Common Findings and Predictive Measures of Opioid Overdoses

Danielle E. Pelletier, Thomas A. Andrew

ABSTRACT

Purpose: This research examines autopsy findings from fatal opiate/opioid intoxications in New Hampshire for cerebral edema, pulmonary edema, and urinary bladder distension in the interest of finding predictability of such cases.

Methods: Autopsy reports of 150 decedents, between 20 and 40 years old, were reviewed. Subjects were divided into three groups as follows: 50 whose cause of death was opioid intoxication excluding fentanyl, 50 who died from fentanyl, and 50 who, lacking intoxication, died from cardiac issues, seizure disorders, or positional asphyxia as the control group. Autopsy reports were reviewed for cerebral edema, pulmonary edema, and urinary bladder distension.

Results: Pulmonary edema was present in 96% of those who died of fentanyl alone and in 94% of those who died of opioids excluding fentanyl. Cerebral edema occurred in 54% of decedents who died of opiates/opioids excluding fentanyl and 8% in those who died solely of fentanyl. Thirty-four percent of the fatal intoxications excluding fentanyl had bladder distension while only 16% of those who died of fentanyl intoxication. The control group found 30% had pulmonary edema, 2% had cerebral edema, and none had bladder distension. The triad occurred in 8% of intoxications and never in the control group.

Conclusion: The results validated correlation between opioid intoxication and pulmonary edema, cerebral edema, and bladder distension. Cerebral edema and bladder distension suggest opioid intoxication, but arise less frequently in fentanyl intoxication. We hypothesize that fentanyl causes death more rapidly than other opioids leading to these results. Given the variations, we do not recommend reliance on postmortem computed tomography *in lieu* of autopsy to evaluate potential fatal intoxications. *Acad Forensic Pathol.* 2017 7(1): 91-98

AUTHORS

Danielle E. Pelletier BS, Office of Chief Medical Examiner, State of New Hampshire

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study, general supervision, writing assistance and/or technical editing.

Thomas A. Andrew MD, Office of Chief Medical Examiner, State of New Hampshire

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study, general supervision, writing assistance and/or technical editing.

CORRESPONDENCE

Danielle E. Pelletier BS, 246 Pleasant Street Suite 218, Concord NH 03301, danielle6elizabeth@gmail.com

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INTRODUCTION

Deaths from opiate/opioid intoxication has become a nationwide problem that has been drastically increasing in the past five years. Since 2000, deaths from drug overdoses has increased 137% and deaths specifically from opiates/opioids has increased 200% (1). New Hampshire has shown to have one of the highest drug overdose rates in the nation (1). In 2011, 157 of the 201 total deaths from drug intoxication were opiate/opioid-related. In 2015, total drug deaths rose to 439, with 397 being opiate/opioid-related. The New Hampshire Office of the Chief Medical Examiner (OCME) projects based on year-to-date data, that in 2016, opiate/opioid deaths will increase to well over 400 out of the projected 494 total drug deaths (2). Over half of the opiate/opioid deaths in 2015 were caused by fentanyl (**Table 1**).

Fentanyl is a synthetic and short-acting opioid analgesic and is 50-100 times more potent than morphine (3). Pharmaceutical fentanyl is known to be misused, but most cases of fentanyl-related deaths in this medicolegal jurisdiction are from illicitly manufactured fentanyl and fentanyl analogues (3). Nonpharmaceutical fentanyl is produced in clandestine laboratories and often sold in disguise making it that much more dangerous on the streets as consumers of illicit agents often do not know the contents of what they are taking (3).

Fentanyl, like other opiates and opioids, act on opioid receptors that are distributed throughout the body. Highly conserved opioid receptor substrates have been demonstrated in a wide range of systems, from neurons in the hippocampus, locus ceruleus, and ventral tegmental area, to the dorsal root ganglia (4). Evidence has supported the concept that opioid receptors positively couple to potassium channels while also negatively modulating calcium channels in many model systems and cell types (4). This alteration of ion channels within the body and their abundance in the peripheral and central nervous system lead to a variety of physiological effects upon receptor activation. Peripheral effects include constipation, urinary retention, hives, and bronchospasm; central effects consist of nausea, sedation, respiratory depression, hypotension, miosis, and cough suppression (4).

