Severe Slowly Resolving Heroin-Induced Pulmonary Edema

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Severe heroin-induced pulmonary edema occurred in three previously healthy young men. Adequate arterial 
PO2 could only be achieved with the use of positive end-expiratory pressure (PEEP). Recovery was characterized by the gradual clearing of the pulmonary infiltrates and a gradual lessening of the severe restrictive ventilatory de-
fects over many weeks. Concomitant aspiration of gastric acid was thought to be the explanation for the severity of these cases. In cases such as these, initial vigorous therapy, including PEEP for hypoxia, corticosteroids for possible aspiration and volume replacement for hypotension, is recommended.

Pulmonary edema is commonly associated with heroin overdose.1-4 Previous reports have emphasized that in most patients with this syndrome the clinical, radiologic and arterial blood gas improvements are rapid and are complete within a few days. Moreover, most patients do not have refractory hypoxemia necessitating artificial ventilation with positive end expiratory pressure (PEEP).

The following three cases seen at this hospital in the past year with severe pulmonary edema secondary to heroin overdose are presented to emphasize the following: (1) The hypoxemia associated with heroin pulmonary edema may be severe but can be managed with PEEP. (2) Concomitant aspiration of gastric acid can occur and systemic corticosteroids should be started as soon as the diagnosis is made. (3) The possibility of intravascular fluid depletion should strongly be considered in these patients who are hypotensive. (4) The pulmonary infiltrates and the severe restrictive ventilatory defects may persist for weeks but do gradually improve.

CASE REPORTS

CASE 1

A 23-year-old man was admitted comatose to this hospital on November 11, 1972. A short time prior to admission he had been found unconscious, cyanotic and frothing at the mouth in his barracks. He was taken to the local dispensary, intubated and given 10 mg nalorphine HCL intravenously and transferred to this hospital. It was thought that he had aspirated gastric material since food particles were obtained from his lungs after intubation. His past medical history was unremarkable except for occasional drug abuse. He subsequently admitted using heroin intravenously on the day of admission. Physical examination revealed a comatose, cyanotic man with shallow respirations and a respiratory rate of 24. His pupils were pinpoint and did not respond to light. Auscultation of the lungs revealed coarse rhonchi and rales throughout both lung fields.

The admission chest x-ray film revealed diffuse alveolar infiltrates. The patient was treated with penicillin and hydrocortisone intravenously for possible aspiration pneumonia. The arterial blood gases after intubation with the patient on a volume type respirator and 100 percent O2 revealed a pH of 7.37, PacO2 of 38 cm H2O and a PaO2 of 22 cm H2O. Over the next 24 hours, much difficulty was encountered in maintaining adequate arterial oxygenation with a volume type respirator. At this time the addition of 5 cm H2O positive end-expiratory pressure with 60 percent inspired O2 resulted in a PaO2 of 66. The patient improved and was extubated 38 hours post-admission. This patient was never hypotensive. He had a low grade fever during the first 72 hours and then spiked to 39.4°C, but no pathogens were ever grown from either the sputum or blood.

A repeat chest x-ray film four days after admission demonstrated only partial clearing of the pulmonary infiltrates. Serial films demonstrated persistence of the infiltrates. The forced vital capacity (FVC) 2½ weeks after admission was 53 percent of predicted, but there was no evidence of obstruction. Repeat pulmonary function tests and a chest x-ray film one week later were unchanged. Arterial blood gases at this time revealed PaO2 of 70, PacO2 of 32 and pH of 7.44.

The patient was asymptomatic and could climb four flights of stairs without difficulty. In February 1973, the FVC had increased to 82 percent of predicted, the arterial blood gases were normal and the chest x-ray film was completely normal.

CASE 2

A 20-year-old man was admitted comatose to this hospital on February 3, 1973. Approximately two hours prior to admission he had been found unresponsive in his barracks.

His past medical history was unremarkable except for occasional heroin abuse. He subsequently admitted using heroin intravenously shortly before he became comatose. On admission he was comatose, cyanotic and nearly apneic. There were rales and rhonchi throughout both lung fields, and there was a regular tachycardia of 130 per minute.

