Drug Induced Pulmonary Disorders

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Scope of the Problem

- 0.5 to 1.2% of adverse drug effects
- 12% of life threatening adverse drug effects
- 26% of drug induced deaths
- Often unrecognized or a diagnosis of exclusion
Pathophysiologic categorization

- Apnea
  - CNS depression
  - respiratory neuromuscular blockade or myopathy
- Bronchospasm
  - allergic, anaphylactic
  - airway irritation
  - pharmacologic effect
- Pulmonary edema
- Pulmonary eosinophilia
- Pulmonary fibrosis
- Pulmonary hypertension
- Oxygen toxicity, ACE inhibitor cough
- Pseudolymphoma, lupus syndrome
Drug Induced Apnea

- CNS depressants
  - Opiods, sedative/hypnotics, ETOH, antihistamines
  - Greater risk in elderly, COPD, overdose
  - Consider additive. E.g. benzos, ETOH
  - High dose $O_2$ in CO$_2$ retainers → hypoxic ventilatory drive

- Neuromuscular blocking agents
  - Post surgical or ventilated patients
  - Additive with aminoglycosides
  - Consider hepatic and renal status

- Respiratory muscle myopathy
  - Prolonged high dose corticosteroids
  - Vaccine induced Guillain-Barre
  - INH via pyridoxine inhibition
Drug Induced Bronchospasm

• Risk
  – Asthma, COPD, non-specific bronchial hyperreactivity

• Beta blockers
  – Non-selective vs. selective vs. mixed α, β blocker vs. partial agonist vs. topical

• Direct airway irritation (parasympathetic)
  – MDI, DPI. Beta agonists, steroids
  – Smoke, N-acetylcysteine (Mucomyst)
  – Sulfites in food/wine (preservative/anti-O₂)

• Anaphylaxis (IgE mediated)
  – Pcn, ceps, sulfas, transfusions
  – peanut oil, benzalkonium preservative

• Anaphylactoid (mast cell degranulation)
  – Iodinated radio contrast media (shell fish), local anesthetics
  – Food coloring (tartrazine)
NSAID induced bronchospasm

- Aspirin: 4-20% of asthmatics
  - 14-23% if nasal polyps
  - Often with vasomotor rhinitis
  - Women > men; onset over age 40
  - COPD not at greater risk
  - Bronchospasm within minutes to hours of ingestion. Also rhinorrhea, flushing of head and neck, conjunctivitis

- Cross reactive with other NSAIDS
  - Acetaminophen? Rare reports

- Pharmacologic, not allergic
  - Selective cyclooxygenase inhibition
  - Unopposed lipooxygenase & relative over expression of leukotrienes.
Pharmacologic/Physiologic Basis of Asthma

Mast cell contents
- Histamine
- Recruit mediators (IL’s, lymphokines, eosinophils)

Mast cell membrane rupture
(phospholipid release)

Arachidonic acid

Lipoxygenase

Cyclooxygenase

Leukotrienes

- LTD4
- LTE4

Prostaglandins

- PGE
- prostacyclin
- thromboxane

Zileuton (Zyflo)

inhibit

Zafirlukast (Accolate)

Montelukast (Singulair)

Block receptor

“Receptors”

Allergen + IgE

Ca++ inflow
(↓ cyclic AMP, ↑ cyclic GMP*)

Phospholipase A₂

*Beta agonists increase cyclic AMP
Anticholinergics decrease cyclic GMP,
Corticosteroids block phospholipase A₂
ACE Inhibitor Induced Cough

• 1-25% (mean 10%) of patients
  – Dry, non-productive, persistent
  – May mimic post URI bronchitis
  – Onset 3 days to one year
  – Remits in 1-4 days after d/c, but up to 4 weeks in some
  – Recurs with re-challenge
  – Cross reacts among all ACEIs
  – Asthma and hyperreactivity not a risk, normal PFTs

