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Review Article

Systemic antimicrobials for putative pathogens: immense snag for antibiotics against melange of microfloral etiology

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ABSTRACT

Inflammation starts and progresses because of biofilm, which is thought to be a main etiologic agent. Restoring the health status of periodontal tissues involves reducing the bacterial burden in periodontal pockets. The use of antibiotics as an adjuvant treatment is necessary in some circumstances, such as aggressive periodontitis, to get rid of harmful bacteria that have deeply penetrated the connective tissue and may later colonise the root surface and cause the illness to return. Penicillin was the first antibiotic historically used to treat periodontal disease and was taken systemically. Amoxicillin was later employed due of its impact on a number of important periodontal bacteria.
Penicillin was the first antibiotic historically used to treat periodontal disease and was taken systemically. Amoxicillin was later employed due of its impact on a number of important periodontal bacteria. In conclusion, despite a number of disadvantages, the use of antibiotics continues to be the most common and successful addition to mechanical periodontal therapy. However, these medications' undeniable drawbacks and restrictions cause the allure of using them to start to wear off. Based on a deeper understanding of the nature and aetiology of periodontal illnesses, this necessitates the search for new complementary treatments of periodontal therapy.Penicillin was the first antibiotic historically used to treat periodontal disease and was taken systemically. Amoxicillin was later employed due of its impact on a number of important periodontal bacteria.

1. Introduction

1.1. Subgingival biofilm

The use of antibiotics in periodontal therapy is justified by the microbial aetiology of inflammatory periodontal disorders. According to Moore et al. (1982), periodontal pockets may have been home to more than 500 different bacterial species. Lesions from periodontitis typically contain multiple potential pathogens rather than a single pathogenic species. Gram-negative anaerobic rods make up the majority of potential periodontal pathogens. However, some pathogens are facultative Gramme positive anaerobic rods and cocci, while others are facultative Gramme negative rods. The microorganisms that make up the subgingival biofilm create an extremely intricate and structured bio-community, thankfully not all of which are found in a single periodontal pocket. A glycocalyx matrix contains bacterial microcolonies that make up the subgingival biofilm. In the biofilm, nutrients are limited and growth is much slower. In addition, the biofilm protects its residents from both internal and external forces. [1]

1. Internal forces include toxic end-products such as lactic acid, which would normally lower the pH and inhibit the growth of many bacteria. In the biofilm,

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many end-products of bacterial metabolism serve as substrates for other species and are thus removed from the environment.
2. External forces include the host's immune response and the presence of toxic chemicals such as antibiotics and other antimicrobial agents.

It is widely acknowledged that a biofilm's inhabitants require an antibiotic dose that is several orders of magnitude higher than that needed to stop planktonic bacteria from growing.

Channels inside the microstructure of the biofilm can be seen using scanning electron microscopy and laser confocal microscopy on in vitro generated biofilms. It is believed that these pathways are required for nutrients to reach bacterial cells and microcolonies that are embedded in the biofilm matrix. Since most antibiotics have very tiny molecules (500 MW or less), it is possible that they could diffuse through these channels and travel through the biofilm with different nutrients. Additionally, it's probable that these antibiotics will stick to the glycocalyx, an extracellular component of the biofilm matrix.

Given that many antibiotics have a positive charge and are often hydrophilic, the idea of direct interaction between an antibiotic and glycocalyx looks to be quite likely. Once attached, the antibiotic is unlikely to reach the biofilm's deepest components, reducing its potency or even making it inert.[2]

According to a different view, resistant bacteria or their byproducts, such as -lactamase, may shield vulnerable bacteria from an antibiotic's effects. These elevated enzyme concentrations are presumably enough to protect both the germs that produce -lactamase and those that do not from penicillins. However, inactivating enzymes are not typically involved in the processes of antibiotic resistance within the oral flora.

The ability of the antibiotic to actually penetrate the bacterial cell or the capacity of the antibiotic to attach to a specific spot within the cell are affected instead by genetic determinants, whether chromosomal or plasmid-mediated. Also suggested is the existence of "persister cells" within the biofilm. In contrast to planktonic cells, these cells may exhibit a phenotype within the biofilm that involves the expression of genotypes or genes that are not necessary for survival in the nutrient-rich environment observed in laboratory conditions. Some genes that improve organism survival may get activated in order to survive in a highly competitive, nutrient-limited environment. These genes might potentially be responsible for the rise in antibiotic resistance. A subpopulation of "super-resistant" cells may develop as a result within the biofilm. Some evidence for the existence of super-resistant cells has been obtained with Pseudomonas aeruginosa**.**

The efficacy of periodontal antibiotic therapy is determined by the antimicrobial spectrum and the pharmacokinetic characteristics of the drug and by local environmental factors including:

1. Drug binding to tissues
2. Protection of pathogens through binding, consumption, or degradation of the drug by non-target microorganisms
3. Biofilm phenomena in plaque protecting the pathogens
4. Total bacterial load relative to the maximum achievable antibiotic concentration
5. Effectiveness of the host defenses
6. Pathogens in periodontal tissues, root surfaces, and extra-dental oral sites not affected by the therapy

2. Rationale for Use of Antibiotics in Periodontics

Suppression or eradication of periodontal infections is a key component of modern periodontal therapy. For periodontal patients who do not respond to traditional mechanical therapy, for those who have acute periodontal infections with systemic manifestations, for prophylaxis in patients with compromised immune systems, and as an adjunct to surgical and non-surgical periodontal therapy, antibiotics and chemotherapeutics have been prescribed.

Nonsurgical scaling and root planing may remove subgingival campylobacter rectus (Rams & Slots, 1993) but is frequently ineffective against porphyromonas gingivalis, prevotella intermedia, Bacteriodes fosythus, Staphylococci and enteric rods (Edwardsson et al 1999. Mombelli et al 2000, Petersilka et al 2002) and may not significantly reduce Actinomyces actinomycetecomitans (Rewert et al 1990, Takamatou et al 1999) or peptostrptococcus micros (Rams et al 1992). Mechanical debridement may fail to remove pathogenic micro-organisms because of their location in subepithelial gingival tissues (A.a) (Christenson et al 1987), crevicular epithelial cells (A, actinomycetemcomitans, P. micros, P. intermedia and P. gingivalis) (Dzink et al 1989, Taylor et al 1999, Rudney et al 2001), collagenous strata (P.gingivalis) (Naito et al 1988), altered cementum and radicular dentinal tubules (Adraines et al 1988, Giuliana 1997) subgingival hard deposits (Serino et al 2001) or furcations or anatomic structures complicating adequate instrumentation. Moreover, periodontal pathogens frequently colonize oral mucosa, tongue dorsum, tonsils and other oral domains and may translocate from non-periodontal site to periodontal crevices (Muller et al 1997, Ouirgnen et al 2001).[2,3]

Systemic antibiotics enter the periodontal tissues and the periodontal pockets via serum and can affect the organisms outside the reach of cleaning instruments or topical anti-infective chemotherapeutics. The following recommendations are given for antimicrobial drugs:

1. Localised juvenile periodontitis is one of the disorders linked with A. actinomycetmcomitans that the tetracyclines are indicated to treat. Other diseases

including rapidly progressing periodontitis may also benefit from their use. For optimal clinical and microbiological success, mechanical debridement should be used in conjunction with tetracycline therapy. Tetracyclines should also be given to patients with A. actinomycetemcomitans who are at risk for developing bacterial endocarditis before receiving routine antibiotic prophylaxis and dental care. Patients who cannot tolerate tetracyclines, have resistant A. actinomycetemcomitans, or were not successfully treated with tetracyclines should be given an alternate regimen of metronidazole (250 mg three times daily) and amoxicillin (500 mg three times daily) for at least 8 days.

2. The standard course of treatment for adults with typical cases of periodontitis includes surgical procedures as well as scaling and root planing. With the probable exception of metronidazole in some moderate-to-advanced cases, antibiotic treatment for these patients has not been demonstrated to be beneficial.
3. Cultural analysis is strongly advised to choose the right antibiotic in patients who have not reacted well to traditional treatment. Some of these individuals have been successfully treated with tetracyclines, metronidazole, Augmentin, a medication made up of metronidazole and amoxicillin, and clindamycin. Treatment for these individuals without microbiological testing increases the possibility of treatment failure, as well as the possibility of a pathogen overgrowth and disease worsening.
4. As with the administration of any drugs, patients must be informed of potential side effects and should be closely monitored during and after antibiotic therapy for any adverse side effects.

