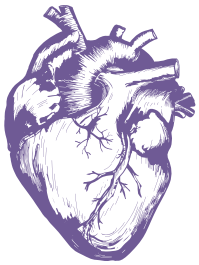


BÖLÜM 18

Sınıf I Antiaritmik İlaçlar

Doğan İLİŞ [1]

GİRİŞ

Kardiyak aksiyon potansiyeli çeşitli iyonlarının hareket döngüsüdür, bu döngü kas kasılmasına yol açan kardiyak miyositlerin depolarizasyonu ve repolarizasyonu sağlar (1). Kardiyak miyositin dinlenme/istirahat fazı, başlangıçta eksi 80 (-80 mV) ile eksi 90 (-90 mV) mV arasında bir dinlenme zar potansiyeline sahiptir. Antiaritmik ilaçlar esas olarak kardiyak aksiyon potansiyelinin çeşitli fazlarında farklı oranlarda iyon hareketini yavaşlatarak etki eder. Aksiyon potansiyeli 5 fazdan meydana gelir **(Şekil 1).**

Faz 0: Aksiyon potansiyelinin "depolarizasyon" fazıdır. Yaklaşık +30 mV'luk membran potansiyeline yol açan bir elektrokimyasal gradyan boyunca sodyum iyonlarının (Na+) hücre içine hızlı hareketiyle oluşur.

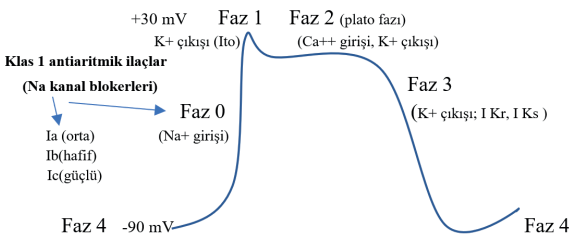
Faz 1: Aksiyon potansiyelinin ilk veya erken repolarizasyon fazı, potasyum (K+) iyonlarının dışarı akışı ile oluşur (Ito kanalları).

Faz 2: "Plato" fazı. Bu fazda dışa doğru K+ iyon hareketini dengeleyen, içe doğru bir kalsiyum iyonu hareketinin görüldüğü fazdır.

Faz 3: Aksiyon potansiyelinin "repolarizasyon" fazıdır. Bu faza, esas olarak K+ iyonlarının elektrokimyasal gradyanları boyunca hücre dışına hareketi neden olur (I Kr, I Ks kanalları ile). Kalp kasının negatif membran potansiyelini geri kazandırır.

Faz 4: Kardiyak miyositin istirahat membran potansiyelinin olduğu evredir (-90 mV) aktif olan pompa Na/K-ATPaz pompasıdır.

Antiaritmik ilaçlar tipik olarak Vaughan-Williams (VW) sınıflandırma sistemine göre kategorize edilmiştir. Sistem, birkaç ajanın birden çok sınıfın özelliklerini gösteresine rağmen ilaçları primer etki mekanizmasına göre sınıflandırır (2-4). Vaughan-Williams (VW) sınıflandırma sistemi 2018 yenilenmiştir (Tablo 1).



Şekil 1. Aksiyon potansiyeli şematik gösterimi

[1] Dr. Öğr. Üyesi, Kafkas Üniversitesi, Tıp Fakültesi, Kardiyoloji AD., ilisdogan@hotmail.com, ORCID iD: 0000-0002-1871-5157

diyovasküler toksisite riski, yapısal kalp hastalığı olan hastalarda daha fazladır (68,69).

İnotropik etkiler: Sol ventrikül ejeksiyon fraksiyonu (LVEF) normal veya minimal düzeyde azalmış (Ef ≥ %40) hastalarda, oral propafenon, KY semptomlarına neden olmadan EF yi azaltabilir (71). Bununla birlikte, önceden ventriküler sistolik disfonksiyonu olan hastalarda aşikâr KY tetikleyebilir (72). Propafenon, QRS süresinde uzama, yeni gelişen sol dal bloğu veya sağ dal bloğu ile ilişkilendirilmiştir (73,74). Diğer antiaritmik ajanlar gibi, propafenon da sürekli ventriküler taşikardiyi (VT) tetikleyebilen proaritmik bir etkiye sahiptir (38). Propafenonun proaritmik etkisi, beta-bloker aktivitesi ile bir şekilde azaltılabilir.

Nörotoksik yan etkileri: Propafenon ile bağlantılı olarak birçok sinir sistemi yan etkileri bildirilmiştir; mide bulantısı, başdönmesi, olağandışı tat ve bulanık görme. Propafenonun neden olduğu ataksi de bildirilmiştir (75).

