J Forensic Sci, Nov 2004, Vol. 49, No. 6
Paper ID JFS04143
Available online at: www.astm.org

CASE REPORT

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Deaths After Intravenous Misuse of Transdermal Fentanyl

ABSTRACT: Fentanyl is a potent synthetic opioid used as a general anesthetic and analgetic. Fatal outcome from intravenous misuse of transdermal fentanyl is rare, and there are few such reports in literature. Here we report two cases of fatal intravenous injection of the content from fentanyl patches. Both were male drug addicts, found dead within a one week interval in the same apartment. Post-mortem femoral blood was screened for amphetamines, cannabinoids, cocaine, and opioids with immunological methods (EMIT II) and further with headspace gas chromatography for alcohol and with liquid chromatography mass spectrometry (LC-MS) for different drugs, including fentanyl. Confirmatory analysis of fentanyl and morphine was performed by gas chromatography-mass spectrometry (GC-MS). In the first case, the toxicological analysis revealed fentanyl (2.7 ng/mL), morphine (31.4 ng/mL), and ethanol (1.1 g/L) in postmortem blood and amphetamine, cannabinoids, morphine, and ethanol (1.4 g/L) in postmortem urine. In the second case, the analysis revealed fentanyl (13.8 ng/mL), 7-aminoclonazepam (57.1 ng/mL), and sertralin (91.9 ng/mL) in postmortem blood and a small amount of ethanol (0.1 g/L) in postmortem urine. Police investigation revealed that both the deceased had bought the patches from the same source. The present cases demonstrate the possibility of intravenous misuse of transdermal patches and the risk of fatal outcome.

KEYWORDS: forensic science, fentanyl, drug abuse, transdermal, fatal intoxication

Fentanyl is a potent synthetic opioid used as a general anesthetic and analgetic. It has a calculated potency 100 times that of morphine (1). The transdermal delivery system for fentanyl (Durogesic® is used in the treatment of opioid-responsive strong chronic pain. In Norway, transdermal patches are available in four dosage strengths from 25–100 μg/h, containing 2.5–10 mg fentanyl, respectively. The patch is constructed as a rectangular, transparent unit composed of four functional layers and a protective peel strip (2). The drug reservoir contains the fentanyl base gelled with hydroxyethyl cellulose and ethanol. Extracting the drug from the patches using a syringe is easy, and consequently it has a potential for abuse. However, the adverse reactions of the drug after intravenous administration of the content in these patches has proven to be fatal (3). There are few reports of such administration in literature (3–8). It is therefore important to build up a database of fentanyl-related fatalities by the intravenous route and to make physicians and others aware of this growing problem. Here we report two cases of fatal intravenous injection of the content of Durogesic patches. Both were male drug addicts, found dead in the same apartment within seven days. The investigation concluded that the deceased had bought the patches from the same source, the son of two physicians.

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Received 3 Apr. 2004; and in revised form 5 June 2004, 24 June 2004; accepted 25 June 2004; published 5 Oct. 2004.

Materials and Methods

Case 1

A 41-year-old man was found dead by a friend in his home. The deceased was cyanotic and apneic, lying on his back on the floor. Cardiopulmonary resuscitation (CPR) was first commenced by the friend and continued by paramedics. However, after some time he was pronounced dead. A syringe and an empty Durogesic patch (fentanyl transdermal system; Janssen-Cilag, 100 μg/h) were found next to the victim. In the apartment the police found used syringes, citric acid, and other equipment for drug abuse. Four days later an autopsy was performed. Post-mortem femoral blood was screened for amphetamines, cannabinoids, cocaine, and opioids with immunological methods (EMIT II) and further with gas chromatography with headspace injection (GC-headspace) for alcohol and with liquid chromatography mass spectrometry (LC-MS) for 63 different drugs, including fentanyl. Confirmatory analysis of morphine and fentanyl were performed respectively by gas chromatography mass spectrometry (GC-MS) and gas chromatography tandem spectrometry (GC-MS-MS). The method used for determination of fentanyl is summarized below.

Extraction procedure: To 1 mL of whole blood, 1 mL internal standard solution (approx. 2.4 ng/mL fentanyl-d5), 0.35 mL 2 M NaOH, and 4 mL ethylacetate/heptane (4/1) were added. The organic layer was then back-extracted with 2.5 mL 0.1 M HCl, and the aqueous layer made alkaline by adding 0.25 mL 2 M NaOH and extracted with 3 mL ethylacetate/heptane (4/1).

