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A Fentanyl Epidemic in Maryland 1992

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ABSTRACT: In early 1992, the Office of the Chief Medical Examiner, State of Maryland, encountered 30 cases where fentanyl was identified in the postmortem specimens. Twenty-five of the decedents were found in Baltimore City and five were found in the surrounding counties. Four of the decedents were female and eight of the victims were white. The blood fentanyl concentrations ranged from 2.2 to 100 μg/L. Ethanol and other abused drugs were detected in 28 of these cases. The cause of death in all cases was ethanol-, drug intoxication, or both.

KEYWORDS: toxicology, fentanyl, epidemic, chromatographic analysis, chemical analysis

Fentanyl is a synthetic narcotic analgesic approximately 50 to 100 times as potent as morphine. It was originally synthesized by Janssen Pharmaceutica in Belgium and introduced in Europe in the 1960s and in the United States in the 1970s for use in the induction of anesthesia and relief of postoperative pain. It is estimated that 70% of all surgical procedures in the U.S. use fentanyl for either of these uses [*1*]. The pharmacokinetics of fentanyl have been reviewed previously [*2*]. There is significant overlap between effective and toxic fentanyl concentrations in plasma. Mean effective analgesic concentrations for postoperative and intraoperative administration range from 1 to 3 μg/L. However, significant respiratory depression occurs at these concentrations. Much higher concentrations have been observed in patients undergoing cardiac surgery, intubation or sternotomy.

Because of its potency and toxicity, fentanyl has been used in many suicidal and accidental overdoses [*3–8*]. The average blood fentanyl concentrations in these cases is 8.1 μg/L, but five of these six cases had blood fentanyl concentrations below 5 μg/L. Tissue distribution studies in some of these cases indicate significant distribution into central compartment tissues such as liver and kidney, but fail to indicate sequestration of the drug in a particular tissue.

In addition to its therapeutic uses, fentanyl and its analogs have been subject to abuse both by health-care professionals and by narcotic addicts. One survey suggested that

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fentanyl was the most frequently abused drug by anesthesiologists [*9*]. Abuse by narcotic addicts has been observed since the 1970s and has occurred mainly in certain regions within the state of California [*10*]. However, within the past several years, there have been pockets of abuse of fentanyl along the Eastern United States. For instance, Wahba and Winek [*11*] reported 19 cases in the Pittsburgh, PA area where 3-methylfentanyl or "China White" was identified. An epidemic of fentanyl overdoses was also observed in New York City in 1991 [*12*].

In February 1992, fentanyl was identified in a series of cases investigated by the Office of the Chief Medical Examiner, State of Maryland. The following is a report of the findings of these cases.

Experimental

Fentanyl Screening

The Diagnostic Products Corporation Coat-a-Count® radioimmunoassay kit was used to screen urine specimens for fentanyl. The assay was performed in accordance with the manufacturer's instruction for the qualitative procedure [*13*]. A negative and a 0.5 μg/L fentanyl calibrator were run in duplicate. Any specimen with counts less than the average of the counts for the positive calibrator was confirmed along with the associated blood specimen.

Fentanyl Confirmation

Materials—Fentanyl citrate was obtained from McNeil Laboratories, Inc. and a 10 mg/L solution as the free base in methanol was prepared. Ethylmorphine hydrochloride was acquired from Alltech-Applied Science and a 10 mg/L solution in methanol served as the internal standard for fentanyl analysis.

Sulfuric acid (H_2SO_4), sodium hydroxide (NaOH) and ammonium hydroxide (NH_4OH) were Baker reagent grade. Methylene chloride, n-butyl chloride, ether and methanol were Fisher HPLC or pesticide grade.

