Respiratory Pharmacology

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Introduction

The respiratory system constitutes vital organs mainly responsible for gas exchange, and their function can be significantly influenced by various medications. While some drugs are designed to treat pulmonary conditions, others may inadvertently cause adverse effects on the lung tissues and other organs. The topic of respiratory pharmacology is expansive, this chapter briefly explores the mechanisms by which medications affect the respiratory system, focusing on both therapeutic and harmful effects.

Therapeutic medications for pulmonary conditions

Bronchodilators

Bronchodilators are a cornerstone of treatment for obstructive lung diseases such as asthma and chronic obstructive pulmonary disease. They work by relaxing the smooth muscles of the airways, thereby improving airflow.

- **Beta-2 Agonists:** These agents activate beta-2 adrenergic receptors on airway smooth muscle cells, leading to increased cyclic AMP (cAMP) levels and subsequent muscle relaxation. These medications can be in inhaled, oral or intravenous forms.

  Side effects: include but are not limited to local effects (throat irritation, cough, paradoxical bronchospasms, hoarseness), and systemic side effects (tachycardia, palpitations, arrhythmias, hypertension, hypokalemia, hyperglycemia, tremors, anxiety, headaches, tachyphylaxis).

- **Anticholinergics:** These agents block muscarinic receptors, preventing acetylcholine-induced bronchoconstriction. These medications are used mainly through the inhaled route.

  Side effects: include but are not limited to local effects (dry mouth, throat irritation, cough, paradoxical bronchospasms, hoarseness), and systemic side effects (tachycardia,

  palpitations, worsening glaucoma, blurry vision, constipation, nausea, dry mouth, urinary retention, dizziness, headaches, cognitive impairment).

- **Corticosteroids:** These agents are anti-inflammatory agents used to manage chronic inflammatory lung diseases. They reduce inflammation by inhibiting the production of pro-inflammatory cytokines and decreasing the infiltration of immune cells into lung tissue. These medications can be in inhaled, oral or intravenous forms.

  Side effects: include but are not limited to local effects (cough, oropharyngeal candidiasis, dysphonia, pharyngitis), and systemic side effects (adrenal insufficiency, Cushing's syndrome, hyperglycemia, hyperlipidemia, hypertension, osteoporosis, myopathy, growth suppression in children, peptic ulcer, pancreatitis, immunosuppression, hypokalemia).

- **Leukotriene modifiers:** block the action of leukotriene, which are inflammatory mediators involved in bronchoconstriction and mucus production. These medications are usually used in the oral form.

  Side effects are not limited to abdominal pain, nausea, indigestion, headaches, dizziness, cough, upper respiratory infections, insomnia, agitation, hallucination, depression, elevated liver functions, rash, eosinophilia).

- **Theophylline:** a non selective Phosphodiesterase Enzyme Inhibitor that causes smooth muscle relaxation (bronchodilation) and suppression of the response of the airways to stimuli (non-bronchodilator prophylactic effects). It increases the force of contraction of diaphragmatic muscles through enhancement of calcium uptake through adenosine-mediated channels. These medications can be oral or intravenous forms.

  Side effects are not limited to tachycardia, cardiac arrhythmias, anxiety, seizures, narrow therapeutic range of toxicity and drug-drug interactions.

Pulmonary Vasodilators

Pulmonary vasodilators are a group of medications used to treat Pulmonary Hypertension (PH), a condition characterized by high blood pressure in the pulmonary arteries. These medications work by relaxing the blood vessels in the lungs, reducing pulmonary vascular resistance, and improving blood flow. There are several classes of pulmonary vasodilators, each with distinct mechanisms of action and side effect profiles.

- **Calcium Channel Blockers (CCBs):** inhibit calcium influx into the vascular smooth muscle cells, leading to relaxation of pulmonary arteries. These medications can be in oral or intravenous forms.

  Side effects are not limited to bradycardia, hypotension, constipation, peripheral edema, constipation.

- **Endothelin Receptor Antagonists (ERAs):** block endothelin-1, a potent vasoconstrictor, leading to vasodilation and inhibition of vascular remodeling. These medications are usually administered in the oral form.

  Side effects are not limited to hepatotoxicity, peripheral edema, anemia, headaches, teratogenicity, nasopharyngitis.

- **Phosphodiesterase-5 (PDE-5) Inhibitors:** increase cyclic guanosine monophosphate (cGMP) levels, leading to vasodilation. These medications are usually administered in the oral form.

  Side effects are not limited to hypotension, headaches, flushing, dyspepsia, visual disturbance, nasal congestion.

- **Prostacyclin Analogues and Prostacyclin Receptor Agonists:** These medications mimic prostacyclin, a natural vasodilator and inhibitor of platelet aggregation. These medications can be administered in the oral, intravenous or inhaled forms.

