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A cluster of fentanyl-related deaths among drug addicts in Sweden

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Abstract

During a 16-month period, nine fatalities occurred among white male drug-addicts, where fentanyl was detected at postmortem toxicological analysis. The street samples associated with these cases confirmed the presence of fentanyl as an additive in low-concentration amphetamine powders with caffeine, phenazone and sugar as cutting agents. In seven of the cases, an acute intoxication by fentanyl was considered to be the immediate cause of death, and in one case, it was likely, but no analysis of fentanyl was performed in blood, and in another case the death was suicide by hanging. This appears to be the first report of a cluster of fentanyl-related deaths outside the United States, and the occurrence of fentanyl in combination with amphetamine has not previously been reported. In addition, in all cases, femoral blood was collected, and samples were handled and analysed according to standardized, quality-controlled procedures. The previous history, circumstances surrounding death, autopsy findings, histology and toxicology examination of each case are presented. The gas chromatographic-mass spectrometric method for fentanyl is also described. Fentanyl concentrations ranged from 0.5 to 17 ng g^{-1} blood, and from 5 to 160 ng ml^{-1} urine. Other drugs found were amphetamine (8 cases), ethanol (5 cases) and benzodiazepines (5 cases). Morphine was found in only one case. The average age of the men was 33.9 years (range 22–44); six were found in their own or friend's apartment, two inside buildings (stairways) and one was found outdoors. We conclude that fentanyl is a dangerous substance that should be considered in drug-addict deaths even outside the United States, particularly when the remaining toxicology is unremarkable, and the cause of death cannot be ascertained. © 1997 Elsevier Science Ireland Ltd.

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1. Introduction

Fentanyl has been used as a narcotic analgesic since 1963 when it was introduced by Janssen Pharmaceutica. It became available as 100 μg ml^{-1} solutions in Sweden in 1967, but these were later (1988) lowered to a concentration of 50 μg ml^{-1}. Since fentanyl has a low molecular weight and is lipid soluble it can also be administrated through the skin. Transdermal patches (Durogesic) were introduced in Sweden during 1995 for chronic opioid-related analgesia. After a rapid distribution into tissues, fentanyl is redistributed into the bloodstream and extensively transformed to inactive metabolites in the liver, with N-dealkylation as the main pathway. Approximately 80% of the given dose will be excreted in the urine within 72 h after administration. Less than 8% is excreted unchanged in the urine [1,2].

Fentanyl (usually Sublimaze) has been reported in overdose cases among medical staff with access to this drug [3–6]. In cases not related to medical staff, other analogues such as 3-methyl-fentanyl and alpha-methyl-fentanyl or illicitly manufactured fentanyl are more common findings. In the United States, fentanyl and its analogues have been found in overdose deaths since 1979 [7–9], usually as clusters isolated both in time and location. Outside the United States there have, to the best of our knowledge, not been any report of deaths caused by acute poisoning by fentanyl. In Sweden, no street samples of, or deaths from fentanyl had been encountered until 1994. Since then, 21 street samples (33 items) of powder mixtures have contained fentanyl as a minor constituent and at least 8 people have died from acute fentanyl poisoning.

2. Methods

The forensic pathology units in Sweden perform approximately 5,500 autopsies annually. Screening for pharmaceutical drugs and alcohol analysis are carried out in virtually all cases, whereas screening for illicit drugs is performed in suspect drug addict cases only. Previously, fentanyl was not analysed at the department of forensic chemistry, but a method was developed when the cases reported here appeared.

Information about the previous history of the cases was obtained from the police reports, and in some cases also from medical records and relatives.

Samples for toxicology were collected and handled according to the Swedish national guidelines [10]. Thus, femoral vein blood was collected from both sides, and pooled; urine was collected from the urinary bladder. Potassium fluoride was added to a concentration of 1%, and the samples were stored at +4°C until analysed (except during transportation) and then frozen. All fentanyl analyses were done retroactively, after initial freezing of the samples.

