Drug - Induced Respiratory Diseases

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Drug-Induced respiratory diseases are becoming increasingly apparent, as more than 40 commonly used drugs are reported to cause pulmonary parenchymal tissue injury(1,2). Drug - induced interstitial lung diseases can be acute or chronic. Due to irreversible damage that may result from drugs, treatment, for lethal diseases have to be withdrawn prematurely. It is difficult to estimate the true incidence of drug induced pulmonary disease because of the lack of specific markers, histologic findings or diagnostic clinical features and also because of sporadic nature of many of these reactions. Pharmacologic agents that may cause pulmonary parenchymal injury can be classified into 2 group (Table 1). The first group involves cytoloxic drugs and the second non cytoloxic drugs.

Mechanisms of drug - Induced pulmonary disease

The lungs, the only organs in man, exposed to both internal and external insults of various types has a number of homeostatic mechanisms for maintaining a balance between damaging inflammatory reaction and protective detoxification pathways. Drugs can affect any of these systems resulting in pulmonary injury.

a) Oxidant - antioxidant system (1)

Drugs such as bleomycin, cyclophosphamide and amiodarone are capable of producing reactive oxygen species (Oxidants) including the superoxide anion (02), hydrogen peroxide (H202), the hydroxyl radical (OH), singlet oxygen (1 02) and hypochlorous acid (HOCL). These oxidants can cause autologous cytotoxicity, unless they are neutralised by antioxidants such as superoxide dismutase (SOD), catalase, glutathione peroxidase, ceruloplasmin and vitamin E. These antioxidant systems are present in virtually every cell in the body. Over production of oxidants by the drugs, thus results in an alteration of normal balance between oxidants and antioxidants, resulting in pulmonary toxicity.

(b) Immunologic system (1,3-5)

Normal resident pulmonary cells are alveolar macrophages and lymphocytes. Drugs can activate resident pulmonary cells, resulting in attracting and activating peripheral inflammatory cells such as polymorphonuclear neutrophils (PMN), eosinophils and monocytes. These activated cells liberate cytotoxic mediators. Experimental pulmonary fibrosis induced by agents such as bleomycin, paraquat, N-nitroso-N-methylurethane

etc. had shown that fibrosis of the alveolar wall first requires "injury" to the alveolar wall, that is, damage to the existing cells and matrix, comprising the lung parenchyma. Most of the injury results from the effector processes of these cell types comprising alveolitis. Bronchoalveolar lavage (BAL) studies (6-8) have demonstrated increased numbers of polymorphonuclear neutrophils in patients with bleomycin, amiodarone, tocainide and phenytoin induced pulmonary injury. A lymphocytic alveolitis in the BAL has been demonstrated in lung damage due to bleomycin, methotrexate, gold salts, amiodarone and nitrofurantoin. Lung eosinophilia have been reported in lung diseases due to bleomycin, procarbazine, nitrofurantoin, gold etc. The relative potency of the effector cells in regard to their ability to injure the alveolar wall is probably, in descending order, neutrophils, alveolar macrophages, eosinophils and lymphocytes. If the damage is sufficient such that normal alveolar architecture cannot be reestablished, a secondary form of "repair", ie. replacement of the normal parenchyma by fibroblasts and their products, takes over. Activated alveolar macrophages release chemoattractants for neutrophils, leukotriene B4, interleukin 1, possibly interleukin 8, oxidants and a variety of growth signals for mesenchymal cells including platelet - derived growth factor (PDGF - B) fibronectin (FN), insulin like growth factor 1 (IGF-1), transforming growth factor - beta (TGF-B), and Tumour Necrosis Factor (TNF). Macrophage derived growth factors are shown in figure 1. Neutrophils release oxidants and potent proteinases such as collagenase and neutrophil elastase. Eosinophils liberate oxidants, collagenase and a variety of other agents such as major basic protein. Lymphocytes release interleukin - 2, migration inhibition factor, monocyte chemotactic factor and oxidants.

Fibronectin and alveolar macrophage derived growth factors (AMDGF), the mediators released by alveolar macrophages play an important role in fibrosis. Fibronectin (FN) recruits fibroblasts to the area of injury. Fibroblast numbers expand as a result of mediators released by macrophages. FN attaches fibroblasts to matrix which is made up of type I and type III collagen. FN also acts as a "competence factor" to move fibroblasts through the early phases of the Cl portion of the cell cycle (G1 is the earliest phase of the cell proliferation cycle and precedes DNA synthesis). AMDGF acts as a growth factor and in the presence of the "competence factor" (FN) induces fibroblasts to move, through the late stages of GI and prolifeate. This ultimately leads to fibrosis by replacement of normal parenchymal cells and matrix by fibroblasts and fibroblast products. However, macrophages are also capable of arresting fibrotic response by releasing two cytokines, TNF- α and IL 1. They interact synergistically to augment production of prostaglandins (PGE 2). PGE 2 is a powerful second messenger that inhibits fibroblast proliferation. Pathogenesis of the fibrotic response is given in Figure 2 (9, 10).

c. Proteolytic system (5).