Respiratory depression is one of the biggest concerns in opioid use because it has shown to lead to pulmonary edema. Healthy lungs are the site of fluid and solute filtration that moves by transvascular hydrostatic and protein osmotic pressure differences. In pulmonary edema, the rate of fluid filtration exceeds the rate of lymphatic removal (5). Pulmonary edema is divided into two main types: cardiogenic (or hydrostatic) and noncardiogenic (or increased permeability) (5). Cardiogenic pulmonary edema results from a marked increase in pulmonary capillary hydrostatic pressure, whereas noncardiogenic pulmonary edema follows an increase in the permeability of the endothelium to

Table 1: Number of Deaths and the Drugs Responsible, Per Year

Opiates/Opioids	Number of Deaths 2011	Number of Deaths 2012	Number of Deaths 2013	Number of Deaths 2014	Number of Deaths 2015
Fentanyl (no other drugs)	5	5	9	77	161
Fentanyl and other drugs (excluding heroin)	12	5	7	31	78
Heroin (no other drugs)	21	21	40	40	31
Heroin and other drugs (excluding fentanyl)	23	16	28	20	13
Heroin and fentanyl	0	0	1	38	44
Other opiates/opioids	96	74	77	88	70
Total deaths caused by opiates/opioids	157	121	162	294	397
Total drug deaths	201	163	192	326	439

fluid and protein (5). Drug-induced pulmonary edema is typically classified as noncardiogenic, but, in fact, shows features of both increased hydrostatic pressure, caused by intense sympathetic stimulation, and increased permeability (5). Drug-induced pulmonary edema can be fatal.

Opioid receptor activation also leads to cerebral edema, with subcellular molecular mechanisms similar to those that produce pulmonary edema. Calcium and sodium ion channels are altered upon activation, causing an accumulation of sodium within the cell and creating an osmotic gradient (6). Cells are flooded with water in response to the change in concentrations and hypoxia depletes cellular energy stores, disabling the sodium-potassium pump (6). This pump failure and the resulting accumulation of sodium causes fluid to move from the extracellular to the intracellular space to maintain osmotic equilibrium, activating intracellular cytotoxic processes (6). This leads to an inflammatory response, creating increased intracranial pressure since the described fluid shifts occur within a rigid environment that does not allow for expansion.

As mentioned above, one of the peripheral effects upon opioid receptor activation is urinary retention. When activated, there is a decreased sensation of bladder fullness by partially inhibiting the parasympathetic nerves involved with the bladder (7). They have also shown to increase the sphincter tone of the urinary bladder by the over-stimulation of the sympathetic nervous system leading to outlet resistance (7). These two working together ultimately lead to urinary retention which, in cases of fatal intoxication, may be seen as a distended bladder in autopsy and postmortem computed tomography (PMCT).

A study published in 2012, by Rohner et al., has shown that urinary bladder distension is much more frequent in cases of fatal drug intoxication than in decedents who were not intoxicated (8). They found a 162.8 mL difference in mean urine volumes between a study group of fatally intoxicated individuals and their control group who had negative toxicology results (8). The authors concluded that they found a positive relationship between intoxication and urinary bladder volumes.

The previous study was supported by another done by Winklhofer et al. published in 2014 that examined whole body PMCT scans of individuals from fatal opioid intoxication in which they found 42% of those intoxicated had a distended bladder (9). The control group found this in only 9.1% of the decedents. This study also showed higher frequencies of pulmonary edema and cerebral edema in the intoxicated individuals. Pulmonary edema was present in 95% of the study group and cerebral edema in 49%. The study saw all three present simultaneously in intoxicated individuals numerous times, but not once in the control group. The triad of cerebral edema, pulmonary edema, and a distended urinary bladder as an indicator of opioid-related deaths had a 26% sensitivity and a 100% specificity, as confirmed by autopsy and toxicology analysis (9).

Past research and these two studies that examine relationships between intoxication and postmortem findings support that these three findings have a strong correlation with opiate/opioid intoxication and encourage further research (**Figure 1**). This study aims to highlight frequent findings and potential predictive measures of opioid overdoses.

METHODS

Subjects were found and collected through query searches from the New Hampshire's Office of Chief Medical Examiner's database.

