PULMONARY EFFECTS OF AMIODARONE – Jamie Taylor, MD

Amiodarone, an iodinated benzofurane derivative used for the suppression of ventricular and supraventricular tachyarrhythmias, can produce a variety of adverse effects, the most serious of which is pulmonary toxicity. Pulmonary toxicity correlates most closely with total cumulative dose, and usually occurs several months to several years after initiation of therapy, and in patients treated with doses of at least 400 mg/day.

Four forms of pulmonary toxicity are associated with the drug:

1. Chronic interstitial pneumonitis is the most common presentation. It is characterized by nonspecific interstitial pneumonitis composed of mononuclear cells, type II cell hyperplasia, fibrosis, and foamy alveolar macrophages. Numerous foamy macrophages in the airspaces is actually a characteristic finding in all patients exposed to amiodarone, which, like other amphiphilic compounds, can cause accumulation of phospholipids within lysosomes due to inhibition of phospholipase A. This form of toxicity presents with an insidious onset of nonproductive cough, dyspnea, and weight loss two or more months after therapy. Chest X-ray shows focal or diffuse interstitial opacities.

2. Organizing pneumonia with or without bronchiolitis obliterans (BOOP) is a form of pulmonary amiodarone toxicity that accounts for about 25% of cases. It also presents with a nonproductive cough, although more acutely than with chronic interstitial pneumonitis. It is also associated with pleuritic chest pain, fever, dyspnea, and patchy alveolar infiltrates on chest X-ray, and crackles and pleural rub on auscultation. It can mimic an infectious pneumonitis.

3. Acute respiratory distress syndrome (ARDS) is a potentially fatal form. Although it is rare, it is of special interest to anesthesiologists because it is characterized by a fulminant course in patients who have undergone surgery or pulmonary angiography. The surgical patients develop acute lung injury one to four days after extubation. Whereas the two angiography patients who developed fatal ARDS showed deteriorating respiratory symptoms within 30 minutes of the procedure. It is characterized by diffuse alveolar damage manifested by acute interstitial pneumonitis with hyaline membranes. There may also be focal areas of organizing airspace exudate, and intraalveolar hemorrhage. It has been hypothesized that the amiodarone had sensitized these susceptible patients to either high concentrations of high FIO₂, or iodinated contrast media.

4. A solitary pulmonary mass has also been reported as a complication of amiodarone therapy.

There are two major hypotheses regarding the pathogenesis: direct drug cytotoxicity, and indirect immunologic (hypersensitivity) reaction. Direct drug cytotoxicity is supported by the long half-life and high affinity for lung tissue that amiodarone has. Amiodarone also alters phospholipid bilayers, altering membrane function, and generates toxic oxygen species. Hypersensitivity reaction has been suggested by the presentation of several patients with lymphocytic infiltration, CD8-T lymphocytosis, and positive IgG immunofluorescence in the lung.

There may also be an association between preexisting lung disease and the development of toxicity, but this finding may be skewed by these patients becoming symptomatic earlier in their course because of limited pulmonary reserve.
The diagnosis of amiodarone toxicity is one of exclusion. Differential diagnosis may include heart failure, infectious pneumonia, pulmonary embolism, and malignancy. The clinical diagnosis is suggested by three or more of the following:

- New or worsening signs or symptoms
- New abnormalities on chest X-ray
- A decrease in total lung capacity (TLC) of 15% or more, or in carbon monoxide diffusing capacity (DLCO) of more than 20%
- Phospholipidosis in lung cells
- Marked CD8+ lymphocytosis in lavage fluid
- Lung biopsy results showing: diffuse alveolar damage; organizing pneumonia; interstitial pneumonitis; or fibrosis
- Improvement in lung manifestations after withdrawal of amiodarone.

Due to the possible development of ARDS following surgery in patients taking amiodarone, open or thoracoscopic lung biopsies are performed only when all other efforts to diagnose the illness, including a trial of drug withdrawal and corticosteroids, have been exhausted.

Treatment consists primarily of stopping amiodarone. Alternative measures can usually be used to control arrhythmias. The toxicity may initially progress due to the long half-life of the drug (45 days), and its accumulation in fatty tissues.

Corticosteroid therapy (prednisone 40 to 60 mg per day, tapered over two to six months) can be lifesaving in severe cases, and when withdrawal is not desirable. Again, toxicity may recur upon steroid withdrawal.

Prognosis – generally favorable. The mortality rate in the literature is 10% (probably less in clinical practice), except in cases of ARDS where it is 50%.

Reference: