Acute Pulmonary Edema Induced by Overdosage of Phenothiazines*

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Three schizophrenic adults with previous histories of using phenothiazine derivatives developed acute pulmonary edema after taking large amounts of these drugs. The clinical manifestations included coma (three), hypothermia (two), tachycardia (two), miosis (two) and hypotension (one). All three patients underwent gastric lavage and were treated supportively. The fulminant pulmonary edema in the three cases resolved within 18 to 40 h. The etiology of pulmonary edema following overdose of phenothiazines remains unknown. The authors hypothesize that the most likely pathogenesis is a drug-induced neurogenic pulmonary edema resulting from a disturbance of hypothalamic function. (Chest 1992; 101:102-04)

Acute pulmonary edema may be caused by ingestion of opiate derivatives, sedatives, or tranquilizers. Common potential drugs include heroin, morphine, methadone, propoxyphene, barbiturates, and tricyclic antidepressants.1-4 Neuroleptic agents, such as phenothiazines, butyrophenones, and thioxanthenes, may occasionally cause neuroleptic malignant syndrome.5-7 The striking clinical characteristics of the neuroleptic malignant syndrome are hyperthermia, diaphoresis, hypertonicity, disorder of consciousness, tachycardia, and respiratory insufficiency. We encountered three cases of acute pulmonary edema following an overdosage of phenothiazines, two cases from chlorpromazine and one from perphenazine. The typical features of the neuroleptic malignant syndrome were absent in each of these cases. To our knowledge, phenothiazine-induced pulmonary edema has not been previously described. Potential mechanisms underlying this drug reaction are discussed, and a central neurogenic cause of the pulmonary edema is hypothesized.

CASE REPORT

A 24-year-old schizophrenic man was brought to the emergency room by his parents in coma of 2 h duration after ingestion of about 180 tablets of chlorpromazine (25 mg per tablet, total about 4,500 mg). The patient had a diagnosis of paranoid schizophrenia since 19 years of age, for which he had been taking about 150 mg of chlorpromazine daily.

Physical examination on admission revealed that the patient was comatose, unresponsive to stimuli. Blood pressure was 80/60 mm Hg (supine position). Pulse was 104 beats per minute; respiratory rate was 15 per minute, and temperature was 35°C. Gastric lavage was immediately performed. An arterial blood gas analysis with the patient breathing ambient air showed pH of 7.26; Po2, 33 mm Hg; Pco2, 46.8 mm Hg. The patient's pupils were constricted equally and unresponsive to light. Auscultation of the lungs revealed diffuse rales over both lung fields, especially at the bases. White blood cell count was 8,800/cu mm with 78 percent polymorphonuclear cells and 22 percent lymphocytes. Serum electrolyte studies showed a serum sodium value of 140 mEq/L; potassium level, 3.4 mEq/L; and chloride value, 106 mEq/L. Liver and kidney functions were normal.

Electrocardiogram showed sinoatrial rhythm, sinus tachycardia, and slight ST depression.

A portable anteroposterior chest roentgenogram revealed both interstitial and alveolar opacities bilaterally and a normal size heart. (Fig 1, left)

The clinical diagnosis was that of coma with acute pulmonary edema caused by overdosage of chlorpromazine.

The patient was treated with oxygen, intravenous administration of fluid, vitamin C, 15 percent potassium chloride, methylprednisolone, hydrochloride, metaraminol bitartrate, and antibiotics. About 7 h later, the patient gradually regained consciousness.

A chest radiograph after 18 h revealed that the acute pulmonary edema had completely resolved (Fig 1, right). Repeat blood gas values were normal.

Case 2 and 3 are summarized in Table 1 (Fig 2).

DISCUSSION

At least 30 different drugs have been reported to cause pulmonary edema.1-3,5 The pathogenesis of phenothiazine-induced pulmonary edema, currently unknown, might be similar to that of pulmonary edema caused by overdosage of heroin or methadone.4,10 Central neurogenic disturbances by the offending drugs likely play a principal role, as the phenothiazines exert their basic therapeutic and adverse effects through dopamine-receptor blockade in the basal ganglia and hypothalamus.5-8 There is evidence to indicate that phenothiazines antagonize dopamine-mediated neurotransmission at the synapses. The effects of phenothiazines on the autonomic nervous system are complex and unpredictable, since the drugs exhibit varying degrees of alpha-adrenergic blocking, muscarinic blocking and adrenergic activity.8

In contrast to the typical cases of neuroleptic malignant syndrome, the present cases showed fulminant pulmonary edema and coma without hyperthermia and muscular rigidity. These manifestations may well be secondary to depression and biochemical

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dysfunction of the hypothalamus by the heavy dosage of the offending drugs. Of course, hypoxemia and cardiovascular complications could accelerate the process.

