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B-Lactam Antibiotics in Daily Dentistry Practice: A Critical Review

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Abstract: Antimicrobial therapy has an essential role in the management of the oro-facial infections of odontogenic origin. The aim of this study, is to report a detailed review about the activity of the β -lactams in the odontostomatological practice. This group of antibiotics is very used in daily practice of dentistry for the prophilaxis and for the aspecific or specific therapy. The etiology of odontogenic infections is usually attributed to the endogenous flora of the mouth and not to the introduction of non-resident bacteria. This infections are typically polymicrobial; however, anaerobes generally outnumber aerobes by at least four fold. B-lactams are a large group of antibiotics in constant evolution, in fact, it includes penicillins, cephalosporins, carbapenems and monobactams. Penicillins are the oldest group of antibiotics, they are very diffused in the dentistry clinic but they hears again a lot the problem of the bacterial resistance. Cephalosporins is also more diffused and their new generations are deserving of attention. Carbapenems and monobactams are molecules relatively new but in constant evolution and they represent a possible future of antibiotics therapy.

Key words: B-lactam, antibiotics, penicillin, cephalosporin, carbapenem, monobactam

INTRODUCTION

Antimicrobial therapy has an essential role in the management of the oro-facial infections of odontogenic origin. The majority of odontogenic infections are self limiting and may drain spontaneously. However, these infections may drain into the anatomical spaces adjacent to the oral cavity and spread along the contiguous fascial planes, leading to more severe infection. Antibiotics is very used in daily practice of dentistry for the prophilaxis and for the aspecific or specific therapy (Flynn *et al*., 2006a, b). The etiology of odontogenic infections is usually attributed to the endogenous flora of the mouth and not to the introduction of non-resident bacteria. This infections are typically polymicrobial and the causal bacteria are generally saprophytes. On the other hand, invasive dental interventions give rise to transient bacteremia. When an oral lesion is contaminated by extrinsic bacteria, the required antibiotic treatment should be provided as soon as possible. B-lactams are a large group of antibiotics in constant evolution, in fact, it includes penicillins, cephalosporins, carbapenems and monobactams. This study will focus the characters of the β- Lactams antibiotics and their used in the dentistry daily practice.

β-lactams: β-lactams represent one of the most efficient antibiotics and in the treating a large variety of infections, including the odontostomatological ones. This kind of antibiotics represent the first choice either in the therapy and in the prophylaxis of the odontogenic infections. Prophylaxis is required in all immunocompromised patients, as well as in individuals with cardiac problems associated with endocarditis, vascular catheters or prostheses (Horstkotte *et al*., 2004). The following antibiotics belong to this class: Penicillins; Cephalosporins; Carbapenems and Monobactams (Flynn *et al*., 2006a, b; Amico *et al*., 2003). The anti-microbial activity of the β-lactams is tied with a β-lactam ring, contained in all these mixtures, so if this last one is opened, it looses the antibiotics activity. The β-lactams differ among themselves for the substitution of a radical in the lateral chain of the β-lactam ring, except for monobactams which present only the β-lactam ring. All the β-lactams act forbidding the synthesis of the cellular wall in the final phase of the peptidoglycan synthesis inhibiting the formation of peptidoglycan cross links in the bacterial cell wall. The β-lactams moiety of penicillin binds to the enzyme (transpeptidase) that links the peptidoglycan molecules in bacteria and this weakens the cell wall of the bacterium (in other words, the antibiotic causes cytolysis or death). In addition, the build-up of peptidoglycan precursors triggers the activation of bacterial cell wall hydrolases which further digest the bacteria's existing peptidoglycan

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(Marin and Gudiol, 2003). When the bacteria lose their cell walls they are then called spheroplasts.

Other actions of β-lactam antibiotics have as a goal the reaching of action sites, called Penicillin-Binding-Proteins (PBP). The β-lactams, nevertheless, aren't able to influence all the batteries because of the introduction of Resistance mechanisms due to three fundamental mechanisms: Reduction of the permeability of the batteries Gram cellular wall Bacterial production of a β -lactamase which hydrolyses the β -lactam ring and alteration of the target proteins PBP (Fig. 1).