3. Practical aspects of Periodontal Antibiotic Therapy

3.1. Microbiological analysis

After traditional mechanical therapy is finished, subgingival microbiota may be analysed microbiologically to determine whether additional therapy, such as antibiotic treatment, is necessary. In order to confirm the elimination or marked suppression of the suspected pathogen(s) and to check for potential superinfecting organisms, such as Gram-negative enteric rods, pseudomonads, and yeasts, reevaluation with microbiological testing at 1 to 3 months after antimicrobial therapy may be useful.

3.2. Antibiotics selection

There haven't been many studies done on the best antibiotics to choose for refractory patients whose subgingival biota has been identified by microbial testing. Furthermore, since the majority of existing antibiotic regimens were created through empirical rather than scientific study, the ideal dose of antibiotics is still unknown.

Tetracyclines may be indicated in periodontal infections in which A. actinomycetemcomitans is the prominent pathogen; however, in mixed infections these antibiotics may not provide sufficient suppression of subgingival pathogens to arrest disease progression.

Metronidazole may arrest disease progression in refractory periodontitis patients with Porphyromonas gingivalis and/or Prevotella intermedia infections.

Clindamycin may be used to treat periodontal infections caused by Peptostreptococcus, ß-hemolytic streptococci, and other oral Gram-negative anaerobic rods since it has shown promise in treating refractory periodontitis. Because of the possibility of pseudomembranous colitis brought on by intestinal overgrowth of Clostridium difficile, clindamycin should only be taken with caution. Sometimes other antibiotics can also lead to pseudomembranous colitis.

Clindamycin might be replaced by amoxicillin-clavulanic acid. Systemic amoxicillin-clavulanic acid therapy has been employed in guided tissue regeneration to reduce periodontal infections and boost clinical attachment. Ciprofoxacin is effective against A. actinomycetemcomitans, enteric rods, pseudomonads, staphylococci, and other periodontal pathogens. For the treatment of mixed anaerobic periodontal infections, ciprofloxacin may be coupled with metronidazole or a ß-lactam medication.[4]

Metronidazole plus amoxicillin provides a relatively predictable eradication of periodontal A. actinomycetemcomitans and P. gingivalis in early-onset forms of periodontitis and in refractory adult periodontitis. Ciproflaxin may substitute for amoxicillin in individuals who are allergic to ß-lactam drugs and are at least years of age.

Selective periodontitis associated microbial species and their in vitro susceptibility is discussed in Table 1 **:**

4. Systemic Antibiotic

Chemotherapeutic agent is a general term for chemical substance that provides a clinical therapeutic benefit.

Definition: Antibiotics are naturally occurring, semi-synthetic or synthetic type of antimicrobial agent that destroys or inhibits the growth of selective micro-organisms, generally at low concentrations.

Chemotherapeutic agents can be administered locally, orally or parentally. Systemic antimicrobials may be necessary for tissues invading organisms whereas, local administration i.e., directly in the periodontal pocket has the potential to provide greater concentrations to the infected area and reduce possible systemic side effects. The commonly used antimicrobial agents in periodontal therapy are discussed in Table 2:

Table 1: Selective periodontitis associated microbial species and their in vitro susceptibility

Anaerobic gram- negative species	Antimicrobial agents					
	Amox	**Aug**	**Tet**	**Met**	**Clin**	**Cip**
Porphyromonas Gingivalis	S	S	S	S	S	S
Prevotella intermedia	V	S	S	S	S	V
Bacteriodes forsythus	S	S	S	S	S	ND
Fusobacterium Spp.	V	S	S	s/v	S	R
Selenomonas Spp.	R	R	s/v	S	S	ND
Spirochetes	S	S	S	S	S	ND
Anaerobic gram- positive species						
Peptostreptococcus micros	S	S	v/r	s/v	S	ND
Eubacterium Spp.	S	S	R	V	S	ND
Facultative gram- negative species						
A. actinomycetemcomitans	V	V	s/v	v/r	R	S
Eikinella corrodens	V	S	s/v	V	R	S
Capnocytophaga Spp.	V	S	s/r	R	S	S
Campylobacter rectus	S	S	S	s/v	S	S
Enteric rods / pseudomonas	R	s/v	R	R	R	S
Facultative gram- positive species						
Staphylococcus Spp.	V	V	R	R	V	S
Enterococcus faecalis	R	S	R	R	R	S
Yeasts						
Candida Spp.	R	R	R	R	R	R

Amox – amoxicillin, S – Sensitive, Aug – Augmentin, V – variable, Clin – Clindamycin, Tet – Tetracycline , R – Resistant, Cip – Ciprofloxacin, Met – Metronidazole, ND – Not documented

Table 2: The commonly used antimicrobial agents in periodontal therapy

Penicillin's	• Amoxicillin • Augmentin (amoxicillin + clavulanic acid)
Tetracycline's	• Tetracycline • Minocycline • Doxycycline
Quinolones	• Ciprofloxacin
Macrolide	• Azithromycin • Erythromycin • Spiramycin
Lincomycin derivative	• Clindamycin
Nitroimidazoles	• Metronidazole • Tinidazole • Secnidazole • Ornidazole

4.1. Penicillin

These are antibiotics having a β-lactum ring. This was first drug to be used clinically in 1941 and was originally obtained from the fungus penicillium notatum but the present source is a high yielding mutant of penicillium chrysogenum.

4.1.1. Structure (Figure 1)

The penicillin nucleus consists of fused thiazolidine ring and β-lactum rings.

Substitutions on the acyl side chain have yielded a wide variety of penicillin compounds with vastly different properties. This includes improved stability to gastric acid, improved absorption and higher serum concentrations and activity against gram negative as well as gram-positive bacteria.

4.1.2. Mechanisms of action

All -lactum antibiotics prevent bacteria from producing their cell walls. Bacteria produce UDP-N-acetylglucosamine and

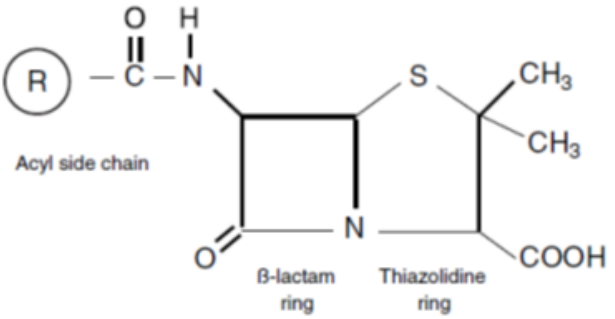

Fig. 1: R – C – NH _ CH _CH

UDP-N-acetylmuramic acid pentapeptide. They combine, cleaving UDP to form lengthy strands. The enzyme transpeptidase cleaves the terminal D-alanine as the last step. The cell wall becomes hard and stable thanks to this cross-linking. Antibiotics that contain -lactum block the transpeptidases to prevent cross-linking. The penicillin

binding proteins (PBPs) that have been discovered on bacterial cell membranes are most likely made up of these enzymes and similar proteins. Each organism possesses a number of PBPs, and PBPs derived from various organisms have varying affinities for various -lactam antibiotics. This information likely explains why they respond differently to different -lactam antibiotics.[4,5]

Cell wall-deficient forms are formed when bacteria divide when -lactam antibiotics are present. The hyperchromatic core of bacteria causes the cell wall-deficient forms to inflate and explode, which results in bacterial lysis. These antibiotics' lytic effects may also result from the inhibition of some bacterial autolysis, which often occurs during bacterial cell division. In the actively proliferating phase (log phase) of bacterial development, b-lactam antibiotics are more deadly. Bacteria are the only organisms that can synthesise peptididoglycans; animals cannot. Penicillin is practically non-toxic to humans because of this.

The most typical negative side effect is allergic hypersensitivity. Any of the penicillins can cause an allergic reaction in someone who is vulnerable. Because penicillin allergies have been reported often, vigilance is suggested.

