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Could chest wall rigidity be a factor in rapid death from illicit fentanyl abuse?

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ABSTRACT

Background: There has been a significant spike in fentanyl-related deaths from illicit fentanyl supplied via the heroin trade. Past fentanyl access was primarily oral or dermal via prescription fentanyl patch diversion. One factor potentially driving this increase in fatalities is the change in route of administration. Rapid intravenous (IV) fentanyl can produce chest wall rigidity. We evaluated post-mortem fentanyl and norfentanyl concentrations in a recent surge of lethal fentanyl intoxications. Methods: Fentanyl related deaths from the Franklin County coroner's office from January to September 2015 were identified. Presumptive positive fentanyl results were confirmed by quantitative analysis using liquid chromatography tandem mass spectrometry (LC/MS/MS) and were able to quantify fentanyl, norfentanyl, alfentanil, and sufentanil. Results: 48 fentanyl deaths were identified. Mean fentanyl concentrations were 12.5 ng/ml (range 0.5 ng/ml to >40 ng/ml). Mean norfentanyl concentrations were 1.9 ng/ml (range none detected to 8.3 ng/ml). No appreciable concentrations of norfentanyl could be detected in 20 of 48 cases (42%) and were less than 1 ng/ml in 25 cases (52%). Elevated fentanyl concentrations did not correlate with rises in norfentanyl levels. In several cases fentanyl concentrations were strikingly high (22 ng/ml and 20 ng/ml) with no norfentanyl detected. Discussion: The lack of any measurable norfentanyl in half of our cases suggests a very rapid death, consistent with acute chest rigidity. An alternate explanation could be a dose-related rapid onset of respiratory arrest. Deaths occurred with low levels of fentanyl in the therapeutic range (1–2 ng/ml) in apparent non-naïve opiate abusers. Acute chest wall rigidity is a well-recognized complication in the medical community but unknown within the drug abuse community. The average abuser of illicit opioids may be unaware of the increasing fentanyl content of their illicit opioid purchase. Conclusion: In summary we believe sudden onset chest wall rigidity may be a significant and previously unreported factor leading to an increased mortality, from illicit IV fentanyl use. Fentanyl and norfentanyl ratios and concentrations suggest a more rapid onset of death given the finding of fentanyl without norfentanyl in many of the fatalities. Chest wall rigidity may help explain the cause of death in these instances, in contrast to the typical opioid-related overdose deaths. Intravenous heroin users should be educated regarding this potentially fatal complication given the increasingly common substitution and combination with heroin of fentanyl.

Introduction

There has been a recent important rise in fentanyl related deaths across the nation, with most deaths involving injection related drug users.[1] The increase in deaths from fentanyl coincides with increasing amounts of non-pharmaceutical fentanyl supplied in combination with or in substitution for heroin via the illicit heroin trade supply.[2] In the past, the primary route of access to fentanyl was diversion of prescription fentanyl, primarily via fentanyl patch diversion.[3] There are several reasons fentanyl may be substituted for heroin; including ease of synthesis, greater potency and the fact that as a schedule II drug, fentanyl carries a lesser penalty to possession than heroin.

It has been suggested that many of these deaths have been related to the increased potency of fentanyl compared to other abused opioids. Fentanyl is approximately 80–100 times more potent than morphine on a weight per weight basis.[4] However, post-mortem values of fentanyl have been reported in the range found with therapeutic administration. Therapeutic use has resulted in serum fentanyl levels in the 11–34 ng/ml range after intravenous administration with fatalities reported in 4.9–27 ng/ml range.[5,6] Post-mortem blood is not serum, however a comparison of post-mortem blood levels and therapeutic serum values established a ratio of one for fentanyl suggesting use and comparison of post-mortem blood is appropriate.[7] Alternate explanations for the discrepancy, such as post-mortem redistribution, have been evaluated and discounted.[5] One factor potentially driving this increase in fatalities that has not previously been evaluated is the change in route of administration: from predominantly oral and dermal to intravenous exposure. Rapid intravenous administration and/or larger intravenous doses of fentanyl can produce skeletal muscle rigidity and specifically chest wall rigidity (i.e., wooden chest).[8–14] Chest wall rigidity does not appear to be dose related as it has been reported with low-dose therapeutic administration.[10,12] The chest wall rigidity phenomenon appears to be uncommon with other
opioids and more likely to be observed in the synthetic lipid soluble compounds such as fentanyl, acetylfentanyl, alfentanil, and sufentanil.[8] Onset of wooden chest is sudden and will produce a rapid inability to ventilate or move the chest wall.[6,14,15] The mechanism appears to be related to activation of the coeruleospinal noradrenergic pathway via the guanine nucleotide regulatory protein following mu-receptor activation in the locus coeruleus.[16,17] The effects may be reversed by rapid administration of naloxone.[8,9,11,14] Death after intravenous fentanyl abuse from chest wall rigidity may produce a number of features: (1) a wide range of fentanyl levels from low to high, as it is not dose related, (2) a lack of or very low levels of the metabolite norfentanyl, and (3) lack of specific anatomical findings on autopsy because chest wall rigidity is lost after death.