Proteolytic enzymes, particularly elastase are produced by polymorphonuclear leukocytes and alveolar macrophages. There are a number

of antiprotease systems in the lower respiratory tract, the most important being the alpha - 1 - protease inhibitor. Reactive oxygen radicals released by drugs such as bleomycin and cyclophosphamide can inactivate alpha - 1 - protease inhibitor resulting in enhanced activity of proteolytic enzymes.

d. Central Nervous System (CNS) (5)

A variety of CNS insults can cause neurogenic pulmonary oedema in which there will be an increased capillary protein leak, This may suggest that pulmonary capillary permeability may be, in part, controlled by the central nervous system. Several drugs such as opiates, major tranquilizers, salicylates and methotrexate may cause pulmonary oedema through their effects on CNS. Presence of plentiful opiate receptors near the medullary respiratory centre may support for neural influences in the development of pulmonary oedema.

Risk factors (5) -

Risk factors predisposing to development of drug - induced pulmonary disease are given in Table 2.

Clinical manifestations

Five distinct syndromes have been described.

1. Pneumonitis / fibrosis (1,5).

Drugs causing pneumonitis/fibrosis are shown in Table 3. Symptoms begin insidiously, progressing over several weeks to months. Symptoms include non-productive cough, dyspnoea on exertion, fatigue and malaise. Significant weight loss can also occur. Bi-basilar end - expiratory crackles can be heard on auscultation. Clubbing may be present. The chest radiograph show bilateral reticular infiltrates. Occasionally chest radiograph is normal, even in the presence of pulmonary symptoms and physiologic abnormalities. Pulmonary function may show a restrictive ventilatory defect with a reduced diffusing capacity. In general, most patients show some residual pulmonary impairment despite appropriate treatment which include discontinuation of the offending drug and institution of corticosteroids.

2. Hypersensitivity pneumonitis (1,5)

Drugs that cause hypersensitivity pneumonitis (HP) are shown in Table 4. HP is characterised by a subacute onset (within hours to days) of dyspnoea, non-productive cough, chills, myalgia, fever and headache. Skin rash may be present in 50% of patients. Auscultation may reveal crackles. 40% of patients will have peripheral eosinophilia. There may be signs of hepatitis in a few cases. The chest radiograph shows diffuse acinar infiltrates, pleural effusions are more common than those of pneumonitis. Pulmonary function shows restriction with mildly reduced diffusing capacity. Lung biopsy may show interstitial and airway eosinophilia with a paucity of fibrosis. Virtually all patients, except those due to methotrexate, recover with few residual pulmonary dysfunction. Treatment includes withdrawal of the drug and institution of corticosteroids.

3. Non-Cardiogenic pulmonary oedema (1,5)

Symptoms occur acutely (over minutes to hours) and usually are associated with overdose of the offending agents. Drugs that cause non - cardiogenic pulmonary oedema are given in Table 5. Prognosis is variable and generally better than other causes of non - cardiogenic pulmonary oedema on removal of the offending agents.

4. Bronchiolitis obliterans (11)

This rare complications is usually due to three drugs namely, gold salts, sulfasalazine and penicillamine. The underlying disease particularly rheumatoid arthritis can cause similar pulmonary pathology in the absence of drugs. Clinical symptoms include insidious onset of cough, dyspnoea and weight loss. Chest radiographs may be normal or show localised infiltrate. Pulmonary function shows an obstructive ventilatory defect. Histology shows areas of inflammation surrounding bronchioles resulting in their obliteration. In a proportion of patients especially due to sulfasalazine and penicillamine, a significant alveolitis is present. Prognosis of this condition is poor. Despite corticosteroid treatment and discontinuation of drugs, residual pulmonary abnormalities will be persisting.

5. Pulmonary renal syndrome (5)

This is a rare complication of penicillamine treatment. Clinical presentation includes hemoptysis, dyspnoea, pleuritic chest pain and uremia. Chest radiographic abnormalities include diffuse acinar, reticular or confluent large round densities. Lung histology shows pulmonary haemorrhage and haemosiderin laden macrophages. Although similar to GoodPasture's Syndrome, there were no typical linear pattern of basement membrane immunoglobulin deposition. Treatment includes immunosuppression and plasmapheresis.