2.1. Analysis of post mortem material

Ethanol was analysed by head-space gas chromatography with flame ionization detection. Amphetamine, opiates and tetrahydrocannabinol were analysed by gas chromatography-mass spectrometry (GC-MS) and medical drugs were analysed using neutral and basic extraction, followed by gas chromatography with nitrogen-phosphorous detection. All methods are internally and externally quality controlled. For fentanyl, GC-MS methods for blood and urine were developed as described below.

2.2. Reagents

Fentanyl and d5-fentanyl were purchased from Radian corp. (Austin, TX) Iso octane, potassium hydroxide and methanol were of analytical grade and purchased from Merck (Darmstadt, Germany). Standard solutions of fentanyl and d5-fentanyl were prepared in methanol and stored frozen. Samples for standard curves and controls were prepared from drug free urine and blood by addition of standard solutions prior to extraction.

2.3. Instrumentation

Radio immuno assay (RIA) of urine samples were performed on an LKB 1275 (Turku, Finland) gamma counter using DPC (Los Angeles, CA) Coat-A-Count RIA kit as proposed by the manufacturer. Threshold was 0.5 ng ml^{-1} urine.

GC-MS analysis was performed on a Hewlett Packard (Palo Alto, CA) HP5890 Series II gas chromatograph interfaced to a HP5972A mass spectrometer. The capillary column was a 30 m HP-5 MS with i.d. 0.25 mm and 0.25 μm film thickness. Helium was used as carrier gas at a constant flow of 1.0 ml min^{-1}. A 2 μL aliquot of the samples was injected in splitless mode using a silanized 250 μL liner, packed with a small plug of silanized glass wool. Injector and interface temperatures were 210°C and 280°C, respectively. The oven temperature was kept at 85°C during the 1 min splitless time and then increased at 25°C min^{-1} to 280°C and kept there for 4.5 min. For quantitation, ion m/z 245.2 for fentanyl and ion m/z 250.2 for d5-fentanyl were used. Qualifiers were ions m/z 189.1 and m/z 146.1 for fentanyl and ions m/z 194.1 and m/z 151.1 for d5-fentanyl.

2.4. Extraction

If urine was available the samples were screened with RIA prior to analysis with GC-MS. Depending on the RIA result, 0.2 to 1.0 ml urine was used for the GC-MS analysis. For blood 0.5 or 1.0 g was used. Urine or blood were added to a 10 ml screw capped glass tube. Internal standard (10 ng) and 0.5 ml 2 M potassium hydroxide were added and the samples were extracted for 10 min with 2 ml iso octane. The samples were then centrifuged for 5 min at 5000 rpm (+5°C) and the organic phase was transferred to a new tube and evaporated under a stream of nitrogen. The residue was reconstituted in 40 μL of iso octane and transferred to GC-MS micro vials for injection.

2.5. Validation

Linear calibration curves were established between 0.5–40 ng ml^{-1} urine and 0.5–10 ng g^{-1} blood. The threshold concentration for detection was set at 0.5 ng ml^{-1} for both urine and blood. For analysis of blood the between-day coefficient of variation (CV) at 2.0 ng g^{-1} and 10.0 ng g^{-1} were 11.6% (n=6) and 5.2% (n=6), respectively. Mean concentrations were 2.08 and 9.97 ng g^{-1}, respectively. For urine at the same levels between-day CV was 10.3% (n=5), and 4.0% (n=5), respectively and mean concentration were 2.26 and 10.3 ng ml^{-1}, respectively. The extraction recovery of fentanyl from blood and urine were 76% (n=5) and 77% (n=5), respectively.

2.6. Analysis of street samples

Street samples were analysed by gas chromatography with FTIR detection and GC-MS for identification of active substances and cutting agents. Amphetamine was quantitated using gas chromatography with flame ionization detection. Sugars were identified using thin layer chromatography (TLC). The analysis of fentanyls in street samples included fentanyl, tiofentanyl, beta-hydroxy-fentanyl, 3-methylfentanyl, alpha-methyl-fentanyl, acetylfentanyl, benzylfentanyl and para-fluoro-fentanyl. Analysis of street samples were performed at the National Laboratory of Forensic Science, Linköping, Sweden.

