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Fentanyl Concentrations in 23 Postmortem Cases from the Hennepin County Medical Examiner's Office*

ABSTRACT: The purpose of this study was to compare blood fentanyl concentrations in fentanyl-related deaths with fentanyl concentrations found incidentally at autopsy, as well as with fentanyl concentrations found in hospitalized patients receiving fentanyl. Between the years 1997 to 2005, 23 fentanyl-positive postmortem cases were identified. Nineteen of 23 (82.6%) cases were deemed to be drug overdoses. Fentanyl alone was responsible for 8 of the 19 (42.1%) overdose deaths. Mean and median fentanyl concentrations were 36 (SD 38) μg/L and 22 μg/L, respectively, range 5–120 μg/L. Seven of the cases were accidental, one undetermined. The remaining 11 of the 19 (57.9%) cases were mixed drug overdoses. Fentanyl concentrations in these cases were 31 (SD 46) μg/L, range 5–152 μg/L. All of the mixed drug overdoses were determined to be accidental. Four cases where fentanyl was considered an incidental postmortem finding were determined to be natural deaths. In hospitalized inpatients (n = 11) receiving fentanyl 2 of the patients receiving fentanyl for chronic pain for more than 3 months had concentrations of 8.5 μg/L and 9.9 μg/L. The other nine inpatient concentrations were less than 4 μg/L. In conclusion, blood fentanyl concentrations found in cases where fentanyl alone was determined to be the cause of death were similar to cases where fentanyl was part of a mixed drug overdose. There was also considerable overlap between fentanyl concentrations in fentanyl-related overdose deaths compared to hospitalized patients being treated for chronic pain. Fentanyl concentrations in postmortem cases must be interpreted in the context of the deceased's past medical history and autopsy findings.

KEYWORDS: forensic science, fentanyl, postmortem, cause of death

Fentanyl is a synthetic opioid widely used as a surgical anesthetic and for management of chronic pain because of its high potency (100 times that of morphine) and rapid onset (2–3 min) (1). From 1990 to 1996, the amount of fentanyl prescribed in the U.S. increased 1000% (2), primarily because of the ability of fentanyl to be delivered transdermally, with the advent of the transdermal patch, in patients with chronic pain. Similar to other opioids, fentanyl has a high abuse potential and is capable of producing severe respiratory depression, muscle rigidity, seizures, hypotension, coma, and death (3). In recent years, there have been a number of fentanyl-related deaths reported (4–8). At the Hennepin County Medical Examiner's Office, Minnesota, the number of fentanyl-related deaths increased from one in 1997 to six deaths in the first 6 months of 2005. The medical examiner, pathologist, or coroner in cases where fentanyl is identified often faces the difficult problem of determining whether fentanyl was an incidental finding or played a role in causing the death. This difficulty arises because patients who are treated with fentanyl for chronic pain may have high blood concentrations due to the development of tolerance and/or progression of their underlying disease. These blood fentanyl concentrations may overlap with the fentanyl concentrations in medical examiner cases, and one is required to determine if fentanyl played a role in the cause of death or was an incidental finding.

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In the current study, we compare blood fentanyl concentrations in fentanyl-related deaths with fentanyl concentrations found incidentally at autopsy, as well as with blood fentanyl concentrations in hospitalized patients receiving fentanyl therapeutically as part of their pain control.

Materials and Methods

The experimental design used in this study was approved by the Institutional Review Board (IRB) for human subjects research. The Hennepin County Medical Examiner's Office (HCMEO) database was searched from January 1997 through June 2005 for cases in which fentanyl was quantitated in either the decedent's blood, and/or liver; based on suspicion of fentanyl use. Hennepin County has a population of 1.1 million people. In general at the HCMEO, blood was collected at autopsy from the inferior vena cava in gray-top tubes containing 17.5 mg of sodium fluoride. Blood and urine were routinely screened by liquid chromatography for a comprehensive identification of drugs, and not specifically to identify fentanyl because of the poor limit of detection (50 μg/L) (Bio-Rad REMEDi® HS Drug Profiling System, Hercules, CA). When requested by the HCMEO, quantitative analysis of blood fentanyl was performed by gas chromatography-mass spectrometry (GCMS) in cases where fentanyl was of high clinical suspicion. There were no cases identified only by screening urine.

