

# BÖLÜM 42

## İLAÇLARA BAĞLI ANJİÖDEM

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### GİRİŞ

Anjiödem; vazodilatasyon ve vasküler permeabilite artışı sonucu gelişen, derin dermal, subkutan ve/veya mukozal ödem ile karakterizedir(1,2). Yüzde, dudaklarda ve dilde şişlik belirgindir. Ekstremitelerde, larinks, genital bölge ve gastrointestinal sistem tutulumu görülebilir(3). Solunum sistemi tutulumu olduğunda yaşamı tehdit edebilir(4). Son yıllarda pek çok farklı ilacın kullanımı ile birlikte anjiödemeye yol açabilen ilaçların çeşitliliği artmıştır. Beta laktam antibiyotikler, nonsteroidal antiinflamatuvar ilaçlar (NSAİİ), anjiotensin dönüştürücü enzim (ACE) inhibitörleri ve diğer antibiyotikler anjiödemeye en sık yol açan ilaç gruplarıdır(5-7).

İlaç ilişkili anjiödemeye, vakaların yaklaşık %50'sinde ürtiker eşlik edebilir ve yaşamı tehdit edici anafilaksi bulgusu olabilir(2).

İlaç ilişkili anjiödem gelişimi, mast hücre aracılı ve bradikinin aracılı mekanizma ile veya mekanizması tam olarak bilinmeyen yollarla ortaya çıkabilir(8,9).

Anjiödem tiplerinin ayrımı, alta yatan nedenin, mekanizma ve tedavilerin birbirinden farklı olması nedeniyle önemlidir.

### MAST HÜCRE ARACILI ANJİÖDEM

Mast hücre aracılı anjiödem, mast hücresi ve bazofillerden histamin ve diğer mediatörlerin salınımı nedeniyle oluşur. Bradikinin ilişkili anjiödemeye göre daha hızlı ortaya çıkar, 24- 48 saatte geriler. Genellikle kaşıntı ve/veya ürtiker ile birlikte görülür(10). Alerjik veya psödoalerjik reaksiyonlar sonucu olarak ortaya çıkabilir(11).

### İmmünglobulin E (IgE) İlişkili Anjiödem (Alerjik Anjiödem)

İlaç ilişkili mast hücre aracılı anjiödemimin en sık formudur. Mast hücrelerinin, daha önceden duyarlanılmış bir ilaca yanıt olarak IgE aracılı degranülasyonu, histamin ve diğer mediatörlerin salınımı sonucu oluşur (tip 1 hipersensitivite)(7). En sık beta

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yonunda daha büyük rol oynar. Bu nedenle DPP4 inhibitörü kullanılırken anjiyödem açısından dikkatli olunmalıdır(23).

## Fibrinolitik Ajanlar

Akut iskemik inme ve tromboz nedeniyle streptokinas ve alteplaz ile tedavi edilen hastalarda anjiyödem bildirilmiştir(40,41). Fibrinolitik ajanlar ile görülen anjiyödemin; kininleri, kompleman sistemini ve fibrinolitik sistemi birbirine bağlayan temas sisteminin aktivasyonu sonucu oluştuğu ve bradikinin aracılı anjiyödem olduğu düşünülmektedir(42).

## Anjiyödem Mekanizması Bilinmeyen İlaçlar

Kalsiyum kanal blokerleri, cilt ve ince bağırsak mukozasında anjiyödem ile ilişkilendirilmiştir ancak mekanizması bilinmemektedir(43,44).

Anjiyödem bildirilen ancak mekanizması tam olarak bilinmeyen diğer ilaçlar; sirolimus, everolimus, amiodaron, metoprolol, ripseridon ve etanercept ve diğer biyolojik ajanlardır(45–50).

