

OPIOİDLER

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ÖZET

Opioidler kanser ağrısının farmakolojik tedavisinin temelini oluştururlar. Bununla beraber kanser ağrısında opioidlerin standart dozları, tavan etkileri ve maksimum dozları yoktur. Hastaya göre titre edilir ve tolere edilebilen yan etkilerle ağrıyı kontrol eden etkin doz belirlenir. Kanser ağrı tedavisinde kullanılan opioidlere bağlı yan etkiler oldukça yaygındır ve çoğu zaman önceden tahmin edilebilir. Yan etkilerin birçoğuna tolerans gelişmektedir. Bu nedenle opioidlerin titre edilerek kullanımı, düşük dozdan başlanması, hasta ve yakınlarının yan etkiler ve bunlarla nasıl baş etmeleri gerektiği konusunda bilgilendirilmeleri çok önemlidir.

GİRİŞ

Opioidler, papaver somniferum bitkisinden elde edilen opium'dan (afyon) türetilmiştir (1, 2) ve bilinen en güçlü analjezik ajanlardır. Opium, afyon tohumundan elde edilen alkaloid karışımını ifade eder. Opiat terimi morfin veya kodein gibi doğal olarak oluşan alkaloidleri tanımlar. Opioid ise opioid reseptörleri üzerine etki eden tüm bileşiklerini tanımlamak için kullanılır. Narkotik ifadesi stupor tarif eden yunanca bir kelimedir ve temel olarak uyku için kullanılan ilaçları tanımlamak için kullanılmıştır. Daha sonra opioidleri tanımlamak için kullanılmışsa da kötüye kullanımı ifade eden adli bir terimdir (3).

1980'li yıllardan önce opioidler özellikle terminal dönem kanser hastalarında tercih edilmekteydi. 1986 yılında Dünya Sağlık Örgütü'nün (DSÖ) üç basamaklı merdiven sistemi ile farmakolojik tedavi ve opioidler kanser ağrısı tedavisinde yapıtaşı olarak kabul edilmiştir. Kanser ağrısı tedavisinde temel ilkeler; optimal ağrı kontrolü sağlamak, bunu sağlarken yan etkilerin minimal olması, hastanın hem fizyolojik hem de psikolojik olarak iyilik hâlini sürdürmek ve yaşam kalitesini yükseltmek olmalıdır. Tüm bunları sağlamak için multimodal ve multidisipliner yaklaşımlar gerekir. Multimodal tedavide farmakoterapi önemli bir yer alır. Ağrının şiddeti analjezik gereksiniminin derecesini belirler. Opioid

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Tablo 12. Epidural hasta kontrollü analjezi

İlaçlar	Bolus doz (ml)	Bazal infüzyon (ml)	Kilitli kalma süresi (dk)
Bupivakain/levobupivakain %0.1-0.125 veya ropivakain %0.2 + fentanil 2-3 µg/ml	5	4	15
Bupivakain/levobupivakain %0.1-0.125 veya ropivakain %0.2 + morfin 0.05-0.1 mg/ml	3	4	15

Tablo 13. İntratekal ilaçların önerilen başlama ve maksimum dozları

İlaçlar	Önerilen başlama dozu	Günlük maksimum doz
Morfin	0.1–0.5 mg/gün	15 mg
Hidromorfon	0.01–0.15 mg/gün	10 mg
Fentanil	25–75 mcg/gün	1000 mcg
Sufentanil	10–20 mcg/gün	500 mcg
Bupivakain	0.01–4 mg/gün	15–20 mg
Klonidin	20–100 mcg/gün	600 mcg
Zikonotid	0.5–1.2 mcg/gün	19.2 mcg

(83). İntratekal uygulama için yaygın olarak kullanılan birçok ilaç mevcuttur. Bu ilaçlardan morfin ve zikonotid FDA tarafından ağrı için onay almıştır. Polianaljezik Konsensüs Konferansı (PACC), intratekal analjeziklerin akılcı kullanımına ilişkin öneriler geliştirmiştir. PACC tarafından intratekal kullanım için tavsiye edilen başlangıç ve maksimum ilaç dozları Tablo 13'te özetlenmiştir. Klasik yan etkiler; kaşıntı, bulantı, kusma, idrar retansiyonu ve solunum depresyonudur. Bununla beraber yan etkilerin çoğu doz bağımlıdır. Ayrıca uzun dönem intratekal opioid kullanımına bağlı granüloma da görülebilmektedir (84).

Diğer yollardan uygulanan opioidlere yanıt vermeyen kanser hastalarında intraventriküler uygulama denenmiştir. Bu ilaç verme yöntemi için Omma-ya rezervuarı kullanılmıştır (85).

