Cefaclor & Linezolid and Their Effectiveness against S. Aureus

Kaixuan Jin
Nanjing Foreign Language School, Nanjing, 210008, China

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Abstract: *Staphylococcus aureus* is a common human pathogen that could cause skin and soft tissue infection. Symptoms and severity of *S. aureus* SSTIs differ significantly, and complicated SSTI might require antibacterial agents to treat. Both linezolid and cefaclor are effective against *S. aureus* infections. Linezolid is an artificially synthesized antibacterial agent. It inhibits bacteria's protein synthesis by binding to bacteria ribosome and prohibiting the translation at an early stage. It could be delivered orally or intravenously. Cefaclor is another human synthesized antibacterial agent. It could inhibit the synthesis of peptidoglycan by binding to a type of penicillin binding protein, causing bacteria cell wall lysis. It is delivered orally. In this work, the structures, mechanisms, limitations and economics of the two antibacterial agents would be briefly discussed and the comparison between them would be shown clearly.

1 INTRODUCTION

The antibacterial properties of oxazolidinones were first discovered in 1984. Years later, a research program on oxazolidinone was performed. After synthesis attempts and evaluations, scientists discovered that linezolid had preferable characteristics and further trials were done. Linezolid was approved in the United States in 2000 and was considered an effective drug against Gram-positive bacteria (Hashemian, Farhadi, Ganjparvar 2018, Ford, Zurenko, Barbachyn 2001). Linezolid could bind with bacteria ribosome and inhibit the translation process at the early stage (Foti, Piperno, Scala, Giuffrè 2021).

Cefaclor originated from a type of fungus and belongs to the cephalosporin family. It is effective against both Gram-negative and Gram-positive bacteria. Cefaclor's mechanism is similar to that of penicillin's (Arsalan, Ahmad, Ali 2017, Jeong, Jang, Cho, Lee 2021).

Staphylococcus aureus is a common type of bacteria (Wertheim, Melles, Vos, van Leeuwen, van Belkum, Verbrugh, Nouwen 2005). Infections caused by *S. Aureus* included skin and soft tissue infections. Abscesses on the skin is an example of *S. Aureus* skin and soft tissue infection (Foti, Piperno, Scala, Giuffrè 2021). Both linezolid and cefaclor are effective in treating infections caused by *S. aureus* (Hashemian, Farhadi, Ganjparvar 2018, Arsalan, Ahmad, Ali 2017).

2 OVERVIEW OF DISEASE

Staphylococcus aureus is a Gram-positive bacterium. It is spherical and its diameter is approximately 1 μm, as shown in figure 1. It was first isolated by Alexander Ogston from an infection in 1880 and in 1882 the term *Staphylococcus* was created by Ogston. Further classifications were completed in the following decades (Lakhundi, Zhang 2018).

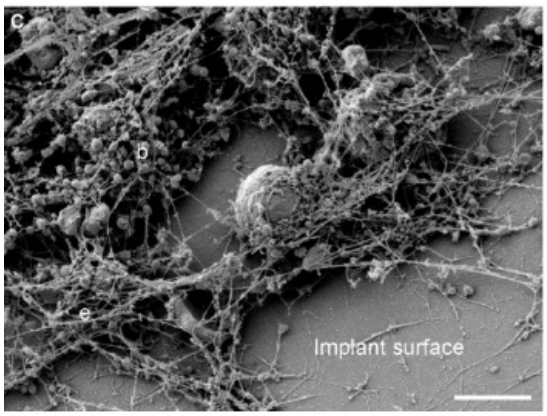

Figure 1: S. aureus (Jensen, Koch, Aalbaek et al. 2017).

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Staphylococcus aureus is one of the most common types of bacteria. About 50% of total human population are continuously or discontinuously carrying *S. aureus* (Wertheim, Melles, Vos, van Leeuwen, van Belkum, Verbrugh, Nouwen 2005). It causes various infections, including different types of skin and soft tissue infections (SSTI), the severity of which could differ significantly (Tong, Davis, Eichenberger, Holland, Fowler 2015).

Abscesses on the skin is a typical SSTI caused by *S. aureus* (Tong, Davis, Eichenberger, Holland, Fowler 2015). Impetigo is another example of *S. aureus* SSTI, shown in figure 2. Among children, impetigo is the most common SSTI caused by bacteria (Bangert, Levy, Hebert 2012). Other types of SSTI could also be caused by *S. aureus*, despite being less common (Tong, Davis, Eichenberger, Holland, Fowler 2015).

