"Robo-Tripping": Dextromethorphan Abuse and its Anesthetic Implications

Kelly A Linn [1]; Micah T Long [1]; Paul S Pagel [1,*]

[1]Anesthesia Service, Clement J. Zablocki Veterans Affairs Medical Center, Milwaukee, Wisconsin, USA

Corresponding author: Paul S Pagel, Anesthesia Service, the Clement J. Zablocki Veterans Affairs Medical Center, Milwaukee, Wisconsin, 53295, USA. Tel: +1-4143842000; Fax: 1-4143842939, E-mail: pspagel@mcw.edu

Introduction: We describe a patient scheduled for elective surgery who regularly consumed approximately 12 to 15 times the maximum recommended daily dose of dextromethorphan. We describe the clinical pharmacology of dextromethorphan and discuss its anesthetic implications.

Case Presentation: A 30-year-old man with a history of a nasal fracture was scheduled to undergo an elective septorhinoplasty. He reported daily consumption of large quantities (1440 to 1800 mg) of dextromethorphan for six years. He was previously treated for dextromethorphan dependency on several occasions with urine dextromethorphan levels exceeding 2000 ng/mL. He described marked dissociative effects when abusing the drug, but had abstained from use for 48 hours before his elective surgery. Considering that dextromethorphan has a relatively short half-life and that the patient did not suffer major withdrawal symptoms after voluntarily discontinuing the drug, the authors proceeded with the case while recognizing that the drug has significant neuropsychiatric and sympathetic nervous system stimulant effects resulting from its actions as a N-methyl-D-aspartate receptor antagonist.

Conclusions: Anesthesiologists need to be aware of dextromethorphan's clinical pharmacology because recreational abuse of the drug has become increasingly common in adolescents and young adults.

Keywords: Dextromethorphan; Sigma Opioid Receptor; Substance Abuse; Addiction; Dissociative Anesthesia; NMDA Receptor Antagonists

1. Introduction

Dextromethorphan is widely available antitussive medication that is a major component of more than 140 cold and cough remedies sold over the counter (1, 2). The drug is a D-isomer of the opioid analgesic levomethorphan and may exert its antitussive effects by activating sigma$_1$ opioid receptors in the medullary cough center. Recommended doses of dextromethorphan (maximum of 120 mg in four divided doses per day) are often associated with a dry mouth, tachycardia, and a reduced ability to concentrate resulting from a mild anticholinergic effect, but acute ingestion of larger doses causes a dissociative state similar to that observed with phencyclidine and ketamine (1, 3, 4) because the drug's primary metabolite is a putative N-methyl-D-aspartate (NMDA) receptor antagonist (5, 6). This latter pharmacological action, combined with easy access to the drug, has contributed to an increase in the recreational abuse of dextromethorphan-containing formulations in adolescents and young adults (7, 8) sometimes termed "robo-ing", "robo-copping", or "robo-tripping" after the popular cough syrup Robitussin DM® (Pfizer, Kings Mountain, North Carolina, USA) (9, 10). In this report, we describe a young man scheduled for an elective septorhinoplasty who regularly consumed approximately 12 to 15 times the maximum recommended

daily dose of dextromethorphan. We describe the pharmacology of dextromethorphan and discuss the anesthetic implications of this drug of abuse. The patient's written consent was obtained for publication of this report.

