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Fentanyl-Related Deaths: Demographics, Circumstances, and Toxicology of 112 Cases

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ABSTRACT: Since 1979, the potent narcotic analgesic fentanyl and its analogs have been synthesized in clandestine laboratories and sold as heroin substitutes. At least 112 overdose deaths have been associated with their use. In this study, toxicology data, autopsy findings, and coroners' investigative reports were reviewed in order to construct a profile of the typical fentanyl overdose victim and to identify any factors that might heighten the risk of death from fentanyl use. The "typical" fentanyl overdose victim was 32.5 ± 6.7 years of age (range, 19 to 57 years), male (78%, compared with 22% female), and Caucasian (50%, compared with 29% Hispanic, 20% Black, and 0.9% Asian). With the exception of his or her age, the typical fentanyl overdose victim is quite similar to the typical heroin user. Nearly all the deaths (94%) occurred in California, yet within the state they were widely distributed throughout 17 counties and 44 cities. Pulmonary edema and congestion and needle puncture sites were consistent postmortem findings. No preexisting medical conditions were identified as possible risk factors. Although most of the fentanyl victims had a prior history of intravenous drug use, morphine or codeine were not commonly found, which suggests that the victims had little or no opiate tolerance. Ethanol was present in 38% of the cases and is thought to be a significant risk factor. Mean fentanyl concentrations in the body fluids were quite low: 3.0 ± 3.1 ng/mL (0.3 ± 0.31 μg/dL) in blood and 3.9 ± 4.3 ng/mL (0.39 ± 0.43 μg/dL) in urine, measured by radioimmunoassay. Although the potency of the analogs and the purity of street samples varies considerably, it is probably the general availability of the drug rather than the potency of a particular analog that determines the incidence of overdose deaths.

KEYWORDS: toxicology, fentanyl, death, epidemiology

On 28 Dec. 1979, two unusual drug-related deaths occurred in Orange County, California. The paraphernalia (syringes, needles, and balloons containing white powder) found near the victim's body and the autopsy findings (recent injection sites, pulmonary edema and congestion) suggested heroin overdose. However, toxicological examination of the body tissues and fluids produced negative findings, and chemical analysis of the white powders showed only lactose and trace amounts of an unidentified substance. During the next six months, there were six similar overdose cases in Orange County which appeared to be related to narcotics, but again the toxicological reports were negative. Reports that the victims were using a drug called either "China white" or "synthetic heroin" at the time of their deaths prompted the U.S. Drug Enforcement Administration

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(DEA) to initiate a special study of street samples identified as "China white." Subsequently, alpha-methylfentanyl, a homologue of the potent, synthetic narcotic analgesic fentanyl was identified as the drug responsible for these overdose deaths [*1,2*]. Over the next five years, a number of fentanyl analogs appeared on the street as heroin substitutes, and at least ten analogs have been identified to date [*3*].

Because the author's laboratory had developed a radioimmunoassay for fentanyl and had had experience in detecting fentanyl in biological samples [*4,5*], the laboratory began receiving specimens from coroners' laboratories, forensic science laboratories, and law enforcement agencies from cases in which heroin was suspected but could not be detected. From 1980 to 1988, over 3000 samples were tested by radioimmunoassay and gas chromatography/mass spectrometry. At least 112 overdose deaths were identified which appear to have been caused by fentanyl or one of its ten analogs. In this report, the author reviews the results from the laboratory's chemical analysis of body fluids and tissues from overdose victims, data obtained from coroners' investigative reports, and the autopsy and toxicology findings in an attempt to describe the phenomenon of fentanyl abuse, construct a profile of the typical fentanyl overdose victim, and identify those factors which may have contributed to the fatal overdose.

Methods and Materials

Analytical Procedures

Blood and urine samples were analyzed by a radioimmunoassay (RIA) [*4,5*] that is quite specific for the known illicit fentanyl analogs—alpha-methylfentanyl, parafluorofentanyl, 3-methylfentanyl, and thienylfentanyl—and does not cross-react with other known drugs of abuse. Also, the antisera do not cross-react with the two primary metabolites in man, norfentanyl and despropionyl fentanyl, or with 4-substituted fentanyls such as alfentanil, sufentanil, and carfentanil; however, 4-substituted fentanyls have not appeared as illicit drugs of abuse to date, probably because they are more difficult to synthesize. To remove any potentially interfering material which might result from tissue decomposition, the samples were extracted with organic solvent, heptane/isoamylol (99:1), prior to analysis. This assay has a practical limit of detection of 0.2 ng/mL (0.02 μg/dL). Although the concentrations of the drug are expressed as nanograms of fentanyl per millilitre, these values represent the concentration of all immunologically reactive materials (drugs and metabolites) present in the sample.

