ISSN: 2456–5474 RNI No.UPBIL/2016/68367 Vol-2* Issue-2* March-2017
Innovation The Research Concept

Application of Clavulanic Acid in Treatment of Diseases

Rajesh K. Srivastava
Assistant Professor,
Deptt.of Biotechnology,
GIT, GITAM University,
Gandhi Nagar Campus,
Rushikonda, Visakhapatnam,
A. P.

Abstract

Clavulanic acid combination with other β-lactam antibiotics has been used successfully to treat various infectious diseases, caused by microorganisms which produce β-lactamase enzyme. There are currently new antibacterial compounds in development and pre-clinical stage to cure the diseases effectively. It is thus necessary to make the best use and safe of currently available agents. Many combination drug /products containing amoxicillin and clavulanic acid is has been used to treatment of diseases effectively and they belongs to the group of medications known as antibiotics. Many bacteria has tendency of keeping β-lactamase enzyme which can make inactive by breakdown of β-lactam ring of the many antibiotic containing in its structures. It is used to treat infections caused by certain bacteria. Amoxicillin works by killing the bacteria that is causing the infection. Clavulanic acid helps make the amoxicillin more effective. This medication is most commonly used to treat various infections of the sinus, ear, lung, skin, and bladder.

Keywords: Keyword: β-lactamase, antibiotics, Clavulanic acid (CA), Diseases, infection

Introduction

Infections are currently ranked as the leading global burden of disease with respiratory diseases playing the most significant role. Antibiotic resistance remains a serious problem, as it was even 50 years ago.The 1970s saw the introduction of a number of important new antimicrobial agents, such as amoxicillin, but despite a high level of clinical success, a serious mechanism of resistance had emerged which could render the penicillins inactive - beta-lactamase production. In 1972, a potent inhibitor of beta-lactamase was identified. It was produced by *Streptococcus clavuligerus* as clavulanic acid. Amoxicillin, with its good oral absorption and broad spectrum antimicrobial activity, has chosen as the antibiotic and co-administered with clavulanic acid in tablet formulation (Gordon, 2010).

Today, there are currently new antibacterial compounds in development and most are at a pre-clinical stage. It is thus necessary to make the best use of currently available agents. The development of higher dosing regimens and pharmacokinetically has enhanced formulations to allow amoxicillin/clavulanate and it has played continue an important role in the treatment of a range of infections, particularly those of the respiratory tract, in both adults and children worldwide (Rollinson et al. 2008).

S. clavuligerus produces over 20 secondary metabolites, including many β-lactam antibiotics such as clavulanic acid, cephamycin C, deacetoxycephalosporin C, penicillin N (an intermediate in cephamycin C pathway) and at least four other clavams. Different carbon sources such as palm oil, olive oil, glycerol can be used for the production of clavulanic acid. Use of olive oil and palm gives better concentration of clavulanic acid than glycerol.But the cost of olive oil is much higher than glycerol. So, considering all necessary parameters for the production glycerol is used as the best suited carbon source (Bellão et al., 2013).

The downstream processing of clavulanic acid involves a series of steps. After the fermentation process, solvent extraction is carried out which follows freeze drying to prepare clavulanic acid crude salt at -20°C. Then ultrafiltration is carried out and nanofiltration can also be done for more concentration followed by centrifugation and ion-exchange charomatography with Amberlite XAD4-ABDA to get pure clavulanic acid.

Clavulanic Acid (CA) Characteristics

Clavulanic acid appears to be active against a wide spectrum of gram positive and gram negative bacteria. It exhibits only weak antibacterial activity and is, therefore, unsuitable for use by itself. Hence, it is used in combination with certain antibiotics for effective clinical and

therapeutic use to overcome problems related to antibiotic resistant pathogenic bacteria.

The combination of amoxicillin and clavulanic acid is used to treat certain infections caused by bacteria, including infections of the ears, lungs, sinus, skin, and urinary tract. Amoxicillin is in a class of medications called penicillin-like antibiotics. Amoxicillin with clavulanic acid is also used to treat some dental infections that are resistant to other penicillins. (Hoban et al., 2003). It works by stopping the growth of bacteria. Clavulanic acid works by preventing bacteria from destroying amoxicillin. Antibiotics will not work for colds, flu, or other viral infections. Amoxicillin and clavulanic acid also is used sometimes to treat certain sexually transmitted diseases (Gordon, 2010).