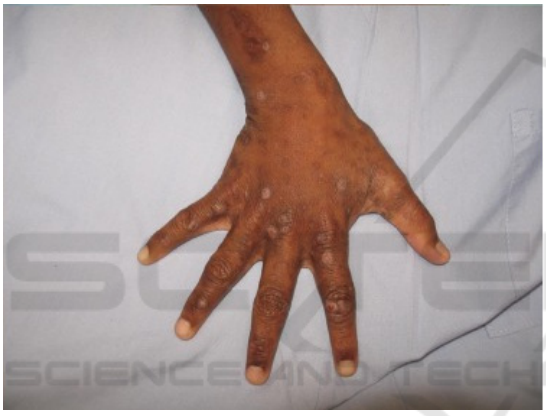

Figure 2: Impetigo complicating other infection (Tong, Davis, Eichenberger, Holland, Fowler 2015).

It remains unclear whether uncomplicated *S. aureus* SSTIs would require antibacterial agents in treatments (Tong, Davis, Eichenberger, Holland, Fowler 2015), but for the complicated SSTI-generally defined as situations where an operation would be needed to cure the infection, or when an extension of the swollen, infected area into deeper structures occur, or situations where serious underlying diseases exist (Sunderkötter, Becker, Eckmann, Graninger, Kujath, Schöfer 2020) -treatments using antibiotics might be required (Tong, Davis, Eichenberger, Holland, Fowler 2015).

3 ABOUT LINEZOLID

3.1 Chemical Structures

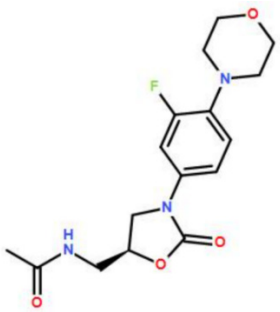

Figure 3: Chemical structure of linezolid.

The empirical formula of linezolid is $C_{16}H_{20}FN_3O_4$ (molecular weight: 337.35 g/mol) (Hashemian, Farhadi, Ganjparvar 2018).

3.2 History

Oxazolidinones-the class linezolid belongs to-were first used in 1978 due to their effectiveness against plant diseases. In 1984, it was discovered that oxazolidinones had antibacterial properties (Hashemian, Farhadi, Ganjparvar 2018). In the 1990s, with the increasing need for potential new antibacterial agents, scientists from Pharmacia Corporation began a biochemistry research program on oxazolidinone. After massive synthesis attempts and evaluations, improvements of antibacterial activity for the chemicals were achieved. Among various chemicals, linezolid showed preferable characteristics and was selected for further clinical test and evaluation. Consequently, the trials proved linezolid's effectiveness in treating various Gram-positive infections (Ford., Zurenko, Barbachyn 2001). In 2000, linezolid was officially approved in the United States (Hashemian, Farhadi, Ganjparvar 2018).

3.3 Mechanism

Linezolid inhibits protein synthesis by binding with bacteria ribosome and prohibiting the translation process. The A-site of 50S subunit of the ribosome would form bonding with linezolid, and the 30S subunit would not be affected. The initiator-tRNA would then be prohibited from binding with the ribosome, which prevents the translation process at an early stage. To be more specific, the binding would occur at the upper part of the peptidyl transferase

center and hydrogen bond would be formed (Hashemian, Farhadi, Ganjparvar 2018, Foti, Piperno, Scala, Giuffrè 2021).

The mechanism of linezolid is unique as linezolid inhibits the synthesis of protein at the early translation stage. Linezolid is effective against not only bacterial ribosome, but archaeal ribosome as well. Human cells would not be inhibited by linezolid (Foti, Piperno, Scala, Giuffrè 2021).

The 5-acylaminomethyl group binds with ribosomes and is a pivotal structure for linezolid's activity. Electron-withdrawing group in the aryl ring (the fluoride atom) could increase the activity of linezolid. Changes with the extra substituents on the proximal aromatic ring do not have direct effect on the activity against bacteria but could alter various characteristics of the chemical (Hashemian, Farhadi, Ganjparvar 2018, (Chellat, Raguž, Riedl 2016).

3.4 Limitation

Drug resistance:

Although the unique mechanism of linezolid makes it difficult for bacteria resistance to develop (Hashemian, Farhadi, Ganjparvar 2018, (Chellat, Raguž, Riedl 2016), bacteria resistance might still be a potential issue. A research which included data from various regions of the world concluded that linezolid had a 99.9% rate of effectiveness against Methicillin-resistant *Staphylococcus aureus* (Shariati, Dadashi, Chegini, van Belkum, Mirzaii, Khoramrooz, Darban-Sarokhalil, 2020), but it is still possible that the percentage of *S. aureus* resistant against linezolid is higher in certain particular areas.

