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# A Cluster of Fentanyl-Laced Heroin Deaths in 2015 in Melbourne, Australia

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## Abstract

The prevalence of opioid use in therapeutic and recreational settings has steadily increased throughout the western world. The addition of fentanyl into heroin products can produce potentially dangerous consequences, even to opioid tolerant individuals who may be unaware of such additions. Following an observed spike of heroin-fentanyl related deaths in Melbourne, Australia, a study was undertaken to determine the prevalence of these cases. All reportable deaths occurring in Victoria during 2015 and submitted to the toxicology laboratory were analysed using LC–MS-MS to confirm the combination of the heroin marker 6-acetylmorphine and/or morphine, and fentanyl. Over 4,000 coronial cases in 2015 underwent toxicological analysis for these drugs, there were nine cases identified that involved fentanyl-laced heroin. There was no specific mention of fentanyl use in any of these cases. All occurred within 2 months and in two distinct locations. The first four deaths occurred within 3 days of each other, in neighboring suburbs. The ages ranged from 25 to 57 years with an average of 40 and median of 37 years, and consisted of eight males and one female. The average and median femoral blood concentration of fentanyl was 18 and 20 ng/mL (range: <1–45 ng/mL), and morphine 140 and 80 ng/mL (range: 20–400 ng/mL), respectively. All nine cases had 6-acetylmorphine detectable in blood. Urine analysis was also performed where available. A syringe, powder and spoon found at the scene of one case were also analysed and found to be positive for both heroin and fentanyl, which supported the likelihood of fentanyl-laced heroin. This is the first reported case series of fatalities involving heroin and fentanyl outside of North America in published literature. These findings may help inform public health and prevention strategies serving to decrease the potential for such fatalities in the future.

## Introduction

The powerful synthetic opioid fentanyl is used therapeutically both as an effective painkiller available in transdermal (Denepax, Durogesoc, Dutran, Fenpatch), transmucosal (Abstral) or lozenge (Actiq) and buccal (Fentora) forms, in addition to induction for anesthesia during surgery by intravenous administration (Aspen, B. Braun, DBL, GH, Sublimaze) (1–4). The availability of fentanyl to outpatients, primarily through the slow release formulation for self-management of chronic pain has increased in recent years (5, 6). Although classified as a Schedule 8 "controlled drug" in Australia, the increase in legitimate use has also coincided with a rise in the incidence of fentanyl misuse from diversion (2), resulting in many reports of fatal fentanyl overdoses, frequently spiking when heroin availability is low (5, 7–27).

Fentanyl has a rapid onset of action and binds to opioid μ-receptors in the brain, however, at 50–100 times greater potency weight-for-weight than heroin or morphine (11, 28, 29). This can cause respiratory central nervous system (CNS) depression within minutes of intravenous use, with the effects of fentanyl and heroin said to be virtually indistinguishable (3, 30–33).

Alarmingly, it has been reported that fentanyl has been included in heroin formulations without the user's knowledge (24, 33, 34), with one Canadian study that suggesting up to 73% of illicit fentanyl use was unbeknownst to the user (33). Heroin (diacetylmorphine) rapidly crosses the blood-brain-barrier to elicit euphoria and is converted via esterase activity mainly into the active metabolite 6-acetylmorphine (6-AM) which is then further metabolized into morphine. The combination of both opioids may exacerbate adverse effects and lead to increased CNS depression with potentially fatal outcomes, even to users with a level of opioid tolerance following a history of heroin use.

Clusters of fentanyl-laced heroin seizures marketed under the street names Tango and Cash, Blue Bag, Drop Dead, Flatline, Fefe, Poison, or China White, has coincided with the discovery of clandestine laboratory fentanyl production in the 1980s, 1990s and 2000s in Northern America (35–37), and limited reports in Europe (17). Accordingly, outbreaks of survival and fatal overdoses with this specific opioid combination have been reported sporadically to occur during these reported seizures in the United States and Canada (10, 12, 23, 24, 33, 35–41).