4.2. Amoxicillin

Amoxicillin, a semi-synthetic penicillin, is well absorbed after oral administration and permeates the gingival crevicular fluid. It has great efficacy against both gram-negative and gram-positive bacteria. Unfortunately, bacterial -lactamases are also very effective against amoxicillin. A variety of bacteria produce the -lactamase enzyme, which hydrolyzes the -lactam ring. All of the penicillin's antibacterial properties are destroyed by hydrolysis of this ring. Amoxicillin's usage as a supplement to periodontal therapy has thus been somewhat restricted. Periodontal pockets frequently contain -lactamases. This could explain why amoxicillin was ineffective, together with the subgingival biofilm's inherent resilience.

Amoxicillin is an aminopenicillin with extended spectrum of activity. Aminopenicillins are produced semisynthetically by replacing the benzyl side chain of penicillin G (benzyl penicillin). Amoxicillin is produced by amino substitution of the side chain. It has:-

1. Better oral absorption
2. Food does not interfere with absorption
3. Higher and more sustained blood levels are produced
4. Incidence of diarrhea is less

Pharmacokinetics: - It is well absorbed orally and is partly excreted in bile and reabsorbed during enterohepatic circulation. However, primary channel of excretion is kidney, but tubular excretion also occurs with a plasma t1/2 of 1 hour.

Dose: - 0.25g – 1g TDS.

Preparations: Amoxycillin, amoxylin, novamox, synamox, 250, 500 mg capsules.

Adverse effects: Diarrhoea though reported but the incidence is less. A high incidence of rashes has been reported in patients with AIDS, EB virus infections and lymphatic leukemia. Concurrent administration of allopurinol also increases incidence of rashes.

Interactions: It is inactivated by hydrocortisone if mixed in intravenous solutions. By inhibiting colonic flora it may interfere with deconjugation and entero-hepatic cycling of oral contraceptives thus causing failure of oral contraception. Probenicid retards renal excretion of amoxicillin by blocking tubular secretion.

4.3. Clavulanic acid

Clavulanic acid is obtained from streptomyces clavuligenus. It is a β-lactamase (penicillinase) inhibitor with no potential antibacterial capacity. *B*-lactamases are a family of enzymes produced by many gram positive and gram negative bacteria that inactivate β-lactam antibiotics by opening the β-lactam ring. It is a progressive inhibitor i.e., binding with β-lactamases is initially reversible but becomes covalent later, and thus inhibition increases with time. After binding it is inactivated therefore known as suicide inhibitor.

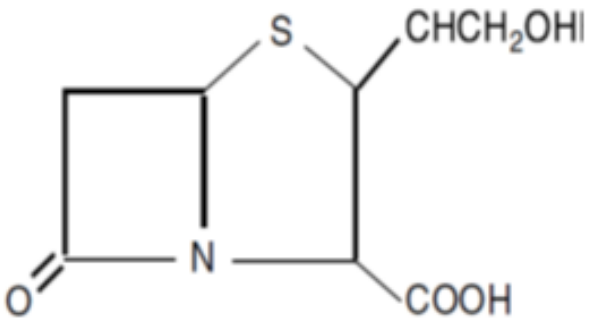

Fig. 2: Structure of clavulanic acid

4.4. Augmentin

A little more than ten years ago, the antibiotic amoxicillin and the -lactamase inhibitor clavulanic acid were combined to create the drug augmentin. An unprotected - lactam ring can be found in clavulanic acid. Many - lactamase enzymes of oral origin are preferentially bound to the clavulanate moiety, have a higher affinity for clavulanic acid than for amoxicillin, and are competitively eliminated from hydrolyzing the - lactam ring in amoxicillin. Thus, the combination of amoxicillin and clavulanic acid may be effective against bacteria that are ordinarily resistant to amoxicillin because they produce -lactamase.

For sites considered to be clinically active, Magnusson et al. (1994) reported an average 2 mm gain in clinical attachment at 3 months after therapy and an average decrease of 2.5 mm in probing pocket depth at 6 months after therapy. These results were obtained using 10 patients with refractory periodontal disease following mechanical debridement and the adjunctive use of Augmentin for 2 weeks.

Pharmacokinetics: It has rapid bioavailability. It has plasma t1/2 of 1 hour matching with that of amoxicillin with which it is used (called co-amoxiclav).

Preparations: Augmentin, Enhancin, Amonate contains amoxicillin 250 mg+ clavulanic acid 125 mg tab.

Adverse effects: Same as for amoxicillin i.e., GI intolerance is poorer especially in children. Other side effects are Candida stomatitis/ vaginitis and rashes. Some cases of hepatic injury have been reported with combination.

4.5. Tetracyclines

They were introduced into the clinical practice in late 1940s by Duggar 1948. Chlortetracycline was the first tetracyclines isolated from the fermentation of products of Streptomyces aurofaciens. When originally introduced, tetracyclines inhibited practically all types of pathogenic micro-organisms, except fungi and viruses; hence the name given broad spectrum antibiotics. The three commonly used drugs of this group are tetracyclines, minocyclines and doxycyclines. It is most commonly prescribed group of antimicrobials in periodontal therapy.[5,6]

4.6. Structure (Figure 3)

These are a class of antibiotics having a nucleus of four cyclic rings

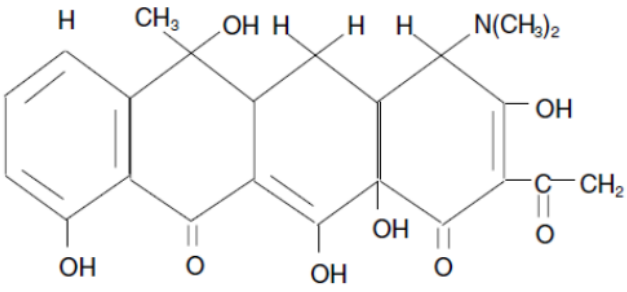

Fig. 3:

4.7. Mechanism of action

The tetracyclines bind to the bacterial 30s ribosomal subunit and inhibit protein synthesis in the bacterial cell. These are normally bacteriostatic antibiotics that do not kill the bacterial cell, but inhibit its growth. However, at high concentrations, such as those achieved with localized delivery of the antibiotic directly into the periodontal pocket, the tetracyclines may exert a bactericidal effect due to their ability to cause alterations in the cytoplasmic membrane. This may result in leakage of nucleotides and other components from the bacterial cell and result in its death. (Figure 4)

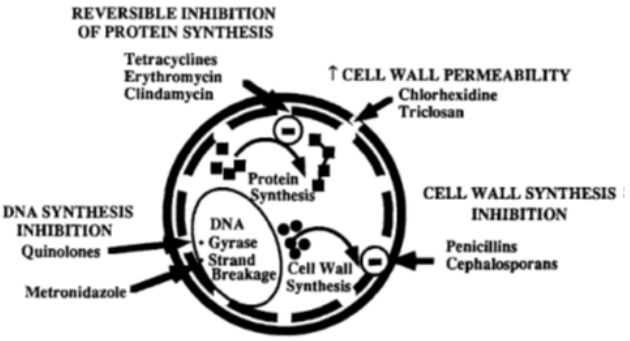

Fig. 4: Elicits the mechanism of action of antibiotics

4.8. Resistance

The minimum inhibitory concentration (MIC), or the dosage needed to halt the growth of 90% of strains, determines the therapeutic range of any antibiotic. Tetracycline resistance is a fairly common phenomenon that is mediated by a number of genetic elements that can be found on plasmids or the bacterial chromosome. An efflux pump's coding may cause resistance because it actively removes the medication from the bacterial cell, preventing a sufficient drug concentration from building up inside the cell. This is a typical method for transmitting tetracycline and, to a lesser extent, doxycycline resistance.