Transient bacteraemia is a known risk factor following oral surgery and invasive dental procedures in patients with altered immune system response and those with a susceptible site of infection (patients with heart valve prostheses or recent joint replacements, etc.) (Maester and Gomez-Lus, 2007; Oliver *et al*., 2004; Planells *et al*., 2006). The most commonly isolated aerobic bacteria in postoperative bacteraemia are Streptococcus Viridans. However, other periodontal pathogenic anaerobic bacteria are found in up to 64% in blood cultures (mixed bacteria or anaerobic bacteria alone). Dental pathogenic bacteria do not appear to be covered by standard amoxicillin or clindamycin prophylactic regimens (Table 1). A personal history of exposure to dental pathogenic bacteria may have an impact on the patient s global health, not only because of classical local or systemic infectious complications, but also because dental pathogenic bacteria have been found in atheromatous plaques in coronary and carotid arteries. This finding along with epidemiological data, suggests that such bacteria may contribute to the progression of vascular arteriosclerotic lesions and the occurrence of cardiovascular and/or cerebrovascular accidents, although the pathogenic mechanisms involved are not yet well known. Taking these facts into consideration and in view of antimicrobial sensitivity data available at present, we believe that the use of amoxicillin/clavulanic acid is the most appropriate option for prophylaxis of all infectious risks associated with bacteraemia of oral origin, due to its broader cover of dental pathogenic bacteria and its pharmacokinetic profile (Lockhart *et al*., 2006; Maestre and Gomez-Lus, 2007; Oliver *et al*., 2004; Planells *et al*., 2006).

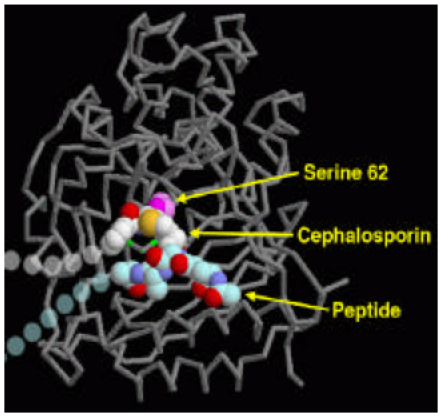

Fig. 1: Inhibitory mechanism of the β-lactam antibiotics

PENICILLINS

This group of β-lactams is the first example of antibiotics. They are formed by a nucleus (6-aminopenicillanic acid) with different lateral chains able to influence the pharmacokinetic peculiarities and the action spectrum. The penicillin interferes with the production mechanism of the bacterial peptidoglycan forbidding the formation of crossed links of the cellular wall. Specific enzymes congregate to form these links which become the PBP of the penicillin (Fig. 2).

The referring penicillin is the benzylpenicillin, known as penicillin G, particularly active towards, Gram + cocci, Gram + bacilli, Gram-cocci and spirochaetal but not towards batteries like the staphylococci, able to produce enzymes as the penicillinases which can destroy the penicillin. This natural penicillin was casually discovered in the 1928 by Fleming, who extracted it from the *penicillum notatum*.

Table 1: Prophylactic antibiotic regimens (Horstkotte *et al*., 2004)

Dental, oral, respiratory and esophageal procedures (P)	
Not allergic to penicillin:	Amoxillin 2.0g (children 50 mg kg^{-1}) p.o. 1h before P
Unable to take oral medication:	Amoxicillin or ampicillin 2.0g (children 50mg kg^{-1}) i.v. 1/2 -1h before P
Allergic to penicillin:	Clindamycin 600mg (children 20mgkg^{-1}) or azithromycin/clarithromycin 500mg (children15 mg kg^{-1}) 1h before P