Fentanyl was quantitated after solid phase extraction from whole blood by gas chromatography mass spectrometry (GCMS) on a Hewlett-Packard 5972 mass selective detector following chromatography on a 5890 gas chromatograph equipped with a 30 m DB-5 capillary column (Agilent Technologies, Palo Alto, CA). Standards and deuterated internal standards were obtained from Cerillant Corp (Austin, TX). For example, 1 mL of whole blood (appropriate

standards, controls, and case) was mixed with 10 μL fentanyl-d5 internal standard (10 ng/mL) and 3 mL of water was added to this solution and vortexed. After sitting for 5 min, it was centrifuged at 1950 g for 15 min, and the pellet was discarded. To the supernatant, 3 mL of 100 mM phosphate buffer was added followed by pH adjustment to 6. This specimen was then transferred onto a preconditioned solid phase extraction column (Bond Elut; Varian, Harbor City, CA). Following treatments with water, 100 mM acetate buffer, and methanol, the column was eluted with methylene chloride, isopropanol, and ammonium hydroxide (78:20:2). The eluant was evaporated at 30–40°C with nitrogen, reconstituted with 0.05 mL ethyl acetate, and transferred for analysis into the autosampler for injection on the GCMS. The MS was operated in the select ion monitoring mode (SIM), and the following ions were scanned: fentanyl quantitating ion 245, qualifier ions 146, 189; fentanyl-d5 quantitating ion 250; and qualifier ions 151,194. Standard curves were derived for each analysis and area ratios for unknowns were used to calculate the corresponding analyte concentration. Quantitation of fentanyl was based upon ratios of integrated ion areas to the corresponding deuterated internal standard. Analytes were identified based upon comparison of relative retention times (within 1% of retention time of calibrators) and ion ratios with the corresponding values of calibrators assayed in the same run. Ion ratios were calculated by dividing the area of the qualifier ion by the area of the quantitative ion and must be within ± 20% of calibrators. Limit of detection, limit of quantitation and limit of linearity were experimentally found to be 2 μg/L, 2 μg/L, and 100 μg/L, respectively. The assay's total precision (% CV) at 2 μg/L was 4.9%.

The Hennepin County Medical Center's pharmaceutical list was searched during one 24-h period for all inpatients receiving fentanyl. Waste blood was collected from 11 patients, and fentanyl blood concentrations were measured by GCMS. Charts were reviewed for therapeutic indications of fentanyl dosing.

Mean, median, and range of fentanyl concentrations were determined. The medical examiner's cases were further analyzed for those cases in which fentanyl was the sole cause of death and those in which fentanyl was part of a mixed drug overdose. The mean and range of fentanyl concentrations were compared amongst the subpopulations and with respect to the cause and manner of death. Statistically significant differences in groups were determined by two-tailed student's *t*-tests and ANOVA with $p < 0.05$ demonstrating significance.

Results

Twenty-three medical examiner cases were identified as suspicious of recent fentanyl use in which the decedent's blood tested positive for fentanyl. Seven cases were found to be exposed at death to fentanyl patches, as indicated in Table 1. In general though, there were poor histories for past chronic or acute fentanyl exposure. Of the 23 cases, 19 (82.6%) were deemed to be drug overdoses. Fentanyl alone was responsible for eight of the 19 (42.1%) overdose deaths. Mean and median fentanyl concentrations were 36 (SD 38) μg/L and 22 μg/L, respectively, range 5–120 μg/L. Seven of the cases were signed out as accidental, one as undetermined. The remaining 11 of the 19 (57.9%) cases were mixed drug overdoses. Other opiates were identified in seven of the 11 mixed drug overdoses, barbiturates in three, and ethanol and benzodiazepines in two. Mean and median fentanyl concentrations were 31 (SD 46) μg/L and 13 μg/L, respectively, range 5–152 μg/L. All of the mixed drug overdoses were signed out as accidental. The four cases where fentanyl was an incidental postmortem finding were signed out as natural deaths. Blood concentrations in this group were 2, 2, 2, and 15 μg/L. The deceased with the blood fentanyl concentration of 15 μg/L was being treated for chronic pain related to metastatic squamous cell carcinoma of the head and neck. This fentanyl level was greater than or equal to three of the fentanyl-only overdose deaths and seven of the mixed drug overdose cases. Table 1 describes the blood fentanyl and other drug concentrations observed by each group in all deaths. Of the 19 fentanyl-related deaths, 10 occurred between January 2004 and July 2005. Seventeen of the 19 occurred after the year 1999.

For comparison, 11 inpatients receiving fentanyl therapeutically were identified over one 24-h period. Two of the patients had fentanyl concentrations of 8.5 μg/L and 9.9 μg/L. These levels were higher than one of the fentanyl-only related deaths (5 μg/L) and two of the mixed drug overdose deaths (5 μg/L and 7 μg/L). Both patients had been receiving multiple opiates, including fentanyl, for chronic pain for more than three months. The other nine inpatient blood fentanyl concentrations were undetectable (less than the LOD). Table 1 also describes the fentanyl concentrations for the 11 inpatients.