  Side effects are not limited to hypotension, flushing, headaches, nausea, vomiting, infusion site reaction.

- **Soluble Guanylate Cyclase (sGC) Stimulators:** enhance the sensitivity of sGC to nitric oxide, leading to increased cGMP levels and vasodilation. These medications are usually administered in the oral form.

  Side effects are not limited to hypotension, headaches, dyspepsia, nausea, vomiting, dizziness, hemoptysis.

- **Nitric Oxide (NO) and Nitric Oxide Donors**: relaxes vascular smooth muscle by increasing cGMP levels. These medications are usually administered in the inhaled form.

  Side effects are not limited to hypotension, methemoglobinemia, headaches, tolerance, rebound pulmonary hypertension.

Mucolytics and Expectorants

Mucolytics, such as acetylcysteine, hypertonic saline, heparin and dornase alfa, work by breaking down the disulfide bonds in mucus, reducing its viscosity and making it easier to clear from the airways. Acetylcysteine also has antioxidant properties, which may provide additional benefits in conditions involving oxidative stress and inflammation. Expectorants, such as guaifenesin, function by increasing the hydration of airway secretions, promoting mucus clearance through ciliary movement and coughing. Mucolytics are usually administered in the inhaled or oral forms, while Expectorants are usually in the oral form.

Side effects of mucolytics can include respiratory irritation, rhinorrhea, increased secretions, and hypersensitivity reactions. Expectorants are usually well tolerated but can cause gastrointestinal effects, dizziness, headaches, and rarely kidney stones.

Antitussives

There are different classes of medications used to suppress coughing. Centrally acting antitussives, such as codeine and dextromethorphan, are the most common and function by inhibiting the medullary cough center in the brainstem. Codeine, an opioid, is effective but carries risks of dependence and side effects, while dextromethorphan, a non-opioid, is widely available over the counter and has a better safety profile. Peripherally acting antitussives, such as benzonatate, work by anesthetizing the stretch receptors in the

lungs and airways, reducing the cough reflex. These medications are usually administered in the oral form.

Side effects of codeine are similar to other opiates including risk of dependence, constipation, dizziness. Other non narcotic medications are well tolerated but can cause gastrointestinal side effects and abdominal pain.

Decongestants

The most common classes to treat allergic or infectious rhinorrhea are antihistamines (e.g. diphenhydramine, cetirizine, loratadine), mast cell stabilizers (Cromolyn), and glucocorticoids. These medications can be used in the oral or nasal form.

Side effects of each class are not limited to: Antihistamines can cause drowsiness, confusion, dry mouth, blurred vision. Cromolyn can cause gastrointestinal symptoms, pruritic, headaches, myalgias, the nasal form has limited side effects. Glucocorticoids as above.

Pulmonary Surfactant

Pulmonary surfactant is a complex mixture of lipids and proteins produced by type II alveolar cells in the lungs. Its primary function is to reduce surface tension at the air-liquid interface of the alveoli, preventing alveolar collapse during exhalation and ensuring efficient gas exchange. Surfactant is composed of approximately 90% lipids (primarily phospholipids) and 10% proteins (including surfactant proteins SP-A, SP-B, SP-C, and SP-D), which play critical roles in stabilizing the surfactant film and modulating immune responses. In premature infants, surfactant deficiency leads to respiratory distress syndrome (RDS). Exogenous surfactant replacement therapy has revolutionized the treatment of neonatal respiratory distress syndrome (RDS), significantly improving survival rates. Beyond its mechanical role, it also contributes to innate immunity by enhancing pathogen clearance and modulating inflammation, highlighting its importance in maintaining lung health. Surfactant can be natural or synthetic and is administered as a liquid format through the endotracheal tube.

Side effects are not limited to hypoxia, airway occlusion, bradycardia, hypotension, pulmonary hemorrhage, air leak, bronchopulmonary dysplasia, retinopathy, and neurodevelopmental delays.

Medications Induced Complications

Respiratory Depression

Respiratory depression is a potentially life-threatening condition characterized by reduced respiratory rate, tidal volume, or complete cessation of breathing through different mechanisms. Opioids suppress the brainstem respiratory centers, Benzodiazepines potentiate GABAergic inhibition in the central nervous system, reducing respiratory drive, Barbiturates directly causes CNS depression, General Anesthetics directly suppress central respiratory drive, Muscle Relaxants cause paralysis of respiratory muscles.