He was intubated and given 15 mg of nalorphine HCL intravenously. Endotracheal suction revealed bloody pulmonary edema fluid with some food particles. After the patient was put on a volume respirator with 50 percent oxygen, the

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light, showed extensive bilateral pulmonary infiltrates. The tubes alveolar infiltrates. A repeat roentgenogram six days after which necessitated intubation. The patient subsequently admitted the use of intravenous heroin just prior to his illness. He became hypotensive shortly after being admitted and metaraminol was used over the next 12 hours to maintain a systolic pressure of 100 mm Hg. He also developed a temperature in the 38.8° to 39.4°C range in the first six hours of hospitalization and remained afebrile for the following 72 hours. Multiple cultures of the blood, sputum and urine grew no pathogens. Because of purulent sputum, the patient was started on tetracycline on the third hospital day and he was afebrile after the sixth day.

The chest x-ray film on admission revealed diffuse bilateral alveolar infiltrates. A repeat roentgenogram six days after admission revealed that the infiltrates had improved but they did not clear completely for more than three weeks. Within two weeks the arterial blood gases at rest were nearly normal. The original spirogram attained one week after admission showed a severe restrictive ventilatory defect without any evidence of obstruction. Over the following six weeks, the patient became completely asymptomatic and the FVC increased to 70 percent of predicted.

Case 3

A 21-year-old man was admitted to the hospital on July 9, 1973. Shortly before admission he had been found staggering around his barracks and shortly thereafter had become comatose. He was taken to the nearest dispensary and upon arrival there became apneic. He was given 0.4 mg naloxone hydrochloride intravenously and there was a spontaneous return of respirations, but he remained semicomatose with pinpoint pupils.

Upon arrival at this hospital he had normal blood pressure, pulse and chest examination. However, a few minutes later fulminant pulmonary edema and cyanosis ensued which necessitated intubation. The patient subsequently admitted the use of intravenous heroin just prior to his illness. He had used heroin on only one previous occasion.

Blood pressure was 110/80, pulse rate 110 and respiratory rate was 50. Physical examination was normal except for cyanosis and diffuse inspiratory and expiratory rales throughout both lung fields. He expectorated copious amounts of blood-tinged pulmonary edema fluid.

The patient was placed on a volume respirator with 60 percent oxygen. Afterwards, Po2 was 31, Paco2 was 42, pH was 7.16 and bicarbonate was 14.2. The chest x-ray film showed extensive bilateral pulmonary infiltrates. The hematocrit was 57 and the white blood cell count was 5,000 with a normal differential. The patient was then given 5 ampules of sodium bicarbonate and placed on 100 percent oxygen with a PEEP of 5 cm H2O. This corrected the acidosis but the Paco2 increased only to 33 mm Hg. The patient then developed atrial fibrillation with a ventricular rate of 190 and was cardioverted. He then became hypotensive and was started on metaraminol. The infusion of four units of salt free albumin over the next several hours alleviated the need for metaraminol. He was also treated with intravenous dexamethasone for three days.

Over the next 72 hours a Po2 above 40 mm Hg could only be maintained with a PEEP of 15 cm H2O. The patient developed left pneumothorax on the third hospital day and right pneumothorax on the fifth hospital day for which chest tubes were inserted. He experienced temperature elevations to 40.0°C over the first week of hospitalization and was treated with cephalothin and gentamicin although multiple blood, sputum and urine cultures grew no pathogens.

Gradually the patient improved and was extubated on the fifth hospital day. Chest x-ray films revealed gradual clearing, but some infiltrates still persisted after almost four weeks. Arterial blood gases gradually improved; however, on August 9, with the patient breathing room air the Po2 was still only 72 with a Paco2 of 37 and a pH of 7.44. Serial spirometry demonstrated a severe restrictive ventilatory defect which continued to improve up until the time of discharge. The FVC was only 9 percent of predicted one week post extubation but gradually increased to 37 percent of predicted over the next three weeks. At this time the patient was asymptomatic and could climb two flights without difficulty.