3. Results

3.1. Case 1

A 29-year-old man with a history of drug abuse was found dead in a casually hired apartment. A large amount of whitish-pinkish foam was seen in and around his mouth. He was fully dressed, and was lying on his back in his bed with his hands clasped behind his nape. On an adjacent desk were found several syringes and needles, and some white powder.

3.2. Case 2

The victim was an obese 26-year-old man, who had been smoking and injecting heroin during the night and who was found dead in a friend's apartment, sitting in a chair with his head leaning against a table. Around his right wrist was a waist-belt tightly applied, and right below it, a fresh injection mark was found. A syringe and a needle were lying on the floor beside him.

3.3. Case 3

A young man, aged 22, was found dead, lying on his back on a couch in his apartment. On an adjacent table, a small bag containing white powder, was found. The

deceased had been abusing drugs for years. The skin could not be accurately examined regarding the possible presence of injection marks due to putrefaction.

3.4. Case 4

A 40-year-old man was found on the first floor in an apartment house, beside the elevators. An ambulance was required, and ECG-registration revealed a slow heart rate of 30 beats min^{-1}; however he was pulseless and did not breathe. Resuscitation attempts were unsuccessful. When the man was discovered, he was fully dressed, but also partly wrapped in a wet towel. A bag with ice was found in his pocket. No syringes or needles were found at the scene. Police investigation revealed that the deceased had been visiting a drug dealer in the building a couple of hours before he was discovered.

3.5. Case 5

The deceased was a 44-year-old man with a long history of drug abuse, particularly of amphetamine. During the last seven months, he had just been drinking alcohol periodically. The night before he was discovered, he had bought (what he was told was) heroin. Later on, he and a friend of his, had injected the drug. The friend later claimed that he himself, had immediately become dizzy, and fallen asleep. Both men were found by a girl-friend the next morning, who called for an ambulance, but the man who died had been dead for hours. He was sitting in a couch, with his clasped hands on his belly, and a syringe was found in an ashtray on the table beside the couch.

3.6. Case 6

This fatality concerns a 42-year-old drug-addict, who was found in the stairway on the second floor of an apartment house, lying face-down, apparently dead. There were no syringes or needles at the scene. No resuscitation was carried out. In a pocket, a small bag with white powder was found. No injuries suggesting a fall were found on the body.

3.7. Case 7

The deceased was a 42-year-old man with a long history of amphetamine abuse. He was found dead in his girlfriend's apartment, lying in the bed. According to the girl-friend, he had been alive just five minutes before she discovered him, holding a syringe, which contained fluid mingled with blood. He seemed unconscious, and she tried to awake him, pouring water over his face. After a few minutes, she dragged him to the floor and started resuscitation. Then she asked a neighbour to call for an ambulance, but the man was dead when the emergency staff arrived. A number of small drug-containing bags were found on a table in the apartment, along with several used needles, syringes and tablets.

3.8. Case 8

An 34 year old male was found dead in his home, hanging in a rope. Only ten minutes previously he and his girl-friend had had an argument. For several years, the deceased had abused drugs, and during the last five days, he had been injecting amphetamine regularly.

3.9. Case 9

A 26-year-old man with a long history of cannabis and peroral amphetamine abuse was found dead, outdoors, next to an underground station, 30 minutes after being seen alive. There were no findings or circumstances suggesting homicide.

A summary of the histological findings, the body mass indexes (*BMI*) and organ weights are displayed in Table 1.

Generally, all victims had some degree of organ congestion, and massive pulmonary edema was apparent in most of the cases. All were HIV negative, but at least five had positive serology for hepatitis C. *BMI* values were generally in the normal or even high range.

The analytical results in blood and urine are shown in Table 2. The place and date of death of the victims are also displayed in this table. In eight of the nine cases, amphetamine was found in blood or urine. Morphine was only found in one case.

