

Contribution of Opiates in Sudden Asthma Deaths

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Abstract: Asthma is a common disease in the United States and is frequently encountered during medicolegal autopsies. Patients are often young and have a witnessed collapse or are found dead. Opiate abuse is also pervasive and is repeatedly seen in death investigations. All cases over a 7-year period involving asthma investigated at the Wayne County Medical Examiner's Office were reviewed for demographics, circumstances, autopsy toxicology findings, and cause and manner of death. Ninety-four cases met these criteria. Ten cases (10.5%) were positive for opiates, 8 listed drugs as the cause of death, and 2 listed asthma. Of cases with established asthma opiate positivity, 8 (80%) were found dead, and only one had a witnessed collapse. Compared with those without opiate abuse, asthmatic patients abusing opiates had a higher mean age, no reported respiratory symptoms immediately preceding death, and higher frequency of being found dead. A discernable difference exists between deaths in asthmatic patients in the presence of opiates and those without. These findings indicate that it may be possible to predict the presence of opiates given history investigation information, thereby focusing toxicology panels to promote cost-effective practices when ordering supportive tests.

Key Words: asthma, opiates, sudden death, found dead, witnessed collapse (*Am J Forensic Med Pathol* 2015;36: 49–52)

Asthma is a commonly encountered disease in the United States, with an estimated 25.5 million people afflicted in 2012 (8152 per 100,000 persons).¹ It is also frequently seen at autopsy during the medicolegal investigation of a death, as victims can be young and pass suddenly and unexpectedly. Deaths attributed to this illness often times occur in those persons with known asthma who have a witnessed collapse or are found dead after experiencing shortness of breath, respiratory distress, or an asthma attack.

Opiate use remains pervasive in the United States, with an estimated 335,000 people over the age of 12 reporting usage of heroin in 2012² and an estimated 4.9 million people over the age of 12 reporting usage of opioid pain relievers for nonmedical purposes in 2012.³ Opioid toxicity is also regularly detected during the medicolegal investigation of a death, as cases with suspicion or knowledge of drug use fall under the jurisdiction of the medical examiner or coroner in the United States.

As a result of the prevalence of both asthma and opioid use in cases routinely autopsied during the medicolegal investigation of a death, the authors wished to compare and contrast the demographics, circumstances, and autopsy findings of individuals with asthma who died suddenly with opioids in their system to those without.

MATERIALS AND METHODS

All cases of sudden death involving asthma patients who were investigated and autopsied by the Wayne County Medical

Examiner's Office in Detroit, Mich, from mid 2007 to mid 2014 were retrospectively identified in CASEManagerfw software (QuincyTech, Acworth, Ga). These were reviewed for age, sex, race, clinical history, presentation, cause of death, gross and microscopic autopsy findings, and toxicology results. All cases with circumstances that did not raise the possibility of the death being caused by asthma (eg, homicides, motor vehicle accidents, suicides, and other diseases such as terminal cancer) were excluded. The clinical histories and presentations were reviewed as to whether there was a previous diagnosis of asthma or treatment for asthma; whether there was shortness of breath, respiratory distress, or an asthma attack immediately before death; and whether the decedent had a witnessed collapse or was subsequently found dead. The autopsy reports were reviewed for the gross findings of hyperinflation of the lungs and mucus plugs in the airways. Figure 1 demonstrates hyperinflated lungs encountered during autopsy. The microscopic examinations of the airways were reviewed for thickened basement membranes, an inflammatory cell infiltrate that included eosinophils, smooth muscle hypertrophy, and goblet cell hyperplasia. Figure 2 demonstrates these microscopic findings in an affected airway. Toxicological analyses performed on peripheral blood samples were reviewed for all positive findings of drugs of abuse except for metabolites of marijuana, which was excluded as the cases from mid 2007 to late 2010 were not tested for such by our toxicology laboratory. Of these, the cases that were positive for opioids were compared qualitatively to all others that met the criteria.