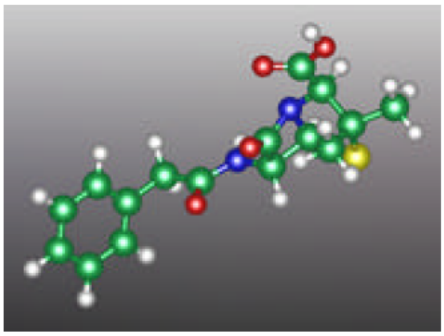

Fig. 2: Tridimensional representation of the penicillin G structure

Actually it is extracted from the *penicillum crysogenum* through fermentative way, which assures better results. Penicillin G is typically given by a parenteral route of administration (not orally) because it is unstable in the hydrochloric acid of the stomach. Because the drug is given parenterally, higher tissue concentrations of penicillin G can be achieved than is possible with phenoxymethylpenicillin. These higher concentrations translate to increased antibacterial activity. The penicillin V, phenoxymethylpenicillin , has the analogous spectrum as the G penicillin but it is better adsorbed through oral way. The streptococci are particularly susceptible to this two kind of penicillin. In the prophylaxis treatment, Penicillin V associated to clavulanic acid and administered via the oral route is known to be effective against odontogenic infections. In the case of allergies to penicillin, an alternative drug is clindamycin. Most acute infections are resolved within 3-7 days (Planells *et al*., 2006). In recent years, the tendency is to reduce general antibiotic use for preventive or therapeutic purposes. The penicillins are elective medicine against actinomycosis and syphilis and are used in the endocarditic cases associated to an aminoglycosidic. Toxicity is pratically insignificant, but the penicillin G can determine an alteration of the piastrinic aggregation and the super-infections of Candida Albicans are not infrequent after a treatment with ampicillin. Allergy to these medicines represents the biggest iper-sensibility reaction. The principal penicillin of dentistry interest are the Aminopenicillins which extend their activity to the Gram + e Gram- micro-organisms. They are penicillin susceptible to the β-lactamase and this is the reason they are associated with substances that inhibit these enzymes like the clavulanic or sulbactam acid (Lauber *et al*., 2007; Limeres *et al*., 2005).

AMOXICILLIN

This aminopenicillin presents a very good activity towards almost all the anaerobic strains and the Streptococci which constitute the oral flora, in particular Actinomyces, Propionibacterium, Peptostreptococus, Veillonella, Fusobacterium and some streptococci that cannot be grouped, like Streptococcus sanguis, Streptococcus mitis and Streptococcus salivarius (Bancescu *et al*., 2006). It results active, moreover, towards the Gram-aerobes and the Streptococcus Pneumoniae and S. Pyogenes. On the contrary, Amoxycillin doesn't result active towards Actinobacillus actinomicetemcomitans e Campylobacter, micro-organisms known as etiologically responsible for the youthful periodontitis. Altrought amoxicillin and ampicillin have similar spectrum and structure, they are totally different for the pharmacokinetic: Amoxicillin owns a faster and more complete absorption through oral way (about 93%), which is not influenced by the contemporary presence of food in the stomach. Amoxocillin is consequently suggested against all the bacterial odontogenic infections supported by susceptible germs, in particular: Pulpitis; Postextraction alveolar osteitis; Periapical Abscess; Perimaxillary adenoflemmone (Diz *et al*., 2006). In the case of pulpitis, such treatment is usually not indicated if the infection only reaches the pulp tissue or the immediately adjacent tissues. In the event of dental avulsion, local antibiotic application is advised, in addition to the provision of systemic antibiotics (Lockhart *et al*., 2004).

AMOXICILLIN + CLAVULANIC ACID

Clavulanic acid is a mixture composed by a β- lactam structure, not endowed with anti-bacterial action on its own, but able to inhibit in a definitive way a lot of β-lactamase. The clavulanic acid faces the β-lactamase enzymes in the external environment of the Gram- bacteria. The contemporary administration of clavulanic acid and amoxycillin determines a "deviation" from the β- lactamase enzymes to the clavulanic acid, thanks to a better affinity, allowing the amoxycillin, still entire in its structure, to express its full bactericide activity. Clavulanic acid is also known as "suicide inhibitor" because, after contracting a specific and irreversible link with the active site of the enzyme, it is destroyed with it. The bacterial activity on β-lactamase productive strains, which are resistant to the sole amoxycillin, is very elevate. Beside restoring the amoxycillin sensibility, the combination enlarges the antibiotics spectrum even to those strains normally not included, such as Staphylococcus aureus and Bacteroides. This two components, amoxycillin and clavulanic acid, present similar pharmacokinetic parameters. The oral absorption results very good and it is not influenced by the contemporary presence of food in the stomach; The bio-availability corresponds, in fact, to more than the 90% for the amoxycillin, while the clavulanic acid goes through the 70%. The maximum levels are reached, from both the components, after about an hour from the oral administration and the profiles of their plasmatic concentration result parallel. The diffusion inside the tissues and the different organic liquids is elevated and in the main cases their concentrations remain within an optimal balance. The elimination principally occurs through the urinary tract and partially, through the bile ducts. Clavulanic acid is metabolised in instable mixtures. The oral administration increases a good compliance toward the patients and it allows an

