

Drug-Induced Pulmonary Disorders

Stephen Richey
Grace on Wings Air Ambulance
Indianapolis, Indiana

Problems in Identifying the Culprit

- Multi-drug regimens
- Concomitant medical issues (cardiac, infectious, metastasis, etc)
- Addition of new medications or new combinations of drugs
- No pathognomonic findings in most cases

Modified from list in "Chemotherapeutic induced lung disease: focus on new agents" (presentation, author not listed)

How to Identify the Culprit

- Maintain a high index of suspicion
- Know the medications that can cause respiratory issues and what they normally do
- Exclude all other diagnoses

Modified from list in "Chemotherapeutic induced lung disease: focus on new agents" (presentation, author not listed)

Drugs Known to Cause Pulmonary Disease

Chemotherapeutic (cytotoxic) Agents

-Azathioprine -Bleomycin -Busulfan
 -Chlorambucil -Cyclophosphamide -Etoposide
 -Melphalan -Mitomycin -Nitrosureas
 -Procarbazine -Vinblastine -Ifosfamide

Chemotherapeutic (non-cytotoxic) Agents

-Methotrexate -Cytosine arabinoside -Bleomycin
 -Procarbazine

Drugs Known to Cause Pulmonary Disease

Antibiotic/Antifungal Agents

-Amphotericin B -Nitrofurantoin -Sulfasalazine
 -Sulfonamides -Pentamidine

Anti-inflammatory Agents

-Aspirin -Gold -Methotrexate
 -NSAIDs -Pencillamine

Immunosuppressive Agents

-Cyclosporine -Interleukin-2

Drugs Known to Cause Pulmonary Disease

Analgesics

-Diacetylmorphine (heroin) -Methadone
 -Naloxone -Ethchlorvynol
 -Propoxyphene -Salicylates

Cardiovascular Medications

-Amiodarone -ACE inhibitors
 -Anticoagulants -Beta-blockers
 -Dipyridamole -Fibrinolytic Agents
 -Protamine -Tocainide

Drugs Known to Cause Pulmonary Disease

Inhaled Substances

- Oxygen
- Hydrocarbons ("huffing")
- Nasally snorted illicit substances
- Albuterol
- Solvents ,etc

Intravenous agents

- Blood/blood products
- Injected contents of capsules
- Ethiodized oil (media)
- Ethanalamine oleate (sodium morrhuate)
- Talc (IVDAs)
- Fat emulsions
- Dextran-70

Drugs Known to Cause Pulmonary Disease

Miscellaneous

- Bromocriptine
- Dantrolene
- Hydrochlorothiazide (HCTZ)
- Methysergide
- Oral contraceptives
- Tocolytic agents
- Tricyclic antidepressants
- L-tryptophan
- Drugs that induce SLE

Drugs Known to Cause Pulmonary Disease

Miscellaneous

- Fenfluramine
- Trans retinoic acid compounds

Drugs Known to Cause Pulmonary Disease

THIS IS NOT AN ALL-INCLUSIVE LIST!

MORE THAN 200 MEDICATIONS HAVE BEEN DESCRIBED AS HAVING SOME RESPIRATORY ISSUE ASSOCIATED WITH THEIR USE (OUTSIDE OF HYPERSENSITIVITY/ALLERGIC REACTIONS)

Drugs Known to Cause Acute Onset of Pulmonary Symptoms

{within 24-48 hours}

- | | |
|--------------------------|----------------|
| -Bleomycin (with oxygen) | -Mitomycin |
| -Procarbazine | -Heroin*/IVDAs |
| -Naloxone* | -Aspirin* |
| -Nitrofurantoin | -Methotrexate |
| -Amphotericin B | -Interleukin-2 |
| -Epinephrine* | -Ethchlorvynol |
| -Fibrinolytic agents | -Protamine |
| -Heparin | -Amiodarone |
| -Dextran-70* | -Tricyclics* |

Drugs Known to Cause Acute Onset of Pulmonary Symptoms

{within 24-48 hours}

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| -Blood products* | -HCTZ* |
| -Fat emulsions | |

Mechanisms of Action

- Parenchymal effects
 - Interstitial pneumonitis
 - Fibrosis/granulomatous disease
 - Hypersensitivity pneumonitis
 - Non-cardiogenic pulmonary edema
 - Pulmonary renal syndrome