The 21 street samples (33 items) encountered in Sweden were sold as either amphetamine or heroin, and correlated well both in time and geographically with the overdose cases (Fig. 1). All street samples contained amphetamine at low concentrations, but no other illicit drugs except fentanyl. Those that were quantitatively analyzed contained from below 1% up to 7%. The cutting agents were caffeine in combination with phenazone (9 cases), caffeine: and sugar (14 cases), only caffeine (7 cases), only phenazone (1 case) and 2 cases with caffeine, phenazone and sugar. No other fentanyl analogues were found in the street samples.

4. Discussion

4.1. Street samples

In Sweden, no street samples of, or deaths due to fentanyl had been encountered until 1994. Between April 1994 and August 1995, 21 street samples (33 items) of powder mixtures have contained fentanyl as a minor constituent. No quantitation of fentanyl was made but it was always present in trace amounts. The cutting agents were caffeine, phenazone and sugar with a maximum concentration of 7% amphetamine. None of the street samples contained heroin. This is unique as all previously reported street samples of fentanyl have been either the pure product [7–9] or a mixture with heroin [2]. These were sold as synthetic heroin or "China White", or under other names usually connected with heroin. The powders encountered in Sweden were either sold as amphetamine or heroin.

Table 1
Body mass index, organ weights and post mortem findings

Case	*BMI*[a]	Organ Weights (gram)						Autopsy Findings
Sex/Age		Brain	Lungs	Heart[b]	Liver	Kidneys	Spleen	
1. M/29	20.89	1,635	870	360 (0.46)	1,875	365	260	Acute organ congestion. Pulmonary emphysema and edema.
2. M/26	37.66	1,400	1,185	450 (0.49)	2,900	435	385	Acute organ congestion. Pulmonary edema. Acule bronchitis. Fatty infiltration of the myocardium.
3. M/22		1,360	1,250	380	1,440		220	Putrefaction.
4. M/40	23.12	1,490	2,235	400 (0.5)	2,540	360	770	Acute organ congestion Pulmonary edema and emphysema. Perivascular fibrosis and stromal condensation in the myocardium. Liver cirrhosis with splenomegaly.
5. M/44	28.06	1,611	1,284	366 (0.44)	1,782	321	259	Acute organ congestion. Pulmonary eduma and emphysema. Liver cirrhosis.
6. M/42	18,61	1,636	1,263	393 (0.62)	2,061	343	182	Hemosederin-laden macrophages in the lungs.
7. M/42	29.06	1,435	1,280	385 (0.46)	2,035	416	294	Acute organ congestion. Pulmonary edema and emphysema. Hemosederin-laden macrophages in the lungs Subendocardial hemorrhages. Liver cirrhosis.
8. M/34	20.42	1,340	1,445	330 (0.56)	1,800	310	180	No remarkable pathological findings of internal organs.
9. M/26	18,08	1,470	760	270 (0.48)	1,120	210	140	Acute organ congestion Patchy supleptomeningeal hemorrhages. Myocardium with focal mytocytolysis in various stages. Foci with hemosederin-laden macrophages in the lungs.

[a]*BMI*-Body Mass Index.
[b]Numbers in parentheses are percent of body weight.

The reason why fentanyl was added to the preparations is unclear. An unintentional contamination of fentanyl to amphetamine preparations constitutes one alternative, but is unlikely as the amphetamine concentrations are much lower than those in other samples of amphetamine that have been quantified. The preparations are therefore more likely to have been intentional fentanyl preparations for introduction to the Swedish market. Thus, the amphetamine could have been added to counteract the central nervous depressant effects of fentanyl in the same way as when cocaine is used together with heroin.

4.2. Toxicological and pathological findings

In case 3, amphetamine was not detected. Thus, we suspected that the deceased might have obtained fentanyl from a medical facility. However, we were unable to find any

