Drug-induced respiratory disease

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Keywords: drugs, respiratory disease, cough, pulmonary adverse effects

Drug-induced lung disease is a relatively common condition caused by an adverse reaction to medication and it is often impossible to predict who will develop lung disease resulting from a drug.[1]

Introduction

Drug-induced lung disease may occur via various mechanisms:

- *Direct toxicity*: This usually takes time before it manifests clinically. The toxic effect is usually dose related, though other factors such as age and renal function can enhance toxicity.
- *Hypersensitivity reaction*: This is not dose related and requires prior sensitization to the drug. It is a result of interactions between the drug and humeral antibodies or sensitized lymphocytes.
- *Pulmonary oedema*: This can occur with various drugs. Pulmonary oedema typically occurs within hours of administration of the drug.
- *Pulmonary haemorrhage*: This is most commonly a complication of anticoagulant therapy or drug-induced thrombocytaemia.
- *Pulmonary granulomas*: These are composed of macrophages reacting to various drugs.[2]

Cardiovascular Drugs

Angiotensin-converting enzyme inhibitors

Angiotensin converting enzyme inhibitors (ACEIs) are rightly so prescribed for the treatment of hypertension, especially in the presence of left ventricular dysfunction and congestive heart failure. In these patients ACEIs decrease morbidity and mortality. Yet, some patients may experience a tedious dry cough which affects their compliance. Cough is the most common adverse effect with this class of drugs and it occurs about five times more often than with placebo. Cough is more common in women and older patients.[3] Approximately 0.1 to 0.2% of patients receiving ACEIs experience more serious adverse effects which can vary from a mild swelling of the face to swelling of the tongue and supraglottic area leading to respiratory compromise.[4] The etiology of ACEI-related side-effects is not completely understood, however, the accumulation of bradykinin is thought to be one explanation. Bradykinin causes vasodilation and capillary leakage leading to side effects. Adverse effects might be seen in some patients and not others due to a possible genetic deficiency of bradykinin-metabolizing enzymes in some patients.[4]

Beta-Blockers

Beta-blockers are frequently prescribed in hypertensive patients or ischaemic heart disease sufferers without taking into consideration whether the patient suffers from asthma. Beta-blockers are contra-indicated in asthma as they can cause bronchospasm. Being competitive inhibitors of beta-adrenoceptors, even small doses of beta-blockers can cause bronchospasm, with manifesting symptoms such as shortness of breath and wheezing.[3] The severity of the bronchoconstrictor response to a given beta blocker is not predictable, and occurs mainly in patients with reversible bronchial obstruction.[5] This can also be extended to topical beta-blockers, such as eye drops. Systemic absorption and thus side-effects can be encountered even with these preparations.

Amiodarone

Atrial fibrillation is a common dysrhythmia frequently treated with antiarrhythmic drug therapy, such as amiodarone. Long-term use of amiodarone may cause pulmonary complications, including pneumonitis

and acute respiratory distress syndrome (ARDS), in up to 10% of patients receiving this drug. However, most of the published cases have been in patients receiving more than 200mg per day of amiodarone (usually 400mg/d or more). Low dose amiodarone poses fewer problems though the Canadian Myocardial Infarction Amiodarone Trial showed that even low-dose amiodarone increased pulmonary toxicity compared to placebo (3.89% vs. 1.2%). Therefore, the clinician must keep in mind that even low-dose amiodarone is associated with some risk for pulmonary toxicity.[6]

Anti-inflammatory agents

Aspirin and NSAIDs

Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed for a variety of medical conditions. Patients commonly take NSAIDs for any type of pain they experience, without even consulting a doctor or a pharmacist. Aspirin and NSAIDs may precipitate asthmatic attacks in approximately 8 per cent of asthma sufferers and these attacks can occasionally proceed to be potentially fatal. Patients with chronic rhinitis and nasal polyps are at greatest risk. Persons with aspirin-induced asthma are usually not previously sensitive to aspirin and this usually appears in the third to fourth decade.[7] After aspirin ingestion, patients who are sensitive to aspirin may present with various symptoms such as rhinorrhea, dyspnoea and cough. These symptoms usually occur over a period of 20 minutes to three hours after ingestion of the drug and can lead to bronchospasm and angioedema. The overproduction of leukotrienes may be implicated in this asthmatic reaction.[8]

Methotrexate

Methotrexate is used in the treatment of rheumatoid arthritis and other connective tissue disorders, as well as in cancer chemotherapy. Pulmonary complications seen in patients who are on anti-inflammatory doses of methotrexate include opportunistic infections, acute interstitial pneumonitis, interstitial fibrosis, and asthma.[7]

Infliximab

Infliximab is used in patients with rheumatoid arthritis and Crohn's disease. It can cause infusion reactions which can occur during or 1-2 hours after infusion. These reactions can cause symptoms such as fever, chills as well as dyspnoea and cough.[9]

Chemotherapeutic drugs

Bleomycin

Bleomycin is deposited in the skin and lungs; hence the most serious adverse effects are seen in these organs.[7] Chronic lung damage secondary to the use of bleomycin is rare though it can progress to pulmonary fibrosis and death in a minority of patients.[10] The role of Interleukin-4 in the development of lung fibrosis is as yet unclear.[11] Risk factors for bleomycin toxicity include total dose of bleomycin given, exposure to high oxygen concentrations, thoracic radiation, decreased renal function, older age and smoking. With doses of bleomycin less than 300mg, the incidence of pneumonitis is 3-5% whilst with doses higher than 500mg the incidence is 20%. Bleomycin-induced pneumonitis usually occurs gradually in the first few months of therapy. Pulmonary function tests should be monitored in order to detect the onset of bleomycin-induced pneumonitis.[10]

Mitomycin-C

Incidence of pulmonary toxicity with Mitomycin-C is about 5% and this includes bronchospasm, acute pneumonitis, haemolytic-uremic-like syndrome, acute lung injury, chronic interstitial pneumonitis, and pleural disease.[7]

Hypnotics and Anxiolytics and Barbiturates

Benzodiazepines

Benzodiazepines are widely prescribed in general practice to relieve anxiety and facilitate sleep. There is still much debate regarding the over use of this class of drugs, especially since benzodiazepines can easily cause dependence the over use of this class of drugs.

