Drug-induced Noncardiogenic Pulmonary Edema*

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NCPE = noncardiogenic pulmonary edema; rIL-2 = recombinant interleukin 2

Gastric aspiration, sepsis, and trauma are well-recognized causes of noncardiogenic pulmonary edema (NCPE). Less appreciated is the fact that various drugs, either taken as standard therapy or as an overdose, may precipitate NCPE. Little is known about the mechanisms involved. A Medline and manual search of the English-language literature was used to generate a bibliography for this review of drug-induced NCPE. Cases were selected that fit currently accepted definitions of NCPE, ie, the simultaneous presence of severe hypoxemia, bilateral infiltrates on chest roentgenogram, and normal pulmonary capillary wedge pressure, with exclusion of other risk factors for NCPE.

The syndrome of NCPE due to ethchlorvynol serves as a model of drug-induced NCPE. Other agents are divided into groups as presented in Table 1. The distinction between groups is somewhat arbitrary but is based on the number of reported cases that fit the above criteria for NCPE. Some drugs typically included on such lists induce syndromes that do not meet these criteria—eg, nitrofurantoin causes an acute pulmonary syndrome that rarely causes severe hypoxemia and for which right heart catheterization has not been performed. Drugs that incite more specific syndromes such as penicillamine and alveolar hemorrhage are excluded. We will not address group 4, although references are available.

**Group 1**

Ethchlorvynol is a hypnotic, sedative drug designed for oral use. The active drug is a liquid in a gelatin capsule. This capsule can be punctured with a needle and the contents aspirated into a syringe for injection. Intravenous (IV) ethchlorvynol abuse is associated with a reversible form of NCPE. Although there have been case reports of pulmonary edema found at postmortem examination after oral ingestion, there is doubt as to whether this is NCPE, cardiogenic pulmonary edema, or postmortem changes.

Within minutes following the IV injection of one to four capsules (500 to 2,000 mg), the patient experiences dyspnea and coughing, and may expectorate a thin, reddish sputum that is probably pulmonary edema fluid. Many patients become somnolent, fall asleep, and awake hours later with continued symptoms. Physical examination reveals tachypnea, tachycardia, and end-inspiratory rales. The chest roentgenographic findings are consistent with NCPE, ie, bilateral interstitial/alveolar infiltrates with a normal-size heart.

Table 1—Classification of Drug-Induced NCPE

<table>
<thead>
<tr>
<th>Group 1 (&gt;10 cases)</th>
<th>Ethchlorvynol</th>
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<tr>
<td>Group 2 (5-10 cases)</td>
<td>Cyclosporine</td>
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<td>Tricyclic antidepressants</td>
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<td></td>
<td>Amiodarone</td>
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<td>Vinca alkaloids and mitomycin</td>
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<td>Bleomycin</td>
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<td>Cytarabine (cytosine arabinoside)</td>
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<td>Group 3 (controversial areas)</td>
<td>Amphotericin and granulocyte infusions</td>
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<td></td>
<td>Insulin and diabetic ketoacidosis</td>
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<td>Group 4 (&lt;5 cases)</td>
<td>Streptokinase</td>
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<td>Trimethoprim-sulfamethoxazole</td>
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<td>Flurazepam</td>
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<td>Lidocaine</td>
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<td>Sclerotherapy</td>
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<td>Nitroprusside</td>
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<td>Intrathecal methotrexate</td>
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nary function studies reveal restrictive disease. Hypoxemia, hypocapnia, and respiratory alkalosis are universally present. Depending on the severity of the respiratory distress, tracheal intubation, mechanical ventilation, and positive end-expiratory pressure (PEEP) may be necessary. Most patients improve within 24 to 36 hours, although the chest roentgenogram, pulmonary function, and arterial blood gas changes may lag behind clinical improvement.