RESULTS

Ninety-four cases that met the criteria were identified. The mean age was 34.6 years (range, 9.5 months to 58 years), and 40 were female, whereas 54 were male. The race distribution was 81 black, 12 white, and 1 Hispanic. There was a previous diagnosis of asthma in 92 cases, and 2 cases were diagnosed based on the gross and microscopic findings at autopsy. There was shortness of breath or respiratory distress before demise in 50 (53%), and 52 (55%) had a witnessed collapse, whereas 34 (36%) were subsequently found dead. Eighteen cases had causes of death that were not related to asthma or drugs, including hypertensive cardiovascular disease (7), arteriosclerotic cardiovascular disease (3), pneumonia (3), dilated cardiomyopathy (2), hypertrophic cardiomyopathy (1), emphysema (1), and morbid obesity (1). No drugs of abuse were found in 50 (53%) of cases.

Sixty-eight cases (72%) listed asthma as the cause of death. The mean age was 32 years (range, 23 months to 58 years), and 27 were female, whereas 41 were male. The race distribution was 59 black, 9 white, and 0 Hispanic. There was a previous diagnosis of asthma in 67 cases. One case had only a history of cerebral palsy, and the diagnosis was based on the gross and microscopic findings at autopsy. There was shortness of breath or respiratory distress before demise in 46 (68%), and 44 (65%) had a witnessed collapse, whereas 19 (28%) were subsequently found dead. No drugs of abuse were found in 48 (70.5%) of cases. One or more drugs were identified in the blood of 18 cases, but not at toxic levels individually or in combination to have caused or contributed to death. Two cases had drug levels that were felt to have caused or contributed to death. Table 1 summarizes the 20 cases with positive toxicology findings.

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FIGURE 1. Hyperinflation of the lungs encountered during autopsy as the chest wall is removed.

Ten cases (10.5%) were positive for opioids on toxicology. The route of administration of the drugs was not determined during the death investigations and thus is unknown. The mean age was 43 years (range, 16–58 years), and 4 were female, whereas 6 were male. The race distribution was 6 black, 3 white, and 0 Hispanic. There was a previous diagnosis of asthma in 9 cases, and 1 case was diagnosed based on the gross and microscopic findings at autopsy. None of the cases had shortness of breath or respiratory distress before the demise, and 1 (10%) had a witnessed collapse, whereas 8 (80%) were subsequently found dead. One case had a history of a cold and severe headache, and it was unclear if there was a witnessed collapse or if the decedent was found dead. Eight of these cases listed drugs as the cause of death, whereas 2 listed asthma as the cause of death. Table 2 summarizes the 10 cases of sudden death with a history of asthma and toxicology positive for opioids.

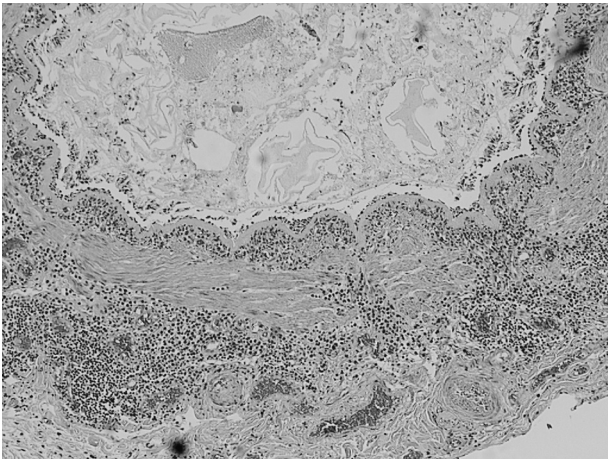


FIGURE 2. Bronchial basement membrane thickening, smooth muscle hypertrophy, and an inflammatory cell infiltrate that includes eosinophils, hematoxylin and eosin stain at $\times 10$ magnification.

TABLE 1. Cases With Asthma as the Cause of Death and Toxicology Findings

Demographics	Presentation	Toxicology Findings in Peripheral Blood
43 white female	SOB, WC	Ethanol
24 black female	FD	Diphenhydramine
49 black female	SOB, WC	Benzoylcegonine
23 black male	SOB, WC	Acetaminophen
52 black male	SOB, WC	Dextromorphan
37 black male	SOB, FD	Chlorpheniramine
15 white female	SOB, WC	Ethanol
32 white female	SOB, WC	Ethanol
20 black male	FD	Quetiapine
15 black male	FD	Diphenhydramine
38 black male	SOB, WC	Ethanol
53 black female	FD	Ethanol
54 black male	FD	Ethanol
23 black female	SOB, WC	Diphenhydramine
53 black female	FD	Methadone, phentermine, diazepam, diphenhydramine
51 white male	FD	Alcohol
54 black female	SOB, WC	Alcohol
48 black female	FD	Morphine (6-MAM negative), benzoylcegonine
45 black female	SOB, WC	Sertraline, trazodone, mirtazapine
57 black female	SOB, WC	Imipramine, desipramine, benzotropine, Haldol, paroxetine

SOB indicates shortness of breath; FD, found dead; WC, witnessed collapse; 6-MAM, 6-monoacetylmorphine.

