

## BÖLÜM 20

# OKSAZOLİDİNONLARIN VE DAPTOMİSİNİN ETKİ SPEKTRUMU VE KULLANIM ALANLARI

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### Giriş

Oksazolidinon grubu antibiyotikler gram pozitif mikroorganizmalar üzerine etkinlik gösterir. Linezolid ve tedizolid bu grupta yer alır. Metisilin dirençli stafilokoklar (MRSA, koagülaz negatif stafilokoklar) ve vankomisin dirençli enterokokların (VRE) da dahil olduğu yumuşak doku enfeksiyonları, hastane veya toplum kökenli pnömoni tedavisinde kullanımı vardır. Uzun süreli kullanımda daha sık görülebilen en önemli yan etkisi miyelosupresyondur. Daptomisin de gram pozitif enfeksiyonların tedavisinde kullanılan lipopeptit grubu antibiyotiktir. MRSA ve VRE'nin etken olduğu bakteriyemi, endokardit, kemik eklem enfeksiyonları tedavisinde kullanılır. Alveolar surfaktan ile inaktive olması nedeniyle pnömoni tedavisinde yeri yoktur. En önemli yan etkisi rabdomiyoliz ve eozinofilik pnömonidir. Bu bölümde gram pozitif enfeksiyonların tedavisinde oldukça önemli yere sahip olan oksazolidinon grubu antibiyotikler ve daptomisinin genel özellikleri, etki spektrumu ve klinik kullanımları ele alınacaktır.

### Oksazolidinonlar

#### Linezolid

##### *Genel özellikler*

Linezolid, gram pozitif mikroorganizmalara karşı bakteriyostatik etkinlik gösteren oksazolidinon grubu bir antibiyotiktir. Bakteri ribozomunun 50S alt birimine

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bağlı kas ağrısı, güçsüzlük gibi semptomlar gözlenebilir. Miyopati varlığında ve serum keratin fosfokinaz değeri normalin üst sınırının 5 katından fazla (veya  $\geq 1000$  U/L) olan vakalarda veya semptom tariflemeyen ve serum keratin fosfokinaz değeri normalin üst sınırının 10 katından fazla (veya  $\geq 2000$  U/L) olan vakalarda daptomisinin kesilmesi önerilir (38). Semptomlar sıklıkla 2-3 içinde geçer. Daptomisin tedavisi alan hastalarda haftada bir olarak serum keratinfosfokinaz değerinin takibinin yapılması gerekir.

Daptomisine bağlı görülebilecek eozinofilik pnömoni diğer bir önemli yan etkidir. Ateş yüksekliği, hipoksemi, diffüz pulmoner infiltrasyon ve bronkoalveoler lavajda eozinofili varlığı ile karakterizedir. Fizik muayenede ince raller duyulur. Bu durumda daptomisin tedavisi kesilir, destekleyici tedavi önerilir. Ayrıca sistemik glukokortikoid tedavisinin de hasta yönetiminde yeri gösterilmiştir (39).

## Kaynaklar

1. Usluer G, Ünal S. Linezolid. *Flora Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Dergisi*. 2005;10 (ek 4); 1-15
2. Moellering R. C. Linezolid: the first oxazolidinone antimicrobial. *Annals of internal medicine*, 2003; 138(2), 135–142. <https://doi.org/10.7326/0003-4819-138-2-200301210-00015>
3. Luque S, Grau S, Alvarez-Lerma F, et al. Plasma and cerebrospinal fluid concentrations of linezolid in neurosurgical critically ill patients with proven or suspected central nervous system infections. *International Journal of Antimicrobial Agents*. 2014;44(5):409-415. doi:10.1016/j.ijantimicag.2014.07.001
4. MacGowan A. P. Pharmacokinetic and pharmacodynamic profile of linezolid in healthy volunteers and patients with Gram-positive infections. *The Journal of antimicrobial chemotherapy*, 2013; 51 Suppl 2, ii17–ii25. <https://doi.org/10.1093/jac/dkg248>
5. Willke A, Doganay M, Söyletir G, Nobel Kitabevi, İstanbul, 2008; cilt 1: 337-41.
6. Crass, R. L., Cojutti, P. G., Pai, M. P., et al, Reappraisal of Linezolid Dosing in Renal Impairment To Improve Safety. *Antimicrobial agents and chemotherapy*, 2019; 63(8), e00605-19. <https://doi.org/10.1128/AAC.00605-19>
7. Douros, A., Grabowski, K., & Stahlmann, R. Drug-drug interactions and safety of linezolid, tedizolid, and other oxazolidinones. *Expert opinion on drug metabolism & toxicology*, 2015; 11(12), 1849–1859. <https://doi.org/10.1517/17425255.2015.1098617>
8. Stalker, D. J., & Jungbluth, G. L. Clinical pharmacokinetics of linezolid, a novel oxazolidinone antibacterial. *Clinical pharmacokinetics*, 2003; 42(13), 1129–1140. <https://doi.org/10.2165/00003088-200342130-00004>
9. Wilcox M. H. Update on linezolid: the first oxazolidinone antibiotic. *Expert opinion on pharmacotherapy*, 6(13), 2005; 2315–2326. <https://doi.org/10.1517/14656566.6.13.2315>
10. Diekema, D. J., & Jones, R. N. Oxazolidinone antibiotics. *Lancet* 2005; 358(9297), 1975–1982. [https://doi.org/10.1016/S0140-6736\(01\)06964-1](https://doi.org/10.1016/S0140-6736(01)06964-1)
11. Ager, S., & Gould, K. Clinical update on linezolid in the treatment of Gram-positive bacterial infections. *Infection and drug resistance*, 2012; 5, 87–102. <https://doi.org/10.2147/IDR.S25890>
12. Larruskain J, Idigoras P, Marimon JM et al. “Susceptibility of 186 Nocardia sp. isolates to 20 an-

