BÖLÜM 5

KARBAPENEMLERİN VE MONOBAKTAMLARIN ETKİ SPEKTRUMU VE KULLANIM ALANLARI

Hividar ALTAN [1]

Giriş

Beta laktam grubu içerisinde yer alan karbapenemler kullanım yeri ve etki spektrumu nedeniyle antibiyotikler içerisinde önemli bir yere sahiptir. Karbapenemler beta laktamlar grubu içerisinde en geniş spektruma sahip gruptur. Bu yüzyılda giderek artan gram negatif ilaç dirençleri nedeniyle özellikle yoğun bakım ünitelerinde karbapenemler giderek artan şekilde kullanılmaktadır. Ancak son zamanlarda karbapenemlere dirençli suşların artışı dikkat çekmektedir. Karbapenemlerden imipenem, meropenem, ertapenem ve doripenem günümüzde klinik kullanımdadır. Monobaktamların ilk üretilen ve şuan kullanımda olan tek üyesi aztreonam karbapenemlerden farklı olarak sadece gram negatif ve aerob etkinliğe sahiptir. Ancak bu dar etkisine rağmen dirençli gram negatif patojenlere etkinliği sayesinde günümüzde aranan bir grup haline gelmiştir.

Karbapenemler

Moleküler yapısı ve etki mekanizması

Karbapenemler Tienamisin derivesi olup *Streptomyces cattleya* 'dan üretilmiştir. Beta laktam türevi antibiyotik olan karbapenemlerin penisilinlerden farklı olarak, C1 atomuna sülfür yerine karbon atomu bağlıdır, karbon atomuna da bir tiazolidin halkası bağlanmıştır. Ayrıca 6- transhidroksimetil grubunun bulunması birçok beta laktamaz üreten bakterilere karşı karbapenem direncini sağlar. Tienamisin öncül maddesinden ilk elde edilen antibiyotik olan imipenem renal di-

[1] Uzm. Dr., Siirt Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği, hividaraltan@gmail.com

rika Enfeksiyon Hastalıkları Derneği (IDSA) tarafından MBL üreten karbapenem dirençli *Enterobacteriaceae* türlerinin neden olduğu ciddi enfeksiyonların tedavisi için önerilmiştir (28,29). Ancak henüz piyasaya sürülmemiştir.

Kaynaklar

1. Drusano GL. An overview of the pharmacology of imipenem/cilastatin. *The Journal of antimicrobial chemotherapy* 1986;18 Suppl E:79-92. doi: 10.1093/jac/18.supplement_e.79.
2. Papp-Wallace KM, Endimiani A, Taracila MA, et al. Carbapenems: past, present, and future. *Antimicrobial agents and chemotherapy* 2011;55:4943-60. doi:10.1128/AAC.00296-11
3. Armstrong T, Fenn SJ, Hardie KR. JMM Profile: Carbapenems: a broad-spectrum antibiotic. *J Med Microbiol*. 2021;70(12):001462. doi:10.1099/jmm.0.001462
4. Zhanel GG, Wiebe R, Dilay L, et al. Comparative review of the carbapenems. *Drugs* 2007;67:1027-52. doi:10.2165/00003495-200767070-00006
5. Fritsche TR, Sader HS, Stillwell MG, et al. Antimicrobial activity of doripenem tested against prevalent Gram-positive pathogens: results from a global surveillance study (2003-2007). *Diagnostic microbiology and infectious disease* 2009;63:440-6. doi: 10.1016/j.diagmicrobio.2009.01.019
6. Unemo M, Golparian D, Limnios A, et al. In vitro activity of ertapenem versus ceftriaxone against Neisseria gonorrhoeae isolates with highly diverse ceftriaxone MIC values and effects of ceftriaxone resistance determinants: ertapenem for treatment of gonorrhea? *Antimicrobial agents and chemotherapy* 2012;56:3603-9. doi: 10.1128/AAC.00326-12
7. Mera RM, Miller LA, Amrine-Madsen H, et al. Acinetobacter baumannii 2002-2008: increase of carbapenem-associated multiclass resistance in the United States. *Microbial drug resistance (Larchmont, NY)* 2010;16:209-15. doi:10.1089/mdr.2010.0052
8. Goldstein EJ, Citron DM, Merriam CV, et al. Comparative in vitro activities of ertapenem (MK-0826) against 469 less frequently identified anaerobes isolated from human infections. *Antimicrobial agents and chemotherapy* 2002;46:1136-40. doi: 10.1128/AAC.46.4.1136-1140.2002
9. Cercenado E, Marín M, Sánchez-Martínez M, et al. In vitro activities of tigecycline and eight other antimicrobials against different Nocardia species identified by molecular methods. *Antimicrobial agents and chemotherapy* 2007;51:1102-4. doi: 10.1128/AAC.01102-06
10. Chavan VV, Dalal A, Nagaraja S, et al. Ambulatory management of pre- and extensively drug resistant tuberculosis patients with imipenem delivered through port-a-cath: A mixed methods study on treatment outcomes and challenges. *PLoS One*. 2020;15(6):e0234651. Published 2020 Jun 16. doi:10.1371/journal.pone.0234651
11. Zumla A. Mandell, Douglas, and Bennett's principles and practice of infectious diseases: *The Lancet. Infectious Diseases*, 2010 May;10(5):303-4. doi: 10.1016/S1473-3099(10)70089-X. Epub 2010 Apr 21.
12. Cannon JP, Lee TA, Clark NM, et al. The risk of seizures among the carbapenems: a meta-analysis. *The Journal of antimicrobial chemotherapy* 2014;69:2043-55. doi: 10.1093/jac/dku111
13. Shayan M, Elyasi S. Cilastatin as a protective agent against drug-induced nephrotoxicity: a literature review. *Expert opinion on drug safety*. 2020;19(8):999-1010. doi:10.1080/14740338.2020.1796967
14. Paterson DL, Depestel DD. Doripenem. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2009;49:291-8. doi:10.1086/600036
15. FDA. *FDA Drug Safety Communication: FDA approves label changes for antibacterial Doribax (doripenem) describing increased risk of death for ventilator patients with pneumonia*. 2014. http://www.fda.gov/Drugs/DrugSafety/ucm387971.htm. 2014. (erişim tarihi: 12/12/2022)
16. Prescott WA, Jr., DePestel DD, Ellis JJ, et al. Incidence of carbapenem-associated allergic-type