KAYNAKLAR

1. Başar HT. (2016) Opioidler. Güneş Tıp Kitabevleri.
2. Sinatra RS, McQuay H. (2009). Oral and parenteral opioid analgesics for acute pain management. Sinatra RS, de Leon-Cassasola OA, Viscusi ER, Ginsberg B. (Eds.) Acute Pain Management. (pp.188-203) Cambridge: Cambridge University Press.
3. Trescot AM, Datta S, Lee M, et al. Opioid pharmacology Pain Physician 2008;11: S133-153.
4. Turhan SÇ. Postoperatif ağrı tedavisi. Türkiye Klinikleri J Anest Reanim-Special Topics 2008;1(3);117-122.
5. Barkin RL, Iusco AM, Barkin SJ. (2006). Opioids used in primary care for the management of pain: a pharmacologic, pharmacotherapeutic, and pharmacodynamic overview. In: Boswell MV, Cole BE. (Eds.), Weiner's pain management: a practical guide for clinicians, (7th ed. pp.789-804). New York:CRP Press/Taylor & Francis group.
6. Butterworth J, Mackey D, Wasnick J. (2015). Klinik Anesteziyoloji (Çev. Ed. Cuhruk H.), (5. Baskı, s.309-328). Ankara:Güneş Kitabevi.
7. Keskinbora K. (2007) Opioid Analjezikler. Erdine S. (Ed). Ağrı. İstanbul: Nobel Tıp Kitabevleri.
8. Ayten Saraçoğlu BŞÇ. Opioidlerle indüklenen hiperaljezi. Türkiye Klinikleri J Anest Reanim 2014;12(1):31-38.
9. Lee HJ, Yeomans DC. Opioid induced hyperalgesia in anesthetic settings. Korean Journal of Anesthesiology 2014;67:299-304. doi: 10.4097/kjae.2014.67.5.299.

