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Noncardiogenic pulmonary edema associated with ultrapotent opioid overdoses

A study of overdose patients presenting to two emergency departments in BC found the incidence of fentanyl-related pulmonary edema was similar to that found in previous studies focusing predominantly on heroin overdoses.

ABSTRACT

Background: Noncardiogenic pulmonary edema is a rare but potentially fatal complication of opioid overdose that must be recognized and managed promptly. The typical presentation includes persistent hypoxia and radiographic findings of bilateral pulmonary infiltrates. Previous studies of pulmonary edema associated with opioids have focused on heroin and not considered drugs such as fentanyl, which make up an increasingly large proportion of the illicit drug supply in BC.

Methods: A retrospective chart review was conducted to determine the incidence of noncardiogenic pulmonary edema in patients with symptoms of opioid overdose presenting to two Vancouver emergency departments from 1 January 2014 to 31 October 2016. Health records were reviewed for all patients who received naloxone or whose chief complaints suggested an opioid overdose. Noncardiogenic pulmonary edema was identified based on radiographic findings of acute bilateral pulmonary infiltrates not attributable to causes other than opioid use.

Results: Reviewers considered 2397 charts. After inclusion and exclusion criteria were applied, 962 charts remained. Radiographic evidence of noncardiogenic pulmonary edema was found in the charts of 11 patients (1.1%). Three of these patients (27%) required intubation. The remaining eight patients were treated with oxygen supplementation alone. Symptoms resolved within 24 hours for the majority of patients. Of the 11 patients, one died after cardiac arrest and all others were eventually discharged.

Conclusions: In cases of ultrapotent opioid overdose, the incidence of noncarcinogenic pulmonary edema and the clinical course of affected patients were similar to those found in previous studies that looked predominantly at heroin overdose cases. This suggests that the risk of developing pulmonary edema from an overdose with an ultrapotent opioid is not greater than the risk posed by an overdose with a less potent opioid such as heroin.

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Background

Noncardiogenic pulmonary edema (NCPE) is an uncommon but potentially fatal complication associated with opioid overdoses that must be recognized and managed promptly. The typical presentation includes persistent hypoxia despite attempts to reverse opioid-induced respiratory depression and radiographic findings of bilateral pulmonary infiltrates. The pathogenesis of this condition was first described in 1880 by William Osler and remains unclear to this day. Possible mechanisms for NCPE include lung injury from direct opioid exposure, tissue hypoxia, inspiration against a closed glottis, and catecholamine surge following naloxone administration.[1]

Previous studies of pulmonary edema associated with opioids have focused on heroin and not considered drugs such as fentanyl, which make up an increasingly large proportion of the illicit drug supply in BC. In April 2016 a public health emergency was declared in the province following an alarming rise in fentanyl-related overdoses and deaths. In the course of 5 years the number of drug-related fatalities increased more than fivefold, rising from 269 deaths in 2012 to 1452 deaths in 2017, with fentanyl being detected in 76% of cases [**Figure**].[2]

Given the high percentage of fentanyl-related deaths identified in British Columbia, a study was proposed to determine the incidence and clinical characteristics of

noncardiogenic pulmonary edema associated with ultrapotent opioids.

Methods

A retrospective chart review was conducted to determine the incidence of noncardiogenic pulmonary edema in patients with symptoms of opioid overdose presenting to emergency departments at two tertiary care hospitals in Vancouver from 1 January 2014 to 31 October 2016.

Health records were reviewed for all patients who received naloxone or whose chief complaints suggested an opioid overdose. Documents pertaining to each hospital visit were considered, including emergency health service notes, nursing notes, consultation summaries, and discharge summaries. Relevant chart information from eligible patients was collected using REDCap software (https://projectredcap.org). Noncardiogenic pulmonary edema was identified based on radiographic findings of acute bilateral pulmonary infiltrates not attributable to causes other than opioid use.

The chart reviews were completed by emergency medicine research assistants and trained medical students. In cases with ambiguous findings, additional reviews were completed by a panel consisting of two medical toxicologists and one emergency nurse.

