

BÖLÜM

GÖZ HASTALIKLARI FARMAKOLOJİSİ

12

Dr. Öğr. Üyesi Özgün Melike GEDAR TOTUK¹

İnsan gözü birçok embriyolojik kökene sahiptir: lens ektodermden, retina ve optik sinir ön beyinden, aksesuar yapılar mezenşimden kaynaklanır. Gözün, özellikle bir duyusal organ olarak benzersizliği görme işlevidir. Bununla birlikte göz, kardiyovasküler, nöronal ve diğer sistemlerin küçük bir örneğidir. Nispeten küçük olmasına rağmen, göz aşırı derecede karmaşık bir organdır. Gözün ebatları da önemlidir, çünkü miyopi veya konjenital glokomda olduğu gibi daha büyük bir göz, görme fonksiyonunu azaltabilir ve hastayı körlük veya retina dekolmanı gibi risklerle karşılaşır.

Kornea ve lens arasındaki ve lens ile retina arasındaki sıvı, düzgün bir görüntü elde etmek için saydam olmalıdır. Normalde kornea ve lensin kan damarları yoktur, besinler etraflarında dolaşan hava ve sıvı yoluyla temin edilir. Göze giden kan akımı karmaşıktr: hem oftalmik arter hem de koroidal pleksus tarafından kan akımı sağlanır. Özellikle koroid, vücuttaki en vasküler alanlardan biridir ve birim alana düşen kan akımı çok yüksektir. Oftalmik arter içindeki kan akışının düzenlenmesi karmaşıktr, çünkü sadece sistemik kan basıncına değil, aynı zamanda kan damarlarını daraltabilecek ve akışı engelleyebilecek göz içi basıncına da (GİB) bağlıdır.

Retina, hem gündüz hem gece yüksek çözünürlüklü görüş için, hem de renkli görme için fazlaca hücre yapısına sahiptir. Diğer omurgalılarda olduğu gibi, insan retinalarının çoğunluğu düşük çözünürlüklü siyah-beyaz çevresel görüşe sahiptir. Sadece küçük bir santral alan okuma gibi aktif görevlerle uğraşır.

¹ Dr. Öğretim Üyesi Bahçeşehir Üniversitesi Tıp Fakültesi Göz hastalıkları Anabilim Dalı

nin klinik kullanım endikasyonları antikolinerjik ilaçlar gibidir. Midriyazise ikincil dar açılı hastada AKG'nu tetikleyebilir. İris dilatator kasının kontraksiyonu pigment granüllerinin ön kamaraya dağılmasına yol açabilir. Gözde ağrı, korneada bulanıklık ve kaş ağrısı yapabilir. Nadiren sistemik toksisiteye yol açacak kadar absorbe olur, kardiyovasküler yan etkiler (hipertansiyon, ventriküler aritmi, kardiyak arrest gibi) önemlidir. Diğer yan etkiler terleme, solukluk, titreme, ajitasyon ve konfüzyondur.

Muskarinik Antagonistler - Midriyazis ve Siklopeji			Midriyasız	Siklopeji
Jenerik İsmi	Marka İsmi	Solusyonun konsantrasyonu (%)	Maksimum etki (dakika) / Düzeltme (gün)	Maksimum etki (dakika) / Düzeltme (gün)
Atropin	Generic Only	0.5, 1	30-40 / 7-12	60-180 / 6-12
Siklopentolat	AK-Pentolate, Cyclogyl	0.5, 1, 2	30-60 / 1	25-76 / 0.25-1
Homatropin	Isopto Homatropine	2, 5	40-60 / 1-3	30-60 / 1-3
Skopolamin	Isopto Hyoscine	0.25	20-30 / 1-3	30-60 / 3-7
Tropikamid	Tropicacyl, Opticetyl, Mydriacyl	0.5, 1	20-40 / 0.25	20-35 / <0.25

KAYNAKLAR

1. Goss CM. The Organs of the Senses, 29th ed. Philadelphia: Lea & Febiger, 1973.
2. Novack GD. Ophthalmic drug delivery: development and regulatory considerations. Clin Pharmacol Ther. 2009;85:539–543.
3. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. Annu Rev Pharmacol Toxicol. 2011;52:275–301.
4. Stone JL, Robin AL, Novack GD, Covert D, Cagle GD. And Objective evaluation of eye-drop instillation in glaucoma patients. Arch Ophthalmol. 2009;127:732–736.
5. Edman P. Biopharmaceutics of Ocular Drug Delivery (Pharmacology and Toxicology). Boca Raton, FL: CRC Press; 1993.