The Victorian Institute of Forensic Medicine (VIFM) is a purpose built statutory authority situated in Melbourne, Australia. The Institute serves a population of over 5 million people across the state of Victoria and performs the medico-legal death investigations of decedents reported to the a Victorian Coroner. The toxicology laboratory within the VIFM receives blood specimens taken during admission of the body to the mortuary, as well as at autopsy where a larger range of biological specimens are collected, in addition to further blood samples.

In this article, we report a cluster of deaths resulting from heroin and fentanyl combinations over a period of 2 months.

## Experimental

### Specimens

Peripheral leg blood (drawn from the femoral vein) was collected as soon as practicable after a body was admitted to the mortuary at the VIFM. These samples were transferred to the laboratory and were analyzed for alcohol, common drugs and poisons on the same day and then stored at 4°C. Where possible, urine samples were collected at autopsy from the same deceased person, along with additional specimens all of which were stored at −20°C until analysis. Blood was collected in 10 mL polypropylene tubes containing 1% sodium fluoride/potassium oxalate preservative.

### Toxicological screening

Blood samples from each case were analyzed by a fully validated liquid chromatography–tandem mass spectrometry (LC–MS-MS) procedure on a Sciex™ 3200 Q-trap™ operating in positive electrospray ionization mode monitoring 132 analytes including amphetamines and other stimulants, antidepressants, antipsychotics, benzodiazepines, cocaine, opioids and some major metabolites (42). This was based on the method previously published using the same mobile phase and column, and the multiple reaction monitoring (MRM) of a minimum of two transitions per drug for each analyte (43). The lower limit of quantification (LLOQ) for fentanyl was 1 ng/mL, whilst 6-AM, morphine and codeine were 10 ng/mL in blood. Similarly, urine specimens were analyzed on an identical LC–MS-MS instrument with the method differing in the extraction technique, and with the inclusion of an additional 103 monitored analytes (231 in total) (44). The LLOQ in urine for was 10 ng/mL for fentanyl, 6-AM, morphine and codeine. In both methods if the concentration of an analyte was below the LLOQ, it was deemed detected above the limit of detection (LOD) if satisfactory ratio of the transitions was observed all at a signal to noise ratio greater than 3:1. In order for comprehensive toxicological screening, both methods were able to detect subtherapeutic levels of the most commonly used drugs and poisons in Australia. Quality controls were run with each analysis. Precision and reproducibility were evaluated at three concentrations and were generally <15% for all reported analytes.

The detection of 6-AM was targeted to conclusively indicate heroin use, however, due to its rapid metabolism in blood to morphine, 6-AM is not commonly detected following the use of heroin. Therefore, where available the analysis of urine was undertaken to provide a longer window of detection.

Occasionally the laboratory received exhibits for analysis as part of death investigations either when the deceased is admitted to the mortuary or via separate delivery from an investigating police officer. Screening of exhibits consisted of methanolic washes or dilutions of the specimen and analysis performed using the laboratory's previously published long-standing general unknown GC–MS technique (45).

### Case selection

Following a perceptible sudden rise in the detection of fentanyl and heroin combinations, a search of the VIFM case management system was performed to identify all reported deaths in 2015 where fentanyl and 6-AM and/or morphine were detected in either blood or urine specimens. Identified cases were reviewed in-depth to ensure that the deceased did not receive medical intervention, have a valid prescription for fentanyl or morphine, or have any other legitimate situation that could explain the fentanyl or morphine use. Additionally, circumstances of the case provided by the initial police investigation were used to determine whether fentanyl may have been a contaminant of heroin, or taken concurrently.

