Pulmonary Disease after Amitriptyline Overdosage

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British Medical Journal, 1973, 1, 716-717

A rapidly fatal diffuse pulmonary consolidation after ingestion of amitriptyline is reported. The disease process was accompanied by noticeable loss of lung compliance, and a gross diffusion defect at alveolar level.

It seems unlikely that the course was that of an aspiration or bronchopneumonia, and clinically and pathologically it resembled the changes seen in surfactant deficiency. It is suggested that amitriptyline in overdosage may interfere with the production of surfactant.

Case Report

A 26-year-old housewife was admitted to an intensive care unit three hours after ingesting an unknown quantity of amitriptyline tablets. She was unconscious but responded to painful stimuli. Tendon reflexes were brisk and the plantar responses were extensor. An electrocardiogram showed a heart rate of 100 beats per minute in sinus rhythm, T-wave flattening in V5 and V6, but no bundle-branch block or ectopic beats. There were no abnormal respiratory signs and laryngeal reflexes were present. There was no history of previous chest disease.

After 24 hours she was responding to all stimuli, and became agitated on tactile stimulation. She was still drowsy and irritable at 48 hours but was able to answer simple questions. At this time, however, her temperature rose to 101°F (38.3°C) and a few rales were audible at both lung bases. Routine chest physiotherapy was unproductive. Cloxacillin and ampicillin were started intramuscularly but during the third hospital day the rales became more extensive and a chest x-ray picture showed patchy areas of consolidation in both lung fields. The temperature varied between 99° and 103°F (37.2°-39.4°C).

During the fourth hospital day she became dyspnoeic over a period of four hours. Her level of consciousness had not deteriorated and all reflexes were now normal. Respiratory rate increased to 60 a minute. There was no evidence of bronchospasm. A chest x-ray picture showed diffuse consolidation throughout both lung fields (Fig. 1). In view of the deterioration and unproductive physiotherapy she was intubated, 30% humidified oxygen in air was given, and bronchial suction was performed. Very little secretion was aspirated and bacteriological culture grew no pathogens. She was attached to a Bennett ventilator which was patient triggered. The inspired oxygen was continued at 30%. The antibiotics were changed to penicillin and streptomycin.

On day six she became increasingly distressed and cyanosed while triggering the ventilator. Blood gases showed P_{aO_2} 42 mm Hg and P_{aCO_2} 70 mm Hg (Fig. 2). Rales were audible throughout the lungs, a chest radiograph confirmed generalized consolidation, and bronchial suction remained unproductive. Positive pressure respiration was started with a Barnet III ventilator using a high tidal volume and a minute volume of 15 litres. Intramuscular hydrocortisone was started.

During the next four days inspired oxygen concentration was 40%, temperature varied between 99° and 101°F (37.2°-38.3°C), further culture of lung secretion grew no pathogens, and the chest x-ray appearances remained unaltered. Daily blood gases

FIG. 1—Chest x-ray picture on day 4, showing confluent shadows throughout both lungs.

FIG. 2—Chart of arterial oxygen and carbon dioxide measurements, inspired oxygen concentration, and ventilator pressure from day 6 until death.

were measured, and inspired oxygen concentration was increased to 50% on the 11th day. On the 14th day after admission the ventilator pressure showed a sharp increase to 50 cm of water, and the next day again increased to 55 cm. The inspired oxygen concentration was increased to 60%.

On this day she suddenly became cyanosed. A radiograph (Fig. 3) confirmed a bilateral pneumothorax, and intercostal drains were inserted in both pleural cavities. Expansion of both lungs

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was achieved but inspired oxygen was increased to 100%. Her general condition rapidly deteriorated and she died on the 17th day.

FIG. 3—Chest x-ray picture on day 14 showing bilateral pneumothoraces, air tracking up the mediastinum, and emphysema of the tissues. Shadowing throughout lung fields persists.

During the last two days of life sputum was aspirated for the first time and *Staphylococcus aureus* was cultured. Treatment was started with erythromycin and kanamycin. No improvement in the chest x-ray appearances had occurred.

At necropsy there was severe confluent consolidation extending throughout both lungs. Histologically there was hyaline membrane deposition within the alveoli. In one section there was early abscess formation. The appearances were similar to those seen in the respiratory distress syndrome in infants.

The consequence of the extensive consolidation was extreme non-compliance, and the pneumothorax was no doubt due to the artificial ventilation of a non-compliant lung. Terminal *Staph. aureus* infection was beginning to cause abscess formation.

Comment

Chest disease developed 48 hours after admission and worsened over the next 24 hours. Disease was at alveolar level with a diffusion defect. Adequate arterial oxygen saturation was achieved only with increasing inspired oxygen concentration, and efficient carbon dioxide elimination was maintained by a high minute volume ventilation. Noticeable decrease in compliance necessitated high ventilator inspiratory pressures.

It seems unlikely that the disease was bronchopneumonia as sputum was scanty, culture was negative, and there was no response to antibiotic therapy. In some respects the illness resembled the syndrome of fluid vomit aspiration (Mendelson, 1946). However, during the 48 hours between gastric lavage

and onset of symptoms the patient had an active laryngeal reflex, recovered consciousness, had not taken oral fluids or been seen to vomit. At no time was bronchospasm present.

The deterioration remains unexplained but clinically, radiologically, and pathologically the disease resembles the respiratory distress syndrome where surfactant is deficient. Severe depression of surfactant biosynthesis results in alveolar instability and abnormal pressure-volume relations. The resulting atelectasis and transudation of fluid is accompanied by vascular shunting hypoxaemia, and pulmonary hypoperfusion (Chu *et al.*, 1965).

Other established causes of surfactant deficiency include prolonged intermittent positive pressure respiration with large tidal volume and exposure to high oxygen concentrations. The pathological process in this patient, however, obviously started before oxygen therapy and ventilation.

A syndrome resembling respiratory distress has been reported secondary to drugs—notably, paraquat weedkiller (Oreopoulos *et al.*, 1968) and busulphan (Leake *et al.*, 1963). It also occurred in a child receiving cyclophosphamide and vincristine (Rodin *et al.*, 1970). The present patient had no access to weedkiller, and it appeared from medical records and relatives' evidence that amitriptyline was the sole drug taken in the suicide attempt. Blood barbiturate and salicylate estimations were negative.

Amitriptyline is rapidly absorbed from the intestinal tract, and plasma levels fall rapidly as the drug is concentrated in the tissues, particularly the brain, heart, and lungs. In these organs levels 180-times plasma level have been found (Hucker and Porter, 1961). Severe overdosage produces coma, hyporeflexia with extensor plantar responses, and sometimes convulsions. Extreme agitation may occur spontaneously or after stimulation. Cardiac side effects have been well documented (Freeman *et al.*, 1969). One fatal case of amitriptyline poisoning reported showed bronchiolitis and interstitial pneumonitis. There was widespread thickening of the alveolar septa, secondary to proliferation of septal cells, engorgement, oedema, and lymphocytic infiltration. The authors speculated that these changes were due to the pharmacological effects of amitriptyline itself (Sunshine and Yaffe, 1963).

The present patient died of an illness resembling the respiratory distress syndrome. It seems likely that this was a direct effect of amitriptyline poisoning. The drug is concentrated avidly in the lungs, and it is suggested that in large quantity it may inhibit surfactant production and thus have caused the clinical and pathological picture described.

We would like to thank Dr. D. W. Barritt for allowing us to report details of a patient under his care, and Dr. O. C. Lloyd for the necropsy report.

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