CASE REPORT

The blue child – amiodarone-induced blue-gray skin syndrome and pulmonary mass in a child

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Key clinical message

Adverse effects of amiodarone are rarely seen in pediatric patients, but may occur if amiodarone is applied for long-term treatment. Two rather rare phenomena are blue-gray skin pigmentation and pulmonary mass. They represent important differential diagnoses from more common clinical complications like pneumonia and drug-induced toxic skin lesions.

Keywords

Amiodarone, arrhythmia, child, pulmonary mass, skin pigmentation.

Introduction

Amiodarone is a widely used and highly effective drug in the treatment of various atrial and ventricular arrhythmias. Severe adverse effects are well known especially in the long-term treatment. Atrial arrhythmias are a frequently encountered clinical challenge in patients with congenital heart disease. Currently, some of these patients may undergo electrophysiologic study with radiofrequency ablation. Yet, drug treatment is still an important treatment option in this group of patients. Actual guidelines provide the clinician with several treatment options of which amiodarone is one of the most effective, although with the cost of a wide range of adverse effects [1]. To the authors knowledge this is the first description reporting an amiodarone-induced blue-gray skin pigmentation and pulmonary mass in a child. CASE: A 13-year-old male patient, weighing 31.7 kg, with congenital Ebstein’s anomaly was referred to our center for cardiac surgery. The patient’s history included a primary univentricular approach with Glenn anastomosis at the age of 10 months, tricuspid valve reconstruction and implantation of a transvenous pacemaker for sick sinus syndrome at the age of 6 years. Due to atrial flutter he was treated with amiodarone (6 mg/kg/day) since the age of 7 years. At the time of admission the patient was in NYHA class III due to congestive heart failure without any pulmonary symptoms. Most strikingly he presented with a blue-gray facial skin pigmentation (Fig. 1). In addition, preoperative X-ray revealed several ominous pulmonary nodules. A computed tomography was performed (Fig. 2) and the suspicion of an abscess forming pneumonia aroused. Yet, blood chemistry was unremarkable and the patient showed no signs of an infection. Reviewing literature these findings were associated with chronic amiodarone intake. Bronchoscopy was performed which showed numerous macrophages with foamy cytoplasm, presumably in the context of lipid sediment, and confirmed the diagnosis. Remarkably, no risk factors were identified in the child that could have predisposed to his condition. Amiodarone was discontinued after success-
ful cardiac surgery with tricuspid valve reconstruction, right atrial reduction plastic, MAZE procedure, removal of the transvenous pacemaker system and implantation of an epicardial pacing system. Postoperative course was uneventful. Follow-up after 1 year showed a thorough disappearance of the blue-gray skin pigmentation and absence of atrial arrhythmia. Noteworthy, the pulmonary nodules showed only incomplete regression after 2 years follow-up.

Discussion

Amiodarone is one of the most effective and commonly used drugs available for treatment of cardiac arrhythmias in the adult and pediatric population. It prolongs the cardiac repolarization through the sodium and calcium channel block and nonselective β-adrenergic inhibition. It has a long plasma half-life of about 57 days and is hepatically metabolized [2]. Many adverse effects are reported, especially in the long-term treatment. Apart from frequent adverse effects like corneal microdeposits, reported in up to 90% of patients, and photosensitivity (25–75%), blue-gray skin discoloration (4–9%), and pulmonary toxicity (1–17%) are rather rare [3]. The incidence of blue-gray skin discoloration in children is estimated <2% [4].

Amiodarone-induced blue-gray skin pigmentation is most often reported to occur following long-term treatment in elderly patients with a predominance of male patients. The exact pathomechanism of blue-gray skin syndrome is still controversial. Several different theories are discussed in literature. These include drug-induced lipidosis, photosensitivity reaction to ultraviolet light, or leukocytoclastic vasculitis [5]. The typical feature of the blue-gray skin syndrome is the strictly facial skin pigmentation. It is speculated that ultraviolet light induces amiodarone and its metabolites to attach to the blood vessel walls and the perivascular tissue. This is associated with local vasodilatation and increased diffusion of amiodarone and its metabolites, resulting in chronic tissue accumulation. Therefore, only sun exposed regions are affected [6]. Molecular mechanisms have been described by Morissette et al. [7] who analyzed skin biopsies of patients with blue-gray skin syndrome and concluded that the vacuolar sequestration of amiodarone occurs at concentrations close to therapeutic levels. It is mediated by V-ATPase and evolves toward persistent macroautophagy and phospholipidosis. In case of discontinuation of amiodarone complete relief of symptoms can be expected.

Amiodarone-induced pulmonary mass is very rarely reported in adults and according to Labombarda F et al. [8], is extremely rare in children. Basically it is thought to represent a subtype of the rather common phenomenon of amiodarone-induced pulmonary toxicity (AIPPT). Facchini and colleagues reported that amiodarone can damage the lung via an indirect immune reaction or direct cytotoxic damage [9]. The different mechanisms of injury contribute to the variability of symptoms onset, ranging from 1 to 6 months. Typically AIPPT presents as infiltration of the pulmonary interstitium with inflammatory cells, interstitial fibrosis, and hyperplasia of type II pneu-

Figure 1. Demonstrating the patient’s blue-gray skin pigmentation.

