

# BÖLÜM 22



## SINIF III - IV ANTİARİTMİK İLAÇLAR

İlke ERBAY<sup>1</sup>

### SINIF-III ANTI ARİTMİK İLAÇLAR

Bu sınıfta temel olarak potasyum kanallarını bloke eden ve repolarizasyon süresini uzatan ajanlar yer almaktadır. Sotalol, amiodaron, dronedaron ve bretilyum gibi anti aritmikler bu gruba aittir.

#### AMIODARON

Bir bitki grubundan izole edilen ve benzofuran türevi olarak 1960 ların sonlarında koroner vazodilatör olarak piyasaya sunulan amiodaron, diğer ilaçların etkisiz kaldığı ya da tolere edilemediği hayatı tehdit edici ventriküler aritmisi olan hastalarda FDA tarafından onaylanmış anti aritmik ajanların başında yer almaktadır.<sup>1</sup>

#### *Elektrofizyolojik Etkileri*

Amiodaron, diğer antiaritmik ajanların özelliklerini de taşımasına rağmen geleneksel olarak sınıf 3 anti aritmik ajanların en önemli üyesidir. Akut etkilerine bakıldığında aktif metaboliti olan dezetilamiodaron, miyokard kasında aksiyon potansiyeli süresini uzatırken Pukinje liflerinde aksiyon potansiyeli süresini kısaltır. Atriyo Ventrikler (AV) nodun ileti süresini uzatarak atriyumlardan ventriküle geçen iletileri azaltır. Bu etkiyi ise hücre membranındaki voltaj bağımlı sodyum (Na<sup>+</sup>) ve kalsiyum (Ca<sup>2+</sup>) kanallarını bloke ederek aksiyon potansiyeli oluşumu için gerekli olan hücre içi Ca<sup>2+</sup> ve Na<sup>+</sup> girişini azaltarak yapar. Na<sup>+</sup> ve Ca<sup>2+</sup> akımları üzerindeki frekansa bağlı etkisi nedeniyle amiodaronun taşikardi sırasındaki etkileri fizyolojik normal kalp hızlarında gösterdiği etkiden daha güçlüdür.<sup>2,3</sup> Amiodaronun

<sup>1</sup> Uzm. Dr., Muş Devlet Hastanesi, Kardiyoloji Bölümü, ilkeerbay@gmail.com

### **Yan Etkileri**

Ciddi hipotansiyonu olan ve hemodinamisi stabil olmayan hastalarda kullanımı kontrendikedir. Hipotansiyon, AV blok, bradikardi görülen sık yan etkiler olup beraberinde beta bloker tedavi alan hastalarda daha fazla görülmektedir. Ayrıca 2. ve 3. derece AV blok varlığında, hipotansif durumlarda, kardiyojenik şokta, ciddi sinüs nodu disfonksiyonu varlığında, aksesuar yolağın antegrad olarak kullanıldığı atriyal fibrilasyonda ve çoğu VT de kullanımı kontrendikedir.<sup>13,19,58</sup>

### **KAYNAKLAR**

1. Singh BN. Amiodarone as paradigm for developing new drugs for atrial fibrillation. *Journal of cardiovascular pharmacology*. 2008;52(4):300-5.
2. Kodama I, Kamiya K, Toyama J. Amiodarone: ionic and cellular mechanisms of action of the most promising class III agent. *The American journal of cardiology*. 1999;84(9):20-8.
3. Kodama I, Kamiya K, Toyama J. Cellular electropharmacology of amiodarone. *Cardiovascular research*. 1997;35(1):13-29.
4. Dan G-A, Martinez-Rubio A, Agewall S, Boriani G, Borggrefe M, Gaita F, et al. Antiarrhythmic drugs—clinical use and clinical decision making: a consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Cardiovascular Pharmacology, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and International Society of Cardiovascular Pharmacotherapy (ISCP). *Ep Europace*. 2018;20(5):731-2an.
5. Kosinski EJ, Albin JB, Young E, Lewis SM, Stevens LeLand O. Hemodynamic effects of intravenous amiodarone. *Journal of the American College of Cardiology*. 1984;4(3):565-70.
6. Remme W, van Hoogenhuyze D. Hemodynamic profile of amiodarone during acute and long-term administration in patients with ventricular dysfunction. *Cardioscience*. 1990;1(3):169-76.
7. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Journal of the American College of Cardiology*. 2018;72(14):e91-e220.
8. Libby P, Bonow RO, Mann DL, Tomaselli GF, Bhatt D, Solomon SD, et al. *Braunwald's Heart Disease-E-Book: A Textbook of Cardiovascular Medicine*: Elsevier Health Sciences; 2021.
9. Allen LB, Genaro-Mattos TC, Anderson A, Porter NA, Mirnics K, Korade Z. Amiodarone alters cholesterol biosynthesis through tissue-dependent inhibition of emopamil binding protein and dehydrocholesterol reductase 24. *ACS chemical neuroscience*. 2020;11(10):1413-23.
10. Plomp T, Wiersinga W, Van Rossum J, Maes R. Pharmacokinetics and body distribution of amiodarone and desethylamiodarone in rats after oral administration. *In vivo (Athens, Greece)*. 1987;1(5):265-79.
11. Soar J, Perkins GD, Maconochie I, Böttiger BW, Deakin CD, Sandroni C, et al. European Resuscitation Council Guidelines for Resuscitation: 2018 update—antiarrhythmic drugs for cardiac arrest. *Resuscitation*. 2019;134:99-103.
12. Chevalier P, Durand-Dubief A, Burri H, Cucherat M, Kirkorian G, Touboul P. Amiodarone versus placebo and class Ic drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis. *Journal of the American College of Cardiology*. 2003;41(2):255-62.
13. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed

- with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *European heart journal*. 2021;42(5):373-498.
14. Rüden LM-ZJ. Einfluss der Art der oralen Antikoagulation auf die intrakardiale Thrombenbildung im Rahmen der elektrischen Kardioversion: Staats-und Universitätsbibliothek Hamburg Carl von Ossietzky; 2021.
  15. Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, et al. Amiodarone versus sotalol for atrial fibrillation. *New England Journal of Medicine*. 2005;352(18):1861-72.
  16. e1 AFADSI. Maintenance of sinus rhythm in patients with atrial fibrillation: an AFFIRM substudy of the first antiarrhythmic drug. *Journal of the American College of Cardiology*. 2003;42(1):20-9.
  17. Tan ES, Rienstra M, Wiesfeld AC, Schoonderwoerd BA, Hobbel HH, Van Gelder IC. Long-term outcome of the atrioventricular node ablation and pacemaker implantation for symptomatic refractory atrial fibrillation. *Europace*. 2008;10(4):412-8.
  18. Connolly SJ, Dorian P, Roberts RS, Gent M, Bailin S, Fain ES, et al. Comparison of  $\beta$ -blockers, amiodarone plus  $\beta$ -blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC study: a randomized trial. *Jama*. 2006;295(2):165-71.
  19. Members ATF, Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Ep Europace*. 2015;17(11):1601-87.
  20. GENG DF, JIN DM, WANG JF, LUO YJ, Wu W. Clinical study of amiodarone-associated torsade de pointes in Chinese people. *Pacing and clinical electrophysiology*. 2006;29(7):712-8.
  21. Grant P. Coumarin anticoagulants and endocrine interactions. *Coumarin Anticoagulant Research Progress*. 2008;1:11.
  22. Cardenas GA, Cabral JM, Leslie CA. Amiodarone induced thyrotoxicosis: diagnostic and therapeutic strategies. *Cleveland Clinic journal of medicine*. 2003;70(7):624-6, 8.
  23. Farhan H, Albulushi A, Taqi A, Al-Hashim A, Al-Saidi K, Al-Rasadi K, et al. Incidence and pattern of thyroid dysfunction in patients on chronic amiodarone therapy: experience at a tertiary care centre in oman. *The open cardiovascular medicine journal*. 2013;7:122.
  24. Kessenich CR, Higgs DA. Understanding amiodarone-induced hypothyroidism. *The Nurse Practitioner*. 2010;35(6):14-5.
  25. Narayana SK, Woods DR, Boos CJ. Management of amiodarone-related thyroid problems. *Therapeutic advances in endocrinology and metabolism*. 2011;2(3):115-26.
  26. Wolkove N, Baltzan M. Amiodarone pulmonary toxicity. *Canadian respiratory journal*. 2009;16(2):43-8.
  27. Ernawati DK, Stafford L, Hughes JD. Amiodarone-induced pulmonary toxicity. *British journal of clinical pharmacology*. 2008;66(1):82-7.
  28. Nacca N, Bhamidipati CM, Yuhico LS, Pinnamaneni S, Szombathy T. Severe amiodarone induced pulmonary toxicity. *Journal of thoracic disease*. 2012;4(6):667.
  29. Loke YK, Derry S, Aronson JK. A comparison of three different sources of data in assessing the frequencies of adverse reactions to amiodarone. *British journal of clinical pharmacology*. 2004;57(5):616-21.
  30. Babatin M, Lee SS, Pollak PT. Amiodarone hepatotoxicity. *Current vascular pharmacology*. 2008;6(3):228-36.
  31. Chang C-C, Petrelli M, Tomaszefski Jr JF, McCullough AJ. Severe intrahepatic cholestasis caused by amiodarone toxicity after withdrawal of the drug: a case report and review of the literature. *Archives of Pathology and Laboratory Medicine*. 1999;123(3):251-6.
  32. Lewis JH, Ranard RC, Caruso A, Jackson LK, Mullick F, Ishak KG, et al. Amiodarone hepatotoxicity: prevalence and clinicopathologic correlations among 104 patients. *Hepatology*. 1989;9(5):679-85.