SONUÇ

Etki ettikleri iyon kanalları ve bu kanallar üzerindeki etki oranları açısından antiaritmik ilaçlar hayatı öneme sahip olan, doğru zamanda doğru hasta için tercih edildiğinde ciddi faydaları olan özel bir gruptur. Bunun yanında, hastada olan çeşitli organ patolojileri ve/veya kullandığı diğer ilaçları ile dikkatlice bilinmesi gerekir. Olası advers etkileri açısından klinisyen uyanık olmalı ve uygun araçlarla uygun zaman aralıklarında takibin önemini unutmamalıdır.

KAYNAKLAR

1. Kingma JH, Suttorp MJ. Acute pharmacologic conversion of atrial fibrillation and flutter: the role of flecainide, propafenone, and verapamil. Am J Cardiol. 1992 Aug 20;70(5):56A-60A; discussion 60A-61A.
2. Shanmugasundaram M, Lotun K. Refractory Out of Hospital Cardiac Arrest. Curr Cardiol Rev. 2018;14(2):109-114.
3. Noss K, Aguero SM, Reinaker T. Assessment of Prescribing and Monitoring Habits for Patients Taking an Antiarrhythmic and Concomitant QTc-Prolonging Antibiotic. Pharmacy (Basel). 2017 Nov 01;5(4)
4. Lai E, Chung EH. Management of Arrhythmias in Athletes: Atrial Fibrillation, Premature Ventricular Contractions, and Ventricular Tachycardia. Curr Treat Options Cardiovasc Med. 2017 Oct 09;19(11):86.
5. American College of Cardiology Foundation/American Heart Association Task Force on Practice. American Association for Thoracic Surgery. American Society of Echocardiography. American Society of Nuclear Cardiology. Heart Failure Society of America. Heart Rhythm Society. Society for Cardiovascular Angiography and Interventions. Society of Thoracic Surgeons. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg. 2011 Dec;142(6):e153-203
6. Fuster V, Rydén LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol. 2011 Mar 15;57(11):e101-98.
7. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Executive summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm. 2018 Oct;15(10):e190-e252.
8. January CT, Wann LS, Alpert JS, et al. ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014 Dec 02;130(23):2071-104.
9. Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2019 Aug 20;140(8):e382-e482.
10. Cohen IS, Jick H, Cohen SI. Adverse reactions to quinidine in hospitalized patients: findings based on data from the Boston Collaborative Drug Surveillance Program. Prog Cardiovasc Dis 1977; 20:151.
11. Morganroth J, Horowitz LN. Incidence of proarrhythmic effects from quinidine in the outpatient treatment of benign or potentially lethal ventricular arrhythmias. Am J Cardiol 1985; 56:585.
12. Roden DM, Woosley RL, Primm RK. Incidence and clinical features of the quinidine-associated long QT syndrome: implications for patient care. Am Heart J 1986; 111:1088.