Discussion

The mortality associated with heroin-induced pulmonary edema is significant. In the two largest reported series,1,2 22 of 177 (12.4 percent) of the patients died. The clinical course of those patients who died was often characterized by refractory hypoxemia, but none was treated with PEEP. The usefulness of PEEP in increasing the arterial Po2 in other situations characterized by refractory hypoxemia is well documented.5,8 Lutch and Murray9 raised the possibility that the PEEP might decrease the cardiac index and thus impair tissue oxygenation even though the arterial Po2 increased. However, recent studies by Nicotra and co-workers6 have shown that the mixed venous oxygen content increases in the patients that benefit from PEEP.

The three patients in this report all appeared to benefit from PEEP. Arterial Po2 above 50 cm H2O could be achieved only with PEEP. There have been only scattered reports of the use of PEEP with opiate-induced pulmonary edema. Leftwich and colleagues7 mention two cases of heroin-induced pulmonary edema that appeared to benefit from PEEP, but did not give details. Schaaf and associates10 reported one case of methadone-induced pulmonary edema that appeared to benefit from PEEP. PEEP has an important role in the management of heroin-induced pulmonary edema and should be instituted whenever an arterial Po2 of at least 50 mm Hg cannot be obtained with an FIO2 of 50 percent. Its early institution should prevent some cases of oxygen toxicity which occur when high inspired concentrations of oxygen are given for more than 24 hours.11 Once therapy with PEEP is started a constant alert for pneumothoraces must be maintained. As many as 50 percent of patients6 receiving PEEP will develop pneumothorax as did one of our patients.

The persistence of pulmonary infiltrates for over three weeks in our patients is distinctly unusual in heroin-induced pulmonary edema. Most of the previously reported cases1,4 have had complete clearing of the pulmonary infiltrates at five days and
almost all have had complete radiologic clearing within 14 days. Schachter and Basta\textsuperscript{12} reported two patients who had persistent pulmonary infiltrates for many weeks after heroin-induced pulmonary edema. However, both these patients had been on respirators for prolonged periods (9 and 18 days) and their chest x-ray films never cleared. In contrast to our patients they remained very symptomatic, had spirometers characterized by an obstructive rather than a restrictive ventilatory defect and had proved bronchiectasis.

Most patients with heroin-induced pulmonary edema initially have a severe restrictive ventilatory defect, which rapidly improves over several weeks.\textsuperscript{3,4} Frand and co-workers\textsuperscript{5} studied 16 patients within the first few days after heroin-induced pulmonary edema and found that the average FVC was only 47 percent of predicted. It increased rapidly but remained reduced even after the chest x-ray film was clear. They followed none of their patients more than ten days. When their patients were last tested after an average of 6.3 days, the mean FVC was 65 percent of predicted.

The patients in the present series had a more severe and persistent restrictive ventilatory defect than did Frand's patients. Their average FVC on the first measurement was only 30 percent of predicted and after four weeks had only increased to 50 percent of predicted. They resemble two cases of severe methadone-induced pulmonary edema reported by Frand and co-workers\textsuperscript{13} both of whom had a severe restrictive ventilatory defect that only improved gradually over many weeks. It should be emphasized that both the persistent infiltrates and the restrictive ventilatory defect do improve with time and therapy with corticosteroids is not necessary.

The explanation for the severity of the initial pulmonary edema, the marked persistence of the roentgenographic abnormalities and the restrictive pulmonary defect is not clear. Katz and associates\textsuperscript{14} have shown that the average protein concentration in pulmonary edema fluid is much higher (98 percent of serum) when the edema is induced by heroin than when it is due to cardiac disease (40 percent of serum). However, there is no reason to believe that the protein content of the pulmonary edema fluid in our patients was any higher than in those patients with less hypoxia who recover completely within 72 hours. A second factor that could explain the persistent infiltrates is oxygen toxicity. However, since none of our patients received greater than 50 percent oxygen for over 24 hours this appears to be unlikely.\textsuperscript{11}

