Heroin-Related Noncardiogenic Pulmonary Edema*

A Case Series

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Study objectives: To examine the current clinical spectrum of noncardiogenic pulmonary edema (NCPE) related to heroin overdose.

Design: Retrospective chart review of all identified patients from August 1994 through December 1998.

Setting: Urban academic hospital.

Patients or participants: Heroin-related NCPE was defined as the syndrome in which a patient develops significant hypoxia (room air saturation < 90% with a respiratory rate > 12/min) within 24 h of a clinically apparent heroin overdose. This should be accompanied by radiographic evidence of diffuse pulmonary infiltrates not attributable to other causes, such as cardiac dysfunction, pneumonia, pulmonary embolism, or bronchospasm, and which resolve clinically and radiographically within 48 h.

Interventions: None.

Measurements and results: Twenty-seven patients were identified during this 53-month period, with a majority being male patients (85%; average age, 34 years). Twenty patients (74%) were hypoxic on emergency department arrival, and 6 patients (22%) had symptoms develop within the first hour. One patient had significant hypoxia develop within 4 h. Nine patients (33%) required mechanical ventilation, and all intubated patients but one were extubated within 24 h. Eighteen patients (66%) were treated with supplemental oxygen alone. Hypoxia resolved spontaneously within 24 h in 74% of patients, with the rest (22%) resolving within 48 h. Twenty patients (74%) had classical radiograph findings of bilateral fluffy infiltrates, but unilateral pulmonary edema occurred in four patients (15%) and more localized disease occurred in two patients (7%).

Conclusion: NCPE is an infrequent complication of a heroin overdose. The clinical symptoms of NCPE are clinically apparent either immediately or within 4 h of the overdose. Mechanical ventilation is necessary in only 39% of patients. The incidence of NCPE related to heroin overdose has decreased substantially in the last few decades.

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Key words: heroin; noncardiogenic; poisoning; pulmonary edema

Abbreviations: ED = emergency department; NCPE = noncardiogenic pulmonary edema; PA = pulmonary artery

Heroin use has increased dramatically in the United States during the past decade, and heroin-related emergency department (ED) visits have increased 110% between 1990 and 1995.1 In 1996, heroin overdose was responsible for 14,300 ED visits as well as 4,178 deaths.2

In certain western cities, the death toll from heroin overdoses has become the largest category of preventable deaths. In San Francisco, more people die of a heroin overdose than all causes of trauma combined.3 The actual mechanism of death caused by a heroin overdose has not been adequately explained.4 The one striking finding is the almost universal occurrence of noncardiogenic pulmonary edema (NCPE) in the fatal overdose.4–6 It is hoped that a better understanding of NCPE in patients with nonfatal heroin overdoses may lead to a partial explanation of the mode of death in a heroin overdose and can lead us in directions that may decrease the death rate from this street drug. An appreciation of the incidence of NCPE in heroin-overdose patients may also give us insight into proper treatment of patients with nonfatal heroin overdoses.

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Clinical Investigations in Critical Care
NCPE is a well-known severe complication of heroin overdose that was first described by William Osler during an autopsy in 1880. The presentation and clinical course of NCPE patients with nonfatal heroin overdoses were first described in 1953, and later in a variety of case series and reports.

A heroin overdose is routinely clinically diagnosed by noting the combination of altered mental status, severely decreased respiratory drive, pinpoint pupils, and circumstantial evidence of drug use. NCPE related to a heroin overdose usually presents as the combination of persistent hypoxia after resolution of opiate respiratory depression along with frothy, pink-tinged pulmonary secretions, and a characteristic radiograph pattern of fluffy diffuse pulmonary infiltrates. Some of these patients require mechanical ventilation to treat their hypoxia. The symptoms usually resolve rapidly with supportive care alone within hours to 1 or 2 days.

NCPE has also been reported with overdoses of methadone, propoxyphene, codeine, buprenorphine, and nalbuphine. There is also an unrelated syndrome of cardiogenic pulmonary edema that has been rarely reported with the use of naloxone or nalmefene to reverse therapeutic doses of opiates after anesthesia.