## KAYNAKLAR

1. Lerch M. Drug-Induced Angioedema. *Chem Immunol Allergy*. 2012;97: 98–105.
2. Inomata N. Recent Advances in Drug-Induced Angioedema. *Allergology International*. 2012;61: 545–557. <https://doi.org/10.2332/allergolint.12-RAI-0493>.
3. Leeyaphan C, Kulthanan K, Jongjarearnprasert K, et al. Drug-induced angioedema without urticaria: Prevalence and clinical features. *Journal of the European Academy of Dermatology and Venereology*. 2010;24(6): 685–691. <https://doi.org/10.1111/j.1468-3083.2009.03489.x>.
4. Kaplan AP, Greaves MW. *Angioedema*. *Journal of the American Academy of Dermatology*. 2005. p. 373–388. <https://doi.org/10.1016/j.jaad.2004.09.032>.
5. Jares EJ, Sánchez-Borges M, Cardona-Villa R, et al. Multinational experience with hypersensitivity drug reactions in Latin America. *Annals of Allergy, Asthma and Immunology*. 2014;113(3): 282–289. <https://doi.org/10.1016/J.ANAI.2014.06.019>.
6. Bertazzoni G, Spina MT, Scarpellini MG, et al. Drug-induced angioedema: Experience of Italian emergency departments. *Internal and Emergency Medicine*. 2014;9(4):

- 455–462. <https://doi.org/10.1007/S11739-013-1007-X>.
7. Stone C, Brown NJ. *Angiotensin-converting Enzyme Inhibitor and Other Drug-associated Angioedema*. *Immunology and Allergy Clinics of North America*. 2017. p. 483–495. <https://doi.org/10.1016/j.iac.2017.04.006>.
8. Giavina-Bianchi P, Aun M V., Motta AA, et al. *Classification of angioedema by endotypes*. *Clinical and Experimental Allergy*. 2015. p. 1142–1143. <https://doi.org/10.1111/cea.12551>.
9. Giavina-Bianchi P, Aun MV, Jares EJ, et al. *Angioedema associated with nonsteroidal anti-inflammatory drugs*. *Current Opinion in Allergy and Clinical Immunology*. 2016. p. 323–332. <https://doi.org/10.1097/ACI.000000000000292>.
10. Busse PJ, Smith T. *Histaminergic Angioedema*. *Immunology and Allergy Clinics of North America*. 2017. p. 467–481. <https://doi.org/10.1016/j.iac.2017.03.001>.
11. Hahn J, Hoffmann TK, Bock B, et al. *Angioedema - An interdisciplinary emergency*. *Deutsches Arzteblatt International*. 2017. p. 489–496. <https://doi.org/10.3238/arztebl.2017.0489>.
12. Antúnez C, Martín E, Cornejo-García JA, et al. Immediate Hypersensitivity Reactions to Penicillins and Other Beta-lactams. *Current Pharmaceutical Design*. 2006;12: 3327–3333.
13. Szczeklik A, Nizankowska-Mogilnicka E, Sanak M. Hypersensitivity to Aspirin and Other NSAIDs: Mechanisms, Clinical Presentation and Management. *Drug Hypersensitivity*. Basel, Karger. 2007; 340–349. <https://doi.org/https://doi.org/10.1159/000104211>.
14. Porebski G, Kwiecien K, Pawica M, et al. Mas-Related G Protein-Coupled Receptor-X2 (MRGPRX2) in Drug Hypersensitivity Reactions. *Frontiers in Immunology*. 2018;9. <https://doi.org/10.3389/fimmu.2018.03027>.
15. McNeil BD, Pundir P, Meeker S, et al. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature*. 2015;519(7542): 237–241. <https://doi.org/10.1038/nature14022>.
16. Yuan F, Zhang C, Sun M, et al. MRGPRX2 mediates immediate-type pseudo-allergic reactions induced by iodine-containing iohexol. *Biomedicine and Pharmacotherapy*. 2021;137(January): 111323. <https://doi.org/10.1016/j.biopha.2021.111323>.
17. Stevenson DD. Aspirin and NSAID sensitivity. *Immunology and Allergy Clinics of North America*. 2004;24(3): 491–505. <https://doi.org/10.1016/j.iac.2004.03.001>.
18. Kowalski ML, Stevenson DD. Classification of Reactions to Nonsteroidal Antiinflammatory Drugs. *Immunology and Allergy Clinics of North America*. 2013;33(2): 135–145. <https://doi.org/10.1016/j.iac.2012.10.008>.
19. Kowalski ML, Asero R, Bavbek S, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs.