Each year, the New Hampshire's Office of Chief Medical Examiner tracks all fatal intoxications that occur within the state for that year. This information is used for statistical purposes as well as research. The OCME case file includes the age of the decedent as well as the specific drugs involved in the fatality. Using these statistics, the two study groups for this research were created. Only autopsy cases of fatally intoxicated individuals from 2012 to 2015 were used, for a total of 587 autopsy cases. All decedents younger than 20 and older than 40 were excluded from the study group. The age range was kept narrow to prevent outliers based on varying physiological conditions in the very young and confounding comorbid-

Figure 1: The triad of findings that can be observed in opioid deaths. Created under contract by professional medical illustrator Diana Kryski.

ities in older decedents. This reduced the number of usable cases to 300. The remaining decedents were then separated based on the drugs involved in the cause of death. This research aimed to reveal differences in postmortem changes between those who

died from fentanyl alone and those who died from other opioids excluding fentanyl; therefore, all deaths caused by multiple opioids including fentanyl were excluded from this study. This further reduced the number of cases to 184, leaving 64 decedents who

died of acute fentanyl intoxication and 120 who died from intoxication by another opioid. Fifty cases were randomly selected from each group.

The control group was likewise created from query searches in the New Hampshire's Office of Chief Medical Examiner computer database, using an age range between 20 and 40 years old, whose cause of death was due to cardiac circumstances such as "spontaneous coronary artery dissection," "myocardial infarction due to arteriosclerotic cardiovascular disease," and "mitral valve prolapse" as examples of the many varying cardiac-related causes of death. This group also contains deaths caused by seizure disorders and positional asphyxia. The group is made up of decedents whose death was not obvious upon presentation and therefore could have been thought to be drug-related, but was later determined otherwise. This will allow the study to reveal how accurate the triad predicts deaths to be caused by opiates/opioids when compared against a group of cases that were thought to be potential drug intoxication cases and were later determined otherwise by autopsy and toxicology. While creating the control group, a few decedents were found to have naloxone in their system even though they were not intoxicated from opiates/opioids. This is because in light of the high rates of opiate/opioid intoxications, administration of naloxone has become routine. The control decedents had to be negative for opioids in their postmortem toxicology. With these parameters, 50 age-matched cases between 2010 and 2015 were selected to represent the control group.

Autopsy and toxicology reports for each of the total 150 cases involved in this study were reviewed and analyzed by two pathologists for the presence or absence of pulmonary edema, cerebral edema, and a distended urinary bladder. The pathologists share the same format in which they record autopsy findings. Pulmonary edema was considered present when foamy, proteinaceous fluid was in the trachea, major bronchi, and/or was expressed from the cut surface of the lungs. The pathologists specifically noted whether the decedents had pulmonary edema versus merely congestion in the lungs. Brain weights of each decedent

were recorded at autopsy in the fresh state. For this study, these weights were compared to a standard range of organ weights developed by The Ohio State University Department of Pathology (10). For males, this range is 1365 g to 1450 g and for females it is 1250 g and 1275 g. Decedents' brains were also examined for flattening of gyri, narrowing of sulci, and fullness within the cranial cavity for determining the presence or absence of cerebral edema. Histological examination aided in the determination of the presence or absence of both pulmonary edema and cerebral edema in these cases. Decedents in this study were considered to have a distended urinary bladder if it contained 400 mL or more of urine. Previous publication by Rohner et al. had used 350 mL as their minimum distended bladder volume (8). Our study used 400 mL to assure distension and significance for this study in these cases. Bladder evacuation prior to autopsy could not be accounted for and is therefore a limitation to this study.

After reviewing the decedents' information and recording the presence or absence of these findings within each decedent, the data was statistically analyzed.

RESULTS

Pulmonary edema was present in almost all cases of intoxication. It was found in 94% of those who died from opiate/opioid intoxication excluding fentanyl and in 96% of those who died from solely fentanyl intoxication. Cerebral edema, however, was found in 54% of those who died from an opiate/opioid intoxication excluding fentanyl and only in 8% of the study group in which fentanyl was responsible for death. Similarly, urinary bladder distension was found less frequently in the fentanyl study group, arising in only 16% compared to 34% in the study group excluding fentanyl in cause of death. In the control group, pulmonary edema was present in 30%, cerebral edema was present in 2%, and bladder distension had occurred in none. The triad of all three being present simultaneously within a decedent occurred in 8% of those intoxicated and not once in the control group of nonintoxicated decedents (**Table 2**).

Statistical Analysis

The correlation between fatal opiate/opioid drug intoxication and the presence of pulmonary edema, cerebral edema, and urinary bladder distension was carried out using Chi-squared (X^2) test. Results were considered significant at $p < 0.05$ (Table 2).