6. Sleath B, Blalock SJ, Carpenter DM, et al. Ophthalmologist-patient communication, self-efficacy, and glaucoma medication adherence. *Ophthalmology*. 2015; 122:748–754.
7. Baudouin C, Labbe A, Liang H, Pauly A, Brignole-Baudouin F. Preservatives in eyedrops: the good, the bad and the ugly. *Prog Retin Eye Res*. 2010; 29:312–334.
8. Brown RH, Novack GD. General principles of ophthalmic medications. In: Morrison J, Pollack I, eds. *Glaucoma: Science and Practice*. New York: Thieme Publishing Company, 2002;354–362.
9. Covert D, Robin AL, Novack GD. Systemic medications and glaucoma patients (letter). *Ophthalmology*. 2005; 112:1849–1853.
10. Zhang T, Xiang CD, Gale D, Carreiro S, Wu EY, Zhang EY. Drug transporter and cytochrome P450 mRNA expression in human ocular barriers: implications for ocular drug disposition. *DrugMetab Dispos*. 2008; 36:1300–1307.
11. Kraft ME, Glaeser H, Mandery K, et al. The prostaglandin transporter OATP2A1 is expressed in human ocular tissues and transports the antiglaucoma prostanoid latanoprost. *Invest Ophthalmol Vis Sci*. 2010;51: 2504–2511.
12. Van Buskirk EM. Adverse reactions from timolol administration. *Ophthalmology*. 1980; 87:447–450.
13. Nordlund JR, Pasquale LR, Robin AL, et al. The cardiovascular, pulmonary, and ocular hypotensive effects of 0,2% brimonidine. *Arch Ophthalmol*. 1995; 113:77–83.
14. Streilein JW. Ocular immune privilege: therapeutic opportunities from an experiment of nature. *Nat Rev Immunol*. 2003; 3:879–889.
15. Novack GD. Pipeline: thoughts generated by the Annual Meeting of the American Society of Clinical Pharmacology and Therapeutics. *Ocul Surf*. 2004; 2:212–214.
16. Perlee LT, Bansal AT, Gehrs K, et al. Inclusion of genotype with fundus phenotype improves accuracy of predicting choroidal neovascularization and geographic atrophy. *Ophthalmology*. 2013; 120:1880–1892.
17. Fauser S, Lambrou GN. Genetic predictive biomarkers of anti-VEGF treatment response in patients with neovascular age-related macular degeneration. *Surv Ophthalmol*. 2015; 60:138–152.
18. Ciulla TA, Starr MB, Maskit S. Bacterial endophthalmitis prophylaxis for cataract surgery: an evidence-based update. *Ophthalmology*. 2002; 109:13–24.
19. Group EES. Prophylaxis of postoperative endophthalmitis following cataract surgery: results of the ESCRS multicenter study and identification of risk factors. *J Cataract Refract Surg*. 2007; 33:978–988.
20. Shorstein NH, Winthrop KL, Herrinton LJ. Decreased postoperative endophthalmitis rate after institution of intracameral antibiotics in a Northern California eye department. *J Cataract Refract Surg*. 2013;39:8–14.
21. Packer M, Chang DF, Dewey SH, et al. Prevention, diagnosis, and management of acute postoperative bacterial endophthalmitis. *J Cataract Refract Surg*. 2011; 37:1699–1714.
22. Buehler PO, Schein OD, Stamler JF, Verdier DD, Katz J. The increased risk of ulcerative keratitis among disposable soft contact lens users. *Arch Ophthalmol*. 1992; 110:1555–1558.
23. Bullock JD, Warwar RE, Elder BL, Northern WI. Temperature instability of ReNu With MoistureLoc: a new theory to explain the worldwide *Fusarium* keratitis epidemic of 2004–2006. *Arch Ophthalmol*. 2008; 126:1493–1498.

