Drug induced pulmonary diseases

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Abstract

Drug reactions present to the clinician as a syndrome that may be due to a number of different causes, the patient's treatment being one possibility. In most clinical instances, a correct clinical diagnosis can be made if the physician is knowledgeable of the drugs which have been implicated in the pathogenesis of drug-induced lung reactions and recognizes the characteristic clinical and roentgenographic features present in each case. Management of pulmonary drug reactions consists in stopping the offending drug and if necessary, substituting a less harmful one. Corticosteroid therapy may be used in some cases.

INTRODUCTION

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 identified only 19 drugs with the potential to cause pulmonary diseases; now, more than 350 drugs have been identified and the search is still on[1]. The introduction of cytotoxic drugs in particular has increased both the range of mechanisms and the frequency of pulmonary drug reactions. The range of reactions is wide, from familial simple pharmacological effects (e.g. opiates causing respiratory depression or beta-blocking drugs causing bronchoconstriction) through less well understood reactions (e.g. aspirin induced asthma, eosinophilic reactions due to sulphonamides or fibrosis due to busulphan) to the infective complications of immunosuppressants. Because of the diverse nature of the drug-induced pulmonary diseases, the correct diagnosis in any individual case will be made only if physicians are knowledgeable of the drugs which have been implicated in the pathogenesis of these reactions and recognize the characteristic clinical and roentgenographic features associated with these drugs.

EPIDEMIOLOGY

The exact frequency of drug induced lung diseases is difficult to determine because of lack of an effective screening tool. Drug induced lung diseases are prevalent in both adults and children. Children receiving chemotherapy for brain tumours or lymphoma may lead to progressive pulmonary fibrosis and this can occur even 17 years after receiving chemotherapy[2].Certain diseases have sex predilection like aspirin induced asthma[3] and ACE inhibitors induced cough[4] are more common in women than in men. Similarly some ethnic groups are more prone to these diseases. Incidence of interstitial lung disease following administration of Geftinib for non small cell lung cancer is higher in Japanese population than rest of the world[5]. Angioedema and cough have been reported more frequently in Nigerian patients receiving ACE inhibitors[4].

ETIOPATHOGENESIS

The common classes of drugs which can cause lung injury are antineoplastic drugs (Busulfan, Methotrexate, Bleomycin, Cyclophosphamide), antibiotics (Nitrofurantoin, Penicillin, Paraaminosalicylicacid, Sulphonamides), antihypertensive drugs, anticoagulants, drugs of abuse (heroin) and many others like Hydrochlorothiazide, Chlorpropamide, Phenytoin, Methysergide etc[6]. In addition to drugs, other potential inducers of respiratory disease are biomolecules(eg Interferons, Immunoglobulins, anti-thymocyte globulin), stem cell modulators (eg All-trans retinoic acid, Granulocyte-colony stimulating factors), transfusion of blood or blood products, stem-cell transplantation, herbs and dietery supplements.

It is very difficult to know the exact mechanism of drug associated injury of the lung as we do not have any specific marker to differentiate drug associated interstitial lung disease from other pharmacologic processes. In addition, usage of many drugs at the same time or in close sequence, a practice that makes the assignment of toxicity to a specific agent difficult. By aiding the identification of more than 1000 proteins or peptides in blood samples, the field of

Proteomics will hopefully allow scientists to identify candidate markers. Drugs cause lung injury as a result of direct pharmacologic action, persistence or metabolism in the tissue or production of a reactive metabolite. The result of this injury ranges from cellular dysfunction to apoptosis and alteration of repair mechanisms essential for replacing critical tissue elements and function. In many cases, drug induced lung disease is dose related, particularly with cytotoxic agents. Other factors such as increasing patient age, decreased renal function, radiation therapy and oxygen therapy may enhance the toxic effects.

TYPES OF REACTIONS

Bronchoconstriction – Aspirin and b-blockers are the two most common drugs causing bronchoconstriction. Aspirin, through its inhibitory action on cyclo-oxygenase pathway and b-blockers, through their direct pharmacological effect on airway smooth muscle can induce an attack of asthma[7].There can be a paradoxical worsening of asthma after inhalation of chromoglycate or of hypotonic nebulized solution of ipratropium bromide[8]. The usual pattern of response to b-blockers is a gradual worsening of patients breathlessness and a failure to respond to treatment with b-agonist drugs. Sometimes the adverse effect of drugs persists for some months after it has been discontinued[9]. A syndrome comprising asthma, nasal polyps and aspirin sensitivity has also been recognized. Other common drugs causing bronchoconstriction are antibiotics and contrast media used in radiology.