**Materials and Methods**

This study took place at San Francisco General Hospital, an urban hospital with > 75,000 ED visits per year. The University of California, San Francisco Committee of Human Research approved this study.

Most heroin overdoses are diagnosed and initially treated by paramedics. After making the presumptive diagnosis of a heroin overdose (a patient with an abnormal level of consciousness, pinpoint pupils, and decreased or absent respirations), the patient is treated with a bag-valve mask and supplemental oxygen along with an IM dose of naloxone, 2 mg. Approximately 70% of the heroin-overdose patients in San Francisco are transported to San Francisco General Hospital. In the ED, heroin-overdose patients (74%) were hypoxic on presentation to the ED, and 6 patients (22%) had severe hypoxia develop during the first hour. One patient (4%) presented with a room air oxygen saturation of 93% and a respiratory rate of 18/min that worsened within 4 h to a room air oxygen saturation of 81%. Characteristic radiographic findings of pulmonary edema developed in this patient.

There were no episodes of hypoventilation in this group of patients. The respiratory rate ranged from 16 to 44/min (average, 24/min). The initial oxygen saturation ranged from 47 to 89% on room air, with an average oxygen saturation of 76%. Thirty-three percent of these patients required mechanical ventilation to achieve adequate oxygenation, while most of the patients (66%) were treated with oxygen via nonrebreather face mask and observation only. There were three patients who presented with hypotension (systolic BP < 90 mm Hg). These episodes resolved spontaneously with < 500 mL of crystalloid fluid resuscitation.

The hypoxic symptoms of a majority of patients (74%) resolved within 24 h, several within 8 h. The other six patients (22%) had resolution of symptoms within 24 to 48 h. All intubated patients but one were extubated within 24 h. This patient required a prolonged ICU stay partially because of an iatrogenic pneumothorax.

Classic chest radiographic findings of bilateral pulmonary edema were noted in 20 of the 27 patients (74%). Interestingly, four patients presented with chest radiographic findings of unilateral pulmonary edema, a finding that has been previously reported.

Three other patients had chest radiographic findings of "patchy atelectasis" (n = 2) and "nodular interstitial pattern" (n = 1). These results were confirmed by one of the authors (E.D.) for appropriateness of the diagnosis of NCPE. Most patients were admitted to the hospital for a variety of other medical reasons, such as pneumonia, possible endocarditis, persistent confusion, cellulitis, etc. Borderline cases (eg, atypical pneumonia) were reviewed by the first author (K.A.S.) for consistency with the diagnosis.

**Results**

There were 1,278 patients who presented with the diagnosis of heroin overdose in our hospital during this 53-month period; 162 of these patients were admitted to the medical service, and a total of 27 patients met the criteria for the diagnosis of NCPE. There were 23 male patients in this NCPE cohort, and the average age was 34 years. There were no repeat cases among the NCPE group. The repeat rate for all heroin-overdose patients has been shown to be extremely small in our city.

All patients but one received prehospital naloxone. Twenty patients (74%) were hypoxic on presentation to the ED, and 6 patients (22%) had severe hypoxia develop during the first hour. One patient (4%) presented with a room air oxygen saturation of 93% and a respiratory rate of 18/min that worsened within 4 h to a room air oxygen saturation of 81%. Characteristic radiographic findings of pulmonary edema developed in this patient.

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patients did not undergo bronchoscopy to definitively rule out aspiration pneumonia, but the absence of an increased WBC count and the very rapid resolution of the symptoms and the radiographic findings make this less likely. Rhabdomyolysis was diagnosed in two of these patients, and they were treated with fluid replacement and sodium bicarbonate. Neither patient developed renal insufficiency.

