Drug-induced pulmonary disease

Part I. Patterns of response

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Pulmonary disease due to an adverse drug reaction often presents a diagnostic challenge to the clinician. An abnormality on the chest roentgenogram and a symptom complex are the most common forms of presentation. The disease is diagnosed only because it is highly suspected, and yet this is often not sufficient. For example, a new infiltrate shown on the chest roentgenogram and a fever may indicate an adverse drug reaction in the immunocompromized patient. However, the patient may also have a life-threatening infection.

This review is intended as a guide to the clinician in the early recognition of a drug reaction by providing a comprehensive description of adverse pulmonary effects due to drugs and a rough estimate of their frequency. *Part I* describes patterns of response, *Part 2* is divided into major categories of drugs, and *Part 3* deals with chemotherapeutic and immunotherapeutic drugs. Reactions such as simple shortness of breath; systemic anaphylaxis; volume overload, i.e., pulmonary edema due to either fluid or salt overdose, or circuitous reactions, e.g., cardiogenic pulmonary edema caused by myocardial depression brought on by a bundle branch block due to tricyclic antidepressants, have not been included. Nor are obsolete or experimental medications included. Brief sections on respiratory de-

pression, illicit drugs, and investigational aids are included. Adverse pulmonary reactions due to radiation therapy and immunotherapy are included in the section concerning chemotherapy to present a comprehensive overview in this rapidly expanding area of medicine. Individual drugs are discussed under the heading of major importance for that medication.

It must be recognized that this review will be inherently incomplete. New reactions are described yearly. The key to successful management is still based on the clinician diagnosing a condition because it is highly suspected.

Hypersensitivity reactions (*Table 1*)

The pulmonary responses to the drugs in this group may be best considered in terms of a hypersensitivity response. Typically there will be symptoms of cough, dyspnea, and fever with the appearance of an infiltrate on the chest roentgenogram. Occasionally there may be a pleural effusion. In some instances, laboratory manifestations characteristic of hypersensitivity responses may be demonstrated, such as peripheral eosinophilia or, more specifically, a positive lymphocyte transformation test (LTT) toward the offending drug. The adverse response usually remits soon after cessation of the drug; corticosteroids may hasten the recovery, although they are generally not needed or used. Only in the timing of the response does this differ from traditional concepts of a hypersensitivity response. The sensitizing time may be measured in days to years (examples will be given under the appropriate drugs).

Table 1. Hypersensitivity pulmonary infiltrates

Without peripheral eosinophilia
Azathioprine
Busulfan
Ibuprofen*
Nitrogen mustard*
Penicillamine
Radiation (acute)
With variable (0% to 80%) peripheral eosinophilia
Bleomycin
Carbamazepine
Chlorpropamide
Cromoglycate
Diphenylhydantoin
Imipramine
Isoniazid
Methotrexate
Nitrofurantoin (acute)
Para-aminosalicylic acid
Penicillin
Pituitary snuff
Procarbazine
Sulfonamides

* Probable.

Carbamazepine has been associated with a diffuse interstitial infiltrate and symptoms of dyspnea, dry cough, and fever in two patients after 5 weeks and 3 months of therapy. Eosinophilia ranged from 11% to 58% and peripheral lymphadenopathy was observed. A lung biopsy specimen in one patient showed interstitial pneumonitis and fibrosis; an LTT was positive in the other. Both cases resolved 1 to 2 days after the drug was discontinued and corticosteroids were initiated.[1,2]

Cases of hypersensitivity pneumonitis due to chlorpropamide have been described.[3] An acute response characterized by dyspnea, an alveolar infiltrate, and bilateral pleural effusions was seen in an atopic patient with mixed connective tissue disease who took ibuprofen.[4] One case of imipramine toxicity occurred within days of initiation of therapy and resolved over 2 weeks after its use was discontinued.[5]

Noncardiogenic pulmonary edema (*Table 2*)

Starling's equation refers to five factors responsible for the transvascular

Table 2. Noncardiogenic pulmonary edema

Acetylsalicylic acid*
Chlordiazepoxide
Colchicine*
Ethchlorvynol*
Fluorescein
Heroin/morphine*
Hydrochlorothiazide
Methadone*
Nitrogen mustard†
Propoxyphene*

* Overdosage only.
† Probable.

flow of fluid. One is the filtration coefficient of permeability of the vascular endothelium. This value is believed to be altered in cases of noncardiogenic pulmonary edema.

