



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

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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.

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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).

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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, anti-histamine, 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 anti-histamine (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

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