KOŁODZIEJ, Magdalena, GORCZYCA, Kamila, JASTRZĘBSKA, Ilona, WĘGOROWSKI, Paweł & WIECZOREK, Michał. The solution to drug resistance of Gram-negative bacteria – Cefiderocol. Journal of Education, Health and Sport. 2023;33(1):17-21. eISSN 2391-8306. DOI
http://dx.doi.org/10.12775/JEHS.2023.33.01.002
https://apcz.umk.pl/JEHS/article/view/43777
https://zenodo.org/record/7962694

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343.
Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159.
Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 29.04.2023. Revised: 10.05.2023. Accepted: 23.05.2023. Published: 23.05.2023.

The solution to drug resistance of Gram-negative bacteria – Cefiderocol

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Abstract

Introduction: A major public health problem is the emergence of anti-gram-negative antimicrobial resistance worldwide. Cefiderocol is a new agent targeting Gram-negative bacteria, including strains with resistance to carbapenems.

Aim of the study: Analysis of the efficiency of cefiderocol in the treatment of infections caused by gram-negative bacteria, the drug's mechanism of action and pharmacokinetics and pharmacodynamics of the drug.

Material and Methods: Search of the PubMed database using the following keywords: cefiderocol, resistance, gram negative bacteria. Only full-length articles were taken into consideration.

Results: The studies show that cefiderocol is active against Enterobacteriaceae, P. aeruginosa, B. cepacia and A. baumannii and effective in the treatment of pneumonia in both non-ventilated and ventilated patients. Moreover, it has been used in the treatment of sepsis as a rescue therapy.

Conclusion: Cefiderocol is an effective treatment for infections caused by gram-negative bacteria. However, more research is needed to learn more about the use of this drug, side effects and resistance mechanisms.

Keywords: cefiderocol, resistance, gram negative bacteria

Introduction

A major public health problem is the emergence of anti-gram-negative antimicrobial resistance worldwide. Cefiderocol is a new agent targeting Gram-negative bacteria, including strains with resistance to carbapenems [1].
Gram-negative bacteria resistant to carbapenems of clinical importance include, first of all, Pseudomonas aeruginosa, Acinetobacter baumannii, Enterobacteriaceae [2]. Enterobacteriacae produce both B-lactamase and extended-spectrum carbapenemase, while Pseudomonas and Acetinobacter produce carbapenemases [3]. Colistin and tigecycline are used as first-line drugs in the treatment of infections caused by these pathogens, but their effectiveness is uncertain, even when used in combination with other drugs. Recently, several new drugs with activity against certain carbapenem-resistant pathogens have either been approved for clinical use or are in the final stages of research. These include meropenem-vaborbactam, ceftazidime-avibactam, ceftolozane-tazobactam and cefiderocol [2].

Materials, Methods and Purpose:

The purpose of this article was to analyse the efficiency of cefiderocol in the treatment of infections caused by gram-negative bacteria, the drug's mechanism of action and pharmacokinetics and pharmacodynamics of the drug. During the search of the PubMed database the following keywords were used: **cefiderocol, resistance, gram negative bacteria**. Only full-length articles were taken into consideration.

The mechanism of action

Cefiderocol is a new cephalosporin with siderophore properties in which the catechol side chain forms a chelated complex with iron [2,4]. Siderophoris an iron chelating agent and facilitates the absorption of iron, which is needed for the survival of the bacteria [5]. The siderophore group absorbs iron from the environment. A complex composed of siderophore iron and of the antibiotic binds the iron transporter on the outside of the bacterial membrane and is actively

transported inside. Thanks to this, it bypasses the defence systems of the microorganism. This action is referred to as the "Trojan horse strategy" and uses an iron transporter to improve the penetration of the antibiotic [6].

Pharmacokinetics and pharmacodynamics of the drug

Structurally, cefiderocol is similar to cefepime and ceftazidime [1,7]. Cefiderocol is eliminated in 60-70% in the urine unchanged, and no accumulation was observed in health patients after a 1-h infusion of 1000 mg [8,9]. The coefficiency of variation in volume of distribution and clearance in subjects with normal renal function for cefiderocol Has been reported as 15.8 (15%) L and 4.70 (27%) L/h. In addition, there is no proof of significant interactions of this new cephalosporin with other medications [5]. The therapeutic dose of cefiderocol is 2g and is usually well tolerated in patients. In addition, no side effects have been reported after the supratherapeutic dose of 4g. Additionally, cefiderocol has no significant effect on ECG parameters, including the QT interval [10].

Studies using cefiderocol

Cefiderocol has been studied in 2 radomized trials. These were phase 3 studies and involved patients with cancer and pneumonia in the second study. Mortality rates were similar with meropenem [11]. One study used cefiderocol to treat A. baumanii infection. It showed that patients who received cefiderocol had a lower risk of 30-day mortality compared to controls [12]. In another study, 65% of patients with nosocomial pneumonia, who were taking cefiderocol, achieved a clinical improvement compared with 67% of those taking meropenem [13]. Cefiderocol was approved in 2019 by the FDA for the treatment of infections caused by gram-negative bacteria, in particular complicated urinary tract infections [14]. The 2021 IDSA guidelines recommend the use of cefiderocol for the treatment of pneumonia [15].

