

# Fatal Intravenous Fentanyl Abuse

## Four Cases Involving Extraction of Fentanyl From Transdermal Patches

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**Abstract:** The transdermal fentanyl system delivers a specific dose at a constant rate. Even after the prescribed application time has elapsed, enough fentanyl remains within a patch to provide a potentially lethal dose. Death due to the intravenous injection of fentanyl extracted from transdermal patches has not been previously reported. We present 4 cases in which the source of fentanyl was transdermal patches and was injected. In all of these cases, the victim was a white male who died at home. Case 1 was a 35-year-old with no known history of drug use, who was found by his wife on the floor of his workshop. Police recovered a fentanyl patch, needle, and syringe at the scene. Case 2 was a 38-year-old with a known history of drug use whose family claimed that he was in a treatment program that used fentanyl patches for unknown reasons. His brother found him dead in bed, and law enforcement officers found a hypodermic needle beside the body; a ligature around his left hand, and apparent needle marks between his first and second digits were also noted. Case 3 was a 42-year-old with a recent attempted suicide via overdose who was found dead at his home. An empty box of fentanyl patches, Valium, Ritalin, and 2 syringes were found at the scene. Case 4 was a 39-year-old found by his mother, who admitted to removing a needle with attached syringe from the decedent's arm. Medications at the scene included hydrocodone, alprazolam, zolpidem, and fentanyl patches. All reported deaths were attributed to fentanyl intoxication, with blood concentrations ranging from 5 to 27  $\mu\text{g/L}$ .

**Key Words:** fentanyl, patch, intravenous injection, death

(*Am J Forensic Med Pathol* 2004;25: 178–181)

Manuscript received August 28, 2002; accepted October 31, 2003.

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ISSN: 0195-7910/04/2502-0178

DOI: 10.1097/01.paf.0000127398.67081.11

Fentanyl overdose is classically associated with intravenous use of  $\alpha$ -methyl-fentanyl (“China White”),<sup>1</sup> a powder form that is chemically different from therapeutic fentanyl. However, fentanyl overdose has also been reported in cases of excessive transdermal application<sup>2</sup> and ingestion<sup>3,4</sup> or inhalation<sup>5</sup> of transdermal patches. Fentanyl is a narcotic analgesic, which primarily binds to opioid  $\mu$ -receptors, producing not only the analgesia for which it is primarily used but also sedation, euphoria, and at high doses, respiratory depression and death.<sup>6</sup> Transdermal fentanyl therapy (Duragesic; Janssen Pharmaceutica, Beerse, Belgium) has been used successfully to treat postoperative pain, as well as pain associated with malignancies, but as with all opioid agents, the potential for abuse exists. The transdermal fentanyl system is designed to deliver a specific dose at a constant rate based on the initial concentration present in the patch. This delivery system effectively limits the peak versus trough concentration, which is a common problem associated with other routes of administration. Following 3 days of continuous therapeutic use, enough fentanyl remains within a patch to provide a potentially lethal dose.<sup>7</sup> We present 4 cases occurring in North Carolina between January 1997 and July 2001 in which the fatal dose of fentanyl was extracted from transdermal patches and injected intravenously.

## MATERIALS AND METHODS

### Case Selection

The case files of the Office of the Chief Medical Examiner (Chapel Hill, NC) were searched from 1991 to 2001 for deaths related to fentanyl. An initial search identified 53 cases,<sup>8</sup> of which only 4 involved intravenous abuse of a transdermal fentanyl patch. Case histories are listed below.

### Toxicologic Analysis

All toxicologic analyses were performed at the Office of the Chief Medical Examiner (Chapel Hill, NC). All cases were screened for volatiles, common drugs of abuse (eg, cocaine and morphine), and other basic drugs. Other tests (eg, fentanyl) were performed as needed.