Confirmation of RIA Results

The samples were confirmed by gas chromatography/mass spectrometry (GC/MS) when the concentration of fentanyl analogs[2] (as determined by RIA) was high enough (>5 ng/mL or >0.5 μg/dL) or when there was a sufficient sample volume for further analysis. When the fentanyl concentrations were less than 1 ng/mL (0.1 μg/dL), the author attempted to analyze for the nor-metabolites in urine, since the metabolites are generally present at concentrations ten times higher than that of the parent drug. This method has been described previously [*6*] and includes a differential pH extraction of 1-mL samples, extractive acylation with pentafluoropropionic anhydride (PFPA), gas chromatography (GC) separation on a fused silica capillary column (DB-1701), and detection by electron capture detector (ECD) or mass spectrometry (MS) with selected ion monitoring.

[2]For the remainder of this paper, any reference to fentanyl implies fentanyl analogs unless otherwise indicated.

Autopsy, Investigative, and Toxicology Reports

Coroners' autopsy reports were obtained for 75 cases (67% of the total cases), investigative reports were obtained for 89 cases (79%), and toxicological reports were obtained for 89 (79%) cases. Any case in which suicide was suspected or in which fentanyl may have been administered during medical treatment was excluded. The investigative reports gave vital statistics for the victim when available, described the circumstances surrounding the death (such as the location of the victim, the presence of paraphernalia, and fresh needle marks), and provided information on the victim's prior drug abuse history obtained from interviews of family and friends and from police records. The toxicology reports listed all drugs and their concentrations found in the body fluids and tissues at autopsy.

Results and Discussion

During the period 1980 to 1988, 112 coroners' cases were identified by the author's laboratory in which fentanyl was suspected as the cause of death. Nearly all the fatalities occurred in California; however, two occurred in Oregon, one each in Arizona and Nevada, and the three most recent deaths occurred in Pennsylvania. The geographical distribution of fentanyl deaths is both curious and paradoxical. The deaths are confined almost exclusively to the state of California (94% of all deaths), yet they are distributed widely throughout the state with deaths identified in 44 cities and 17 counties. Curiously, none of the fentanyl deaths were from Los Angeles, which is the largest city in the state and has the greatest number of heroin deaths per year. Similarly, only two fentanyl deaths were found in the second largest city, San Francisco. This cannot be explained by the lack of samples analyzed because the laboratory routinely received samples from these two cities during the study period. In addition, this laboratory has analyzed over 600 urine specimens from Los Angeles drug treatment or probation programs and no fentanyl-positive samples were found.

As shown in Fig. 1, fentanyl deaths followed a cyclic pattern, with small increases occurring in 1980, 1982, 1983, and again in 1988. The largest increase, by far, occurred in 1984, which accounts for 40% (45) of the deaths to date. Similar yearly fluctuations have been reported for heroin [*7–10*] and are thought to be due either to an increase in

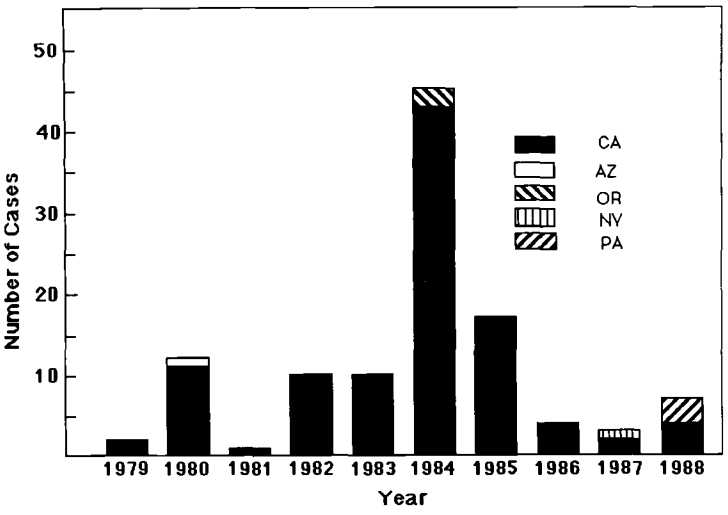

FIG. 1—*Number of fentanyl-related deaths by year and geographical location.*

the amount or potency of the heroin available [9,11–14] or to the appearance of toxic adulterants or cutting agents [7]. The surge in fentanyl deaths in 1984 is most likely due to an increase in both the availability and the potency of the drug. During this time, fentanyl became more widely available throughout the state. For example, more than half of the deaths in 1984 (31 of 45) occurred in San Diego, a site where no fentanyl-related deaths had previously been identified. It was also at this time that 3-methylfentanyl, one of the most potent analogs, was first observed on the streets. The distribution of fentanyl does not appear to be linked to the distribution of heroin in California. Data from the California Department of Alcohol and Drug Programs show that heroin use, measured by three indicators—overdose deaths, emergency room mentions, and admissions to drug treatment programs—increased gradually from 1980, peaked in 1985, then declined [15]. Also, during this period over 30% of the heroin fatalities occurred in Los Angeles and San Francisco, cities which accounted for less than 2% of the California fentanyl fatalities.

