Bölüm 10

ANTİHİSTAMİNİKLERİN KARDİYOVASKÜLER ETKİLERİ

Erol GÜRSOY[1]

GİRİŞ

Antihistaminikler gelişmiş ülkelerde en sık reçete edilen ilaçlar arasındadır(1). Terapotik aralığı geniş olması nedeni ile çoğu formu reçetesiz de alınabilmektedir. Antihistaminikler, histamin ile yarışarak onların etkilerini azaltır veya ortadan kaldırırlar. Alerjik hastalıklar ve uyku bozuklukları tedavisinde kullanılmaktadır. Klasik antihistaminikler, difenhidramin, klorfeniramin, hidroksizin, bromfeniramin, siproheptadin gibi etkili moleküllerdir, ancak kullanımları antikolinerjik ve sedatif özellikleri nedeni ile kısıtlıdır. Klasik antihistaminiklerin etkileri, yan etkileri ve diğer ilaçlarla etkileşimleri iyi bilinmektedir. Bu nedenle zamanla sedatif ve antikolinerjik yan etkileri olmayan nonsedatif H1 antihistaminikler ve H2 reseptör blokerleri geliştirilmiştir. Nonsedatif olarak değerlendirilen yeni antihistaminiklerin zamanla daha sık kullanılması ile ilaç etkileşimleri ve birçok yan etki ve ortaya çıkmıştır. Nonsedatif H1 antihistaminikler, sedatif ve antikolinerjik etkilerinin olmaması nedeniyle alerjik hastalıkların tedavisi için yaygın olarak reçete edilir; bununla birlikte, terfenadin ve astemizol gibi bazı nonsedatif antihistaminiklerin, özellikle aşırı dozda veya imidazol grubu antifungallerinin veya makrolid grubu antibiyotiklerinin birlikte alınmasıyla QT uzamasına ve Torsades de Pointes (TdP) olarak bilinen ventriküler aritmilere neden olduğu artık bilinmektedir(2). Tüm bu ilaçlar, farmakolojik etkileri bilinerek ve doğru dozlarında kullanıldığı zaman güvenlidir.

[1] Uzm. Dr. Koç Üniversitesi Hastanesi, Kardiyoloji Kliniği, drerolgursoy@gmail.com

en acil sorunlara, yani, özellikle genetik kökenli olanlar olmak üzere, bu nadir fakat potansiyel olarak ölümcül kardiyotoksik belirtilere yatkınlaştırıcı faktörlerin rolü, belirli moleküllerin detoksifikasyonunda yer alan metabolik yollar çeşitli zorluklara yanıt vermek için önümüzde durmaktadır.

Şimdiye kadar elde edilen ilerlemeler, klinisyenlere ve hastalara gelişmiş bir güvenlik profili ile karakterize edilen ilaçlar sağlamaya kesin olarak yardımcı olmuş olsa da, QT uzamasının tamamen tarihsel değeri olan bir advers ilaç reaksiyonu olarak kabul edilmesinden önce bu yönde daha fazla çalışmaya ihtiyaç vardır. Kardiyak yan etkiler antihistaminik kaynaklı olabileceği gibi genetiğe bağlı olarak da oluşabilmektedir. Genetik nedenli kardiyak yan etkiler karciğer enzimlerinin hastalar arasında farklılık göstermesine ve iyon kanallarındaki mutasyona bağlı olarak gözükürken, ilaç kaynaklı yan etkiler ise HERG1 kanalının blokajı nedeni ile gözükür. Kardiyak hastalık riski olan hastalarda ilaç etkileşimlerine çok dikkat etmek gerekir.