Sensitivity, specificity, and positive/negative predictive values were calculated using the data obtained in this study. The sensitivity of pulmonary edema in both study groups was notably higher than the sensitivities of cerebral edema and urinary bladder distension for opiate/opioid-related deaths (94% in the study group excluding fentanyl in cause of death and 96% in the study group of fatal fentanyl intoxications) (Tables 3 and 4). The specificity of all three, especially that of cerebral edema and urinary bladder distension, are also very high (Tables 3 and 4). In the study group of those who died of opiate/opioid intoxication excluding fentanyl, the positive predictive value of cerebral

edema is 96% and that of urinary bladder distension is 100%. The negative predictive value for the accuracy of absence of pulmonary edema is 92% (Table 3).

In the study group of individuals who died of fentanyl intoxication, the specificity for opiate/opioid-related death, when looking at cerebral edema and urinary bladder distension, are both high, but their sensitivity values are small (Table 4). Similarly, to the other study group, the positive predictive values for the triad are high, all above 75%. The negative predictive value for pulmonary edema in opiate/opioid-related deaths is 96% (Table 4).

DISCUSSION

This study supports a relationship between opiate/opioid intoxication and the presence of pulmonary edema, cerebral edema, and urinary bladder distension due to the much higher frequencies of the three within individuals who died from fatal opiate/opioid intox-

Table 2: Frequencies of Pulmonary Edema, Cerebral Edema, and Urinary Bladder Distension at Autopsy

Autopsy Findings	Pulmonary Edema	Cerebral Edema	Bladder Distension
Study group (excluding fentanyl)	47/50 (94%)	27/50 (54%)	17/50 (34%)
Study group (fentanyl only)	48/50 (96%)	4/50 (8%)	8/50 (16%)
Control group	15/50 (30%)	1/50 (2%)	0/50 (0%)
<i>p</i> -value	$p < 0.002$	$p < 0.002$	$p < 0.002$

Table 3: Sensitivity, Specificity, Positive and Negative Predictive Values of Study Group Excluding Fentanyl in Cause of Death

Study Group Excluding Fentanyl in Cause of Death	Pulmonary Edema	Cerebral Edema	Bladder Distension
Sensitivity for opiate/opioid-related death	94%	54%	34%
Specificity for opiate/opioid-related death	70%	98%	100%
Positive predictive value	76%	96%	100%
Negative predictive value	92%	68%	60%

Table 4: Sensitivity, Specificity, Positive and Negative Predictive Values of Study Group of Fentanyl Deaths

Study Group of Fentanyl Deaths	Pulmonary Edema	Cerebral Edema	Bladder Distension
Sensitivity for opiate/opioid-related death	96%	8%	16%
Specificity for opiate/opioid-related death	70%	98%	100%
Positive predictive value	76%	80%	100%
Negative predictive value	95%	52%	54%

ications than in a control group of cardiac, seizure, and asphyxiation deaths who had negative toxicology reports. Pulmonary edema was found in nearly every case of intoxication regardless of the opiate/opioid involved and therefore, pulmonary edema is extremely predictive to an opiate/opioid overdose. Cerebral edema, however, had interestingly differing results between the two study groups. Cerebral edema was present in over half of those intoxicated from opiates/opioids excluding fentanyl and only in 8% of those who died from intoxication caused solely by fentanyl. Similarly, urinary bladder distension was more frequent in the study group that excluded fentanyl in cause of death than in the fentanyl study group. These differences are likely a reflection of the specific pharmacological effects of fentanyl in comparison to other opioids and opiates. Given its much higher potency, fentanyl and its analogues cause death too rapidly to allow for the accumulation of cerebral edema or urinary bladder distension. All three were still present more commonly in those intoxicated than those in the control group and all three postmortem findings were found simultaneously in individuals in 8% of the combined study groups and never in the control group. Having noted that, the finding of all three within one individual is highly predictive to an opiate/opioid overdose. In our experience, so far, nonopiate/opioid central nervous system depressants such as benzodiazepines and barbiturates seem to lack this rate of reoccurrence of this triad in autopsy.

Unfortunately, bladder evacuation could not be accounted for in this study when obtaining the data. It is information that the pathologists do not receive upon autopsy and certainly limits the study.