Benzodiazepines are also weak respiratory depressants. When administered as monotherapy, respiratory depression with diazepam may be detectable at doses of 0.2mg/kg (14mg dose for a 70kg person). The resulting increase in CO_2 is slight, clinically insignificant, and may be attributable to decreased tidal volume. However, respiratory depression with benzodiazepines can be clinically significant when used in combination with other respiratory depressants or if allowed to accumulate to toxic levels. Elderly patients are at particular risk from longer acting agents such as flurazepam and diazepam. This should be of concern to clinicians when considering the high amount of prescriptions issued for diazepam, especially to the elderly. Often benzodiazepines may be prescribed concomitantly. Lorazepam and temazepam are eliminated primarily by glucuronidation, which is less dependent on microsomal enzymes, and are unlikely to be influenced by hepatic dysfunction or increasing age. Moreover, they do not have active metabolites and have a shorter half-life (15 hours). As a result, they are safer than the other benzodiazepines.[12]

Barbiturates

Barbiturates are still sometimes prescribed for patients suffering from epilepsy. These are strongly associated with drug-induced respiratory depression and are, therefore, contra-indicated in patients with severe respiratory disease. Barbiturates are thought to induce respiratory depression by desensitization of the medulla to hypercapnia and these agents inhibit the respiratory rate and affect the depth and volume of inspiration. Phenobarbitone should be therefore prescribed with great caution.[12]

Antimicrobial drugs

Nitrofurantoin

Nitrofurantoin, commonly prescribed for urinary tract infections, may cause pulmonary disease with eosinophilia. Initially the patient presents with fever, dyspnoea, cough and pulmonary infiltrates, and there is often marked

peripheral blood eosinophilia. There may be an acute presentation, developing hours to days after initiation of treatment and complications usually resolve within 15 days of discontinuation of nitrofurantoin. Long term therapy with nitrofurantoin may eventually cause pulmonary fibrosis. This may occur from two months to five years after initiation of therapy and the patient will present with exertional dyspnoea and a non-productive cough and fatigue. This chronic form represents direct tissue damage from oxidants.[7,13]

Sulphonamides and sulpha containing drugs

Sulphonamides, commonly used to treat urinary tract infections as a combination in co-trimoxazole, are known to cause pulmonary eosinophilia which tends to occur 10-14 days after exposure. The patient presents with fever, blood eosinophilia and new pulmonary opacities.[13] Sulfasalazine, indicated for ulcerative colitis, Crohn's disease and rheumatoid arthritis, can cause lung complications such as eosinophilia and fibrosing alveolitis.

Tetracyclines

Minocycline can cause pulmonary eosinophilia, which is characterised by pulmonary infiltrates on the chest X-ray, chest symptoms such as dyspnoea, and eosinophilia in blood and bronchoalveolar lavage fluids. These symptoms may be severe enough to lead to transient respiratory failure.[13]

Illicit drugs

Cannabis, the most widely used illicit drug, contains carcinogens similar to those found in tobacco smoke, and hence chronic heavy marijuana use may predispose people to chronic obstructive lung disease.[14] Heroin is a derivative of morphine and can cause slow breathing by stimulation of mu receptors. Heroin reduces the brain's responsiveness to changes in PCO_2 and with high doses, it can also depress the brain's response to hypoxia. This results in severe respiratory depression progressing to apnoea. Therefore, fatal heroin overdose is nearly always caused by respiratory arrest.[15] Cocaine may cause wheezing which occurs from exacerbated asthma or hypersensitivity pneumonitis. Cocaine use may also lead to non-cardiogenic pulmonary oedema or to diffuse alveolar hemorrhage. Long-term users of crack, a chemical derivative of cocaine, can suffer from bronchitis and other breathing problems.[16]

Miscellaneous Drugs

Several other drugs can affect the respiratory system. Bromocriptine, a stimulant of dopamine receptors, can cause pulmonary fibrosis and pleural disease[7] as well as nasal congestion.[17] Antidepressant and antipsychotic agents have been associated with pulmonary oedema.[7] Venlafaxine, a serotonin and noradrenaline reuptake inhibitor, may potentially cause pneumonitis.[18] Some propellants found in inhalers which are intended to relieve respiratory problems, may actually cause cough. Doxazosin, an alpha-adrenoceptor blocking drug, may cause rhinitis and a potential side-effect of candersartan, an angiotensin-II receptor antagonist, is upper respiratory-tract and influenza-like symptoms including rhinitis and pharyngitis.[19]

Conclusion

This paper has only reviewed the more commonly used medications and illicit drugs. However, currently there are at least 150 agents which have the potential to cause pulmonary disease. Early diagnosis is important since stopping the drug usually reverses toxicity, whereas unrecognized toxicity can be progressive and even fatal. Therefore, both doctors and pharmacists in the clinical settings should be on the alert for possible associations between medication and lung related symptoms.

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