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Amiodarone toxicity in two post-operative congenital heart disease patients

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ABSTRACT

Amiodarone is a class III antiarrhythmic medication known for its efficacy in treating tachyarrhythmias. The pulmonary complications including acute lung toxicity are well documented in the adult population, however much less so in pediatrics. We describe two pediatric congenital heart disease patients with suspected amiodarone induced pulmonary toxicity in the post-operative period. Case 1 presented with acute respiratory distress syndrome accompanied by periods of pulmonary hemorrhage post-operatively; after multiple courses of methylprednisolone and discontinuation of amiodarone, she showed significant clinical improvement with normalization of her CXR. Case 2 presented as hypoxemic with acute respiratory distress syndrome, and had notable clinical improvement after cessation of amiodarone with pulse dose methylprednisolone and inhaled budesonide.

1. Introduction

Amiodarone is a commonly used antiarrhythmic medication that is effective in both supraventricular and ventricular tachyarrhythmias. However, prolonged use has known toxic effects in as many as 73% of individuals involving the thyroid, hepatic, cardiac, ocular, and pulmonary organs [1–3]. Although pulmonary toxicity is not the most common at an estimated rate of 5–7% in adults [4], it is one of the most serious if undetected and can be fatal in up to 20% of those affected [5]. Although presentation is often subacute or chronic, rapid progression to respiratory failure is known to occur in some patients. Fogoros et al. [3] found amiodarone pulmonary toxicity as therapy limiting in all cases; however 50% had complete resolution of pneumonitis with drug cessation and steroid initiation. Unfortunately, existing publications only describe cohorts of adults and there are no clear guidelines for steroid dosing. Few cases are documented in the pediatric literature, and are particularly sparse in the post-congenital heart disease population [6,7]. Prompt recognition of clinical presentation and optimal steroid dosing in this group could lead to shortened hospital stays, less morbidity, and improved mortality. We report two congenital heart disease pediatric patients with highly suspected amiodarone induced pulmonary toxicity in the post-operative period.

2. Case Reports

2.1. Case #1

A 16 year old female with Ebstein's anomaly underwent Cone repair, tricuspid annuloplasty, right reduction atrioplasty, and partial PFO closure. POD 1 she had ventricular tachycardia followed by pulseless electrical activity requiring defibrillation and epinephrine. Amiodarone infusion was started that day at 5 μg/kg/min without bolus. Chest x-ray on POD 3 revealed worsened haziness/pulmonary edema, and frothy pink secretions from the endotracheal tube. Echocardiogram revealed normal left ventricular function. Patient was started on ECMO later on POD 3, continued until POD 10. Work up for coagulopathy was negative. Amiodarone was discontinued on POD 5 in the absence of further arrhythmias.

Patient returned to the operating room on POD 9 for mediastinal exploration, Glenn procedure, and tricuspid valve replacement. She failed extubation on POD 14 with development of ventricular tachycardia and pulmonary hemorrhage. Amiodarone was started once again with 150 mg loading dose, followed by infusion at 5 μg/kg/min. Bronchoscopy on POD 28 showed no focal bleeding source, but mucosa appeared hyperemic and inflamed with brown secretions, suggestive of prior diffuse bleeding process. Bronchoalveolar lavage specimen was positive for presence of foamy macrophages. Chest x-ray continued to

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reveal bilateral symmetric opacification consistent with pulmonary edema vs. hemorrhage.

Amiodarone infusion was changed to oral on POD 32, which was the last day of documented sanguineous secretions from the endotracheal tube. Stress dose hydrocortisone with taper had been started since POD 2 for hemodynamic concerns; however IV methylprednisolone was then started on POD 33 at 1 mg/kg/day (60 mg/day) [Wt ~ 60 kg] due to concern for ARDS for a 2 week course. This was followed by a taper consisting of oral prednisone ~0.5 mg/kg for 1 weeks, then 0.25 mg/kg for 4 days, followed by hydrocortisone 10 mg Q8 and eventually weaned to near physiologic dosing (15 mg/m^2/day) over 12 days per endocrinology recommendations. Patient also had pulmonary toilet regimen consisting of 3% hypertonic saline, atrovent QID, and incentive spirometry. Oral amiodarone was discontinued on POD 40. Patient was successfully extubated on POD 49 to BiPAP, 9 days after stopping amiodarone.