10. Dhaliwal A, Gupta M. (2021) Physiology, Opioid Receptor. StatPearls: StatPearls Publishing.
11. Han W, Ide S, Sora I, et al. A possible genetic mechanism underlying individual and interstrain differences in opioid actions: focus on the mu opioid receptor gene. *Annals of the New York Academy of Sciences* 2004;1025:370-375. doi: 10.1196/annals.1307.045.
12. Overholser BR, Foster DR. Opioid pharmacokinetic drug-drug interactions. *The American Journal of Managed Care* 2011;17:S276-287.
13. Smith HS. Opioid metabolism. *Mayo Clinic Proceedings* 2009;84(7):613-624. doi: 10.1016/S0025-6196(11)60750-7.
14. Eichelbaum M, Ingelman-Sundberg M, Evans WE. Pharmacogenomics and individualized drug therapy. *Annu Rev Med* 2006;57:119-137. doi: 10.1146/annurev.med.56.082103.104724.
15. Ingelman-Sundberg M, Sim SC, Gomez A, et al. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoeconomic and clinical aspects. *Pharmacology & Therapeutics* 2007;116:496-526. doi: 10.1016/j.pharmthera.2007.09.004.
16. Kiang TK, Ensom MH, Chang TK. UDP-glucuronosyltransferases and clinical drug-drug interactions. *Pharmacology & Therapeutics* 2005;106:97-132. doi: 10.1016/j.pharmthera.2004.10.013.
17. Kilpatrick GJ, Smith TW. Morphine-6-glucuronide: Actions and mechanisms. *Medicinal Research Reviews* 2005;25:521-544. doi: 10.1002/med.20035.
18. Projean D, Morin P-E, Tu T, et al. Identification of CYP3A4 and CYP2C8 as the major cytochrome P450 s responsible for morphine N-demethylation in human liver microsomes. *Xenobiotica* 2003;33: 841-854. doi: 10.1080/0049825031000121608.
19. Vree T, Van Dongen R, Koopman-Kimenai P. Codeine analgesia is due to codeine-6-glucuronide, not morphine. *International Journal of Clinical Practice* 2000;54:395-398.
20. Mikus G, Bochner F, Eichelbaum M, et al. Endogenous codeine and morphine in poor and extensive metabolisers of the CYP2D6 (debrisoquine/sparteine) polymorphism. *Journal of Pharmacology and Experimental Therapeutics* 1994;268:546-551.
21. Labroo RB, Paine MF, Thummel KE, et al. Fentanyl metabolism by human hepatic and intestinal cytochrome P450 3A4: implications for interindividual variability in disposition, efficacy, and drug interactions. *Drug Metabolism and Disposition* 1997;25:1072-1080.
22. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clinical Pharmacokinetics* 2004;43:879-923. doi: 10.2165/00003088-200443130-00004.
23. Grönlund J, Saari TI, Hagelberg NM, et al. Exposure to oral oxycodone is increased by concomitant inhibition of CYP2D6 and 3A4 pathways, but not by inhibition of CYP2D6 alone. *British Journal of Clinical Pharmacology* 2010;70:78-87. doi: 10.1111/j.1365-2125.2010.03653.x.
24. Collier JK, Christrup LL, Somogyi AA. Role of active metabolites in the use of opioids. *European Journal of Clinical Pharmacology* 2009;65: 121-139. doi: 10.1007/s00228-008-0570-y.
25. King S, Forbes K, Hanks G, et al. A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: a European Palliative Care Research Collaborative opioid guidelines project. *Palliative Medicine* 2011;25:525-552. doi: 10.1177/0269216311406313.
26. Bosilkovska M, Walder B, Besson M, et al. Analgesics in patients with hepatic impairment. *Drugs* 2012;72:1645-1669. doi: 10.2165/11635500-000000000-00000.
27. Peechakara BV, Gupta M. Codeine. *StatPearls*. StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC., Treasure Island (FL), 2022.
28. Jin J. Risks of codeine and tramadol in children. *Jama* 2017;318:1514-1514. doi: 10.1001/jama.2017.13534.
29. Nosek K, Leppert W, Puchala Ł, et al. Efficacy and Safety of Topical Morphine: A Narrative Review. *Pharmaceutics* 2022;14(7):1499. doi: 10.3390/pharmaceutics14071499.
30. Charles E. Inturrisi DSC, Arthur G. Lipman. (2018). Opioid Analgesics. Ballantyne JC (5.ed). *Bonica's Management of Pain*. Wolters Kluwer.
31. Pergolizzi Jr. JV, Seow-Choen F, Wexner SD, et al. Perspectives on Intravenous Oxycodone for Control of Postoperative Pain. *Pain Practice* 2016;16:924-934. doi: 10.1111/papr.12345.
32. Choi BM. A new therapeutic option for postoperative pain management with oxycodone HCl injection. *Korean Journal of Anesthesiology* 2016;69:211-218. doi: 10.4097/kjae.2016.69.3.211.
33. Sadiq NM, Dice TJ, Mead T. Oxycodone. *StatPearls*. StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC., Treasure Island (FL), 2022.
34. Lussier D, Richarz U, Finco G. Use of hydromorphone, with particular reference to the OROS® formulation, in the elderly. *Drugs & Aging* 2010;27:327-335. doi: 10.2165/11318320-000000000-00000.
35. Furlan AD, Reardon R, Weppler C. Opioids for chronic noncancer pain: a new Canadian practice guideline. *Cmaj* 2010;182:923-930. doi: 10.1503/cmaj.100187.
36. Reisli, R. Kronik bel-boyun ağrılı hastada opioid analjezikler. *TOTBİD Dergisi* 2017;16:139-147. doi: 10.14292/totbid.dergisi.2017.21.
37. Leppert W. Tramadol as an analgesic for mild to moderate cancer pain. *Pharmacological Reports* 2009;61:978-992. doi: 10.1016/s1734-1140(09)70159-8.
38. Tamaskar R, Parran Jr TV, Heggi A, et al. Tramadol versus buprenorphine for the treatment of opiate withdrawal: a retrospective cohort control study. *Journal of Addictive Diseases* 2004;22:5-12. doi: 10.1300/j069v22n04_02.
39. Dhesi M, Maldonado KA, Maani CV. Tramadol. *StatPearls*. StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC., Treasure Island (FL), 2022.
40. Hudak ML, Tan RC. Neonatal drug withdrawal. *Pediatrics* 2012;129: e540-560. doi: 10.1542/peds.2011-3212.
41. Jordan MR, Morrisonponce D. Naloxone. *StatPearls*. StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC., Treasure Island (FL), 2022.
42. Singh D, Saadabadi A. Naltrexone. *StatPearls*. StatPear-

