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Side effects and efficacy of low-dose amiodarone in rhythm disorders

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Abstract

Amiodarone is one of the most widely used antiarrhythmic drugs, which is the most effective drug for maintaining sinus rhythm. Taking this drug correlates with side effects such as pulmonary toxicity, thyroid dysfunction, neurotoxicity, hepatotoxicity, and skin manifestations. In addition, in some cases, amiodarone remains as a first-line therapy to maintain sinus rhythm. The side effects of amiodarone depend on the dose and duration of the drug. Systematic reviews and meta-analyses have shown the safety profile of a low dose of amiodarone, defined as 200 mg and a very low dose of amiodarone 100 mg. Due to the use of catheter ablation, the use of a low dose of amiodarone is sufficient. In this literature review, we have cited the side effects of a low dose of amiodarone. In addition, although there is evidence of a safer low-dose spectrum, it is not free from side effects and needs to develop an algorithm for early detection of adverse events, as well as studying the effectiveness according to modern research methods, such as an implantable heart monitor, which in turn is of undoubted interest.

Keywords: low doses of amiodarone, side effects, safety, amiodarone.

Introduction

Amiodarone, a dilodinated benzofuran derivative similar in structure to thyroxine, contains two iodine atoms [1]. Amiodarone is originally known since 1967 as an antianginal drug, later antiarrhythmic effects were identified. Amiodarone is characterized by the Vaughn-Williams classification as having "Class III" properties [2]. Its mechanism of action involves blocking potassium, sodium channels, delaying intracellular calcium and non-competitive blocking alpha and beta adrenoreceptors. These pharmacological properties make amiodarone effective for both therapy of supraventricular and ventricular arrhythmias, and prevention of recurrent AF [1, 2, 3]. Oral bioavailability of amiodarone is approximately 30-50%, due to the benzene ring, amiodarone has a high lipophilicity. In view of which when taken with food rich in fats absorption of the drug is increased by 2.4-3.8 times in comparison with fasting intake [4]. Its side effects are related to its pharmacodynamics and pharmacokinetics, as the highest amiodarone content is found in the liver, lungs, fatty tissues, thyroid gland, kidneys, heart, skin, adrenal glands, testes, eyes and lymph nodes [5].

The dose and duration of administration of amiodarone are the most important factors of adverse events. Previously, the maintenance dose for the treatment of arrhythmias ranged from 200 mg / day to 800 mg / day. After detecting dose dependence and side effects, a lower dosage was taken, which ranges from 100 mg/day to 200 mg/day [6]. Therefore, it is sufficient to prescribe a low dose of antiarrhythmic drugs to maintain sinus rhythm in atrial fibrillation [7, 8, 9].

This drug has been studied for a long time, which, although it is an effective drug, has a wide range of side effects and leads to damage to the thyroid gland, lungs, liver, and nervous system, depending on the dose and duration of use [10].

Despite studies researching standard-dose amiodarone therapy, the severity of side effects with low-dose amiodarone remains incompletely investigated.

Purpose: to evaluate the range of application and safety of low-dose amiodarone in patients with cardiac rhythm disorders.

Objective: to analyze the use and evaluation of the side effects of a low dose of amiodarone according to literature sources.

Methods: A literature search was conducted in the Pubmed, Medline, Cochrane databases by October 2023 for the keywords low doses of amiodarone, safety, side effects. Studies have been included that have reported side effects of amiodarone. These studies included systematic reviews and meta-analyses, randomized controlled trials (RCTs), clinical cases, and a series of clinical cases with 95% confidence intervals (CI). We have reviewed more than 519 articles. After the deletion of 484 articles, 35 articles were retained for further review.

Results

A systematic review and meta-analysis of 2 studies showed that the use of a low dose of amiodarone, defined as 200 mg, showed clinical safety in comparison with higher doses as a second-line treatment after catheter ablation [6, 8, 11]. Similar systematic reviews report complications even with a low dose of amiodarone, defined as 200 mg and a very low dose of 100 mg [10]. On the contrary, Blackman et al. conducted a survey among cardiologists in European countries and concluded that very low doses of amiodarone are used daily by cardiologists and have a low side effect profile [12].