2. Case Presentation

A 30-year-old, 116 kg, 180 cm man with a history of symptomatic persistent nasal congestion after a nasal fracture was scheduled to undergo an elective septorhinoplasty. His past medical history was notable for insulin dependent diabetes mellitus, essential hypertension treated with lisinopril, tobacco use, and depression. He also described a history of oxycodone and ethanol abuse. The patient reported that he abstained from using these substances during the previous ten months, but he did admit that he was consuming large quantities [1440 to 1800 mg per day (between 48 and 60 tablets)] of dextromethorphan on a daily basis for the past six years. He obtained the dextromethorphan from a local pharmacy. He had been treated in our institution for dextromethorphan detoxification and dependency on several occasions, most recently one month before the planned septorhinoplasty. Urine dextromethorphan levels were greater than 2000 ng/mL during the patient's detoxifi-

cation admissions. The patient stated that dextromethorphan gave him "dumb and numb" feelings so that he "did not have to think [about] problems." He described marked fatigue and depressed mood on days that he did not ingest dextromethorphan, but he denied physical signs and symptoms of drug withdrawal. The patient stated that he voluntarily did not use dextromethorphan during the previous 48 hours in anticipation of his elective surgery. The patient's wife supported this assertion. The physical examination and laboratory findings were unremarkable. The liver function tests were normal. A random urine drug screen performed one month before surgery was negative for ethanol, amphetamines, barbiturates, benzodiazepines, cocaine metabolites, and opioids. We did not obtain a urine drug screen on the day of surgery because routine drug testing does not detect dextromethorphan (1) and the patient was not displaying signs and symptoms of acute intoxication with dextromethorphan or other drugs of abuse.

Considering that dextromethorphan has a relatively short half-life (4) and that the patient had not suffered any withdrawal symptoms after discontinuing the drug, the authors elected to proceed with the case and the patient was transported to the operating room. Anesthesia was induced using fentanyl (2 mg/kg), lidocaine (1 mg/kg), propofol (1.5 mg/kg), and rocuronium (0.6 mg/kg) and maintained using sevoflurane (end-tidal concentrations of 1.5 to 2% in an air-oxygen mixture; fractional inspired oxygen concentration of 0.5), fentanyl (1.5 mg/kg), and hydromorphone (0.2 mg) after endotracheal intubation. The patient's vital signs remained within 20% of baseline levels throughout the case. He was extubated in the operating room at the end of case. Postoperative pain was treated using intravenous hydromorphone (1.2 mg in divided doses) in the postanesthesia care unit and was subsequently managed using oral hydrocodone with acetaminophen after the patient was discharged from the hospital later that day. He reported excellent pain control (visual analog scale of 3/10) when he was seen in the otolaryngology clinic for routine follow-up on the 3rd postoperative day. The remainder of his postoperative course was unremarkable.

3. Discussion

Descriptions of recreational dextromethorphan abuse have appeared in the peer-reviewed medical literature with increasing frequency (4, 7, 10-12) since the phenomenon was first reported in Europe in the mid-1960s (13, 14). A recent survey of the National Poison Data System quantified the incidence of dextromethorphan abuse in the United States as 15.7 cases per 1 million citizens (8), but dextromethorphan abuse has not been previously documented in Iran (15). The drug is particularly popular among teenagers and young adults because it is unregulated, inexpensive or easily stolen from retailers, readily obtained from a variety of commercial sources including the internet, and consumed orally (1, 2, 4, 16).

The peak plasma concentration and the usual duration of clinical effect are 2.5 and 6 hours, respectively, after ingestion of the drug (4, 17). Dextromethorphan is rapidly metabolized to dextrorphan by hepatic cytochrome P^{450} 2D6 in most subjects with a plasma half-life of 2 to 4 hours, but approximately 5% of individuals of northern European extraction have a deficiency of this enzyme that may cause rapid accumulation of the parent drug (5). This specific pharmacokinetic polymorphism renders the subset of individuals substantially more susceptible to drug toxicity (17).