- Allergy: European Journal of Allergy and Clinical Immunology. 2013;68: 1219–1232. <https://doi.org/10.1111/all.12260>.
20. Kowalski ML, Woessner K, Sanak M. Approaches to the diagnosis and management of patients with a history of nonsteroidal anti-inflammatory drug – related urticaria and angioedema. *Journal of Allergy and Clinical Immunology*. 2015;136(2): 245–251. <https://doi.org/10.1016/j.jaci.2015.06.021>.
  21. Asero R. Intolerance to nonsteroidal anti-inflammatory drugs might precede by years the onset of chronic urticaria. *Journal of Allergy and Clinical Immunology*. 2003;111(5): 1095–1098. <https://doi.org/10.1067/mai.2003.1444>.
  22. Doña I, Blanca-López N, Cornejo-García JA, et al. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: Patterns of response. *Clinical and Experimental Allergy*. 2011;41(1): 86–95. <https://doi.org/10.1111/j.1365-2222.2010.03651.x>.
  23. Hudey SN, Westermann-Clark E, Lockey RF. Cardiovascular and Diabetic Medications That Cause Bradykinin-Mediated Angioedema. *Journal of Allergy and Clinical Immunology: In Practice*. 2017;5(3): 610–615. <https://doi.org/10.1016/j.jaip.2017.03.017>.
  24. Kalambay J, Ghazanfar H, Martes Pena KA, et al. Pathogenesis of Drug Induced Non-Allergic Angioedema: A Review of Unusual Etiologies. *Cureus*. 2017;9(8): e1598. <https://doi.org/10.7759/cureus.1598>.
  25. Kostis WJ, Shetty M, Chowdhury YS, et al. ACE Inhibitor-Induced Angioedema: a Review. *Current Hypertension Reports*. 2017;20(7): 1–7. <https://doi.org/10.1007/s11906-018-0859-x>.
  26. Thalanayar PM, Ghobrial I, Lubin F, et al. Drug-induced visceral angioedema. *Journal of Community Hospital Internal Medicine Perspectives*. 2014;4(4): 25260. <https://doi.org/10.3402/jchimp.v4.25260>.
  27. Davin L, Marechal P, Lancellotti P, et al. *Angioedema: a rare and sometimes delayed side effect of angiotensin-converting enzyme inhibitors*. *Acta Cardiologica*. 2019. p. 277–281. <https://doi.org/10.1080/00015385.2018.1507477>.
  28. Miller DR, Oliveria SA, Berlowitz DR, et al. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. *Hypertension*. 2008;51(6): 1624–1630. <https://doi.org/10.1161/HYPERTENSIONAHA.108.110270>.
  29. Kostis JB, Kim HJ, Rusnak J, et al. Incidence and characteristics of angioedema associated with enalapril. *Archives of Internal Medicine*. 2005;165(14): 1637–1642. <https://doi.org/10.1001/archinte.165.14.1637>.
  30. Brown T, Gonzalez J, Monteleone C. *Angiotensin-converting enzyme inhibitor-induced angioedema: A review of the literature*. *Journal of Clinical Hypertension*. 2017. p. 1377–1382. <https://doi.org/10.1111/jch.13097>.
  31. Elliott WJ. Long-term follow-up of 111 patients with angiotensin-converting enzyme inhibitor-related angioedema. *Yearbook of Cardiology*. 2012;2012: 45–47. <https://doi.org/10.1016/j.ycar.2012.01.097>.
  32. Campbell DJ, Krum H, Esler MD. Losartan increases bradykinin levels in hypertensive humans. *Circulation*. 2005;111(3): 315–320. <https://doi.org/10.1161/01.CIR.0000153269.07762.3B>.
  33. Haymore BR, Yoon J, Mikita CP, et al. Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: A meta-analysis. *Annals of Allergy, Asthma and Immunology*. 2008;101(5): 495–499. [https://doi.org/10.1016/S1081-1206\(10\)60288-8](https://doi.org/10.1016/S1081-1206(10)60288-8).
  34. Makani H, Messerli FH, Romero J, et al. Meta-analysis of randomized trials of angioedema as an adverse event of renin-angiotensin system inhibitors. *American Journal of Cardiology*. 2012;110(3): 383–391. <https://doi.org/10.1016/j.amjcard.2012.03.034>.
  35. Telmisartan T, Assessment R. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *The Lancet*. 2008;372(9644): 1174–1183. [https://doi.org/10.1016/S0140-6736\(08\)61242-8](https://doi.org/10.1016/S0140-6736(08)61242-8).
  36. Rasmussen ER, Pottegård A, Bygum A, et al. Angiotensin II receptor blockers are safe in patients with prior angioedema related to angiotensin-converting enzyme inhibitors – a nationwide registry-based cohort study. *Journal of Internal Medicine*. 2019;285(5): 553–561. <https://doi.org/10.1111/joim.12867>.
  37. White WB, Bresalier R, Kaplan AP, et al. Safety and tolerability of the direct renin inhibitor aliskiren: A Pooled analysis of clinical experience in more than 12,000 patients with hypertension. *Journal of Clinical Hypertension*. 2010;12(10): 765–775. <https://doi.org/10.1111/j.1751-7176.2010.00352.x>.
  38. Toh S, Reichman ME, Houstoun M, et al. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. *Archives of Internal Medicine*. 2012;172(20): 1582–1589. <https://doi.org/10.1001/2013.jamainternmed.34>.
  39. McMurray JJV, Packer M, Desai AS, et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: Rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact. *European Journal of Heart Failure*. 2013;15(9): 1062–1073. <https://doi.org/10.1093/eurjhf/hft052>.
  40. Beitzke M, Ottomeyer C, Hennerici MG, et al. Raising Awareness of Orolingual Angioedema as a Complication of Thrombolysis in Acute Stroke Patients. 2009; 307–309. <https://doi.org/10.1159/000201558>.