13. Coplen SE, Antman EM, Berlin JA, et al. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. Circulation 1990; 82:1106.
14. Flaker GC, Blackshear JL, McBride R, et al. Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators. J Am Coll Cardiol 1992; 20:527.
15. Reimold SC, Chalmers TC, Berlin JA, et al. Assessment of the efficacy and safety of antiarrhythmic therapy for chronic atrial fibrillation: observations on the role of trial design and implications of drug-related mortality. Am Heart J 1992; 124:924.
16. Podrid PJ, Lampert S, Graboys TB, et al. Aggravation of arrhythmia by antiarrhythmic drugs--incidence and predictors. Am J Cardiol 1987; 59:38E.
17. Koster RW, Wellens HJ. Quinidine-induced ventricular flutter and fibrillation without digitalis therapy. Am J Cardiol 1976; 38:519.
18. Morganroth J. Risk factors for the development of proarrhythmic events. Am J Cardiol 1987; 59:32E.
19. Minardo JD, Heger JJ, Miles WM, et al. Clinical characteristics of patients with ventricular fibrillation during antiarrhythmic drug therapy. N Engl J Med 1988; 319:257.
20. Roden DM, Hoffman BF. Action potential prolongation and induction of abnormal automaticity by low quinidine concentrations in canine Purkinje fibers. Relationship to potassium and cycle length. Circ Res 1985; 56:857.
21. Levine JH, Spear JF, Guarnieri T, et al. Cesium chloride-induced long QT syndrome: demonstration of afterdepolarizations and triggered activity in vivo. Circulation 1985; 72:1092.
22. El-Eraky H, Thomas SH. Effects of sex on the pharmacokinetic and pharmacodynamic properties of quinidine. Br J Clin Pharmacol 2003; 56:198.
23. Benton RE, Sale M, Flockhart DA, et al. Greater quinidine-induced QTc interval prolongation in women. Clin Pharmacol Ther 2000; 67:413.
24. SHORT DS. The syndrome of alternating bradycardia and tachycardia. Br Heart J 1954; 16:208.
25. Grayzel J, Angeles J. Sino-atrial block in man provoked by quinidine. J Electrocardiol 1972; 5:289.
26. SHULMAN NR. Immunoreactions involving platelets. I. A steric and kinetic model for formation of a complex from a human antibody, quinidine as a haptene, and platelets; and for fixation of complement by the complex. J Exp Med 1958; 107:665.
27. Cohen MG, Kevat S, Prowse MV, et al. Two distinct quinidine-induced rheumatic syndromes. Ann Intern Med 1988; 108:369.
28. Teichman SL, Ferrick A, Kim SG, et al. Disopyramide-pyridostigmine interaction: selective reversal of anticholinergic symptoms with preservation of antiarrhythmic effect. J Am Coll Cardiol 1987; 10:633.
29. Konishi T, Kadoya M, Ikeguchi S, et al. Combined effect of disopyramide and bethanechol: use of bethanechol to prevent anticholinergic side effects of disopyramide without reduction of antiarrhythmic efficacy. J Cardiovasc Pharmacol 1989; 14:341.
30. Tsuchishita Y, Fukumoto K, Kusumoto M, et al. Effects of serum concentrations of disopyramide and its metabolite mono-N-dealkyldisopyramide on the anticholinergic side effects associated with disopyramide. Biol Pharm Bull 2008; 31:1368.
31. Di Bianco R, Gottdiener JS, Singh SN, et al. A review of the effects of disopyramide phosphate on left ventricular function and the peripheral circulation. Angiology 1987; 38:174.
32. Casedevant B, Sabaut D, Clementy J, et al. [Letter: Syncopes through the inversion of points in connection with the absorption of disopyramide]. Nouv Presse Med 1975; 4:2339.
33. Choudhury L, Grais IM, Passman RS. Torsades de pointes due to drug interaction between disopyramide and clarithromycin. Heart Dis 1999; 1:206.
34. Hayashi Y, Ikeda U, Hashimoto T, et al. Torsades de pointes ventricular tachycardia induced by clarithromycin and disopyramide in the presence of hypokalemia. Pacing Clin Electrophysiol 1999; 22:672.
35. Ray WA, Murray KT, Meredith S, et al. Oral erythromycin and the risk of sudden death from cardiac causes. N Engl J Med 2004; 351:1089.
36. Rubinstein E. Comparative safety of the different macrolides. Int J Antimicrob Agents 2001; 18 Suppl 1:S71.
37. Granowitz EV, Tabor KJ, Kirchhoffer JB. Potentially fatal interaction between azithromycin and disopyramide. Pacing Clin Electrophysiol 2000; 23:1433.
38. Podrid PJ, Lampert S, Graboys TB, et al. Aggravation of arrhythmia by antiarrhythmic drugs--incidence and predictors. Am J Cardiol 1987; 59:38E
39. Wald RW, Waxman MB, Colman JM. Torsade de pointes ventricular tachycardia. A complication of disopyramide shared with quinidine. J Electrocardiol 1981; 14:301.
40. Schweitzer P, Mark H. Torsade de pointes caused by disopyramide and hypokalemia. Mt Sinai J Med 1982; 49:110.
41. Tzivoni D, Banai S, Schuger C, et al. Treatment of torsade de pointes with magnesium sulfate. Circulation 1988; 77:392.
42. Tzivoni D, Keren A, Stern S, et al. Disopyramide-induced Torsade de Pointes. Arch Intern Med 1981; 141:946.
43. Stec GP, Lertora JJ, Atkinson AJ Jr, et al. Remission of procainamide-induced lupus erythematosus with N-acetylprocainamide therapy. Ann Intern Med 1979; 90:799
44. Reidenberg MM, Drayer DE. Procainamide, N-acetylprocainamide, antinuclear antibody and systemic lupus erythematosus. Angiology 1986; 37:968.
45. Danielly J, DeJong R, Radke-Mitchell LC, et al. Procainamide-associated blood dyscrasias. Am J Cardiol 1994; 74:1179.
46. Ellrodt AG, Murata GH, Riedinger MS, et al. Severe neutropenia associated with sustained-release procainamide. Ann Intern Med 1984; 100:197.
47. Rademaker AW, Kellen J, Tam YK, et al. Character of