For all steps, the mixture was shaken for 10 min followed by centrifugation at 3500 rpm for 10 min. The organic layer from the last extraction step was evaporated to dryness at 60°C under a stream of nitrogen, and the residue was dissolved in 30 μL butyl acetate.

Analysis: GC-MS-MS analysis was performed using a Hewlett-Packard 5890 GC attached to a ThermoFinnigan TSQ detector. A fused-silica capillary column Rtx-5MS (15 m × 0.25 mm I.D., 0,1 μm film thickness) from Restek was used. The injection port was in splitless mode. Analyses were performed at a helium flow-rate of 1 mL/min, and the temperature settings were: injection temperature 280°C; initial column temperature 200°C; initial hold time 1 min; temperature rate 25°C/min; final column temperature 320°C; final hold time 1 min; transfer line temperature 300°C, and ion source temperature 150°C. The ionization mode was positive chemical ionization with ammonia as reagent gas and argon as collision gas. The transitions 337.2 → 188.2 (fentanyl) and 342.2 → 188.1 (fentanyl d5) were monitored in the multiple reaction monitoring (MRM) mode. Urine was screened for amphetamines, cannabinoides, benzodiazepines, cocaine, opiates, and methadone with immunological methods (EMIT II) and further with alcohol dehydrogenase (ADH) for alcohol. Confirmatory analysis of amphetamine, morphine, and tetrahydrocannabinol-acid in urine was performed by GC-MS and for alcohol by GC-headspace.

Case 2

One week later, a 42-year-old male, well-known drug addict, was found dead by two of his friends in the same apartment as the subject in Case 1. He was lying on a sofa, facing downward. He was dead when paramedics arrived at the scene, and no rescusitation attempt was made. Around his left upper arm there was a belt, probably used as a tourniquet. A used syringe was found on the sofa. On a table next to the victim, the packing of a Durogesic patch (fentanyl transdermal system; Janssen-Cilag, 100 μg/h), and equipment for drug abuse were found. An autopsy was performed four days later. Femoral blood and urine were analyzed as mentioned above. 7-aminoclonazepam and sertraline were screened with LC-MC and confirmatory analysis was performed with liquid chromatography with fluorescence detection and gas chromatography with nitrogen/phosphorus detection (GC-NPD), respectively.

Results

In Case 1, external examination of the body showed a few petechiae on both eyelids and in the left conjunctiva. There were four recent skin puncture wounds in the left cubital fossa and one in the left wrist; two of the needle marks were due to the resuscitation attempt. No other signs of violent injury were found. Internal examination showed pulmonary edema and enlarged lymph nodes in the liver hilus, but no other macroscopical signs of disease. Histological examination showed chronic active hepatitis. The Durogesic patch had a small puncture mark, the reservoir was totally empty, and neither the content of the patch, nor the used syringes were analyzed. Postmortem toxicological analysis revealed the following: Blood: fentanyl 2.7 ng/mL (0.008 μmol/L), morphine 31.4 ng/mL (0.11 μmol/L), ethanol 1.1 g/L. Urine: amphetamine, cannabinoids, and morphine: Positive. Ethanol 1.4 g/L. The cause of death was determined to be a combination of fentanyl, morphine, and ethanol intoxication, and opioids were considered to be the most important agents.

In Case 2, external examination of the body showed no signs of violence, except for recent puncture marks in both cubital fossae. Internal examination showed pulmonary edema, pale liver, enlarged lymph nodes in the liver hilus, and some white tablets in the stomach. Histological examination showed chronic active hepatitis. The used syringe was not analyzed. Postmortem toxicological analysis revealed the following: Blood: fentanyl 13.8 ng/mL (0.041 μmol/L), 7-aminoclonazepam 57.1 ng/mL (0.2 μmol/L), sertralin 91.9 ng/mL (0.3 μmol/L). Urine: ethanol 0.1 g/L. The cause of death was determined to be fentanyl intoxication.

Discussion

Fentanyl is a potent synthetic opioid. Traditionally it is used as an anesthetic adjuvant. It is also administered transdermally in the treatment of strong chronic pain. The active agent is absorbed from the patch through the skin. The advantage of transdermal use is a constant release, resulting in a consistent therapeutic serum concentration. Several ways of misuse have been reported, including inhalation, ingestion, and transdermal and intravenous administration (3–8). Only a few fatal cases after intravenous administration of the content in fentanyl patches have been reported (3,8). The amount of fentanyl injected after extraction from a patch is variable, making the outcome unpredictable. An intravenous bolus of 2 μg/kg can lead to a serum-concentration of 11 ng/mL (9). In a large series of fatalities from fentanyl-abuse, the mean blood-concentration was 3 ng/mL (10). Poklis has reported a range in serum-concentration of 0.1–5 ng/mL (11). In comparison, an effective analgetic serum-concentration is 0.3–0.7 ng/mL (12).

