

# How Drugs Affect The Lungs

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## Abstract

Drug-induced lung disease is a major source of iatrogenic injury. The numbers of drugs that adversely affect the respiratory system continues to increase and more than 350 (and still counting) have been identified and their effects pose a great challenge to all physicians. Awareness of drug-induced pulmonary disease is essential to make a proper diagnosis for management of such patients. Here we review the various drugs known to induce lung injury and the various patterns of injury seen.

## BACKGROUND

The number of drugs that adversely affect the respiratory system continues to increase, and their effects pose a great challenge to all physicians. A review in 1972<sup>1</sup> identified only 19 drugs with the potential to cause pulmonary disease; now, more than 350 (and counting) have been identified.

Awareness of drug-induced pulmonary disease is increasing. The sole purpose of one clinical study group, the Groupe d'Etudes de la Pathologie Pulmonaire Iatrogene (GEPP), is to provide information regarding individual cases, to collect and update literature on drug-induced lung disease, to publish updated lists of offending compounds, and to provide warnings when adverse effects of drugs are recognized.

## LIMITED KNOWLEDGE

Our understanding of the mechanisms of drug-associated injury of the lung is limited compared to our knowledge of diseases in other tissues (eg, liver), and no specific markers are known to differentiate drug-associated interstitial lung disease from other pathological processes. In addition, many drugs are used at the same time or in close sequence, a practice that makes the assignment of toxicity to a specific agent difficult

## FREQUENCY

Exact frequency of drug-induced lung disease is difficult to determine, and any estimate is probably an underestimate because no effective screening tool is available. One of the best resources is Pneumotoxonline. This site grades evidence that a given drug is responsible for a specific lung disease in 4 categories based on 1-5 isolated case reports, approximately 10 cases, 20-100 cases, and more than 100

cases

## AGE

Drug associated lung diseases may affect any age group. Infants, children and adults may all develop lung disease.

## RACE

Some ethnic groups are at increases risk for adverse reactions to drugs. e.g.-when gefitinib is used in cases of advanced non-small-cell lung cancer (NSCLC), the incidence of interstitial lung disease is higher in Japanese populations (1.9%) than in the rest of the world (0.3%).ACE-Is and cough have been reported in Thai patients (Suriyachan, 1995)<sup>2</sup>.Angioedema and cough have been reported in Nigerian patients receiving ACE-Is (Ajayi, 2000)<sup>3</sup>

## SEX

Certain drugs have a sex predilection.e.g.aspirin induced asthma is more common in women than in men. Cough due to ACE-Is<sub>4</sub> is more common in women than in men.

## RISK FACTORS

Drug-induced lung disease is often dose related, particularly with cytotoxic<sub>5</sub> agents, such bleomycin, busulphan, and carmustine<sub>6</sub>. Other factors, such as increasing patient age, decreased renal function, radiation therapy, oxygen therapy, and other associated cytotoxic drug therapy may enhance the toxic effects.

## PATTERNS OF DRUG-ASSOCIATED LUNG DISEASES

The patterns<sub>7,8</sub> usually seen when drugs affect lungs are as

follows—

### **HYPERSENSITIVITY PNEUMONITIS**

It is usually seen with methotrexate, chrysotherapy, cyclophosphamide, Nitrofurantoin, and antidepressants.

It has acute presentation with fever, nonproductive cough, myalgia and is often associated with peripheral and tissue eosinophilia<sub>9,10</sub>. Chest radiograph reveals interstitial or mixed interstitial-alveolar infiltrates. Pulmonary Function studies show a restrictive ventilatory defect with decreased diffusing capacity. Diagnosis is made by Bronchoscopy and Sensitization. BAL (Bronchoalveolar Lavage) has a characteristic Lymphocytic predominant picture constituting 40-80% of all cells. All are CD3 lymphocytes with CD4 to CD8 ratio less than one usually. Antibodies to the offending drug may be seen in the BAL Fluid.

Prognosis is favorable as patient usually recovers with steroids or on dechallenge.

### **EOSINOPHILIC PNEUMONITIS**

Eosinophilic syndromes<sub>11</sub> are usually seen with methotrexate, sulfasalazine, Amiodarone, minocycline, para-amino salicylic acid, nitrofurantoin and NSAIDs.