## Results

Of the nearly 6,600 coronial cases received at the VIFM in 2015, ~4,200 underwent toxicological analysis in the laboratory of which there were 168 overdoses involving heroin. Table I describes nine cases that fit the selection criteria and were toxicologically analyzed and confirmed to contain a combination of 6-AM (and/or morphine) and fentanyl. The ages ranged from 25 to 57 years with an average age of 40 (median of 37) and consisted of eight males and one female. All blood samples were collected on admission to the mortuary from the peripheral leg region within 24 h of death, in an attempt to limit the postmortem redistribution of the drugs. Concentrations ranged from 2 to 45 ng/mL in eight cases with quantifiable fentanyl, with another case detecting fentanyl <1 ng/mL. The average concentration was 18 ng/mL (median 20 ng/mL). Five cases were found to have 6-AM quantifiable concentrations, with the remaining four cases detecting 6-AM <10 ng/mL. All nine cases had free morphine concentrations in blood that ranged from 20 to 400 ng/mL, with an average of 140 ng/mL (median of 80 ng/mL). Free codeine was detected in the blood of six cases. Urine results largely complemented blood results except for Case 3 where there was no presence of fentanyl in the urine, although there was a significant concentration of 19 ng/mL in the blood. Available urine was not always examined if a cause of death could either be established

**Table I.** A cluster of users fatally overdosing on a combination of fentanyl and heroin over a short period within melbourne's inner east (A) and outer south-east (B) regions

| Case | Date of death in 2015[a] | Sex age (y) | Region | Circumstances | Blood concentration (ng/mL) | | | Urine concentration (ng/mL) | | | Other drugs detected in blood or urine (if analyzed) | Exhibits |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 6-AM | Morphine | Fentanyl | 6-AM | Morphine | Fentanyl | | |
| 1 | September (late) | M 57 | A | Methadone permit | 30 | 300 (C) | 22 | Urine analysis not performed | | | Methadone, methamphetamine, Δ9-THC | – |
| 2 | September (late) | F 37 | A | 10-yr heroin user. Methadone permit | 60 | 400 (C) | 20 | Urine analysis not performed | | | Methadone, diazepam, nordiazepam, oxazepam | – |
| 3 | September (late) | M 46 | A | Syringe in close proximity | 20 | 100 | 19 | 500 | ND (C) | ND | Amphetamine, cocaine, benzoylecgonine, Δ9-THC | – |
| 4 | October (early) | M 25 | A | Recent heroin user. Syringe found *in situ* | <10[b] | 30 | 2 | 30 | 3000 (C) | <10[b] | Fluoxetine, olanzapine, quetiapine, temazepam | – |
| 5 | October (early) | M 34 | B | 20-yr heroin user | <10[b] | 20 (C) | 27 | 60 | >1000[c] (C) | 1200 | Paracetamol, buprenorphine | Syringe, powder and spoon = heroin and fentanyl |
| 6 | October (mid) | M 37 | A | Syringe in close proximity | 10 | 40 (C) | 5 | <10[b] | >1000[c] (C) | <10[b] | Diphenhydramine, mirtazapine, oxazepam, paracetamol | – |
| 7 | October (late) | M 32 | B | Syringe found *in situ* | <10[b] | 20 (C) | 3 | 40 | 300 (C) | <10[b] | Δ9-THC | – |
| 8 | November (late) | M 52 | A | Unconscious in toilet block | <10[b] | 80 | <1[b] | <10[b] | 4000 (C) | <10[b] | Ethanol, methamphetamine, Δ9-THC, diazepam, temazepam, oxazepam | – |
| 9 | November (late) | M 37 | A | Heroin user. Methadone permit. Syringe in proximity | 20 | 300 (C) | 45 | Urine analysis not performed | | | Methadone, promethazine, Δ9-THC | – |
| X[d] | September (late) | F 23 | B | GHB and alprazolam user, drug paraphernalia at scene | ND | ND | 12 | No urine available | | | GHB, alprazolam, amphetamine, zolpiclone | Powder = heroin and fentanyl |

[a]Early, mid and late = 1st to 10th, 11th to 20th and 21st to end of each month, respectively.
[b]Drug detected below lower limit of quantitation (LLOQ) but above limit of detection (LOD).
[c]Drug reported above the upper limit of quantitation (ULOQ).
[d]Demonstrates additional evidence of fentanyl-laced heroin, however, not included in the case series as heroin was not determined in the available biological specimens.
ND, not detected, (C), codeine detected.

by the blood results and/or urine analysis was not specifically requested by the pathologist or coroner (i.e., Cases 1, 2 and 9).