A study by G E Kochiadakis in 2000 compared the effectiveness of drugs such as amiodarone, propafenone and sotalol in patients with atrial fibrillation. As well as a similar study conducted in 2004 comparing low doses of amiodarone (200 mg) and propafenone (450 mg) in patients with AF. In both studies, the authors concluded that amiodarone is the most effective drug, but most often causes side effects, including non-cardiac ones [13, 14]. In 2020, a retrospective study by RongDa Huang studied the comparison of amiodarone and propafenone in patients with AF after catheter ablation. According to the results of this study, it was revealed that amiodarone was associated with a lower frequency of rhythm disruptions [15].

Jong et al indicated the lowest dose of amiodarone in 2006 in a study examining the effectiveness of low doses of amiodarone in maintaining sinus rhythm after cardioversion in atrial fibrillation. In this study, there was no withdrawal of the drug, and therefore it was concluded that there was a low profile of NSAIDs requiring drug withdrawal [16].

In the studies of Mahrian et al., the parallel administration of a very low dose of amiodarone 100 mg and 50 mg compared with placebo in patients with unstable ventricular tachycardia (VT) was studied. During which, in the group receiving 100 mg, complete suppression of unstable VT was revealed, which shows the clinical efficacy of a very low dose of amiodarone [17].

In a retrospective study in patients with coronary heart disease with tachyarrhythmias, such as supraventricular tachycardia and VT, the use of a low dose of AMD less than 200 mg showed that no recurrence of tachyarrhythmia was observed for 2.9 years with SVT and 3.2 years with VT in 36% and 65% of patients, respectively, for 3 years. In 23% of cases, the frequency of side effects was associated with thyroid dysfunction [18].

Next, consider a series of adverse events associated with taking a low dose of 200 mg amiodarone.

There is a description of cases in patients taking AMD at a dose of 200 mg for 2 to 5 years, the appearance of hemoptysis, acute respiratory distress syndrome, which also proves that the duration of administration is important. Exclusion of other potential diseases and improvement after discontinuation of the drug are important in diagnosis [19, 20, 21, 22]. In another description of a series of cases, there is a report of three patients who received AMD at a dose of 200 mg for an average of 6.6 months. The patients were male, 75, 93 and 85 years old, with a history of smoking, whose first complaints were shortness of breath without signs of heart failure. According to the CT scan, alveolar pneumonitis was exposed. The treatment of this complication was the withdrawal of AMD and the administration of corticosteroids with complete recovery [23].

There are descriptions of cases with changes in the skin of a blue-gray, semi-matte skin tone [24, 25, 26].

Some life-threatening side effects have been reported in patients treated with amiodarone only briefly, although such extremely undesirable events occur very rarely [27].

In a meta-analysis conducted by Ruzieh et al., eliminating amiodarone and placebo, they concluded that low doses of amiodarone were not associated with a statistically significant increase in the incidence of adverse events from the lungs, but were still associated with adverse events from the thyroid gland and liver [28].

A very rare case of a woman having a hallucination for the first time after taking AMD for AF paroxysm is described. After the drug was replaced, the side effects were leveled [29].

Amiodarone is known to have non-cardiac side effects, including hepatotoxicity. Among the least common are pseudoalcoholic cirrhosis. The cases of patients with these complications when taking a dose of amiodarone 200 mg per day for several years with the possible exception of other causes of cirrhosis are presented [30, 31, 32].

Since the release of the systematic review by Chokesuwattanaskul et al., articles have been published, clinical cases describing the more frequent detection of side effects when using low AMD. But there is no unified assessment of side effects and their detailed identification, as well as the frequency of these examinations are not described. They also demonstrated the conclusions that, compared with amiodarone at a dose of 200 mg/day, the cumulative estimated frequency of common side effects was 0.11 (95% CI: 0.04–0.27), while the frequency of side effects requiring drug withdrawal was 0.02 (95% CI: 0.01–0.06) for a dose of 100 mg/day [11]. Another point of view was expressed by the author A. Reiffel, that low doses of amiodarone are not quite as safe as they seem [33].