She remained on BiPAP and developed worsening respiratory distress on POD 70. At that time, LV function remained normal. She had finished a long course of broad spectrum antibiotics and infection was thought unlikely. She was euvolemic. It appeared that worsening respiratory distress had started after the steroid wean. In absence of other etiology for respiratory distress, amiodarone induced pulmonary toxicity was suspected. CT thorax done during this time showed diffuse ground glass and consolidative airspace opacities bilaterally. Bedside pulmonary function testing (PFT) was suggestive of severe restrictive airway pattern. IV Methylprednisolone was started 60 mg/day for another 2 week course followed by 30 mg daily for maintenance with which she had dramatic improvement and came off BiPAP. Review of serial chest radiographs showed acute respiratory distress syndrome-like picture coinciding with amiodarone initiation and improvement with its cessation and steroid therapy (Fig. 1). Both Pediatric and Adult Pulmonary services felt amiodarone induced pulmonary toxicity was very likely with history dramatic improvement post-discontinuation of amiodarone and initiation of prednisone. Allergy/Immunology agreed with Pulmonary and felt primary immunodeficiency was unlikely with limited infection history prior to this admission.

Patient was discharged home on POD 116 on room air with slow steroid taper plan down from 30 mg PO once daily, and was weaned off steroids 3 months later at the outpatient pulmonary visit. Her restrictive pattern had improved to moderate by that visit, and 9 months later her restrictive pattern had resolved.

2.2. Case #2

A 9 month old male with hypoplastic left heart syndrome underwent Norwood Procedure with Sano modification on day 8 of life. Due to recurrent episodes of supraventricular tachycardia (SVT) before and during surgery, he received a total of 17.5 mg/kg amiodarone bolus followed by amiodarone infusion at 5–15 μg/kg/min, later converted to oral form. Recurrent episodes of SVT required oral reload of amiodarone and initiation of propranolol. He remained on maintenance oral amiodarone and propranolol.

Post-operative course was complicated by recurrent respiratory failure secondary to diaphragm palsy requiring two diaphragm plications. He successfully extubated on POD 43 and remained in the hospital for social concerns, feeding, and growing. On POD 118 he became severely hypoxic requiring high flow nasal cannula, 100% oxygen and nitric oxide. Sepsis work-up, echocardiogram and cardiac catheterization did not reveal an etiology of hypoxia. On POD 142, he was intubated for persistent hypoxic respiratory failure and ARDS of unclear etiology. Bronchoalveolar lavage was not conducted due to critical clinical condition. With prolonged exposure to amiodarone, amiodarone induced toxicity was suspected. CT thorax revealed bilateral, diffuse ground glass opacities consistent with this suspicion (Fig. 2). Amiodarone was discontinued and pulse dose methylprednisolone was initiated at 30 mg/kg/day on POD 147 for three consecutive days to be repeated every month. This pulse dosing was suggested by the pulmonology service based upon previous experience with interstitial lung disease. As an adjunct, inhaled budesonide twice a day was added on POD 152 as a novel approach to accelerate improvement.

Patient extubated successfully on POD 160 and received another 3 day monthly steroid burst before second stage repair on POD 198. He was extubated four days after second stage surgery and discharged home on POD 28 on 1 L/min nasal oxygen supplementation and no steroid medications. Oxygen supplementation was discontinued 2 months post-discharge at outpatient pulmonology follow up.

3. Discussion

Amiodarone is a commonly used antiarrhythmic agent in children after cardiac surgery. Amiodarone is a highly lipophilic drug which is extensively distributed into tissues and has side effects involving multiple organs. Pulmonary toxicity is the most serious and life threatening [2]. However, most cases of amiodarone induced pulmonary toxicity are reversible if treated early and have good prognosis. Our understanding of amiodarone toxicity comes mostly from adult literature [4], with limited information available in the pediatric cardiac population [6,7].

Amiodarone induced pulmonary toxicity can have a variety of clinical presentations [8]. The most common form, interstitial pneumonitis, has an insidious onset of non-productive cough, dyspnea and fever associated with parenchymal infiltrates in diffuse interstitial pattern on chest x-ray. The onset of symptoms may be as early as two months or may occur after several years of treatment.

Amiodarone induced pulmonary toxicity can also have an acute onset with radiographic changes of predominantly alveolar pattern with patchy distribution. It can present as acute respiratory failure and/or acute respiratory distress syndrome. This tends to occur < 1 week after amiodarone initiation, and is characterized by pulmonary edema and hypoxemia in the absence of cardiac failure or fluid overload. It may be difficult to distinguish from infectious etiologies due to presence of fever and acute onset.

Surgical intervention (cardiac or non-cardiac) in patients who have been receiving amiodarone is considered a risk factor for development of amiodarone induced pulmonary toxicity post-operatively [2,4]. Physical exam will reveal bilateral rales. Blood testing may show elevated white blood cell count, elevated Lactate Dehydrogenase, Erythrocyte Sedimentation Rate, and C Reactive Protein. Pulmonary function testing typically reveals a restrictive pattern with reduced forced vital and total lung capacity in addition to a reduced diffusing capacity (DLCO) [9]. Radiologic imaging will generally reveal reticular or ground glass opacities, with diagnosis generally hinging on high clinical suspicion and radiologic evidence. Histopathologic findings from bronchoalveolar lavage are highly variable. Lipid-laden “foamy” macrophages are questionable in utility, as up to 50% of patients exposed to amiodarone without any toxicity may have these findings [10]. However, absence of these cells may make pulmonary toxicity unlikely.

