JOURNAL OF FORENSIC SCIENCES

J Forensic Sci, July 2011, Vol. 56, No. 4
doi: 10.1111/j.1556-4029.2011.01730.x
Available online at: onlinelibrary.wiley.com

CASE REPORT

TOXICOLOGY

Cristian Palmiere,[1] *M.D.; Christophe Brunel,*[2] *M.D.; Frank Sporkert,*[1] *Ph.D.; and Marc Augsburger,*[1] *Ph.D.*

An Unusual Case of Accidental Poisoning: Fatal Methadone Inhalation*

ABSTRACT: In this report, the authors present a case of unusual, accidental methadone intoxication in a 40-year-old man, who had inhaled methadone powder. The drug dealer was a pharmacy technician; methadone had been stolen from a pharmacy and sold as cocaine. After having inhaled methadone powder, he suffered cardiopulmonary arrest. He was admitted to hospital where he died after 24 h of intensive care. The autopsy revealed congestion of internal organs and cerebral and pulmonary edema. Microscopically, the heart showed no changes. The toxicological analyses performed on blood and urine taken at the hospital revealed methadone, cannabinoids, and ethanol. The blood methadone concentration was 290 μg/L. The urine methadone concentration was 160 μg/L. Midazolam and lidocaine, which were administered to the patient at the hospital, were also detected in the blood. The cause of death was determined to be methadone intoxication. The literature has been reviewed and discussed. To date, and to our knowledge, only very few cases of accidental death resulting from methadone inhalation have been described up to the case presented herein.

KEYWORDS: forensic science, forensic pathology, substance abuse, methadone, intoxication, inhalation

Methadone is a synthetic opioid agonist used for maintenance of withdrawal and management of narcotic addicts and for the relief of moderate-to-severe pain. Recreationally, methadone is abused for its sedative and analgesic effects (1–3).

We present a case of unusual accidental methadone intoxication, having occurred in a 40-year-old man, who had inhaled methadone powder. The powder was sold as cocaine, and nine other people were intoxicated at the same time in two different locations of the same region. Six people were arrested by the police. Among the six was a pharmacy technician, who provided stolen methadone in pure form.

While methadone intoxication is really not unusual in forensic practice, the route of administration of the drug in this case appears unusual. To date and to our knowledge, only very few cases of accidental death resulting from methadone inhalation have been reported previously.

Case Report

Case History

The case concerns a 40-year-old man, who decided to spend a Saturday night with four other people. Everybody drank alcohol and smoked cannabis. After dinner, one person suggested to the others to snort cocaine, which he could obtain quickly. Everybody agreed and the person called the dealer. One hour later, they received cocaine at home and prepared some lines. Everybody snorted, except one person, who had cocaine with him and who snorted his own drug. After snorting, this latter person went to the restroom. Upon returning to the dining room, he found the other four people unconscious. He immediately called for help. Three of the four people were unconscious but were still breathing. The fourth person was unconscious and was not breathing. Cardiopulmonary resuscitation was started by the only conscious person for 30 min. Upon arrival, rescuers found one individual in asystolic with pulseless electrical activity. They kept performing the cardiopulmonary resuscitation for 35 min during which a sinus rhythm was restored. While being transferred to the hospital, the patient received epinephrine, naloxone, and flumazenil. He was admitted to the hospital with a Glasgow Coma Scale of 3, hemodynamic instability (pH 6.8, lactate 13.7 mM), and hypothermia (31.1°). The multislice computed tomography (CT) revealed diffuse cerebral edema. The toxicological analyses performed at the hospital showed alcohol in blood, cannabinoid metabolites, and methadone in urine. The patient rapidly developed multiorgan failure, including hepatic and renal failure, rhabdomyolysis, disseminated intravascular coagulation, and respiratory and heart failure. From a neurological point of view, the patient presented with a nonreactive coma with bilateral mydriasis. The electroencephalogram showed no electrical activity in the brain.

The patient died as a result of cardiac arrest after 24 h of intensive care.

The other people intoxicated were also admitted to the hospital, where they regained consciousness after some hours. Toxicological analyses showed methadone in urine in all cases.