24. Martin DF, Parks DJ, Mellow SD, et al. Treatment of cytomegalo-virus retinitis with an intraocular sustained-release ganciclovir implant. *Arch Ophthalmol.* 1994; 112:1531–1539
25. Musch DC, Martin DF, Gordon JF, Davis MD, Kuppermann BD. Treatment of cytomegalovirus retinitis with a sustained-release ganciclovir implant. The Ganciclovir Implant Study Group. *N Engl J Med.* 1997; 337:83–90.
26. Group TVS. A randomized controlled clinical trial of intravitreous fomivirsen for treatment of newly diagnosed peripheral cytomegalovirus retinitis in patients with AIDS(1). *Am J Ophthalmol.* 2002;133:467–474.
27. Foulks GN. DEWS report: a mission completed. *Ocul Surf.* 2007;5:65–66.
28. Nichols KK, Foulks GN, Bron AJ, et al. The international workshop on meibomian gland dysfunction: executive summary. *Invest Ophthalmol Vis Sci.* 2011; 52:1922–1929.
29. Smith JA, Albeitz J, Begley C, et al. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf.* 2007; 5:93–107.
30. Sullivan DA, Hammitt KM, Schaumberg DA, et al. Report of the TFOS/ARVO Symposium on Global Treatments for Dry Eye Disease: an unmet need. *Ocul Surf.* 2012; 10:108–116.
31. Pflugfelder SC, Geerling G, Kinoshita S, et al. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf.* 2007; 5:163–178.
32. Novack GD. Pipeline: why aren't there more pharmacotherapies for dry eye. *Ocul Surf.* 2014; 12:227–230.
33. Sheppard JD, Torkildsen GL, Lonsdale JD, et al. Lifitegrast ophthalmic solution 5.0% for treatment of dry eye disease: results of the OPUS-1 phase 3 study. *Ophthalmology.* 2014; 121:475–483.
34. Friedman DS, Wolfs RC, O'Colmain BJ, et al. Prevalence of open-angle glaucoma among adults in the United States. *Arch Ophthalmol.* 2004; 122:532–538.
35. Jiang X, Varma R, Wu S, et al. Baseline risk factors that predict the development of open-angle glaucoma in a population: the Los Angeles Latino Eye Study. *Ophthalmology.* 2012; 119:2245–2253.
36. Hochberg C, Maul E, Chan ES, et al. Association of vision loss in glaucoma and age-related macular degeneration with IADL disability. *Invest Ophthalmol Vis Sci.* 2012; 53:3201–3206.
37. Ramulu P. Glaucoma and disability: which tasks are affected, and at what stage of disease? *Curr Opin Ophthalmol.* 2009; 20:92–98.
38. Kass MA, Heuer DK, Higginbotham EJ, et al. for the Ocular Hypertension Treatment Study Group. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol.* 2002; 120:701–713.
39. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the early manifest glaucoma trial. *Arch Ophthalmol.* 2002; 120:1268–1279.
40. Group GLTR. The Glaucoma Laser Trial (GLT) and Glaucoma Laser Trial follow-up study: 7. Results. *Am J Ophthalmol.* 1995;120:718–731.

41. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology*. 2001; 108:1943–1953.
42. Panel AAO. Preferred Practice Pattern: Primary Open-Angle Glaucoma. San Francisco, CA: American Academy of Ophthalmology; 2010. <http://www.aao.org/preferred-practice-pattern/pri-mary-openangle-glaucoma-ppp--october-2010>.
43. Panel AAO. Preferred Practice Pattern: Primary Open-Angle Glaucoma Suspect. San Francisco, CA: American Academy of Ophthalmology; 2010. <http://www.aao.org/preferred-practice-pattern/primary-openangle-glaucoma-suspect-ppp--october-20>.
44. Society EG. Terminology and Guidelines for Glaucoma, 4th ed. Savona, Italy: Publ-Comm; 2014
45. Singh K, Sit AJ. Intraocular pressure variability and glaucoma risk: complex and controversial. *Arch Ophthalmol*. 2011; 129:1080–1081.
46. Gedde SJ, Schiffman JC, Feuer WJ, Herndon LW, Brandt JD, Budenz DL. Treatment outcomes in the tube versus trabeculectomy (TVT) study after five years of follow-up. *Am J Ophthalmol*. 2012;153:789–803.
47. Budenz DL, Barton K, Feuer WJ, et al. Treatment outcomes in the Ahmed Baerveldt Comparison Study after 1 year of follow-up. *Ophthalmology*. 2011; 118:443–452.
48. Robin AL, Ramakrishnan R, Krishnadas R, et al. A long-term dose-response study of mitomycin in glaucoma filtration surgery. *Arch Ophthalmol*. 1997; 115:969–974.
49. Goldmann H. Out-flow pressure, minute volume and resistance of the anterior chamberflow in man. *Doc Ophthalmol Adv Ophthalmol*. 1951; 5-6:278–356.
50. Brubaker RF. Goldmann's equation and clinical measures of aqueous dynamics. *Exp Eye Res*. 2004; 78:633–637.
51. Bacharach J, Dubiner HB, Levy B, Kopczynski CC, Novack GD, Group A-CS. Double-masked, randomized, dose-response study of AR-13324 vs. latanoprost in patients with elevated intraocular pressure. *Ophthalmology*. 2015; 122:302–307.
52. Kiel JW, Kopczynski C. Effect of AR-13324 on episcleral venous pressure in Dutch belted rabbits. *J Ocul Pharmacol Ther*. 2015;31:146–151.
53. Wang R-F, Williamson JE, Kopczynski C, Serle JB. Effect of 0.04%AR-13324, a ROCK and norepinephrine transporter inhibitor, on aqueous humor dynamics in normotensive monkey eyes. *J Glaucoma*. 2015; 24:51–54.
54. Williams RD, Novack GD, van Haarlem T, Kopczynski C; AR-12286 Phase 2A Study Group. Ocular hypotensive effect of the Rhokinase inhibitor AR-12286 in patients with glaucoma and ocular hypertension. *Am J Ophthalmol*. 2011; 152:834–841.e1.
55. Tanihara H, Inoue T, Yamamoto T, Kuwayama Y, Abe H, Araie M. Phase 2 randomized clinical study of a rho kinase inhibitor, K-115, in primary open-angle glaucoma and ocular hypertension. *Am J Ophthalmol*. 2013; 156:731–736.
56. Tanihara H, Inatani M, Honjo M, Tokushige H, Azuma J, Araie M. Intraocular pressure-lowering effects and safety of topical administration of a selective ROCK inhibitor, SNJ-1656, in healthy volunteers. *Arch Ophthalmol*. 2008; 126:309–315.
57. Toris CB, Camras CB, Yablonski ME. Effects of PhXA41, a new prostaglandin F2 alpha analog, on aqueous humor dynamics in human eyes. *Ophthalmology*. 1993; 100:1297–1304.

