



CASE REPORT

Deaths due to abuse of dextromethorphan sold over-the-counter in Pakistan



Humera Shafi ^{a,*}, Muhammad Imran ^a, Hafiz Faisal Usman ^a,
Muhammad Sarwar ^a, Muhammad Ashraf Tahir ^a, Rabia Naveed ^a,
Muhammad Zar Ashiq ^a, Ammar M. Tahir ^b

^a Punjab Forensic Science Agency, Thokar Niaz Baig, Multan Road, Lahore, Pakistan

^b Ohio University, Medical School Athens, OH 45701, United States

Received 31 March 2015; revised 30 June 2015; accepted 20 July 2015

Available online 28 August 2015

KEYWORDS

Dextromethorphan;
Liquid chromatography;
Synergistic effect

Abstract Dextromethorphan is the most commonly used over-the-counter anti-tussive and expectorant medicine at therapeutic doses. Due to easy availability, euphoric high and hallucinogenic effects at larger doses, dextromethorphan popularity amongst the drug abusers is growing day by day. It is often mixed with alcohol, opiates, cannabinoids or other drugs of abuse for recreational purposes despite their lethal synergistic effects. More than 50 deaths were reported the first time in Pakistan after consuming cough syrups containing dextromethorphan, manufactured by two local pharmaceutical industries. All deceased had the history of drug abuse. We report the deaths of nineteen males, ages ranged from 17 to 45 years, in two major cities of Pakistan who purposefully ingested large doses of dextromethorphan for recreational purposes and died as a result of direct toxic effects of the drug. Toxicological analysis revealed high levels of dextromethorphan ranging from 7.3 to 41.7 mg/L in the peripheral blood, 4.2–92.6 mg/kg in the liver and 9.9–349.6 mg/L in the gastric content by high performance liquid chromatography. The dextromethorphan concentrations in all subjects significantly exceeded the therapeutic range and were consistent with concentrations reported in other cases of dextromethorphan abuse and toxicity. Besides dextromethorphan other drugs of abuse like cannabinoids, opiates, benzodiazepines, ethanol and chlorpheniramine were also detected. The cause of death was determined to be acute dextromethorphan intoxication with lethal synergistic effect of other co-ingested drugs of abuse. The deaths resulted in the prosecution of all individuals involved in manufacturing, distribution or sale of the cough syrup.

© 2015 The International Association of Law and Forensic Sciences (IALFS). Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Dextromethorphan (DXM) is amongst the most abused over-the-counter (OTC) anti-tussive medications due to its easy availability for consumption. Buying a bottle of cough syrup

* Corresponding author at: House No. 75, Sector/Block 4-A-II, Township, Lahore, Pakistan. Tel.: +92 3234229144, +92 3217487427.

E-mail address: humera.shafi@yahoo.com (H. Shafi).

Peer review under responsibility of The International Association of Law and Forensic Sciences (IALFS).

<http://dx.doi.org/10.1016/j.ejfs.2015.07.002>

2090-536X © 2015 The International Association of Law and Forensic Sciences (IALFS). Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

containing DXM is as simple as going to the store for grocery. Its popularity amongst drug abusers is growing day by day owing to highly dose dependent effects of DXM.^{1,2} It acts as cough suppressant at therapeutic doses but at larger doses it produces intoxication, euphoric high, hallucinations, out of body experiences, and dream-like visions.^{3,4} DXM is a non-controlled drug which is structurally related to codeine (opiate) but lacks opiate-like analgesic activity. It is manufactured as a white powder, but consumption is by swallowing gel capsules, tablets, or cough syrup. In cough and cold preparations, DXM is present in combination with analgesic, decongestant, antihistamine, and/or expectorant/mucolytic agents.¹⁻⁴ Therapeutic level of DXM reported in the literature ranges from 0.005 to 0.06 mg/L in blood whereas the lethal levels range from 3.3 to 9.5 mg/L in the blood and 31–230 mg/kg in the liver.^{1,2}

Drug abusers also mix DXM with alcohol, cannabinoids, opiates and benzodiazepines to create an even stronger but dangerous effect. Its effects are similar to dissociative hallucinogens like phencyclidine (PCP) and lysergic acid diethylamide (LSD) but not long lasting as compared to PCP and LSD.⁸ DXM causes psychological addiction. FDA issued a warning in May 2005 about the dangers of DXM abuse involving over-the-counter products and DXM obtained from illicit sources.⁵ In 2005 and 2006, nearly 1 million (1.7%) and about 3.1 million persons aged 12–25 (5.3%) had misused an over-the-counter (OTC) cough and cold medication to get high.^{6,7} Several deaths had been reported in the literature as a result of direct toxic effects of DXM owing to its growing popularity amongst young teens and young adults for recreational purposes.^{2,11,13}

More than 50 deaths were reported in two incidents in Pakistan after ingesting cough syrup containing DXM in 2013. In this article, we report the deaths of nineteen subjects who purposefully ingested cough syrup containing DXM for recreational purposes in combination with other drugs of abuse including benzodiazepines, opiates, cannabinoids, chlorpheniramine and ethanol. They died as a result of direct toxic effects of DXM as well as lethal synergistic effect of co-ingested drugs of abuse.