Some seasonal variations in heroin deaths have been reported [7,16], with an increase in deaths during the summer and fall months. Other investigators have observed abrupt month-to-month changes, but no seasonal variation [7,11,16]. The author's data suggest slightly more fentanyl deaths in the late fall and winter months, with the fewest deaths in May, but this does not appear significant (data not shown).

Demographics

Table 1 compares demographic data for fentanyl deaths with data for individuals admitted to heroin or general drug treatment programs in California. The "typical" fentanyl overdose victim was 32.5 ± 6.7 years of age (range, 19 to 57), male (78%, compared with 22% female), and Caucasian (50%, compared with 29% Hispanic, 20%

TABLE 1—*Demographic data for fentanyl-related deaths, admissions for heroin treatment in California, and total admissions for drug treatment in California.*

	Fentanyl Deaths[a]	Heroin Treatment[b]	Total Admissions[b]
Age, years			
Mean	32.5 ± 6.7		
Range	19–57		
Age Groups, %			
0–17	0	<1	4
18–20	2	2	5
21–25	15	14	18
26–30	21	29	27
31–44	57	48	40
45 +	5	7	6
Race, %			
Asian	1	1	1
Black	20	14	16
Caucasian	50	49	50
Hispanic	29	36	33
Sex, %			
Female	22	38	37
Male	78	62	63
Employment Status, %			
Employed	32		29
Unemployed	9		51
Unknown	71		

[a]Data obtained from 89 coroners' or police investigative reports.
[b]Data obtained from Ref 15 for fiscal years 1982–1983 to 1986–1987.

Black, and 0.9% Asian). In comparison, the distribution of ethnic groups in California is approximately 59% Caucasian, 23% Hispanic, 8% Black, and 10% Asian. With the exception of age data, the demographic data for fentanyl overdose victims are very similar to those for persons entering drug treatment in California for heroin or other drugs.

According to the investigative reports, 32% of the victims were employed at the time of death. Most were employed as laborers; however, six individuals had occupations that required a special training (for example, nurse-anesthetist, electronic technician, chemist). As shown in Table 2, most of the victims had a prior history of drug dependence (65%) and four individuals were thought to be enrolled in a drug treatment program. When other drug use was reported, heroin was the most often used drug, followed by alcohol, cocaine, and amphetamine. Preexisting medical problems were uncommon; however, depression and pain were mentioned in five cases, followed by diabetes, hypertension, and obesity. Thus, other than drug dependency, the deceased appeared to have few medical problems.

TABLE 2—*Medical and drug use history of fentanyl overdose victims.*[a]

Category	Number
Prior Drug Use	
Yes	58
Yes, but not recently	7
No	4
Not known or no mention	20
Drug Used	
Heroin	28
Heroin and other drugs	6
Alcohol and other drugs	6
Cocaine	3
Amphetamine	2
Intravenous, drug unknown	2
Not known or not mentioned	47
Medical History	
Depression	5
Pain	4
Hypertension	3
Diabetes	2
Obesity	2
Cirrhosis	1

[a]Data obtained from 89 coroners' and police investigative reports.

Circumstances

As shown in Table 3, the victims were generally found dead (56%) or comatose and unresponsive (44%). Only five of the individuals found comatose could be resuscitated; of these, one survived one day after hospitalization, two for four days and two for five days. The victims were usually found in their own or a friend's or relative's residence; however, in three cases they were brought to an emergency room for treatment. When found in a residence, the victims were typically in the bathroom (31%) or bedroom (30%), and occasionally in the living room (17%). The next most common sites were an automobile (generally their own) or hotel, and they were rarely found on the street or in a "shooting gallery."

Paraphernalia was found in 62% of the cases and was typical of that found in a heroin overdose: syringes, spoons or bottle caps used as "cookers," and paper, tinfoil, or balloons

TABLE 3—*Place of death and circumstances.*[a]

	Number (%)
Location	
Own residence	47 (53)
Auto	11 (12)
Friend or relative's residence	10 (11)
Hotel or motel	7 (8)
Street, alley or roadside	4 (5)
Hosptial	3 (3)
Bay	1 (1)
Cafe	1 (1)
Laundromat	1 (1)
Not specified	4 (5)
Where Found[b]	
Bathroom	20 (31)
Bedroom	19 (30)
Living room	11 (17)
Hallway	2 (3)
Not specified	12 (19)
Condition	
Dead	50 (56)
Comatose	39 (44)
Paraphernalia	
Yes	55 (62)
No	21 (24)
No report	13 (15)
Tracks	
Yes	81 (91)
No	5 (6)
Not reported	3 (3)

[a]Data from a review of 89 investigative reports.
[b]Data from those found in a residence, hotel, or motel (64 reports).

containing traces of powder. In Pittsburgh, the drug was generally found in the cutoff corners of plastic sandwich bags.