## Fentanyl Screen

The specimens were screened by enzyme linked immunoassay, with a 1  $\mu\text{g/L}$  cutoff concentration (Orasure Technologies, Bethlehem, PA) utilizing a Biochem Personal Laboratory Autoanalyzer (Allentown, PA). The assays were performed in accordance with the manufacturers instructions and as validated for use in the Office of the Chief Medical Examiner Toxicology Laboratory.<sup>9</sup>

## Fentanyl Confirmation and Quantification

Quantification and confirmation analyses were performed by first isolating fentanyl by basic extraction<sup>6</sup> of a 1- to 5-mL (g) specimen. Underivatized specimens were analyzed on an Agilent Technologies (Wilmington, DE) gas chromatograph/mass spectrometer (GC/MS). The GC/MS system was composed of an Agilent 6890 gas chromatograph, a 5973 mass selective detector (MSD) and a 7683 liquid auto-sampler. The GC/MS was fitted with a HP-1MS capillary column (30 m  $\times$  0.25 mm inside diameter  $\times$  0.25- $\mu\text{m}$  film thickness). A 13.19-minute run time occurred after 1- $\mu\text{L}$  splitless injection into a 275°C injection port equipped with 0.4-mm gooseneck liner with base-deactivated fused silica wool. Oven temperature programming began at 125°C, holding for 1.00 minute, then ramping at 3 intervals: 35°C/minute to 195°C, 7°C/minute to 230°C and 32°C/minute to a final temperature of 300°C, holding for 3 minutes. Helium was used as the carrier gas at a linear velocity 61 cm/s; flows included a septum purge of 15.0 mL/minute at 2.0 minutes and a constant column flow of 2.6 mL/minute. The MSD was operated in selective ion mode, with a transfer line temperature of 280°C.

## CASE PRESENTATIONS

### Case 1

A 35-year-old Caucasian man with no known history of drug use was working in his workshop at home one evening. His wife reported that at approximately 12:30 AM, she asked him to come into the house, but that he stated that he would probably continue building porch swings through the night. His father, who stated that he “appeared OK,” last saw him alive at 2:30 AM. At approximately 5:00 AM, the decedent’s wife found him lying on the floor of his workshop. Paramedics were unable to resuscitate him. Police investigating the scene found a fentanyl patch, a needle, and syringe in the workshop. External examination of the body revealed no evidence of trauma, except for a 3/4-inch recent contusion with some yellow discoloration at its margins in the left antecubital fossa and a faint petechial-like contusion along a vein on the right forearm. Pulmonary congestion and edema, with a combined lung weight of 920 g, were the only other significant autopsy findings. Toxicological analysis of aortic blood was remarkable for a fentanyl concentration of 5  $\mu\text{g/L}$ ,

as well as a concentration of 0.8 mg/L of propoxyphene (generally considered to be a nontoxic concentration), and therapeutic concentrations of amitriptyline (0.08 mg/L) and its metabolite nortriptyline (0.33 mg/L). No other organic bases were detected, and testing for norpropoxyphene was not performed. The cause of death was attributed to “fentanyl poisoning,” with the manner of death listed as accident.

### Case 2

A 38-year-old Caucasian man with a history of drug use was living with his relatives. His family claimed that he had begun a treatment of his drug use in a program that used “morphine patches” for unknown therapeutic purposes. He was last seen alive at 10:00 PM, at which time he complained of nausea. His brother found him dead in bed the following morning at 8:15 AM. Resuscitative efforts were attempted but were unsuccessful. Law officers found a hypodermic needle in the bed beside the body and a ligature on his left hand, with apparent needle marks between the thumb and forefinger. On external examination at the time of autopsy, scars were noted in the right antecubital fossa as well as over each wrist, including a relatively recent puncture site over the dorsum of the left hand, between the thumb and second digit. Internal examination revealed pulmonary congestion and edema, with a combined lung weight of 1500 g, and cardiomegaly (450 g). A focus of granulomatous inflammation was present within the left lung with caseous necrosis, which was found to be due to *Coccidioides immitis* on silver stains. Focal chronic hepatitis and moderate coronary atherosclerosis were also identified. Toxicologic studies of aortic blood were positive for a 27  $\mu\text{g/L}$  concentration of fentanyl, with no other substances identified. The cause of death was listed as “fentanyl poisoning” with the manner of death as accident.