- ls Publishing Copyright © 2022, StatPearls Publishing LLC., Treasure Island (FL), 2022.
43. Yaksh T, Wallace M. Opioids, Analgesia, and Pain Management. (2017). In Brunton LL, Hilal-Dandan R, Knollmann BC (Eds). *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*, 13e. McGraw-Hill Education, New York, NY.
 44. McDaid C, Maund E, Rice S, et al. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) for the reduction of morphine-related side effects after major surgery: a systematic review. *Health Technol Assess* 2010;14:1-153. doi: 10.3310/hta14170.
 45. Holzer P. Opioid receptors in the gastrointestinal tract. *Regulatory Peptides* 2009;155:11-17. doi: 10.1016/j.regpep.2009.03.012.
 46. Holzer P. Pharmacology of opioids and their effects on gastrointestinal function. *The American Journal of Gastroenterology Supplements* 2014;2:9. doi: 10.1038/ajgsup.2014.4.
 47. Camilleri M, Drossman D, Becker G, et al. Emerging treatments in neurogastroenterology: a multidisciplinary working group consensus statement on opioid-induced constipation. *Neurogastroenterology & Motility* 2014;26:1386-1395. doi: 10.1111/nmo.12417.
 48. Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. *The American Journal of Surgery* 2001;82: S11-S18. doi: 10.1016/s0002-9610(01)00782-6.
 49. Brock C, Olesen SS, Olesen AE, et al. Opioid-induced bowel dysfunction. *Drugs* 2012;72:1847-1865. doi: 10.2165/11634970-000000000-00000.
 50. Mahajan G, Wilsey B, Fishman SM. (2005). Opioid therapy: adverse effects including addiction, SPEC-Essentials of Pain Medicine and Regional Anesthesia (Reprint) (pp. 113-123). Elsevier Inc.
 51. Leppert W. Oxycodone/naloxone in the management of patients with pain and opioid-induced bowel dysfunction. *Current Drug Targets* 2014;15:124-135. doi: 10.2174/13894501113149990210.
 52. Xu XS, Etropolski M, Upmalis D, et al. Pharmacokinetic and pharmacodynamic modeling of opioid-induced gastrointestinal side effects in patients receiving tapentadol IR and oxycodone IR. *Pharmaceutical Research* 2012;29:2555-2564. doi: 10.1007/s11095-012-0786-5.
 53. Holzer P. New approaches to the treatment of opioid-induced constipation. *European Review for Medical and Pharmacological Sciences* 2008;12:119.
 54. Chey WD, Webster L, Sostek M, et al. Naloxegol for opioid-induced constipation in patients with noncancer pain. *New England Journal of Medicine* 2014;370:2387-2396. doi: 10.1056/NEJMoa1310246.
 55. Poulsen JL, Brock C, Olesen AE, et al. Evolving paradigms in the treatment of opioid-induced bowel dysfunction. *Therapeutic Advances in Gastroenterology* 2015;8:360-372. doi: 10.1177/1756283X15589526.
 56. Lacy BE, Levy LC. Lubiprostone: a novel treatment for chronic constipation. *Clin Interv Aging* 2008;3:357-364. doi: 10.2147/cia.s2938.
 57. Laugsand EA, Kaasa S, Klepstad P. Management of opioid-induced nausea and vomiting in cancer patients: systematic review and evidence-based recommendations. *Palliative Medicine* 2011;25:442-453. doi: 10.1177/0269216311404273.
 58. Knezevic NN, Tverdohleb T, Knezevic I, et al. Unique pharmacology of tapentadol for treating acute and chronic pain. *Expert Opin Drug Metab Toxicol* 2015;11:1475-1492. doi: 10.1517/17425255.2015.1072169.
 59. Vella-Brincat J, Macleod A. Adverse effects of opioids on the central nervous systems of palliative care patients. *Journal of Pain & Palliative Care Pharmacotherapy* 2007;21:15-25. doi: 10.1080/j354v21n01_05
 60. Dasgupta N, Funk MJ, Proescholdbell S, et al. Cohort Study of the Impact of High-Dose Opioid Analgesics on Overdose Mortality. *Pain Med* 2016;17:85-98. doi: 10.1111/pme.12907.
 61. Ko MC. Neuraxial opioid-induced itch and its pharmacological antagonism. *Handb Exp Pharmacol* 2015;226:315-335. doi: 10.1007/978-3-662-44605-8_17.
 62. Webster LR, Choi Y, Desai H, et al. Sleep-disordered breathing and chronic opioid therapy. *Pain Med* 2008;9:425-432. doi: 10.1111/j.1526-4637.2007.00343.x.
 63. Yue HJ, Guillemineault C. Opioid medication and sleep-disordered breathing. *Med Clin North Am* 2010;94:435-446. doi: 10.1016/j.mcna.2010.02.007.
 64. Kosciuzuk U, Knapp P, Lotowska-Cwiklewska AM. Opioid-induced immunosuppression and carcinogenesis promotion theories create the newest trend in acute and chronic pain pharmacotherapy. *Clinics (Sao Paulo)* 2020;75: e1554. doi: 10.6061/clinics/2020/e1554.
 65. de Vries F, Bruin M, Lobatto DJ, et al. Opioids and Their Endocrine Effects: A Systematic Review and Meta-analysis. *J Clin Endocrinol Metab* 2020;105:1020-1029. doi: 10.1210/clinem/dgz022.
 66. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;64:e139-e228. doi: 10.1016/j.jacc.2014.09.017.
 67. Minozzi S, Amato L, Jahanfar S, et al. Maintenance agonist treatments for opiate-dependent pregnant women. *Cochrane Database Syst Rev* 2020;11:CD006318. doi: 10.1002/14651858.CD006318.pub4.
 68. McCance-Katz EF, Sullivan LE, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. *Am J Addict* 2010;19:4-16. doi: 10.1111/j.1521-0391.2009.00005.x.
 69. Kanner RM, Foley KM. Patterns of narcotic drug use in a cancer pain clinic. *Ann N Y Acad Sci* 1981;362:161-172. doi: 10.1111/j.1749-6632.1981.tb12804.x.
 70. Hser YI, Evans E, Grella C, et al. Long-term course of opioid addiction. *Harv Rev Psychiatry* 2015;23:76-89. doi: 10.1097/hrp.0000000000000052.
 71. Drewes AM, Jensen RD, Nielsen LM, et al. Differences between opioids: pharmacological, experimental, clinical and economical perspectives. *British Journal of Clinical Pharmacology* 2013;75:60-78. doi: 10.1111/j.1365-