2. Case histories

2.1. Incident 1 – Lahore, Pakistan

An incident of more than 30 deaths occurred in Lahore city of Pakistan due to ingestion of cough syrup containing DXM. Autopsy specimens of twelve males with ages ranging from 18 to 45 years were submitted for forensic postmortem toxicology. All subjects had the history of ingesting cough syrup manufactured by a local pharmaceutical industry. Interviews with families and friends of deceased reported that they were drug abusers. The autopsy reports submitted with postmortem specimens revealed an opiate-type overdose resulting in pulmonary and cerebral oedema, congested lungs and other airways and no signs of trauma or antecedent natural disease. No fragments of tablets or capsules were present in the gastric contents of all deceased. Postmortem toxicology was performed on specimens of whole blood and gastric contents belonged to twelve deceased. Toxicology revealed a peripheral blood DXM concentration ranged from 7.3 to 41.7 mg/L by liquid

chromatography. Chlorpheniramine (sedating anti-histamine) was also detected but not quantitated. All subjects tested positive for the presence of opiates, eight for cannabinoids, and two for benzodiazepines by immunoassay. Gastric contents of one deceased also contained 1.1 g/dL ethanol. The cause of death in all deceased was determined to be acute DXM intoxication, and the manner of death was ruled accidental in nature. Presence of one or more co-ingested drugs of abuse suggested the lethal synergistic effect.

Three additional teenage males, who survived after toxic dose of DXM, informed the police that they became ill soon after ingesting the cough syrup and subsequently vomited. The surviving individuals told the police that they had purchased the DXM cough syrup bottles from local pharmacies on multiple occasions. They further told police that they had abused the same amount of medication in the past without ill side effects.

2.2. Incident 2 – Gujranwala, Pakistan

A second incident of more than 20 DXM-related deaths occurred in Gujranwala city of Pakistan and was linked to the abuse of an over-the-counter cough syrup containing DXM manufactured by another National pharmaceutical industry. Postmortem specimens of seven deceased, ages ranging from 17 to 45 years, submitted for toxicological analysis included liver and gastric contents. Blood specimens were not submitted for analysis. Autopsy reports submitted with specimens showed the same opiate-type overdose with significant pulmonary oedema as in the incident 1. Postmortem toxicology revealed high levels of DXM ranging from 4.2 to 92.6 mg/kg in the liver and 9.9–349.6 mg/L in gastric contents. All subjects also tested positive for the presence of opiates, three for cannabinoids and two were positive for the presence of benzodiazepines by immunoassay. In five deceased, 0.02–0.43 g/dL ethanol was also found in the gastric contents. The cause of death in all subjects was determined to be the drug intoxication by ingestion of DXM in the presence of other drugs of abuse, and the manner of death was accidental.

Both incidents and all deaths were linked to the cough syrup containing DXM, manufactured by two local pharmaceutical industries. The owners of both industries told the investigators that they bought the DXM (active ingredient in cough syrup) in bulk from India, manufactured the syrup, and sold it as over-the-counter medication. Both pharmaceutical industries were sealed and all the individuals involved were arrested.

3. Discussion

Dextromethorphan (DXM) is the principal active ingredient of cough and cold medications, in combination with antihistamine (like chlorpheniramine, pheniramine, brompheniramine), analgesic (such as aspirin, acetaminophen), expectorant (or mucolytic agent like guaifenesin) and/or decongestant (like pseudoephedrine, phenylephrine). DXM is a dextrorotatory isomer of 3-methoxy-N-methyl-methorphan and structurally related to codeine but lacks analgesic activity. It is a NMDA receptor antagonist. Like ketamine and phencyclidine, the dissociative and hallucinogenic effects of DXM are due to its binding to the NMDA receptor.⁹ It is metabolized in