Questioned by the physicians, they all related the same version of the incident, that is they wanted to snort cocaine and snorted a

[1]University Center of Legal Medicine, 21 Rue du Bugnon, 1011 Lausanne, Switzerland.
[2]University Center of Legal Medicine, 1 rue Michel-Servet, 1211 Genève 4, Switzerland.

*Presented at the 58th Annual Meeting of the American Academy of Forensic Sciences, February 20–25, 2006, in Seattle, WA.

Received 24 Feb. 2010; and in revised form 6 May 2010; accepted 16 May 2010.

white powder believed to be cocaine. Snorting was immediately characterized by an unusual "burning sensation" in the nose followed by, a little time later, respiratory difficulties and loss of consciousness.

Autopsy Findings

The body was transferred to the University Centre of Legal Medicine for autopsy. The CT-scan examination of the body was negative. The external examination was unremarkable, except for multiple signs of medical intervention. The significant internal gross findings were marked pulmonary edema and general congestion of the internal organs. The brain was edematous and congested. The trachea and bronchi were filled with frothy, serous, or serosanguineous fluid. No identifiable pill components or fragments were found in the stomach contents or upper gastrointestinal tract. The neuropathological investigation was negative.

Microscopically, the heart showed no changes. The histological examination revealed hepatic steatosis, generalized congestion, cerebral and pulmonary edema, and desquamation of the ciliated respiratory epithelium, as well as alveolar and interstitial macrophages, which contained anthracotic pigment.

Under plane-polarized light, rare birefringent, finely granular material was found consistent with crystalline powder.

Toxicological Findings

Toxicological tests were performed on blood and urine taken at the hospital upon the patient's admission and on the hair taken at the autopsy.

These included blood ethanol determination and screening for common drugs and illegal substances by gas chromatography-mass spectrometry (GC-MS), high-performance liquid chromatography with diode-array detection, and headspace-gas chromatography-flame ionization detection.

Methadone and its metabolite (2-ethylidene-1,5-dimethyl-3, 3-diphenyl-L-pyrrolidine [EDDP]), tetrahydrocannabinol and its metabolites (11-hydroxy-delta-9-tetrahydrocannabinol and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol), and ethanol (106 mg/dL) were detected in the blood. Midazolam and lidocaine, which were administered to the patient while in hospital, were also detected. The blood methadone concentration was 290 μg/L, and the blood EDDP concentration was below the limit of quantitation (<50 μg/L).

Methadone, EDDP, and tetrahydrocannabinol metabolites were detected in urine. The urine methadone concentration was 160 μg/L, and the urine EDDP concentration was below the limit of quantitation (<50 μg/L).

Cocaine, benzoylecgonine, 3,4-methylenedioxymethamphetamine, 3,4-methylenedioxyamphetamine, amphetamine, and methamphetamine were detected in hair.

The cause of death was determined to be methadone intoxication.

Analyses were also performed on the white powder brought to the hospital using GC-MS, gas chromatography-nitrogen phosphorus detector, and capillary electrophoresis and revealed the presence of 90% R,S-methadone base.

Police Investigation

A total of 10 people were admitted in two different hospitals the same night: two groups of five people in two different locations of the same region. Only one person died, after 24 h of intensive care. All people were admitted with essentially the same clinical features (unconsciousness and respiratory difficulties) and all related the same story: they had wanted to buy cocaine and received white crystalline powder from two different dealers, which they subsequently snorted. All people were admitted to a hospital with a diagnosis of "intoxication with an unknown substance," which had led, for five of them, to serious adverse clinical effects.

In all cases, the toxicological analyses revealed the presence of methadone in both blood and urine, but no presence of cocaine.

Six people were arrested by the police. Among them, a pharmacy technician, who provided stolen methadone in pure form, which was sold as cocaine.

Discussion

Methadone is a long-acting μ-receptor agonist with pharmacologic properties qualitatively similar to those of morphine (4). It is available as methadone hydrochloride powder, which can be used for the preparation of oral, rectal, and parenteral solutions. In many countries, methadone is also commercially available for oral, rectal, and parenteral administration (1). Methadone is prescribed for the relief of moderate-to-severe pain, in opiate-dependence detoxification treatment, as well as for maintenance in heroin and narcotic addiction. Recreationally, it is used for its euphoric, sedative, and analgesic effects (2).

Methadone was first synthesized in the late 1930s by two physicians, Max Bockmühl and Gustav Ehrhart, in the course of ongoing research into compounds with both analgesic and spasmolytic properties (5).