Gas Chromatograph/Mass Spectrometer—Fentanyl analysis was performed on a Hewlett Packard 5890 gas chromatograph interfaced with a model 5970 mass selective detector (GC/MS). A DB-1 fused silica capillary column (0.20 mm id × 12 m) with 1 mL/min carrier gas (helium) flow provided the analytical separation. The injector was at 200°C and operated in the spitless mode. The oven temperature began at 100°C for one min and increased by 25°C/min to 280°C, holding for six min. The mass spectrometer was operated in the selected ion monitoring (SIM) mode, with the following ions being monitored: m/z = 146, 189, 245, and 313. Ion abundance ratios of m/z = 146/245 and 189/245 were used as qualifying ion ratios for fentanyl. Confirmation was based upon comparison of retention time and ion ratio data of sample extracts with standards. Quantification was based on the area ratio of fentanyl (m/z = 245) to internal standard (m/z = 313) in comparison to standards.

Extraction—To 5 mL standard, or fluid were added 2 mL 0.1 NaOH, 50 μL internal standard solution and 20 mL n-butyl chloride:ether (3:1). After mechanical rotation and centrifugation the organic layer was separated and extracted with 3 mL of 1 N H_2SO_4. The acid layer was removed, alkalinized with 0.5 mL NH_4OH and extracted with 5 mL methylene chloride. The methylene chloride was transferred to a conical tube and evaporated to dryness at 40°C. The residue was reconstituted in 50 μL methanol and 2 μL were injected into the GC/MS.

Results and Discussion

All the decedents were initially tested comprehensively for alcohol and drugs. This testing included the following: methanol, ethanol, acetone, and isopropanol by headspace gas chromatography, color tests for salicylate, acetaminophen and ethchlorvynol, acid/neutral drug screening by gas chromatography-nitrogen-phosphorus detection, basic drug screening by gas chromatography-nitrogen-phosphorus detection and morphine by radioimmunoassay. Table 1 provides a summary of the results.

The identification of fentanyl in the initial case occurred from the basic drug screen. This screen identifies commonly encountered drugs such as antidepressants, antihistamines, benzodiazepines, many narcotic analgesics and phenothiazines, phencyclidine, quinine and sympathomimetic amines. It was then decided to retrospectively screen all cases containing morphine received since the beginning of the calendar year 1992. As the incidence of fentanyl cases increased, some cases were encountered that contained only cocaine in the urine but were otherwise without a cause of death. Therefore, the screening for fentanyl increased to those cases containing either cocaine or morphine. When a case was encountered that was positive only for quinine but subsequently tested positive for fentanyl, it was decided to screen all urine specimens for fentanyl whenever a comprehensive drug screen was requested by the pathologist.

The fact that fentanyl was identified in the routine screening process is quite unusual; fentanyl is usually present in such small amounts in the biological fluids that a special immunoassay analysis is required. The radioimmunoassay kit used for screening had previously been evaluated [*14*] and provided excellent sensitivity; a 0.5 μg/L cut-off standard was run with each batch. The extraction of fentanyl for GC/MS was the same as used for the basic drug screen with only one modification: n-butyl chloride:ether (3:1) was used for the initial extraction instead of n-butyl chloride. The presence of the ether reduced any emulsions which developed during the extraction process. This was critical because of the low detection limits required. This requirement also necessitated the use of selected ion monitoring in the GC/MS. Three ions were selected: m/e = 245, 189, and 146. Fentanyl has excellent chromatographic characteristics on a methylsilicone column and thus, no derivatization was necessary. The limit of detection of fentanyl in blood was 0.5 μg/L.

The blood fentanyl concentrations measured in these 30 cases produced a wide range of values: 2.2 to 100 μg/L. The blood concentrations are also provided in Table 1. The average concentration was 18 μg/L, but the median concentration was 11 μg/L. Thirteen cases had concentrations less than 10 μg/L while the remaining cases were greater than 10 μg/L. No correlation between fentanyl concentration and the presence of ethanol and other drugs was readily apparent other than the fact that most cases indicated prior use of narcotics or cocaine. In general, the blood fentanyl concentrations measured in these deaths were higher than measured in overdoses from therapeutically prepared fentanyl. This is not surprising because the effect of tolerance to narcotics in abusers is well documented.