Physical and Chemical Properties

It forms a methyl ester which has a molecular weight (by mass spectroscopy) of 213.0635 which corresponds to the formula C_9 H_{11} NO_5. It appears as off-white crystalline powder. It competitively and irreversibly binds to beta-lactamases, including types II, II, IV and IV, and penicillinases produced by *Staphylococcus* spp. As a potent inhibitor of β-lactamase its presence in preparations of amoxycillin makes the combined product active against most strains of*Staphylococcus aureus* and some *Escherichia coli*, also against *Bacteroides* spp. and *Klebsiella* spp.

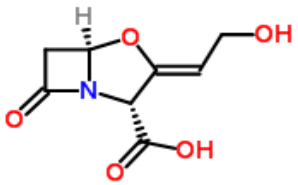

Figure 1: Structure of Clavulanic Acid with Molecular Formula: $C_8H_9NO_5$ and weight 199.16076

Perspective of Antibiotic Activity

CA is a major β-lactam antibiotic and discovered independently as the product of the organism *Streptomyces clavuligerus. S. clavuligerus* has been isolated in 1971 in a screening programme for producers of β-lactam compounds with improved resistance to β-lactamases. Ironically, the selection of *S. clavuligerus* is due to its ability to produce cephamycin C, and CA. It has only discovered when the strains from this first screen are subsequently examined for the production of β-lactamase inhibitors. In addition, a number of other species that produce clavam metabolites that are structurally related to CA (they carry the fused bicyclic β-lactam/oxazolidine ring system) have been described. However, Clavulanic acid with its 3R, 5R stoichiomistry is the only one among the metabolites in showing the β-lactamase inhibitory activity. All the others have the 3S, 5S stereochemistry and show no β-lactamase inhibition, although some have antibacterial or antifungal properties. Following its discovery, the chemical structure of CA is identified by Howarth et al. This compound is found to be an analog of the basic penicillin structure. In CA molecule, oxygen atom is substituted for sulphur, a characteristic of penicillin. As such, CA derivatives all contain an oxazolidine ring structure. The combined effective inhibition of β-lactamase and antibacterial activity of CA make it very important, both clinically and economically (Howarth et al., 1976). CA, in its plant in Lendava and the finished product in Prevalje. The consolidated sales of coamoxiclav in the US market exceeded $100 million in 2003 making the US Lek's biggest market. Thus commercial products such as Augmentin™ and Timentin™, combinations of CA together with amoxicillin or ticarcillin, respectively have made CA, a product valued in excess of a billion dollars/annum and created a powerful incentive to understand the biochemistry and genetics which underpins the production of this compound.

Applications

Pharmacological Actions of Clavulanic Acid

The effectiveness of a β-lactamase inhibitor/β-lactam combination against Gram-negative pathogens depends on many interplaying factors, one of which is the penetration of the inhibitor across the outer membrane.Farmer et al measured the relative penetrations of CA,sulbactum,tazobactum and BRL 42715 into two strains of *Klebsiella pneumonia* producing TEM-1- β-lactamase ,two strains of *Klebsiella pneumoniae* producing either TEM-1 or K-1, and two strains of Enterobacter cloacae each producing a class C β-lactamase . It was shown that CA penetrated the outer membranes of all these strains more readily than the other β-lactamase inhibitors. For the strains of E. coli and K. pneumoniae, CA penetrated approximately 6–19 times more effectively than tazobactum 2-9 times more effective than sulbactam, and 4–25 times more effectively than BRL 42715. The superior penetration of CA observed in this study contributed to the efficacy of CA/β-lactam and 4–25 times more effectively than BRL 42715. The superior penetration of CAobserved in this study contributed to the efficacy of CA/β-lactam combinations in combating β-lactam resistant bacterial pathogens.

Hoban et al. (2003) compared the in vitro activity of amoxycillin–CA with four comparator oral antimicrobial agents; ampicillin, azithromycin, cefuroxime and trimethoprim–sulphamethoxazole against 4536 recent clinical isolates covering 29 species isolated in the US and Canada between 1997 and 1999. Based upon minimum inhibitory concentrations (MICs), amoxycillin–CA was the most active agent against many Gram-positive species (Hoban et al. 2003).