alternative therapeutic approach, even better than the intravenous one, in pathological forms resistant to β-lactams supported by micro-organisms which produce β-lactamase (Lockhart *et al*., 2004). This combination is consequently indicated in serious oral pathologies such as: Postextraction alveolar osteitis; Osteomyelitis; Periodontal Abscess; Periodontitis. Besides, Amoxicillin/clavulanic acid is efficacious in reducing the incidence of Inflammatory complications following third molar extraction but should not be prescribed in all cases (Lacasa *et al*., 2007; Santamaria *et al*., 2005).

AMPICILLIN

It was the first semi-synthetic penicillin with wide spectrum and oral way administration and this constitutes a milestone in the antibiotic therapy. Concerning the oral cave micro-organisms, the ampicillin has practically the same spectrum and the same intrinsic antibacterial activity as the amoxycillin has. The bacteria resistance towards ampicillin, like the one towards amoxycillin, is realized through resistant plasmids that confer a multiple resistance through the β-lactamase production. Ampicillin has a good stability in a acid ambiance, so it can be administered through oral way, but its absorption is very variable and in any case modest, only the 30-40% and it is remarkably conditioned by food. Through this way, gastric intolerance phenomena and intestinal dismicrobism can be frequent. The intravenous absorption, instead, results optimal, with haematic peaks about an hour after the administration, so ampicillin is better when intravenous administration is indicated. The half-life is about an hour and the linkage with plasmatic proteins is about 20%. It is principally expelled in unmodified way through renal way, but, for 20-30 %, through the bile ducts; a part goes into enter hepatic circulation, so it is partially eliminated through faecal way. The unwished effects relatively frequent in ampicillin are the allergic reactions of benign kind, such as erythema, itchiness, nettle rash, whereas the anaphylactic shock, that nevertheless occurs when the medicine is administered through intravenous way, is rare. In the odontostomatologic field, amoxycillin is preferred for the better oral absorption (Lockhart *et al*., 2006).

BACAMPICILLIN

It is a semi-synthetic penicillin ester of the ampicillin. Like the other ester, this medicine was formulated to obviate the inconvenient irregular absorption of ampicillin through oral way. Bacampicillin is a wide spectrum antibiotic that moreover presents the characteristic of being a pro-medicine, so it is lacking in antibacterial activity but lively, administred through oral way, it is activated after its absorption through its hydrolyzation by means of not specific esterases, with both tissue and haematic origin. It is without any doubt an advantage because this ester of Ampicilline presents a really elevated intestinal absorption (98%) with a biodegradability of 40% higher than Ampicillin, so permitting on the one hand an early and elevate concentrations of medicine in blood and tissues and on the other hand the nearly total absence of a biological active medicine in the intestine, with the consequent lacking of intestinal inconveniences peculiar to synthesis penicillin administrated through oral way. Gastric disorders (dyspepsia, nausea, gastralgia) may be attributed to the association of FANS, considering that many patients referred the disappearance of these disorders when they suspended the anti-inflammatory therapy and continued with the sole antibiotic. Definitely, Bacampicillin, for the width of its spectrum of action, for the modest collateral effects, for the comfortable assumption and for the fast therapeutic effect is a good remedy for the odontogenic diseases.