Ribosome protection is a different kind of resistance. With this mechanism, tetracycline antibiotics are not removed from the bacterial cell but are prevented from binding to the 30S ribosomal subunit. This mechanism generally conveys resistance equally to all tetracyclines.[1–5]

4.9. Pharmacological properties

The primary doxycycline and minocycline tetracycline derivatives differ from the parent molecule by minute changes to the chemical elements linked to the fundamental ring structure. These modest modifications in the chemical structure make both doxycycline and minocycline more lipophilic than the parent molecule, resulting in greater adsorption following systemic distribution and better penetration into the bacterial cell. Thus, doxycycline and minocycline can be used in smaller and less frequent doses. Doxycycline and minocycline are often the most used tetracyclines because of this and the widespread

resistance to tetracycline-HCl.All three semi-synthetic tetracyclines—tetracycline derived from chlortetracycline and doxycycline derived from oxytetracycline—are tetracycline hydrochloride, doxycycline, and minocycline. Doxycycline and minocycline both have higher oral absorption rates and are more extensively protein bound and have more prolonged half-life than tetracycline hydrochloride.[7]

In the GIT, tetracycline hydrochloride, a chelating drug, will chelate Ca2+, Mg2+, and Al3+. Numerous food ingredients contain these ions, particularly calcium. So it's best to take tetracycline either one hour before or two hours after eating. Doxycycline and minocycline are not affected by food when being absorbed. Tetracycline cannot pass through the lipid bilayer of the bacterial cell wall, however doxycycline and minocycline can since they are both more lipid soluble than tetracycline.

Antibacterial effects: These medications typically function as bacteriostats, killing both gram-positive and gram-negative bacteria.

4.9.1. Adverse effects

1. GIT disturbances – diarrhea is high with tetracyclines, nausea and vomiting, rarely severe colitis, oesophageal ulcerations (common with doxycycline only).
2. Overgrowth of resistant strains.
3. Photosensitivity mainly in form of sunburn is high with doxycycline.
4. Skin rashes are rare.
5. Hypersensitivity reactions are rare.
6. Vestibular disturbances (minocycline only).
7. Increase in intracranial pressure but in infants.
8. Kidney damage may occur in existing kidney disease with the exception of doxycycline which is safe.

4.10. Interactions of tetracyclines

1. Antagonism with bactericidal antibiotics.
2. Impaired absorption when given with Antacids.
3. Failure of contraception so contraceptive pills not effective.
4. It increases the serum digoxin and lithium carbonate levels.
5. When given with warfarin enhances the anticoagulant effect.
6. Carbamazepine and phenytoin reduces the concentration of doxycycline and minocyclines.

4.11. Contraindication of tetracyclines

1. Pregnancy and breast feeding: as it causes staining of teeth and git disturbances in neonates.
2. Child less than 8 years: staining of teeth.
3. Hepatic disease it causes fatty changes especially during pregnancy.
4. Systemic lupus erythematosus it causes exacerbation of lesions.
5. With patients taking calcium supplements it causes chelating action.

Preparations: Tetracycline – Achromycin, hostacycline, Idilin- 200- 500 mg capsules.

Doxycycline – Tetradox, Biodoxi, Duracyclin, Doxy caps, R-doxy – 100mg capsules.

Minocycline – Cyanomycin 50, 100 mg capsules.

5. Periodontal Implication

5.1. Systemic administration of tetracyclines

Tetracycline systemic administration has historically been widely used as an additional form of periodontal therapy. Tetracycline was known to be inhibitory for a wide range of bacteria that are frequently seen in association with periodontally diseased locations prior to the middle of the 1980s. Tetracycline was thus among the first antibiotics to undergo in-depth scientific examination with a focus on treating periodontal disorders.

In the tetracycline group, the mean probing depth and attachment level somewhat improved. Clinically significant outcomes were frequently attained following the supplementary use of tetracycline in the management of localised aggressive periodontitis. Despite a strict 3-month follow-up period, Lindhe (1981) found that up to 25% of patients with localised severe periodontitis receiving supplementary tetracycline medication experienced resumed disease activity.[1–7]

Tetracyclines as an adjunct to SRP may yield benefits in certain patients, particularly some with localized aggressive periodontitis and in some patient's refractory to previous mechanical therapy.

5.2. Local delivery of tetracyclines

It makes sense that local distribution of an antibiotic into the periodontal pocket would result in a higher, more effective drug concentration than systemic treatment might. Sulcular medicine concentrations frequently reach the equivalent of 1 mg/ml (1,000 g/ml) due to the amount of substance administered. For the majority of bacteria that show resistance to systemically given concentrations, this threshold is regarded as bactericidal.

One particular infection location is the periodontal pocket. According to microbiology, the idea of applying a locally administered antibiotic after manually removing subgingival plaque from only the locations that are thought to require therapy seems perfect. The idea behind mechanical debridement is that it disrupts and moves the biofilm.

Antibiotics applied locally at concentrations far higher than those that can be achieved systemically help eliminate

remaining germs at a specific spot. Each of the antibiotics tetracycline, doxycycline, and minocycline has been included.

Both doxycycline and tetracycline have undergone thorough testing. Tetracycline, 12.7 mg tetracycline-HCl in an ethylene-vinyl acetate copolymer fibre (Actisite), and doxycycline, 10% doxycycline hyclate in a gel delivery method (Atridox). Both technologies have been shown to provide statistically significant improvements in clinical attachment level and probing pocket depth in a number of clinical investigations.

The most lipophilic of the tetracyclines, minocycline, has also been added to minocycline-HCl microspheres (Arestin), a local delivery system. Although clinical trials have not been as extensive as with the other two, a multicenter trial reported significant improvement in probing pocket depth in subjects treated with minocycline and SRP compared to SRP plus vehicle or SRP alone.[7–9]

Local versus systemic application of tetracyclines

They have the ability to concentrate in the gcf after systemic administration. The drugs exhibit substantivity to dentine whilst maintaining antimicrobial activity within the periodontal pocket (Bjorutan 1983). The mechanism of tetracyclines sequestration is uncertain but may be related to the binding of the drug to and its subsequent release from the root surface, or to chelation with calcium ions in crevicular fluid. The local higher concentration of the tetracyclines enhances their bacteriostatic actions and inhibits the development of resistant strains.

The local delivery of tetracyclines can produce concentrations of 1300ug/ ml with minimal unwanted effects (Tonnetti et al. 1990, Heijl et al. 1991). Plasma conc. of tetracyclines following a systemic dose of 250mg every 6 hrs is approx. 2- 3ug/ ml. After placement of tetrayclines fibers, the maximum detectable serum concentration was ≤ 0.1 ug/ml (Rapley et al 1992) thus ensuring minimal systemic unwanted effects.[7–9]

Other properties of tetracyclines which are of value in the management of periodontal disease:

1. Collagenase inhibition
2. Inhibition of bone resorption
3. Anti- inflammatory actions
4. Promote the attachment of fibroblasts and connective tissue to the root surfaces

Previously, it was believed that the tetracycline antibiotic's broad-spectrum antibacterial impact on the microbial flora was the sole cause of the favourable response that resulted from the supplementary use of the drug. Tetracyclines are now known to be powerful inhibitors of the matrix metalloproteinases family of enzymes, which breaks down extracellular matrix components like collagen. Each type of cell found in periodontal tissue produces matrix metalloproteinases, which are essential in the development of periodontitis. When a disease is present, infiltrating polymorphonuclear leukocytes secrete more matrix metalloproteinases-8 and matrix metalloproteinases-9.

Subantimicrobial dose doxycycline (SDD), 20 mg bid (Periostat), improves clinical indices without having any discernible impact on the subgingival flora or leading to an increase in antibiotic resistance, according to a number of double-blind, placebo-controlled clinical investigations. At 3, 6, and 9 months of treatment, participants who got SRP plus SDD had significantly greater gains in clinical attachment level and pocket probing depth than those who received SRP alone.

That SDD had no discernible impact on the typical flora at any of these locations is not surprising. SDD at 20 mg bid results in steady state concentrations of about 0.4 g/ml and peak serum levels of 0.7-0.8 g of doxycycline. Compared to typical MICs (minimally inhibitory concentration), this doxycycline concentration is substantially lower. . The drug has been proven safe and does not seem to exert a detectable effect on the normal microflora. Its usage may be most beneficial when widespread disease is present, in the treatment of periodontitis patients with underlying systemic disease, e.g. diabetes, and perhaps as a follow-up after the use of an adjunctive antibiotic.