58. Weinreb RN, Toris CB, Gabelt BT, Lindsey JD, Kaufman PL. Effects of prostaglandins on the aqueous humor outflow pathways. *Surv Ophthalmol.* 2002;47 Suppl 1: S53–S64.
59. Schenker HW, Yablonski ME, Podos SM, et al. Fluorophotometric study of epinephrine and timolol in human subjects. *Arch Ophthalmol.* 1981; 99:1212–1226.
60. Coakes RL, Brubaker RF. The mechanism of timolol in lowering intraocular pressure. *Arch Ophthalmol.* 1978; 96:2045–2048.
61. Strahlman E, Tipping R, Vogel R. A double-masked, randomized 1-year study comparing dorzolamide (Trusopt), timolol, and betaxolol. International Dorzolamide Study Group. *Arch Ophthalmol.* 1995; 113:1009–1016.
62. Adamsons I, Clineschmidt C, Polis A, et al. The efficacy and safety of dorzolamide as adjunctive therapy to timolol maleate gel solution in patients with elevated intraocular pressure. *J Glaucoma.* 1998; 7:253–260.
63. Lichter PR, Newman LP, Wheeler NC, Beall OV. Patient tolerance to carbonic anhydrase inhibitors. *Am J Ophthalmol.* 1978; 85:495–502.
64. Gharagozloo NZ, Relf SJ, Brubaker RF. Aqueous flow is reduced by the alpha-adrenergic agonist, apraclonidine hydrochloride (ALO2145). *Ophthalmology.* 1988; 95:1217–1220.
65. Robin AL. The role of apraclonidine hydrochloride in laser therapy for glaucoma. *Trans Am Ophthalmol Soc.* 1989; 87:729–761.
66. Toris CB, Gleason ML, Camras CB, Yablonski ME. Effects of brimonidine on aqueous humor dynamics in human eyes. *Arch Ophthalmol.* 1995; 113:1514–1517.
67. Novack GD. Medicinal cannabis for glaucoma. *Curr Opin Ophthalmol.* in press.
68. Robin AL, Novack GD, Covert DW, Crockett RS, Marcic TS. Adherence in glaucoma: objective measurements of once-daily and adjunctive medication use. *Am J Ophthalmol.* 2007; 144:533–540.
69. Novack GD. Pipeline: what does it mean when a company says that a product is “approvable”? *Ocul Surf.* 2005; 3:63–64.
70. Jesner S. Der humor aqueus des Auges in seinen beziehungen zubleutdruck und nerventreizung. *Pflugers Arch Eur J Physiol.* 1880;23:14–44.
71. Feldman-Billard S, Dupas B, Sedira N, et al. Hypoglycaemia is associated with the absence of a decrease in diurnal macular thickness in patients with diabetic macular oedema. *Diabetes Metab.* 2013;39:169–173.
72. Yablonski ME, Burde RM, Kolker AE, Becker B. Cataracts induced by topical dexamethasone in diabetics. *Arch Ophthalmol.* 1978;96:474–476.
73. Fairbairn WD, Thorson JC. Fluorometholone: anti-inflammatory and intraocular pressure effects. *Arch Ophthalmol.* 1971;86:138–141.
74. Bodor N. Soft drugs: principles and methods for the design of safe drugs. *Med Res Rev.* 1984;4:449–469.
75. Novack GD. Pipeline: decoding the package insert: indications. *Ocul Surf.* 2003;1:150–151.
76. Cannan RK. The Drug Efficacy Study of the National Research Council's Division of Medical Sciences, 1966–1969, 1968. Washington, DC: National Academy of Sciences. <http://www.nasonline.org/about-nas/history/archives/collections/des-1966-1969-1.html?referrer=https://www.google.com/>.
77. Jaffe GJ, Ben Nun J, Guo H, Dunn JP, Ashton P. Fluocinolone acetonide sustained drug delivery device to treat severe uveitis. *Ophthalmology.* 2000;107:2024–2033.