In our literature review, we can note the weaknesses that do not reflect all the side effects that AMD has.

Conclusion

There are very few randomized studies examining the efficacy and safety of a low dose of amiodarone after catheter ablation. Currently, there are no systematic reviews and meta-analyses, controlled studies confirming the effectiveness of a particular treatment, the clinical safety profile is evaluated everywhere, which is also not fully disclosed. Based on the pharmacokinetics study the principal finding is that a very low dose of amiodarone (100 mg every day) is effective in maintaining sinus rhythm in patients with AF. Amiodarone is commonly utilized for treating both supraventricular and ventricular arrhythmias. While this drug is a very effective antiarrhythmic agent, it also leads to many well-known side effects involving a variety of organs such as the thyroid, liver, lungs, and eyes including many that are dose- and duration-dependent.

Table 1 Side effects of a low dose of amiodarone

№	The title of the article	Authors	Design	Indications for the use of amiodarone	The dose and duration of taking amiodarone	Side effects	The authors' conclusions
1	Amiodarone-induced Hemoptysis: A Rare Presentation of Amiodarone-induced Pulmonary Toxicity Occurs at a Low Dose	Busch, Clayton D et al, 2019 [19]	Case report	AF	200 mg/day, 5 years	Hemoptysis, diffuse alveolar hemorrhage	The manifestation of the side effect of amiodarone can be detected at any dose.
2	Acute respiratory failure on a low dose of amiodarone – is it an underdiagnosed and undertreated condition?	Mijo Meter et al, 2021 [20]	Case report	AF	200 mg/day, 5 years	Acute respiratory distress syndrome	It is important in making a diagnosis to exclude other potential diseases and improve after discontinuation of the drug
3	Amiodarone-related pneumonitis	Sheng-Nan Chang, 2007 [23]	Case report	AF	200 mg/day, 6.6 months	Shortness of breath without signs of heart failure	The treatment of this complication was the withdrawal of AMD and the administration of corticosteroids with complete recovery
4	New-onset hallucinations with amiodarone: a case report.	Jessica Molinaro, 2022 [29]	Case report	AF	200 mg twice a day, 7 days	Visual and auditory hallucinations	The hallucinations disappeared on the third day after the withdrawal of amiodarone, which may be due to the two-phase elimination of amiodarone from the body and an improvement in the condition
5	A low dose of amiodarone-indused sinoatrial node dysfunction: a case report	Ayurzana et al, 2022 [34]	Case report	AF	100 mg/day, 2 month	A long sinus pause (4-7,9 seconds)	Amiodarone decline palpitations, but develop sinoatrial node dysfunction
6	"Blue-grey syndrome" – A rare adverse effect of amiodarone	Hana Kuncipálová, 2018 [35]	Case report	AF	200 mg/day, 6 years	blue-gray discoloration of the face, neck, earlobe and back of the hands	Prolonged use of even a low dose of amiodarone can lead to the appearance of skin pigmentation with subsequent disappearance after discontinuation of the drug

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References

1. Narayana SK, Woods DR, et al. Management of amiodarone-related thyroid problems. *Ther Adv Endocrinol Metab.* 2011; 2: 115–126. https://doi.org/10.1177/2042018811398516.
2. Freedman MD, Somberg JC, et al. (). Pharmacology and Pharmacokinetics of Amiodarone. *The Journal of Clinical Pharmacology.* 1991; 31(11): 1061–1069. https://doi.org/10.1002/j.1552-4604.1991.tb03673.x.
3. Oates JA, Wood A, et al. Amiodarone. *New England Journal of Medicine.* 1987; 316(8): 455–466. https://doi.org/10.1056/nejm198702193160807.
4. Hamilton, D., Nandkeolyar, S., et al. Amiodarone: A Comprehensive Guide for Clinicians. *American Journal of Cardiovascular Drugs.* 2020; 20: 549–558. https://doi.org/10.1007/s40256-020-00401-5.