Mechanisms of Action

Parenchymal effects
Interstitial pneumonitis

Frequently presents with a dry hacking cough and a varying degree of dyspnea

Can present from very mild to severe, acute to chronic onset

Crackles and increased radiographic marking peripherally and over the bases are common early findings

If cause not identified, removed and/or treated, progression can lead to "honeycomb" appearance of a chest film

Mechanisms of Action

Parenchymal effects
Interstitial pneumonitis

At a microscopic level, one finds varying degrees of fibrosis associated with mononuclear infiltrates and the presence of abnormal/atypical type I pneumocytes




Image from list in "Chemotherapeutic induced lung disease: focus on new agents" (presentation, author not listed)

Mechanisms of Action

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Mechanisms of Action

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Mechanisms of Action

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Mechanisms of Action

- Parenchymal effects
 - Pulmonary renal syndrome

Mechanisms of Action

- Airway effects
 - Bronchospasm
 - Inflammation

Mechanisms of Action

- Pleural inflammation/damage
 - Most often seen with trans retinoic acid therapy
- Pulmonary vasculature effects
 - Mostly vasoconstrictive in nature, but drug-associated thromboembolic events also fall into this category

Bleomycin

Associated with a syndrome similar to idiopathic pulmonary fibrosis with increased numbers of fibroblasts, as well as eosinophils and neutrophils present both in biopsy and BAL samples

Believed to be an oxidative stress mediated direct toxicity

Vascular issues associated with increased levels of cytokines and TGF-beta

Similar issues reported with mitomycin, cyclophosphamide and busulfan

Bleomycin

Risk Factors For Respiratory Complications

-OXYGEN THERAPY (NO SAFE THRESHOLD)

-Dose >450 units

-Radiation to the thorax

-Advanced age (>70 years)

-Elevated creatinine

Incidence of clinical toxicity is about 4-5% but may be subclinically present in up to 25% based on PFT changes

Bleomycin

-Treatment with systemic corticosteroids is indicated and is associated with high rates of clinical improvement in a series of 10 cases (Chest, 1984)

-Avoid further doses of the medication and further radiation treatments and minimize use of oxygen whenever possible.

-However, mortality rates still were 30% for early mortality and 30% for late mortality.

Amphotericin-B

- Chills, fever, hypotension and tachypnea are common complications of administration in many patients
- Most often about 1 to 3 hours after the initiation of the infusion
 - Often persists for an hour after cessation
- Symptoms may also result from overdose of the medication, which can be lethal especially in children

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Amphotericin-B

- More serious specifically pulmonary pathology includes:
- Pulmonary hypertension (mostly with liposomal formulations) (Camecchia and Kurtzke, 1960)
 - Bronchiolitis obliterans (Levine SJ et al, 1991)

Amphotericin-B

- Assessment should include chest x-ray and arterial blood gases
- Once stabilized, pulmonary function tests may be indicated
- Treatment is largely supportive

Amiodarone

- Most common significant complication (5-10%) is a pulmonary that can lead to onset of a rapidly progressive ARDS (Martin and Miller, 1985)
- Alveolar or interstitial infiltration
- Commonly associated with doses above 400 mg/day for at least 2 months (McNeil and Firouz-Abadi, 1992; Retz and Martin, 1992; Rubin et al, 1991; Fraire et al, 1993)

Amiodarone

Other Predisposing Factors:

- Age greater than 60 (Dusman et al, 1990)
- Pre-treatment DLCO <80 (Dusman et al, 1990)
- Other pre-existing abnormality on CXR or PFT

Amiodarone

- Onset may be acute (mimicking infectious processes) or chronic (dyspnea on exertion, dry cough, unexplained weight loss, etc)
- Presence of a fever may be a dominant finding
- Symptoms may persist after discontinuation of therapy due to long half-life of drug (up to 54 days)

Amiodarone

- Treatment consists of either withdrawal or reduction in dose (<400 mg/day)
- Corticosteroid therapy has been noted to result in resolution of infiltrates.