While central venous pressures were not measured, left ventricular failure as a cause for the edema was not likely, as the edema cleared despite the administration of intravenous fluids. In addition, the heart sizes and contours on the portable chest films were normal. The cardiovascular effects of phenothiazines are complex, the most common phenomena being tachycardia, orthostatic hypotension, and electrocardiographic changes. Indeed, there was sinus tachycardia, slight ST depression on ECG, and hypotension in case 1. However, the electrocardiograms in the remaining two cases were essentially normal.

Direct toxicity of the offending agents on the pulmonary capillary membranes leading to a capillary permeability edema is also unlikely, given the rapidity of resolution of the pulmonary edema in these cases over 18 to 40 h.

Included in the differential diagnosis of the diffuse pulmonary infiltrates in these cases are drug hypersensitivity, gastric aspiration, and pneumonia. All of the three cases had been using phenothiazines chronically for years, without any skin rash or allergic reactions. The sudden changes, therefore, were not likely to be caused by drug hypersensitivity. None of the patients had blood eosinophilia. Because the three cases had undergone gastric lavage in the emergency room, the possibility of aspiration of gastric contents may be considered. Landay and his colleagues, in a review of 60 such cases, noted that roentgenographic
Table 1—Case Histories

<table>
<thead>
<tr>
<th>Age, Sex</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>24, Male</td>
<td>Paranoid schizophrenia for 5 years. 150 mg chlorpromazine orally daily to prevent onset of disease</td>
<td>Ten year history of schizophrenia with about 100 mg chlorpromazine orally every day</td>
<td>Six-year history of schizophrenia. Five to six perphenazine tablets (10-12 mg) per day</td>
</tr>
<tr>
<td>32, Female</td>
<td>Ingestion of about 4,500 mg chlorpromazine once</td>
<td>≥2,000 mg chlorpromazine once, orally (80 to 100 tablets 25 mg chlorpromazine)</td>
<td>Swallowing 100 2 mg tablets of perphenazine (total about 200 mg)</td>
</tr>
<tr>
<td>48, Female</td>
<td>30 min</td>
<td>30 min</td>
<td>60 min</td>
</tr>
<tr>
<td>Major clinic manifestation on admission</td>
<td>Coma, hypothermia, hypotension, tachycardia miosis</td>
<td>Coma</td>
<td>Coma, hypothermia, tachycardia, miosis</td>
</tr>
<tr>
<td>Blood gases on admission</td>
<td>pH 7.36, Po2 33 mm Hg, Pco2 46.8 mm Hg</td>
<td>pH 7.38, Po2 44 mm Hg, Pco2 35 mm Hg</td>
<td>pH 7.35, Po2 42 mm Hg, Pco2 36 mm Hg</td>
</tr>
<tr>
<td>Other laboratory data</td>
<td>Blood cell counts, electrolytes, kidney &amp; liver function all within normal limits</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>Sinoatrial rhythm, sinus tachycardia &amp; slight ST depression</td>
<td>Diffuse, poorly defined infiltrates throughout both lungs with decreased lung volumes. Bilateral pulmonary opacities with decreased lung volumes. Cardiac shadow is normal. (Fig 2)</td>
<td>Clear or normal</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Bilateral diffuse, pulmonary opacities. The size &amp; contour of the heart is normal (Fig 1, left)</td>
<td>Gastric lavage, oxygen, IV fluid, vitamin C, KCL, methylphenidate, metaraminol, antibiotics Bilateral pulmonary opacities with decreased lung volumes Cardiac shadow is normal. (Fig 2)</td>
<td>Gastric lavage, oxygen, IV fluid</td>
</tr>
<tr>
<td>Therapy</td>
<td>Gastric lavage, oxygen, IV fluid, vitamin C, KCL, methylphenidate, metaraminol, antibiotics</td>
<td>Cardiac shadow is normal. (Fig 2)</td>
<td>Gastric lavage, oxygen, IV fluid</td>
</tr>
<tr>
<td>Outcome</td>
<td>7 h after admission patient regained consciousness; 18 h later, acute pulmonary edema completely resolved. (Fig 1, right)</td>
<td>24 h after admission patient completely recovered. Acute pulmonary edema cleared.</td>
<td>About 4 h after admission patient gradually regained consciousness. Chest x-ray taken 40 h after admission was normal.</td>
</tr>
</tbody>
</table>

changes often worsen for several days in uncomplicated cases, but improvement is generally manifested within the first week after aspiration. Most patients also develop fever. In contrast, the three patients reported here were afebrile, and the pulmonary infiltrates cleared rapidly.

Chlorpromazine and perphenazine, both phenothiazine derivatives, are widely used in the management of psychotic conditions. The diagnosis of phenothiazine-induced pulmonary edema should be suspected in any patient with potential access to these drugs who presents with coma and diffuse pulmonary infiltrates.

The treatment, apart from withdrawal of the offending agent, is essentially supportive.

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