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Piperacillin/Tazobactam: an update for clinical use

Alice R. C. e C. Costa,[1] Andréia Patrícia Gomes,[1] Eduardo Vinícius V. Varejão,[2] Romario Brunes Will,[1] Walter Tavares,[3] Luiz Alberto Santana,[1] Rodrigo Siqueira-Batista[1,4*]

Abstract

Introduction: Piperacillin-tazobactam, a broad-spectrum penicillin, is an important option in the treatment of infections, especially in critically ill patients who exhibit high rates of resistance to various antimicrobial agents. Understand this medication and updates on its clinical use is of paramount significance to guide precise therapeutic choices aimed at the optimization of patient care. Objective: To describe the main pharmacological and therapeutic as-pects of piperacillin-tazobactam, highlighting its clinical application and updates related to its use. Methodology: A narrative review of the literature was conducted in order to provide an update on the most relevant aspects related to piperacillin-tazobactam, including (1) a brief history; (2) chemical structure; (3) mechanism of action; (4) resistance mechanisms; (5) spectrum; (6) major clinical uses; and (7) adverse effects. Results: The safe use of piperacillin-tazobactam requires rapid testing for antimicrobial resistance patterns, thus discouraging its empirical use in cases of ESBL-producing microorganisms. In patients undergoing renal replacement therapy, antibiotic goals must be established promptly. For critically ill patients, monitoring pharmacodynamic and pharmacokinetic variability is essential. Conclusion: Piperacillin-tazobactam remains a vital drug in the management of critically ill patients, while requiring constant updates. In addition, further studies are required, especially concerning its continuous use and the selection of alterna-tives to carbapenem-resistant medications.

1. Faculdade de Medicina, Universidade Federal de Viçosa, Viçosa, MG, Brazil.
2. Departamento de Medicina e Enfermagem, Universidade Federal de Viçosa, Viçosa, MG, Brazil.
3. Departamento de Química, Universidade Federal de Viçosa, Viçosa, MG, Brazil.
4. Faculdade de Medicina, Centro Universitário Serra dos Órgãos, Teresópolis, RJ, Brazil.
5. Faculdade de Medicina, Faculdade Dinâmica do Vale do Piranga, Ponte Nova, MG, Brazil.

*Correspondence address:
E-mail: lmecs@ufv.br
ORCID: https://orcid.org/0000-0002-3661-1570

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Introduction

Penicillins are part of a group of antibiotics called beta-lactams, chemically characterized by having a beta-lactam ring fused to a thiazolidine ring. This bicyclic structure corresponds to 6-aminopenicillanic acid (6-APA), the structural backbone of all penicillins. Various penicillins, both natural ones obtained from fermentation of *Penicillium chrysogenum* (penicillins G and V) and semisynthetic ones, differ from each other by the type of side chain attached to the amino group of the 6-APA structural backbone (Figure 1). The penicillin group is usually divided into five classes: natural penicillins (G and V); penicillinase-resistant penicillins

(methicillin, nafcillin, and isoxazolyl); aminopenicillins (amoxicillin and ampicillin); carboxypenicillins (carbenicillin and ticarcillin); and ureidopenicillins (azlocillin, mezlocillin, and piperacillin).[1]

The penicillins group occurred was discovered in 1928 by Alexander Fleming, after he observed that the contamination of a culture of *Staphylococcus aureus* with the fungus *Penicillium notatum* (currently *Penicillium chrysogenum*) resulted in the lysis of bacterial cells. The substance responsible for the antibacterial activity of the fungus was named penicillin and went on to revolutionize the prognosis of bacterial diseases.[2] A significant breakthrough in the development of new antibiotics came with the isolation of the structural backbone of penicillins, 6-aminopenicillanic acid (6-APA), from which various other penicillins were developed through chemical alterations in the side chain attached to the amino group of this central structure. Even today, the penicillin group is responsible for changing the prognosis of many diseases, and is the subject of numerous studies, for example, on use in critically ill patients as an alternative to carbapenems, which seem to be responsible for an increase in the selection of resistant bacteria.[3]

The primary mechanism of action of penicillins is the inhibition of bacterial cell wall synthesis. This group binds to peptidoglycan-binding proteins, more commonly known as penicillin-binding proteins (PBPs), which are responsible for essential enzymatic activities in the biosynthesis of new peptidoglycan molecules, a crucial component in the formation of the bacterial cell wall. Binding to these proteins results in a defect in cell wall construction, which leads to cell lysis.[1,2]

The expanded spectrum of piperacillin against Gram-negative bacteria, wish distinguishes it from other penicillins, is a result of its high affinity with the PBPs of these microorganisms, including strains of *Pseudomonas aeruginosa*, *Enterobacteriaceae*, *Bacteroides* spp, and *Enterococcus faecalis*.[4,5] On the other hand, tazobactam is a beta-lactamase inhibitor, sulfone of penicillanic acid that irreversibly binds to beta-lactamase enzymes, thereby forming a stable acyl-enzyme complex that allows piperacillin to be effective against bacteria producing beta-lactamas-es.[4,5] The combination of piperacillin and tazobactam makes piperacillin with the broadest spectrum penicillin of all .[5]

In Brazil, Piperacillin-tazobactam is currently used in hospital infections caused by various microorganisms, generally involving critically ill patients.[2] Due to the high resistance rates related to the drugs of choice in the treatment of these patients, especially among microorganisms that produce extended-spectrum beta-lactamase (ESBL), piperacillin-tazobactam has been considered as a possible alternative in treatment. Furthermore, these patients have pathophysiological changes thataffect the outcome of treatments and require the best therapeutic choices, including customized doses due to the severity of the condition.[6,7] As a result, constant reviews are necessary to update therapeutic choices.

Recognizing the importance of updates on this subject, this article aims to review our knowledge of the antibiotic piperacillin-tazobactam, by describing the main commonly accepted, such as mechanism of action, resistance mechanisms, among others, combined with up-to-date information regarding clinical use to assist healthcare professionals in their decision-making.

Methodology

This scientific article on methodological characteristics contains a narrative literature review was conducted, which is characterized as "*not using explicit and systematic criteria for literature search and critical analysis*" (p. 2) and not employing "*sophisticated and exhaustive search strategies*" (p. 2).[8] This review aims to update the most important pharmacological and thera-

peutic aspects related to piperacillin-tazobactam. Unlike a systematic review, therefore, which aims to answer a specific question related to a particular subject matter issue, the literature research used does not require a detailed description of the "*methodology for searching for references, nor [of] the criteria used in the evaluation and selection of the works consulted*" (p. 50)[9], to achieve its purpose of outlining a "*state of the art of a particular subject, from a theoretical or contextual perspective*" (p. 1).[10]

In this context, we proceeded with the identification and meticulous analysis of bibliographic sources, including articles, books, and publications from reputable scientific institutions. This process was conducted based on the researchers' prior knowledge, including a rigorous approach to the comprehensive reading of such sources, followed by a critical evaluation aimed at extracting the most pertinent and relevant information. The sources consulted, written in both English and Portuguese, served as the foundation for organizing the following topics that constitute this study: (1) brief history; (2) chemical structure; (3) mechanism of action; (4) resistance mechanisms; (5) spectrum; (6) major clinical uses; and (7) adverse effects.

Brief history

Penicillin was discovered by Alexander Fleming in 1928, through the observation of the *Penicillium notatum* fungus (now called *Penicillium chrysogenum)* fungus, which contaminated a culture of *Staphylococcus aureus* at St. Mary's Hospital in London.[1,2] Fleming realized that the fungus produced an antimicrobial substance, which came to be named penicillin.[2] In 1940, Florey, Chain, and colleagues isolated penicillin, thus enabling the commercialization of penicillin G, which revolutionized the prognosis of infectious disease cases.[1,2] The emergence of organisms that produce beta-lactamases stimulated the development of components resistant to the hydrolysis of these mi-croorganisms and the search for agents that were more effective than penicillin G against Gram-negative organisms. In 1959, Batchelor and colleagues successfully simplified the isolation of 6-aminopenicillanic acid (6-APA), which forms the central core of penicillin G. This discovery marked the beginning of the field of semi-synthetic penicillin, with part of the product being obtained through fermentation and part obtained artificially through the introduction of radicals into the core structure. The discovery enabled the production and teting of various semi-synthetic peni-cillins, such as methicillin against beta-lactamase-producing *Staphylococcus aureus*, and ampicillin against selected Gram-negative bacilli, among others. Since then, ongoing research has sought drugs with various pharmacological and antimicrobial properties.[1,2]

Piperacillin, a member of the ureidopenicillin group, resulted from research aimed at identifying beta-lactams that are highly effective against *Pseudomonas* spp., have a broad spectrum of action, and are less toxic than aminoglycoside antibiotics. This antibiotic was introduced in 1976, as a derivative of ampicillin formed by the addition of a hydrophilic heterocyclic group to the gamma-amino group.[2,4] This modification gave piperacillin a broad spectrum of action against Gram-negative bacteria, in part due to its increased affinity with penicillin-binding protein (PBP)-3.[5] However, piperacillin is inactivated by plasmid-derived beta-lactamases produced by some microorganisms, and is therefore often combined with tazobactam, a derivative of sulfone of penicillanic acid, to enhance its effectiveness against such microorga-nisms.[2,4]

Chemical structure

Piperacillin is a synthetic penicillin derived from ampicillin, with the chemical name (2S,5R,6R)-3,3-dimethyl-7-oxo-6-[(2R)-2-[(4-ethyl-2,3-dioxo-1-piperazinyl)formamido]-2-phenylacetamido]-4-thia-1-azabicyclo[3.2.0]-heptan-2-carboxylic acid (Figure 1).[11]

Its structure features the beta-lactam ring, which is common to all antimicrobials referred to as beta-lactams, including peni-cillins. A lactam corresponds to a cyclic amide.[12,13] Amides are characterized by the presence of a nitrogen atom directly bonded to a carbonyl group. Therefore, in lactams, the nitrogen and the carbonyl carbon are part of a cyclic structure. The Greek prefix "beta" indicates that the cycle consists of a total of four atoms.[14] In penicillins, the beta-lactam ring is fused to a five-mem-bered thiazolidine ring. This bicyclic structure forms the structural backbone of all penicillins, and this structure is known as 6-aminopenicillanic acid (6-APA), biosynthetically formed by the cyclization of a dipeptide formed by the condensation between L-cysteine and D-valine. Am-picillin, as a side chain, has the (R)-2-amino-2-phenylacetyl group attached to the nitrogen at position 6 (N-6) of the central 6-APA skeleton. This structure is chemically formed by the linkage of this nitrogen to the carboxylic acid group of D-phenyl-glycine. Piperacillin, on the other hand, is synthesized from ampicillin by linking the amino group of the D-phenylglycine portion to a 4-ethylpiperazin-2,3-dione carbonyl group. Thus, piperacillin contains a piperazine ring in its structure, from which is derived (Figure 1).[11]

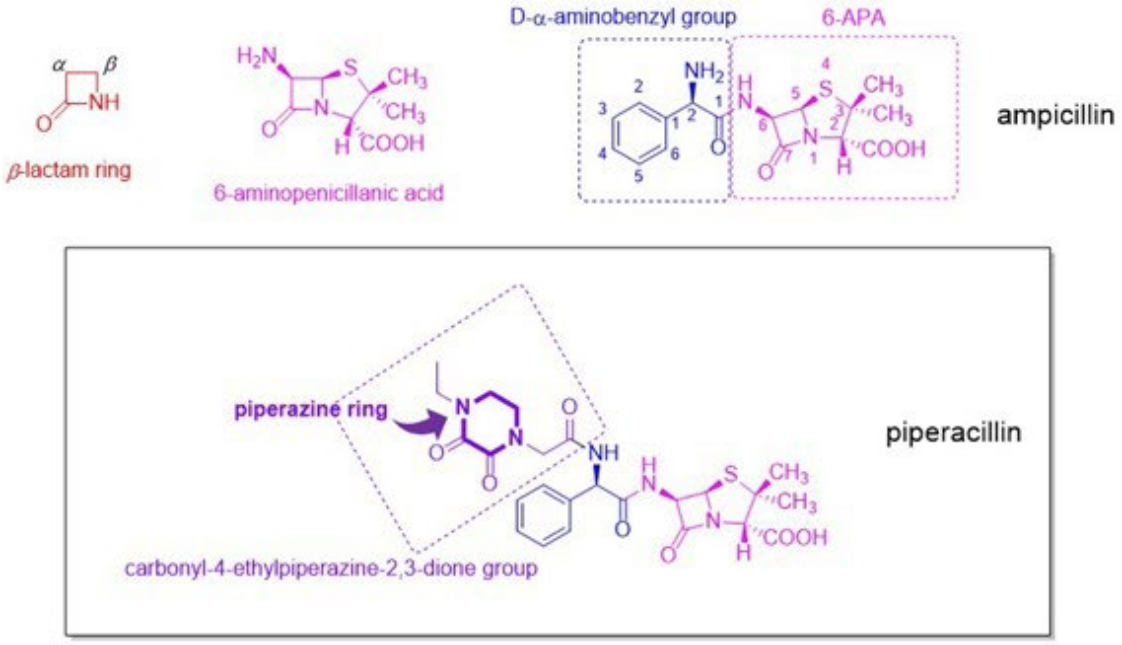

Figure 1. Chemical structures of the beta-lactam ring, 6-aminopenicillanic acid, ampicillin, and piperacillin. Note the piperazine ring as a constituent of the side chain in piperacillin.

Source: Self-generated image based on references.[12,15]

Mechanism of action

The drug's mechanism of action is related to the presence of the beta-lactam ring. The drug binds to penicillin-binding proteins (PBPs), located on the external surface of the cytoplasmic membrane, thereby preventing the formation of peptidoglycans, which are essential components of the bacterial cell wall, anda causes the osmotic lysis of bacterial cells.[2]

Piperacillin belongs to the group of penicillins that act by inhibiting the synthesis of the bacterial cell wall. Bacteria require several enzymes to biosynthesize and link the constitu-

ents of their cell walls, and PBP is responsible for the enzymatic activity of transglycosidases, transpeptidases, carboxypeptidases, and endopeptidases. Bacteria produce four types of PBPs, including high-molecular-weight PBP, low-molecular-weight PBP, which catalyze transpeptidation and carboxypeptidation, respectively, in cell wall assembly, and high-molecular-weight PBP class A, which are bifunctional enzymes with transpeptidase and transglycosylase domains. Penicillins bind to these proteins, by inhibiting enzymatic actions and, consequently, the biosynthesis of new peptidoglycan molecules — the essential component of the bacterial cell wall —and their incorporation into the developing bacterial cell wall. As a result, the cell in development has a defect in the formation of its cell wall, leading to osmotic lysis. Furthermore, the antibiotic action of penicillins also depends on the autolytic action of the bacteria's own enzymes on their cell walls, breaking down the old cell walls and enabling the bactericidal effect of the drug, since the new cell wall will be defective. However, cells that are not actively multiplying or are osmotically protected can survive the presence of penicillin. This suggests that the bactericidal effect of penicillins is directly related to the cell cycle and that the binding of penicillin to PBPs disrupts an essential event, wich possibly occurs during cell division.[1]

Resistance mechanisms

Four main resistance mechanisms exist: the destruction of antibiotics by beta-lactamases; the inability to effectively penetrate Gram-negative bacteria; the efflux through the membrane; and the low affinity of antibiotics to bind to PBPs.[1,16]