Cough – Though any drug causing bronchoconstriction can induce cough but dry cough caused by ACE inhibitors is of special mention as it is rarely if ever accompanied by bronchoconstriction. The cough usually starts after several months of treatment and is of a dry irritant nature. It ceases within a few days of stopping the drug. There is some evidence that administration of cromoglycate reduces the severity and frequency of cough in such patients[10]. But it is better to change the treatment to angiotensin 2 antagonists.

Bronchiolitis obliterans organizing pneumonia – A syndrome of progressive breathlessness associated with increasing airflow obstruction has been described with the use of a number of drugs. The breathlessness is progressive, although the rate varies from a rapid progression over weeks to a slow course over years. Drug associated BOOP has been reported from use of several different types of medications, including anti-inflammatory and immunosuppressive agents such as bleomycin sulphate, gold and methotrexate; antibiotics such as sulfasalazine, cephalosporins and amphotericin B; illicit use of cocaine and a massive dose of L-tryptophan. Minocycline associated BOOP has been reported in a woman who was taking this medication for acne[11]. Phenytoin related BOOP with rapid improvement after corticosteroid therapy has been reported[12] .There are case reports of patients having nitrofurantoin induced BOOP and their condition improved when nitrofurantoin was withdrawn and corticosteroid treatment commenced[13].

Alveolitis – Two patterns of drug induced alveolitis has been described. Mild eosinophilic pneumonitis is characterized by cough, breathlessness and fever of subacute to chronic onset with bilateral diffuse micronodular or patchy infilterates on radiography. There is often blood eosinophilia and lung biopsy may show inflammatory cells and eosinophils. Vasculitis may also be present. The condition usually recovers with withdrawl of drug and steroids. Common drugs associated with this condition are antibiotics(nitrofurantoin[14],sulphonamides,paraaminosalicylic acid); anticonvulsants(phenytoin,carbamazepine);antiarrhythmics(amiodarone,procainamide) and cytotoxic agents (bleomycin, mitomycin, busulphan).In contrast to the non-cytotoxic drugs; the usual pulmonary injury with cytotoxic therapy is a progressive pulmonary fibrosis with relatively little of an inflammatory component and a tendency to cause irreversible lung damage. The second pattern described is of acute eosinophilic pneumonitis. This condition is typically caused by minocycline. Characteristic features are fever, skin-rash, an eosinophilic BAL fluid and has a favourable outcome on cessation of therapy.

Acute noncardiogenic pulmonary edema – A variety of drugs –including opiates, aspirin, amiodarone, blood, blood products and tocolytic agents-can cause pulmonary vascular permeability alterations resulting in pulmonary edema. It occurs sometimes as an idiosyncratic reaction though usually in response to an excessive dose. In all cases, widespread bilateral alveolar or alveolar-interstitial infilterates are noted. The most frequent causes of drug induced pulmonary edema are overdoses of aspirin and opiates. Patients admitted to hospital with high salicylate levels after an overdose(>40 mg/dl) are at risk of developing acute pulmonary edema. The severity and outcome of these cases are quite variable. Most often the pulmonary edema is rapidly reversible. In some patients, however severe lung injury occurs and the clinical course progresses to the point where the case fulfills criteria for adult respiratory distress syndrome(ARDS).

Pulmonary vascular disease – Acute alveolar haemorrhage and recurrent alveolar haemorrhage have been reported to occur in response to some drugs like oral anticoagulants, fibrinolytic agents and platelet glycoprotein inhibitors. Patients present with hemoptysis and chest radiographs show alveolar infilterates as well as diffuse ground glassing. In some cases, the alveolar haemorrhage occurs as part of a pulmonary-renal syndrome that is very similar to goodpasture's disease. On the other hand oestrogen containing oral contraceptives have been shown to increase the risk of pulmonary thromboembolism in women by about six to nine times as well as of thrombotic stroke and myocardial infarction.

Hypersensitivity pneumonitis – Common drugs causing hypersensitivity pneumonitis are methotrexate, cyclophosphamide, nitrofurantoin, antidepressants and chrysotherapy. Patient gets sensitized to the drug and develops cough and breathlessness with lymphocytic predominant bronchoalveolar lavage fluid. It has a favourable outcome and usually recovers with steroids or on dechallenge.

Pleural and mediastinal fibrosis[15] – Methysergide, used for migraine can cause fibrosis of the pleura and underlying lung and it is a dose-related complication. Patient develops shortness of breath after several years of treatment. Interestingly, all the other drugs that have been reported to cause pleural fibrosis are blockers of neurotransmission. Practolol, b-blocker may cause pleural, mediastinal and peritoneal fibrosis. Ergotamine and bromocriptine can also cause pleuro-pulmonary fibrosis. The course of pleural fibrosis is progressive, with a restrictive pattern of lung function. However, the condition remits when the drug is stopped and in most instances there is reduction in symptoms and some improvement in lung function, though residual fibrosis remains on the chest film.