- timicrobial agents.” *Antimicrobial agents and chemotherapy* 2011 ; vol. 55,6 2995-8. doi:10.1128/AAC.01279-10
13. Lifan, Z., Sainan, B., Feng, S., et al. Linezolid for the treatment of extensively drug-resistant tuberculosis: a systematic review and meta-analysis. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*, 2019; 23(12), 1293–1307. <https://doi.org/10.5588/ijtld.18.0822>
  14. Stevens, D. L., Dotter, B., & Madaras-Kelly, K. A review of linezolid: the first oxazolidinone antibiotic. *Expert review of anti-infective therapy*, 2004; 2(1), 51–59. <https://doi.org/10.1586/14787210.2.1.51>
  15. Zyvox® (linezolid) [package insert]. New York: Pharmacia and Upjohn Company; 2017.
  16. Hashemian, S. M. R., Farhadi, T., & Ganjparvar, M. Linezolid: a review of its properties, function, and use in critical care. *Drug design, development and therapy*, 2018; 12, 1759–1767. <https://doi.org/10.2147/DDDT.S164515>
  17. Baddour LM, Wilson WR, Bayer AS, et al. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. *Circulation*. 2015;132(15):1435-1486. doi:10.1161/CIR.0000000000000296
  18. Lee M, Lee J, Carroll MW, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. *The New England journal of medicine*, 2012; 367(16), 1508–1518. <https://doi.org/10.1056/NEJMoa1201964>
  19. Gerson SL, Kaplan SL, Bruss JB, et al. Hematologic effects of linezolid: summary of clinical experience. *Antimicrobial agents and chemotherapy*, 2002; 46(8), 2723–2726. <https://doi.org/10.1128/AAC.46.8.2723-2726.2002>
  20. Narita, M., Tsuji, B. T., & Yu, V. L. Linezolid-associated peripheral and optic neuropathy, lactic acidosis, and serotonin syndrome. *Pharmacotherapy*, 2007; 27(8), 1189–1197. <https://doi.org/10.1592/phco.27.8.1189>
  21. Ortiz-Covarrubias A, Fang E, Prokocimer PG, et al. Efficacy, safety, tolerability and population pharmacokinetics of tedizolid, a novel antibiotic, in Latino patients with acute bacterial skin and skin structure infections. *The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases*, 2016; 20(2), 184–192. <https://doi.org/10.1016/j.bjid.2015.12.007>
  22. Roger, C., Roberts, J. A., & Muller, L. Clinical Pharmacokinetics and Pharmacodynamics of Oxazolidinones. *Clinical pharmacokinetics*, 2018; 57(5), 559–575. <https://doi.org/10.1007/s40262-017-0601-x>
  23. Flanagan, S., Bartizal, K., Minassian, S. L., et al. In vitro, in vivo, and clinical studies of tedizolid to assess the potential for peripheral or central monoamine oxidase interactions. *Antimicrobial agents and chemotherapy*, 2013; 57(7), 3060–3066. <https://doi.org/10.1128/AAC.00431-13>
  24. Kosmidis, C., & Levine, D. P. Daptomycin: pharmacology and clinical use. *Expert opinion on pharmacotherapy*, 11(4), 2010; 615–625. <https://doi.org/10.1517/14656561003598893>
  25. Hair, P. I., & Keam, S. J. Daptomycin: a review of its use in the management of complicated skin and soft-tissue infections and Staphylococcus aureus bacteraemia. *Drugs*, 2007; 67(10), 1483–1512. <https://doi.org/10.2165/00003495-200767100-00008>
  26. Dvorchik, B. H., Brazier, D., DeBruin, M. F., & Arbeit, R. D. Daptomycin pharmacokinetics and safety following administration of escalating doses once daily to healthy subjects. *Antimicrobial agents and chemotherapy*, 2003; 47(4), 1318–1323. <https://doi.org/10.1128/AAC.47.4.1318-1323.2003>