Figure 2. A: Chest X-ray showing nodular pulmonary infiltration. B: Computer tomography showing the nodular lesions with the aspect of abscess forming pneumonia.
mocytes. On biopsy, the presence of foamy macrophages confirms exposure to amiodarone. While AIPT mostly appears as diffuse parenchymal infiltration, the occurrence of amiodarone-induced pulmonary mass is thought to be due to a selective accumulation of the drug in a prior lung lesion [10]. As reported in literature, patients with amiodarone-induced pulmonary mass typically present with dyspnea, cough, and fever, which can easily be mistaken as symptoms of pneumonia. Most patients respond well to withdrawal of amiodarone and prednisolone can be added to promote healing.

After all, the adverse effects of amiodarone are rarely seen in pediatric patients. This may be due to the fact that amiodarone is mainly used for the acute treatment of arrhythmias, for example in the postoperative setting. But even if amiodarone is used in the outpatient setting to treat for example supraventricular arrhythmias in infants, there is a substantial number of patients who expect spontaneous disappearance of their arrhythmia and treatment is only needed for a time period of months in contrast to the long-term treatment of atrial fibrillation or ventricular arrhythmias in adults that often require treatment for several years. Nevertheless, adverse effects similar to those reported in adults can be seen in children if amiodarone is applied for long-term treatment. Consequently, close monitoring of possible adverse effects, early dose reduction in amiodarone and effective sun protection of exposed regions are of particular importance to prevent adverse effects of long-term amiodarone treatment in children. As there currently exists a wide range of effective antiarrhythmic drugs for children available on the market, alternative substances should always be considered if a long-term treatment is expected [1].

Conclusion

Long-term administration of amiodarone can cause severe side effects in children even if an approved dosage is prescribed. Close monitoring of possible adverse effects, early dose reduction of amiodarone and effective sun protection of exposed regions may prevent adverse effects of long-term amiodarone treatment. The use of alternative substances should be considered.

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Conflict of interest

None.

References

1. Brugada, J., N. Blom, G. Sarquella-Brugada, C. Blomstrom-Lundqvist, J. Deanfield, J. Janousek, et al. 2013. Pharmacological and non-pharmacological therapy for arrhythmias in the pediatric population: EHRA and AEPC Arrhythmia Working group joint consensus statement. Europace 15:1337–1382.
2. Gonzalez-Arriagada, W. A., A. R. Santos Silva, P. A. Vargas, O. P. de Almeida, and M. A. Lopes. 2013. Facial pigmentation associated with amiodarone. Gen. Dent. 61: e15–e17.
3. Vassallo, P., and R. G. Trohman. 2007. Prescribing amiodarone an evidence-based review of clinical indications. JAMA 298:1312–1322.
4. Coumel, P. L., and J. Fidelle. 1980. Amiodarone in the treatment of cardiac arrhythmias in children: one hundred thirty-five cases. Am. Heart. J. 100:1063–1069.
5. Wiper, A., D. H. Roberts, and M. Schmitt. 2007. Amiodarone-induced skin pigmentation: Q-switched laser therapy, an effective treatment option. Heart 93:15–15
6. Bahadir, S., R. Apaydin, U. Cobanoilu, Z. Kapicioilu, Y. Ozora, M. Gökçe, et al. 2000. Amiodarone pigmentation, eye and thyroid alterations. J. Eur. Acad. Dermatol. Venereol. 14:194–195.
7. Morissette, G., A. Ammoury, D. Rusu, M. C. Marguery, R. Lodge, P. E. Poubelle, et al. 2009. Intracellular sequestration of amiodarone: role of vacuolar ATPase and macroautophagic transition of the resulting vacuolar cytopathology. Br. J. Pharmacol. 157:1531–1540.
8. Labombarda, F., P. Ou, B. Stos, J. de Blic, E. Villain, and D. Sidi. 2008. Acute amiodarone-induced pulmonary toxicity: an association of risk factors in a child operated by arterial switch operation. Congenit. Heart. Dis. 3:365–367.
9. Facchini, G., S. Forte, P. Podda, F. Piro, and S. Carlone. 2008. Pulmonary masses in a patient with blue-gray cutaneous hyperpigmentation. Eur. Rev. Med. Pharmacol. Sci. 12:113–116.
10. Rodriguez-Garcia, J. L., J. C. Garcia-Nietob, F. Ballestab, E. Prietoa, M. A. Villanuevaa, and J. Gallardoa. 2001. Pulmonary mass and multiple lung nodules mimicking a lung neoplasm as amiodarone-induced pulmonary toxicity. Eur. J. Intern. Med. 12:372–276.