Other pulmonary reactions – Drugs can also cause lung disease in an indirect manner like hypoventilation and respiratory failure may be provoked by overdose of narcotics or sedatives, particularly in the elderly or in those with previous airflow obstruction. Drugs acting on the immune system, used in the management of cancer, transplantation and vasculitic diseases can cause opportunistic pulmonary infections.

DIAGNOSIS

Recognition of drug-induced lung disease is difficult because the clinical ,radiologic and histologic findings are nonspecific. The diagnosis is based on a history of drug exposure, histologic evidence of lung damage and exclusion of other causes of lung injury[16].The key to the diagnosis of drug-induced pulmonary disease is awareness of the possibility. Patient should be asked about all the drugs taken and any drug with unfamiliar names should be checked in reference books. First of all, appropriate base-line investigations should be carried out and the offending drug should be stopped. Base line investigations should include chest radiography, lung function testing, erythrocyte sedimentation rate, temperature records, total and differential cell counts and HRCT thorax. In case of doubt among a number of drugs, challenge test can be carried out but it should be performed only under hospital supervision. Lung biopsy, Gallium scanning and bronchoalveolar lavage can also play an important role in the differential diagnosis.

Although conventional chest radiography 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 radionuclide imaging have a role in detecting lung toxicity early when it is still reversible.

Radiological manifestations – Busulfan causes diffuse linear opacities, which may occasionally become reticulonodular. Bleomycin toxicity includes subpleural linear and/or nodular opacities at the lung bases. Methotrexate causes linear and/or reticulonodular opacities early in the process, followed by acinar filling. Bilateral basal interstitial opacities are commonly caused by nitrofurantoin. A common form of granulomatous reaction is caused by methotrexate, nitrofurantoin and chronic aspiration of mineral oils, which leads to the formation of chronic basilar, often conglomerate masses. Heroin or methadone overdose is often associated with pulmonary edema with widespread air-space consolidation. Amiodarone therapy is associated with alveolar and interstitial infilterates, peripheral consolidation, and pleural thickening adjacent to the consolidation.

HRCT thorax – The HRCT findings of chemotherapeutic drug-induced lung disease reflect the histologic findings[17]. Interstitial pneumonitis and fibrosis result in ground-glass opacities, focal areas of consolidation and irregular linear opacities that tend to involve the lower zones of the lungs. Acute respiratory distress syndrome results in bilateral predominantly dependent air-space consolidation with onset occurring within days of chemotherapy administration. Approximately 6% of individuals receiving amiodarone

develop pulmonary toxicity[18]. The most common HRCT finding of amiodarone toxicity is diffuse interstitial thickening or less commonly as nodular areas of subpleural consolidation. Amiodarone is an iodine containing compound; therefore, parenchymal lesions often show high attenuation with a range from 82 to 174 HU. Although this finding is helpful in suggesting amiodarone-induced pulmonary toxicity, it is not pathognomonic. Nitrofurantoin toxicity on HRCT shows air-space consolidation with a basilar predominance, a pattern consistent with cardiogenic pulmonary edema. Less commonly, chronic pneumonitis and fibrosis may ensue. On HRCT ,this appearance mimics idiopathic pulmonary fibrosis with bilateral predominantly basilar reticular opacities. Methotrexate toxicity reveals interstitial pneumonitis and ocassinally centrilobular nodules or a localized nodular air-space filling pattern. The use of illicit drugs like intravenous injection of talc may result in talcosis. HRCT shows diffuse micronodularity resulting from a foreign-body granulomatous response. The micronodules may become confluent and progress to conglomerate parahilar masses, which tend to have high attenuation caused by talc accumulation.[19,20].

So, in conclusion the HRCT manifestations of drug-induced lung disease imitate other entities such as infection, pulmonary fibrosis and disease recurrence.

MANAGEMENT

Management of drug induced pulmonary reactions consists in stopping the offending drug and, if necessary, substituting a less harmful one. Corticosteroid therapy may be used in some cases. In malignancy, pulmonary side-effects are relatively common and sometimes fatal as the cessation of drug can cause relapse of disease. Hyposensitisation or induction of tolerance can be tried if the drug is considered essential. The main interest of this subject currently centres on the induction of tolerance to aspirin and non steroidal anti-inflammatory drugs[21]. However it should be done with great care as serious reactions can occur.

Finally, we can say that the knowledge of adverse pulmonary drug reactions is very important for the pulmonary physicians for better management of patients.

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