Clinical Pharmacology & Toxicology Pearl of the Week

~Amiodarone – Part 5 - Lung Toxicity~

The following is part of a series of reviews detailing potential for specific organ toxicity of amiodarone after exposure, including basic information, diagnosis, and management.

Case

- 86 yo M with chronic kidney disease and atrial flutter admitted with rapid ventricular rate in the setting of diarrheal illness secondary to *Giardia*
- Heart rate is difficult to control despite use of high-dose metoprolol, digoxin, and verapamil
- Symptomatic benefit from successful cardioversaion sinus rhythm a few years prior
- Initial amiodarone load 10 g (600-800 mg/d divided doses) then maintenance (usually 200 ± 100 mg/d)

Clinical question: What should health care practioners consider when initiating or managing patients on amiodarone in regards to pulmonary toxicity?

Epidemiology of Lung Toxicity

- Incidence rates of adverse pulmonary events in patient using amiodarone reported at 129 per 10, 000 patient years in one meta-analysis

Pathology of Lung Toxicity

- Direct damage via cytotoxic effect when concentrations are high enough to:
  - Induce production of free oxygen radicals at a rate greater than natural clearance
  - Inhibit phospholipase sufficiently to cause excessive accumulation of phospholipids in tissues
- Indirect toxicity via immunologic mechanisms (proposed)
  - Reported CD-8 positive lymphocytosis in some studies of bronchoalveolar lavage may indicate possible hypersensitivity pneumonitis phenotype, but not widely studied

Risk Factors

- Age > 60
- Total Cumulative Dose frequently reported as being a risk factor. This is a misinterpretation of effects of increasing concentration prior to steady state that is no reached for up to a year. It is not scientifically possible for a drug with first order kinetics that does not cause continues damage in every person exposed. Rather, it is a surrogate parameter for progressively increasing pre-steady-state concentrations that skew the data collected from studies lasting less than three years (virtually all studies). As concentrations increase, patients receiving too high a daily dose become more likely to develop concentrations exceeding a threshold for toxicity (akin to antibiotic time over minimum inhibitory concentration). Total Cumulative Dose is not a limit when the dosing rate produces concentrations below the toxic threshold at the point or reaching steady state.
- Daily dose - studies report higher association of toxicity > 400 mg/day (high steady-state concentration)
  - Previous reported higher incidence of 5-15% was at doses higher than generally used today
  - Higher doses push the bell curve of patient concentration higher with a larger percent above toxic threshold
  - All cases of pulmonary fibrosis in trials were seen in patients receiving amiodarone at a maintenance dose of ≥ 300 mg/d
- Exposure to high concentrations of supplemental O2, alone or with mechanical ventilation promotes O2 radicals.
- Duration of exposure

    - Risk highest in those on amiodarone for 6-12 months (when concentrations hit steady-state peak)
- Pre-existing lung disease has been proposed but not well characterized
    - In patients with abnormal chest radiograph or reduced pulmonary reserve
    - May represent patients who become symptomatic earlier in their course due to reduced pulmonary reserve

Clinical Findings

- Patients most commonly present with a sub-acute history of progressive dyspnea, cough, malaise, fever, and pleuritic chest pain
- Symptom onset is usually 6-12 months from initiation of amiodarone but can occur at any time after drug initiation (or even without exposure to amiodarone in placebo-controlled trials)
    - Studies have reported toxicity from 6 days to 60 months of drug initiation (time independence?)
    - Prior to the first month of dosing, there is almost no amiodarone in the lungs

Laboratory testing

- Elevation in serum ALT may be an early sign of excess drug exposure, thus increasing probability of pulmonary toxicity
- Amiodarone concentrations greater than 4 μmol/L increase the risk of pulmonary toxicity

Imaging Features

- Chest X-ray findings are non-specific, can reveal patchy or diffuse infiltrates
- High resolution CT is modality of choice
    - Usually hyperdense (iodine), asymmetric, bilateral peripheral consolidation with patchy ground glass opacities (the latter sign being extremely non-specific)
    - Interstitial fibrosis
    - Can infrequently present with masses that must be ruled out as cancer
- Nuclear medicine
    - Gallium-67 scan is sensitive but not specific for diagnosis and not used frequently