Other drugs detected in either the blood or urine of each case were as follows: an antipsychotic and anthistamine in one case; analgesics, antidepressants, cocaine and amphetamines in two cases; benzodiazepines on three occasions; and cannabis and other opioids (methadone or buprenorphine) on four occasions. The concurrent use of some of these drugs with the heroin and fentanyl combination may have exacerbated death in the case series (Table I).

Of the nine cases included in this study, the first four occurred over a 3-day period all located within an ~3 $km^2$ radius in Melbourne's inner east suburbs (region A). This area is well known for illicit drug use, specifically heroin. Following a 2-week period another death occurred and then over a month later another two deaths were reported in this region—a total of seven. During the period of these latter three deaths, two more deaths occurred in neighboring suburbs ~35 km south-east of Melbourne (region B).

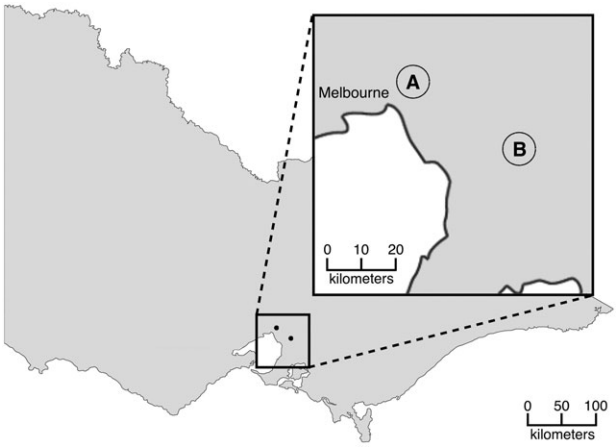


**Figure 1.** Map of the Victorian state showing the two distinct regional clusters A (inner east of Melbourne) and B* (outer south-west ~35 km from Melbourne) where the 9 fentanyl and heroin combination deaths occurred. *Region where exhibits were located have confirmed by the laboratory to contain fentanyl-laced heroin.

Figure 1 describes the proximity between the deaths and demonstrates the two distinct clusters. All deaths were indicated as combined drug toxicity, many dying with the needle *in situ* or in close proximity.

A syringe, powder and a spoon were found at the scene in Case 5 and all of these exhibits returned a positive result for a combination of heroin and fentanyl. An additional case, 'Case X' was received during the study period that had a blood fentanyl concentration of 12 ng/mL, but no indication of heroin use and no urine was available for further analysis, hence, it was not included in this study. However, powder found at the scene was received with this case, and upon analysis of this exhibit it also returned positive for heroin and fentanyl. The location of this case was within region B (Figure 1) and showed a similar composition to the exhibit specimens from Case 5.

## Discussion

The increased use of opioids has been observed in Australia (46, 47) and throughout the world (48, 49), including a sharp rise of licit and illicit fentanyl use which has commonly resulted in death when abused (5, 18, 22). Over the last few decades, clusters of deaths caused by fentanyl-laced heroin have been reported. Table II summarizes the current available literature that demonstrated explicit fentanyl and heroin use with, at least, fentanyl blood concentrations collected from peripheral sites and provided. These reports originated from mid-2005 onwards and only from the United States. In Wayne County, Michigan, in an 11-month period between 2005 and 2006, the Medical Examiner's Office documented 101 fentanyl and heroin-related fatalities, of which over a third were female (10). During a similar timeframe, there were 107 fentanyl deaths in Massachusetts, combined with opiates, cocaine or both, 16 of which were with illicit morphine use and 1 had detectable 6-AM (40). However, this study was not included in Table II as it could not conclusively demonstrate fentanyl and heroin use in combination. At the same time over 18 months, Cook County, Illinois, experienced a series of approximately 350 fentanyl intoxication deaths, with 15% (~52) also indicating heroin use (12). New Jersey monitored all 2006 cases and observed 86 deaths directly from this combination (23). The last