Autopsy Findings

Autopsy reports were available in 75 of the 112 cases. As shown in Table 4, pulmonary edema and congestion were the most consistent postmortem findings and were present in all but one of the fentanyl deaths. Other common findings were old needle puncture scars and new injection sites (with hemorrhage into surrounding subcutaneous tissue), which were reported in all but 4 cases (data not shown). In addition, generalized visceral and cerebral congestion or signs of early postmortem decomposition were frequently found when the bodies were discovered some time after death (data not shown).

The mean lung weight, often used as an endpoint in opiate epidemiological studies, was 726 + 187 g for the fentanyl victims (range, 300 to 1200 g). This is lower than that typically found in heroin overdose deaths. Levine and Grimes found an average lung weight of 800 g in their study of 40 heroin deaths [*17*], while Helpern and Rho [*16*] and Wetli et al. [*18*] reported mean lung weights in excess of 1000 g. In comparison, only 6 of the fentanyl victims had lung weights greater than 1000 g. These autopsy findings and

TABLE 4—*Autopsy findings.*[a]

Organ System	Number (%)
Lungs[b]	
Pulmonary edema	74 (97)
Pulmonary congestion	73 (96)
Bronchopneumonia	17 (23)
Granulomas	9 (12)
Aspiration of gastric contents	5 (7)
Laryngeal edema	2 (3)
Liver	
Hepatitis	7 (9)
Fatty changes	6 (8)
Chronic inflammation	5 (7)
Cardiovascular	
Cardiomegaly	3 (4)
Atherosclerosis	3 (4)

[a]Data obtained from 75 autopsy reports.
[b]Mean weight 726 ± 187 g; range ± 300–1200 g.

the circumstances at the death scene suggest that fentanyl death occurs rapidly, similar to the "sudden death" occasionally reported with heroin overdose [*19*]. In contrast, bronchopneumonia, which is generally associated with a slower death, was reported in only 17 cases. Although no firm conclusions can be drawn regarding anaphylaxis in response to injected excipient matter, granulomas were reported in only 9 cases and laryngeal edema was reported in only 2 cases. Aspiration of gastric contents was also uncommon, mentioned in only 5 cases. Rapid cessation of respiration seems the most likely cause of death and is consistent with the pharmacological properties of the fentanyls, which are highly lipophylic and reach the brain rapidly after intravenous administration [*20*]. Clinical studies with fentanyl have shown that respiratory depression is maximum within 2 to 5 min [*21*].

Liver pathology was noted in only 18 of the autopsy reports and consisted of fatty changes, chronic inflammation, and hepatitis. The only other organ with any pathological changes was the heart, with cardiomegaly and atherosclerosis mentioned in 3 cases. In no case did a pathologist describe a cardiac lesion significant enough to suggest cardiac stress as a cause of the visceral or pulmonary congestion. It is interesting that, despite a relatively long history of intravenous drug use, the fentanyl victims were relatively healthy and preexisting medical problems were relatively rare.

Toxicology Findings

Fentanyl Concentrations—Figure 2 shows the distribution of fentanyl concentrations in the blood and urine, determined by RIA. Fentanyl concentrations in blood ranged from 0.2 to >50 ng/mL (0.02 to >5μg/dL), and the concentrations in urine ranged from 0.2 to >800 ng/mL (0.02 to >80 μg/dL). If we exclude those cases in which relatively large concentrations were found, the mean drug concentrations were 3.0 ± 3.1 ng/mL (0.3 ± 0.31 μg/dL) in blood and 3.9 ± 4.3 ng/mL (0.39 ± 0.43 μg/dL) in urine. The blood and urine concentrations exceeded 50 ng/mL in 5 cases and 3 cases, respectively. In one case, the blood concentration exceeded 800 ng/mL. Similar drug concentrations have been reported in other fentanyl case studies [*22–24*].