The epidemic of fentanyl deaths in Maryland was relatively evenly distributed over a three-month period (January to April 1992). During this three-month period, fentanyl-related deaths were also noted in California, Massachusetts, and South Carolina. The periodicity of these deaths were in contrast to the 1991 episode in the New York City area, where all deaths occurred within a one-week span in February 1991 [*12*].

The majority of the 30 cases in Maryland involved males (87%). Of the 30 decedents, 22 were black (73%). The age range was from 18 to 61, with a mean and median age of 34. Twenty-five deaths occurred in Baltimore City, while the five deaths occurred in three surrounding counties. Fourteen cases were found dead at the scene, either in residences or on the street.

Other drugs were detected in 28 of the 30 cases. The most common drugs found in

TABLE 1—*Summary of toxicologic results in 30 fentanyl related deaths.*

No.	Case	Blood-fentanyl (μg/L)	Blood-ethanol concentration (% w/v)	Urine/bile-morphine (positive/negative)	Blood-morphine (μg/L)	Urine/bile-cocaine (positive/ negative)	Blood-cocaine (μg/L)
1	36 WM	4.2	negative	positive	230	positive	100
2	32 WM	11	negative	positive	110	positive	negative
3	36 BM	2.2	negative	positive	negative	negative	—
4	40 BM	6.6	negative	positive	300	positive	negative
5	23 BF	28	negative	positive	negative	negative	—
6	38 BM	6.4	negative	positive	negative	positive	negative
7	40 WM	17	0.05	codeine	negative	negative	—
8	21 WM	11	0.03	negative	—	negative	—
9	37 BM	23	negative	positive	negative	negative	—
10	45 WM	9	negative	positive	140	negative	—
11	28 BF	7.9	0.11	positive	negative	positive	negative
12	31 BM	19	0.02	positive	negative	positive	negative
13	33 BM	7.1	0.22	negative	—	positive	negative
14	40 WM	17	negative	negative	—	negative	—
15	37 WM	13	negative	negative	—	negative	—
16	29 BM	9.3	negative	negative	—	positive	negative
17	18 BM	2.4	negative	positive	negative	positive	negative
18	38 WF	3	negative	positive	negative	positive	negative
19	35 BM	22	negative	positive	negative	negative	—
20	19 BM	13	negative	positive	negative	negative	—
21	61 BM	100	negative	positive	negative	positive	negative
22	35 BF	54	negative	negative	—	positive	400
23	35 BM	17	0.09	positive	negative	positive	100
24	42 BM	30	negative	positive	negative	positive	100
25	49 BM	4.3	0.03	positive	negative	positive	100
26	30 BM	5.6	0.01	positive	negative	positive	300
27	24 BM	23	0.05	positive	negative	negative	—
28	20 BM	9.6	negative	negative	—	negative	—
29	37 BM	53	0.18	positive	negative	negative	—
30	38 WM	11	negative	negative	—	positive	negative

addition to fentanyl were morphine/codeine (22 cases), cocaine (17 cases), and ethanol (10 cases). Other drugs detected in these cases were oxycodone, propoxyphene, normeperidine, salicylate, acetaminophen, diphenhydramine, and chlorpheniramine.

All 30 deaths included in this study were attributed to alcohol and drug intoxication, or both. There were no incidences where fentanyl was detected as incidental findings in deaths due to other causes. This is different from the identification of other abused drugs in cases investigated by this Office. For example, cocaine, heroin as morphine and phencyclidine have been detected in homicides and motor vehicle accidents as well as in deaths due to drug intoxications.

Seizures of street samples were analyzed by the Drug Enforcement Agency's Special Testing Laboratory. These samples contained fentanyl hydrochloride of varying purities (0.6 to 6.7%) diluted with quinine, mannitol, lactose, and inositol. The fentanyl hydrochloride was believed to be clandestinely manufactured because the citrate salt is prepared for therapeutic use. In addition, the presence of impurities such as quinine are not normally found in pharmaceutical preparations.