Two major categories of drugs produce the response. Overdose of sedative or narcotic medications produces the most frequent examples. Most patients in this group also have some degree of central nervous system depression; it is unclear whether this response is due to a drug effect, to neurogenic pulmonary edema, or to a combination of the two. The other group of drugs characteristically produces an idiosyncratic response that occurs within minutes to hours after absorption and shows no manifestations of a hypersensitivity response other than the acute onset of pulmonary infiltrates.

Chlordiazepoxide has been found to cause noncardiogenic pulmonary edema when the oral capsule is mixed and injected intravenously.[6] This response has not been seen when either form of the drug was used correctly. Colchicine, recently reported to produce this response, was fatal over a 42-hour period in a patient who ingested 150 mg of colchicine powder.[7] Three cases of acute dyspnea associated with alveolar infiltrates were described following the oral ingestion of 50-mg tablets of hydrochlorothiazide. In two patients, the symptoms started within 45 minutes; in one, there was no response to epinephrine.[8, 9] Phenylbutazone has also been cited as a cause of noncardiogenic pulmonary edema.[10]

Symptoms of ethchlorvynol overdosage include coma, hypotension, hypothermia, and respiratory arrest as well as noncardiogenic pulmonary edema.[11] The edema has been reproduced in experimental animals and is believed to be the result of a direct effect on the alveolar capillary membrane and not to a central mechanism, hypoxemia, or acidosis.[11, 12]

Interstitial pneumonitis/fibrosis (*Table 3*)

Many drugs have the potential for causing either interstitial pneumonitis or interstitial fibrosis. In some cases, in-

Table 3. Interstitial pneumonitis/fibrosis

Alpha-adrenergic nasal sprays
BCNU
Bleomycin
Busulfan
Carbamazepine
Chlorambucil
Cromoglycate
Cyclophosphamide
Diphenylhydantoin*
Drug-induced SLE
Gold
Intravenous use of "illicit" drugs
Iodine (radioactive)
Melphalan
Mercaptopurine
Methotrexate
Methysergide
Mineral oil
Mitomycin
Nitrofurantoin
Penicillamine
Pituitary snuff
Procarbazine
Radiation (acute)

* Possible.

terstitial pneumonitis has many of the features of a hypersensitivity state and the difference may be semantic rather than real. In other cases, there are few features of a hypersensitivity state, and interstitial pneumonitis represents only the inflammatory state preceding the fibrosing process. Drugs manifesting this response are discussed in other sections.

Pleural effusions (*Table 4*)

With the exception of anticoagulants, the drugs listed that may be associated with an acute pleural effusion have been reported as doing so as part of a hypersensitivity pneumonitis. Conversely, the remainder of the drugs listed in *Table 1* capable of causing hypersensitivity pneumonitis, but not listed on *Table 4*, are not known causes of a pleural effusion. Anticoagulants are discussed below.

Chronic pleural effusion refers to an effusion developing after the chronic use of a medication. In some instances this is a manifestation of a prolonged hypersensitivity-like response (methotrexate and procarbazine) or is associated with an interstitial fibrosis (busulfan and methotrexate).

Table 4. Pleural effusion

Acute
Anticoagulants (hemorrhagic)
Bleomycin
Ibuprofen*
Methotrexate
Nitrofurantoin
Para-aminosalicylic acid
Penicillin
Procarbazine
Radiation
Chronic
Busulfan
Drug-induced SLE
Methotrexate
Methysergide
Mitomycin
Procarbazine

* Probable.

Pulmonary vascular responses (*Table 5*)

In the past, drugs were frequently implicated as a cause of systemic and pulmonic angiitis. In many instances the proof was tenuous. In others the patient had a disease that is now considered to include vasculitis as part of its pathologic process.

Busulfan and cromoglycate are included since biopsy specimens of patients with hypersensitivity reactions to these drugs may also show an inflammatory vascular response. It is unclear what role the angiitis, per se, plays in the development of these disease processes. Illicit drugs are capable of causing angiitis and hypertension; the drugs and their diluents are given intravenously and are filtered by the pulmonary capillaries where they produce adverse effects. Corticosteroids are mentioned as causing pulmonary vasculitis,[13] but this has not been proved. In a review of autopsy findings in rheumatoid arthritis, pulmonary vasculitis was observed in 29% of patients who had received corticosteroids, but not in

Table 5. Pulmonary vascular disease

Pulmonary angiitis
Busulfan
Corticosteroids*
Cromoglycate
Intravenous use of "illicit" drugs
Radiation (acute)
Sulfonamides*
Pulmonary hypertension
Alpha-adrenergic nasal sprays
Estrogens
Intravenous use of "illicit" drugs
Decreased pulmonary vascular resistance
Digitalis

* Possible.

those who had not received corticosteroids.[13] Sulfonamides were also mentioned in the older literature as a cause of pulmonary vasculitis,[14] but on review, the association was tenuous at best.