Discussion

Our study demonstrates considerable overlap between fentanyl concentrations in fentanyl-related deaths and fentanyl concentrations found incidentally at autopsy, as well as with fentanyl concentrations found in hospitalized patients receiving fentanyl. These results are similar to other results reported in the literature regarding medical examiner cases (4–8). However, our study, although small in numbers, is the first to demonstrate overlapping fentanyl blood levels in medical examiner case fatalities with living patients receiving fentanyl for pain control while being hospitalized. Unfortunately, accurate associated histories were not available in medical examiner cases; with only evidence of seven cases found with transdermal patches at the time of death. In a study of 112 fentanyl-related deaths, the mean fentanyl concentration at autopsy was 3.0 μg/L, with a range of 0.2 μg/L to greater than 50 μg/L (7). In comparison, in eight cases where fentanyl was an incidental finding at autopsy, and clearly not the cause of death, the average blood concentration was 3.6 μg/L, with a range of undetectable to 7 μg/L (6). The primary reason for the overlap between blood fentanyl concentrations in hospitalized patients and incidental findings at autopsy, and cases where fentanyl played a role in the decedent's death, is the development of tolerance in chronic users (9,10). In the inpatient cases and the medical examiner case in which fentanyl was an incidental finding (Table 1), the subjects were being treated with fentanyl for the treatment of chronic pain. Two hospitalized patients had been receiving fentanyl for over 3 months.

Our study did not show a higher mean and median blood fentanyl concentration in cases where fentanyl alone was determined to be the cause of death when compared to cases where fentanyl was part of a mixed drug overdose ($p = 0.3$); in agreement with a recent study of fentanyl-related deaths in Canada (8). The lack of statistical significance may be the result of the relatively small number of cases; a limitation of our study. A larger study of 223 postmortem cases, however, did report differences in average postmortem fentanyl concentrations of 30 μg/L and 17 μg/L in fentanyl-only deaths and mixed drug overdoses, respectively (4).

We have also demonstrated postmortem blood fentanyl levels can range up to 15 μg/L for therapeutic management of cancer pain. This is in contrast to the suggestion that postmortem blood fentanyl levels following therapeutic administration range to 7 μg/L (6). In a study of 23 fentanyl-positive autopsy cases, a 46-

TABLE 1—*Blood fentanyl concentrations in medical examiner cases and hospitalized patients being treated for pain.*

Case no.	Fentanyl dose (μg/h)	Blood Fentanyl (μg/L)	Other drugs detected	Cause of death	Manner of death
Fentanyl-only related deaths					
1	100 (transdermal patch)	5	Blood clonazepam (<4 μg /L)	Fentanyl toxicity	Accident
2	150 (transdermal patch)	10	Liver amitriptyline (8 mg/kg) Liver nortriptyline (2 mg/kg)	Fentanyl toxicity	Accident
3	–	15	None	Fentanyl toxicity	Accident
4	–	19	Urine droperidol Urine diphenhydramine Urine hydrocodone and metabolites Urine nalbuphine Urine trazadone and metabolite	Fentanyl toxicity	Accident
5	–	25	Liver nortriptyline (19 mg/kg) Blood levetiracetam (18 mg/L) Blood topiramate (11.9 mg/L) Blood trazadone (880 μg /L)	Fentanyl toxicity	Accident
6	–	34	Blood cocaine (0.05 mg/L) Blood benzoylecgonine (0.31 mg/L) Blood ethanol (0.057 g/dL)	Fentanyl toxicity	Accident
7	–	62	Blood amitriptyline (<25 μg/L) Blood nortriptyline (63 μg/L)	Fentanyl toxicity	Undetermined
8	300	120	Urine dihydrocodeine, urine propoxyhene & metabolites Urine venlafaxine	Fentanyl toxicity	Accident
Mixed drug overdoses					
9	150 (transdermal patch)	5	Blood methadone (0.54 mg/L) Blood free oxycodone (0.07 mg/L) Blood trazadone (246 μg /L)	Mixed drug overdose (fentanyl, methadone)	Accident
10	–	7	Blood benzoylecgonine (0.33 mg/L) Blood ethanol (0.022 g/dL) Blood butalbital (0.45 mg/L) Blood oxycodone (14 μg/L)	Mixed drug overdose (fentanyl, barbiturates, oxycodone, ethanol)	Accident
11	75 (transdermal patch)	10	Blood total morphine (3.23 mg/L)	Opiate overdose	Accident
12	–	11	Blood ethanol (0.062 g/dL)	Mixed drug overdose (fentanyl & ethanol)	Accident
13	–	12	Blood acetaminophen (<10 mg/L) Blood alprazolam (13 μg/L) Blood tramadol (1500 μg/L)	Mixed drug overdose (benzodiazepines and fentanyl)	Accident
14	–	13	Blood tramadol (240 μg/L) Blood D-desmethyltramadol (120 μg/L) Blood norfentanyl (3.1 μg/L) Blood diphenhydramine (10 μg/L) Blood cyclobenzaprine (0.020 mg/L)	Mixed drug overdose (fentanyl & tramadol)	Accident
15	–	14	Blood total morphine (0.38 mg/L)	Opiate overdose	Accident
16	–	16	Liver amitriptyline (1 mg/L) Liver nortriptyline (9 gm/kg) Blood propoxyphene (0.338 mg/L) Blood norpropoxyphene (0.708 mg/L)	Mixed drug overdose (fentanyl & propoxyphene)	Accident
17	–	20	Blood phenobarbital (7.0 mg/L) Blood nordiazepam (72 μg/L) Blood diazepam (58 μg/L)	Mixed drug overdose (fentanyl, benzodiazepines, and barbiturates)	Accident
18	75 (transdermal patch)	90	Blood hydrocodone (0.24 mg/L)	Mixed drug overdose (hydrocodone and fentanyl)	Accident
19	–	152	Blood methadone (1.86 mg/L) Blood alprazolam (120 μg/L) Blood ethanol (0.027 g/dL)	Mixed drug overdose (fentanyl, alprazolam, ethanol, and methadone)	Accident
Incidental fentanyl finding					
20	20	2	Liver nordiazepam (1500 μg/L) Liver diazepam (300 μg/kg) Liver temazepam (<200 μg/kg) Blood dihydrocodeine/hydrocodone 850 μg/L)	Arteriosclerotic heart disease	Natural (history of metastatic breast cancer)
21	–	2	Blood venlafaxine & metabolite	Hypertensive heart disease	Natural (chronic pain syndrome)
22	–	2	Blood total morphine (1.08 mg/L) Blood free morphine (0.22 mg/L) Blood benzoylecgonine (2.03 mg/L)	Arteriosclerotic heart disease	Natural (history of chemical dependency)
23	–	15	Urine oxycodone	Metastatic carcinoma of the tongue	Natural

