CASE REPORT

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Fatal Fentanyl Intoxication Following Excessive Transdermal Application*

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ABSTRACT: The case history and toxicological findings of a fatal fentanyl intoxication due to the application of multiple transdermal patches are presented. An 83 year-old white female with terminal cancer was found dead with three 100 mg/h fentanyl patches on her chest. The autopsy and subsequent histological studies revealed extensive areas of gastric carcinoma, a large atrial tumor, ulceration of esophagus, metastasis of peripancreatic lymph nodes and a recent surgical removal of part of the lower lobe of the left lung. Toxicological analysis by GC/MS yielded fentanyl concentrations of blood, 25 ng/mL; brain, 54 ng/g; heart 94 ng/g; kidney 69 ng/g; and liver 104 ng/g. The cause of death was determined to be fentanyl overdose and the manner of death was ruled undetermined as the investigation was unable to conclusively establish whether this was an accidental overdose, a suicide, an assisted suicide, or possibly a homicide. This case demonstrates the need for caution in self-administration of transdermal fentanyl patches, in particular, the dangers inherent in the application of multiple patches which can result in the release of potentially toxic or lethal doses.

KEYWORDS: forensic science, forensic toxicology, death, fentanyl, transdermal administration, drug overdose, poisoning

Fentanyl is a synthetic narcotic analgesic of high potency (80 times morphine) and short duration of action (1). Due to lessened side effects, including shorter duration of respiratory depression, fentanyl is the analgesic of choice in surgical procedures performed in the U.S.A. Plasma concentrations of fentanyl of 2 to 5 ng/mL are sufficient to induce surgical analgesia and respiratory depression (2). In addition to use as a surgical analgesic, fentanyl is also prescribed for the management of chronic pain for patients requiring opiate analgesia. Recently, fentanyl has become available in 2.5, 5, 7.5, and 10 mg transdermal patches which release 25, 50, 75, and 100 μg/hr, respectively, for over 72 h (3). Measurable serum concentrations of fentanyl occur within 2 h of application of the patches (4). Blood, serum, and plasma concentrations are similar to those obtained following equivalent I.V. doses (3,5). Fentanyl has a large apparent volume of distribution (60–300 L) and is primarily metabolized in the liver by dealkylation (2). The elimination of fentanyl is highly dependent on the age and physiological status of the patient.

Fentanyl's therapeutic popularity has not been without problems. As a potent narcotic, fentanyl has become an abuse problem among health professionals, including anesthesiologists, physicians, pharmacists, and nurses (6,7). Recreational abuse of fentanyl is extremely dangerous due to the low concentrations necessary to induce respiratory depression. Several overdose deaths of health professionals have been reported (8–11).

More recently, however, recreational abuse of fentanyl by non-health professionals has been reported involving ingestion, injection, or smoking of fentanyl transdermal patches (12–14). As the use of transdermal patches increases for the management of chronic pain, it appears that other forms of therapeutic mis-adventures may be occurring. For example, patients may apply more than one patch at a time in order to experience enhanced pain relief. As the patches are capable of delivery therapeutic doses of fentanyl, placement of multiple patches would result in fentanyl toxicity including death.

The following case is presented as an example of fentanyl toxicity, as a direct result or compounding factor, in the death of an elderly woman found with multiple fentanyl transdermal patches on her body.

Case Report

Autopsy Findings

An 83-year-old white female was found dead with three 100 ug/h fentanyl patches on her chest. The woman had been diagnosed with terminal cancer and was using fentanyl patches for treatment of pain. The autopsy and subsequent histological studies revealed extensive areas of gastric carcinoma, a large antral tumor, ulceration of esophagus, metastasis of peripancreatic lymph nodes and a recent surgical removal of part of the lower lobe of the left lung. A careful examination of the body revealed no apparent injection sites.

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Toxicological Analysis

Initial Analysis—Blood was initially screened for ethanol using an enzymatic/radiant energy technique; salicylates by trinders reagent and morphine by radioimmunoassay (RIA). Urine as analyzed for amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, and phencyclidine by enzyme immunoassay (Emit II, Bahring Diagnostics, San Jose, CA). Additionally, both blood and urine were screened for fentanyl by RIA (Diagnostic Products, Los Angles, CA) (15).

Quantitative Fentanyl Analysis

GC/MS quantitation of fentanyl was based on previously published methods (16–18). To separate 5.0 g samples of heart, liver, kidney, and brain tissue were added 5.0 mL of distilled water. The samples were then homogenized in a mini-adapted Waring Blender. To 5.0 mL aliquots of tissue homogenates and 2.0 mL aliquots of calibrators, drug free blood, and autopsy blood samples was added 50 ng/mL of fentanyl-d5 (Radian Corp. Austin, TX) as the internal standard. To each aliquot 2.0 mL of pH 9 saturated borate buffer was added, followed by 8.0 mL of n-chlorobutane. The aliquots were vortexed for 15 min, then centrifuged for 5 min and the organic top layer was drawn off into a new tube. Then 2.0 mL 0.1M HCl was added to each extract which was the vortexed for 15 min and centrifuged for 5 min. The bottom aqueous layers were then removed using a 2 mL glass pipette and placed into clean 15 mL centrifuge tubes. The pH of the solutions were then adjusted to greater than pH 9 with the addition of 1.0 mL of 2 N NaOH. The solution was extracted with 3.0 mL of n-chlorobutane by vortexing for 10 min followed by centrifuging for 5 min and organic layers were then transferred to clean 12 by 75 mm test tubes and evaporated to dryness in a Savant Evaporator/Concentrator for 20 min (initial 10 min with radiant cover on). The residues were reconstituted with 500 μL n-chlorobutane, vortexed, and evaporated to dryness at 80°C under dry nitrogen. The resultant residues were reconstituted with 50 μL of n-chlorobutane of which 2.5 μL aliquots were injected into the GC/MS.