The primary resistance mechanism to piperacillin is enzymatic inactivation of the drug caused by the production of beta-lactamases by microorganisms. Beta-lactamases are enzymes that catalyze the hydrolysis of the beta-lactam ring and are divided into four classes (A to D), based on the similarity of amino acid sequences and molecular structure. Classes A and C are the most clinically significant, and class A enzymes are generally effectively inhibited by beta-lactamase inhibitors, unlike class C. However, point mutations can give rise to class A enzymes with an extended spectrum to penicilins, third-generation cephalosporins and aztreonam, referred to as extended-spectrum beta-lactamases (ESBL). The number of microorganisms producing ESBLs has increased in the recent past, and questions have been raised about the efficacity of piperacillin-tazobactam is effective against these bacteria.[4] Class B enzymes are produced by some non-lactose-fermenting Gram-negative microorganisms, with plasmid-mediated enzymes having the broadest spectrum and resistance to all beta-lactam antibiotics except aztreonam.[1] Tazobactam can inhibit class A beta-lactamases but not class B.[4]

Another important resistance mechanism is the drug's inability to penetrate its site of action, with the outer membrane of Gram-negative bacteria functioning as a barrier for this purpose. These microorganisms contain beta-lactamases in the periplasm between the outer cytoplasmic membrane and the outer lipopolysaccharide membrane, a strategy developed to keep PBPs away from beta-lactam antibiotics. However, some porins that allow the passage of mole-cules through this barrier depending on size, structure, and charge. Antibiotics that meet these requirements can pass through and bind to PBPs, but the absence or deletion of an essential porin, often associated with beta-lactamase activity, can lead to possible antibiotic resistance. Efflux is a third mechanism in which the drug that enters the periplasmic space is expelled from the membrane before it can act on PBPs. Usually, this efflux mechanism is accompanied by the destruction of antibiotics by beta-lactamases.[1] The primary mechanism that confers resistance to piperacillin-tazobactam is resistance due to structural differences in PBPs.[4] The action of PBPs in cell wall synthesis and assembly is essential, and the low affinity of PBPs

for beta-lactam antibiotics allows the antibiotic's effectiveness to be circumvented. This form of resistance occurs either through mutations in PBP genes that reduce binding affinity or through the presence of an additional low-affinity PBP.[1]

Spectrum

Piperacillin is a broad-spectrum antibiotic that is effective against strains of *Streptococcus* spp, *Neisseria* spp, *Haemophilus* spp, and other microorganisms of the *Enterobacteriaceae* family, such as *Klebsiella* spp, *Enterobacter* spp, *Serratia* spp, and indole-positive *Proteus*.[1,2] Additionally, it has an effective response against anaerobic cocci and bacilli and can inhibit approximately 60 to 90% of *Pseudomonas aeruginosa* strains at concentrations below 16 micrograms/ml. However, it is hydrolyzed by beta-lactamases of classes A and B, and it is often combined with tazobactam to enhance effectiveness against beta-lactamase-producing organisms.[1] The combination of piperacillin-tazobactam present in vitro antibacterial activity against *Escherichia coli* and *Klebsiella pneumoniae* producing ESBL, although it is less potent against ESBL-non-producing isolates. In clinical practice, bacteria such as *Enterobacter* sp, *Citrobacter* sp, *Burkholderia* sp, *Sal-monella* sp, and *Stenotrophomonas maltophilia* are resistant to piperacillin-tazobactam.

Main clinical uses

In Brazil, due to its efficacy against enterobacteria, anaerobes, and enterococci, piperacillin-tazobactam is prescribed for surgical intra-abdominal infections and hospital-acquired infections caused by *P. aeruginosa, Acinetobacter, Serratia, Klebsiella*, and indole-positive *Proteus*.[2,5] In the treatment of skin and soft tissue infections, pneumonia, intra-abdominal infections, polymicrobial infections, and febrile neutropenia in combination with an aminoglycoside, its efficacy is equal to or greater than antibiotics with a similar spectrum.[1] However, recent studies have concluded that empirical treatment with piperacillin-tazobactam is not recommended, a finding which was also observed in infections caused by #P. aeruginosa#.[3,17,18,19] Regarding empirical use for patients with hospital-acquired sepsis and unknown-source septic shock, a study in Australia recognized a lack of more robust evidence for this recommendation.[17] Furthermore, the same study rejected the recommendation of piperacillin-tazobactam over carbapenems for ESBL producers, which was also certified in other reviews that even mention the reduced effectiveness of piperacillin-tazobactam when associated with carbapenem resistance.[3,17,18,19] Evidence exists for the use of piperacillin-tazobactam in the treatment of urinary tract infections caused by ESBL-producing *Enterobacteriaceae* if susceptibility is confirmed. However, the most appropriate approach to the treatment of ESBL-producing microorganism infections is to conducti tests aimed to identifying resistance patterns and susceptibility in order to guide the best therapy.[6,7]