Aspirin

- ...or more appropriately, the entire family of salicylates
- Toxic doses are associated with direct stimulation of respiratory centers which results in respiratory alkalosis with or without metabolic acidosis
- Acidosis in severe cases is associated with pulmonary edema, neurological symptoms and portends a poor outcome. (Proudfoot AT, presentation 1993)

Aspirin

- The development of pulmonary edema in these patients is a positive feedback loop which leads to worsening of acidosis due to decrease in minute ventilation as the compensatory hyperventilatory response breaks down
- Pulmonary edema is almost a classic finding in overdose of bismuth subsalicylate (Pepto-Bismol) (Sainsbury SJ, 1991)

Aspirin

- Chronic salicylate intoxication can induce multiple organ system failures including ARDS and other symptoms that mimic sepsis:
 - Fever
 - Leukocytosis with left shift in WBCs
 - Hypotension
 - Acute renal failure
 - DIC
 - Encephalopathy

Aspirin

Hence why it is known as the “salicylate pseudosepsis syndrome” (Leatherman and Schmitz, 1991)

Occult salicylate toxicity must be considered as a differential in all sepsis cases without a clear and provable origin.

ARDS has been linked to aspirin overdoses even without the other aforementioned findings (Montgomery et al, 1994)

Aspirin

Treatment is geared towards several goals:

- Correction of acidosis
- Correction of electrolyte imbalances (especially hypokalemia which may be partially masked by the acidosis)
 - Rehydration
- Eliminate the drug from circulation (urinary alkalization vs. dialysis)
- Cooling measures (discontinue when body temperature reaches 38.5 degrees C)

Aspirin

Clinical pearls:

- Give sodium bicarbonate as boluses to get the arterial pH above 7.25 then use mix bicarbonate into rehydration fluids
- Do not give potassium until adequate urine flows have been established
- Watch for drops in ionized calcium as you correct acidotic states
- Use dextrose solutions as rehydration fluids to avoid hyponatremia

Heroin/Intravenous Drug Abuse

- Beyond the obvious issues of respiratory depression associated with the use of heroin and other narcotics and related infections, one of the main primary issues associated with narcotic abuse is pulmonary edema
 - "Heavy wet lungs noted at autopsy"
- Exact mechanism somewhat debated, but likely a combination of cardiac depression, decreased tidal volumes and vasodilation

Heroin/Intravenous Drug Abuse

- This is not a “young person” problem, as 50 and 60 year old IVDAs are not uncommon.
- Most other pulmonary complications are either are a result of impure manufacturing process, drug “cocktails”, poor injection site hygiene or questionable diluting practices
 - Septic thrombophlebitis
 - Pulmonary “talcosis”
- Pulmonary fibrosis/granulomas associated with agents used to “cut” intravenous drugs

Heroin/Intravenous Drug Abuse

- Early onset emphysematous changes associated with heroin users
- NOTE: 95% of IVDAs also smoke
 - “Needle fragment embolus”
- Mycotic aneurysms of the pulmonary arteries
- One of the few ways you have a chance to see tetanus in a first world setting...

“Crack” Cocaine

- Formerly known as “freebase”
- Multiple pulmonary conditions have been documented in association with its use
- Focal air-space disease (bullae formation, etc)
 - Atelectasis
 - Brochiolitis obliterans
 - Pulmonary infarction
 - Pulmonary edema
- Pneumothorax/pneumomediastinum

“Crack” Cocaine

- Thermal airway injury
- Aspiration of foreign bodies
 - Carbonaceous deposits
 - Bronchospasm
- Pulmonary hypertension
- Pulmonary hemorrhage

Nasally Snorted Abused Drugs

- Exact effects will vary based on the drug in question
- Interstitial disease due to inhaled impurities (cellulose, talc, silica, etc)

Methamphetamine

- Increased incidence of pneumonia (likely multi-factorial)
- ”Flash pulmonary edema”

Inhalant Abuse

-Nearly any chemical can be "huffed"

"NO ONE EVER WENT BROKE
UNDERESTIMATING THE STUPIDITY OF
THEIR FELLOW MAN."

Inhalant Abuse

-Petroleum distillates are associated with pulmonary hemorrhage and a chemical pneumonitis

-Xylene is associated with pulmonary edema and hemorrhage (not to mention that it's carcinogenic as well....)

-Ethylene glycol is associated with respiratory failure (exact mechanism is not well described but may be due to pulmonary edema)

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-Methyl ethyl ketone can cause emphysema

QUESTIONS?

STEPHEN L. RICHEY
stephen.richey@gmail.com
Grace on Wings Air Ambulance
www.graceonwings.org