Note Added in Proof

As a result of the investigation triggered in part by the findings discussed in this paper, nine individuals were indicted in United States District Court for the District of Maryland on a variety of charges related to the sale and distribution of Fentanyl. All were found guilty. In the subsequent sentencing hearing, the judge ruled that the Fentanyl distributed by these defendants was a causative agent in most if not all of the thirty deaths reported. With this ruling, mandatory sentences of life in prison without parole were imposed on seven of the defendants. In addition, in 1993 the Maryland legislature added Fentanyl and its analogs to its smuggling statute making the importation of 4g or more of the drug into the State a crime punishable by at least ten years in prison.

References

[1] Henderson, G. L., "The Fentanyls," *American Association for Clinical Chemistry In-Service Training and Continuing Education*, Vol. 12, No. 2, Aug. 1990, pp. 5–17.

[2] Mather, L. E., "Clinical Pharmacokinetics of Fentanyl and its Newer Derivatives," *Clinical Pharmacokinetics*, Vol. 8, 1983, pp. 422–446.

[3] Garriott, J. C., Rodriguez, R., and DiMaio, V., "A Death from Fentanyl Overdose," *Journal of Analytical Toxicology*, Vol. 8, No. 6, Nov.–Dec., 1984, pp. 288–289.

[4] Levine, B., Kauffman, G., and Caplan, Y. H., "The Determination and Distribution of Fentanyl in a Postmortem Case," American Academy of Forensic Sciences, 39th Annual Meeting, San Diego, CA, Feb. 1987.

[5] Pare, E. M., Monforte, J. R., Gault, R., and Mirchandani, H., "A Death Involving Fentanyl," *Journal of Analytical Toxicology*, Vol. 11, No. 6, Nov.–Dec., 1987, pp. 272–275.

[6] Matejczyk, R., "Fentanyl Related Overdose," *Journal of Analytical Toxicology*, Vol. 12, No. 4, July–Aug., 1988, pp. 236–238.

[7] Chaturvedi, A. K., Rao, N. G. S., and Baird, J. R., "A Death Due to Self-Administered Fentanyl," *Journal of Analytical Toxicology*, Vol. 14, No. 6, Nov.–Dec., 1990, pp. 385–387.

[8] Levine, B., Goodin, J. C., and Caplan, Y. H., "A Fentanyl Fatality Involving Midazolam," *Forensic Science International*, Vol. 45, 1990, pp. 247–251.

[9] Ward, C. F., Ward, G. C., and Saidman, L. J., "Drug Abuse in Anesthesia Training Programs. A Survey: 1970 through 1980," *Journal of the American Medical Association*, Vol. 250, No. 7, Aug. 19, 1983, pp. 922–925.

[10] Henderson, G. L., "Fentanyl Related Deaths: Demographics, Circumstances and Toxicology of 112 Cases," *Journal of Forensic Sciences*, Vol. 36, No. 2, March 1991, pp. 422–433.

[11] Wahba, W. and Winek, C. L., "Fatalities Due to 3-Methylfentanyl," Society of Forensic Toxicologists, 19th Annual Meeting, Chicago, IL, Oct. 1989.

[12] McGee, M. P., Marker, E. K., Jovic, M., and Stajic, M., "Fentanyl Related Deaths in New York City," American Academy of Forensic Sciences, 44th Annual Meeting, New Orleans, LA, Feb. 1992.

[*13*] Coat-a-Count® Fentanyl package insert, Diagnostic Products Corporation, Los Angeles, CA.
[*14*] Watts, V. W. and Caplan, Y. H., "Evaluation of the Coat-A-Count ^{125}I Fentanyl RIA: Comparison of ^{125}I RIA and GC/MS-SIM for Quantification of Fentanyl in Case Urine Specimens," *Journal of Analytical Toxicology*, Vol. 14, No. 5, Sept.–Oct. 1990, pp. 266–272.

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