KAYNAKLAR

1. Woosley RL. Cardiac actions of antihistamines. *Annual review of pharmacology and toxicology*. 1996;36(1):233-252.
2. Yap YG, Camm AJ. Potential cardiac toxicity of H1-antihistamines. Histamine and H1-antihistamines in allergic disease. 2002:405-436.
3. Dale HH, Laidlaw PP. The physiological action of β-iminazolylethylamine. *The Journal of physiology.* 1910;41(5):318-344.
4. MacGlashan D. Histamine: a mediator of inflammation. *Journal of Allergy and Clinical Immunology.* 2003;112(4):S53-S59.
5. Zimmermann AS, Burhenne H, Kaever V et al. Systematic analysis of histamine and N-methylhistamine concentrations in organs from two common laboratory mouse strains: C57Bl/6 and Balb/c. *Inflammation Research.* 2011;60(12):1153-1159.
6. Levi R, Owen D, Trzeciakowski J. Actions of Histamine on the pharmacology of histamine receptors. 1982;236.
7. Serafin W. Histamine, bradykinin, and their antagonists. *Goodman & Gilman's the pharmacological basis of therapeutics.* 1996.
8. Genovese A, Spadaro G. Highlights in cardiovascular effects of histamine and HI-receptor ansgonists. *Allergy*. 1997;52:67-78.
9. Folkow B, Hjeger K, Kahlson G. Observations on Reactive Hyperaemia as Related to Histamine on Drugs Antagonizing Vasodilatation Induced by Histamine and on Vasodilator Properties of Adenosinetri phosphate. *Acta Physiologica Scandinavica.* 1948;15(3):264-278.
10. Black JW, Duncan W, DURANT CJ et al. Definition and antagonism of histamine H 2-receptors. Nature. 1972;236(5347):385-390.
11. Durant GJ, Ganellin CR, Parsons ME. Chemical differentiation of histamine H1-and H2-receptor agonists. *Journal of medicinal chemistry.* 1975;18(9):905-909.

12. Bove AA, Dewey JD. Effects of serotonin and histamine on proximal and distal coronary vasculature in dogs: comparison with alpha-adrenergic stimulation. *The American journal of cardiology.* 1983;52(10):1333-1339.
13. Levi R, Allan G. Histamine-mediated cardiac effects: *Elsevier.* New York, New York, USA; 1980.
14. Levi R, Allan G, Zavecz J, editors. Cardiac histamine receptors. Federation proceedings; 1976.
15. Levi R, AJ P. Modification of the effects of histamine and norepinephrine on the sinoatrial node pacemaker by potassium and calcium. 1978.
16. Simons FER, Simons KJ. Histamine and H1-antihistamines: celebrating a century of progress. *Journal of Allergy and Clinical Immunology.* 2011;128(6):1139-1150. e4.
17. Handley DA, Magnetti A, Higgins AJ. Therapeutic advantages of third generation antihistamines. Expert opinion on investigational drugs. 1998;7(7):1045-1054.
18. Kim J, Ogai A, Nakatani S. et al. Impact of blockade of histamine H2receptors on chronic heart failure revealed by retrospective and prospective randomized studies. *Journal of the American College of Cardiology.* 2006;48(7):1378-1384.
19. Hill S, Ganellin C, Timmerman H. et al. *International Union of Pharmacology.* XIII. Classification of histamine receptors. Pharmacological reviews. 1997;49(3):253-278.
20. Simons FER, Simons KJ. The pharmacology and use of H1-receptor-antagonist drugs. *New England Journal of Medicine.* 1994;330(23):1663-1670.
21. Goldberg MJ, Spector R, Chiang C. Transport of diphenhydramine in the central nervous system. *Journal of Pharmacology and Experimental Therapeutics.* 1987;240(3):717-722.
22. Meltzer E. Comparative safety of H1 antihistamines. *Annals of allergy.* 1991;67(6):625-633.
23. Huxtable RF, Landwirth J. Diphenhydramine poisoning treated by exchange transfusion. *American Journal of Diseases of Children.* 1963;106(5):496-500.
24. Hollister LE. Hydroxyzine hydrochloride: possible adverse cardiac interactions. *Psychopharmacology communications.* 1975;1(1):61-65.
25. Monahan BP, Ferguson CL, Killeavy ES et al. Torsades de pointes occurring in association with terfenadine use. *Jama.* 1990;264(21):2788-2790.
26. Cantilena LR, Ferguson CL, Monahan BP. Torsades de Pointes Occurring in Association With Terfenadine Use-Reply. *Jama.* 1991;266(17):2376-2380.
27. Craft TM. Torsade de pointes after astemizole overdose. *British medical journal* (Clinical research ed). 1986;292(6521):660.
28. Smith WM, Gallagher JJ. " Les torsades de pointes": An unusual ventricular arrhythmia. *Annals of internal medicine.* 1980;93(4):578-584.
29. Yun C-H, Okerholm RA, Guengerich FP. Oxidation of the antihistaminic drug terfenadine in human liver microsomes. Role of cytochrome P-450 3A (4) in N-dealkylation and C-hydroxylation. *Drug metabolism and Disposition.* 1993;21(3):403-409.
30. Yumibe N, Huie K, Chen K-J, et al. Identification of human liver cytochrome P450s involved in the microsomal metabolism of the antihistaminic drug loratadine. *International archives of allergy and immunology.* 1995;107(1-3):420.
31. Pessayre D. Effects of macrolide antibiotics on drug metabolism in rats and in humans. *International journal of clinical pharmacology research.* 1983;3(6):449-458.
32. Woosley RL, Chen Y, Freiman JP, et al. Mechanism of the cardiotoxic actions of terfenadine. *Jama.* 1993;269(12):1532-1536.