The use of cefiderocol

Cefiderocol is active against Enterobacteriaceae, P. aeruginosa, B. cepacia and A. baumannii [16]. In addition, it is active in vitro against all classes of beta-lactamases that are produced by Gram-negative bacteria (classes A, B and D) [17]. It is used to treat pneumonia [18] in both non-ventilated and ventilated patients. Additionally, cefiderocol is one of the treatment options for ventilator-associated pneumonia [19]. Moreover, it has been used in the treatment of sepsis as a rescue therapy and is used in patients with complications of urinary tract infections [20].

Table 1. Range of activity of individual drugs

Ceftolozane-tazobactam	Pseudomonas aeruginosa, Enterobacteriaceae
Ceftazidime-avibactam	Enterobacteriaceae, Pseudomonas aeruginosa, Stenotrophomonas maltophilia
Cefiderocol	Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter baumannii, Stenotrophomonas maltophilia

Source: Own study based on: [20–23].

Discussion

Cefiderocol is a new cephalosporin that is active against carbamenem-resistant Gram-negative bacteria both in vivo and in vitro. No clinically significant adverse effects have been reported in studies conducted with this drug. The impact of cefiderocol on the iron economy is not yet well explained [24] however the mechanism of action of the drug provides its high concentration in the blood. In addition, the mechanisms of resistance to this drug have not been thoroughly studied [6].

Conclusion

Cefiderocol is an effective treatment for infections caused by gram-negative bacteria. It is necessary to optimize the use of new antibiotics, guaranteeing patients the best treatment, while delaying the emergence of resistance to cefiderocol. However, more research is needed to learn more about the use of this drug, side effects and resistance mechanisms.

References:

1. Sato, T.; Yamawaki, K. Cefiderocol: Discovery, Chemistry, and In Vivo Profiles of a Novel Siderophore Cephalosporin. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2019**, *69*, S538–S543, doi:10.1093/cid/ciz826.
2. Doi, Y. Treatment Options for Carbapenem-Resistant Gram-Negative Bacterial Infections. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2019**, *69*, S565–S575, doi:10.1093/cid/ciz830.
3. Kanj, S.S.; Bassetti, M.; Kiratisin, P.; Rodrigues, C.; Villegas, M.V.; Yu, Y.; van Duin, D. Clinical Data from Studies Involving Novel Antibiotics to Treat Multidrug-Resistant Gram-Negative Bacterial Infections. *Int. J. Antimicrob. Agents* **2022**, *60*, 106633, doi:10.1016/j.ijantimicag.2022.106633.
4. Kohira, N.; West, J.; Ito, A.; Ito-Horiyama, T.; Nakamura, R.; Sato, T.; Rittenhouse, S.; Tsuji, M.; Yamano, Y. In Vitro Antimicrobial Activity of a Siderophore Cephalosporin, S-649266, against Enterobacteriaceae Clinical Isolates, Including Carbapenem-Resistant Strains. *Antimicrob. Agents Chemother.* **2016**, *60*, 729–734, doi:10.1128/AAC.01695-15.
5. Bilal, M.; El Tabei, L.; Büsker, S.; Krauss, C.; Fuhr, U.; Taubert, M. Clinical Pharmacokinetics and Pharmacodynamics of Cefiderocol. *Clin. Pharmacokinet.* **2021**, *60*, 1495–1508, doi:10.1007/s40262-021-01063-5.
6. Terreni, M.; Taccani, M.; Pregnolato, M. New Antibiotics for Multidrug-Resistant Bacterial Strains: Latest Research Developments and Future Perspectives. *Molecules* **2021**, *26*, 2671, doi:10.3390/molecules26092671.
7. Gijón Cordero, D.; Castillo-Polo, J.A.; Ruiz-Garbajosa, P.; Cantón, R. Antibacterial Spectrum of Cefiderocol. *Rev. Espanola Quimioter. Publicacion Of. Soc. Espanola Quimioter.* **2022**, *35 Suppl 2*, 20–27, doi:10.37201/req/s02.03.2022.
8. Lee, Y.R.; Yeo, S. Cefiderocol, a New Siderophore Cephalosporin for the Treatment of Complicated Urinary Tract Infections Caused by Multidrug-Resistant Pathogens: Preclinical and Clinical Pharmacokinetics, Pharmacodynamics, Efficacy and Safety. *Clin. Drug Investig.* **2020**, *40*, 901–913, doi:10.1007/s40261-020-00955-x.