the liver by CYP2D6 to dextrophan and by CYP3A4/5 to 3-methoxymorphinan.¹⁰ Reported signs and symptoms associated with mild to moderate DXM intoxication includes euphoria, stupor, hyperexcitability, laughing, nystagmus, mydriasis, nausea, vomiting and diaphoresis. Dissociative psychotic disorders including hallucinations, delusions, rhabdomyolysis, hyperthermia, seizures, coma and death occur with intensive abuse^{1-4,11-13}. DXM also has competitive 5HT₁ agonist activity and inhibits the serotonin reuptake therefore creating the potential for interaction with selective serotonin reuptake inhibitors (SSRI) like fluoxetine¹⁴ and paroxetine,¹⁵ the co-ingested anti-histamines like chlorpheniramine and, to a lesser extent, diphenhydramine.¹⁶ Co-administration or overdosing or co-ingestion of drugs with serotonergic effects results in a life threatening serotonin syndrome.¹⁷ Therefore, co-ingested drugs have potential significance in evaluating a DXM death.

Total daily dose of DXM to relief cough is 90–120 mg which is given four times a day in divided doses. Its single dose (30 mg) given four times daily for a week achieved peak plasma concentrations averaged 2.4 µg/L (range 0.5–5.9 µg/L) in rapid metabolizers and 207 µg/L (182–231 µg/L) in poor metabolizers¹⁸ DXM has very low cross-reactivity on opiate or phencyclidine immunoassays and in therapeutic doses it is generally not detected in routine toxicological analysis. Recommended analytical cut-off concentration of DXM to perform drug-impaired driving analysis is 20 µg/L.¹⁹ A specific immunoassay is also available for DXM.²⁰

Several DXM-related deaths had been reported in impaired drivers in Wisconsin²¹ where whole blood DXM concentrations averaged 51 µg/L (range 5–1800 µg/L). In another incident, five drivers in Washington State died after consuming 1500 mg DXM.²² All of them had documented abuse histories of recreational DXM abuse and their blood DXM concentration averaged 790 µg/L (range 470–1220 µg/L).

In most of the cases related to DXM toxicity, cough and flu preparations were abused where DXM was compounded with other drugs, most notably the sedating antihistamine, chlorpheniramine. An adult suicidal poisoning case was reported by Kintz and Mangin²³ in which concentrations of DXM and antihistamine terfenadine determined were 5090 µg/L and 7200 µg/L respectively. The terfenadine concentration was highly elevated and undoubtedly contributed to this death. Two DXM-related deaths were reported by Rammer et al.²⁴ The first death was a suicidal ingestion by an 18 year old woman and the blood DXM concentration found was 9200 µg/L. The second case had blood DXM concentration of 3300 µg/L. Nine deaths were reported by Yoo et al.²⁵ related to combined abuse of DXM and zipeprol with a median DXM concentration of 1800 µg/L (ranged 1100–18,000 µg/L). Pediatric literature also reported the deaths in infants due to administration of inappropriately large doses of cough and flu preparations containing DXM. Cause of death declared in these cases was DXM overdose as well as multiple drug intoxication.^{26,27}

The reported acute dose of DXM for dissociative hallucinogenic effects by the drug abusers is 150–1500 mg or more^{3,4} which is well above the recommended therapeutic antitussive dose (90–120 mg). Five deaths were reported in three incidents in Florida, Washington and Virginia states of America due to abuse of DXM sold over the internet.²⁸ In these deaths, blood DXM concentrations averaged 1890 µg/L (ranged 950–3230 µg/L).

The incidents of dextromethorphan-related deaths reported in this article were of healthy males in their late teens. Each had some history of abusing large amounts of DXM cough syrup specifically for its hallucinogenic effects. They were all ignorant of the toxicity related to DXM overdose as well as the lethal synergistic effects of co-ingested drugs of abuse that they were using in addition to DXM. Lethal levels of DXM reported in the literature ranged from 3.3 to 9.5 mg/L in the blood and 31–230 mg/kg in the liver whereas the concentrations of DXM determined in these nineteen deaths ranged 7.3–41.7 mg/L in blood, 4.2–92.6 mg/kg in the liver and 9.9–349.6 mg/L in gastric contents. In addition to DXM, the presence of other drugs of abuse especially chlorpheniramine, benzodiazepines, opiates, cannabinoids and ethanol suggested the multiple drug intoxication. The concentrations of DXM obtained in these cases are highly elevated and undoubtedly contributed to these deaths. The most probable mechanism of deaths is the generalized CNS and respiratory depressions due to DXM overdose and lethal synergistic effect of co-ingested drugs. All manufacturers and distributors of DXM cough syrups were arrested and are being prosecuted. The case is in the court and verdict is yet to come.

Funding

None.

Conflict of interest

None declared.

Ethical approval

Necessary ethical approval was obtained from the institute ethics committee.