Although 3-methylfentanyl is the most potent of the known fentanyl analogs and is approximately 50 times more potent than fentanyl, it was not the most common drug found in these overdose deaths. Surprisingly, norfentanyl, the metabolite of fentanyl and

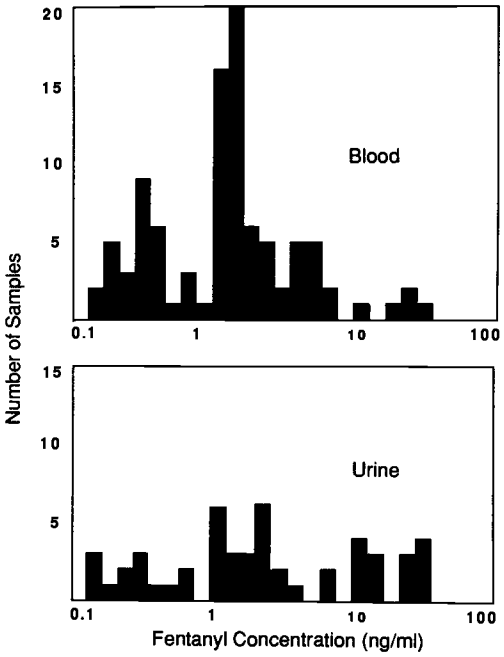

FIG. 2—*Concentrations of the drug found in the blood and urine of fentanyl overdose victims. Values were determined by radioimmunoassay and are expressed in nanograms per milliliter. Values represent the concentration of all immunologically reactive material (drug and metabolites) present in the sample.*

alpha-methylfentanyl, was found approximately twice as often as nor-3-methylfentanyl. This may be due to the fact that the very potent fentanyl analogs have a greater safety margin. For example, it has been shown in experimental animals that 3-methylfentanyl has a safety margin of 1:1662 compared with 1:255 for fentanyl [25]. Alternatively, the more common finding of norfentanyl may simply reflect the greater availability of fentanyl, since our statistics include the large number of deaths occurring in San Diego, which were all due to fentanyl.

Other Drugs Found—Other than the fentanyls, ethanol was the most common drug found at autopsy and was present in 34 (38%) of those cases for which toxicological findings were available (see Table 5). The blood alcohol was greater than 0.1% (100

TABLE 5—*Other drugs found at autopsy.*[a]

Drug	Number
Ethanol	34
Cocaine	18
Morphine/codeine	13
Diazepam/nordiazepam	8
Methamphetamine/amphetamine	5
Propoxyphene/norpropoxyphene	3
Amitriptiline	1
Doxylamine	1
Methadone	1

[a]Data obtained from toxicology reports for 89 cases.

mg/dL) in 20 of these cases, greater than 0.05% (50 mg/dL) in 30 cases, and exceeded 0.2% (200 mg/dL) in 3 cases. Cocaine was the next most common drug found (18 cases), followed by morphine/codeine (13 cases), methamphetamine (5 cases), diazepam (8 cases), and propoxyphene (3 cases). Amitriptyline and doxylamine were also found, each in only one case. These results are surprising since most of the decedents had a prior history of intravenous heroin use; therefore, one might expect residual levels of morphine or codeine or both to be detected. And even though 4 individuals were thought to be enrolled in methadone treatment programs, methadone was found in only one case.

Discussion

Interpretation of the results presented herein are limited by (1) the fact that there is a bias in the samples selected for testing, (2) the anecdotal quality of the investigative reports, and (3) the fact that not all samples found positive by RIA were confirmed by an alternative method, such as GC/MS.

It should be emphasized that the author's laboratory received samples only from cases which appeared to be an opiate overdose, but where no drug (or only trace levels) could be found. Thus, if significant concentrations of opiates or a combination of other drugs were found at an autopsy, the cause of death would be considered an opiate or mixed drug overdose and the case would not have been referred to this laboratory. Also, this study is not a prospective study in which a systematic sampling of overdose cases was conducted but represents analysis of suspect samples submitted by coroners and toxicologists. During the study period, however, fentanyl and the phenomenon of "designer drugs" received considerable attention and it was well known that this laboratory was testing for these drugs. As a result, over 3400 samples from a number of locations with a significant heroin problem throughout the United States were submitted to this laboratory for analysis. Therefore, it is reasonable to assume that the data presented herein are a representative sampling of fentanyl-related deaths.

Data from the investigative reports describing the circumstances at the death scene should be considered cautiously since the body may have been moved, paraphernalia may have been removed by friends or relatives, and those interviewed may be reluctant to reveal the extent of drug use by the deceased. In many cases, there was simply very little known about the deceased.