The neuropsychiatric and sympathetic nervous system effects of dextromethorphan are dose-related (1, 3, 4). Trance-like euphoria or stupor, hyperexcitability, depersonalization, altered mental status, dyskinesia, delayed response times, disordered speech, and vivid auditory and visual hallucinations occur as the ingested dose of dextromethorphan increases above 2 mg/kg (1, 3). Indeed, the current patient described a dissociative stupor and depersonalization when he was abusing dextromethorphan. Respiratory depression, tachycardia, hypertension, seizures, and death may result from severe acute dextromethorphan intoxication (1, 4, 7, 8, 16) whereas chronic abuse of the drug has been associated with frank psychosis (2). These actions are very similar to those described with other NMDA receptor antagonists. Thus, it appears likely that the anesthetic implications of acute dextromethorphan abuse may be quite similar those associated with abuse of ketamine or phencyclidine, but at present, no data have been published to verify this contention. The concomitant presence of antihistamines or sympathomimetic drugs in common cough and cold formulations may influence the clinical manifestations of dextromethorphan abuse (4). In addition to NMDA receptor antagonist activity, dextromethorphan and its metabolite dextrorphan are specific serotonin reuptake inhibitors (SSRI) (2). As a result, acute intoxication of dextromethorphan has been linked to serotonin syndrome, particularly when the drug is ingested in the presence of another SSRI or a serotonergic agonist [e.g. azapirones such as buspirone (anxiety or depression); triptans including sumatriptin (migraine or cluster headaches)]. Dextromethorphan abuse is particularly likely to cause serotonin syndrome in patients treated with the SSRI antidepressant medication paroxetine because the latter drug also inhibits cytochrome P^{450} 2D6 activity.

Dextromethorphan is often combined with the chlorphenamine in many commercially available cough and cold preparations (e.g. Coricidin®, Schering-Plough, Kenilworth, New Jersey, USA). This antihistamine exerts serotonergic effects independent of dextromethorphan, and abuse of this combined formulation further increases the risk that serotonin syndrome may develop (18). Serotonin syndrome has also been reported with ingestion of dextromethorphan alone (19) via NMDA antagonist-mediated 5-HT2A receptor activation (20). Se-

rotonin toxicity may contribute to hyperreflexia, muscle rigidity, and autonomic nervous system instability (21) observed when large doses of dextromethorphan are consumed. Finally, polysubstance abuse is very common among dextromethorphan users (3), and simultaneous use of other drugs may certainly affect the overall clinical presentation of dextromethorphan toxicity. Abuse of dextromethorphan with amphetamine or cocaine may also increase the risk of serotonin syndrome. Notably, the risk of an unfavorable outcome is substantially greater when dextromethorphan is abused with other illicit substances (4).

Unlike our patient who openly admitted and had been previously treated for long standing abuse of dextromethorphan, the diagnosis of acute or chronic dextromethorphan abuse most likely requires a high index of suspicion, but may be suggested with a carefully conducted history and physical examination in the perioperative setting. Patients with acute dextromethorphan intoxication commonly exhibit signs and symptoms similar to those associated with stimulant, phencyclidine, or ketamine abuse, and exclusion of these more common abused drugs using a urine drug screen may indirectly infer a diagnosis of dextromethorphan abuse. Indeed, routine drug screening does not detect dextromethorphan when recommended doses are ingested (1), but false positive results suggesting the presence of phencyclidine or opioids may sometimes be observed when large quantities of the drug are consumed (22). High performance liquid chromatography is required to quantify plasma dextromethorphan concentration (5). As observed in the current patient, other laboratory tests are most often noncontributory in patients with acute or chronic dextromethorphan intoxication. Prolonged QT interval has been previously reported in acute dextromethorphan intoxication (23), but this abnormality was not observed in our patient's electrocardiograms during his detoxification admissions.