Alpha-adrenergic nasal sprays have been associated with interstitial fibrosis and obliterated pulmonary vessels on histologic examination. This response is seen in patients who chronically use sprays excessively and may be caused by the effects of repeated vascular constriction. The chest roentgenogram shows normal parenchyma with prominent pulmonary vasculature. Pulmonary function testing (PFT) reveals a drop in diffusing capacity (D_LCO) proportional to the degree of pulmonary hypertension.[15]

Estrogen-containing medications are also capable of causing pulmonary hypertension. This response must be separated into two distinct groups of patients; those with congenital heart disease and those without. The relationship for the former seems well established although uncommon; for the latter the relationship remains only suggestive.

An Eisenmenger complex with reversal of their shunts and marked pulmonary hypertension after treatment with oral contraceptives was reported to have developed in three patients with congenital cardiac septal defects and mild preexistent pulmonary hypertension. This was responsible for the death of one of the three; the authors reported that there was no apparent relationship to recurrent pulmonary emboli as a cause of the pulmonary hypertension.[16] The situation is less well defined in patients with no preexistent heart disease. There have been case reports implicating oral contraceptives as a cause of primary pulmonary hypertension in patients who have taken the medication from 6 months to 5 years. In one study, three of six patients had factors that may have predisposed them to pulmonary hypertension (family history, corrected ductus arteriosus, and connective tissue disease); the other three were apparently normal.[17] Another report discussed autopsy results in patients known to have taken oral contraceptives for an average of 5 months before death. Thickening of the arterial walls was seen in this small series with occasional evidence of thrombosis.[18]

Digitalis has been shown to cause decreased pulmonary vascular resistance in man. The cause, constancy, and importance of this finding are unknown.[19]

Pulmonary parenchymal calcification (*Table 6*).

Calcium deposition in the lungs rarely occurs. It is seen with soft tissue calcification such as that caused by the milk–alkali syndrome or hypercalcemic states from other causes. Agents known to have precipitated calcium deposition include antacids,[20] calcium,[21] phosphorus,[22] and high doses of vitamin D.[14]

Parenchymal hemorrhage (*Table 7*)

A drug-related pulmonary embolus leading to pulmonary infarction is the most frequently cited reason for hemoptysis when the hemoptysis is a manifestation of an adverse drug effect. However, this is not the only cause. Pulmonary hemorrhage and hemoptysis can be a manifestation of a penicillamine-induced Goodpasture's syndrome

Table 6. Parenchymal calcification

Antacids
Calcium
Phosphorus
Vitamin D

(*Part 2*), lipoid pneumonia (*Part 2*), or chronic radiation pneumonitis (*Part 3*).

Spontaneous pulmonary hemorrhage has been reported in patients who had taken anticoagulants orally for 13 days to 3 years. Presenting symptoms were dyspnea, hemoptysis, and cough; and the roentgenogram showed either hemoptysis or an infiltrate.[23] Anticoagulants may also cause hemothorax in patients being treated for pulmonary embolus. The presenting symptom is pleural effusion with a decreasing hematocrit.[24]

Mediastinal manifestations (*Table 8*)

Although not necessarily a pulmonary disease, this group of adverse responses presents as an abnormality on the chest roentgenogram. Occasionally diphenylhydantoin will produce a pseudolymphoma syndrome manifested as peripheral lymphadenopathy. However, mediastinal lymphadenopathy occurs only rarely in this group of patients. It regresses 1 to 2 weeks after the drug has been withdrawn.[14] Potassium iodide was reported to produce fever, cough, and pruritus with hilar and mediastinal lymphadenopathy, which cleared upon discontinuance of the drug.[25] Transient hilar adenopathy may accompany a hypersensitivity-like response to methotrexate and in a recent review was reported to occur in 3 of 29 cases.[26] Mediastinal lipomatosis due to the use of corticosteroids is discussed in *Part 3*.