- 2125.2012.04317.x
72. Fine PG, Portenoy RK, on Evidence AHEP. Establishing "best practices" for opioid rotation: conclusions of an expert panel. *Journal of Pain and Symptom Management* 2009;38:418-425. doi: 10.1016/j.jpainsymman.2009.06.002
73. O'Brien T, Christrup L, Drewes A, et al. European Pain Federation position paper on appropriate opioid use in chronic pain management. *European Journal of Pain* 2017;21:3-19. doi: 10.1002/ejp.970.
74. Ripamonti C, Bandieri E, Roila F. Management of cancer pain: ESMO clinical practice guidelines. *Annals of Oncology* 2011;22: vi69-vi77. doi: 10.1093/annonc/mdr390.
75. McQuay H, Moore R. (1997). Opioid problems, and morphine metabolism and excretion. Dickenson AH, Besson J-M (Eds) *The Pharmacology of Pain* (pp.335-360). Berlin Heidelberg:Springer-Verlag.
76. Bandieri E, Chiarolanza A, Luppi M, et al. Prescription of opioids in Italy: everything, but the morphine. *Annals of Oncology* 2009;20:961-962. doi: 10.1093/annonc/mdp041.
77. Hanks G, De Conno F, Cherny N, et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *British Journal of Cancer* 2001;84:587-593. doi: 10.1054/bjoc.2001.1680.
78. Wood DE. National Comprehensive Cancer Network (NCCN) clinical practice guidelines for lung cancer screening. *Thoracic Surgery Clinics* 2015;25:185-197. doi: 10.1016/j.thorsurg.2014.12.003.
79. Żukowski M, Kotfis K. The use of opioid adjuvants in perioperative multimodal analgesia. *Anaesthesiology Intensive Therapy* 2012;44: 42-46.
80. Eti Z. (2007) Postoperatif ağrı tedavisi. Erdine S. (Ed). Ağrı. İstanbul: Nobel Tıp Kitabevleri.
81. Hartrick CT, Pestano CR, Ding L, et al. Patient considerations in the use of transdermal iontophoretic fentanyl for acute postoperative pain. *J Pain Res* 2016;9:215-222. doi: 10.2147/jpr.S89278.
82. Raj PP. (2007). Sürekli bölgesel analjezi. Erdine S. (ed). Ağrı. İstanbul:Nobel Tıp Kitabevleri.
83. Bujedo BM. Current evidence for spinal opioid selection in postoperative pain. *The Korean Journal of Pain* 2014;27:200-209. doi: 10.3344/kjp.2014.27.3.200.
84. Deer TR, Pope JE, Hayek SM, et al. The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practices and Guidelines. *Neuromodulation* 2017;20:96-132. doi: 10.1111/ner.12538. doi: 10.1111/ner.12538.
85. Karavelis A, Foroglou G, Selviaridis P, et al. Intraventricular administration of morphine for control of intractable cancer pain in 90 patients. *Neurosurgery* 1996;39:57-61. doi: 10.1097/00006123-199607000-00012.