The drug was given the trade name Dolophine from the Latin "dolor" meaning pain and "fin" meaning end (6). The use of methadone as a maintenance drug in heroin addicts began in the U.S. only in 1964, when Dr. Vincent Dole and Dr. Marie Nyswander pioneered the use of a particular form of synthetic opiate for narcotic maintenance (7).

Methadone is primarily a μ-receptor agonist and may mimic endogenous opioids and affect the release of other neurotransmitters (acetylcholine, norepinephrine, substance P, and dopamine). This action accounts for analgesic and antitussive properties, respiratory depression, sedation, decrease in bowel motility, increase in biliary tone, hormone regulation, and increase in prolactin and growth hormone release, miotic pupils, nausea, and hypotension (8).

Methadone activates μ, κ, and δ receptors, possesses moderate antagonistic effect to the *N*-methyl-D-aspartate receptor and strongly inhibits the reuptake of serotonin and noradrenaline in the central nervous system. These three mechanisms of action could explain better analgesia and less tolerance to analgesic effects of methadone in comparison with morphine, observed in experimental research and in patients (5).

While methadone shares properties of central nervous system and respiratory depression with other opioids, methadone is a particularly potent blocker of the delayed rectifier potassium ion channel, resulting in prolongation of cardiac repolarization, prolonged QT interval on the electrocardiogram, and torsade de pointes in susceptible individuals. Several case reports, as well as series of cases, have described the occurrence of a potentially fatal arrhythmia with the use of methadone (9,10).

During a 4-year prospective study evaluating all patients who consecutively had sudden cardiac death and underwent investigation by the medical examiner in the metropolitan area of Portland, it was shown that 72 of 178 sudden deaths had methadone in their blood.

Of those with methadone in the therapeutic range, 77% had no cardiac abnormalities found at autopsy and only one had an additional opioid (oxycodone).

Chugh et al. concluded that, given the significantly lower prevalence of structural heart disease in methadone group, even at therapeutic levels, methadone was a likely cause of sudden death (9).

Methadone, as other outpatient opioids, is preferably administered orally. The oral route of methadone administration is the most commonly used in clinical practice and the most frequently reported in the literature (1,5).

Subcutaneous administration is usually a substitute for the oral route (5).

Methadone may also be used locally as a mouthwash for the management of painful oral ulcers, in powder as an analgesic on open wounds, as well as intrathecally and/or epidurally in patients with chronic and postoperative pain, sublingually and intranasally (5).

The rectal route of administration is considered an alternative to the oral route in patients with nausea, vomiting, dysphagia, bowel obstruction, and malabsorption. Furthermore, it is an alternative to repeated parenteral injections in patients with immunologic deficiencies or bleeding disorders, and where high-tech analgesic infusion systems may not be available (1).

Dale et al. (11) investigated the pharmacokinetics and the pharmacodynamics of orally, nasally, and intravenously administered methadone in young healthy volunteers. Eight healthy volunteers were given nasal methadone (50 mg/mL in aqueous solution) as a 100-μL spray in each nostril. The methadone effect was measured by noninvasive infrared pupillometry contemporaneous with blood sampling. The study revealed that nasal methadone administration achieved rapid absorption, with a maximum plasma concentration occurring within 7 min. Intranasal methadone had a rapid onset of action, resulting in a maximum effect at 30 min, which was only slightly slower than that of intravenous administration. Moreover, oral and nasal methadone bioavailabilities were equal and relatively high. Last, the duration of effect of a single methadone dose administered by inhalation was similar to that reported for oral and intravenous formulations in chronic pain and postoperative clinical studies (11).

Pharmacokinetic studies on nasal administration of opioids and studies in postoperative patients with opioids and in patients with cancer pain treated with nasal opioids demonstrated that drugs that could be, and actually were, administered by inhalation were absorbed rapidly (maximum serum concentrations achieved between 5 and 49 min), confirming that the nasal mucosa has features that may allow for very rapid uptake of xenobiotics (12–24).

In 1948, the first fatality from methadone was recorded by Bieter and Hirsch in a 54-year-old man, who was given hypodermic injections of methadone (50 mg) in three doses over 8 h and who developed cyanosis and hypotension. They also recorded severe respiratory depression in a 15-year-old boy who was given, by mistake, a 25-mg methadone hypodermic injection (25).