5. Bílek R, Danzig V. Antiviral activity of amiodarone in SARS-CoV-2 disease. *Physiol Res.* 2022; 71(6): 869-875. Epub 2022 Nov 25. https://doi.org/10.33549/physiolres.934974.
6. Chokesuwattanaskul R, Shah N, et al. Low-dose Amiodarone Is Safe: A Systematic Review and Meta-analysis. *J Innov Card Rhythm Manag.* 2020; 11(4): 4054-4061. https://doi.org/10.19102/icrm.2020.110403.
7. Gu J, Liu X, et al. Extensive antiarrhythmic drugs after catheter ablation of persistent atrial fibrillation, *Acta Cardiol.* 2012 Aug;67(4):407-14. https://doi.org/10.1080/ac.67.4.2170681.
8. Xiuli X, Choumi T, et al. Administration of antiarrhythmic drugs to maintain sinus rhythm after catheter ablation for atrial fibrillation: a meta-analysis*, Cardiovasc Ther.* 2015 Aug;33(4):242-6. https://doi.org/10.1111/1755-5922.12133.
9. Ad N, Holmes S, et al. Amiodarone after surgical ablation for atrial fibrillation: Is it really necessary? A prospective randomized controlled trial, *J Thorac Cardiovasc Surg.* 2016 Mar;151(3):798-803. https://doi.org/10.1016/j.jtcvs.2015.07.034.
10. Vorperian VR, Havighurst TC, et al. Adverse effects of low dose amiodarone: a meta-analysis*, J Am Coll Cardiol.* 1997 Sep; 30(3):791-8. https://doi.org/10.1016/s0735-1097(97)00220-9.
11. Gao Y, Zhang P, Liang X. Effects of low-dose amiodarone and Betaloc on the treatment of hypertrophic cardiomyopathy complicated with malignant ventricular arrhythmias. *Pak J Med Sci.* 2014;30(2):291–294
12. Blackman DJ, Ferguson JD, et al. Dose of amiodarone in atrial fibrillation – neither guidelines nor clinical practice reflect available evidence, *Eur Heart J.* 2002 Jun; 23(11):908. https://doi.org/10.1053/euhj.2002.3244.
13. Kochiadakis GE, Marketou ME, et al. Amiodarone, sotalol, or propafenone in atrial fibrillation: which is preferred to maintain normal sinus rhythm? *Pacing Clin Electrophysiol.* 2000 Nov; 23(11 Pt 2):1883-7. https://doi.org/10.1111/j.1540-8159.2000.tb07044.x.
14. Kochiadakis GE, Igoumenidis NE, et al. Long-term maintenance of normal sinus rhythm in patients with current symptomatic atrial fibrillation: amiodarone vs propafenone, both in low doses, *Chest.* 2004 Feb; 125(2):377-83. https://doi.org/10.1378/chest.125.2.37.
15. Huang RD, Lin JJ, et al. Comparison of Amiodarone and Propafenone in Blanking Period after Radiofrequency Catheter Ablation in Patients with Atrial Fibrillation: A Propensity Score-Matched Study, *Biomed Res Int.* 2020 Jun 26;2020:1835181. https://doi.org/10.1155/2020/183518.
16. Jong GP, Chang MH, et al. Long-term efficacy and safety of very-low-dose amiodarone treatment for the maintenance of sinus rhythm in patients with chronic atrial fibrillation after successful direct-current cardioversion. *Chin Med J (Engl).* 2006;119(24):2030–5, PMID: 17199952 https://doi.org/10.3389/fphys.2021.606931
17. Mahmarian JJ, Smart FW, et al. Exploring the minimal dose of amiodarone with antiarrhythmic and hemodynamic activity. *Am J Cardiol.* 1994 Oct 1;74(7):681-6. https://doi.org/10.1016/0002-9149(94)90309-3.
18. Iwasawa S, Uyeda T, et al. Efficacy and Safety of Low-Dose Amiodarone Therapy for Tachyarrhythmia in Congenital Heart Disease. *Pediatr Cardiol.* 2018 Jun;39(5):1016-1022. https://doi.org/10.1007/s00246-018-1853-4.