The specific anesthetic implications of acute or chronic dextromethorphan abuse have not been described in the peer-reviewed literature to date. Considering that sympathetic nervous system stimulation is a characteristic feature of dextromethorphan toxicity (as it is with other NMDA receptor antagonists including phencyclidine and ketamine) (24), it would appear likely that administration of vasoactive drugs, including intravenous and volatile anesthetics, should be approached with caution in dextromethorphan abusers because of the potential for hemodynamically significant drug interactions. This hypothesis has yet to be formally examined to date. As is the case with the generalized neuroexcitation associated with abuse of other NMDA receptor antagonists, dextromethorphan-induced agitation, delusions, and hallucinations may theoretically be mitigated using benzodiazepines before surgery. Nevertheless, the relative efficacy of benzodiazepines in such a perioperative application has not been specifically documented. In the current

patient, benzodiazepines were not administered for conscious sedation or during anesthetic induction because these drugs may delay discharge in patients undergoing ambulatory surgery. The patient also had abstained from abusing dextromethorphan in anticipation of elective surgery and did not display clinical signs or symptoms of acute dextromethorphan intoxication. Thus, the use of benzodiazepines was not directly indicated based solely on the consequences of acute dextromethorphan intoxication, in the authors' opinion. It is also unclear whether the sigma$_1$-opioid agonist and NMDA receptor antagonist properties of acute or chronic dextromethorphan abuse affect perioperative opioid requirements. Our patient's postoperative pain after septorhinoplasty was easily managed using conventional doses of intravenous followed by oral opioids despite his history of chronic dextromethorphan abuse, suggesting that clinically significant opioid tolerance did not occur. Finally, whether acute dextromethorphan intoxication is capable of reducing opioid requirements during and after surgery similar to subanesthetic doses of ketamine also remains to be established.

Management of dextromethorphan toxicity is almost entirely supportive because there is no known antidote for the drug. Three case reports described the use of the nonselective opioid antagonist naloxone to reverse dextromethorphan-induced respiratory depression (11, 25, 26), but the relative value of naloxone for the treatment of other manifestations of dextromethorphan toxicity remains unclear (1). Another report suggested that propofol may be useful for the management of acute dextromethorphan intoxication complicated by serotonin syndrome (19). These observations are intriguing, but the precise implications of these reports (11, 19, 25, 26) on the perioperative management of the acute or chronic dextromethorphan abuser undergoing emergent or elective surgery are currently unknown. Chronic dextromethorphan abusers may suffer from symptoms of psychological withdrawal (2, 3, 12). Indeed, our patient described pronounced fatigue and depressed mood immediately after discontinuing dextromethorphan use. Such individuals may benefit from admission for detoxification and substance abuse treatment with the goal of attaining abstinence from the drug before elective surgery is contemplated.

Authors' Contributions

Kelly A. Linn cared for the patient for the patient in the operating room and wrote drafts of the manuscript. The author has read the final draft of the manuscript and approves it for submission. Micah T. Long cared for the patient for the patient in the operating room and wrote drafts of the manuscript. The author has read the final draft of the manuscript and approves it for submission. Paul S. Pagel wrote and edited drafts of the manuscript. The author has read the final draft of the manuscript and approves it for submission.

Funding/Support

This work was supported entirely by departmental funds.