The mechanism of bacteria resistance against Linezolid could be associated with mutation of 23S rRNA as linezolid binds with the ribosome at the 23S part (Hashemian, Farhadi, Ganjparvar 2018).

Adverse effects:

Recorded side effects caused by linezolid include the follows:

(a) Two patients were reported to develop peripheral neuropathy (caused by damage to neurological tissues outside of the brain and spinal cord (Vital, Vital, Bouillot-Eimer, Brechenmacher, Ferrer, Lagueny, 2004)) after a prolonged linezolid treatment (Rho, Sia, Crum, Dekutoski, Trousdale, 2004).

(b) Anemia-a condition where blood haemoglobin (a protein transporting oxygen) concentration is relatively low for a person's age and gender (Sama, Chiamo, Taiwe, Njume, Sumbele 2021) -could occur due to linezolid's direct effect on red cells (Hashemian, Farhadi, Ganjparvar 2018,) (Vinh, Rubinstein 2009).

3.5 Drug Economics

A research has been carried out to determine the cost for patients who acquired methicillin-resistant *Staphylococcus aureus* pneumonia in hospitals in the United States. The patients received intravenous linezolid in the standard dose 600 mg every 12 hours, 2 doses/day. The patients received antibiotics for 10 days (20 doses). Among all costs generated during the treatment, drug cost using linezolid was $2189. Assuming that cost for intravenous linezolid did not vary significantly due to different factors, a conclusion could be made that the average cost per standard dose (600 mg) of intravenous linezolid was approximately $109.45 (Patel, Shorr, Chastre, Niederman, Simor, Stephens, Charbonneau, Gao, Nathwani 2014).

Linezolid could be changed from intravenous to oral among patients who are clinically stable (Hashemian, Farhadi, Ganjparvar 2018). The cost for patients might therefore decrease.

4 ABOUT CEFACLOR

4.1 Chemical Structure

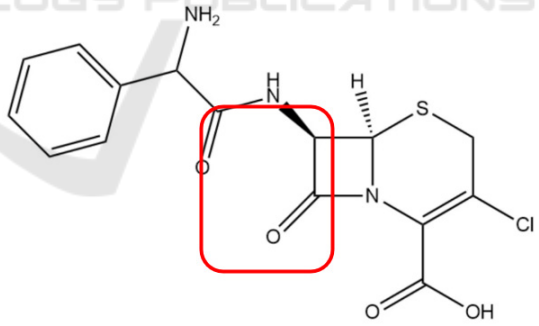

Figure 4: Chemical structure of cefaclor.

The empirical formula of cefaclor is $C_{15}H_{14}ClN_3O_4S$ (molecular weight: 368g/mol).

4.2 History

Cefaclor was originated from the fungus named Acremonium (Arsalan, Ahmad, Ali 2017). Cefaclor belongs to the second generation of the cephalosporin family - antibacterial drugs that have β-lactam as their activity center and resemble penicillin in mode of

action. Cefaclor is more effective against Gram-negative bacteria and less effective against Gram-positive bacteria compared to the first generation of cephalosporins (Arsalan, Ahmad, Ali 2017, Jeong, Jang, Cho, Lee 2021).

4.3 Mechanism

The β-lactam ring is responsible for cefaclor's anti-bacterial activity (Arsalan, Ahmad, Ali 2017).

Cefaclor's mechanism is shown in figure 5. Penicillin-binding proteins are proteins which are responsible for the final steps of the synthesis of peptidoglycan-a pivotal substance in the formation of bacteria cell walls (Sharifzadeh, Dempwolff, Kearns, Carlson 2020). Cefaclor would bind to a particular type of penicillin binding protein, which consequently lead to the prohibition of the synthesis of peptidoglycan and the lysis of cell wall. The mechanism is similar to that of penicillin's (Jeong, Jang, Cho, Lee 2021).

Peptidoglycans are pivotal substances for bacterial cell walls while the substance is not found in human cells. Cefaclor's damage to human cells is therefore minimized (Jeong, Jang, Cho, Lee 2021).