TABLE 1—*Continued.*

Hospitalized patients			
Case no.	Fentanyl concentration (μg/L)	Dose	Significant history
1	9.9	300 μg/h, transdermal	History of squamous cell carcinoma of rectum
2	8.5	100 μg/h, transdermal	History of chronic pain syndrome
3	4.0	150 μg/h, I.V.	Pneumonia with acute respiratory distress syndrome. Fentanyl for sedation while mechanically ventilated
4	3.7	125 μg/h I.V.	Acute interstitial pneumonia with respiratory failure Fentanyl for sedation while mechanically ventilated
5	ND	Unknown	Hypoxemic respiratory failure. Mechanically ventilated
6	ND	Unknown	Congestive heart failure with pulmonary edema. Mechanically ventilated
7	ND	Unknown	Pneumonia with sepsis. Fentanyl for sedation while mechanically ventilated
8	ND	25–50 μg/h, transdermal	History of chronic pain due to peripheral vascular disease
9	ND	25 μg/h, transdermal	Locked-in syndrome due to basal ganglia stroke
10	ND	Unknown	Pain due to incarcerated hernia
11	ND	25 μg/h, transdermal	Hospice care. Therapy-related myelodysplastic syndrome

Urine findings are qualitative; ND, none detected.

year-old male was found to have a blood fentanyl concentration of 14 μg/L. The cause of death was determined to be coronary artery atherosclerosis. The decedent was found with a fentanyl patch on his chest that was not prescribed, raising the question of whether this was actually a fentanyl-related death (6). We also report fentanyl concentrations of 9.9 μg/L and 8.5 μg/L in two hospitalized patients treated with fentanyl for chronic pain, suggesting that the therapeutic range may be higher than previously suggested in chronic users who gain tolerance (10). A limitation of our study that should be noted is that since the limit of detection for the urine screening method for fentanyl is 50 μg/L, it is possible that the number of cases related to fentanyl may be underestimated, as lower concentrations of fentanyl would be missed by the REMEDi® (a liquid chromatography screen) if not suspected. Also, as blood was collected from the inferior vena cava site, our postmortem fentanyl concentrations might be elevated compared to studies where blood is drawn from a peripheral site. Although there are no studies to date regarding true postmortem redistribution of fentanyl (where multiple blood draws are obtained from the same site over time), one can conclude that the redistribution may contribute to higher blood levels as postmortem time to autopsy increases due to the large volume of distribution of fentanyl. Although this may make our postmortem fentanyl concentrations higher than studies where blood is drawn from peripheral sites, this would not alter our finding that there is significant overlap between therapeutic concentrations of fentanyl and lethal levels. Further it is not known either whether postmortem redistribution does occur at peripheral sites either. In conclusion, our findings add evidence to the literature that supports the interpretation of fentanyl concentrations in postmortem cases, reemphasizing that interpretations must be made with caution, and in the context of the decedent's past medical history and autopsy findings, and not as an isolated toxicology finding.

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