Drug-Induced Interstitial Lung disease

Many medications side effects can manifest as pneumonitis, fibrosis or lung edema that can occur acutely, sub acutely, or with chronic use. Manifestations include progressive shortness of breath, hypoxia, worsening lung functions measured by pulmonary functions, and worsening radiological infiltrates.
Common mechanisms include Oxidative Stress with the generation of reactive oxygen species leading to cellular damage, Immune-Mediated Reactions with hypersensitivity or autoimmune responses targeting lung tissue, Direct Cytotoxicity directly causing damage to alveolar epithelial or endothelial cells, and Altered Surfactant Production or function, leading to atelectasis or edema.
Common medications include chemotherapeutic drugs (Bleomycin, Methotrexate), antibiotics (Nitrofurantoin, Sulfonamides), Antiarrhythmics (Amiodarone, Tocainide), Immune checkpoint inhibitors (Nivolumab, Pembrolizumab), Illicit drugs (Cocaine, Heroin).

Drug-Induced Bronchoconstriction

Drug-induced bronchoconstriction refers to the narrowing of the airways caused by certain medications, leading to symptoms such as wheezing, shortness of breath, and coughing. This adverse effect is particularly problematic for individuals with pre-existing respiratory conditions like asthma or chronic obstructive pulmonary disease (COPD). Common culprits include nonsteroidal anti-inflammatory drugs

(NSAIDs) such as aspirin, which inhibits cyclooxygenase (COX) enzymes and shift arachidonic acid metabolism toward the production of bronchoconstrictive leukotrienes. Beta-blockers, especially non-selective ones like propranolol, can also trigger bronchoconstriction by blocking beta-2 adrenergic receptors in the airways, which are essential for bronchodilation. Additionally, angiotensin-converting enzyme (ACE) inhibitors may cause cough and bronchospasm due to the accumulation of bradykinin, a peptide that promotes inflammation and airway constriction.

Drug-Induced Pulmonary Hypertension

Drug-induced pulmonary hypertension is a condition in which certain medications lead to increased pulmonary arterial pressure, resulting in right heart strain and compromised oxygenation. Symptoms often include progressive dyspnea, fatigue, and, in severe cases, right heart failure. Various drugs, including appetite suppressants (e.g., fenfluramine, dexfenfluramine), selective serotonin reuptake inhibitors (SSRIs), amphetamines, and some chemotherapy agents (e.g., dasatinib), have been implicated in triggering or exacerbating PH. These drugs may cause endothelial dysfunction, vasoconstriction, inflammation, or vascular remodeling within the pulmonary arteries.

Vasopressors and Inotropes effect on pulmonary circulation

Systemic vasopressors, such as norepinephrine, epinephrine, dopamine, Angiotensin are commonly used to support blood pressure in critically ill patients. However, their potent vasoconstrictive effects can contribute to or exacerbate pulmonary hypertension (PH). These agents increase systemic vascular resistance (SVR) but may also elevate pulmonary vascular resistance (PVR), leading to right ventricular afterload and potential right heart failure.

- Norepinephrine and epinephrine, through their α-adrenergic stimulation, can cause pulmonary vasoconstriction, but also can augment the right ventricular function through inotropic effect of the B1 receptors.

- Vasopressin is less likely to cause increased pulmonary pressures despite the presence of vasopressin receptors in the pulmonary artery, in fact, studies suggest it may even have a pulmonary vasodilatory effect through the action on V1 receptors and can help to decrease pulmonary arterial pressure and potentially alleviate pulmonary hypertension in certain situations.

- Inotropes like dobutamine and milrinone, which enhance myocardial contractility, can have mixed effects on pulmonary circulation. Dobutamine reduces PVR through β2-mediated pulmonary vasodilation, improving right ventricular output, but may also cause systemic hypotension. Milrinone, a phosphodiesterase-3 inhibitor, lowers both SVR and PVR, reducing right ventricular afterload and improving cardiac output.

- Midodrine, an oral α_1-adrenergic agonist primarily used for orthostatic hypotension, and for patients in ICU to reduce the amounts of intravenous vasopressors. has not been strongly linked to causing pulmonary hypertension in most clinical scenarios. Data on midodrine and Pulmonary Hypertension are limited, however, its vasoconstrictive effects on systemic vasculature could theoretically increase pulmonary vascular resistance in susceptible individuals, particularly those with pre-existing pulmonary hypertension or right heart dysfunction. Unlike systemic vasopressors, midodrine has minimal direct pulmonary vasoconstrictive effects, but its chronic use could contribute to increased afterload on the right ventricle in patients with compromised pulmonary circulation.

Pleural Effusion

Some medications can cause abnormal accumulation of fluid in the pleural cavity, which can impair breathing and oxygenation. Mechanisms can include drug induced lupus (e.g. hydralazine, procainamide), increased capillary permeability or direct toxicity to pleural tissues (chemotherapeutic drugs).

Pulmonary Edema

Certain medications can cause fluid accumulation in the alveoli, impairing gas exchange and leading to hypoxia. It can be cardiogenic (due to heart failure) like intravenous fluids, corticosteroids, NSAIDs, or non-cardiogenic (due to alveolar-capillary membrane damage and capillary leak) like opioids, heroin, salicylates.