Finally, this laboratory was not able to obtain GC and MS confirmation of fentanyl and its analogs in all cases. GC/MS confirmation was achieved in the body fluids of 40 cases and in the powder samples, vials, or syringe associated with another 11 cases. Often, there was too little sample remaining for confirmation, since these samples had been analyzed repeatedly, often by more than one laboratory, before being referred to this laboratory. More importantly, the drug levels present in the body fluids were extraordinarily low in all but a very few cases. Of the 105 blood and 55 urine samples tested, 57 samples had fentanyl concentrations (determined by RIA) of 1 ng/mL (0.1 μg/dL) or less. In the few published reports of fatal overdose involving the pharmaceutical Sublimaze® (fentanyl citrate), concentrations in blood and urine ranged between 3 and 27 ng/mL and 6 and 93 ng/mL, respectively [*22–24*]. The illicit analogs of fentanyl have never been administered to human subjects under controlled conditions, and thus there is no information available about their dose-response relationships; however, clinical studies with the parent drug fentanyl have shown that plasma levels above 2 to 3 ng/mL are associated with respiratory depression [*26*]. It is possible, therefore, that the concentrations of the drug (determined by radioimmunoassay) found in the body fluids of fentanyl overdose victims may range from 0.2 to 100 ng/mL; more typically, they will range from 0.2 to 10 ng/mL.

Despite these limitations, a picture does emerge for the "typical" fentanyl overdose death. He is a male of age 32 with a prior history of intravenous drug use, who is using the drug in isolation, perhaps to conceal his drug use (most were found in the bathroom or bedroom). The demographics for the fentanyl victims are quite similar to those for the typical heroin addict in California seeking treatment, which suggests that fentanyl use presents no greater risk to any sex, age, or racial group than does heroin. Nor is there evidence that any preexisting medical problem increases the risk of death from fentanyl use.

The mean age (32.6 years) of the fentanyl victim is slightly higher than that reported for those individuals seeking treatment for heroin or other drug dependency in California, and slightly higher than that reported in most epidemiological studies of heroin overdose. Typically, the heroin overdose victim is in his or her mid-twenties. The range of ages reported in nine studies was 22.4 to 29 years [*14,16,18,27–32*]; however, one study reported a mean age of 31.5 [*33*]. Although age-dependent changes in brain sensitivity to fentanyl have been demonstrated (the analgesic dose decreases 50% from age 20 to 89) [*34*], this is probably not a significant factor since the changes were small or nonexistent in the 20- to 40-year-old age group. From the data available, there appears to be a difference in mean ages between the fentanyl and heroin users; however, the significance of this finding is unclear. At the very least, it is not the young, inexperienced heroin user who is at greatest risk.

There are two factors which seem to heighten the risk of death for the fentanyl user: diminished tolerance and the concurrent use of ethanol. Morphine and codeine were seldom found in the blood, which suggests the victims had not used heroin recently. And although four individuals were reportedly enrolled in methadone programs, methadone was found in only one case, and at trace levels. Ethanol has been repeatedly mentioned as a complicating factor in heroin overdose [*7,10,18,27,29,31,33,35–37*] and some studies have found ethanol present in greater than 70% of the cases [*35*]. This potentially lethal interaction between heroin or fentanyl and ethanol must be emphasized to all those involved in treating drug dependency.

Fentanyl deaths seem to occur rapidly, probably as a result of acute respiratory depression. Most victims were found dead, often with syringes in hand or close to the body. Bronchopneumonia or aspiration of gastric contents were not typically found, and toxic adulterants such as quinine (although rare in California) or procaine are not likely contributing factors.

Although the fentanyl analogs are remarkably potent (alpha-methylfentanyl and 3-methylfentanyl are approximately 200 and 6000 times as potent as morphine, respectively [25]), the incidence of fentanyl-related deaths is probably determined by the general availability of the drug, rather than the relative potency of the analogs. These deaths are generally due to the use of clandestinely manufactured drug rather than to the diversion of pharmaceutical fentanyl since Sublimaze vials were found at the scene in only three cases. Also, when fentanyl rather than an analog was identified, it was contaminated with benzylfentanyl, an inactive analog, but a likely precursor for the illicit synthesis of fentanyl.

To date, most fentanyl-related deaths have been limited to California and the incidence has decreased markedly since 1984. Whether fentanyl use will continue to decrease and remain primarily in California is unknown. These drugs may simply be an anomaly in the overall problem of drug abuse. However, any optimism should be tempered by the fact that at least three clandestine fentanyl laboratories have been discovered outside of California, the most recent one in Pittsburgh, Pennsylvania [*38–40*], and because of the extreme potency of these compounds, a single laboratory could easily supply the demands of a large heroin-using population. Finally, as national and international efforts to restrict

the flow of illicit drugs from foreign sources increase or become more effective, manufacturing synthetic heroin substitutes like the fentanyls in domestic clandestine laboratories could become an attractive alternative.

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References

[1] Allen, A., Cooper, D. and Kram, T. "China White: α-Methyl Fentanyl," *Microgram*, Vol. 14, No. 3., March 1981, pp. 26–32.