Clearly, pulmonary edema alone is not specific to opiate/opioid intoxication. Since this research highlights the relative lack of urinary distension and cerebral edema in fentanyl deaths, reliance on the PMCT triad of pulmonary edema, cerebral edema, and urinary retention to guide toxicological analysis for likely opiate/opioid intoxication would not detect cases of fatal fentanyl intoxication, which has been the leading cause of drug deaths in New Hampshire for the past three years. Previous references use PMCT imaging

to guide similar studies that leads this study to comment on the limitations of virtual autopsy compared to autopsy to fully evaluate drug deaths.

CONCLUSION

Opioid receptor activation has shown to have peripheral and central nervous system effects that, in cases of fatal intoxication, can be seen postmortem via virtual autopsy and traditional autopsy. Pulmonary edema, cerebral edema, and urinary bladder distension have shown to be frequent findings in cases of fatal drug intoxication by the analysis of PMCT scans and autopsy findings. Pulmonary edema is extremely frequent in all cases of fatal opiate/opioid intoxication whereas cerebral edema and urinary bladder distension have shown to be opiate/opioid dependent, arising much less frequently in those who die from solely fentanyl. This is likely because fentanyl, due its substantially increased potency, induces its fatal effects too rapidly to allow the body to accumulate cerebral edema, high urine volumes, and urinary bladder retention. Given these findings, reliance on the triad in PMCT, although not used in this study, would miss cases of fatal fentanyl intoxication, which has become the leading agent of drug deaths in the state of New Hampshire. The simultaneous presence of all three is still highly predictive to an opiate/opioid overdose both in virtual autopsy and autopsy.

REFERENCES

- 1) Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths – United States, 2000–2014. *MMWR Morb Mortal Wkly Rep*. 2016 Jan 1; 64(50-51):1378–82. PMID: 26720857. <https://dx.doi.org/10.15585/mmwr.mm6450a3>.
- 2) Fallon K. Weekly report provided to OCME stakeholders. Concord (NH): New Hampshire Office of the Chief Medical Examiner; 2016 Aug 11. 1 p.
- 3) Algren DA, Monteilh CP, Punja M, et al. Fentanyl-associated fatalities among illicit drug users in Wayne County, Michigan (July 2005–May 2006). *J Med Toxicol*. 2013 Mar; 9(1):106–15. PMID: 23359211. PMCID: PMC3576499. <https://dx.doi.org/10.1007/s13181-012-0285-4>.
- 4) Al-Hasani R, Bruchas MR. Molecular mechanisms of opioid receptor-dependent signaling and behavior. *Anesthesiology*. 2011 Dec; 115(6):1363–81. PMID: 22020140. PMCID: PMC3698859. <https://dx.doi.org/10.1097/ALN.0b013e318238bba6>.
- 5) Murray JF. Pulmonary edema: pathophysiology and diagnosis. *Int J Tuberc Lung Dis*. 2011 Feb; 15(2):155–60. PMID: 21219673.

- 6) Jha SK. Cerebral edema and its management. *Med J Armed Forces India*. 2003 Oct; 59(4):326-31. PMID: 27407555. PMCID: PMC4923559. [https://dx.doi.org/10.1016/S0377-1237\(03\)80147-8](https://dx.doi.org/10.1016/S0377-1237(03)80147-8).
- 7) Durant PA, Yaksh TL. Drug effects on urinary bladder tone during spinal morphine-induced inhibition of the micturition reflex in unanesthetized rats. *Anesthesiology*. 1988 Mar; 68(3):325-34. PMID: 3344988. <https://doi.org/10.1097/0000542-198803000-00002>.
- 8) Rohner C, Franckenberg S, Schwendener N, et al. New evidence for old lore – urinary bladder distension on post-mortem computed tomography is related to intoxication. *Forensic Sci Int*. 2013 Feb 10; 225(1-3):48-52. PMID: 22565114. <https://dx.doi.org/10.1016/j.forsciint.2012.03.029>.
- 9) Winklhofer S, Surer E, Ampanozi G, et al. Post-mortem whole body computed tomography of opioid (heroin and methadone) fatalities: frequent findings and comparison to autopsy. *Eur Radiol*. 2014 Jun; 24(6):1276-82. PMID: 24599624. <https://dx.doi.org/10.1007/s00330-014-3128-7>.
- 10) Department of Pathology resident's homepage [Internet]. Columbus: Ohio State University, Wexner Medical Center; 2016 [cited 2016 Dec 9]. Available from: <http://www.pathology.med.ohio-state.edu/residents/autopsy.asp>.