• Reduced metabolism of bradykinin, substance P, and prostaglandins
  – Inflammation/ stimulation of irritant lung receptors

• Angiotensin receptor blockers may be substituted.
Pulmonary Edema

• Increased pulmonary capillary hydrostatic pressure
  – Excess IV fluid administration
    • NSAID fluid retention
  – Left ventricular failure (CHF)
    • Anthracyclines, beta blockers
  – Low oncotic pressure (albumin)

• Secondary disruption of alveolar epithelium, interstitial lymphedema, and cellular exudation

• Cough, tachypnea, dyspnea, tachycardia, rales, hypoxemia, infiltrates on CXR.
Opioid Induced Pulmonary Edema

• IV heroin overdose most common
  – Hypoxemia → pulmonary vasoconstriction/hypertension
  – ? Direct toxic effect on alveolar capillary membrane → alveolar edema fluid

• Also idiosyncratic reaction to moderate to high medical doses
  – morphine, methadone, meperidine, propoxyphene

• Onset from minutes post IV dose to 2 hours with PO
  – Mild: cough and rales
  – Severe: cyanosis, hypoxemia, fast shallow respirations, hypotension, fluid on CXR
  – Therapy: Naloxone, O₂, ventilator
  – Clinical improvement in 24-48 hrs; CXR clear in 2-5 days; abnl PFT for weeks; 1-10% mortality
Pulmonary Edema: infrequent causes

- Injection of contrast media into pulmonary circulation during angiocardiology
- IV bleomycin, vinblastine, cyclophosphamide
- Interleukin 2 (Aldesleukin) and muromonab CD3 (OKT-3)
- Ritodrine and terbutaline when used as tocolytics
- Salicylate overdoses
- Paradoxical with high dose hydrochlorothiazide
- Tricyclic antidepressant OD
Pulmonary Hypertension

• Pulmonary artery vasoconstriction
  – Right ventricular afterload
  – Right sided heart failure, failure to perfuse lungs and left heart, edema
  – Exertional dyspnea, chest pain, syncope
• Usually idiopathic or secondary to hypoxia (cor-pulmonale)
• Anorexics:
  – fenfluramine, dexfluramine.
  – Potassium channel inhibition
  – Increased serotonin levels
  – Co-existent valvular heart disease
• Cocaine, oral contraceptives
Pneumonitis

• Non specific acute or chronic inflammation of lung tissue

• Pneumonia: pneumonitis accompanied by formation of an exudate in the interstitial and cellular portions of the lung.
  – Bacterial and viral
  – Chemical (e.g., aspiration)

• Hypersensitivity response to a drug
Pulmonary Eosinophilia (Loeffler’s Syndrome)

- Specific form of drug induced pneumonitis
  - May be mistaken for pneumonia, pulmonary edema or acute asthma
  - Fever, chills, non-productive cough, dyspnea (chest pain/SOB), bilateral pulmonary infiltrates. Rare cyanosis.
  - Lung biopsy: perivascularitis with infiltration by eosinophils, macrophages, proteinaceous edema fluid

- 50% with eosinophils in blood or bronchopulmonary lavage fluid

- Onset within days to weeks of starting therapy. Sometimes delayed for months

- Resolves rapidly after D/C; Rapid recurrence with rechallenge
Drugs Associated with Pneumonitis

• Nitrofurantoin
  – also causes chronic fibrosis

• Dantrolene
  – May be delayed onset (months to years) and slower to resolve.
  – Pleural effusions and pleuritic pain

• Minocycline

• Phenytoin
  – Onset 3-6 weeks
  – Lymphadenopathy, maculopapular rash also common

• Sulfonamides (including topical cream)

• Carbamazepine, tricyclics, penicillins, methotrexate
Pulmonary Fibrosis

• May or may not be preceded by pneumonitis

• Early phase: perivascular, peribronchiolar, interstitial, alveolar inflammation and pulmonary edema