41. Walls RM, Pollack C V. CASE REPORT Successful Cricot-hyrotomy After Thrombolytic Therapy for Acute Myocardial Infarction : A Report of Two Cases. 2000;(February): 188–191.
42. Agostoni A, Gardinali M, Frangi D, Cafaro C, Conciato L, Sponzilli C, Salvioni A, Cugno M CM. Activation of Complement and Kinin Systems After Thrombolytic Therapy in Patients With Acute Myocardial Infarction A Comparison Between Streptokinase and Recombinant. *Circulation*. 1994; 2666–2671.
43. Southward J, Irvine E, Rabinovich M. Probable Amlodipine-Induced Angioedema. 2009;43. <https://doi.org/10.1345/aph.1L527>.
44. Turcu AF, White JA, Kulaga ME, et al. Calcium Channel Blocker-associated Small Bowel Angioedema. 2009;43(4): 338–341.
45. Mahé E, Kreis H. Angioedema in Renal Transplant Recipients on Sirolimus. 2007;2006: 205–209. <https://doi.org/10.1159/000099584>.
46. Mackenzie M, Wood LA. Lingual angioedema associated with everolimus. 2010;(August 2009): 107–109. <https://doi.org/10.3109/02841860903246599>.
47. Burches E, Ferrer M. Amiodarone-induced angioedema Is alternative medicine acceptable in allergology ? 1988; 1199–1200.
48. Tal A Der. Angioedema Following the Intravenous Administration of Metoprolol \*. 1990; 1922–1923. <https://doi.org/10.1378/chest.106.6.1922>.
49. Talaei A, Rad SF, Moghani MB, et al. Acquired Angioedema Induced by Risperidone. 2018;12(3): 2016–2018. <https://doi.org/10.17795/ijpbs-4807>.Case.
50. Sendur OF, Turan Y, Berkit IK, et al. Angio-oedema in a Patient Treated with Etanercept for Rheumatoid Arthritis. 2009; 488–490. <https://doi.org/10.1111/j.1742-7843.2009.00401.x>.