CEPHALOSPORINS

Cephalosporins are bactericide medicines with an activity both against Gram+ and Gram - germs. They inhibit the bacterial cell synthesis with a mechanism similar to the penicillin one. They are largely distributed to the main part of corporeal liquids and tissues with concentrations which are generally enough to control infections, especially in presence of inflammations. The penetration in the eye vireo and in the Cephalic Rachidian Liquor (CRL) is generally relatively poor. Cefuroxime and some cephalosporins of 3rd generation arrive in the LCR at some levels sufficiently elevated to solve meningitis. Cephalosporins tied in reversible way with plasmatic proteins: only the free quote results pharmacologically active. Cefoperazone is produced above all by the bile. Ceftriazone, even if it isn't produce by the bile as much as cefoperazone is, is eliminated in a significative way (33-67%) through this way. All the others cephalosporins and their metabolites (when there are ones) are eliminated above all through the urinary tract, usually through tubular secretion and glomerular filtration. Cephalosporins constitute a rather numerous group of β-lactam antibiotics which have in common a basic nucleus, the 7-aminocephalosporanic acid, structurally very similar to the penicillin one. Cephalosporins are indicated in the therapy of infections supported by Gram- bacilli and Gram+ cocci but they haven't advantage compared to penicillin

towards Gram- bacilli. All the antibiotics belonging to this class differentiate themselves only for some pharmacokinetic characteristics (Asbel and Levison, 2000). The widely quoted cross-allergy risk of 10% between penicillin and cephalosporins is a myth. Cephalothin, cephalexin, cefadroxil and cefazolin confer an increased risk of allergic reaction among patients with penicillin allergy. Cefprozil, cefuroxime, cefpodoxime, ceftazidime and ceftriaxone do not increase risk of an allergic reaction (Pichichero, 2006). Cephalosporins are divided in four generations: I generation Cephalosporins: They have a good effectiveness towards Gram+ cocci (with the exception of enterococci and meticillin-resistant staphylococci and coagulase+ and coagulase-) and towards the main part of strains of E. coli, P. mirabilis e K. pneumonias. Cefalexina, Cefradina and Cefadroxil are well absorbed after the oral administration. II generation Cephalosporins: These ones present an increased activity against Gram- among which these is H influenzae, but not so good towards Gram+. Cefaclor, cefossitina, cefmetazolo belong to this class of antibiotics. III generation Cephalosporins: These medicines have an excellent activity against Gram- such as Enterobacteriaceaebut they are little active against Gram+. Cefoperazone, cefotaxime, ceftriazone are some exempla of this kind of medicines. IV generation Cephalosporins: They present a spectrum completely analogous to the III generation cephalosporins but they are more resistant to β-lactamase hydrolysis codified by plasmids or chromosomes. Cefepime is one of them. Also, Cefepime's twice-daily dosage and increased activity against Enterobacteriaceae may offer some advantages over older cephalosporins.

CARBAPENEMS

Carbapenems are the choice for mixed nosocomial and multiresistant bacterial infections. They presents a very wide bacterial spectrum, the wider among the β-lactams. They have a rapid bactericide activity dues to a fast crossing of bacterial wall by D2 porine and to a great stability in the hydrolytic action operated by almost all the plasmidic and chromosomal β-lactamase. Carbapenems are some β-lactam antibiotics endowed with a sole nucleus structure, where the sulphur atom is substituted for a carbon one. They are derived from olivanic acid, which is a β-lactamase inhibitor. They inhibit many aerobic and anaerobic cocci and a great number of Gram- species. The spontaneous selection of micro-organisms resistant to carbapenems is a very exceptional event. They are endowed with a rapid capacity to enter the bacteria and an immediate and high affinity with their goal. Meropem and imipenem, which is associated with cilastina, belong to this group. Imipenem and meropenem, members of the carbapenem class of beta-lactam antibiotics, are among the most broadly active antibiotics available for systemic use in humans (Hellinger and Brewer, 1999). They are active against streptococci, methicillin-sensitive staphylococci, Neisseria, Haemophilus, anaerobes and the common aerobic gram-negative nosocomial pathogens including Pseudomonas. Resistance to imipenem and meropenem may emerge during treatment of P. aeruginosa infections, as has occurred with other beta-lactam agents; Stenotrophomonas maltophilia is typically resistant to both imipenem and meropenem. Like the penicillins, the carbapenems have inhibitory activity against enterococci. The carbapenems should be considered for treatment of mixed bacterial infections and aerobic gram-negative bacteria that are not susceptible to other beta-lactam agents (Mouton, 2000).