6. Quinolones

Subantimicrobial dose doxycycline (SDD), 20 mg bid (Periostat), improves clinical indices without having any discernible impact on the subgingival flora or leading to an increase in antibiotic resistance, according to a number of double-blind, placebo-controlled clinical investigations. At 3, 6, and 9 months of treatment, participants who got SRP plus SDD had significantly greater gains in clinical attachment level and pocket probing depth than those who received SRP alone.

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6.1. Mechanism of action

It inhibits the DNA gyrase, an enzyme necessary for producing coiling of bacterial DNA. DNA gyrase consists of two subunits A and two subunits B. Subunit A carries out nicking of DNA and subunit B introduces negative supercoils. Again, subunit A reseals the strands. Ciprofloxacin binds to subunit A with high affinity and interferes with strand cutting and resealing action. The bactericidal action probably results from digestion of DNA by exonucleases whose production is signaled by damaged

DNA.[10]

6.1.1. Pharmacokinetics:

1. Rapidly absorbed orally but food delays its absorption.
2. Oral bioavailability is 60 - 80%
3. It has high tissue penetrability and is excreted primarily in urine.

6.1.2. Adverse effects

It has a good safety record; side effects may occur in 10% patients but are generally mild. The side effects includes: -

1. GIT problems like nausea, vomiting, bad taste, anorexia. Gut flora is not affected and hence no diarrhea.
2. CNS effects include dizziness, headache, restlessness, anxiety, insomnia, confusion, and tremor and possibly reflect GAMA antagonistic action.
3. Skin / hypersensitivity reaction may occur though rarely serious. These are rash, pruritis, photosensitivity, urticaria, swelling of lips, etc. it is avoided in children as it causes damage to cartilage of weight bearing joints.

6.1.3. Interactions

1. Plasma concentration of theophyllin, caffeine and warfarin are increased by ciprofloxacin, hence toxicity of these drugs may occur.
2. NSAIDS may enhance CNS toxicity of ciprofloxacin; seizures are reported in such cases.
3. Antacids, sucralfate and iron preparations given concurrently reduce absorption of ciprofloxacin.

6.1.4. Contraindications

Ciprofloxacin is excreted in human breast milk and may cross the placenta barrier. Thus, it is contraindicated during lactation and pregnancy.

6.1.5. Preparations

Cifran, Ciplox, Ciproflox – 250 mg, 500 mg, and 750 mg tabs

7. Lincomycin Derivatives (Clindamycin)

The spectrum of activity of clindamycin, a lincosamide derivative, is similar to that of azithromycin. Although it has a significant activity against anaerobes, it inhibits the majority of gram-positive cocci. Gram-negative bacteria are unaffected, though. In people with penicillin allergies, it is a second-line alternative medication. Clindamycin is often bacteriostatic but is bactericidal for some organisms. Clindamycin inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit and is primarily bacteriostatic. The majority of gram-positive bacteria, including facultative and anaerobic species, are susceptible to the medication's effects. It is particularly effective against periodontal flora-related gram-negative anaerobes. However, the common periodontal flora resident and potential periodontal pathogen Eikenella corrodens is naturally resistant to clindamycin. Additionally, A. actinomycetemcomitans exhibits intrinsic in vitro resistance to this medication.

7.1. Mechanism of action

Clindamycin works by inhibiting protein synthesis at the bacterial 50S ribosomal subunit, thus interferes with the process of peptide-chain formation in bacteria. It also may inhibit the binding of aminoacyle transfer ribonucleic acid (tRNA) or the translocation of messenger ribonucleic acid (mRNA) following amino acid binding on the ribosome, further disrupting protein synthesis.

7.2. Pharmacokinetics

Clindamycin is well absorbed orally (90%) and food does not decrease its absorption. It penetrates most skeletal and soft tissues but not CSF and brain. It accumulates in neutrophils and macrophages. After metabolism it is excreted in urine.

7.3. Interactions

Potential for antagonism occurs with macrolides and chloramphenicol which also acts at ribosome level and may competitively inhibit the action. These drugs should not be used in combination with clindamycin.

7.3.1. Preparations

Dalcap, Dalcin – 150 mg capsules

7.3.2. Adverse effects

Due to its acidic nature and to its effect on the gram- negative intestinal bacteria, adverse effects such as diarrhea, abdominal cramping, oesophagitis and stomach irritation are relatively common. There have been numerous reports of pseudomembranous colitis linked to the use of clindamycin.[11,12]

7.4. Periodontal implications

Gordon et al. (1985) selected 13 subjects refractory to previous periodontal therapy consisting of mechanical debridement, periodontal surgery, and the adjunctive use of both tetracycline and a β-lactam antibiotic. The patients received mechanical debridement at 3-month intervals and were extensively monitored at monthly intervals for disease activity. If disease activity was detected and microbial sampling indicated sensitivity to clindamycin, the patient received a thorough scaling and was placed on clindamycin-HCL for 7 days. Of the 13 patients entered, 11 experienced

no further loss of clinical attachment. The proportion of active sites decreased from an average of 10.7% to 0.5% per patient per year. At 24 months, a mean gain of 1.5 mm of clinical attachment was present.

8. Macrolides

Azithromycin is the new azalide congener of erythromycin and has an extended spectrum, improved pharmacokinetics, better tolerability and drug interaction profiles.

8.1. Mechanism of action

It acts by inhibiting bacterial protein synthesis. It combines with 50s ribosome subunit and interferes with translocation i.e. the ribosome fails to move along the mRNA to expose the next codon. As an indirect consequence peptide chain may be prematurely terminated. Synthesis of larger proteins is specifically suppressed. [13]

8.2. Antibacterial action

In the stomach, azithromycin is stable over a range of pH values. It works well against gram-negative bacteria and anaerobes. A significant quantity of azithromycin can be found in most tissues for 7 to 10 days after taking 500 mg QID orally for 3 days. Azithromycin is present in tissue samples from periodontal lesions at much higher levels than in healthy gingiva. According to some theories, azithromycin has a concentration that is 100–200 times higher in fibroblasts and phagocytes than in the extracellular compartment. Phagocytes actively transport azithromycin to areas of inflammation; once there, it is immediately released when the phagocytes burst during phagocytosis.

8.3. Adverse effects

It causes mild gastric upsets, abdominal pain, headache and dizziness. It has no interaction with hepatic cytochrome P-450 enzymes, theophyllin, carbamazepine, warfarin, terfenadine and cisapride.

Preparations: Zithromax,Azithral, Azixok – 250 mg capsules, 100 mg kid tablets.

Two macrolides erythromycin and spiramycin have been found to play role in periodontal disease**.**

After numerous doses, Erythromycin only partially penetrates gingival fluid, reaching mean levels below 1 g/ml. Most periodontal infections are not susceptible at the levels found in the periodontal pocket, including A. actinomycetemcomitans, F. nucleatum, E. corrodens, S. sputigena, and a sizable number of "black-pigmented Bacteroides." It seems doubtful that erythromycin would be a helpful adjuvant in the treatment of periodontitis, unless under extremely specific situations, based on in vitro susceptibility studies.

Spiramycin has been used extensively as an oral penicillin replacement for infections in several parts of Europe and to a lesser extent in Canada. In comparison to other macrolide antibiotics, this one has the benefit of reaching high concentrations in a variety of organs and tissues, where they stay for extended periods of time even after serum levels decline.

Susceptibility testing of this agent demonstrates that many periodontal microorganisms (unpublished data) are resistant to levels that can be achieved in serum following multiple doses (at least 2 μg/ml).96 Short-term clinical studies have demonstrated a positive effect on clinical parameters in adult periodontitis patients

9. Nitroimidazoles

Metronidazole, a 5-nitroimidazole compound, specifically targets anaerobic microorganisms but has essentially no activity against aerobic or microaerophilic bacteria. Initially, metronidazole was thought to interact with biochemical pathways present only in obligate anaerobes.