Compared with the cases that listed asthma as the cause of death, those with asthma using opiates showed a higher mean age (43 years compared with 32 years), no history of shortness of breath or respiratory distress immediately before death (0% compared with 68%), and a more frequent presentation of being found dead (80% compared with 28%). Table 3 summarizes this comparison.

DISCUSSION

Asthma is a chronic inflammatory disorder of the airways characterized by hyperreactivity, with reversible airflow obstruction, and respiratory symptoms of an attack that can include shortness of breath or respiratory distress.⁴ Substance abuse is a well-known trigger of asthma exacerbations, and it increases the morbidity and mortality of asthma.⁵ Previous studies have published deaths in asthma patients who had illicit drugs in the system at the time of death. Hughes and Caverly⁶ reported 2 deaths in asthmatic patients after inhaling heroin, in which both experienced respiratory symptoms and collapsed after using heroin. Weitzman et al⁷ reported 63 asthma deaths in which 8 had positive toxicology for illicit drugs of which morphine and cocaine were equally common. Donoghue et al⁸ reported 92 deaths in asthmatic patients with toxicology testing done, with 31.5% of the cases positive for illicit drugs of which cocaine was the most prevalent. Mohiuddin et al⁹ reported 22 asthma deaths in which 4 had positive toxicology for illicit drugs.

In contrast with these studies, we found opiates or narcotic pain medication to be by far the most common type of drug abused. This is not unique to asthma deaths and is in keeping with opiates being the most common drug of abuse in our population,

TABLE 2. Cases With History and Presentation Suggestive of Asthma and Positive for Opioids

Demographics	History and Presentation	Gross Findings	Microscopic Findings	Peripheral Blood Toxicology	Cause of Death
Black male, aged 38 y	+dx, FD	Hyperinflation, no plugs	TBM, rare plugs, and eosinophils	Morphine, +6-MAM	Heroin toxicity
Black male, aged 16 y	+dx, cold and headache	Normally inflated, no plugs	TBM, no plugs, or eosinophils	Methadone	Methadone toxicity
Hispanic male, aged 61 y	-dx, FD	Normally inflated, no plugs	TBM, rare plugs, and eosinophils	Doxepin, fentanyl	Doxepin and fentanyl toxicity
Black male, aged 53 y	+dx, FD	Hyperinflation, no plugs	TBM, rare plugs, and eosinophils	Morphine, +6-MAM, cocaine, +BEG	Cocaine and heroin toxicity
White female, aged 35 y	+dx, FD	Normally inflated, no plugs	TBM, no plugs, or eosinophils	Morphine, -6-MAM, diazepam, tramadol, olanzapine	Multiple drug toxicity
Black female, aged 32 y	+dx, WC	Hyperinflation, no plugs	TBM, no plugs, or eosinophils	Morphine, +6-MAM, cocaine, +BEG	Cocaine and heroin toxicity
Black male, aged 53 y	+dx, FD	Normally inflated, no plugs	TBM, rare plugs, and eosinophils	Morphine, +6-MAM, cocaine, +BEG	Cocaine and heroin toxicity
White male, aged 43 y	+dx, FD	Normally inflated, no plugs	TBM, no plugs, or eosinophils	Morphine, +6-MAM, cocaine, +BEG, alprazolam	Cocaine and heroin toxicity
White female, aged 53 y	+dx, FD	Hyperinflation and plugs	TBM, florid plugs, and eosinophils	Methadone, diazepam, phentermine, diphenhydramine	Asthma
Black female, aged 48 y	+dx, FD	Hyperinflation and plugs	TBM, florid plugs, and eosinophils	Morphine, -6-MAM, +BEG	Asthma

DX indicates diagnosis; FD, found dead; WC, witnessed collapse; TBM, thickened basement membrane; 6-MAM, 6-monoacetylmorphine; BEG, benzoylecgonine.

excluding marijuana.¹⁰ We also found a slightly older age at death in those asthma patients who used these drugs, and the most frequent presentation was being found dead without any preceding respiratory symptoms.