Various animal models have been used to determine the natural course, the pathophysiology, and the mechanisms involved in ethchlorvynol-induced NCPE. Hemodynamic changes following the IV injection of ethchlorvynol, 10 to 55 mg/kg, include an immediate but transient fall in cardiac output and systemic blood pressure in sheep, swine, and dogs. These parameters return to baseline within five minutes. Moderate pulmonary hypertension ensues within one minute of drug injection and persists for up to 24 hours in sheep. The increase in pulmonary artery pressure is partly mediated by cyclooxygenase products since it can be blunted by the prior administration of nonsteroidal anti-inflammatory agents. Hypoxemia is universal and persists for hours.

Alveolar capillary membrane (ACM) permeability is increased as evidenced by the flux of albumin and large-molecular-weight dextrans from the pulmonary vasculature to the fluid-filled alveoli in the anesthetized dog. Similarly, in the awake sheep chronic lung lymph fistula model, protein-rich lung lymph increases within 30 to 60 minutes following injection, and in three to four hours peaks at three to four times baseline levels. The lymph flow returns toward normal within 24 hours and by 48 hours has returned to baseline. Antithistamines, nonsteroidal anti-inflammatory agents, and corticosteroids do not blunt the increased ACM permeability. Lung wet/dry weights are increased within hours of ethchlorvynol injection. Surprisingly, and in contrast to histologic findings, bronchoalveolar lavage in sheep reveals a marked influx of neutrophils within the first hour after ethchlorvynol injection. However, when these animals are made leukopenic, or in the isolated dog lung perfused with leukocyte-poor solutions, the increase in ACM permeability persists following ethchlorvynol injection. Ethchlorvynol may have a direct effect on pulmonary vascular endothelial cells.

There is histologic evidence of interstitial and intra-alveolar hemorrhagic edema, which is patchy and diffuse, without evidence of leukocyte trapping. Electron microscopy reveals endothelial blebs and an increase in the number of transendothelial vesicles. There is some damage to the type 2 alveolar cell.

Heroin and related narcotics induce a multitude of deleterious effects on the respiratory system, including acute hypercapnic, hypoxemic respiratory failure; decreased vital capacity; increased AaO2 gradient; V/Q mismatching; lung perfusion defects; and NCPE. The pulmonary edema follows closely on IV injection. Clinical signs and symptoms are characterized by tachypnea, tachycardia, hypoxemia, and bilateral alveolar infiltrates on chest roentgenogram. Endotracheal intubation, mechanical ventilation, and the application of PEEP may be necessary to maintain ventilation and gas exchange. Chest roentgenogram abnormalities return toward normal within two to four days, and most patients are ventilator independent within 24 to 48 hours. The restrictive changes in pulmonary function and hypoxemia improve more slowly and are usually normal within a week. Alveolar hypoxia, hypersensitivity to heroin, impurities in the heroin, release of vasoactive substances, etc, have all been implicated in the etiology of heroin-induced NCPE, but all theories are purely speculative. The incidence of heroin pulmonary edema seems to have decreased over the years.

Tocolytic agents, which include terbutaline, ritodrine, salbutamol, and isoxsuprine, suppress premature uterine contractions during pregnancy. These β-adrenergic agonists increase intracellular cAMP levels, thus decreasing muscular contraction. The incidence of pulmonary edema varies, occurring in 0 to 4.4 percent of pregnant women taking these agents. The pulmonary edema occurs during current or recent (<24 hours) usage or appears less than 12 hours postpartum when tocolytic therapy has failed. Dyspnea is the most common complaint, followed by chest pain and cough that may be associated with pink, frothy sputum. Bilateral alveolar infiltrates are present on the chest roentgenogram. Hypoxemia (the PaO2 averages 50 mm Hg; FIO2; 0.21) and hypocapnia (the PaCO2 averages 28 mm Hg) are present. Fluid overload purportedly occurs in 70 percent. Rapid clinical improvement (<24 hours) is the norm, although a small percentage (<8 percent) of patients may need mechanical ventilatory support. Mortality is low for both mother and fetus.

The cause of the pulmonary edema is unclear, but it may be due to a combination of heart failure, pulmonary venoconstriction, capillary leak syndrome, intravascular fluid volume overload, and reduced serum oncotic pressure, thus representing a combination of cardiogenic and NCPE. Most of these hypotheses are speculative at best. In one case report, a high protein value was found in the pulmonary edema fluid, suggesting the presence of increased capillary permeability.