We evaluated post-mortem fentanyl and norfentanyl concentrations in illicit intravenous fentanyl associated fatalities and describe a recent surge of lethal fentanyl intoxications related to illicit intravenous fentanyl abuse.

Methods

All deaths from Franklin County Coroner's Office from January 2015 to September 2015 were searched to identify lethal fentanyl intoxications. Lethal fentanyl intoxications were identified from the coroner's legal verdict. Cases were excluded if fentanyl was not listed as a cause of death in the coroner's legal verdict. Cases identified as fentanyl overdoses were separated as to whether or not the metabolite norfentanyl was detected. The coroner's verdict was determined after a four level process that included: (1) death scene investigation performed by trained medicolegal death investigators including the collection of drug paraphernalia if present for chemical analysis and review of decedent's past medical history and medical records when available, (2) forensic pathology findings from autopsy, (3) forensic toxicology analysis of blood and urine, and (4) comprehensive review by a panel of medical examiners and forensic toxicologists who apply all available information to best determine the primary cause of death. All available information produced from each of these sources was used in the determination of cause of death for every case reported in this paper. All deaths investigated and examined by the Franklin County Coroner's Office, Columbus, OH receive routine toxicological analysis. Routine post-mortem toxicological testing includes enzyme linked immunosorbant assay (ELISA) blood panel, alkaline drugs in blood by gas chromatography mass spectrometry (GC/MS), acidic/neutral drugs in blood by GC/MS, alkaline/acidic/neutral drugs in urine by GC/MS, and an electrolytes/clinical chemistries panel in vitreous humor. Fentanyl is included in the routine ELISA screening panel and detected when present above a cut-off concentration of 1 ng/ml (Immunoassay, Pomona, CA). ELISA fentanyl test sensitivity has been demonstrated at 0.1 ng/ml to produce a four standard deviation from zero concentration-measured absorbance. ELISA test specificity has been shown to be 100% cross-reactive with fentanyl at 0.5 ng/ml. Presumptive positive fentanyl ELISA results are confirmed by quantitative analysis using liquid chromatography tandem mass spectrometry (LC/MS/MS). The LC/MS/MS confirmation assay uses a Thermo Scientific LTQ Linear Ion Trap (San Jose, CA) and is able to quantify fentanyl, norfentanyl, alfentanil, and sufentanil. Whole blood sample preparation for LC/MS/MS analysis is achieved by mixed-mode hydrophilic/cation exchange solid phase extraction (#CS2DAU206, UCT, Bristol, PA). LC/MS/MS fentanyl analysis was validated and found to have a linear range of 1–40 ng/ml and a limit of detection of 0.5 ng/ml for all four compounds. Drug related evidence or paraphernalia, collected during the death investigation response, was analyzed by GC/MS and used to support toxicological findings and may indicate the drug’s route of administration. Ante mortem blood drawn at hospital admission was subpoenaed for toxicological analysis if the decedents stayed any significant time in the hospital prior to death. Of the 39 Post-mortem samples 37 were femoral samples and two were heart blood from the two infants. For purposes of comparing incidence of fentanyl deaths the number of fentanyl related deaths from the 12 months of 2014 was compiled. We reviewed emergency responder records, in cases where available, as part of the medical record collected by the coroner’s office, investigator’s reports for evidence of drug paraphernalia at scene and history of IV drug use and autopsy findings.