Although studies have shown linkage between asthma deaths and drug abuse, the process in which opiates exacerbate asthma is still unclear. The mechanism is most likely multifactorial. For instance, circulating opiates stimulate the release of histamine into the bloodstream. The histamines, in turn, activate the parasympathetic nervous system resulting in pulmonary smooth muscle bronchoconstriction. In addition, heroin itself has been shown to degranulate mast cells and trigger the mediators of inflammation.¹¹ Furthermore, opiates cause pulmonary edema and depression of the central nervous system's respiratory compensatory mechanisms.

The fact that judgment is impaired while under the influence of drugs must be considered because drug users with asthma may not adequately comprehend or treat their respiratory symptoms, or may delay seeking additional medical attention until it is too late.¹¹

The socioeconomic of Wayne County's mostly inner-city population must also be taken into account. Social-behavioral interactions can lead to people not seeking treatment for respiratory symptoms and being diagnosed with asthma, not continuing asthma treatments despite ongoing symptoms, and not seeking additional medical treatment in the face of an ongoing acute asthma attack.¹²

A limitation of our study is that we did not know the route of administration of the opiates, particularly heroin. Insufflation or snorting heroin is the most regularly reported route of administration in Detroit, as in most major US cities.¹³ Thus, this method is the most likely route of administration in our cases although it cannot be confirmed. Studies have shown that both intravenously and intradermally administered opiates can cause bronchospasm,¹³ suggesting that the route of administration may not be a significant factor in triggering the onset of an asthma attack.

It is clear that not every individual with a previous diagnosis of asthma who experiences respiratory symptoms before death dies from asthma. In our 94 cases of sudden death in asthmatic

TABLE 3. Comparison of Cases With History and Presentation Suggestive of Death From Asthma, Cases With Death Due to Asthma, and Cases of Asthmatic Patients Who Have Narcotics in Their System

	All Cases (94)	Asthma as COD (68)	Positive for Narcotics (10)
Age	34.6 y (range, 9.5 mo to 58 y)	32 y (range, 23 mo to 58 y)	43 y (range, 16–53 y)
Sex	40 female/54 male	27 female/41 male	4 female/6 male
Race	81 black/12 white/1 Hispanic	59 black/9 white/0 Hispanic	6 black/3 white/1 Hispanic
Previous diagnosis	92	67	9
SOB/RD before demise	50 (53%)	46 (68%)	0
Witnessed collapse	52 (55%)	44 (65%)	1
Found dead	34 (36%)	19 (28%)	8

COD indicates cause of death; SOB, shortness of breath; RD, respiratory distress.

patients, there was no diagnosis before death in 2 cases, and asthma was determined to be present in these 2 cases based on the gross and microscopic findings at autopsy. The presentation of shortness of breath or respiratory distress before a witnessed collapse was present in 53% and 55% of these cases, respectively. Of these 94 cases, 68 were determined to have died as a result of asthma. Of the 68 cases with asthma as the cause of death, the presentation of shortness of breath or respiratory distress before a witnessed collapse was present in 68% and 65% of these cases, respectively. Of the 68 asthma deaths, 20 cases (29%) had positive toxicology findings, and in only 2 of them, drugs were felt to have contributed directly to the death as well. Thus, we must consider each case carefully with regards to the history and presentation, circumstances surrounding the death, gross and microscopic findings at autopsy, and toxicology findings to determine if the cause of death was from asthma or simply with asthma as a chronic condition that did not contribute to death.

We identified a subset of asthma patients who also abused opiates or narcotic pain medications. Compared with the cases of asthma as the cause of death, asthmatic patients using opiates showed a higher mean age, no history of shortness of breath or respiratory distress immediately before death, and a more frequent presentation of being found dead. Thus, it may be possible, based on the clinical history and circumstances surrounding the death, to favor drugs versus asthma as the likely cause of death before additional studies such as histology and toxicology. As death investigation systems evolve under changing government policies and budgets, responsible financial decisions often become a point of scrutiny, and justification for supportive studies, such as toxicology and histology, may be required. Based on our data, although histology is needed in all possible asthma cases, it may be possible to modify toxicology panels to include only the common drugs of abuse based on the age and history/presentation of sudden death in those with asthma.

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