Salicylate-induced NCPE may be associated with acute overdose (more common in younger adults) or long-term ingestion (more common in the elderly), with toxic serum levels. In general, the syndrome is identified when the patient presents with salicylate

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toxicity, although development of pulmonary edema may be delayed. While the edema generally resolves quickly with standard supportive therapy, death has been reported. Four reviews of consecutive patients admitted to the hospital with salicylate toxicity identified 29 (7 percent) of 397 patients with NCPE. Age, long-term salicylate ingestion, and cigarette smoking are probable risk factors. Bronchoalveolar lavage performed in one patient revealed an increased percentage of polymorphonuclear cells and decreased percentage of macrophages. Proteinuria has been identified in patients with salicylate toxicity, an indication of increased vascular permeability.

At least 14 cases (12 women, two men) of NCPE attributed to an idiosyncratic reaction to thiazides have been reported. An additional case in a man has been seen at our hospital (personal communication, S. Zeilander, M.D.). Most cases are due to hydrochlorothiazide, although chlorothiazide also evokes the syndrome. Usually the reaction occurs with the first or second exposure to the drug at a dose of 25 or 50 mg. Within minutes to hours, the patient experiences dyspnea, sometimes with wheezing, and often with nonspecific chest pain. Hypotension and bilateral rales are found on physical examination. Chest roentgenograms reveal alveolar and/or interstitial infiltrates. Symptoms usually resolve in 24 hours, although they may last several days. Drug rechallenge can cause recurrence. Limited immunologic investigations, including RBC rosetting, T- and B-lymphocyte enumeration and function, and complement levels were normal in one patient; a second patient had a positive patch test. In one additional case, the patient also developed an erythematous rash, possibly representing a true allergic response.

Protamine sulfate causes both immediate anaphylaxis and delayed reactions (within one hour). Patients with the immediate anaphylactic response are generally skin-test positive and have had previous exposure to protamine (leukapheresis donors, NPH or protamine zinc insulin, fish allergies). The delayed reaction is characterized by NCPE and decreased systemic vascular resistance. Skin tests in this group are negative. Mortality is high (30 percent) despite vigorous supportive therapy. Skin testing of those previously exposed and slow infusion of a low dose of protamine may prevent these syndromes. Postulated mechanisms relate to mast cell degranulation, complement activation, and the effects of protamine on endothelial and epithelial permeability and ATP content.

Recombinant interleukin 2 (rIL-2) produces tumor regression in a certain percentage of patients with far advanced, otherwise untreatable cancers. However, promising as this treatment may be, it is associated with a multitude of side effects, including a purported "capillary leak" syndrome resulting in peripheral and pulmonary edema. Human and animal studies show that rIL-2 administration is associated with increases in pulmonary microvascular permeability, lung parenchymal infiltration with large lymphoid cells and neutrophils, hypoxemia, systemic hypotension, and positive fluid balance. These abnormalities do not seem to be caused by the rIL-2 itself, but may be mediated by cytokines and other cellular constituents activated by rIL-2. In humans, the only means available to reverse this increased permeability pulmonary edema is to discontinue the rIL-2 therapy. A variety of substances, including corticosteroids, nonsteroidal anti-inflammatory drugs, and pentoxifylline have been used in animals to blunt the vascular permeability with variable results.

**GROUP 2**

Cyclosporine can induce NCPE after as long as 24 days of drug administration. Initial postulates that the reaction was due either to infusion through a central vein (thus exposing the pulmonary vasculature to a high concentration of the drug) or to IV solvents are not tenable because the syndrome has been well documented with oral use. NCPE is not always associated with elevated serum cyclosporine levels and is most likely an idiosyncratic reaction to the drug itself. The pulmonary edema resolves when the drug therapy is discontinued.

A review of 56 consecutive patients admitted to the hospital with tricyclic antidepressant overdose identified five patients with NCPE, with aspiration confidently eliminated as the cause in three. Interstitial edema was noted on chest roentgenograms of an additional five patients. The specific agent was not identified for any of these patients.

