromethorphan and terfenadine. Blood toxicology results showed a dextromethorphan concentration of 5090 µg/L, total dextrorphan concentration of 1400 µg/L, and the antihistamine terfenadine at a concentration of 7200 µg/L. The terfenadine concentration is highly elevated and undoubtedly contributed to this death.

Rammer et al. (30) reported two deaths with blood dextromethorphan concentrations. The first, a suicidal ingestion by an 18-year-old woman, had blood dextromethorphan and dextrorphan concentrations of 9200 and 2900 µg/L, respectively. The second had blood dextromethorphan and dextrorphan concentrations of 3300 and 1500 µg/L, respectively. Yoo et al. (31) reported nine combined dextromethorphan and zipeprol deaths with a median dextromethorphan concentration of 1800 µg/L (range from 1100 to 18,000 µg/L); however, in all but the 18,000 µg/L dextromethorphan case, the zipeprol concentrations alone appeared high enough to account for death.

Dextromethorphan-related deaths are also reported in the

pediatric literature, usually involving infants (less than 1 year old). In these cases, multiple drugs are typically present as a result of inappropriately large doses of cough or flu preparations for the child for therapy or sedation. Boland et al. (32) reported the death of a two-month old infant with brompheniramine (400 µg/L), ephedrine (14,000 µg/L), and dextromethorphan (500 µg/L), and Marinetti et al. (33) reported six infant deaths with dextromethorphan present in concentrations ranging from 30 to 550 µg/L. The cause of death in four of these cases was certified as multiple drug intoxication.

The acute doses reported by the user community for the dissociative, hallucinogenic drug experience with dextromethorphan [150–1500 mg or more (3,4)] are well above the normal recommended antitussive dose and will result in blood concentrations well in excess of therapeutic values. Severe toxicity associated with dextromethorphan abuse was documented in the case of a 15-year-old boy who ingested 600 mg (300 mg in the evening and 300 mg in the morning for a total of 9.7 mg/kg), resulting in seizures, mydriasis, nystagmus, cyanosis, and apnea, although blood drug concentrations were not reported (34).

The deaths reported here were all of otherwise healthy males in their late teens. Each had some history of abusing dextromethorphan and was taking large amounts of the drug specifically for its intoxicating/hallucinogenic effects. The blood dextromethorphan concentrations were all in excess of 950 µg/L, which suggests a lower threshold for lethality than previously reported cases. The principal findings in each case were of heavy congested lungs, a common finding in drug overdose deaths. None of the deaths was witnessed, so the symptomology necessary to diagnose serotonin syndrome was not documented; however, that, and generalized CNS depression, are the most likely mechanisms of death. As was true in this case, sale or distribution of a drug for illicit use that results in the death of another creates liability for the provider and may lead to criminal prosecution.

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