**Discussion**

We have presented the clinical characteristics of the largest case series of heroin-related NCPE since the 1960s. NCPE is an infrequent complication of patients who present with an acute heroin overdose. The symptoms of significant hypoxia with an adequate respiratory rate usually occur rapidly after treatment. The radiographic findings are usually bilateral fluffy infiltrates, but a percentage of patients can have unilateral or lobar disease. Only 33% of these patients require intubation. Most patients required only supplemental oxygen, and most of these patients’ symptoms resolve within 24 h.

The epidemiology of NCPE has changed over the last 40 years. Earlier retrospective case series of heroin-overdose patients admitted to the hospital have described a NCPE rate of 48 to 80%. The full denominator, including heroin-overdose patients admitted to and discharged from the hospital, was not available in these studies. More recent case series of patients presenting with heroin overdoses have a NCPE rate of 0.8% to 2.4%, similar to our rate of 2.1%.

The decreased rate of NCPE in patients with nonfatal heroin overdoses can be partially explained by including the full denominator of heroin-overdose patients admitted to and discharged from the hospital. But this alone cannot explain all of the difference. These earlier case series occurred before naloxone was readily available. This specific narcotic antagonist may be instrumental in decreasing the number of patients with nonfatal heroin overdoses with NCPE. The improvement of emergency medical services with the earlier prehospital administration of naloxone and oxygen may also add to this improvement.

This early experience with high rates of NCPE is the likely reason for the extended recommended observation period of 12 to 24 h that is commonly quoted. Because NCPE is a relatively uncommon event in heroin-overdose patients and usually presents early, a 1-h to 2-h observation period should be adequate for these patients. One prospective study demonstrated that these patients rarely return to the hospital for subsequent treatment.

The pathophysiology of NCPE related to heroin overdose has never been adequately explained. This is of interest not because of its relative infrequency in nonfatal heroin overdose, but because of its almost universal occurrence in fatal heroin overdose. This may suggest that this entity may be a partial explanation for the mode of death in a heroin overdose.

The investigations into the cause of heroin-related NCPE have been limited. Hemodynamic evaluation of a total of 11 patients with heroin-related NCPE demonstrated normal or increased cardiac output, normal pulmonary capillary pressure, and only moderately elevated pulmonary artery (PA) pressure. Pulmonary fluid analysis of patients with this syndrome confirmed a much higher protein concentration, as compared to edema fluid from patients with congestive heart failure, consistent with the hypothesis that leaky pulmonary capillaries and not pump failure are the likely cause of heroin-related NCPE.

The only animal model of opiate-induced pulmonary edema examined the effect of morphine on the pulmonary vasculature in perfused, normally oxygenated cats and dogs. A large dose of morphine caused a highly variable increase in pulmonary vascular resistance via venous vasoconstriction. Animals with a mild-to-moderate increase in PA pressure recovered spontaneously and returned to baseline. The animals with a marked increase in PA pressure had pulmonary edema develop within 20 to 30 min. The increase in PA pressure was reversed by chlorpheniramine, a histamine type 1-receptor antagonist. Pretreatment with naloxone blunted this response but had no effect in posttreatment.

Histamine has been implicated as a possible mediator of NCPE related to heroin overdose. Human lungs are rich in histamine, and opiates have been shown to cause its systemic and local release. Histamine has been shown to increase pulmonary lymph flow and capillary permeability. One study of patients with fatal heroin overdoses demonstrated a modest correlation with elevated trypsin levels (a postmortem histamine surrogate), as compared to control subjects.

**Conclusion**

To our knowledge, this is the largest case series of NCPE reported in several decades. NCPE is an infrequent complication of nonfatal heroin overdoses, with an incidence of 2.1% in our hospital. The symptoms of significant hypoxia with an adequate respiratory rate usually occur rapidly after treatment. The radiographic findings are usually bilateral fluffy...
infiltrates, but a significant percentage of patients can have unilateral or lobar disease. Only 33% of these patients require mechanical ventilation. A majority of patients only required supplemental oxygen, and symptoms in most of these patients resolved within 24 h.

REFERENCES

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