9.1. Mechanism of action

It is now understood that metronidazole's cytotoxic metabolites directly interact with bacterial DNA and perhaps other macromolecules to cause cell death. Metronidazole is reduced at the 5-nitro position upon entrance into an anaerobic cell by electron transport proteins that are a component of anaerobic metabolic energy-producing pathways. A continuous concentration gradient is produced by changing the metronidazole molecule, favouring the diffusion of more metronidazole into the cell. The parent chemical is reduced to produce a large number of transiently harmful free radicals. Cell death results from these free radicals' interactions with macromolecules, particularly DNA. Although some anaerobic bacteria, such as Fusobacterium species, can become resistant to metronidazole, this is a rather uncommon occurrence and seems to be caused by a decline in the bacterium's capacity to actively lower the 5-nitro position.

9.2. Pharmacokinetics

It is almost completely absorbed from small intestine and widely distributed in the body attaining therapeutic concentrations in body fluids including GCF. It is metabolized in liver and excreted in urine. Its plasma t1/2 is 8 hours.

9.2.1. Adverse effects

They are relatively frequent but not serious. They include –

1. Anorexia, nausea, metallic taste and abdominal cramps (12%). Looseness of stool is uncommon.

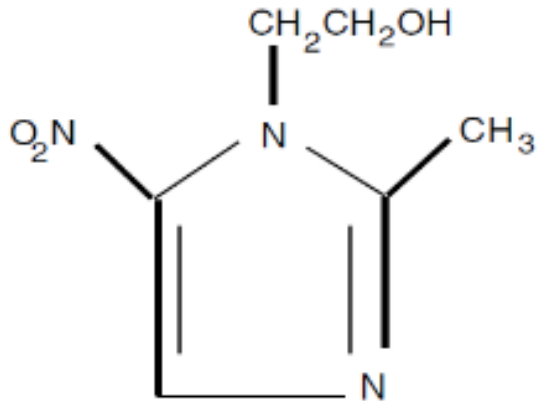

Fig. 5: Structure of metronizadole

2. Headache, glossitis, dryness of mouth, dizziness, rashes and transient neutropenia.
3. Prolonged administration may cause peripheral neuropathy and CNS effects, seizures have followed very high doses.
4. Thrombophlebitis of injected vein if solution is not well diluted.

9.2.2. Contraindications

In neurological disorders, blood dyscrasias, first trimester of pregnancy, chronic alcoholism.

9.2.3. Interactions

1. Intolerance to alcohol occurs among patients taking metronidazole.
2. Enzyme inducers like phenobarbitone and rifampicin may reduce its therapeutic effect.
3. Cimetidine may reduce its metabolism; its dose may need to be decreased.
4. Metronidazole reduces renal elimination of lithium.

9.2.4. Preparations

Tiniba, Tridazole, Abdogyl, Fasigyn – 300, 500, 1000 mg tablets.

9.3. Secnidazole

A congener of metronidazole with the same spectrum of activity and potency. Absorption after oral administration is rapid and complete but metabolism is slower with a plasma t1/2 of 17 – 29 hours. After 48 hours of a single 2 gm dose plasma concentration still remains within range of MIC values against sensitive organisms. A single dose of 2 gm has been found to yield cure rate equal to multiple doses of metronidazole and tinidazole. Side effects profile is similar to metronidazole and incidence is 2 – 10%.[12]

9.4. Preparations

Secnil, Seczol, Nomeba – 500, 1000 mg tablets.

9.5. Contraindications

1. Affects the activity of hepatic enzymes involved with the metabolism of ethanol, producing unpleasant symptoms due to the accumulation of acetaldehyde in the blood. Alcohol ingestion is strictly contraindicated in patients receiving metronidazole.
2. Crosses the placenta barrier, entering the fetal circulation system. It is also secreted in breast milk.
3. Because of the association of metronidazole with tumorigenicity in some animals, the drug is contraindicated in pregnant women or nursing mothers.

9.6. Periodontal implications

Effect of systemic metronidazole on clinical and microbial parameters:

Metronidazole easily reaches concentrations above the MICs via penetrating the gingival crevicular fluid. The number of teeth requiring periodontal surgery or extraction owing to periodontitis is reduced when metronidazole is used in conjunction with mechanical debridement, according to studies by Loesche et al. (1992) including adults with periodontitis.

Adversive juvenile periodontitis, particularly localised juvenile periodontitis, have been treated with metronidazole as an adjuvant. Despite not completely eliminating A. actinomycetemcomitans, treatment significantly decreased its levels. A. actinomycetemcomitans is particularly resistant to metronidazole in vitro, in contrast to the majority of other gram-negative periodontopathogens. As a result, using metronidazole in addition to mechanical debridement is not seen to be the best option for treating juvenile periodontitis.[11,12]

9.6.1. Local delivery of metronidazole

Elyzol is a 25% metronidazole dental gel made of a blend of mono- and triglycerides and metronidazole benzoate. Using a syringe device, the formulation is injected into the periodontal pocket as a liquid, changing instantly to a gel upon contact with the gingival fluid. After being inserted, metronidazole benzoate progressively transforms into metronidazole and supplies the periodontal pocket with high concentrations of the medication for about 24 hours. In most cases, two applications of the dental gel spaced one week apart are advised.

Ornizadole: Today, in addition to subgingival irrigation with chlorexidine mouthrinse, antimicrobials are utilised to treat periimplantitis. One gramme of ornidazole, which works against anaerobic microbes, is administered every day for ten days.

10. Combination Therapy

Combination drug therapy may be useful in periodontitis that involves a variety of periodontopathic species with differing antimicrobial susceptibilities. Combination therapy should include drugs that exhibit synergy or additive effects in vitro. However, some antibiotics through combination antagonism can lead a reduction, rather than an increase, in antimicrobial activity. Antagonism occurs between bacteriostatic tetracyclines and bactericidal ß-lactam antibiotics.

11. Metronidazole & Amoxicillin

Both non-A.actinomycetemcomitans and A.a related periodontitis have shown benefit from the adjunctive use of metronidazole and amoxicillin.The effects of metronidazole and amoxicillin alone, adjunctive metronidazole & amoxicillin with SRP, and SRP alone were compared in studies by Berglundh et al. (1998) and Lopez et al. (2000) in patients with advanced or progressing chronic periodontitis. According to Lopez et al. (2000), metronidazole and amoxicillin administered as the only therapy at 4-month intervals stopped the progression of the disease and markedly improved clinical indicators. According to Berglundh et al. (1998), combined mechanical and antibiotic therapy was superior to mechanical therapy alone in terms of improving the clinical and microbiological characteristics of the disease while antibiotic therapy alone was less successful than SRP.[4–6]

A. actinomycetemcomitans has been suggested to be eradicated with this combination. Van Winkelhoff and coworkers (1989) observed that the combination of 250 mg metronidazole and 375 mg amoxicillin each 3 times a day for one week was effective at eliminating this organism in all but one patient in a group of 11 patients with localised juvenile periodontitis and 11 patients with rapidly-progressive periodontitis who were all infected with A.a. Due to severe diarrhoea, the one patient who still had A.a at the 9–11-month follow-up assessment was unable to take the antibiotic treatment.[12–14]

Fifteen patients with localised juvenile periodontitis who had previously received treatment and were experiencing progressive attachment loss and subgingival infection with A.a. were given metronidazole and amoxicillin. Following 7 days of treatment with this combination of antibiotics, this organism was undetectable in all sites monitored in all patients and there was immediate improvement in several clinical parameters. At present, it appears to be the treatment of choice for localized aggressive periodontitis and for other forms of A. actinomycetemcomitans associated periodontitis.[15]

It is rather surprising that the combination of metronidazole and amoxicillin appears to be effective in killing A. actinomycetemcomitans. According to in vitro susceptibility studies, this bacterium is frequently resistant to the penicillins and is not susceptible to metronidazole, as was previously discussed. With amoxicillin suppressing the facultative and aerobic bacteria and metronidazole inhibiting the anaerobes, this combination is predicted to target a wide range of periodontal organisms. The effectiveness against A. actinomycetemcomitans, however, goes beyond a straightforward additive effect of these two drugs. The combination of amoxicillin, metronidazole, and the hydroxymetabolite of metronidazole has been shown to be effective against this pathogen by Pavicic and colleagues (1994).[1–8]

Insufficient numbers of patients have been treated with metronidazole and amoxicillin to determine the success of this regimen. Tetracyclines should still be regarded as the first medication of choice for treating A. actinomycetemcomitans associated periodontal disease until greater percentages of patients are treated with metronidazole and amoxicillin.