Statistical analysis comparing fentanyl concentrations with groups of norfentanyl concentrations uses Mann–Whitney/ Wilcoxon Two-Sample Test and ANOVA. For the two sample test the Norfentanyl concentrations were placed in two groups for comparison of none detected (<0.5 ng/ml) and detected.

This study received review by the institutional review board at Nationwide Children's hospital and was considered exempt.

Results

From January 2015 to September 2015, 48 deaths were identified as lethal fentanyl intoxications, which was a 128% increase over 21 fentanyl deaths the previous full year (2014) (Figure 1). Most fentanyl-related deaths prior to January 2015 were attributed to misuse or abuse of fentanyl transdermal patches. The mean age, during this nine-month period of 2015, was 33 years with 46 adults (ranges 20–62 years) and two infants (11 months and 14 months). There were 32 (67%) males and 16 females (33%). Of the 48-fentanyl deaths, 43
received autopsies, with five cases receiving external view and samples drawn for toxicology. Intravenous use was definitively established in 23 cases based on syringes found with or attached to the body at the scene and witness accounts. Three cases were established as oral ingestion (two infant ingestions of a parent’s illicit “heroin” purchase and one transdermal patch). The remaining cases (n=22) were believed to be IV abuse based on the decedents history of IV abuse and track marks on the body.

These fentanyl related deaths displayed mean and median fentanyl concentrations of 12.5 ng/ml and 11 ng/ml, respectively, with a range from 0.5 ng/ml to >40 ng/ml (Table 1). Mean concentrations of norfentanyl were 1.9 ng/ml with a range of none detected (<0.5 ng/ml) to 8.3 ng/ml. No appreciable concentrations of norfentanyl could be detected in 20 of 48 cases (42%) and were less than 1 ng/ml in 25 cases (52%).

Elevated fentanyl concentrations did not correlate with rises in norfentanyl levels. In several cases fentanyl concentrations were strikingly high (22 ng/ml and 20 ng/ml) with no norfentanyl detected. The range of fentanyl concentrations in cases with and without norfentanyl detection overlapped considerably and was not significant, suggesting a lack of dose response (Table 1). In 16 cases (33%) heroin metabolites (6-Monoacetylmorphine (6-MAM)) or morphine were detected and may suggest concurrent use of heroin or a combination of fentanyl within the illicit substance being abused. Presence of morphine may be from previous administrations and not necessarily this use.

In two descendants, with no metabolite detected on autopsy, emergency responder run sheets recorded lack of chest wall expansion with attempts at ventilation and unable to intubate. After administration of 2 mg of naloxone intubation and ventilation were successful, although resuscitation was not successful. The first decedent was found on the bathroom floor with two needles lying next to him. The second decedent, found in his bedroom, was noted to be awake less than 10 min prior to the call to 911 for assistance. Both were noted to have previous history of heroin abuse.

**Discussion**

Opioid induced acute onset of chest wall rigidity was first described by Hamilton and Cullen in 1953. The reported incidence of fentanyl induced chest wall rigidity after intravenous administration during use in anesthesia varies from a low of 8% to a high of nearly 100% if the dose administered exceeded 0.25 mcg/kg administered at 150 mcg/min.[6] Serum concentration (Cmax) and effective-site concentration did not appear to predict onset of rigidity; however rigidity was associated with unconsciousness.[6] Slower rates of administration (30 mcg/min and 50 mcg/min) appear to produce a milder form of rigidity (decreased chest wall compliance) with lower doses and with maintenance of consciousness.[6,18,20] Age and gender did not affect incidence of rigidity.[19]

Outside the clinical setting however, rigidity has not been an expected complication, as illicit heroin abuse has historically been by oral or cutaneous exposure using fentanyl infused patches.[3] Recently the constituents of opiates sold as “heroin” have been changing, with decreasing actual heroin content and the substitution of fentanyl.[2] With the rapid increase in availability of illicit fentanyl abused intravenously, we are seeing a disproportionate number of fatalities when compared to previous years where heroin was the primary opioid being abused intravenously.[1]