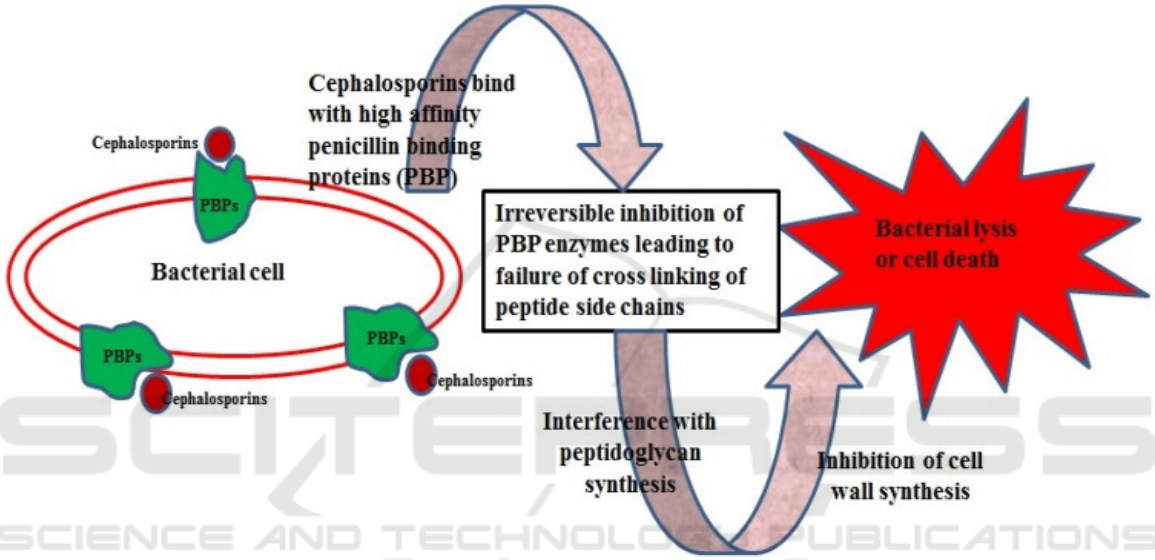

Figure 5: Mechanisms of cephalosporins, including cefaclor (Das, Madhavan, Selvi, Das 2019).

4.4 Limitation

Drug resistance:

Drug resistance among bacteria has always been a significant globally issue. Resistant rate would vary across different regions due to various factors (Arsalan, Ahmad, Ali 2017). Percentage of resistance against cefaclor among *S. aureus* recorded in the last ten years is shown in the table below.

Table 1: Bacteria resistance against cefaclor (Arsalan, Ahmad, Ali 2017).

% Resistance	Year	Region	Reference
14.0	2015	Pakistan	(Ayub, Fatima, Naqvi, Sheikh, Ali, Ayub 2015)
15.0	2015	Serbia	(Stojanovic-Radic, Dimitrijevic, Stankovic, Aleksic, Pejcic 2016)
66.66	Before 2012	India	(Shaifali, Gupta, Mahmood, Ahmed 2012)
21.0	2011	Pakistan	(Arsalan, Naqvi, Sabah, Bano, Ali 2014)

The mechanism of resistance against cefaclor is related to bacteria's production of β-lactamase, a substance that could break down the β-lactam ring in cefaclor and decrease cefaclor's effectiveness (Arsalan, Ahmad, Ali 2017).

Damage to the environment:

Cefaclor belongs to cephalosporins. Cephalosporin wastewater could pose threats to the environment. The wastewater mainly contains toxic organic chemicals, inorganic salts which could

potentially threat survival of organisms in natural environment (Das, Madhavan, Selvi, Das 2019, Yang, Zuo, Li, Wang, Yu, Zhang 2016, Guo, Chen 2015).

Adverse effects:

(a) Diarrhoea (approximately 5.6% of patients) have been reported after use of cefaclor. The effect is relatively minor (Turik, Johns 1998).

(b) Hypersensitivity cases have been observed but the cases are not life-threatening (Arsalan, Ahmad, Ali 2017, Murray, Singer, Singer, Veldman 1980).

4.5 Drug Economics

Cefaclor is an oral antibacterial drug. Cost for the drug would vary depending on brands and types. A 250 mg capsule of cefaclor might cost $1.5 to $2.1.

5 DISCUSSION

Linezolid has oral and intravenous way of delivery, while cefaclor is an oral antibacterial agent. Various relatively serious adverse effects induced by linezolid are reported, but it is possible that some side effects could be reduced by appropriate control of time or dose while using the drugs.

Linezolid has a relatively unique mechanism and has a lower rate of resistance among *S. aureus* compared to cefaclor. It is possible that future study could make linezolid & cefaclor more effective against resistant bacteria by altering part of their structures. Other characteristics of the drugs, such as solubility, might also be improved in future studies.

6 CONCLUSION

The review mainly compared the origins, mechanisms, limitations and drug economics of Linezolid and Cefaclor. Their effectiveness against infections caused by *S. aureus,* a typical type of pathogen, was also briefly discussed. There are similar issues for antibacterial agents with different mechanisms, such as the global spread of drug resistant bacteria. In future studies, both drugs might be improved to become more effective against drug-resistant bacteria. Modifications of a drug's structure, for instance, might improve the drug's reactivity or stability.

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