They may resemble acute or chronic eosinophilic pneumonia. Minocycline is notoriously associated with acute eosinophilic pneumonia. Most commonly a Loeffler's syndrome is noted, with dyspnea, cough, blood eosinophilia, and transient pulmonary infiltrate. Diagnosis is made by Bronchoscopy with BAL Fluid characteristically Eosinophilic. prognosis is favorable as patient usually recovers with steroids or on dechallenge.

### **FIBROTIC NONSPECIFIC INTERSTITIAL PNEUMONITIS**

Drugs that typically cause this pattern<sub>12</sub> are Amiodarone and chemotherapy including bleomycin, busulphan, and chlorambucil.

Manifestations are usually slowly progressive cough, dyspnea, weight loss, and clubbing.

Radiographic findings are usually reticular infiltrates starting in the sub pleural region of the lung bases and progressing to include the entire lung with areas of ground glassing. Diagnosis is by radiography especially the role of HRCT Thorax .

Outcome is usually unfavorable in such cases.

### **DESQUAMATIVE INTERSTITIAL PNEUMONITIS**

Drugs usually associated with this form of interstitial lung disease are methotrexate<sub>13</sub>,

### **INTERFERONS AND ETANERCEPT-D2E7**

Patient usually presents with slowly progressive cough and dyspnea. Histopathologically, Condition is characterized by alveolar accumulation by macrophages. Diagnosis is made by radiography. Mosaic pattern is usually visible on X-ray and HRCT Thorax. Patients generally have a favourable outcome with the role of stopping the causative drug. Steroids have also a role to play.

### **NONCARDIOGENIC PULMONARY EDEMA**

A large variety of drugs are known to cause such condition that include Cytosine arabinoside , beta2-receptor agonists, blood, blood products, narcotics and diuretics.

The syndrome of noncardiogenic pulmonary edema manifests as acute respiratory distress occurring over several hours. Physical examination demonstrates diffuse crackles, and laboratory examination shows significant hypoxemia.

In most instances this is due to capillary endothelial injury, causing increased permeability edema<sub>14</sub>. Chest roentgenograms show diffuse ill-defined acinar infiltrates and normal heart size. Bronchoscopy is diagnostic with BAL Fluid characteristically watery.

Prognosis is favourable and patient generally improves with supportive treatment.

### **PULMONARY VASCULAR DISEASE**

The incidence of pulmonary veno-occlusive disease, characterized by the occlusion of pulmonary venules with subsequent elevated pulmonary arterial pressures, is increased in patients receiving cytotoxic agents for the treatment of malignancy. The diagnosis usually requires an open lung biopsy.

Alphaadrenergic nasal sprays have been associated with interstitial fibrosis and obliteration of pulmonary vessels. Estrogen-containing drugs as well as appetite suppressants have been associated with development of pulmonary hypertension<sub>15</sub>.

Prognosis is usually poor.

### **ALVEOLAR HAEMORRHAGE**

Acute and recurrent alveolar haemorrhages are known to occur in response to certain drugs. The drugs include

Penicillamine, cocaine, Oral anticoagulants, fibrinolytic agents, platelet glycoprotein inhibitors, nitrofurantoin and mineral oil. Patient usually present with haemoptysis and chest radiograph reveals diffuse alveolar infiltrates or diffuse ground glassing. Characteristic feature of alveolar haemorrhage is capillaritis or bland haemorrhage. BAL Fluid is haemorrhagic and this is diagnostic.

Outcome is usually favourable with removal of causative drug.

### BRONCHIOLITIS OBLITERANS

Number of drugs like methotrexate, gold are known to cause bronchiolitis obliterans without pathologic features of organizing pneumonia.

Patient usually present with severe, progressive, fixed obstructive ventilatory defect. These drugs are used in treatment of rheumatoid arthritis, a disease that can itself be complicated by bronchiolitis obliterans as a systemic manifestation. Thus the distinction between the collagen vascular and drug associated bronchiolitis may be difficult.

### LUPUS SYNDROME

Drugs may exacerbate underlying lupus, induce lupus in a predisposed patient, or cause the disease. It is estimated that more than 90% of cases of drug-induced lupus are caused by diphenylhydantoin, hydralazine, isoniazid, or procainamide.

Patients with drug-induced lupus can develop a variety of systemic symptoms, including fever, myalgia, rash, arthralgias, arthritis, and serositis<sup>16</sup>. The lungs and pleurae are involved in 50% to 75% of cases of drug induced lupus<sup>14</sup>. Patterns of response can be pleural effusion with or without pleuritic pain, diffuse interstitial pneumonitis, and alveolar infiltrates<sup>14</sup>.