Ethics approval for the study was obtained from the UBC Clinical Research Ethics Board (certificate H16-01446).

Results

Reviewers considered 2397 charts describing a possible drug overdose or naloxone administration. After applying inclusion and exclusion criteria [**Table**], 962 charts remained to be reviewed for evidence of NCPE, patient demographic characteristics, patient management, and patient disposition.

Radiographic evidence of NCPE was found in the charts of 11 patients (1.1%). No repeat cases of NCPE were found.

The combined mean age of all 962 patients whose charts were reviewed was 40 years (range 19 to 96). Of these, 714 patients were male (74.2%) and 248 were female (25.8%).

The mean age of the patients with NCPE was 49 years. Four patients were female with a mean age of 40 (range 32 to 46) and seven patients were male with a mean age of 51 (range 17 to 65).

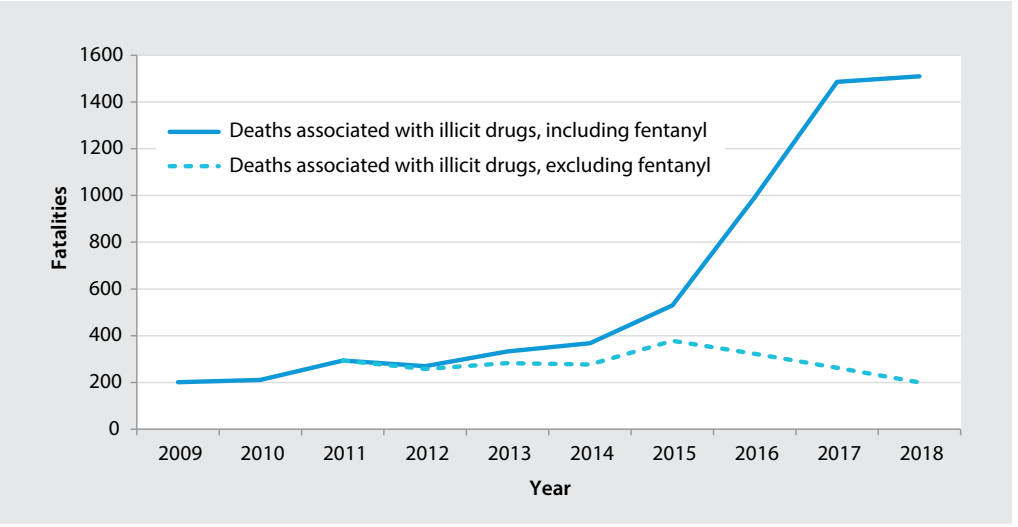

FIGURE. Comparison of illicit drug overdose deaths in BC including and excluding fentanyl, 2009 to 2018. Source: British Columbia Coroners Service.

Management

Of the 11 patients who developed NCPE, 9 received naloxone from emergency health services before arriving at the hospital and 2 received naloxone in the ED. No patients underwent bystander naloxone resuscitation. One patient received 4 mg of naloxone after he was found in cardiac arrest from intranasal fentanyl use, and all others received initial naloxone doses between 0.2 mg and 1.2 mg.

Three patients (designated 1, 2, and 3) were intubated, one in the field when he was found in cardiac arrest secondary to opioid toxicity, and two in the ED due to respiratory failure.

Patient 1 was found in asystol 1 hour after overdosing on intranasal fentanyl. He was intubated and resuscitated. Subsequently he was found to have sustained severe and irreversible hypoxic brain injury and the decision was made by the family to withdraw care.

Patient 2 was initially found in respiratory arrest. He became tachypneic and extremely agitated after naloxone resuscitation, eventually requiring sedation with midazolam. He was intubated after he continued to decompensate, with oxygen saturation of 77%, respiratory rate of 28 breaths per minute, and systolic blood pressure of 77 mm Hg. Patient 2 was intubated for 30 hours and after extubation left hospital against medical advice.

Patient 3 was also found in respiratory arrest and was intubated for failure to maintain airway patency. Following naloxone resuscitation, he opened his eyes and became tachypneic at 30 breaths per minute but was unable to vocalize. Ventolin and epinephrine were administered with no response, three more doses of naloxone were administered, and then he was intubated for impending respiratory failure. This patient self-extubated 2 days later and received 7 days

TABLE. Criteria for study of patients with opioid-related noncardiogenic pulmonary edema.