Clavulanic Acid In Lower Respiratory Tract Infections

It has found it role when given as oral antibiotics in treatment of community-acquired lower respiratory tract infections. Amoxicillin/CA has been shown first choice treatments for community-acquired lower respiratory tract infection since its introduction nearly 25 years ago. Since then, it has become the "gold standard" against which most new oral antimicrobials are compared, but none of these newer

agents has demonstrated a superior efficacy. On the contrary, two recent studies comparing amoxicillin/CA with azithromycin, cefixime, or cipro- floxacin in the treatment of acute exacerbations of chronic bronchitis have demonstrated a higher efficacy rate for amoxicillin/CA (Jacobson et al.,1997) . The increasing rate of treatment failure with penicillin and other β-lactam antibiotics in pharyngotonsillitis caused by group A β-hemolytic streptococci (GABHS) has prompted the search for alternative antimicrobials. Both clindamycin and amoxicillin/CA have excellent clinical activity in pharyngotonsillitis. Mahakit et al. (2006) compared the clinical and bacteriologic efficacy and tolerability of oral clindamycin with those of oral amoxicillin/CA in the outpatient treatment of acute recurrent GABHS pharyngotonsillitis. In this study, in patients with acute recurrent GABHS pharyngotonsillitis, oral clindamycin 300 mg BID and oral amoxicillin/CA 1g BID achieved comparable rates of bacteriologic eradication at 12 days and 3 months and comparable clinical cure rates at 3 months.Patients who receive clindamycin had significantly greater cure rates at 12 days (Mahakit et al., 2006).

Clavulanic Acid In Urinary Tract Infections

Adjei and Opoku (2004) studied the effect of CA on urinary tract infections in African infants. Urinary tract infection (UTI) causes significant illness in the first 2 years of life. The diagnosis in most developing countries is often overlooked due to the tedious nature of obtaining urine from young infants who would not void voluntarily. Misdiagnosis very often led to avoidable ill health and long-term renal damage. There is a need to diagnose UTI in febrile infants to alert clinicians. A prospective study of febrile infants aged up to 12 months on admission was undertaken in a 6-months period. Urine specimen was obtained by supra pubic aspiration and investigated. Out of 150 urine samples screened for UTI, 45 (30%) had positive bacterial growth. E. coli (32%) and Proteus sp. (22%) formed more than 50% of the total isolates. The Gram-positive bacterium isolated was S. aureus representing 11%. All isolates were susceptible to cefuroxime and resistant to ampicillin. Susceptibility to amoxicillin/CA was 77.8% and to nitrofurantoin was 67% (Adjei and Opoku 2004)

Clavulanic Acid In Pregnancy

Czeizel et al. (2001) studied the human teratogenic potential of augmentin (amoxicillin + CA) treatment during pregnancy, and concluded it unlikely to increase the risk of congenital abnormalities in newborn infants when used in usual therapeutic dose. However, the number of cases and controls was limited; therefore, further multicenter–multinational studies are needed for the final risk assessment Czeizel et al., 2001).

Side Effects

Amoxicillin and clavulanic acid may cause side effects. Patient should consult with the doctor if any of these symptoms are severe or do not go away. Patient can face the problem of diarrhea which is indicated by having the symptom of loose motion (Howarth et al., 1976). He can have the trouble of upset stomach with vomiting problem. It can exhibit the mild skin rash. Other more symptoms can be seen and experienced, doctor should be called immediately. First problem severe skin rash and itching and hives may be noticed. Others may be having in difficulty in breathing or swallowing, wheezing, vaginal itching and discharge, yellowing of the skin or eyes (Nilsson-Ehle wt et al., 1985).

Conclusions

Clavulanic acid (CA) has properly of potent inhibitor of β-lactamase enzyme occurred in most pathogenic microorganism. Several species of bacteria such as *Streptomyces clavuligerus* or other microorganisms has produced it. Other β-lactam antibiotics and clavulanic acid combination has been treated various infectious diseases, caused by pathogenic microorganisms which produce β-lactamase enzyme. New antibacterial compounds are in development and most are at a pre-clinical stage. It is thus necessary to make the best use of currently available agents. During pregnancy, there are increase the risk of congenital abnormalities in newborn infants and it used in usual therapeutic dose to cure it. Effect of CA can observe in treatment of urinary tract infections in African infants. Amoxicillin/CA has been shown effective treatments of community-acquired lower respiratory tract infection since its introduction nearly 25 years ago.

Acknowledgement

I am thankful to Ritu Agrwal and Sahana Kolli, B. Tech students of 2014 batch who worked on literature survey part during their project.

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