Table 7. Parenchymal hemorrhage

Anticoagulants
Estrogens
Lymphangiographic dyes
Mineral oil
Penicillamine
Radiation

Table 8. Mediastinal manifestations

Lymphadenopathy
Diphenylhydantoin
Potassium iodide
Methotrexate
Widening
Corticosteroids (lipomatosis)

Drug-induced lupus erythematosus (*Table 9*)

Many drugs have been implicated as causative factors in the systemic lupus erythematosus (SLE) syndrome,[14, 27, 28] and it is estimated that they play an activating role in 5% to 12% of cases.[27] Whether the drug exposes a latent case of SLE or actually causes the disease is still controversial. Animal experiments have not helped to clarify this issue. Acetylator status may be important as cases of hydralazine or isoniazid-related SLE are noted more frequently in slow acetylators of these drugs.

In spontaneous SLE, the lungs and pleura are affected in 50% to 75% of

Table 9. Drug-induced SLE

Alpha methyldopa
Diphenylhydantoin
Digitalis
Ethosuximide
Gold
Griseofulvin
Hydralazine
Hydrochlorothiazide
Isoniazid
Mephenytoin
Oral contraceptives
Para-aminosalicylic acid
Penicillin
Phenylbutazone
Primidone
Procainamide
Propylthiouracil
Reserpine
Streptomycin
Sulfonamides
Tetracycline
Trimethadione

cases, whereas they are involved in 80% of cases of drug-induced SLE.[29] Patterns of responses include pleural effusion with or without pleuritic pain, pleuritic chest pain with or without effusion, atelectasizing pneumonitis, diffuse interstitial pneumonitis, and alveolar infiltrates.[27] Positive biochemical markers of SLE are found more frequently than are systemic signs, and pleuropulmonary manifestations usually defervesce with removal of the agent.

It is estimated that more than 90% of cases of drug-induced SLE are caused by diphenylhydantoin, hydralazine, isoniazid, or procainamide.[29] Sulfonamides implicated include acetazolamide, sulfadiazine, sulfamethoxypyridazine, sulfasalazine, and sulfisoxazole.[27]

Hydralazine differs from most drugs in this category in that only 25% of patients will have pleuropulmonary symptoms. In one review,[30] 87% of symptomatic patients were found to have roentgenographic abnormalities: pleural thickening, 57%; pleural effusion, 36%; pulmonary fibrosis, 21%; elevated hemidiaphragm, 7%; segmental atelectasis, 7%; and migratory pneumonitis, 7%. Hydralazine-induced SLE is seen in 10% to 20% of patients receiving prolonged therapy with doses greater than 400 mg/day (although it has been reported in patients receiving therapy for less than one month and receiving less than 100 mg/day).[30, 31] It is more common in women (50% to 90%), Caucasians, and slow acetylators.[30, 31]

In a prospective study of 102 patients receiving isoniazid, 22% had positive antinuclear antibodies (ANA) by 12 months; 19% were positive by 3 months. No patient had a positive LE cell preparation or clinically active SLE, although it is unclear whether the drug was withdrawn after seroconversion.[32]

Drug-induced SLE due to procainamide is a time rather than dose-dependent phenomenon. For example, in one study, clinical SLE developed in 50% of patients by 3 months; by one year all patients had positive ANAs.[33] In another study of 42 patients followed up for 5 years, a positive ANA developed in 88%, and 29% had symptoms of drug-induced SLE.[34] The syndrome usually disappears within a few days to weeks after the drug has been withdrawn; occasionally corticosteroids are necessary to control symptoms.

Respiratory depressants (*Table 10*)

This section deals with drugs with adverse reactions due to either a blockade of the peripheral nervous system or due to an effect on the central nervous system, but with an initial manifestation of hypoventilation. Drugs that consistently produce this effect, either desired as with anesthetic agents or undesired as with narcotics, are not reviewed.