[2] Kram, T. C., Cooper, D. A., and Allan, A. C., "Behind the Identification of China White," *Analytical Chemistry*, Vol. 53, 1981, pp. 1379–1386.

[3] Henderson, G. L., "Designer Drugs: Past History and Future Prospects," *Journal of Forensic Sciences*, Vol. 33, No. 2, March 1988, pp. 569–575.

[4] Henderson, G. L., Frincke, J., Leung, C. Y., Torten, M., and Benjamini, E., "Antibodies to Fentanyl," *Journal of Pharmacology and Experimental Therapeutics*, Vol. 192, No. 2, Feb. 1975, pp. 489–496.

[5] Schleimer, R., Benjamini, E., Eisele, J., and Henderson, G. L., "Pharmacokinetics of Fentanyl as Determined by Radioimmunoassay," *Clinical Pharmacology and Therapeutics*, Vol. 23, No. 2, Feb. 1978, pp. 188–194.

[6] Hammargren, W. R. and Henderson, G. L., "Analyzing Normetabolites of the Fentanyls by Gas Chromatography/Electron Capture Detection," *Journal of Analytical Toxicology*, Vol. 12, 1988, pp. 183–191.

[7] Cherubin, C., McCusker, J., Baden, M., Kavaler, F., and Amsel, Z., "The Epidemiology of Death in Narcotic Addicts," *American Journal of Epidemiology*, Vol. 96, No. 1, July 1972, pp. 11–22.

[8] Alexander, M., "Surveillance of Heroin-Related Deaths in Atlanta," *Journal of the American Medical Association*, Vol. 229, No. 6, 5 Aug. 1974, pp. 677–678.

[9] *Epidemiology of Heroin: 1964–1984*, Division of Epidemiology and Statistical Analysis, National Institute on Drug Abuse, Rockville, MD, 1985.

[10] Zimney, E. L. and Luke, J. L., "Narcotic-Related Deaths in the District of Columbia: 1971–1979," *Journal of Forensic Sciences*, Vol. 26, No. 3, July 1981, pp. 462–469.

[11] Desmond, D., Maddux, J., and Trevino, A., "Street Heroin Potency and Deaths from Overdose in San Antonio," *American Journal of Drug and Alcohol Abuse*, Vol. 5, No. 1, 1978, pp. 39–49.

[12] DuPont, R. and Greene, M., "The Dynamics of a Heroin Addiction Epidemic," *Science*, Vol. 181, No. 4101, 24 Aug. 1973, pp. 716–722.

[13] Gottschalk, L. A., McGuire, F. L., Heiser, J. F., Dinovo, E. C., and Birch, H., *Drug Abuse Deaths in Nine Cities: A Survey Report*, NIDA Monograph No. 29, National Institute on Drug Abuse, Washington, DC, 1979.

[14] Greene, M. H., Luke, J. L., and DuPont, R. L., "Opiate Overdose Deaths in the District of Columbia, Part II—Methadone-Related Fatalities," *Journal of Forensic Sciences*, Vol. 19, No. 3, July 1974, pp. 575–584.

[15] *Drug Abuse Trend Report: Fiscal Years 1982 83–1986/87*, California Department of Alcohol and Drug Programs, Sacramento, CA, 1988.

[16] Helpern, M. and Rho, Y., "Deaths from Narcotism in New York City, Incidence, Circumstances, and Postmortem Findings," *New York State Journal of Medicine*, Vol. 66, 15 Sept. 1966, pp. 2391–2408.

[17] Levine, S. B. and Grimes, E. T., "Pulmonary Edema and Heroin Overdose in Vietnam," *Archives of Pathology*, Vol. 95, No. 5, May 1973, pp. 330–332.

[18] Wetli, C. V., Davis, J. H., and Blackbourne, B. D., "Narcotic Addiction in Dade County, Florida," *Archives of Pathology*, Vol. 93, No. 3, April 1972, pp. 330–343.