adverse effects of prophylactic lidocaine in the coronary care unit. Clin Pharmacol Ther 1986; 40:71.
48. Chopra MP, Thadani U, Portal RW, et al. Lignocaine therapy for ventricular ectopic activity after acute myocardial infarction: a double-blind trial. Br Med J 1971; 3:668.
49. Gianelly R, von der Groeben JO, Spivack AP, et al. Effect of lidocaine on ventricular arrhythmias in patients with coronary heart disease. N Engl J Med 1967; 277:1215.
50. Lown B, Vassaux C. Lidocaine in acute myocardial infarction. Am Heart J 1968; 76:586.
51. DeToledo JC. Lidocaine and seizures. Ther Drug Monit 2000; 22:320.
52. Pfeifer HJ, Greenblatt DJ, Koch-Weser J. Clinical use and toxicity of intravenous lidocaine. A report from the Boston Collaborative Drug Surveillance Program. Am Heart J 1976; 92:168.
53. Schumacher RR, Lieberson AD, Childress RH, et al. Hemodynamic effects of lidocaine in patients with heart disease. Circulation 1968; 37:965.
54. Johansson BW, Stavenow L, Hanson A. Long-term clinical experience with mexiletine. Am Heart J 1984; 107:1099.
55. Talbot RG, Julian DG, Prescott LF. Long-term treatment of ventricular arrhythmias with oral mexiletine. Am Heart J 1976; 91:58.
56. Velebit V, Podrid P, Lown B, et al. Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. Circulation 1982; 65:886.
57. Campbell RW. Arrhythmogenesis--a European perspective. Am J Cardiol 1987; 59:49E.
58. Sami M, Lisbona R. Mexiletine: long-term efficacy and hemodynamic actions in patients with ventricular arrhythmia. Can J Cardiol 1985; 1:251.
59. Shanks RG. Hemodynamic effects of mexiletine. Am Heart J 1984; 107:1065.
60. Stein J, Podrid P, Lown B. Effects of oral mexiletine on left and right ventricular function. Am J Cardiol 1984; 54:575.
61. Sasaki K, Yamamoto T, Kishi M, et al. Acute exanthematous pustular drug eruption induced by mexiletine. Eur J Dermatol 2001; 11:469.
62. Lee SP, Kim SH, Kim TH, et al. A case of mexiletine-induced hypersensitivity syndrome presenting as eosinophilic pneumonia. J Korean Med Sci 2010; 25:148.
63. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991; 324:781.
64. Pritchett EL, Wilkinson WE. Mortality in patients treated with flecainide and encainide for supraventricular arrhythmias. Am J Cardiol 1991; 67:976.
65. Vik-Mo H, Ohm OJ, Lund-Johansen P. Electrophysiologic effects of flecainide acetate in patients with sinus nodal dysfunction. Am J Cardiol 1982; 50:1090.
66. Hellestrand KJ, Bexton RS, Nathan AW, et al. Acute electrophysiological effects of flecainide acetate on cardiac conduction and refractoriness in man. Br Heart J 1982; 48:140.
67. Williams AJ, McQuinn RL, Walls J. Pharmacokinetics of flecainide acetate in patients with severe renal impairment. Clin Pharmacol Ther 1988; 43:449.
68. Ravid, S, Podrid, et al. Safety of long term propafenone therapy for cardiac arrhythmia: Experience with 774 patients. J Electrophysiol 1987; 1:580.
69. Podrid PJ, Anderson JL. Safety and tolerability of long-term propafenone therapy for supraventricular tachyarrhythmias. The Propafenone Multicenter Study Group. Am J Cardiol 1996; 78:430.
70. Schlepper M. Propafenone, a review of its profile. Eur Heart J 1987; 8 Suppl A:27.
71. Baker BJ, Dinh H, Kroskey D, et al. Effect of propafenone on left ventricular ejection fraction. Am J Cardiol 1984; 54:20D.
72. Brodsky MA, Allen BJ, Abate D, et al. Propafenone therapy for ventricular tachycardia in the setting of congestive heart failure. Am Heart J 1985; 110:794.
73. de Soyza N, Terry L, Murphy ML, et al. Effect of propafenone in patients with stable ventricular arrhythmias. Am Heart J 1984; 108:285.
74. Podrid PJ, Lown B. Propafenone: a new agent for ventricular arrhythmia. J Am Coll Cardiol 1984; 4:117.
75. Odeh M, Seligmann H, Oliven A. Propafenone-induced ataxia: report of three cases. Am J Med Sci 2000; 320:151.