33. Epstein AE, Olshansky B, Naccarelli GV, Kennedy Jr JI, Murphy EJ, Goldschlager N. Practical management guide for clinicians who treat patients with amiodarone. *The American journal of medicine.* 2016;129(5):468-75.
34. Mäntyjärvi M, Tuppurainen K, Ikäheimo K. Ocular side effects of amiodarone. *Survey of ophthalmology.* 1998;42(4):360-6.
35. Wang A-G, Cheng H-C. Amiodarone-associated optic neuropathy: clinical review. *Neuro-Ophthalmology.* 2017;41(2):55-8.
36. Raizman MB, Hamrah P, Holland EJ, Kim T, Mah FS, Rapuano CJ, et al. Drug-induced corneal epithelial changes. *Survey of ophthalmology.* 2017;62(3):286-301.
37. Jaworski K, Walecka I, Rudnicka L, Gnatowski M, Kosior DA. Cutaneous adverse reactions of amiodarone. *Medical science monitor: international medical journal of experimental and clinical research.* 2014;20:2369.
38. Kounis NG, Frangides C, Papadaki PJ, Zavras GM, Goudevenos J. Dose-dependent appearance and disappearance of amiodarone-induced skin pigmentation. *Clinical cardiology.* 1996;19(7):592-4.
39. Monk B. Amiodarone-induced skin pigmentation and multiple basal-cell carcinomas. *Br J Dermatol.* 1995;133(1):148-9.
40. Orr CF, Ahlskog JE. Frequency, characteristics, and risk factors for amiodarone neurotoxicity. *Archives of neurology.* 2009;66(7):865-9.
41. Charness ME, Morady F, Scheinman MM. Frequent neurologic toxicity associated with amiodarone therapy. *Neurology.* 1984;34(5):669-.
42. Werner EG, Olanow CW. Parkinsonism and amiodarone therapy. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society.* 1989;25(6):630-2.
43. Gautier P, Guillemare E, Marion A, Bertrand J-P, Tourneur Y, Nisato D. Electrophysiologic characterization of dronedarone in guinea pig ventricular cells. *Journal of cardiovascular pharmacology.* 2003;41(2):191-202.
44. Zareba KM. Dronedarone: a new antiarrhythmic agent. *Drugs Today (Barc).* 2006;42(2):75-86.
45. Wegener FT, Ehrlich JR, Hohnloser SH. Dronedarone: an emerging agent with rhythm and rate controlling effects. *Journal of Cardiovascular Electrophysiology.* 2006;17:S17-S20.
46. Kathofer S, Thomas D, Karle CA. The novel antiarrhythmic drug dronedarone: comparison with amiodarone. *Cardiovascular Drug Reviews.* 2005;23(3):217-30.
47. Koch-Weser J. Bretylium. *New England Journal of Medicine.* 1979;300(9):473-7.
48. Anderson JL, Askins JC, Gilbert EM, Miller RH, Keefe DL, Somberg JC, et al. Multicenter trial of sotalol for suppression of frequent, complex ventricular arrhythmias: a double-blind, randomized, placebo-controlled evaluation of two doses. *Elsevier;* 1986. p. 752-62.
49. Anderson JL, Prystowsky EN. Sotalol: an important new antiarrhythmic. *American heart journal.* 1999;137(3):388-409.
50. Samanta R, Thiagalingam A, Turner C, Lakkireddy DJ, Kovoor P. The use of intravenous sotalol in cardiac arrhythmias. *Heart, Lung and Circulation.* 2018;27(11):1318-26.
51. Kopelman HA, Woosley RL, Lee JT, Roden DM, Echt DS. Electrophysiologic effects of intravenous and oral sotalol for sustained ventricular tachycardia secondary to coronary artery disease. *The American journal of cardiology.* 1988;61(13):1006-11.
52. Finks SW, Rogers KC, Manguso AH. Assessment of sotalol prescribing in a community hospital: opportunities for clinical pharmacist involvement. *International Journal of Pharmacy Practice.* 2011;19(4):281-6.
53. Gowda RM, Khan IA, Punukollu G, Vasavada BC, Sacchi TJ, Wilbur SL. Female preponderance in ibutilide-induced torsade de pointes. *International journal of cardiology.* 2004;95(2-3):219-22.
54. Abi-Mansour P, Carberry PA, McCowan RJ, Henthorn RW, Dunn GH, Perry KT, et al. Conversion efficacy and safety of repeated doses of ibutilide in patients with atrial flutter and atrial fibrillation. *American Heart Journal.* 1998;136(4):632-42.

55. Tande PM, Bjørnstad H, Yang T, Refsum H. Rate-dependent class III antiarrhythmic action, negative chronotropy, and positive inotropy of a novel Ik blocking drug, UK-68,798: potent in guinea pig but no effect in rat myocardium. *Journal of cardiovascular pharmacology*. 1990;16(3):401-10.
56. Suttorp MJ, Polak PE, van't Hof A, Rasmussen HS, Dunselman PH, Kingma JH. Efficacy and safety of a new selective class III antiarrhythmic agent dofetilide in paroxysmal atrial fibrillation or atrial flutter. *The American journal of cardiology*. 1992;69(4):417-9.
57. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *European heart journal*. 2021;42(36):3599-726.
58. De Simone A, De Pasquale M, De Matteis C, Canciello M, Manzo M, Sabino L, et al. Verapamil plus antiarrhythmic drugs reduce atrial fibrillation recurrences after an electrical cardioversion (VEPARAF Study). *European heart journal*. 2003;24(15):1425-9.