19. Busch CD, Heiberger CJ et al. Amiodarone-induced Hemoptysis: A Rare Presentation of Amiodarone-induced Pulmonary Toxicity Occurs at a Low Dose. *Cureus.* 2019 Jul 31; 11(7):e5289. https://doi.org/10.7759/cureus.5289.
20. Meter M, Prusac IK, et al. Acute respiratory failure on a low dose of amiodarone – is it an underdiagnosed and undertreated condition? *Respir Med Case Rep.* 2021 Sep 5:34:101500. https://doi.org/10.1016/j.rmcr.2021.101500.
21. Ott MC, Khoor A, et al. Pulmonary toxicity in patients receiving low-dose amiodarone. *Chest.* 2003 Feb;123(2):646-51. https://doi.org/10.1378/chest.123.2.646.
22. Gefter WB, Epstein DM, et al. Lung disease caused by amiodarone, a new antiarrythmic agent, *Radiology*. 1983 May; 147(2):339-44. https://doi.org/10.1148/radiology.147.2.6836114.
23. Chang SN, Hwang JJ, et al. Amiodarone-related pneumonitis. *J Formos Med Assoc.* 2007 May;106(5):411-7. https://doi.org/10.1016/S0929-6646(09)60328-4
24. Kounis NG, Frangides C, et al. Dose-dependent appearance and disappearance of amiodarone-induced skin pigmentation. *Clin Cardiol.* 1996 Jul;19(7):592-4. https://doi.org/10.1002/clc.4960190713.
25. Fishman TJ, Spencer S, et al. Amiodarone induced "Blue man syndrome"; an unusual presentation*. Heart and lung.* November 25, 2019 doi.org/10.1016/j.hrtlng.2019.11.005.
26. Kaur A, Mehta D, et al. A Rare Case of Blue-Gray Discoloration Induced by Low-Dose Amiodarone. *The American Journal of Cardiology*, 16, 2022 doi.org/10.1016/j.amjcard.2022.11.045
27. Singhal A, Ghosh P, et al. Low dose amiodarone causing pseudo-alcoholic cirrhosis, *Age Ageing.* 2003 Mar; 32(2):224-5. https://doi.org/10.1093/ageing/32.2.224.
28. Ruzieh M, Moroi M, et al. Adverse Events for Amiodarone Versus Placebo. *Am J Cardiol.* 2019 Dec 15; 124(12):1889-1893. https://doi.org/10.1016/j.amjcard.2019.09.008.
29. Molinaro J, DeVries P, et al. New-onset hallucinations with amiodarone: a case report*. Ann Gen Psychiatry*. 2022 Aug 24;21(1):34. https://doi.org/10.1186/s12991-022-00409-y.
30. Singhal A, Ghosh P, et al. Low dose amiodarone causing pseudo-alcoholic cirrhosis, Age Ageing. 2003 Mar; 32(2):224-5. https://doi.org/10.1093/ageing/32.2.224.
31. Arkun A, Van Deusen S, et al. Hepatic dysfunction and neurotoxicity in a patient receiving long-term low-dose amiodarone therap*, J Emerg Med.* 2010 Apr;38(3):337-9. https://doi.org/10.1016/j.jemermed.2008.01.006.
32. Cohen-Lehman J, Dahl P, et al. Effects of amiodarone therapy on thyroid function. *Nat Rev Endocrinol.* 2010;6(1):34–41 https://doi.org/10.1038/nrendo.2009.225
33. Reiffel J. Reduced-dose Antiarrhythmic Drugs: Valuable or Valueless? *J Innov Card Rhythm Manag.* 2020 Apr; 11(4): 4063–4067. https://doi.org/10.19102/icrm.2020.110404.
34. Ayurzana et al. A low dose of amiodarone-indused sinoatrial node dysfunction: a case report. *Cardiometry.* 2022; 22: 118-120. https://doi.org/10.18137/cardiometry.2022.22.118120.
35. Kuncipálová H, et al "Blue-grey syndrome" – A rare adverse effect of amiodarone. *Cor et Vasa.* 2018; 60 (6): e638-e644. https://doi.org/10.1016/j.crvasa.2018.03.003.