Although Case 1 did have “foamy” macrophages, as previously noted this is not a specific finding. Therefore, bronchoalveolar lavage may be used if amiodarone toxicity is suspected in the authors opinion, and is not mandatory to make the diagnosis. Lung biopsy findings may support the diagnosis but are often non-diagnostic and carry risk, hence judicious use in a stable patient is ideal. Amiodarone induced pulmonary toxicity should be a diagnosis of exclusion and can often be made from constellation of strong clinical suspicion and laboratory findings in addition to resolution of symptoms after medication cessation and/or glucocorticoid trial [6].

Treatment of amiodarone induced pulmonary toxicity consists of discontinuation of amiodarone. Because of accumulation in fatty tissues and long half-life, pulmonary toxicity may continue to progress after discontinuation. Most literature supports use of systemic

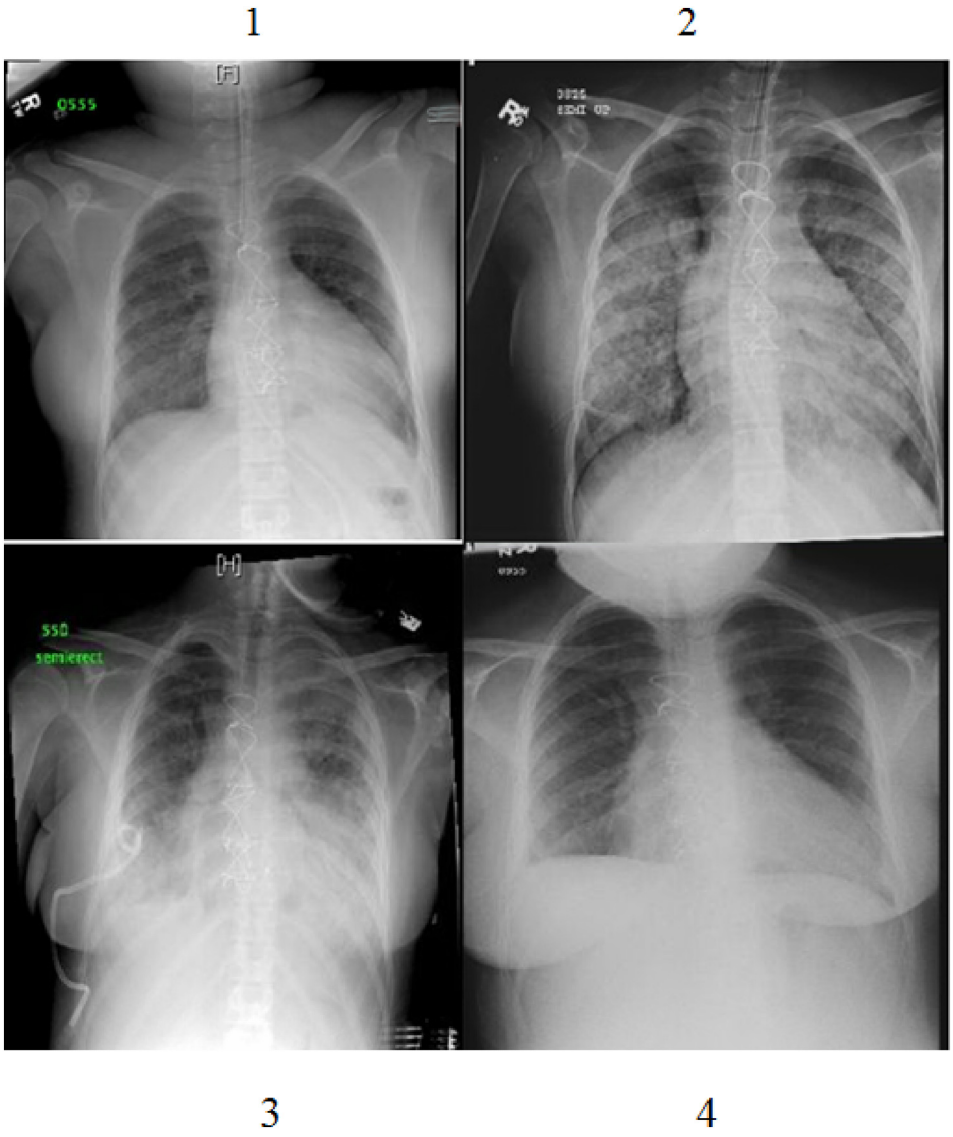

Fig. 1. Serial chest x-ray imaging in Case #1.
1) Top Left: 1 day prior to amiodarone initiation.
2) Top Right: 3 weeks post-amiodarone initiation.
3) Bottom Left: 1 month post-amiodarone discontinuation.
4) Bottom Right: 2.5 months post-amiodarone discontinuation.

