Drug News

Co-Amoxyclav in ENT Infections

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Upper respiratory tract infections are amongst the most common illnesses associated with significant morbidity. The most frequently occurring ENT infections are acute tonsillitis, acute sinusitis pharyngitis, acute & chronic otitis media. Otitis media is a disease of infancy and early childhood, with a peak age specific incidence among children between the ages of 6-18 months. The other ENT infections mentioned are not restricted to any particular age group. The predominant organisms isolated from patients suffering from ENT infections are *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella cartarrhalis, Staphylococcus aureus, Pseudomonas aeruginosa.*

The management of ENT infections depends on the selection of an appropriate antibiotic. Decongestants and anti-histaminics may provide some relief, but are often of limited help in resolution of symptoms. The antibiotic of choice should have a spectrum of activity that includes *S. pneumoniae* and *H. influenzae,* limited side effects, availability in a convenient dosage schedule, palatability when provided in suspension, and it should be cost effective. **Augmentin** (a formulation of amoxicillin and potassium clavulanate) is a broad spectrum antibiotic effective against a wide range of pathogenic bacteria encountered in respiratory tract infections. Its special formulation has the property of irreversibly inactivating β-lactamase enzymes, which are responsible for the resistance of many of these pathogens to β-lactam antibiotics. There has been an increase in the prevalence of β-lactamase producing pathogens in ENT infections. Hence , Co-amoxyclav finds extensive use in the treatment of ENT infections.

Co-amoxyclave

History

In 1977, researchers at Beecham Laboratories discovered clavulanic acid, a substance produced naturally by the organism *Streptomyces clavuligerus* that had the property of inhibiting β-lactamases. When combined with penicillin, clavulanic acid blocks the active site of the enzyme β-lactamase, enabling the penicillin to produce its cidal effect on the bacteria.

Co-amoxyclav is a combination of clavulanic acid (as potassium clavulanate) with amoxicillin, the most widely used of the broad-

spectrum pencillins. This has renewed the efficacy of amoxicillin against strain that have become resistant to β-lactam antibiotics over the years. The similarity of the absorption profile of amoxicillin and clavulanic acid ensures their compatibility. The production of β- lactamse enzymes by a number of pathogens such as *S. pneumoniae* and *H. influenzae* has restricted the effectiveness of amoxicillin in general practice. Hence, the combination of clavulanic acid with amoxicillin has clearly extended the usefulness of a tried and proven first-line antibacterial agent.

Chemistry

Amoxicillin trihydrate

The actively bactericidal component of Co-amoxyclav is amoxicillin-(6R)-6(a-D-p-Hydroxyphenyl-glycylamino) penicillanic acid, presented as amoxicillin trithydrate in the oral form, and as amoxicillin sodium in the injectable form.

Potassium clavulanate

The component that confers protection against β-lactamases is potassium clavulanate-potassium (Z)-(3R, 5R)-2 -(beta Hydroxyethylidine) clavan -3 -carboxylate.

Mechanism of action

β-lactamase inactivation

The molecular structure of potassium clavulanate mimics that of amoxicillin, enabling it to bind at the active site of the b -lactamase and irreversibly block the enzme's activity. Amoxicillin inhibits the bacterial enzyme transpeptidase, thus disrupting the integrity of the bacterial cell wall by preventing cell wall synthesis. Amoxicillin is therefore rapidly bactericidal in growing or replicating cells.

Pharmacokinetics

Absorption after oral administration : Amoxicillin and clavulanate are pharmacokinetically compatible and possess similar absorption profiles, elimination characteristics and serum half lives. It is rapidly absorbed and reaches peak serum levels one hour after dosing. Doubling the dosage of Coamoxyclav apporoximately doubles the serum levels. The absolute bio-availability of clavulanic acid is about 60% , food has no effect on the bio-availabilities of amoxicillin and clavulanate. In adults, following injection 1.2g IV Co-amoxyclav, serum concentrations of amoxicillin and clavulanate are well in excess of those considered necessary for therapeutic efficacy. The ENT and fluid concentrations exceed the MIC values of the majority of the most likely pathogens such as *Haemophilus influenzae, Streptococci* and *Staphylococci.* The corresponding clavulanic acid concentrations are adequate to inactivate b-lactamases produced by these or other b-lactamase producing organisms. A pharmacokinetic study with Co-amoxyclav in patients with tonsillitis, showed good penetration of amoxicillin and clavulanic acid into the tonsils and 100% favourable response to therapy. (Agren et al, 1990). Mean elimination half-life of both clavulanic acid and amoxicillin is around 1 hour, they are mainly eliminated via urine. Amoxicillin is excreted mostly unchanged by tubular secretion, (55-84%) of the administered dose is recoverable from the urine within 6 hours of administration. Clavulanate is more extensively metabolized, clavulanic acid is excreted mainly by glomerular filtration and only 32-44% of the administered dose is recoverable unchanged from the urine.

Microbiology

The antibacterial spectrum of Co-amoxyclav is well established. As per the National Committee for Clinical Laboratory Standards (NCCLS) in the U.S, MICs of amoxicillin / clavulanic acid £ 8/4, 16/8 or ³ 32/16 mg/L indicate susceptible, moderately susceptible or resistant respectively, for species other than Staphylococcus and

Haemophilus (Todd & Benfield, 1990). For both of these species an MIC of ≤ 4/2 mg/L indicates susceptible and values of ≥ 8/4 or ≥ 8/16 mg/L are considered to indicate resistance of Staphylococcus and Haemophilus species (Todd & Benfield, 1990).