[19] Johnston, E. H., Goldbaum, L. R., and Whelton, R. L., "Investigation of Sudden Death in Addicts," *Medical Annals of the District of Columbia*, Vol. 38, No. 7, July 1969, pp. 375–380.
[20] Herz, A. and Teschemacher, H. J., "Activities and Sites of Antinociceptive Action of Morphine-Like Analgesics and Kinetics of Distribution Following Intravenous, Intracerebral and Intraventricular Application," *Advances in Drug Research*, Vol. 6, 1971, pp. 79–119.
[21] Harper, M. H., Hickey, R. F., Cromwell, T. H., and Linwood, S., "The Magnitude and Duration of Respiratory Depression Produced by Fentanyl and Fentanyl Plus Droperidol in Man," *Journal of Pharmacology and Experimental Therapeutics*, Vol. 199, No. 2, Nov. 1976, pp. 464–468.
[22] Garriott, J. C., Rodriquez, R., and DiMaio, V. J., "A Death from Fentanyl Overdose," *Journal of Analytical Toxicology*, Vol. 8, Nov. Dec. 1984, pp. 288–289.
[23] Gillespie, T. J., Gandolfi, A. J., Davis, T. P., and Morano, R. A., "Identification and Quantification of Alpha-Methylfentanyl in Post Mortem Specimens," *Journal of Analytical Toxicology*, Vol. 6, May-June 1982, pp. 139–142.
[24] Matejczyk, R., "Fentanyl Related Overdose," *Journal of Analytical Toxicology*, Vol. 12, 1988, pp. 236–238.
[25] Van Bever, W. F. M., Niemegeers, C. J. E., and Janssen, P. A. J., "Synthetic Analgesics. Synthesis and Pharmacology of the Diastereomers of *N*-[3-Methyl-1-(2-Phenyethyl)-4-Piperidyl]-N-Phenylpropanamide and *N*-[3-Methyl-1-(1-Methyl-2-Phenethyl)-4-Piperidyl]-*N*-Phenyl-Propanamide," *Journal of Medicinal Chemistry*, Vol. 17, No. 10, Oct. 1974, pp. 1047–1051.
[26] Cartwright, P., Prys-Roberts, C., Gill, K., Dye, A., Stafford, M., and Gray, A., "Ventilatory Depression Related to Plasma Fentanyl Concentrations During and After Anesthesia in Humans," *Anesthesia and Analgesia*, Vol. 62, 1983, pp. 966–974.
[27] Greene, M. H., Luke, J. L., and Dupont, R. L., "Opiate 'Overdose' Deaths in the District of Columbia: 1. Heroin-Related Fatalities," *Medical Annals of the District of Columbia*, Vol. 43, No. 4, April 1974, pp. 175–181.
[28] Huber, D., Stivers, R., and Howard, L., "Heroin-Overdose Deaths in Atlanta: An Epidemic," *Journal of the American Medical Association*, Vol. 228, No. 3, 15 April 1974, pp. 319–322.
[29] Feuer, E. and French, J., "Descriptive Epidemiology of Mortality in New Jersey Due to Combinations of Codeine and Glutethimide," *American Journal of Epidemiology*, Vol. 119, No. 2, Feb. 1984, pp. 202–207.
[30] Duberstein, J. and Kaufman, D., "A Clinical Study of an Epidemic of Heroin Intoxication and Heroin-Induced Pulmonary Edema," *American Journal of Medicine*, Vol. 51, No. 6, Dec. 1971, pp. 704–714.
[31] Richards, R. G., Reed, D., and Cravey, R. H., "Death from Intravenously Administered Narcotics: A Study of 114 Cases," *Journal of Forensic Sciences*, Vol. 21, No. 3, July 1976, pp. 467–482.
[32] Helpern, M., "Fatalities from Narcotic Addiction in New York City: Incidence, Circumstances, and Pathologic Findings," *Human Pathology*, Vol. 3, No. 1, March 1972, pp. 13–21.
[33] Baselt, R. C., Allison, D. J., Wright, J. A., Scannell, J. R., and Stephens, B. G., "Acute Heroin Fatalities in San Francisco," *Western Journal of Medicine*, Vol. 122, No. 6, June 1975, pp. 455–458.
[34] Scott, J. C. and Stanski, D. R., "Decreased Fentanyl and Alfentanil Dose Requirements with Age. A Simultaneous Pharmacokinetic and Pharmacodynamic Evaluation," *Journal of Pharmacology and Experimental Therapeutics*, Vol. 240, No. 1, Jan. 1987, pp. 159–166.
[35] Luke, J. L. and Levy, M. E., "Heroin-Related Deaths—District of Columbia, 1980–1982," *Journal of the American Medical Association*, Vol. 250, No. 4, July 2/29, 1983, pp. 463–464.
[36] Garriott, J. and Sturner, W., "Morphine Concentrations and Survival Periods in Acute Heroin Fatalities," *New England Journal of Medicine*, Vol. 289, No. 24, 13 Dec. 1973, pp. 1276–1278.
[37] Nakamura, G. R., "Toxicologic Assessments in Acute Heroin Fatalities," *Clinical Toxicology*, Vol. 13, No. 1, 1978, pp. 75–87.
[38] Phillips, E., "China White Chemist, Accomplice Convicted," *The Pittsburgh Post-Gazette*, 9 June 1988, p. 1.
[39] Lewis, N., "Chemist Sentenced in D.C. Drug Case," *Washington Post*, 29 Nov. 1986, p. C1.
[40] Du Pont Chemist Faces Designer Drug Charges," *Chemical and Engineering News*, 1985, p. 5.

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