Drug-induced lupus can be differentiated easily from spontaneous lupus. The female-to-male ratio is 1:1 in drug-induced lupus while it is 9:1 in spontaneous lupus. Complement and immune complexes are normal in drug induced lupus but elevated in spontaneous form.. In more than 95% of cases of drug induced lupus, antihistone antibodies are present but other auto antibodies are absent, including those directed against double stranded DNA<sup>16</sup>.

### ALVEOLAR HYPOVENTILATION

Respiratory depression is a well known side effect of many centrally acting therapeutic agents, particularly sedatives and opiates. Alveolar hypoventilation may occur with drugs that

impede neuromuscular transmission or diaphragmatic muscle function like aminoglycosides and polymyxins.

Usually the effect is insignificant except in those with underlying lung disease.

### BRONCHOSPASM

Evidence of increased airway resistance is seen in normal persons and patients with asymptomatic asthma who use propranolol and other beta-adrenergic antagonists<sup>17</sup>. The same findings have been shown to occur in asthmatic patients receiving timolol eyedrops for glaucoma.

Aspirin produces bronchospasm in about 4% of asthmatic patients<sup>4</sup> and similar symptoms are seen with other NSAIDs. In asthmatic persons with nasal polyps, the incidence may be as high as 75%.<sup>9</sup> Aspirin-induced bronchospasm generally becomes apparent in the third to fourth decade of life and is more common in women.

Interestingly some inhalational preparations used in the treatment of bronchospasm (eg,albuterol) can induce cough or bronchospasm because of materials other than the bronchodilator agent in the preparation.

Treatment is usually to avoid drugs known to cause bronchospasm.

### PLEURAL DISORDERS

Pleural effusion may occur with drugs like amiodarone, anticoagulants, bleomycin, bromocriptine, busulfan, interleukin-2, methotrexate and methysergide.

Hemothorax or mediastinal hematoma can be a complication of anticoagulants while Pneumothorax may complicate systemic chemotherapy and illicit drug use. Pleural effusions that resolve spontaneously or with discontinuation of the drug are seen in drug-induced systemic lupus erythematosus while an acute pleural effusion in association with drugs can also been seen as part of a hypersensitivity reaction.

### ROLE OF IMAGING

Although conventional chest radiology is the first imaging option in evaluating patients for pulmonary manifestations of drug toxicity, the limitations of the pattern approach often predicate the use of other imaging techniques in addition to clinical and laboratory evaluation. In select cases, HRCT and radio nuclide imaging have a role in detecting lung toxicity early when it is still reversible or in differentiating drug toxicity from other lung pathology.

Common radiological patterns

FOCAL ALVEOLAR OPACITIES---Aminosalicylic acid, Penicillin, Sulfonamides, Mineral oil aspiration

B) DIFFUSE alveolar opacities-----

PULMONARY OEDEMA---- Cocaine, Cytosine-arabioside, Heroin, Interleukin-2, Morphine, OKT3, Ritodrine, Salicylates, Terbutaline, Tricyclics

PULMONARY HEMORRHAGE-----Cocaine, Penicillamine, Quinidine, Anticoagulants

c) Diffuse interstitial opacities----

Methotrexate, Nitrofurantoin, Procarbazine, Carmustine, Bleomycin, Busulphan,

Cyclophosphamide, Methotrexate, Mitomycin-C, Amiodarone, Gold, Oxygen, Tocainide

D) Pulmonary nodules-----

Amiodarone, Bleomycin, Cyclosporine, Mineral oil aspiration

### CONCLUSION

A large number of drugs that can have an adverse effect on lung and the larger number of clinical situations in which drug toxicities must be considered make a thorough understanding of drug-induced pulmonary disorders essential for all medical practitioners and students of pulmonary biology.

It is important to note that each of these clinical syndromes can be caused by a variety of drugs for example intravenous Terbutaline; opiates and aspirin can all cause acute non-cardiogenic pulmonary oedema. Conversely a single drug can also cause several forms of pulmonary toxicities, as exemplified by the ability of NSAIDs to cause pulmonary edema, bronchospastic exacerbation and hypersensitivity lung disease. One should also remember that the most common presentation in a patient is usually an abnormality on the chest radiograph and a symptom complex. Early diagnosis is very important and requires the physician to be vigilant in the appropriate clinical settings. The diagnosis is usually one of exclusion. Stopping the drug is usually the sufficient therapy for most drug toxicities, but

corticosteroids administration may also be needed in some cases.

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