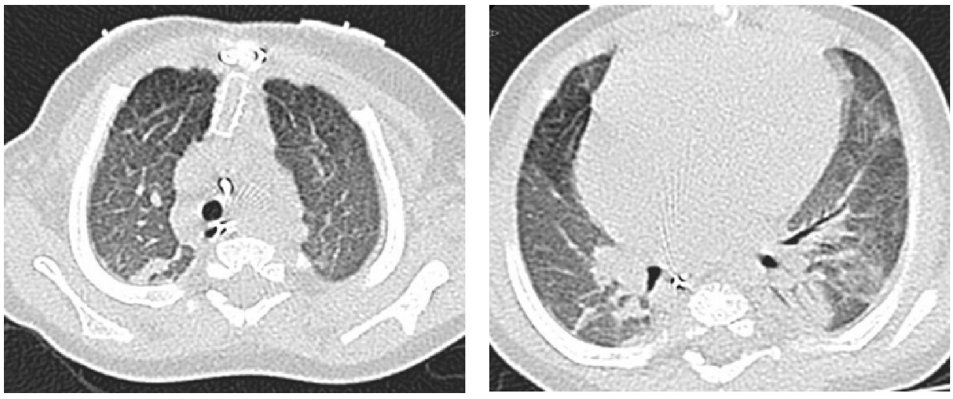

Fig. 2. Computed tomography thorax in Case #2. Ground glass opacities characteristic of amiodarone induced pulmonary toxicity on POD #146.

Table 1
Key features supporting clinical diagnosis of amiodarone induced pulmonary toxicity [8].

	Case 1	Case 2
Onset post-amiodarone initiation	Yes	Yes
Negative cardiac etiology	Yes	Yes
Bronchoalveolar lavage findings (foamy macrophages)	Yes	Not conducted (unstable)
Radiologic findings (new diffuse, ground glass opacities)	Yes (CT)	Yes (CT)
Pulmonary function testing (restrictive pattern)	Yes	Not conducted (patient age)
Lung biopsy[a]	Not conducted	Not conducted
Clinical/radiologic improvement post-amiodarone cessation/steroid initiation	Yes	Yes

[a] Considered not necessary to prove toxicity in patients with new onset respiratory symptoms and compatible radiologic and pulmonary function testing.

glucocorticoids, particularly in patients with severe manifestations [10]. The dose and duration of treatment with glucocorticoids is variable in reported literature. A case of a 3-month old with transposition of the great arteries has been published, with post-arterial switch progressively worsening respiratory distress. Cessation of amiodarone and 2 mg/kg prednisolone (duration unspecified) were thought to lead to improvement [6]. In another case an adolescent with tetralogy of Fallot on amiodarone for 4 years developed interstitial lung disease that improved with cessation of amiodarone and 40 mg/day of prednisolone (duration unspecified) [7]. As it stands, there are no controlled trials but literature suggests 40 to 60 mg/day of oral prednisone with slow taper to be an appropriate regimen [11]. Systemic glucocorticoids should be continued for about 4–12 months to prevent relapse of symptoms.

Despite the difficulty in achieving certainty in diagnosis, both patients presented were strongly suspected to have amiodarone induced pulmonary toxicity after full evaluation based upon timeline of drug initiation, signs and symptoms, laboratory and radiologic findings, and recovery with drug cessation and steroid treatment (Table 1). It is uncertain which steroid regimen between our patients was optimal. Pulse systemic steroids are thought by some providers to have less of a side effect profile. The patient in case 2 did not show initial improvement initially with pulse systemic steroids, hence the addition of inhaled steroids. Use of inhaled steroids is not reported in literature for amiodarone induced pulmonary toxicity and its effect in this case is uncertain. However clinical improvement did coincide with its initiation and we believe it should be considered in systemic steroid refractory cases.

Despite new emerging anti-arrhythmic medications, amiodarone remains one of the top choices in treatment of tachyarrhythmias in children after surgery for congenital heart disease. With the multifactorial etiology of hypoxia and respiratory failure after congenital heart surgery, diagnosis of amiodarone induced pulmonary toxicity may not be easily suspected. Delays in the diagnosis can add to morbidity and potentially mortality if the toxicity is not promptly treated. However, prognosis is good with early treatment.

4. Conclusion

Amiodarone induced pulmonary toxicity can have acute or insidious onset and considerably complicate post-operative course after cardiac surgery in children. However, a keen clinical index of suspicion, willingness to discontinue potential offending agents, and therapy with steroids may rapidly improve patient status and lead to improved outcomes.

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Declarations of Interest

None.

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