33. Rampe D, Wible B, Brown AM, et al. Effects of terfenadine and its metabolites on a delayed rectifier K+ channel cloned from human heart. *Molecular pharmacology.* 1993;44(6):1240-1245.
34. Wood SG, John B, Chasseaud L, et al. The metabolism and pharmacokinetics of 14C-cetirizine in humans. *Annals of allergy.* 1987;59(6 Pt 2):31-34.
35. Affrime M, Lorber R, Danzig M, et al. 3 month evaluation of electrocardiographic effects of loratidine in humans. *Journal of Allergy and Clinical Immunology*; 1993: MOSBY-YEAR BOOK INC 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-63318.
36. Honig P, Baranjuk J. Adverse effects of H1-receptor antagonists in the cardiovascular system. Histamine and H1-receptor antagonists in allergic diseases New York: Marcel Dekker. 1996:383-412.
37. Markham A, Wagstaff AJ. Fexofenadine. *Drugs.* 1998;55(2):269-274; discussion 275.
38. Yap YG, Camm J. Risk of torsades de pointes with non-cardiac drugs: doctors need to be aware that many drugs can cause QT prolongation. *British Medical Journal Publishing Group*; 2000.
39. Lessard É, Yessine M-A, Hamelin BA, et al. Diphenhydramine alters the disposition of venlafaxine through inhibition of CYP2D6 activity in humans. *Journal of clinical psychopharmacology.* 2001;21(2):175-184.
40. Perticone F, Adinolfi L, Bonaduce D. Efficacy of magnesium sulfate in the treatment of torsade de pointes. *American heart journal.* 1986;112(4):847-849.
41. Sanguinetti MC, Jurkiewicz NK. Two components of cardiac delayed rectifier K+ current. Differential sensitivity to block by class III antiarrhythmic agents. *Journal of General Physiology.* 1990;96(1):195-215.
42. Nerbonne JM, Kass RS. Molecular physiology of cardiac repolarization. *Physiological reviews.* 2005;85(4):1205-1253.
43. Shieh C-C, Coghlan M, Sullivan JP, et al. Potassium channels: molecular defects, diseases, and therapeutic opportunities. *Pharmacological reviews.* 2000;52(4):557-594.
44. Priori SG, Rivolta I, Napolitano C. Genetics of long QT, Brugada, and other channelopathies. Cardiac Electrophysiology: Fourth Edition: *Elsevier Inc.*; 2004. p. 462-470.
45. Napolitano C, Priori SG, Schwartz PJ. Torsade de pointes. *Drugs.* 1994;47(1):51-65.
46. Borchert B, Lawrenz T, Stellbrink C. Long and short QT syndrome. *Herzschrittmachertherapie & Elektrophysiologie.* 2006;17(4):205-210.
47. Warmke J, Drysdale R, Ganetzky B. A distinct potassium channel polypeptide encoded by the Drosophila eag locus. *Science.* 1991;252(5012):1560-1562.
48. Sanguinetti MC, Jiang C, Curran ME, et al. A mechanistic link between an inherited and an acquird cardiac arrthytmia: HERG encodes the IKr potassium channel. *Cell.* 1995;81(2):299-307.
49. Splawski I, Shen J, Timothy KW, et al. Spectrum of mutations in long-QT syndrome genes: KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. *Circulation.* 2000;102(10):1178-1185.
50. Antzelevitch C. Role of transmural dispersion of repolarization in the genesis of drug-induced torsades de pointes. *Heart rhythm.* 2005;2(11):S9-S15.
51. Roy M-L, Dumaine R, Brown AM. HERG, a primary human ventricular target of the nonsedating antihistamine terfenadine. *Circulation.* 1996;94(4):817-823.
52. Suessbrich H, Waldegger S, Lang F, et al. Blockade of HERG channels expressed in Xenopus oocytes by the histamine receptor antagonists terfenadine and astemizole. *FEBS letters.* 1996;385(1-2):77-80.