**Table II.** Summaries of epidemics in the literature describing deaths where both illicit fentanyl and heroin use were confirmed in the studied cohort

| Period | Location | No. of deaths | Peripheral blood (mean/median [range]) | | | | | | Author |
|---|---|---|---|---|---|---|---|---|---|
| | | | 6-AM [ng/mL] | $n$[a] | Morphine [ng/mL] | $n$[a] | Fentanyl (ng/mL) | $n$[a] | |
| 2005 (July)–2006 (May) | Wayne County, Michigan, USA | 101 | – | | – | | –/20 [4–69] | 32 | Algren *et al.* (10) |
| 2005 (September)–2007 (April) | Cook County, Illinois, USA | ~52 | – | | – | | 23/17 [0.8–164][b] | ~52 | Denton *et al.* (12) |
| 2006 (January–December) | New Jersey, USA | 86[c] | – | | – | | 23/– [–] | 86 | Hempstead *et al.* (23) |
| 2006 (April–August) | Philadelphia, Pennsylvania USA | 7[d] | Not detected | 0 | 161/161 [118–204] | 2 | 23/27 [5–47] | 7 | Wong *et al.* (35) |
| 2013 (November)–2014 (April) | Montgomery County, Florida, USA | 18[d] | 15/9 [7–27] | 5 | 164/105 [20–623] | 14 | 12/9 [1–60] | 14 | Marinetti *et al.* (39) |
| 2015 (September–November) | Melbourne, Victoria, AUS | 9 | 30/20 [<10–60] | 9 | 140/80 [20–400] | 9 | 18/20 [<1–45] | 9 | This article |

[a]The number of peripheral bloods analysed to provide blood concentrations (i.e., central and/or heart bloods excluded).
[b]For all fentanyl related deaths of which 85% were found to be fentanyl only, potentially giving rise to the higher observed range.
[c]Study does not state whether central or peripheral blood was analysed.
[d]Central and peripheral bloods.

cohort of cases were located in Philadelphia and involved seven deaths (35). Following this year and a half epidemic in the north eastern US states, the government issued several warnings through the media and fentanyl producing clandestine laboratories were shut down (12). However, more recently in late 2013, an additional 18 deaths were recorded in the southern state of Florida over a 5-month period (39), sparking another spate of warnings from US governing agencies. The latest episode of cases seems to be an isolated occurrence, with no further published deaths in this timeframe.

In Canada a public heath issue emerged when fentanyl detected in heroin overdose deaths increased dramatically over the 2012–2014 period from 13 to 90 deaths (38). As suggested in the US studies, it was indicated that users were not aware of the potent opioid added to their products. This led Amlani *et al.* (33) to perform a prospective study across 17 supervised injection sites in British Columbia to determine the prevalence of fentanyl in the urine of surveyed users. Of all, 23% of the 242 participants tested positive for fentanyl, however, 73% of this cohort did not know they were consuming it. Five participants in the study that tested positive to fentanyl reported an overdose in the week prior. This alarming statistic demonstrates the vulnerability of users in potentially obtaining street drugs laced with fentanyl.

The opioids heroin and morphine are CNS depressants causing a reduced rate and depth of breathing and may cause cessation of the breathing reflex, particularly with the additive effect of fentanyl use, further increasing the risk of death (3, 30–33). There is little difference between the fentanyl dose required for its desired euphoric effects and the dose that causes toxicity (30). It is known that there is considerable overlap between therapeutic and toxic concentrations of opioid drugs, predominantly due to the level of tolerance to the drug at the μ-receptor (50). Therapeutic transdermal patch use has given rise to fentanyl postmortem concentrations of up to 7 ng/mL (51). There has been suggestion that concentrations above this, particularly with concomitant drug use, may be considered potentially toxic (40). Palmer describes the significant overlapping of fentanyl concentrations when comparing the ranges for deceased following intravenous or transdermal patch use, with the later generally having higher concentrations (52). The mean measured fentanyl blood concentration in six transdermal fentanyl fatalities was 21 ng/mL (10–38 ng/mL) (9). Reports of oral administration of fentanyl from transdermal patches in seven cases in Toronto, Canada, described postmortem concentrations from 7 to 97 ng/mL (15). Overall the studies described in Table II, including our study, generally show lower levels of fentanyl concentrations than deaths caused solely due to fentanyl (9, 50, 53).