Table 2
Toxicological findings

Case	Femoral blood ($\mu g\ g^{-1}$)	Urine ($\mu g\ ml^{-1}$)	Site/Date
1	Ethanol 0.51 Amphetamine 0.8 Nordiazepam 0.1 Fentanyl 0.004	Ethanol 0.78 Fentanyl 0.011	Malmö 1994-04-28
2	Amphetamine 0.2 Morphine 0.02 7-aminoclonazepam 0.15 Fentanyl N.A.	Fentanyl 0.029	Malmö 1994-07-05
3	Ethanol 0.30 Fentanyl 0.005	N.A.	Borlänge 1994-08-O8
4	Amphetamine 2.2 Codeine 0.1 Propoxyphene 0.1 Fentanyl 0.017	Fentanyl 0.064	Helsingborg 1994-10-08
5	Ethanol 3.0 Amphetamine 0.05 Nordiazepam 0.1 Fentanyl 0.005	Ethanol 3.4 Fentanyl 0.005	Vaggeryd 1995-02-02
6	Ethanol 1.6 Amphetamine 0.1 Fentanyl 0.006	Ethanol 1.7 Fentanyl 0.076	Värnamo 1995-02-16
7	Amphetamine 3.9 Orfenadrine 0.2 Diazepam 0.1 Nordiazepam 0.1 Fenazon 0.6 Fentanyl 0.009	Amphetamine>100 Fentanyl 0.160	Jönköping 1995-04-01
8	Amphetamine 0.3 Norephedrine 0.5 Diazepam 0.1 THC 0.004 Fentanyl 0.0005	Ethanol 0.13 Fentanyl 0.012	Växjö 1995-07-28
9	Amphetamine 1.1 THC 0.003 Fentanyl 0.002	N.A.	Stockholm 1995-08-01

Results for ethanol are presented as $mg\ ml^{-1}$ blood or urine.
N.A.-Not available.

medical records that supported this theory. In all other cases, amphetamine was detected along with fentanyl. This is also in accordance with the analytical results of the examination of the street samples. Of the nine cases presented, one death was by certainty not due to intoxication, but hanging. The blood concentration of fentanyl in this case was four times lower than in any of the intoxications. The median blood concentration of fentanyl in the intoxication cases was 6.8 ng. The levels of fentanyl detected in these cases are of the same magnitude as in previously reported cases [2], even though analysis was carried out long time after the ordinary toxicological examination, suggesting that no significant degradation of fentanyl during the storage