Inclusion criteria	Exclusion criteria
• Patient presented to the emergency department with symptoms of opioid overdose, 1 January 2014 to 31 October 2016. • Patient was treated with naloxone.	• Health records did not contain enough information for review. • Health record review indicated that patient did not have opioid overdose.

of treatment for an aspiration pneumonia before discharge.

Of the eight patients who were not intubated, four were persistently hypoxic with oxygen saturations ranging from 77% to 87% despite naloxone administration and adequate respiratory rate response. One of these patients developed a respiratory rate of 34 breaths per minute with oxygen saturation of 77% on 6 L of oxygen and coughed up pink frothy sputum following the reversal of opioid toxicity. She was admitted to a ward and discharged within 48 hours. Another patient was transferred to the ICU for recurrent hypoxia and re-sedation requiring a naloxone infusion. All patients were treated with oxygen supplementation by nasal prong or simple face mask to maintain oxygen saturations above 92%.

In our study, symptoms resolved in 75% of patients within 24 hours and in 25% of patients by 48 hours.

Disposition

Of the 11 patients with NCPE, one died and the rest were eventually discharged.

Looking at the eight patients who were not intubated, hypoxic symptoms resolved within 24 hours in six patients, and by 48 hours in the other two. Regarding disposition from the ED, one patient was admitted to the ICU for monitoring because of recurrent episodes of hypoxia, four were admitted to a ward, and three were discharged home.

Of the four patients admitted to a ward, one patient was admitted for treatment of rhabdomyolysis and one was admitted because he developed *Clostridium difficile* infection following antibiotic treatment in the ED for a presumed aspiration pneumonia. This patient had a WBC count of 15.3 x 10^9 /L but was afebrile and his sputum culture results were negative. Radiographs revealed "patchy opacities" and "findings of probable mild edema." Aspiration pneumonia could not be definitively ruled out in this case, but is unlikely.

Conclusions

To our knowledge, this is the first study to consider noncardiogenic pulmonary edema in patients presenting to the ED with symptoms of ultrapotent opioid use. NCPE is a well-recognized but rare complication of opioid use that has been studied in cases involving heroin but not in cases involving ultrapotent opioids such as fentanyl. In British Columbia, where a public health emergency was declared following a rise in fentanyl-related overdoses and deaths, we found an NCPE incidence of 1.1%, which is similar to the previously reported incidence from heroin use.

Three retrospective studies of NCPE associated with heroin use have shown incidence rates of 0.8%,[3] 2.4%,[4] and 2.1%.[5] This last rate found by Sporer and Dorn[5] is notable for being from the most recent and largest case series (N= 27) of heroin-associated NCPE.

Higher incidence rates were found in two older studies. For example, a retrospective study of 149 heroin overdose patients presenting to a New York inner-city hospital between 1968 and 1970 reported 71 cases of pulmonary edema (48%).[6] Another study of 39 patients with heroin-related symptoms presenting to Johns Hopkins Hospital between 1964 and 1969 reported eight cases of pulmonary edema (21%).[7] The two studies, however, considered only heroin overdose patients admitted to hospital and were therefore subject to significant selection bias. One would expect a higher proportion of NCPE cases in admitted patients than in those presenting to the emergency department with heroin overdose symptoms.

Both our study and Sporer and Dorn's found similar intubation rates (27% and 33%,[5] respectively) and reported that all other patients were managed with supplemental oxygen by nasal prong or simple face mask. In all cases, respiratory failure was apparent within the first half hour following reversal of the overdose. Patients who were not intubated also followed similar clinical courses in the two studies. In our study, symptoms resolved in 75% of patients within 24 hours and in 25% of patients by 48 hours. In Sporer and Dorn's study, symptoms resolved in 74% of patients within 24 hours and in 26% of patients by 48 hours.[5] These findings suggest that ultrapotent opioids are not associated with higher rates of respiratory failure requiring intubation than heroin.