78. Lowder C, Belfort R Jr, Lightman S, et al. Dexamethasoneintravitreal implant for noninfectious intermediate or posterioruveitis. Arch Ophthalmol. 2011;129:545–553.
79. Keates RH, McGowan KA. Clinical trial offlurbiprofen to maintainpupillary dilation during cataract surgery. Ann Ophthalmol.1984;16:919–921.
80. Flach AJ, Dolan BJ, Irvine AR. Effectiveness of ketorolactromethamine 0.5% ophthalmic solution for chronic aphakic andpseudophakic cystoid macular edema. Am J Ophthalmol. 1987;103:479–486.
81. Flach AJ, Stegman RC, Graham J, Kruger LP. Prophylaxis ofaphakic cystoid macular edema without corticosteroids. Ophthal-mology. 1990;97:1253–1258.
82. Liesegang TJ.Viscoelastics. Int Ophthalmol Clin. 1993;33:127–147.
83. Bainbridge JW, Mehat MS, Sundaram V, et al. Long-term effect ofgene therapy on Leber's congenital amaurosis. N Engl J Med.2015;372:1887–1897.
84. Barnard AR, Groppe M, MacLaren RE. Gene therapy forchoroideremia using an adeno-associated viral (AAV) vector. Cold Spring Harb Perspect Med. 2015;5:a017293.85.
85. Haller JA, Stalmans P, Benz MS, et al. Efficacy of intravitrealocriplasmin for treatment of vitreomacular adhesion: subgroupanalyses from two randomized trials. Ophthalmology. 2015;122:117–122.
86. AREDS. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDSReport no. 8. Arch Ophthalmol. 2001;119:1417–1436.
87. TAP Study Group. Photodynamic therapy of subfoveal choroidalneovascularization in age-related macular degeneration withverteporfin: one-year results of 2 randomized clinical trials—TAP report 1. Arch Ophthalmol. 1999;117:1329–1345.
88. Bressler SB, Qin H, Melia M, et al. Exploratory analysis of theeffect of intravitreal ranibizumab or triamcinolone on worsening ofdiabetic retinopathy in a randomized clinical trial. JAMA Ophthalmol. 2013;131:1033–1040.
89. Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. Ophthalmology. 1980;87:1044–1049.
90. Frueh BR, Felt DP, Wojno TH, Musch DC. Treatment ofblepharospasm with botuli-num toxin. A preliminary report. ArchOphthalmol. 1984;102:1464–1468.
91. Chia A, Chua WH, Wen L, Fong A, Goon YY, Tan D. Atropinefor the treatment of childhood myopia: changes after stoppingatropine 0.01%, 0.1%, and 0.5%.Am J Ophthalmol. 2014;157:451–457.
92. Siatkowski RM, Cotter SA, Crockett RS, Miller JM, Novack GD,Zadnik K. Two-ye-ar multicenter, randomized, double-masked,placebo-controlled, parallel safety and efficacy study of 2%pirenzepine ophthalmic gel in children with myopia.J AA-POS.2008;12:332–339.
93. Tan DTH, Lam DS, Chua WH, Shu-Ping DF, Crockett RS, GroupAPS. One-year multi-center, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gelin children with myopia.Ophthalmology. 2005;112:84–91.
94. Repka MX, Kraker RT, Holmes JM, et al. Atropine vs patching fortreatment of moderate amblyopia: follow-up at 15 years of age of arandomized clinical trial.JAMA Ophthalmol. 2014;132:799–805.
95. Gary D. Novack, Alan L. Robin. Ocular Pharmacology The Journal of Clinical Pharmacology 2016; 56(5):517-527