High concentrations of P. gingivalis, P. intermedia, and A. actinomycetemcomitans have been found in HIV periodontitis and HIV gingivitis areas, according to Murray and colleagues. In 85% and 74% of HIV-periodontitis sites and 83% and 65% of HIV-gingivitis sites, respectively, "Black-pigmented Bacteroides" and A. actinomycetemcomitans were discovered. Amoxicillin and metronizadole administration may be a successful adjunct in treating HIV-associated periodontal disease that cannot be controlled with scalings and chlorhexidine mouthrinse due to the susceptibility of "black-pigmented Bacteroides" to metronidazole and A. actinomycetemcomitans to combination of metronidazole and amoxicillin.

According to the information that is now available, systemic metronidazole and amoxicillin can help mechanical debridement manage, if not completely eradicate, A. actinomycetemcomitans. According to certain studies, this regimen is also effective in treating adult cases of aggressive periodontitis that are unresponsive to previous treatments. Pseudomonas and gram-negative enterics, which are thought to inhabit 14% of advanced lesions in the United States and possibly even more in underdeveloped nations, are unaffected by metronidazole and amoxicillin.

If E. corrodens were present, this combination probably wouldn't be suggested. Periodontal lesions frequently contain E. corrodens, which has been named as a potential periodontal pathogen. Metronidazole is not an effective treatment for this bacterium. It is important to stress that metronidazole and amoxicillin shouldn't be administered randomly.

Thus, culture and susceptibility testing is strongly recommended as an important aid in the selection of the most efficacious antibiotic. It must also be noted that metronidazole & amoxicillin should not be administrated to patients sensitive to penicillins.[13]

12. Metronidazole and Ciprofloxacin

When enteric rods, pseudomonads, or A. actinomycetemcomitans are present, the combination of metronidazole and ciprofloxacin has been recommended as an adjuvant therapy for periodontal infections. Due to its mode of action on bacterial DNA replication, the quinolone antibiotic ciprofloxacin is bactericidal in nature. It has very low activity against obligatory gram-negative anaerobes but high activity against a variety of facultative and aerobic gram-negative bacteria. Like the majority of quinolones, ciprofloxacin is often well tolerated. In some cases, using metronidazole and ciprofloxacin as an adjuvant to periodontal therapy may be beneficial. However, sensitivity testing and cultural considerations should be included in its selection. It is extremely improbable that the combination of metronidazole and ciprofloxacin would be beneficial in the treatment of periodontitis caused by traditional gram-negative anaerobic bacteria.

13. Metronidazole and Augmentin

In the vast majority of periodontal situations, metronidazole and amoxicillin-clavulanate does not actually provide any real advantages over metronidazole and amoxicillin. Since the clavulanate moiety is highly acidic, patients frequently find it difficult to tolerate it. However, penicillin-resistant E. corrodens periodontal infections may be treated with metronidazole and Augmentin. Due to the synthesis of -lactamase, this organism can become resistant to amoxicillin and is only moderately resistant to metronidazole. Therefore, E. corrodens that produces -lactamase is resistant to amoxicillin but vulnerable to amoxicillin-clavulanate. After resolution of the periodontal infection, the patient should be placed on an individually tailored maintenance program. Supragingival plaque control in the supportive periodontal therapy phase may help prevent recolonization by putative periodontal pathogens. [13,14,16]

14. Pharmacokinetic Principles of Antimicrobial Therapy

Antibiotic chemotherapy is used to support host defences in containing and getting rid of microorganisms that have momentarily outpaced the host's defences. The efficacy of antimicrobial therapy is determined by the inherent activity of the antibiotic against the target bacterium and several pharmacokinetic properties of the medicine. The ability to pass through membranes (absorption), diffuse through extracellular fluid (distribution), undergo biotransformation by hepatic enzymes (metabolism), and be eliminated from the body through renal or faecal routes (excretion) are all pharmacokinetic factors that antimicrobial agents share with other medications. The acidic dissociation constant (pK), lipid solubility, plasma protein binding, volume of distribution (amount of drug dispersion through intracellular and extracellular fluids), and type of hepatic metabolism or renal excretion are additional distinctive pharmacokinetic characteristics that each antimicrobial agent exhibits. The main factors that determine a drug's half-life—the amount of time it takes for its peak concentration to decrease by half in a given body fluid or compartment—and, consequently, the ideal dosing interval—are its volume of distribution and its hepatic and renal excretion ratios. Antimicrobial therapy provides a variety of variables not seen with the pharmacological management of other diseases since it targets a living microbe with a physiology that differs significantly from the host.

The type and virulence of the pathogen, the site of infection, the potential for surgical drainage, the ability of the antibiotic to reach the infected site, the post-antibiotic effects, adverse drug reactions, and the effectiveness of the host defence are all factors that affect the clinical outcome of antimicrobial therapy. Nevertheless, proper attention to pharmacokinetic principles can greatly facilitate treatment success.

14.1. Antimicrobial dosing principles

The amount of a medication that yields the most benefit with the least degree of side effects is considered the optimal dose. The right amount of antimicrobial drugs is adequate to help eradicate the infecting pathogen(s) with little negative impact on the host's physiology and the ecology of the microbes.

When an antibiotic's half-life is greater than 3 hours or when a delay of more than 12 hours before therapeutic blood levels are reached, an antibiotic loading dose should be employed. Since orofacial infections are acute, therapeutic blood levels must be reached sooner than 12 hours despite the fact that the majority of antibiotics used to treat them have half-lives of less than 3 hours. An initial dose of 1-2 grams of penicillin V or a cephalosporin {such as cephalexin (cefalexin) or cephradine (cefradine)} or 1 gram of erythromycin followed by 500 milligram maintenance doses of each in adults (one-half these doses in children less than 60 pounds) is appropriate. To achieve steady-state blood levels, the antibiotic should ideally be administered at dosage intervals of 3-4 times its serum half-life. The serum halflives of penicillin V, cephradine, cephalexin and erythromycin are about 0.75, 0.70, 1.2 and 1.4 hours respectively. Penicillin V, cephradine and cephalexin should be administered approximately every 4 hours and not 6 hours as commonly stated. Steady-state blood levels are very important with the beta lactam agents but less so with bacteriostatic agents possessing significant post antibiotic effects. [16]

Although the concentration of the antibiotic in the infected tissue plays a major role in treatment success, it also appears that the total amount of time an

antibiotic concentration is at or above the minimal inhibitory concentration for the organism(s) is significant. According to recent research, bactericidal antimicrobial agents' activities are either concentration- or time-dependent, in contrast to bacteriostatic drugs, which include erythromycin, tetracyclines, and clindamycin, which are active at any conceivable concentration.

Because the death rate is related to the drug concentration, the antibacterial action of aminoglycosides, quinolones, and metronidazole is vitally dependent on high drug concentrations at the infected site. Large intermittent dosages (peak and trough blood levels, pulse dosing) are far more effective for the aminoglycosides than several tiny doses.

The aminoglycosides, quinolones, and metronidazole have no effect on the division of microbial cells. The activity of beta-lactam antibiotics, on the other hand, such as penicillins and cephalosporins, is less dependent on tissue concentrations and more closely tied to the length of time that microorganisms were exposed to the chemical.