References

1. Chyka PA, Erdman AR, Manoguerra AS, Christianson G, Booze LS, Nelson LS, et al. Dextromethorphan poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol* 2007;**45**(6):662–77.
2. Levine DA. “Pharming”: the abuse of prescription and over-the-counter drugs in teens. *Curr Opin Pediatr* 2007;**19**(3):270–4.
3. The Third Plateau: A Dextromethorphan (DXM) Harm Reduction and Safety Information Site.
4. Dextroverse-A DXM community Site.
5. Federal Drug Administration: Drug Safety and Risk Management Site.
6. Drug Abuse Warning Network Site.
7. National Survey on Drug Use and Health Site.
8. National Institute on Drug Abuse Site.
9. Siu A, Drachtman R. Dextromethorphan: a review of N-methyl-D-aspartate receptor antagonist in the management of pain. *CNS Drug Rev* 2007;**13**(1):96–106.
10. Takashima T, Murase S, Iwasaki K, Shimada K. Evaluation of dextromethorphan metabolism using hepatocytes from CYP2D6 poor and extensive metabolizers. *Drug Metab Pharmacokin* 2005;**20**(3):177–82.
11. Babu K, Boyer EW, Hernon C, Brush DE. Emerging drugs of abuse. *Clin Ped Emerg Med* 2005;**6**:81–4.

12. Ganetsky M, Babu KM, Boyer EW. Serotonin syndrome in dextromethorphan ingestion responsive to propofol therapy. *Pediatr Emerg Care* 2007;**23**(11):829–31.
13. Murphy S, Brewerton T. Abuse of over-the-counter dextromethorphan by teenagers. *South Med J* 1993;**86**(10):1151–3.
14. Navarro A, Perry C, Bobo WV. A case of serotonin syndrome precipitated by abuse of the anticough remedy dextromethorphan in a bipolar patient treated with fluoxetine and lithium. *Gen Hosp Psychiatry* 2006;**28**(1):78–80.
15. Skop BP, Finkelstein JA, Mareth TR, Magoon MR, Brown TM. The serotonin syndrome associated with paroxetine, an over-the-counter cold remedy, and vascular disease. *Am J Emerg Med* 1994;**12**(6):642–4.
16. Hellbom E. Chlorpheniramine, selective serotonin reuptake inhibitors (SSRIs) and over the counter (OTC) treatment. *Med Hypotheses* 2006;**66**(4):689–90.
17. Mohammad-Zadeh LF, Moses L, Gwaltney-Brant SM. Serotonin: a review. *J Vet Pharmacol Ther* 2008;**31**(3):187–99.
18. de Zeeuw RA, Jonkman JHG. Genetic differences in oxidative drug metabolism. In: Proceedings of the international association of forensic toxicologists, Groningen, The Netherlands; 1988. p. 53–64.
19. Farrell LJ, Kerrigan S, Logan BK. Recommendations for toxicological investigation of drug impaired driving. *J Forensic Sci* 2007;**52**(5):1214–8.
20. Rodrigues WC, Wang G, Moore C, Agrawal A, Vincent MJ, Soares JR. Development and validation of ELISA and GC–MS procedures for the quantification of dextromethorphan and its main metabolite dextrorphan in urine and oral fluid. *J Anal Toxicol* 2008;**32**(3):220–6.
21. Cochems A, Harding P, Liddicoat L. Dextromethorphan in Wisconsin drivers. *J Anal Toxicol* 2007;**31**(4):227–32.
22. Logan BK. Combined dextromethorphan and chlorpheniramine intoxication in impaired drivers. *J Forensic Sci* 2008.
23. Kintz P, Mangin P. Toxicological findings in a death involving dextromethorphan and terfenadine. *Am J Forensic Med Pathol* 1992;**13**(4):351–2.
24. Rammer L, Holmgren P, Sandler H. Fatal intoxication by dextromethorphan: a report on two cases. *Forensic Sci Int* 1988;**37**:233–6.
25. Yoo Y, Chung H, Kim E, Kim M. Fatal zipeprol and dextromethorphan poisonings in Korea. *J Anal Toxicol* 1996;**20**:155–8.
26. Boland DM, Rein J, Lew EO, Hearn WL. Fatal cold medication intoxication in an infant. *J Anal Toxicol* 2003;**27**(7):523–6.
27. Marinetti L, Lehman L, Casto B, Harshbarger K, Kubiczek P, Davis J. Over-the-counter cold medications – postmortem findings in infants and the relationship to cause of death. *J Anal Toxicol* 2005;**29**(7):738–43.
28. Logan BK, Goldfogel G, Hamilton R, Kuhlman J. Five deaths resulting from abuse of Dextromethorphan sold over the internet. *J Anal Toxicol* 2009;**33**:99–103.