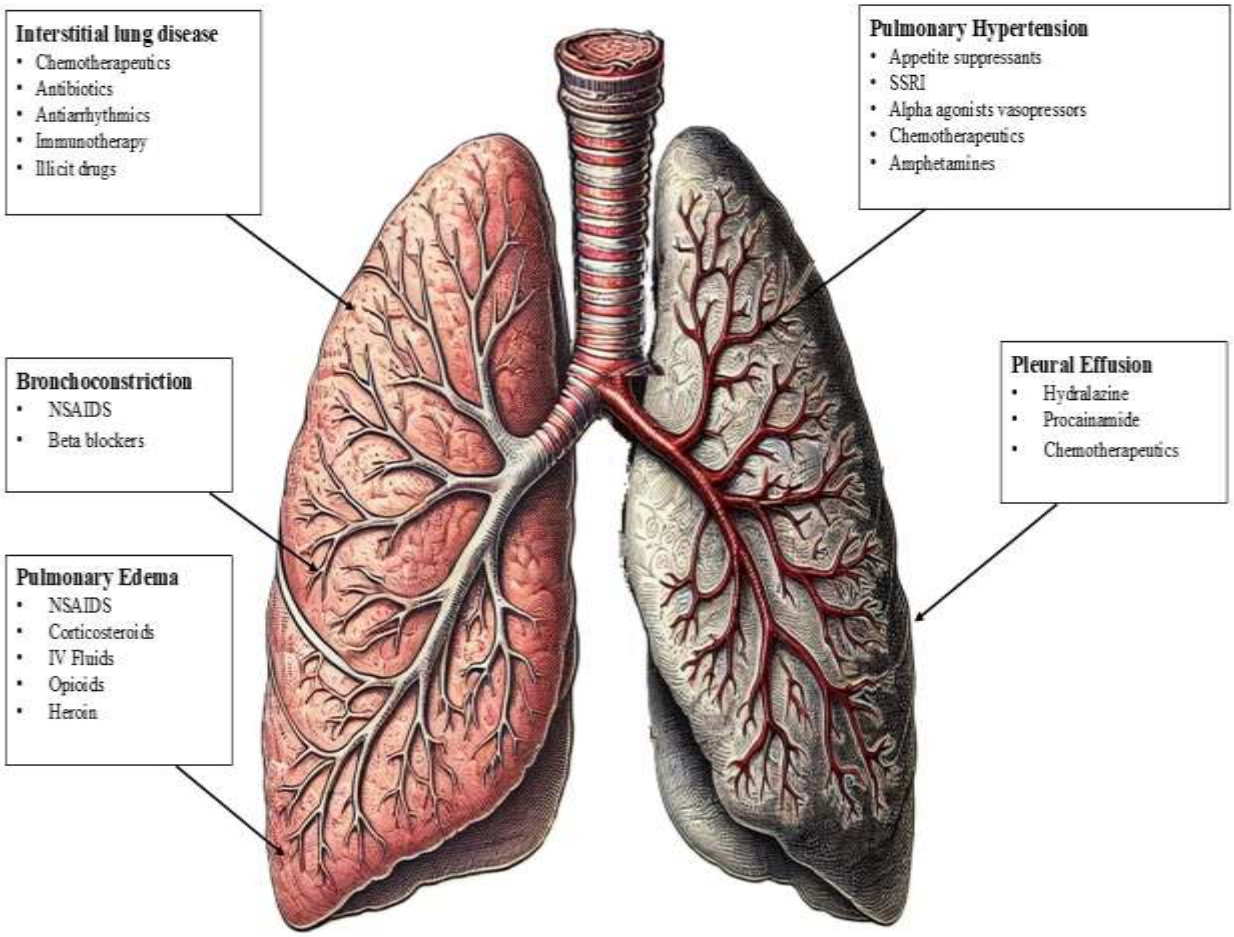

Figure 1 Schematic summary of medications induced side effects on the bronchial tree, pulmonary circulation, interstitial lung tissues and alveoli. Right side (Left lung showing pulmonary circulation in red), Left side (Right lung showing bronchial tree in grey and lung tissue in pink). Image is AI generated and not designed to be anatomically correct.

Conclusion

The field of respiratory pharmacology encompasses a diverse range of medications that influence pulmonary function, either as therapeutic agents or as contributors to respiratory complications. Understanding the mechanisms of drug-induced effects on the respiratory system is essential for optimizing patient care and minimizing adverse outcomes and integrating knowledge of drug-induced pulmonary effects into clinical practice, healthcare providers can tailor pharmacologic interventions to enhance respiratory function while mitigating risks. Continued research and vigilance in monitoring drug-related pulmonary complications will further improve patient safety and therapeutic efficacy in respiratory medicine.

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