Screening tests (1,5)

1. Diffusing capacity for carbon monoxide (TLCO)

TLCO appears to be a sensitive, but relatively nonspecific test as a predictor of drug-induced pneumonitis especially in bleomycin or amiodarone-induced pneumonitis. Patients who never develop clinical disease had also shown a reduced TLCO.

2. Lung volumes

A redution in lung volumes is a restrictive ventilatory defect, appears to be a specific test, but is not very sensitive. Patients with lung disease have rarely shown normal lung volumes.

3. Computed tomographic scanning

The detection of fibrosis by CT scanning has been correlated with lung volume measurements CT abnormalities were detected in patients with normal chest radiographs. However, CT may not differentiate reversible pneumonitis from irreversible fibrosis. CT may prove to be sensitive and specific test in predicting development of drug-induced lung disease.

4. Chest radiographs

Chest radiographs are both nonspecific and insensitive in detecting pulmonary disease. An abnormal chest radiograph is a late manifestation of drug-induced lung disease.

5. *Gallium scanning*

Positive gallium scans i.e. uptake of gallium-67 in area of acute inflammation, in the absence of abnormal chest radiographs have been reported in drug-induced lung diseases. However, there are no proper studies to evaluate gallium scanning in drug-induced lung disease.

6. Soluble mediators

Soluble mediators such as serum angiotensin converting enzyme have been described in all patients receiving bleomycin, but most of them do not develop pulmonary fibrosis. This is a fertile field for future research *in* drug-induced lung disease.