We propose this increase in mortality may, in part, be due to the well-known complication of acute chest wall rigidity associated with intravenous fentanyl use. Death from an opioid overdose is usually not immediate but has a process of central nervous system and respiratory depression associated with a period of agonal respirations during which circulation and metabolism of drugs continue.[21–23] Sudden death after IV heroin abuse is infrequent but has been reported.[23,24] Reports of sudden death after IV heroin abuse appear to be a dose-related phenomenon, with the cases in the short survival groups having the highest morphine levels.[24,25] The high percentage of sudden deaths associated with fentanyl in our study are concerning but may not necessarily be a dose-related event. We did not see the highest fentanyl levels in cases without the metabolite norfentanyl, nor was there a trend toward higher fentanyl concentration in cases without norfentanyl detected. Fentanyl metabolism is extensive and rapid. The primary metabolite norfentanyl appeared in plasma within 2 min after intravenous administration, and maintained concentrations of >1 ng/ml for at least 8 h.[26]

The lack of any measurable norfentanyl formation in half of our cases suggests a very rapid death, that would be consistent with acute chest rigidity. Onset of chest wall rigidity and unconsciousness would produce rapid onset of apnea.[6] An alternate explanation could be a dose-related rapid onset of respiratory arrest. We have recorded deaths with low levels of fentanyl in the therapeutic range of 1–2 ng/ml in apparent non-naive opiate abusers (based on coroner’s investigation), found with drug syringes next to the body and no other anatomical or pharmaceutical cause of death on autopsy.

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**Table 1. Fentanyl concentrations in fatal fentanyl overdoses (OD).**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Mean fentanyl concentration (SD) in ng/ml</th>
<th>Median fentanyl concentration in ng/ml</th>
<th>Range fentanyl concentration in ng/ml</th>
<th>Mean norfentanyl concentration ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl OD with norfentanyl undetectable (&lt;0.5 ng/ml)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15</td>
<td>9.3 (7.0)</td>
<td>7.2</td>
<td>1.2–22</td>
</tr>
<tr>
<td>Fentanyl OD with norfentanyl ≥0.5–1 ng/ml&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8</td>
<td>12.5 (6.5)</td>
<td>12.5</td>
<td>5.5–23</td>
</tr>
<tr>
<td>Fentanyl OD with norfentanyl &gt;1 ng/ml&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16</td>
<td>17.5 (9.3)</td>
<td>17</td>
<td>2.9 to &gt;40</td>
</tr>
<tr>
<td>Fentanyl OD - blood drawn antemortem&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9</td>
<td>8.6 (8.7)</td>
<td>9</td>
<td>0.5–0.99 to 29</td>
</tr>
</tbody>
</table>

<sup>a</sup>Analysis performed on post-mortem blood.

<sup>b</sup>Analysis performed on serum.
Acute chest wall rigidity has been recorded in cases with low dose intravenous fentanyl administration.[11,13] Acute chest wall rigidity is not a recognized complication of intravenous fentanyl within the drug abuse community and would be unexpected and sudden. The average abuser of illicit opioids may be unaware of the increasing fentanyl content of their illicit opioid purchase.[2] This same group is not likely aware that fentanyl specifically has additional risk of death from chest wall rigidity.

Conversely, half of the decedents had measurable norfentanyl concentrations, suggesting survival long enough to produce metabolites and a more “traditional” onset of dose-related respiratory depression progressing to hypoxia and death.

There are several limitations to our study. The data suggests that these fentanyl-related deaths are rapid, but not necessarily caused by chest wall rigidity. Alternate explanations such as sudden apnea/respiratory arrest should be considered for further research. Fentanyl is metabolized in the liver to norfentanyl via the CYP 3A4 enzyme. Inhibitors of CYP 3A4 may impair or slow production of the metabolite norfentanyl. Protease inhibitors, such as atazanavir and ritonavir, which may be prescribed to HIV positive patients, are inhibitors of CYP3A4. A limitation to our study is we did not measure HIV status or presence of protease inhibitors, which may impact production of nor-fentanyl.

In summary, we believe sudden onset chest wall rigidity may be a significant and previously unreported factor leading to an increased mortality, even amongst non-naive abusers of opioids, involving illicit intravenous fentanyl use. Fentanyl-associated deaths are increasing dramatically. Fentanyl and norfentanyl ratios and concentrations suggest a more rapid onset of death given the finding of fentanyl without norfentanyl in many of the fatalities. Chest wall rigidity may help explain the cause of death in these instances, in contrast to the typical opioid-related overdose deaths. Intravenous heroin users should be educated regarding this potentially fatal complication given the increasingly common substitution and combination with heroin of fentanyl.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References