References

1. Schwartz RH. Adolescent abuse of dextromethorphan. *Clin Pediatr (Phila).* 2005;**44**(7):565–8.
2. Miller SC. Dextromethorphan psychosis, dependence and physical withdrawal. *Addict Biol.* 2005;**10**(4):325–7.
3. Ziaee V, Akbari Hamed E, Hoshmand A, Amini H, Kebriaeizadeh A, Saman K. Side effects of dextromethorphan abuse, a case series. *Addict Behav.* 2005;**30**(8):1607–13.
4. Romanelli F, Smith KM. Dextromethorphan abuse: clinical effects and management. *J Am Pharm Assoc (2003).* 2009;**49**(2):e20–5.
5. Silvasti M, Karttunen P, Tukiainen H, Kokkonen P, Hanninen U, Nykanen S. Pharmacokinetics of dextromethorphan and dextrorphan: a single dose comparison of three preparations in human volunteers. *Int J Clin Pharmacol Ther Toxicol.* 1987; **25**(9):493–7.
6. Szekely JI, Sharpe LG, Jaffe JH. Induction of phencyclidine-like behavior in rats by dextrorphan but not dextromethorphan. *Pharmacol Biochem Behav.* 1991;**40**(2):381–6.
7. Murray S, Brewerton T. Abuse of over-the-counter dextromethorphan by teenagers. *South Med J.* 1993;**86**(10):1151–3.
8. Wilson MD, Ferguson RW, Mazer ME, Litovitz TL. Monitoring trends in dextromethorphan abuse using the National Poison Data System: 2000-2010. *Clin Toxicol (Phila).* 2011;**49**(5):409–15.
9. Darboe MN. Abuse of dextromethorphan-based cough syrup as a substitute for licit and illicit drugs: a theoretical framework. *Adolescence.* 1996;**31**(121):239–45.
10. Darboe MN, Keenan GR, Jr, Richards TK. The abuse of dextromethorphan-based cough syrup: a pilot study of the community of Waynesboro, Pennsylvania. *Adolescence.* 1996;**31**(123):633–44.
11. Katona B, Wason S. Dextromethorphan danger. *N Engl J Med.* 1986;**314**(15):993.
12. Miller SC. Coricidin HBP cough and cold addiction. *J Am Acad Child Adolesc Psychiatry.* 2005;**44**(6):509–10.
13. Degkwitz R. [Dextromethorphan (Romilar) as an Intoxicating Agent]. *Nervenarzt.* 1964;**35**:412–4.
14. Jorgensen F. [Abuse of dextromethorphan]. *Ugeskr Laeger.* 1967;**129**(36):1148–50.
15. Sahraian A, Sharifian M, Omidvar B, Javadpour A. Prevalence of substance abuse among the medical students in Southern Iran. *Shiraz E Med J.* 2010;**11**(4):198–202.
16. Logan BK, Goldfogel G, Hamilton R, Kuhlman J. Five deaths resulting from abuse of dextromethorphan sold over the internet. *J Anal Toxicol.* 2009;**33**(2):99–103.
17. Bem JL, Peck R. Dextromethorphan. An overview of safety issues. *Drug Saf.* 1992;**7**(3):190–9.
18. Monte AA, Chuang R, Bodmer M. Dextromethorphan, chlorphenamine and serotonin toxicity: case report and systematic literature review. *Br J Clin Pharmacol.* 2010;**70**(6):794–8.
19. Ganetsky M, Babu KM, Boyer EW. Serotonin syndrome in dextromethorphan ingestion responsive to propofol therapy. *Pediatr Emerg Care.* 2007;**23**(11):829–31.
20. Kim HS, Park IS, Lim HK, Choi HS. NMDA receptor antagonists enhance 5-HT2 receptor-mediated behavior, head-twitch response, in PCPA-treated mice. *Arch Pharm Res.* 1999;**22**(2):113–8.
21. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med.* 2005;**352**(11):1112–20.
22. Banerji S, Anderson IB. Abuse of Coricidin HBP cough & cold tablets: episodes recorded by a poison center. *Am J Health Syst Pharm.* 2001;**58**(19):1811–4.
23. Kaplan B, Buchanan J, Krantz MJ. QTc prolongation due to dextromethorphan. *Int J Cardiol.* 2011;**148**(3):363–4.
24. Pagel PS, May JA. Evaluation of the patient with alcohol or drug addiction. In: Longnecker D, Brown DL, Newman MF, Zapol W editors. *Anesthesiology.* 2 ed. New York: McGraw-Hill Education; 2012. pp. 315–31.
25. Shaul WL, Wandell M, Robertson WO. Dextromethorphan toxicity: reversal by naloxone. *Pediatrics.* 1977;**59**(1):117–8.
26. Schneider SM, Michelson EA, Boucek CD, Ilkhanipour K. Dextromethorphan poisoning reversed by naloxone. *Am J Emerg Med.* 1991;**9**(3):237–8.