The most plausible explanation is that the patients also aspirated acidic gastric liquid at the time their sensorium was depressed by the heroin. Since we did not measure the pH of the material aspirated from the pharynx or trachea, we have no proof that this was the case, although food particles were aspirated from the lungs of two patients. The aspiration of acidic gastric contents leads to fulminating pulmonary edema in both the clinical\textsuperscript{19} and experimental\textsuperscript{16-18} setting, and produces a picture similar to that seen with heroin-induced pulmonary edema. The pulmonary edema develops within the first few hours of aspiration, not necessarily immediately. If the patient survives, the chest x-ray film usually becomes normal within the first week. The patients are usually febrile in the period following the aspiration and this is thought to be due to chemical pneumonitis rather than bacterial infection.\textsuperscript{15} However, some patients do develop a superimposed bacterial infection which can lead to severe bronchiectasis and chronic pulmonary insufficiency.\textsuperscript{12}

The hypotension associated with aspiration pulmonary edema is thought to be at least partially due to the loss of large amounts of fluid into the lung.\textsuperscript{15} In experimental studies in dogs, the plasma volume has decreased by as much as 35 percent,\textsuperscript{16} following aspiration. The rapid response of the hypotension to the infusion of salt free albumin in one of our patients (No. 3) supports this hypothesis. Since the pulmonary edema fluid secondary to both heroin-induced\textsuperscript{14} and aspiration-induced\textsuperscript{18} pulmonary edema contains a high concentration of protein, we feel that a judicious trial of salt free albumin or plasma is indicated in hypotensive patients with heroin-induced pulmonary edema.

Experimentally it has been shown that the administration of systemic corticosteroids at the time of aspiration decreases the degree of hypoxia,\textsuperscript{17} increases the rate of resolution of the infiltrate\textsuperscript{18} and decreases the extent of the lesions microscopically.\textsuperscript{19} We feel that systemic corticosteroids should be given to all patients with heroin-induced pulmonary edema since it is often impossible to determine whether or not the patient aspirated.

After reviewing our three cases and those in the literature, we recommend the following therapeutic maneuvers in patients with severe heroin-induced pulmonary edema: (1) Corticosteroids systemically as soon as the diagnosis is made. (2) The employment of PEEP if an arterial $P_O_2$ of 50 cm $H_2O$ cannot be maintained with 50 percent oxygen. (3) A judicious trial of plasma or salt-free albumin if hypotension occurs.

\textbf{References}

16 Awe WC, Fletcher WS, Jacob SW: The pathophysiology of aspiration pneumonitis. Surgery 60:232-239, 1966

**ANNOUNCEMENTS**

**Taos Lung Disease Symposium**

The Third Annual Taos Lung Disease Symposium will be held February 28-March 2 in Taos. For information and an application, write the New Mexico Thoracic Society, 214 Truman Avenue NE, Albuquerque 87108.

**Critical Care Medicine Meeting**

The Society of Critical Care Medicine will hold its annual meeting in Anaheim, California February 16-19. For information, write Dr. David Allan, Children's Memorial Hospital, 2300 Children's Plaza, Chicago 60614.

**Fifth Aspen Radiology Conference**

The Aspen Institute for Humanistic Studies, Aspen, Colorado will be the site for the Fifth Annual Radiology Conference, March 3-7. The Conference is designed for physicians and scientists interested in diagnostic radiology, nuclear medicine and radiation therapy and will explore the impact of clinical and technological advances on radiologic practice. Further information may be obtained from Dr. Maurice O'Connor, Conference Director, Division of Radiology, Denver General Hospital, Denver 80204.

**Thromboembolism: Diagnosis and Treatment**

The American Heart Association (Council on Thrombosis), Florida Heart Association and Heart Association of Greater Miami will present a course on Thromboembolism: Diagnosis and Treatment, at the Doral Beach Hotel, Miami Beach, February 27, 28 and March 1. For further information, contact George E. Stewart, Jr., American Heart Association, 44 East 23rd Street, New York City 10010.