### Case 3

A 42-year-old Caucasian man was found dead in his home, lying prone in the hallway, with his eyeglasses broken and hanging from his face. He had last been known to be alive on the previous day at 10:30 PM, when he had answered a phone call. At the scene, a bottle of diazepam with 11 pills missing from the prescribed number, a methylphenidate tablet, and 2 syringes (1 empty and 1 filled with a clear liquid), as well as an empty box of fentanyl patches were recovered. He had a history of ethanol and multisubstance abuse and was seen in his local emergency room the week prior to his death for treatment of an attempted suicide by Percocet and Restoril overdose, as well as self-inflicted abrasions and lacerations, and ethanol intoxication. Following a work-up, gastric decontamination, and observation, he was sent to a psychiatric hospital for involuntary commitment. It was not determined how he came to be at his home on the day of his death. External examination was unremarkable, with the exception of abundant healed apparently self-inflicted incised wounds

on the wrists, abdomen, and forearms. No fentanyl patches were found on the body. Pulmonary congestion and edema, with a combined lung weight of 1920 g, cardiomegaly (450 g), with mild coronary atherosclerosis, and mild hepatic steatosis were found at autopsy. Aortic blood was sent for toxicologic analyses and was positive for 17  $\mu\text{g/L}$  of fentanyl, 0.49 mg/L of paroxetine, low concentrations of cocaine (0.061 mg/L) and its metabolite, benzoylecgonine (0.36 mg/L), and diazepam (0.15 mg/L). Fentanyl overdose was listed as the cause of death and the manner of death was classified as suicide.

#### Case 4

A 39-year-old Caucasian man complained of a fever, sore throat, and malaise. He was seen in his local urgent care facility and given hydrocodone cough syrup. Two weeks later, he was found unresponsive in the bathroom of his home by his mother, who admitted removing a needle with attached syringe from his arm. Also found at the scene were 2 empty bottles of hydrocodone, a one-third full bottle of hydrocodone syrup, empty bottles of alprazolam and zolpidem, 2 additional syringes, and 2 empty wrappers from fentanyl patches. He was taken to the local emergency room, where he was pronounced dead. Further investigation revealed a history of drug use, asthma, depression, and psychosis. At the time of autopsy, old needle puncture sites were found within bilateral antecubital fossae, with a relatively recent needle puncture in the left antecubital fossa. Microscopic examination of these sites revealed dermal foreign body giant cells with polarizable material. Internal findings included cardiomegaly (510 g) with left ventricular hypertrophy and hepatosplenomegaly. Numerous foreign body giant cells with polarizable material were present within the lungs, surrounding the pulmonary blood vessels. Toxicologic analysis of femoral blood was positive for 13  $\mu\text{g/L}$  of fentanyl, 0.083 mg/L of hydrocodone, and 0.076 mg/L of oxycodone. Testing of the syringe found at the scene was positive for fentanyl. The cause of death was determined to be fentanyl toxicity, with hydrocodone and oxycodone listed as significant contributing factors. The manner of death was determined to be accident.

#### DISCUSSION

Fentanyl, developed by Janssen Pharmaceutica, was originally introduced in the United States in 1968 for use as an intravenous analgesic-anesthetic drug. The abuse of fentanyl has classically been by health care professionals who had access to the controlled drug. In the 1980s, a street version began to appear, resulting in many deaths. "China White," or  $\alpha$ -methyl-fentanyl, was found to be up to 1000 times more potent than heroin<sup>1</sup> and with demographics similar to those of heroin abuse.<sup>10</sup> In particular, Caucasian men with an average age of 32 years old and a prior history of intravenous drug use were most likely to abuse China White,

usually in combination with other drugs (alcohol, cocaine, other opiates). The FDA approved Duragesic (Janssen Pharmaceutica, Beerse, Belgium), the first transdermal fentanyl system, in 1990 for use in the control of chronic and post-surgical pain.

Since their introduction in 1990, transdermal fentanyl patches have been abused in a number of ways. Edinboro et al<sup>2</sup> reported a case of an 83-year-old female with terminal cancer who was found to have fatal levels of fentanyl in her blood (25  $\mu\text{g/L}$ ) after applying 3 patches to her chest. Arvanitis and Satonik<sup>3</sup> described a case of a 38-year-old man who was found unresponsive on 3 separate occasions after chewing transdermal fentanyl patches. He was treated successfully with naloxone the first 2 times, but the final time, he was found dead with a fentanyl patch in his oropharynx. Complete postmortem evaluation and toxicologic analyses were not complete at the time of publication. Another case of intentional oral ingestion of fentanyl patches was reported by Purucker and Swann,<sup>4</sup> who described a 24-year-old woman who reported to her local emergency room complaining of pain due to miscarriage, as well as chronic pain and muscle spasms. She received an intramuscular injection of meperidine and a fentanyl patch was applied for continued pain relief. She was found shortly thereafter in the lavatory, unresponsive and apneic. She was successfully resuscitated, and an empty Duragesic (Janssen Pharmaceutica) patch was found in her wallet, with bite marks found on the polyester backing and none of the fentanyl gel remaining in the patch. Neither a urine drug screen nor serum fentanyl level was obtained. Marquardt and Tharratt<sup>5</sup> reported a case of a 36-year-old man who became apneic, hypotensive, and tachycardic following heating of a fentanyl patch with subsequent inhalation of the evolving vapors, which was witnessed by his girlfriend. Naloxone was administered and he was able to be resuscitated; urine or serum drug screens were not performed at that time. This man subsequently died as a result of further inhalation abuse of fentanyl patches, and (according to Marquardt and Tharratt<sup>5</sup>) he was found at autopsy to have the following fentanyl concentrations: femoral blood, 2.66 ng/mL; urine, 41 ng/mL; and liver, 122 ng/mL.