MONOBACTAMS

They have a selective spectrum turned against aerobic Gram- bacilli (*Enterobacteriaceae*, *P. aeruginos*). They present an elevate and intrinsic antibacterial activity and a remarkable resistance towards endo- β-lactamase, a fair tissue wide spreading and a very reduced toxicity. They are a good choice in case of allergy towards penicillin and cephalosporins. Among these antibiotics we mention aztreonam. Aztreonam is not nephrotoxic, is weakly immunogenic and has not been associated with disorders of coagulation. Aztreonam may be administered intramuscularly or intravenously; the primary route

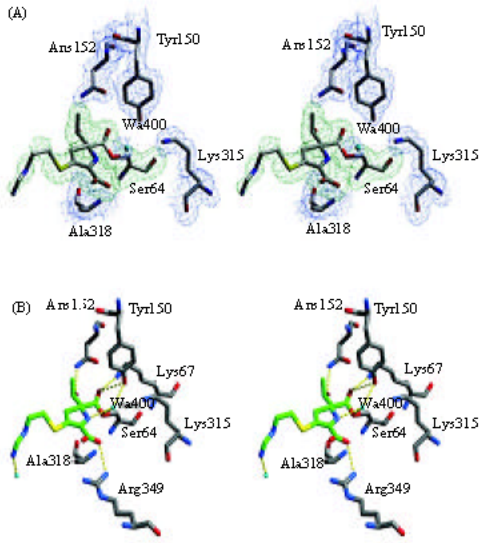

Fig. 3: Mechanism of inhibitory action of the β-lactamase of Imipem

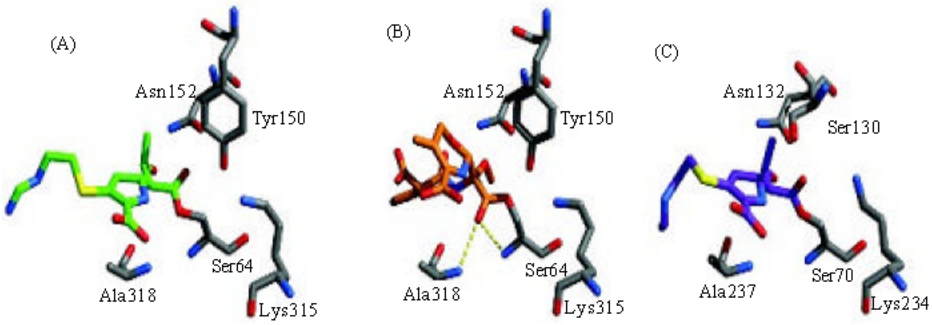

Fig. 4: Mechanism of inhibitory action of the β-lactamase of Imipem (the carbon molecule of Imipem is green in A e purple in C)

of elimination is urinary excretion. Aztreonam is used primarily as an alternative to aminoglycosides and for the treatment of aerobic gram-negative infections. It is often used in combination therapy for mixed aerobic and anaerobic infections. Concurrent initial therapy with other antimicrobial agents is recommended before the causative organism has been determined in patients who are seriously ill or at risk for gram-positive or anaerobic infection (Asbel and Levison, 2000; Hellinger and Brewer, 1999; Mouton, 2000) (Fig. 3 and 4).

CONCLUSION

Odontogenic infections are typically polymicrobial. The pathogenesis of odontogenic infections is dependent on a synergistic relationship between aerobic and anaerobic bacteria. Historically, the penicillins have been used as first-line agents in the treatment of odontogenic infections. The increasing prevalence of ß-lactamase production in dental pathogens and the coincident reports of clinical failures have decreased the usefulness of these agents.In view of antimicrobial sensitivity data available at present, we believe that the use of amoxicillin/clavulanic acid is the most appropriate option for prophylaxis of all infectious risks associated with bacteraemia of oral origin, due to its broader cover of dental pathogenic bacteria and its pharmacokinetic profile. Cephalosporins are indicated for the prophylaxis and treatment of bacterial infections caused by susceptible organisms. First-generation cephalosporins are predominantly active against Gram-positive bacteria and successive generations have increased activity against Gram-negative bacteria (albeit often with reduced activity against Gram-positive organisms). The carbapenems offer a broad antimicrobial spectrum and meropenem has an improved safety profile compared with imipenem. Aztreonam is a useful alternative for patients with aerobic gram-negative infections who are allergic to penicillin. The emergence of resistant organisms, however, is an increasing problem with the frequent use of these antibiotics.

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