9. Saisho, Y.; Katsube, T.; White, S.; Fukase, H.; Shimada, J. Pharmacokinetics, Safety, and Tolerability of Cefiderocol, a Novel Siderophore Cephalosporin for Gram-Negative Bacteria, in Healthy Subjects. *Antimicrob. Agents Chemother.* **2018**, *62*, e02163-17, doi:10.1128/AAC.02163-17.
10. Sanabria, C.; Migoya, E.; Mason, J.W.; Stanworth, S.H.; Katsube, T.; Machida, M.; Narukawa, Y.; Den Nagata, T. Effect of Cefiderocol, a Siderophore Cephalosporin, on QT/QTc Interval in Healthy Adult Subjects. *Clin. Ther.* **2019**, *41*, 1724-1736.e4, doi:10.1016/j.clinthera.2019.07.006.
11. Nordmann, P.; Shields, R.K.; Doi, Y.; Takemura, M.; Echols, R.; Matsunaga, Y.; Yamano, Y. Mechanisms of Reduced Susceptibility to Cefiderocol Among Isolates from the CREDIBLE-CR and APEKS-NP Clinical Trials. *Microb. Drug Resist. Larchmt. N* **2022**, *28*, 398–407, doi:10.1089/mdr.2021.0180.
12. Karaba, S.M.; Hirsch, E.B.; Heil, E.L. In a Pinch: Cefiderocol for CRAB Infections. *Antimicrob. Agents Chemother.* **2022**, *66*, e0006522, doi:10.1128/aac.00065-22.
13. Ribeiro, M.; Sousa, C.A.; Simões, M. Harnessing Microbial Iron Chelators to Develop Innovative Therapeutic Agents. *J. Adv. Res.* **2022**, *39*, 89–101, doi:10.1016/j.jare.2021.10.010.
14. Kawaguchi, N.; Katsube, T.; Echols, R.; Wajima, T. Population Pharmacokinetic Analysis of Cefiderocol, a Parenteral Siderophore Cephalosporin, in Healthy Subjects, Subjects with Various Degrees of Renal Function, and Patients with Complicated Urinary Tract Infection or Acute Uncomplicated Pyelonephritis. *Antimicrob. Agents Chemother.* **2018**, *62*, e01391-17, doi:10.1128/AAC.01391-17.
15. Soriano, A.; Pueyo, J.M. Mechanism of Action of Cefiderocol. *Rev. Esp. Quimioter.* **2022**, *35*, 16–19.
16. Katsube, T.; Echols, R.; Wajima, T. Pharmacokinetic and Pharmacodynamic Profiles of Cefiderocol, a Novel Siderophore Cephalosporin. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2019**, *69*, S552–S558, doi:10.1093/cid/ciz828.
17. Maseda, E.; Suárez de la Rica, A. The Role of Cefiderocol in Clinical Practice. *Rev. Esp. Quimioter.* **2022**, *35*, 39–44, doi:10.37201/req/s02.06.2022.
18. Ribeiro, M.; Sousa, C.A.; Simões, M. Harnessing Microbial Iron Chelators to Develop Innovative Therapeutic Agents. *J. Adv. Res.* **2022**, *39*, 89–101, doi:10.1016/j.jare.2021.10.010.
19. Poulakou, G.; Lagou, S.; Karageorgopoulos, D.E.; Dimopoulos, G. New Treatments of Multidrug-Resistant Gram-Negative Ventilator-Associated Pneumonia. *Ann. Transl. Med.* **2018**, *6*, 423, doi:10.21037/atm.2018.10.29.
20. Chumbita, M.; Monzo-Gallo, P.; Lopera-Mármol, C.; Aiello, T.F.; Puerta-Alcalde, P.; Garcia-Vidal, C. New Treatments for Multidrug-Resistant Non-Fermenting Gram-Negative Bacilli Infections. *Rev. Esp. Quimioter.* **2022**, *35 Suppl 3*, 51–53, doi:10.37201/req/s03.12.2022.
21. Matesanz, M.; Mensa, J. Ceftazidime-Avibactam. *Rev. Espanola Quimioter. Publicacion Of. Soc. Espanola Quimioter.* **2021**, *34 Suppl 1*, 38–40, doi:10.37201/req/s01.11.2021.
22. Zhanel, G.G.; Chung, P.; Adam, H.; Zelenitsky, S.; Denisuik, A.; Schweizer, F.; Lagacé-Wiens, P.R.S.; Rubinstein, E.; Gin, A.S.; Walkty, A.; et al. Ceftolozane/Tazobactam: A Novel Cephalosporin/β-Lactamase Inhibitor Combination with Activity against Multidrug-Resistant Gram-Negative Bacilli. *Drugs* **2014**, *74*, 31–51, doi:10.1007/s40265-013-0168-2.
23. Gorczyca, K.; Obuchowska, A.; Kimber-Trojnar, Ż.; Wierzchowska-Opoka, M.; Leszczyńska-Gorzelak, B. Changes in the Gut Microbiome and Pathologies in Pregnancy. *Int. J. Environ. Res. Public. Health* **2022**, *19*, 9961, doi:10.3390/ijerph19169961.

24. Saisho, Y.; Katsube, T.; White, S.; Fukase, H.; Shimada, J. Pharmacokinetics, Safety, and Tolerability of Cefiderocol, a Novel Siderophore Cephalosporin for Gram-Negative Bacteria, in Healthy Subjects. *Antimicrob. Agents Chemother.* **2018**, *62*, e02163-17, doi:10.1128/AAC.02163-17.