We have previously reported a case of a 19-month-old child who mistakenly received a 30-mg methadone suppository administered by her father instead of an antipyretic suppository and for whom the cause of death was determined to be methadone intoxication (26).

Methadone inhalation has rarely been observed in clinical and forensic medicine.

Carson and Feickert (3) reported a case of a 25-year-old man, who died of substance abuse that included methadone, for whom the route of administration of the drug(s) appeared to have been inhalation. Blood toxicology was positive for cannabinoids, sertraline, nicotine, and methadone.

Byard et al. (27) reported a case of a 21-year-old man, with a known history of paint sniffing, whose death was attributed to the combined effect of toluene inhalation and methadone.

Gossop et al. (28) investigated variations in routes of administration for heroin, nonprescribed methadone, nonprescribed benzodiazepines, cocaine powder, crack cocaine, and amphetamines among 1053 drug abusers recruited for 54 residential and community drug misuse programs. They noted that for some substances (nonprescribed methadone and nonprescribed benzodiazepines), the main route of administration was oral, with a minority of users taking these drugs by injection. Crack cocaine was mainly taken through smoking, although a minority reported regular crack injection. Other drugs were used regularly by more than one route. Heroin was used both by injection and by "chasing the dragon" (heroin vapor inhalation). Cocaine powder was used by injection and by inhalation. Amphetamines were used by injection, by mouth, and also, although less often, by inhalation.

Many inhaled substances are known to traverse respiratory mucosae rapidly, facilitately, and to act systemically, a common example being nicotine inhaled from cigarette smoke (28).

In the presented case, 10 people in two different locations of the same region were intoxicated with methadone powder, which was inhaled as cocaine. They were all admitted to a hospital. The clinical features presented by all were essentially the same: respiratory difficulties having appeared some minutes after powder inhalation, followed by loss of consciousness. Toxicological analyses of the urine samples performed at the hospital showed methadone in all cases. One person died 24 h later. The blood analyses revealed the presence of methadone and metabolites, cannabinoids, and ethanol. Toxicological tests performed on the hair revealed that the deceased was a regular stimulant user and that he also occasionally used cocaine. No methadone was found in the hair, suggesting that the person was not a methadone user. On the other hand, the relation between blood (290 μg/L) and urine (160 μg/L) methadone levels and the low EDDP concentrations suggest that the person was transferred to the hospital shortly after methadone inhalation.

The mentioned pharmacokinetic studies on nasal administration of opioids allow us to put forward the hypothesis that, in the case herein presented, the blood concentrations of methadone at the moment of inhalation had to be greater than the concentrations measured in blood 2 h after inhalation. This supports the hypothesis of a very rapid methadone uptake and distribution to the central nervous system and a very rapid appearance of symptoms of intoxication, as reported by all the intoxicated people described herein.

References

1. Ripamonti C, Zecca E, Bruera E. An update on the clinical use of methadone for cancer pain. Pain 1997;70(2–3):109–15.
2. Couper FJ, Chopra K, Pierre-Louis ML. Fatal methadone intoxication in an infant. Forensic Sci Int 2005;153(1):71–3.
3. Carson HJ, Feickert BL. Identification at autopsy of pulverized pills in lungs of a first-time methadone user. J Forensic Leg Med 2009;16(8): 494–6.
4. Brunton LL, editor. Goodman & Gilman's. The pharmacological basis of therapeutics, 11th edn. New York, NY: McGraw-Hill Medical Publishing Division, 2006.
5. Leppert W. The role of methadone in cancer pain treatment—a review. Int J Clin Pract 2009;63(7):1095–109.
6. Shah S, Diwas S. Methadone: does stigma play a role as a barrier to treatment of chronic pain? Pain Physician 2010;13:289–93.
7. DiMaio DJ, DiMaio T. Fatal methadone poisoning in children: report of four cases. J Forensic Sci 1973;18(2):130–4.
8. Anderson IB, Kearney TE. Use of methadone. West J Med 2000; 172(1):43–6.
9. Chugh SS, Socoteanu C, Reinier K, Waltz J, Jui J, Gunson K. A community-based evaluation of sudden death associated with therapeutic levels of methadone. Am J Med 2008;121(1):66–71.

