Clinical Pharmacology & Toxicology Pearl of the Week

Amiodarone – Part 5 - Lung Toxicity

The following is part of a series of reviews detailing specific organ toxicity of amiodarone, 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 successsful 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, but only scientifically possible if toxicity were produced at lowest concentrations. It is a surrogate parameter for progress towards steady state, when drug exposure peaks and toxicity is most likely to happen at area under the concentration-time curve spent above the concentration threshold for toxicity (akin to antibiotic time over minimum inhibitory concentration). There is no limit to total cumulative dose, only to dosing rate/concentration.
- Daily dose - studies report higher association of toxicity > 400 mg/day (high steady-state concentration)
  - Previous reported incidence of 5-15% at doses higher than this
  - 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
- 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 the drug in placebo-controlled trials)
    - Studies have reported toxicity from 6 days to 60 months of drug initiation (time independence?)

Laboratory testing

- Elevation in serum ALT suggests excess drug exposure, thus increasing probability of pulmonary toxicity
- Amiodarone concentrations greater than 4 umol/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
    - Interstitial fibrosis
    - Can infrequently present with masses that may be mistaken for 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 is an indicator for pulmonary toxicity (high specificity and sensitivity given that it is used to define diagnosis)

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.)
- Common histologic finding is a chronic interstitial pneumonia
- Usually has presence of foam 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 should be held with any reasonable suspicion of amiodarone adverse effect while investigations of possible causes are carried out, as control of arrhythmia endures for weeks after cessation.
- 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)
- Duration of glucocorticoid treatment is usually between 4-12 months
- Mortality of hospital-treated amiodarone-induced lung toxicity is 21% to 33%

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 principles of pharmacology suggest that drug effect is proportional to concentration and measuring serum amiodarone concentration provides at least a rough insight into the patient's level of exposure to the drug
- Expected serum amiodarone concentrations at steady state are 1-2 umol/L
- Lower than expected concentrations suggest risk 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 findings

Take Home Points

- Although pulmonary toxicity due to amiodarone is actually rare at 1.29% /patient-yr., it is a notorious aspect of amiodarone therapy and does 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 being able 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, and corticosteroids may be considered in consultation with respirology if a significant symptom burden outweighs the risk of steroid effects

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA. Click HERE for more details.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.

References

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