GC/MS analysis was performed on a Hewlett-Packard (Avondale, CA) 5890 GC equipped with a 12.5 m by 0.2 mm (ID) by 0.33 μm (film thickness) cross linked 5% phenyl silicone capillary column with a 12 m guard column (Restek, Bellefonte, PA) connected to a Hewlett-Packard 5971-A mass selective detector. Data processing was performed with a HP Chemstation (Version 3.2 software) in the scan mode monitoring m/z ions from 44–600. The GC/MS was operated in the splitless mode with a helium carrier gas linear velocity of 20 mL/min. Initial oven temperature was 200°C for 1 min with an injection port temperature of 250°C. The temperature was ramped at 15°C/min to a final temperature of 280°C which was held for 2.5 min. Data were collected in the SIM mode monitoring m/z ions 245, 146, 189 (fentanyl) and 250, 151, 194 (fentanyl-d5) with a dwell time of 50 ms for each ion.

Calibration

Fentanyl working standard (1μg/mL) was prepared by diluting 1:100 with methanol a 100 μg/mL fentanyl stock standard (Radian Corp.). A calibration curve (0.5, 2.0, 10.0, and 50.0 ng/mL fentanyl) was prepared by adding the appropriate volume of fentanyl working standard to 2.0 mL of drug free whole blood. The calibrators were vortexed and allowed to equilibrate 1 h prior to use.

Results

Initial toxicological analysis of blood and urine failed to disclose the presence of commonly encountered drugs of abuse and alcohol. RIA fentanyl analysis yielded 14 ng/mL in urine and 10 ng/mL in blood (extrapolated from the urine calibration curve). The results of GC/MS fentanyl analysis of the decedents' blood and tissues are presented in Table 1. Fentanyl blood and tissue concentrations greatly exceed those associated with therapeutic administration (4–6) and are consistent with or greatly exceed those previously reported in cases of fatal intoxication (8–11,14,19,20). Fentanyl blood concentrations in these cases ranged from 0.1–28 ng/mL with liver and kidney valves ranging up to 76 and 42 ng/mL, respectively.

The cause of death was determined to be fentanyl overdose and the manner of death was ruled undetermined. The investigation was unable to conclusively establish whether this was an accidental overdose, a suicide, an assisted suicide, or possibly a homicide.

Discussion

The use of fentanyl transdermal release patches provides the advantages of maintaining a constant therapeutic serum concentration similar to constant I.V. infusion while circumventing erratic gastrointestinal absorption and first pass metabolism of oral preparations (3,4). Thus, these dosage forms have proven efficacious for the long term management of cancer related pain. No doubt the out-patient prescribing of transdermal patches will increase in the future. To prevent fentanyl toxicity, both patient and care giver must be properly instructed on the use and hazards of fentanyl patches.

In this case, the decedent was instructed to apply one 100 ug/h patch once every 2–3 days as indicated for cancer related pain. Application of a single 100 μg/h transdermal fentanyl patch would be expected to result in a maximal plasma fentanyl concentrations of 2 to 3.8 ng/mL at 25–72 h after application (4). It appears that the application of multiple transdermal fentanyl patches resulted in an overdose for this woman. Theoretically, three 100 μg/h patches would be expected to produce a blood fentanyl concentration of approximately 10 ng/mL within 24 h of application. The blood concentration of fentanyl in this case was 25 ng/mL indicating that this woman may have been using multiple patches for several days. Additionally, due to her age, the metabolism of fentanyl may have been markedly decreased. Therefore it is possible that the time frame for development of toxicity would have been shortened. The high concentrations of fentanyl in the tissues may also indicate reduced metabolism. Unfortunately, we did not analyze the specimens for fentanyl metabolites as primary reference materials were unavailable from commercial supplies and request to the manufacturer of the drug were not answered. Clearance of unchanged fentanyl via the kidney is less than 8% of an I.V. dose. In this case, kidney concentrations were higher than

TABLE 1—*Toxicological findings.*

Tissue	Fentanyl Concentration
Blood	25 ng/mL
Brain	54 ng/g
Heart	94 ng/g
Kidney	69 ng/g
Liver	104 ng/g

previously reported cases involving I.V. deaths. This high concentration would not be expected under normal conditions for a transdermal delivery system and could be the result of increased unchanged fentanyl available for excretion via the kidneys.

Conclusion

This case demonstrates the need for caution in self-administration of transdermal fentanyl patches, in particular, the dangers inherent in the application of multiple patches which can result in the release of potentially toxic or lethal doses. This same caution would apply to nonprofessional care givers assisting in the application of fentanyl patches. It is important to keep in mind that the metabolism of fentanyl in the elderly is slowed and must be considered as a factor in the high concentrations achieved in this case. The potential for misuse of transdermal fentanyl patches (foul play, assisted suicide, and therapeutic mis-adventures) must be considered in any death associated with fentanyl toxicity.

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