• Later phase: Collagen and elastin deposition in interstitium of alveolar walls resulting in fibrosis, loss of gas exchange
  – Lung stiffening, restrictive lung disease

• Symptoms: Dry cough, pleuritic chest pain, shortness of breath
Mechanism of Pulmonary Fibrosis

- Activation of oxidative reactions toxic to protein sulfhydryl groups, membrane lipids and nucleic acids
  - oxygen free radical production and peroxidation (superoxide, hydrogen peroxide, hydroxyl radicals)
  - Bleomycin, cyclophosphamide, nitrofurantoin, paraquat

- Reduction of antioxidant defense systems
  - superoxide dismutase, catalase, glutathione peroxidase, and \( \alpha \) tocopherol
  - Carmustine, cyclophosphamide, nitrofurantoin
Drugs Causing Fibrosis

• High dose oxygen therapy
  – >50% FIO$_2$ > 24-48 hours

• **Amiodarone**
  – Risk > 400 mg/day; 4-6% incidence
  – Onset 4 wks to 6 years
  – Progressive exertional dyspnea, cough, weight loss, low grade fever
  – Rare: rapid progression and respiratory failure.
  – PFT monitoring not helpful except CO diffusing capacity.
  – Value of steroids unknown

• Nitrofurantoin

• **Cytotoxic drugs (most common)**
  • Paraquat
  • Methysergide, gold salts, phenytoin
Cytotoxic Drug Risk Factors

- Cumulative dose
- Increasing age
- Concurrent or prior radiotherapy
- Oxygen therapy
- Combination cytotoxic drugs
- Preexisting lung disease
Nitrosoureas

- BCNU (Carmustine)
  - 20-30% incidence
  - Less common: lomustine, semustine
- Inhibit glutathione reductase
- Cumulative doses 580-2100 mg/m²
- Inflammatory infiltrates usually absent.
- Dyspnea, tachypnea, non-productive cough starting 1 month to 3 yrs of therapy
  - May occur as late as 17 years after therapy
- Symptoms progress over time with mortality rates 15-90% (difficult to quantitate)
Bleomycin

• Major dose limiting factor of this drug
  – Chronic progressive fibrosis most common (10% at cumulative doses >450-500 units)
  – Rare acute hypersensitivity with fatalities as low as 100 units
• Generates superoxide anions
  – Worse with radiation, high O$_2$ (even months after drug d/c’d)
  – Protection by superoxide dismutase and catalase?
  – More inflammation than other drugs
• Steroids more helpful for acute form than for chronic
Alkylating Agents

• Mitomycin and cyclophosphamide most common
  – Also chlorambucil, melphalan and uracil mustard
  – Nitrogen mustard and thiotepa not reported
• Up to 4% with symptoms, 46% at autopsy
• Average 4 yrs therapy before onset, (some after drug d/c’d), slow progression
• 60% recover with or without steroids
• Rare with cumulative doses <500 mg unless radiation, high dose O₂, or combined with other toxic drugs
Antimetabolites

• Methotrexate best characterized
  – Hypersensitivity pneumonitis with pulmonary edema and eosinophilia most common. Usually reversible and may not recur with rechallenge
  – 10% later develop fibrosis. Chills, fever, malaise before dyspnea, cough, chest pain.
  – Rare granulomatous development

• Less with azathioprine, 6 MP, procarbazine
Miscellaneous Pulmonary Toxicity

• Drug induced lupus syndrome with pleuritic changes
  – Procainamide, hydralazine, INH
  – Pleuritic chest pain, joint and muscle pain, rash, fever, pleural effusions, + ANA

• Retroperitoneal fibrotic reaction
  – Methysergide

• Pseudolymphoma and generalized lymphadenopathy
  – Phenytoin

• Talc granulomatous reaction from IV Ritalin

• Pneumothorax from IV heroin in neck veins