Though the exact pathophysiology of NCPE remains unknown, autopsy results have shown that nearly all patients who have died after an opioid overdose have findings of pulmonary edema. This suggests that the cause of the pulmonary edema may be a primary effect of opioids rather than a response to naloxone or the associated opioid withdrawal response.[8,9] If this is the case, then the increased efficiency of emergency medical services in providing naloxone in the field may have reduced the incidence of heroin-related NCPE over the past 50 years in the same way that prehospital care appears to have reduced heroin-related deaths.[4] All patients in our study were given naloxone prior to imaging, so it is difficult to separate the effects of the opioid from the effects of the naloxone in the development of NCPE. Additionally, not all patients showed overt clinical signs of pulmonary edema, so it was difficult to establish the time of onset.

Limitations of study

The study was subject to the limitations expected with a retrospective chart review methodology, including those related to incomplete or missing chart information and variations in physician practice patterns. This last limitation is especially relevant regarding the decision to obtain a chest radiograph. Our results could be an underestimation of the true incidence of NCPE, as some treating physicians may not have sent mildly symptomatic patients for radiographs. In addition, ED charts do not always accurately account for comorbid conditions and we may have unwittingly included cases of pulmonary edema attributable to causes other than opioid overdose.

Finally, the use of ultrapotent opioids in the cases studied is difficult to establish definitively, as these synthetic opioids are often found as contaminants in the illicit drug supply

and are not detected on typical urine screening tests. There is often no clinical utility in testing specifically for ultrapotent opioids, so the presence of these opioids is not reported. However, it appears that fentanyl is pervasive in the British Columbia opioid drug supply as it has been detected in up to 76% of illicit drug-related deaths,[2] and up to 86% of street drugs tested.[10,11]

Implications of study

The incidence of NCPE in patients treated for ultrapotent opioid overdoses and their clinical course, including intubation rates and time to symptom resolution, were similar to those found in previous studies that looked predominantly at heroin overdoses. This suggests that the risk of developing pulmonary edema from an ultrapotent opioid overdose is not greater than the risk posed by an overdose with a less potent opioid such as heroin. ■

Acknowledgments

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Competing interests

None declared.

References

1. Radke JB, Owen KP, Sutter ME, et al. The effects of opioids on the lung. Clin Rev Allergy Immunol 2014; 46:54-64.
2. BC Coroners Service. Illicit drug overdose deaths in BC. Posted 19 March 2019. Accessed 6 May 2019. www2.gov.bc.ca/assets/gov/birth-adoption-death-marriage-and-divorce/deaths/coroners-service/statistical/illicit-drug.pdf.
3. Smith DA, Leake L, Loflin JR, Yealy DM. Is admission after intravenous heroin overdose necessary? Ann Emerg Med 1992;21:1326-1330.
4. Bertini G, Russo L, Cricelli F, et al. Role of a prehospital medical system in reducing heroin-related deaths. Crit Care Med 1992;20:493-498.
5. Sporer KA, Dorn E. Heroin-related noncardiogenic pulmonary edema: A case series. Chest 2001;120: 1628-1632.
6. Duberstein JL, Kaufman DM. A clinical study of an epidemic of heroin intoxication and heroin-induced pulmonary edema. Am J Med 1971;51:704-714.
7. Morrison WJ, Wetherill S, Zyroff J. The acute pulmonary edema of heroin intoxication. Radiology 1970; 97:347-352.
8. 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;24:1276-1282.
9. Karch SB, Stephens BG. Toxicology and pathology of deaths related to methadone: Retrospective review. West J Med 2000;172:11-14.
10. Amlani A, McKee G, Khamis N, et al. Why the FUSS (Fentanyl Urine Screen Study)? A cross-sectional survey to characterize an emerging threat to people who use drugs in British Columbia, Canada. Harm Reduct J 2015;12:54.
11. Vancouver Coastal Health. 86% of drugs checked at Insite contain fentanyl. [news release] Posted 31 August 2016. Accessed 6 May 2019. www.vch.ca/about- us/news/news-releases/86-of-drugs-checked-atinsite-contain-fentanyl.