Pulmonary Function Testing

- Reveals a restrictive pattern
    - Reduction in DLCO by 15% from baseline may be suggestive for pulmonary toxicity (although used to define diagnosis, amiodarone alters the surfactant layer reducing DLCO to some degree in all patients)

Bronchoscopy

- Flexible bronchoscopy and bronchoalveolar lavage (BAL) can be helpful in diagnosis when there is uncertainty or necessary to rule out other causes (infection, malignancy, etc.). Inclusion bodies in cells from BAL are not diagnostic
- A common histologic finding is a chronic interstitial pneumonia
- BAL usually reveals presence of foamy cells due to accumulation of phospholipids in alveolar macrophages
    - Presence is not helpful in diagnosis, but absence of same makes amiodarone toxicity unlikely

Treatment

- Drug dosing can be safely suspended while any reasonable suspicion of amiodarone adverse effect is investigated, as it takes at least 6 weeks for serum concentration to fall below a threshold of efficacy. Once toxicity is ruled in or out, dosing can resume as appropriate.
- In long-term discontinuation, alternative anti-arrhythmic agents should be explored with cardiology

- Although there is no supporting evidence, significantly symptomatic patients with impairment of respiratory function are often treated with glucocorticoid therapy (prednisone 40-60 mg/day). This can be dangerous if an infectious cause is misdiagnosed as drug toxicity.
- Duration of glucocorticoid treatment is usually between 4-12 months
- Mortality of hospital-treated amiodarone-induced lung toxicity is 21% to 33% in the population sick enough to receive high-dose amiodarone

Monitoring

- Patients should be counseled on monitoring for worsening respiratory symptoms upon initiation of drug
- Interval monitoring requires a baseline chest X-ray and pulmonary function testing
- Some guidelines recommend interval monitoring for respiratory symptoms and chest X-ray every 6-12 months but evidence is lacking. Annual X-ray or symptom-prompted X-ray make clinical sense.

Measure Serum Amiodarone Concentration

- The core principle of pharmacology is that a drug's effect is proportional to its concentration. Thus, measuring serum amiodarone concentrations provides at least a rough insight into the patient's level of exposure to the drug
- Expected serum amiodarone concentrations for efficacy at steady state are 1-2 μmol/L.
- Lower than expected concentrations suggest likelihood of inefficacy and low probability of adverse effect
- High serum concentrations (> 4 umol/L) suggest high risk for adverse effect
- Concentrations less than 2 umol/L are seldom associated with adverse effects and extra efforts should be made to find a more likely cause of concerning pulmonary findings

Take Home Points

- Although pulmonary toxicity due to amiodarone is rare at 1.29% /patient-year, it is a notoriously associated with amiodarone therapy and can carry significant mortality
- Symptom onset is usually within 6-12 months of initiation but has been reported at any time. Drug pharmacology would argue that very early onset is difficult to attribute to very low drug exposure
- Patients should be counseled on monitoring for onset of symptoms
- Baseline chest X-ray and pulmonary function testing is imperative to rule out pre-existing infiltrates or decreased DLCO. Repeated tested can be based on symptoms or done annually.
- Diagnosis of pulmonary toxicity due to amiodarone has a higher probability when there is:
    - A new elevation of serum ALT above normal in a patient on amiodarone (warning sign)
    - New or worsening respiratory symptoms
    - New infiltrates on radiograph or CT imaging of the chest
    - Reduction in diffusion capacity (DLCO) by >15-20%
    - Presence of phospholipid accumulation in alveolar cells (not pathognomonic)
    - Marked CD8+ lymphocytosis in bronchoalveolar lavage fluid
    - Biopsy showing organizing pneumonia, diffuse alveolar damage, interstitial pneumonitis or fibrosis
    - Improvement in symptoms (slowly) after withdrawal of drug (recognizing that the drug concentrations decrease by 1-2% per day)
- Once diagnosed, amiodarone should be discontinued. Corticosteroids may be considered in consultation with respirology if severity of the symptom burden outweighs the risk of steroid effects

References

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The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

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