The peripheral blood mean, median and maximum concentrations of fentanyl in our study are comparable to those determined in the 2005–2006 studies, with the exception of the 164 ng/mL maximum observed in the Cook County Illinois cohort (12). This higher maximum concentration may have result from fentanyl use in isolation, as it was not possible to distinguish between fentanyl-laced heroin and lone fentanyl use in this study. Therefore if sole fentanyl use was included, higher purity levels of fentanyl in these drug batches may have been required in order to cause the fatal overdoses observed in this cohort. The recent epidemic in Montgomery County of 18 deaths produced similar 6-AM and morphine blood concentrations, however, with lower mean and median fentanyl concentrations. This may be explained by lower levels of fentanyl compared to heroin in the street batches of drugs from the previous US and this current study. Additionally the postmortem interval is unknown for each study, thus postmortem redistribution of fentanyl may vary between the studies.

Although US and Canadian studies have demonstrated the risk fentanyl-tainted heroin poses to illicit drug users, Australia had not observed such a trend prior to this study. Even with public health alert schemes such as the Australian Illicit Drug Reporting System (IDRS) that are intended to identify emerging drug trends, this outbreak was not publicized in the media or through government agencies. Specifically, a IDRS bulletin published on the injecting behaviors of 888 surveyed Australian users in the same 2015 year when these deaths occurred, suggested that only 10 individuals abused fentanyl (54). However, there was no indication that heroin and fentanyl were used in combination. This signifies that forensic institutions are often the first to become aware of specific drug trends when sudden spikes of related deaths are observed.

There is evidence from the US that some street products are sold as illicit fentanyl and not just as a heroin product (39). Some users abuse prescription fentanyl by injecting the extracted fentanyl from the transdermal patch (9, 13, 14, 26, 27, 32), or swallowing the patches themselves (15, 55). However, the cases in this series did not demonstrate the intravenous fentanyl misuse of transdermal patches, pills or powders in combination with heroin, but most likely as a fentanyl-laced heroin product (quite possibly from the same illicit batch), as implied by the analysis of exhibits found at the scene of these deaths which all contained the opioid combination.

Presumptively, the motivation to include fentanyl in heroin formulations is to increase the drug high, however, the resulting mixtures are extremely dangerous with a high mortality rate. The circumstances of each case in this study suggested recent and potentially fatal use of heroin and fentanyl, often combined with a range of other therapeutic and recreational drugs to produce mixed drug toxicity. It is noteworthy that the deceased in this study were not opioid-naive and had a history of heroin use, suggesting heroin combined with fentanyl may have been responsible for these increased toxicity in at least some of the cases. In addition to this opioid combination, other μ-receptor agonists should also be monitored, especially given the emergence of newer opioids like acetyl fentanyl (56), and the continued abuse of pharmaceutical opioids such as methadone and oxycodone (47, 57).

## Conclusion

Forensic toxicology laboratories should be aware of the increased use of illicit fentanyl either in the place of, or in addition to, heroin products. There is no evidence in these cases of intentional heroin overdose, or awareness of the opioid combination in the product administered. Many of the deceased had a history of heroin use suggesting that increased toxicity from this potent combination contributed to the deaths of these individuals. The observed increase of fentanyl detected in these overdoses, as well as the risk of unintentional administration, presents an emerging public health concern. This study assists in providing relevant and timely information to the public, medical community and public health bodies.

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## Conflict of Interest

The authors declare that there is no conflict of interest.

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