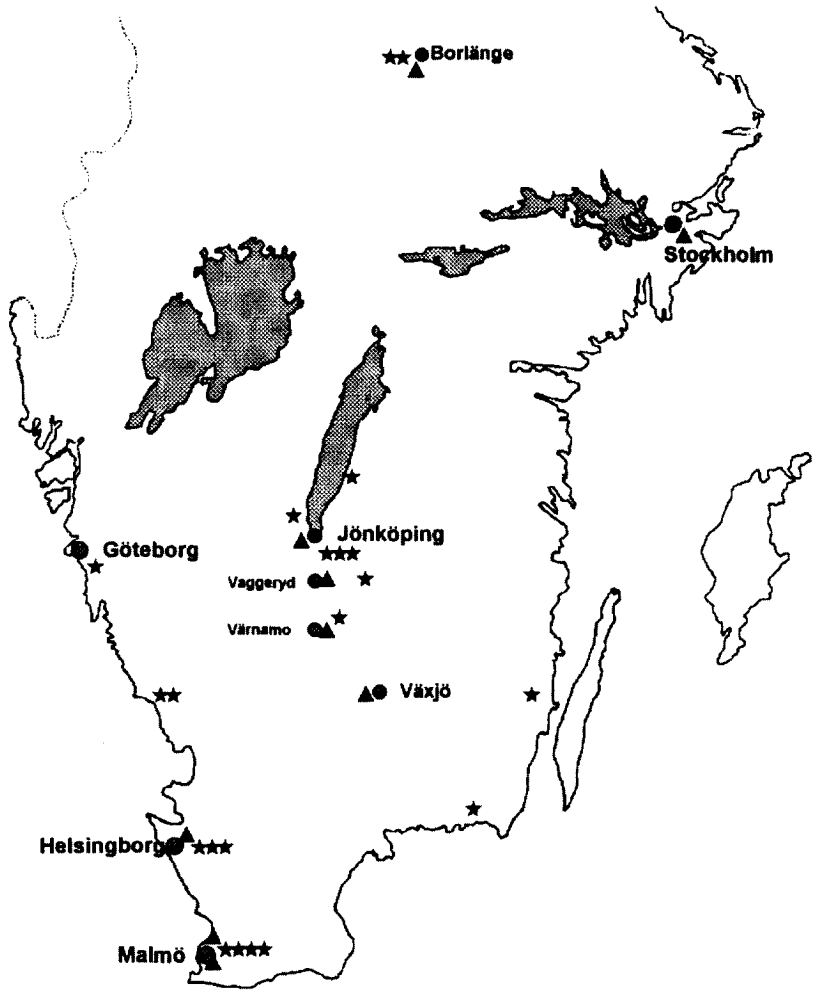

Fig. 1. Map of southern part of Sweden with locations of the suspected overdose cases (triangle), and the street samples of fentanyl (star).

occurred. All blood samples were collected from the femoral veins in order to minimize the risk for artefactual high levels due to postmortem redistribution.

As fentanyl is not included in the routine drug screen, the first positive case (number 6) was revealed when a street sample containing fentanyl was found at the death scene.

The cases from 1994 were discovered when a retrospective investigation was carried out on all autopsy samples, where the main analytical finding was amphetamine, and the time and place of death matched any of the street samples containing fentanyl. In two of these cases, fentanyl had been suspected but no analytical method was available at that time. Another investigation was carried out on samples collected from 98 autopsy cases from all Sweden during a two month period, where overdose from illegal drugs was

suspected as the cause of death. Fentanyl was not found in any of these cases using RIA screening in urine. Since case 9 (August 1995) no additional fentanyl-related deaths or street samples of fentanyl have been encountered. Hence, the deaths described here forms a cluster, that appeared when a limited amount of fentanyl powder was distributed in a certain part of the country, even though the time frame was extended.

Whenever fentanyl was found, it was likely to have caused death or contributed to death, which supports the opinion that this drug is highly toxic. Its analgetic effect is considered to be approximately 100 times that of morphine on weight per weight basis [1]. Although fentanyl rarely causes histamine release as opposed to most other opioids [2], significant pulmonary edema was seen in most of the cases despite the lack of other opioids (apart from case 2). The toxicity of fentanyl is potentiated by ethanol, neuroleptics, hypnotics and benzodiazepines [2]. On the other hand, muscle rigidity caused by fentanyl may be counteracted by benzodiazepines. In case 5, a potentiation of the toxicity of fentanyl by ethanol was likely. It is also possible that the comparatively high concentrations of amphetamine in cases 4 and 7 have contributed to death. However, much higher concentrations can be seen without severe symptomatology and conversely, intracerebral bleedings may be encountered when concentrations are below 0.5 $\mu g\ g^{-1}$ blood (unpublished observations). Thus, amphetamine's contribution to these fatalities is difficult to assess.

In five cases, benzodiazepines were detected, but these findings were probably of minor importance since the concentrations were low. The lungs from three of the deceased contained foci of haemosiderin-laden macrophages, compatible with, although not pathognomonic of, previous bleedings owing to mixed drug abuse of many year's duration [11,12]. This number should be considered to be a minimum, since the amount of lung tissue available for histology examination varied between the cases. This also applies to the heart specimens. In case 9, recent and older pathologic changes were found, suggesting that an acute heart dysfunction may have contributed to the death of this young man.

As judged by the *BMI*-index and past history, the drug addicts in this series were not in bad physical condition, in fact, several of them were obese.

5. Conclusion

We conclude that fentanyl is a dangerous substance that should be looked for in drug-addict deaths even outside the United States, particularly when the remaining toxicology is unremarkable, and the cause of death cannot be ascertained. Also, the analysis of street samples containing only small amounts of amphetamine, should include a search for fentanyl and its analogues. The GC-MS method described, is rapid and has sufficient sensitivity to detect fentanyl in blood and urine at subnanogram levels. Successful introduction of fentanyl as a substitute for heroin on the Swedish drug market seems unlikely, for several reasons, especially as the potency of fentanyl and its analogues together with the difficulties involved in preparing homogenous powders makes it more hazardous than heroin.

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