Figure 1

Macrophage derived growth factors

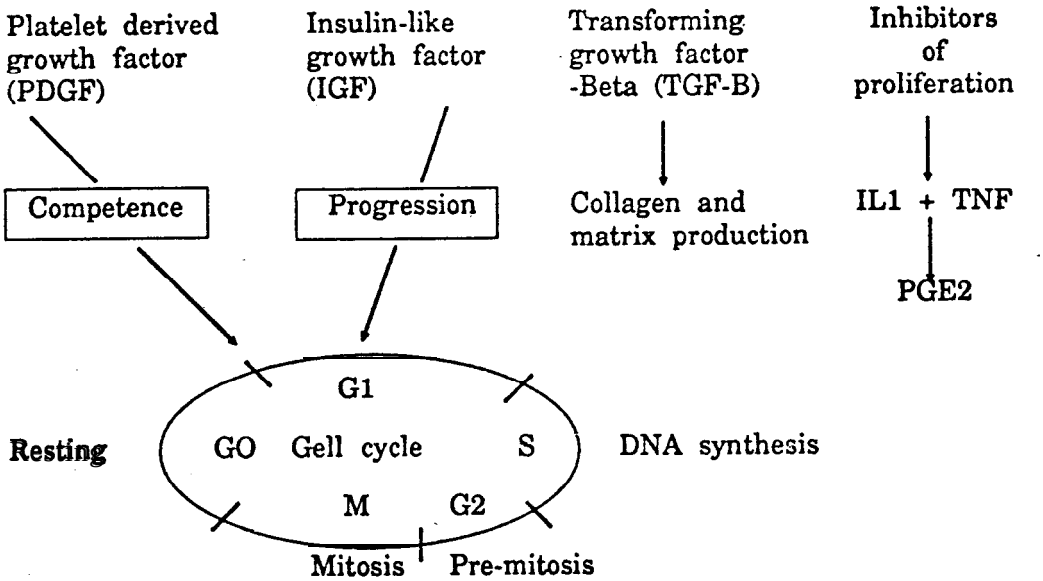

Figure 2

Pathogenesis of the fibrotic response

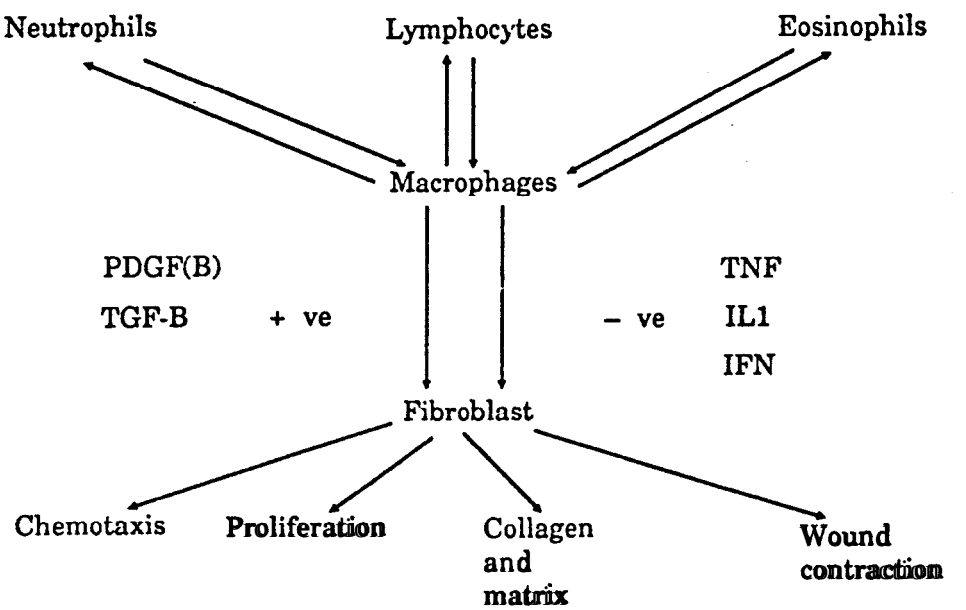

Table 1

Pharmacologic agents that cause Pulmonary Parenchymal Injury

Cytotoxic drugs	*Non Cytotoxic drugs*
Antibiotics	Antibacterial agents
Bleomycin	Nitrofurantoin
Mitomycin	Amphotericin
Neocarzinostatin	Sulfasalazine
Alkylating Agents	Analgesics
Busulfan	Aspirin
Cyclophosphamide	Opiates
Chlorambucil	Heroin
Melphalan	Propoxyphene
Nitrosoureas	Methadone
Carmustine (BCNU)	Sedatives
Semustine (Methyl CCNU)	Etchlorvynol
Lomystine (CCNU)	Chlordiazepoxide
Chlorozotocin	Anticonvulsants
Antimetabolites	Diphenylhydantoin
Methotrexate	Carbamazepine
Azathioprine	Diuretics
Mercaptopurine	Hydrochlorothiazide
Cytosine arabinoside	Major Tranquilizers
Miscellaneous	Haloperidol
Procarbazine	Fluphenazine
VM - 26	Antiarrhythmics
Vinblastine	Amiodarone
Vindesine	Lidocaine
	Tocainide
	Procainamide
	B adrenergic blockers
	Practolol
	Propranolol
	Pindolol
	Miscellaneous
	Gold salts
	Penicillamine
	Isoniazid
	Colchicine

Table 2

Risk factors predisposing to development of drug induced pulmonary diseases

Risk Factor	*Drug(s) Implicated*
Cumulative dose	Bleomycin, carmustine (BCNU), amiodarone
Unit dose:	Amiodarone, Heroin, Proproxyphene methadone, Ethchlorvynol, Chlordiazepoxide, Haloperidol, Colchicine, Imipramine.
Route of Administration:	Bleomycin
Frequency of Administration:	Methotrexate
Oxygen therapy:	Bleomycin, Mitomycin, Cyclophosphamide, Nitrofurantoin
Radiotherapy:	Bleomycin, Busulfan, Mitomycin
Other Drug therapy:	Bleomycin, BCNU, Cyclophosphamide, Mitomycin, Methotrexate, Vinca alkaloids
Age:	Bleomycin
Previous Pulmonary diseases:	BCNU, Amiodarone
Blood component transfusions :	Mitomycin, Amphotericin
Renal failure:	Bleomycin
Steroid tapering or adrenalectomy:	Methotrexate
Pulmonary angiography:	Amiodarone

Table 3

Drugs that cause pneumonitis/fibrositis

Cancer Chemotherapeutic agents	*Other Drugs*
Bleomycin	Nitrofurantoin
Mitomycin	Sulfasalazine
Busulfan	Amiodarone
Neocarzinostatin	Tocainide
Cyclophosphamide	Gold salts
Chlorambucil	Penicillamine
Melphalan	
Carmustine (BCNU)	
Semustine (Methyl CCNU)	
Lomustine (CCNU)	
Chlorozotocin	
Methotrexate	

Table 4

Drugs that cause hypersensitivity pneumonitis

Bleomycin	Paraaminosalicyclic acid
Methotrexate	Penicillin
Procarbazine	Cromolyn
Azathioprine	Dantrolene
Mercaptopurine	Methylphenidate
Sulfasalazine	Mephenesin carbamate
Nitrofurantoin	Hydralazine
Diphenylhydantoin	Mecamylamine
Carbamazepine	Ampicillin
Chlorpropamide	Febarmate
Imipramine	Salazopeyrin
Isoniazid	Naproxen
Sulfadimethoxine	

Table 5

Drugs that cause non - cardiogenic pulmonary oedema

Cancer chemotherapeutic Drugs	*Other Drugs*
Mitomycin	Amphotericin
Cyclophosphamide	Heroin
Methotrexate	Propoxyphene
Cytosine arabinoside	Methadone
VM - 26	Ethchlorvynol
	Chlordiazepoxide
	Haloperidol
	Lidocaine
	Terbutaline
	Ritodrine
	Isoxsuprine
	Imipramine
	Colchicine

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