More than 4 to 5 times the minimal inhibitory concentration of penicillins does not lead to greater microbial killing and may even have the opposite effect, known as the "Eagle effect," whereby extremely high beta-lactam concentrations lead to a slower rate of microbial killing. Beta-lactams and vancomycin, which impede the formation of cell walls, are sluggish time-dependent killers of bacteria that need to be undergoing cell division. Since bacteria divide at various rates and times, beta-lactams should ideally always be present in the affected area. In order to maintain tissue concentrations of penicillins and cephalosporins above the minimal inhibitory concentration for as long as feasible, it is important to dose with beta-lactam medicines in order to maximise the length of exposure to active drug levels. An important consequence to concentration vs time dosage is the idea of the postantibiotic effect. The persistent inhibition of bacterial growth following prior exposure to an antibiotic agent is known as the postantibiotic effect. The type of antibiotic agent, medication concentration, length of therapy, and pathogen targeted all have a significant impact on the postantibiotic effect.Since bacteria divide at different periods, beta-lactams should ideally be present continually in the affected area. A postantibiotic effect is more persistent with antibiotics acting intracellularly by affecting ribosomal protein synthesis (erythromycin, tetracyclines or clindamycin) or nucleic acid (DNA) synthesis (quinolones or metronidazole). The beta-lactams and vancomycin only have a significant postantibiotic effect against Staphylococcus aureus; erythromycin and tetracycline may maximally show a 5 to 10 hour postantibiotic effect against Streptococcus pyogenes and Streptococcus pneumoniae;and aminoglycosides may demonstrate a 2 to 7 hour postantibiotic effect against Escherichia coli, Klebsiella pneumoniae and Pseudomonas aeruginosa.[1–5]

14.2. Antibiotic dosing variables

According to the Ficks principle, antimicrobial drugs passively diffuse through tissue barriers (capillaries, interstitial fluids, and cell walls) from a higher to a lower concentration. The lipid solubility, pH of the surrounding tissue, and the acid dissociation constant (pK) of the antibiotic all affect how easily it may reach the site of action (highly charged molecules can not readily penetrate membranes). Tetracyclines, erythromycin, and quinolones are examples of highly lipophilic (lipid-soluble) antimicrobial drugs that penetrate tissue barriers more effectively than -lactams, aminoglycosides, and vancomycin, which are examples of highly water-soluble antimicrobial agents.

Antibiotics' affinity for plasma protein (serum albumin) can range from 80 to 96% (clindamycin, doxycycline, and oral antistaphylococcal penicillins), to 50-80% (penicillin V and G, erythromycin, and tetracycline), to less than 25%. (ciprofloxacin, ampicillin, amoxicillin, cephalexin, cephradine, metronidazole and aminoglycosides). Protein binding of antibiotics may increase with infection, inflammation, malignancy and diabetes, and decrease with liver disease (cirrhosis), burns and malnutrition.[4,6,8]

The ratio of the vascular bed's surface area to the volume of the tissue compartment that has to be supplied determines the antibiotic concentration at the infection site. The antimicrobial concentration (aside from beta lactams) may be comparable to blood in areas with a high vascular bed to volume ratio (high vascularity and low infection volume), as seen in areas of inflammation with little purulence or edoema, whereas in areas with a low vascular bed to volume ratio (low vascularity and high infection volume), the antimicrobial concentration may be significantly lower than serum.

14.3. Antimicrobials in special conditions

14.3.1. Pregnancy

The beta-lactams, erythromycin (except the estolate salt) and azithromycin are generally considered safe in pregnancy. The safety of clindamycin and clarithromycin has not been established in pregnancy. Clarithromycin should be used in pregnancy only when no alternative therapy is available. The tetracyclines and erythromycin estolate are contraindicated in pregnancy, and metronidazole should be avoided in the first trimester. Chloramphenicol is the only antibiotic absolutely contraindicated in nursing mothers.

14.3.2. Patient's age

Antimicrobial agent pharmacokinetics may change depending on the patient's age. When adjusted for body

weight, antibiotic dosages for children are similar to those for adults. The blood supply to muscles, the plasma protein binding, the activity of the kidneys and liver, the amount of body fat, and the amount of total body water and extracellular fluid are all reduced in newborns. The serum half-lives of penicillins can be 3–4 times longer in preterm infants and neonates than in adults. Elderly adults have less total body water, less lean body mass (more fat), less gastric acid, less time for the stomach to empty, and less kidney and liver function. Antibiotics (quinolones, aminoglycosides, beta-lactams, and vancomycin) largely excreted via the kidneys may require a lower dosage or longer intervals between doses for these people.

14.4. Renal and hepatic impairement

The metabolism and excretion of antimicrobial substances may be restricted by impaired renal or hepatic function. A lower dose or a longer gap between doses may be necessary for antibiotics that are excreted through the kidneys. Penicillin G and V, ampicillin, amoxicillin, methicillin, cephalexin, most cephalosporins, erythromycin and ciprofloxacin should be decreased with severe renal failure; cefazolin, aminoglycosides, vancomycin, imipenem with any renal impairment; and cephaloridine and all tetracyclines except doxycycline are contraindicated with any renal impairment. In the case of severe liver illness, dosages for metronidazole, enoxacin, perfloxacin, and probably the macrolides should be reduced.

With renal impairment, clindamycin, doxycycline, metronidazole, cefaclor, and the oral antistaphylococcal penicillins typically do not need to be dose adjusted. [1,3,5,6,8]

15. Duration of Antibiotic Therapy

The idea that taking antibiotics calls for a "complete course" of treatment is a common fallacy in antibiotic therapy. Conceptual blunders about a predetermined "course" of antibiotic therapy result from a number of false premises:

1. Long-term antibiotic therapy eliminates resistant bacteria.
2. This is a contradiction in terms because, according to the definition of microbial resistance, antimicrobial agents cannot harm resistant microorganisms, and continued use of antimicrobial agents only helps to favour the development of resistant species.
3. Since the organisms are only inhibited but not completely eradicated, "rebound" infections that reoccur require prolonged antibiotic therapy.
4. Particularly if the infection's source is successfully eliminated, acute orofacial infections typically not recur.
5. Antibiotic dosages and duration of therapy can be extrapolated from one infection to another: This is not possible given the variability in infectious processes. [16,17]

16. Conclusion

The minimum amount of time that will avoid a clinical and microbiological relapse is the optimal length of antibiotic therapy. Clinical improvement of the patient as assessed by remission of the infection is the sole practical reference for measuring the success of antimicrobial treatment and, consequently, the length of medication. Acute orofacial infections typically start quickly and last 2–7 days maximum, especially if the underlying cause is addressed and/or removed. If the infection's expected course is 3 days, as determined by clinical experience and its nature, then 3 days of antibiotic medication are sufficient; if it takes 5 days, then 5 days of therapy are required. Antibiotic medication should be stopped when clinical evidence shows that the infection is either fairly likely to clear or has already done so.

The idea behind systemic antibiotic therapy in periodontics is that certain microorganisms cause destructive periodontal disease and that the antibiotic agent can reach concentrations higher than those required to kill or inhibit the pathogen(s) in vivo. By eliminating subgingival germs that are still present after traditional mechanical periodontal therapy, systemic periodontal antibiotic therapy seeks to help host defences in resolving the infection and reinforce mechanical periodontal treatment. The capacity of pathogens to enter periodontal tissues, their residence in anatomical tooth structures that are inaccessible to periodontal instruments, or the effectiveness of the host's defensive mechanisms may allow them to evade the effects of mechanical treatment.

Patients with periodontitis who are resistant to traditional mechanical periodontal treatment may benefit from systemic antibiotic therapy.

Depending on the host defence and dental hygiene efforts, some subgingival bacteria can be suppressed for a long time by single antimicrobial medication therapy. With complex mixed periodontal diseases, combination medication therapy that aim to broaden the antibacterial range and take advantage of antibiotic synergy may be required. Systemic antibiotic therapy should be used sparingly and cautiously due to the rising resistance of medical and oral infections to conventional antibiotics.

When possible, primary surgical intervention should always be preferred over the use of antibiotics. On the other hand, extensive culture and in vitro sensitivity studies must be used to purposefully select antimicrobial medicines for the treatment of severe periodontitis.

Identification of the organism is necessary to prevent polyantimicrobial therapy from selecting highly antibiotic resistant bacteria with the potential for local and systemic pathogenicity. Additionally, a range of bacteria with various antibiotic sensitivity and resistance patterns might

be involved in periodontal diseases. If at all possible, mechanical debridement performed before to or together with antibiotic treatment should be used to remove tissue barriers and inoculum effects in periodontal infections. We may soon be faced with a new breed of oral microorganisms with enhanced defences that will ensure the survival of the species, allow for greater pathogenicity, and transfer genetic material coding for increased virulence and antibiotic resistance to other oral and nonoral microorganisms, unless antimicrobial agents against periodontal disease are used wisely.

17. Source of Funding

None.

18. Conflicts of Interest

There are no conflicts of interest.

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