Transdermal fentanyl therapy consists of a patch composed of 4 layers with an outer protective liner. The 4 layers include a polyester film backing; the drug reservoir, which contains a mixture of fentanyl, alcohol, and hydroxyethyl cellulose; a membrane that controls the rate of fentanyl delivery; and a silicone adhesive, which also contains fentanyl. The rate-limiting step in absorption is through the lipophilic, keratinous stratum corneum by passive diffusion.<sup>11</sup> Extraction of the contents of the drug reservoir followed by intravenous injection of the fentanyl effectively bypasses this rate-limiting step and provides a bolus dose. This unique method of abuse, therefore, increases a person's risk of fatal overdose by rapidly administering larger than the usual in-

**TABLE 1.** Brief case summaries and toxicology results

| Case No. | Age, y | History of drug use | Specimen                       | Fentanyl concentration (µg/L) | Additional drugs                                                  | Cause of death     | Manner of death |
|----------|--------|---------------------|--------------------------------|-------------------------------|-------------------------------------------------------------------|--------------------|-----------------|
| 1        | 35     | No                  | Aortic Blood                   | 5                             | Propoxyphene, amitriptyline, nortriptyline                        | Fentanyl poisoning | Accident        |
| 2        | 38     | Yes                 | Aortic blood                   | 27                            | None                                                              | Fentanyl poisoning | Accident        |
| 3        | 42     | Yes                 | Aortic blood                   | 17                            | Diazepam, nordiazepam, cocaine, benzoylcegonine                   | Fentanyl overdose  | Suicide         |
| 4        | 39     | Yes                 | Aortic blood/<br>femoral blood | 22/13                         | Alprazolam, propoxyphene, norpropoxyphene, oxycodone, hydrocodone | Fentanyl toxicity  | Accident        |

travenous dose of fentanyl than would be administered without respiratory support and much greater than the dose administered via the transdermal time-release method intended by the patch design.

A single prior case of nonfatal intravenous abuse of a transdermal fentanyl patch was reported by DeSio et al<sup>12</sup> in which the subject was a 21-year-old female with a history of chronic abdominal pain and a history of classic “drug-seeking” behavior. She apparently had 2 episodes of respiratory arrest following self-injection of the contents of fentanyl patches, to which she readily admitted. The actual amount of fentanyl extracted from the patch and injected was not quantified, nor was a urine drug screen or a blood level reported.

All cases presented in this report were Caucasian men between the ages of 35 and 42 years, and all but 1 had a known prior history of drug use. Three of the 4 men also had other substances detected in their blood, including cocaine, benzodiazepines, oxycodone, and propoxyphene (Table 1). None of the men had a history of chronic pain syndrome, and except for Case 2, in which the decedent apparently obtained the fentanyl patch from a drug treatment program; it is unknown how the men obtained the fentanyl patches.

The 4 cases presented in this report demonstrate the importance of careful scene investigation and interviews as an invaluable part of the postmortem examination. In all cases, fentanyl patches and needles with syringes were found at the scene, as well as physical evidence of intravenous injection found on the body at the time of autopsy. Fentanyl, while acting pharmacologically similar to opiates, has a much different chemical structure and is not detected by standard

narcotic screening tests. In the cases presented, it is highly improbable that the intravenous abuse of fentanyl extracted from transdermal patches would have been considered or detected without thorough investigation of the scene and the decedent’s history.

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