10. Andrews CM, Krantz MJ, Wedam EF, Marcuson MJ, Capacchione JF, Haigney MC. Methadone-induced mortality in the treatment of chronic pain: role of QT prolongation. Cardiol J 2009;16(3):210–7.
11. Dale O, Hoffer C, Sheffels P, Kharasch ED. Disposition of nasal, intravenous, and oral methadone in healthy volunteers. Clin Pharmacol Ther 2002;72(5):536–45.
12. Dale O, Hjortkjær R, Kharasch ED. Nasal administration of opioids for pain management in adults. Acta Anaesthesiol Scand 2002;46:759–70.
13. Schwagmeier R, Boerger N, Meissner W, Striebel HW. Pharmacokinetics of intranasal alfentanil. J Clin Anesth 1995;7:109–13.
14. Striebel HW, Kramer J, Luhmann I, Rohierse-Hohler I, Rieger A. Pharmakokinetische Studie zur intranasalen Gabe von Fentanyl. Der Schmerz 1993;7:122–5.
15. Takala A, Kaasalainen V, Seppala T, Kalso E, Olkkola KT. Pharmacokinetic comparison of intravenous and intranasal administration of oxycodone. Acta Anaesthesiol Scand 1997;41:309–12.
16. Eriksen J, Jensen NH, Kamp-Jensen M, Bjarno H, Friis P, Brewster D. The systemic availability of buprenorphine administered by nasal spray. J Pharm Pharmacol 1989;41:803–5.
17. Shyu WC, Mayol RF, Pfeffer M, Pittman KA, Gammans RE, Barbhaiya RH. Biopharmaceutical evaluation of transnasal, sublingual, and buccal disk dosage forms of butorphanol. Biopharm Drug Dispos 1993;14:371–9.
18. Striebel HW, Pommerening J, Rieger A. Intranasal fentanyl titration for postoperative pain management in an unselected population. Anaesthesia 1993;48:753–7.
19. Striebel WH, Malewicz J, Hermanns K, Castello R. Intranasal meperidine titration for postoperative pain relief. Anesth Analg 1993;76:1047–51.
20. Schwesinger WH, Reynolds JC, Harshaw DH, Frakes LA. Transnasal butorphanol and intramuscular meperidine in the treatment of postoperative pain. Adv Ther 1992;9:123–9.
21. Dershwitz M, Walsh JL, Morishige RJ, Connors PM, Rubsamen RM, Shafer SL, et al. Pharmacokinetics and pharmacodynamics of inhaled versus intravenous morphine in healthy volunteers. Anesthesiology 2000;93:619–28.
22. Gourlay GK, Wilson PR, Glynn CJ. Pharmacodynamics and pharmacokinetics of methadone during the perioperative period. Anesthesiology 1982;57:458–67.
23. Helmers JH, Noorduin H, Van Peer A, Van Leeuwen L, Zuurmond WW. Comparison of intravenous and intranasal sufentanil absorption and sedation. Can J Anaesth 1989;36:494–7.
24. Zeppetella G. An assessment of the safety, efficacy and acceptability of intranasal fentanyl citrate in the management of cancer-related breakthrough pain: a pilot study. J Pain Symptom Manage 2010;20:253–8.
25. Bieter RN, Hirsh SA. Methadone in internal medicine. Ann N Y Acad Sci 1948;51(Art 1):137–44.
26. Palmiere C, Staub C, La Harpe R, Mangin P. Parental abuse and accidental death in children. J Forensic Sci 2010;55(3):819–21.
27. Byard RW, Gilbert JD, Terlet J. Death associated with volatile substance inhalation—histologic, scanning electron microscopic and energy dispersive X-ray spectral analyses of lung tissue. Forensic Sci Int 2007;171 (2–3):118–21.
28. Gossop M, Marsden J, Stewart D, Treacy S. Routes of drug administration and multiple drug misuse: regional variations among clients seeking treatment at programmes throughout England. Addiction 2000;95(8): 1197–206.

Additional information and reprint requests:
Cristian Palmiere, M.D.
Centre Universitaire Romand de Médecine Légale
21 Rue du Bugnon, 1011 Lausanne
Switzerland
E-mail: Cristian.Palmiere@chuv.ch