reactions among patients with versus patients without a reported penicillin allergy. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2004;38:1102-7. doi:10.1086/382880

17. Sodhi M, Axtell SS, Callahan J, et al. Is it safe to use carbapenems in patients with a history of allergy to penicillin? *The Journal of antimicrobial chemotherapy* 2004;54:1155-7. doi:10.1093/jac/dkh454
18. Cunha BA, Hamid NS, Krol V, et al. Safety of meropenem in patients reporting penicillin allergy: lack of allergic cross reactions. *Journal of chemotherapy (Florence, Italy)* 2008;20:233-7. doi:10.1179/joc.2008.20.2.233
19. Kula B, Djordjevic G, Robinson JL. A systematic review: can one prescribe carbapenems to patients with IgE-mediated allergy to penicillins or cephalosporins? *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014;59:1113-22. doi:10.1093/cid/ciu587
20. Romano A, Viola M, Guéant-Rodriguez RM, et al. Imipenem in patients with immediate hypersensitivity to penicillins. *The New England journal of medicine* 2006;354:2835-7. doi:10.1056/NEJMc053529
21. Romano A, Viola M, Guéant-Rodriguez RM, et al. Brief communication: tolerability of meropenem in patients with IgE-mediated hypersensitivity to penicillins. *Annals of internal medicine* 2007;146:266-9. doi:10.7326/0003-4819-146-4-200702200-00005
22. Miller AD, Ball AM, Bookstaver PB, et al,. Epileptogenic potential of carbapenem agents: mechanism of action, seizure rates, and clinical considerations. *Pharmacotherapy* 2011;31:408-23. doi:10.1592/phco.31.4.408
23. Kaye KS, Bhowmick T, Metallidis S, et al. Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection: The TANGO I Randomized Clinical Trial. *Jama* 2018;319:788-99. doi:10.1001/jama.2018.0438
24. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and Safety of Meropenem-Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial. *Infectious diseases and therapy* 2018;7:439-55. doi:10.1007/s40121-018-0214-1
25. Young K, Painter RE, Raghoobar SL, et al. In vitro studies evaluating the activity of imipenem in combination with relebactam against Pseudomonas aeruginosa. *BMC microbiology* 2019;19:150. doi:10.1186/s12866-019-1522-7
26. Motsch J, Murta de Oliveira C, Stus V, et al. RESTORE-IMI 1: A Multicenter, Randomized, Double-blind Trial Comparing Efficacy and Safety of Imipenem/Relebactam vs Colistin Plus Imipenem in Patients With Imipenem-nonsusceptible Bacterial Infections. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2020;70:1799-808. doi:10.1093/cid/ciz530
27. Kishiyama JL, Adelman DC. The cross-reactivity and immunology of beta-lactam antibiotics. *Drug safety* 1994;10:318-27. doi:10.2165/00002018-199410040-00006
28. Tamma PD, Aitken SL, Bonomo RA, et al. Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa). *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2021;72:e169-e83. doi:10.1093/cid/ciac268
29. Paul M, Carrara E, Retamar P, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2022;28:521-47.