The use of antibiotics in the empirical treatment of *Pseudomonas* spp infections is risky and uncertain, and the use of piperacillin-tazobactam is not recommended due to the increasing resistance rates, according to a recent study. Therefore, rapid detection of resistance patterns and susceptibility to antimicrobials should be prioritized.[20] Of course, since we are dealing with severe and potentially life-threatening infections, treatment should always be initiated based on the monitoring the presumed sensitivity/resistance profiles of the agent and later adjusted accordinng to culture results.

As previously mentioned, piperacillin is widely used in a hospital environments due to its effectiveness in the treatment of infections that typically affect patients in these settings. However, this usage presents another challenge since critically ill patients require

specific treatment due to physiopathological changes that impact pharmacokinetics and cause variability in treatment effectiveness.[6,21] In such cases, there are good indications for continuous infusions and therapeutic drug monitoring, but further studies are needed to recommend this practice.[6] Establishing the required dose in critically ill patients is a challenge, and it is essential to achieving pharmacokinetic and pharmacodynamic goals. One study showed that defining these goals had more impact on the likelihood of achieving the target than the use or intensity of continuous renal replacement therapy, and it is necessary to define soft or more stringent targets, or even individualized goals depending on the patient, must be defined.[21]

Adverse effects

As in the case of most penicillins, hypersensitivity reactions have been described, ranging from rashes to anaphylaxis, superinfections, neurological toxicity at high doses, and irritative effects on blood vessels leading to phlebitis. During long-term administration at high doses, neutropenia may occur, which is reversible upon drug withdrawal. Less frequen-tly, hypokalemia and changes in bleeding time occur.[1,2,16] Despite drug-related fixed drug eruptions being widely described in association with piperacillin-tazobactam, a recent case of generalized fixed drug eruption was published, which appears to be related to drug reexposure.[7] In addition, specific dos-ing helps reduce adverse effects, while overexposure to piperacillin-tazobactam seems to be associated with increased mortality.[17,21]

It should be emphasized that the action of the drug against anaerobes can, collaterally, determine colonization by multi-resistant microorganisms, particularly in a hospital environments. Intestinal microbiota are predominantly composed of such agents and, therefore, we can result in the emergence of multidrug-resistant infections, including fungal infections such as *Candida* spp, may emerge.[22]

Conclusions

The antibiotic piperacillin-tazobactam is routinely used, primarily in situations that require decisive interventions, and a comprehensive and up-to-date understanding of the drug can assist in the therapeutic choices made on a daily basis. The safe use of this antibiotic for infections now depends on rapid testing of resistance and susceptibility to antimicrobials, and the empirical use of piperacillin-tazobactam or its use for ESBL-producing microorganisms is not recommended. In situations involving patients with renal replacement therapy, it is important to quickly achieve appropriate antibiotic goals, which require meeting pre-determined targets, must be achieved quickly. For critically ill patients, awareness of pharmacodynamic and pharmacokinetic variability is essential. However, several studies reviewed for this article revealed the need for additional research in clinical practice to address doubts and provide certainties, such as the recommendation for continuous therapy. Furthermore, growing concerns about resistance tto antibiotic underscores the need to consider alternatives, for example, to the currently used carbapenem. Although current studies indicate that piperacillin-tazobactam may not be the best alternative for all situations in critical patient care, new studies and new needs may shape innovative developments in this story.

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