NCPE developed in eight patients taking long-term amiodarone therapy who underwent surgery with general anesthesia. These patients were easily extubated postoperatively but subsequently (usually within 18 to 72 hours) experienced the acute onset of dyspnea rapidly progressing to NCPE. Many risk factors for NCPE may be present in these patients—e.g., prolonged pump time, high inspired oxygen tension, major surgery. Fentanyl or sufentanil was administered to seven of eight patients. Preoperative amiodarone pulmonary toxicity may be a contributing factor but was not clinically apparent in four of these patients. Wood et al described two patients receiving amiodarone who developed NCPE and died following pulmonary angiography. In addition, four patients described by Tuzcu et al may also represent NCPE secondary to amiodarone therapy.

Vinca alkaloids and mitomycin C in combination cause NCPE that appears within one half to five hours of drug administration. Patients may require intubation and mechanical ventilation for 12 to 36 hours.
and some fatalities have been reported. Most patients had prior exposure to a vinca alkaloid and mitomycin C. Reexposure to vinblastine caused the same reaction in two patients.30,31 One patient developed a prolonged respiratory illness after apparent recovery from vinblastine/mitomycin-induced NCPE.36

Nine patients who received bleomycin developed fatal NCPE after surgery for a primary carcinoma.40,41 A high intraoperative inspired oxygen tension may be either the cause or a cofactor in the development of NCPE in this population.41 The use of colloids rather than crystalloids also may have been contributory. Following a protocol that minimized both inspired oxygen tension and colloid infusions, more than 200 subsequent patients were treated by these investigators without the development of NCPE.

Sixteen of 125 patients developed NCPE after treatment with high- and intermediate-dose cytarabine (cytosine arabinoside) as therapy for acute adult leukemia.42,43 Typically dyspnea and tachypnea occur after a “silent” interval of 1 to 28 days. Fatality rates are high (75 percent). Resolution of the edema may take two to three weeks.

GROUP 3

Hypoxemia, widened AaO2 gradients, and frank NCPE have been observed in patients treated for diabetic ketoacidosis.44,45 In those patients with NCPE, treatment regimens were similar and included colloid and insulin administration, and potassium and phosphate replenition. Pulmonary artery catheters revealed low pulmonary capillary wedge pressures, and a high pulmonary edema fluid colloid osmotic pressure has also been noted.46,47 Hypoalbuminemia was a prominent feature in some patients with NCPE and diabetic ketoacidosis.47 A report of two patients who intentionally overdosed on insulin and experienced NCPE48 supports the contention that insulin is the causative agent in those cases associated with diabetic ketoacidosis. Matz49 suggests that the actions of insulin in decreasing colloid osmotic pressure—due to its effects on plasma volume, serum albumin, and sodium and water retention—result in both pulmonary and cerebral edema.

In 1981, Wright et al50 reported the acute onset of dyspnea and hypoxemia with interstitial infiltrates on chest roentgenogram in 14 (64 percent) of 22 patients receiving amphotericin B and leukocyte transfusions for a variety of diseases including leukemia, lymphoma, and neuroblastoma. The cause for this relationship is unclear but may relate to the known effects of amphotericin on leukocyte function, ie, inhibition of chemotaxis, decreasing viability, and inducing pulmonary leukostasis.51 Additionally, the pulmonary complications may be due to underlying pulmonary fungal infection, congestive heart failure, bacteremia, or fungemia.

CONCLUSION

Although altered capillary permeability has been demonstrated in the pathogenesis of drug-induced NCPE, the mechanisms leading to loss of vascular integrity remain to be elucidated. Nevertheless, the syndrome is clearly associated with several agents that have vastly different pharmacologic functions. Animal models exist with which to explore the mechanism of vascular injury at both cellular and molecular levels. Clinically, drug-induced NCPE resolves quickly with supportive therapy and discontinuation of treatment with the offending agent, although fatalities have been reported with a number of these drugs.

An expanded reference list is available from the authors upon request.

REFERENCES

Drug-induced Noncardiogenic Pulmonary Edema (Reed, Glauser)