In our two cases the fentanyl concentrations were in the range of previously reported fatalities. Theoretically, oral intake of fentanyl from the patches could have occured. However, in Case 1, puncture marks on the patch indicate that the content was extracted with a syringe. Together with recent skin puncture marks, we believe this is an indication of intravenous abuse. The intake of ethanol, 7-aminoclonazepam, and sertralin was probably oral. In Norway, street heroin usually contains 6-monoacetylmorphine and codeine. Since these substances were not detected in the toxicological analyses from blood or urine in the two cases, it cannot be completely ruled out that morphine could have been taken orally. In Case 2 it would be expected that a completely opened patch was found at the scene, on the victim or perhaps in the internal organs if the drug had been taken orally. The actual patch was never found in this case. However, this man was a well known drug-addict, and the only drug detected was fentanyl. With these facts, combined with the findings of recent needle marks on the victim, we believe that intravenous abuse was most likely. Due to the effective constant release of the drug in the treatment of pain, prescription of transdermal patches will probably increase in the future. A substantial amount, which ranged from 28–84% of the original fentanyl concentration, remained in used patches, even after three days, in a group of patients with cancer pain (13). This represents an important source of drug for potential abuse.

Conclusion

Fentanyl patches are used by many cancer patients. The liquid content is easy to recover and therefore to abuse. Physicians should be aware of the potential for misuse of both used and new transdermal patches, their complications, and the risk of fatal outcome. An effective disposal policy should be implemented in places where transdermal fentanyl is used, and patches should be removed from deceased patients and destroyed. Physicians, police, forensic

pathologists, and toxicologists should consider the possibility of intravenous use in deaths associated with fentanyl when needle-marks are found. When needle-marks are absent, the potential for transdermal or oral abuse also should be considered.

References

1. Gutstein HB, Akil H. Opioid analgetics. In: Hardman JG, Limbird LE, Goodman Gilman A, Eds. Goodman and Gilman: The pharmacological basis of therapeutics. 10th ed. New York: McGraw-Hill, 2001;569–619.
2. Gupta SK, Southam M, Gale R, Hwang SS. System functionality and physiocochemical model of fentanyl transdermal system. J Pain Symptom Manage 1992;7:17–26.
3. Reeves MD, Ginifer CJ. Fatal intravenous misuse of transdermal fentanyl. Med J Aust 2002;177(10):552–3. [PubMed]
4. Marquardt KA, Tharratt RS. Inhalation abuse of fentanyl patch. J Toxicol Clin Toxicol 1994;32(1):75–8. [PubMed]
5. Kramer C, Tawney M. A fatal overdose of transdermally administered fentanyl. J Am Osteopath Assoc 1998;98(7):385–6. [PubMed]
6. Flannagan LM, Butts JD, Anderson WH. Fentanyl patches left on dead bodies–potential source of drug for abusers. J Forensic Sci 1996;41(2):320–1. [PubMed]
7. DeSio JM, Bacon DR, Peer G, Lema MJ. Intravenous abuse of transdermal fentanyl therapy in a chronic pain patient. Anesthesiology 1993;79(5):1139–41. [PubMed]
8. Kuhlman JJ, McCaully R, Valouch TJ, Behonick GS. Fentanyl use, misuse, and abuse: A summary of 23 postmortem cases. J Anal Toxicol 2003;27:499–504. [PubMed]
9. Fung DL, Eisele JH. Fentanyl pharmacokinetics in awake volunteers. J Clin Pharmacol 1980;20(11–12):652–8. [PubMed]
10. Henderson GL. Fentanyl-related deaths: demographics, circumstances, and toxicology of 112 cases. J Forensic Sci 1991;36(2):422–33. [PubMed]
11. Poklis A. Fentanyl: a review for clinical and analytical toxicologists. J Toxicol Clin Toxicol 1995;33(5):439–47. [PubMed]
12. Gourlay GK, Kowalski SR, Plummer JL, Cousins MJ, Armstrong PJ. Fentanyl blood concentration—analgesic response relationship in the treatment of postoperative pain. Anesth Analg 1988;67(4):329–37. [PubMed]
13. Marquardt KA, Tharratt RS, Musallam NA. Fentanyl remaining in a transdermal system following three days of continous use. Ann Pharmacother 1995 Oct.;29(10):969–71. [PubMed]

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