Effect of co-amoxyclav on beta-lactamase producing bacteria (Slocombe et al, 1984).

	MIC (mcg/ml)
Microorganism	**Co-amoxyclav**
S. aureus	1.0
S.epidermidis	1.0
H.influenzae	0.25
M. catarrhalis	0.25
N. gonorrhoeae	1.0
K. pneumoniae	4.0
E. coli	8.0
P.mirabilis	4.0
P. vulgaris	2.0
B. fragilis	0.5

β-lactamases are enzymes that catalyze the hydrolysis of β-lactam ring. In gram positive bacteria the β-lactamases are secreted into the outside environment, in the gram negatives the β-lactamases remain within the periplasmic space. The indiscriminate use of β-lactam antibiotics has been associated with the rise in the number of β-lactamase producing organisms. An increase in the prevalence of β-lactamase producing *Haemophilus influenzae* in ENT infections has been noted. These strain are increasingly becomng resistant to antibiotics like ampicillin.

β-lactamase inhibitors, such as clavulanic acid act as 'suicide inhibitors', binding to β-lactamases and preventing them from destroying β–lactamase. β-lactamase producing anaerobes such as Bacteroides spp., found in tonsils have the capability of conferring protection to β-lactam sensitive organisms , which are present in close proximity. This phenomenon is known as '***indirect pathogenicity***'. As a result bacterial strains which were otherwise susceptible to β-lactam antibiotics are now showing a trend towards resistance. It has been suggested that penicillin-sensitive *Streptococcus pyogenes* could be responsible for chronic recurrent tonsillitis of protected by β-lactamase-producing anaerobes, particularly of the Bacteroides species.

Until recently *Streptococcus pneumoniae* the causative organism of diseases like pneumoniae, sinusitis and otitis media was thought to be consistently susceptible to β-lactam antibiotics. The emergence of drug-resistant *Streptococcus pneumoniae* strains (DRSP) threaten to complicate the management of these illnesses. B-Lactam antibiotics, kill pneumococci by inactivating more than one high molecular weight penicillin-binding proteins (high-Mr PBP). The development of resistance occurs by the development of altered forms of the high-Mr PBP thus preventing binding of the β-lactam antibiotic to it. **In January 1995, NCCLS granted Co-amoxyclav separate and more favourable measurements against DRSP than of oral penicillin, oral ampicillin and most oral cephalosprins.**

Clinical efficacy in ENT infections.

Overall, the clinical and bacteriological efficacy of Co-amoxyclav has been shown for a wide range of infections yielding clinical cure and improvement rates of about 90% (Slocombe et al, 1984). There is no evidence in recent years to show that there has been a change in either the bacteriological or clinical efficacy of this drug. Effectiveness of Co-amoxyclav is ackonwledged against aerobes such as *S. Pneumoniae* and *H. influenzae* and also against anaerobes such as *B. fragilis* in acute, mixed and chronic infections.

Compared with other agents, Co-amoxyclav has one of the most comprehensive ranges of antibacterial coverage for acute sinusitis in children.

Efficacy of selected antimicrobial agents for the common pathogens in acute sinusitis (Stafford, 1990).

Antimicrobial agent	S.pneumoniae	H. influenzae β lactamase		M. catarrhalis β lactamase	
		negative	positive	negative	positive
Amoxicillin	+	+	-	+	-
Co-amoxyclav	+	+	+	+	+

+Effective - Not effective

In a trial of 50 adult patient with a variety of ENT infections, bacterial eradication was achieved in 93% of cases of mixed infection (Stafford, 1990). Co-amoxyclav achieved a good or excellent clinical result in 88% of patients. Treatment of ENT infections in 44 children with Co-amoxyclav showed excellent clinical and bacteriological results against infection due to both amoxicillin-sensitive and amoxicillin-resistant organisms. The overall success rate was 100% (Baba, 1982).

Amoxicillin-clavulanic acid can be a potential alternative in the treatment of streptococcal pharyngitis. Two comparative studies against phenoxymethyl penicillin have shown improved outcomes with amoxicilin-clavulanic acid. (Scaligone et al, 1997) The amoxicillin with clavulanate combination showed a good efficacy of 94.3% in a study conducted by Boschi et al (1992).

Infections of the middle ear are said to be most common infections in the world. The starting point is acute otitis media which may develop into chronic otitis media. Inadequate antibiotic therapy and incomplete resolution of infection at the acute stage may promote or contribute to middle ear effusions and recurrent otitis media. The antibiotic chosen must be effective against aerobic and anaerobic organisms including β-lactamase producing organisms.

Co-amoxyclav was compared with cefaclor in the treatment of a total of 133 infants and children with acute otitis media. Clinically, Co-amoxyclav proved superior to cefaclor , with a clinical success rate at 10 days of 98.4% compared to 95.7% for cefaclor (Kaleida et al, 1987). A further comparison of Co-amoxyclav with cefaclor found that the bacteriological success rate for-Co-amoxyclav was significantly better than that for cefaclor (jacobsson et al, 1988).

In a recent multicentre study of 1277 young children with otitis media, clinical effectiveness of Co-amoxyclav was evaluated as good or very good in 91.2% of cases. Co-amoxyclav proved to be outstandingly effective, well tolerated and easy to use (Cohen et al, 1989).

Amoxicillin-clavulanic acid can be expected to find a similar therapeutic niche to that once held by amoxicillin . i. e. a broad spectrum orally active agent effective in an environment of increasing β lactamase resistance.

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