Some aminoglycoside antibiotics (*Table 10*) have been found to produce a competitive neuromuscular blockade

Table 10. Respiratory depressants

Antibiotics
Aminoglycosides
Gentamicin
Kanamycin
Neomycin
Streptomycin
Tobramycin
Polymyxins
Colistin
Polymyxin B
Other
Viomycin
Hypnotic/sedatives
Barbiturates
Chlordiazepoxide
Diazepam*
Others
Propranolol*

* Possible.

that can be reversed by the administration of calcium or neostigmine. The minimal effective doses (MED) vary widely between the drugs and species. In cats, the MED for gentamicin is 50 mg/kg, for tobramycin it is 40 mg/kg, and for neomycin it is 30 mg/kg.[35] Factors reported to potentiate this response are renal failure due to either drug accumulation or hypocalcemia, or both, simultaneous use of anesthetic agents or muscle relaxants (especially ether), preexistent neuromuscular disease (such as myasthenia gravis), overdosage, hypothermia, respiratory acidosis, and hypermagnesemia.[14, 36, 37] The critical factor in the development of the syndrome appears to be the blood level of the drug rather than the route of administration. Usually respiratory muscle paralysis is the first manifestation and occurs 10 to 30 minutes after administration.[36]

Polymyxin B and colistin have a neuromuscular blocking effect similar to the aminoglycosides. The onset is 1 to 26 hours after administration and the paralysis may persist as long as 72 hours.[38] This response is not dose- or serum-level-related and has been observed with any route of administration including the subcutaneous and topical routes. The syndrome occurs more commonly in patients with hypocalcemia. The mechanism is believed to be calcium depletion at the neuromuscular junction, and calcium is given intravenously. Prodromal symptoms include cranial nerve palsies, paresthesias (especially around the mouth), pruritus, ataxia, nystagmus, fever, nausea, and hallucinations.[38, 39] Viomycin produces an effect similar to the aminoglycoside, but less commonly.[40]

Hypnotics appear capable of producing a centrally mediated respiratory depression. Differences are seen between the various groups in their ability to cause this depression. The effect is more clearly demonstrated in patients with hypercapnic chronic obstructive pulmonary disease (COPD).

Respiratory depression due to barbiturates is dose related. It affects both the drive for respiration and the mechanism responsible for the rhythmic character of respiratory movements. Patients with preexisting lung disease may manifest more changes and at smaller doses than patients without pulmonary disorders.[41] One study in hypercapnic emphysematous patients given 1 grain of phenobarbital for insomnia showed a decrease in minute ventilation by 4.22 liters, an increase in the $PaCO_2$ of 22.9 torr (or mm Hg, from 58.8 to 81.7 torr), and a decrease in the pH from 7.38 to 7.13.[42]

The constancy of respiratory depression in the benzodiazepine class of drugs is less well established. Hypoventilation due to chlordiazepoxide appears to exist solely in patients with preexistent hypercapnic respiratory failure. A study was performed in seven patients with hypercapnic ($PaCO_2 > 54$ torr) COPD. A dose of 30 mg/day increased the $PaCO_2$ and decreased the FEV_1 in six of the seven patients; the seventh had been receiving benzodiazepine tranquilizers chronically.[43]

In several studies, it has been suggested that diazepam is capable of producing respiratory depression.[44–46] Most of these studies have serious flaws in their methodology; the most consistently demonstrable response was hypoventilation. However, the degree of hypoventilation recorded tended to normalize blood gas measurements that reflected a pretreatment respiratory alkalosis; patients went from a hyperpnic state to a eupneic state, not from eupnea to hypopnea. Other studies have failed to show hypoventilation in patients given diazepam.[47, 48] The above findings

were observed in patients given doses ranging from 40 mg/day orally in a stable condition to 0.66 mm/kg intravenously in the acute stage. Patients with hypercapnic COPD did not appear to have a response that differed significantly from normal subjects.

A number of studies have been performed on the benzodiazepines (chlordiazepoxide and diazepam) supporting at least some degree of respiratory depression; however, only in patients with preexistent, hypercapnic respiratory failure were the results most consistently positive.

Propranolol has been reported to cause blunting of the hypercapnic drive to respiration. A study was undertaken in six young healthy subjects. A single 80-mg dose given orally produced a depressed responsiveness to inhaled CO_2, which resembled that seen in hypercapnic COPD patients. There were no changes in air flow rates and arterial blood gas measurements were not performed.[49] Another group[50] could find no such effect with oral doses as high as 320 mg. A further study reported hypopnea caused by propranolol. However, this decrease in ventilation was proportional to decreases in the cardiac output; the change in minute ventilation and carbon dioxide output was significantly correlated with an r value of 0.85, tending to maintain normal values for end-tidal CO_2 tensions.[51] It seems likely that propranolol exerts no independent effects on the ventilatory drive.

A number of stereotyped responses have been presented by which adverse drug effects may become manifest. Drug categories will be discussed in *Part 2* and chemotherapeutic drugs in *Part 3*.

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