27. Sauermann, R., Rothenburger, M., Graninger, W., & Joukhadar, C. Daptomycin: a review 4 years after first approval. *Pharmacology*, 2008; 81(2), 79–91. <https://doi.org/10.1159/000109868>
28. Silverman, J. A., Mortin, L. I., Vanpraagh, A. et al. Inhibition of daptomycin by pulmonary surfactant: in vitro modeling and clinical impact. *The Journal of infectious diseases*, 2005; 191(12), 2149–2152. <https://doi.org/10.1086/430352>
29. Vena A, Falcone M, Comandini E, et al. Daptomycin plus trimethoprim/sulfamethoxazole combination therapy in post-neurosurgical meningitis caused by linezolid-resistant *Staphylococcus epidermidis*. *Diagnostic microbiology and infectious disease*, 2013; 76(1), 99–102. <https://doi.org/10.1016/j.diagmicrobio.2013.01.021>
30. Chuma M, Nakamoto A, Bando T, et al. Association Between Statin Use and Daptomycin-related Musculoskeletal Adverse Events: A Mixed Approach Combining a Meta-analysis and a Disproportionality Analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 2022; 75(8), 1416–1422. <https://doi.org/10.1093/cid/ciac128>
31. Humphries, R. M., Pollett, S., & Sakoulas, G. A current perspective on daptomycin for the clinical microbiologist. *Clinical microbiology reviews*, 2013; 26(4), 759–780. <https://doi.org/10.1128/CMR.00030-13>
32. Moore, C. L., Osaki-Kiyan, P., Haque, N. et al. Daptomycin versus vancomycin for bloodstream infections due to methicillin-resistant *Staphylococcus aureus* with a high vancomycin minimum inhibitory concentration: a case-control study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 2012; 54(1), 51–58. <https://doi.org/10.1093/cid/cir764>
33. Sakoulas, G., Golan, Y., Lamp, K. et al. Daptomycin in the treatment of bacteremia. *The American journal of medicine*, 2007; 120(10 Suppl 1), S21–S27. <https://doi.org/10.1016/j.amjmed.2007.07.012>
34. Chaftari AM, Hachem R, Mulanovich V, et al. Efficacy and safety of daptomycin in the treatment of Gram-positive catheter-related bloodstream infections in cancer patients. *International journal of antimicrobial agents*, 2010; 36(2), 182–186. <https://doi.org/10.1016/j.ijantimicag.2010.03.015>
35. Cantoni, L., Glauser, M. P., & Bille, J. Comparative efficacy of daptomycin, vancomycin, and cloxacillin for the treatment of *Staphylococcus aureus* endocarditis in rats and role of test conditions in this determination. *Antimicrobial agents and chemotherapy*, 1990; 34(12), 2348–2353. <https://doi.org/10.1128/AAC.34.12.2348>
36. Skiest D. J. Treatment failure resulting from resistance of *Staphylococcus aureus* to daptomycin. *Journal of clinical microbiology*, 2006; 44(2), 655–656. <https://doi.org/10.1128/JCM.44.2.655-656.2006>
37. Knoll, B. M., Spieler, P. J., Kubiak, D. W. et al. Neutropenia associated with prolonged daptomycin use. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 2013; 56(9), 1353–1354. <https://doi.org/10.1093/cid/cit023>
38. Daptomycin (Cubicin) Product Information. Merck and Co, Inc; Whitehouse, NJ 8/2020
39. Hirai J, Hagihara M, Haranaga S, et al. Eosinophilic pneumonia caused by daptomycin: Six cases from two institutions and a review of the literature. *Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy*, 2017; 23(4), 245–249. <https://doi.org/10.1016/j.jiac.2016.09.001>