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Properties of each drug in triple antibiotic paste used in dentistry: A short communication

Authors:

1. Arun T, 2. Ponnudurai Arangannal, 3. Jeevarathan J, 4. Vijayakumar M, . Aarthi J, 6. Amudha S

Affiliation of the authors

- Arun T, Post graduate student, Department of Paedodontics, Sree Balaji Dental College, BIHER, Pallikarani, Chennai.
- Ponnudurai Arangannal MDS, Professor and Head of the department, Sree Balaji Dental College, BIHER, Pallikarani, Chennai.
- Jeevarathan MDS, Professor, Sree Balaji Dental College, BIHER, Pallikarani, Chennai
- Vijayakumar.M, Senior Lecturer, Sree Balaji Dental College, BIHER, Pallikarani, Chennai
- Aarthi J, Reader, Sree Balaji Dental College, BIHER, Pallikarani, Chennai.
- Amudha S, Reader, Sree Balaji Dental College, BIHER, Pallikarani, Chennai.

Abstract

This review is about ‘triple antibiotic paste’ (TAP) and its properties which used in dentistry. TAP is a combination of 3 antibiotics, ciprofloxacin, metronidazole, and minocycline. Despite the problems and pitfalls research pertaining to this paste has unveiled, it has been vastly used in endodontic treatments. The paste's applications vary, from vital pulp therapy to the recently introduced regeneration and revascularisation protocol. Studies have shown that the paste can eliminate the root canal microorganisms and prepare an appropriate matrix for further treatments. This combination is able to remove diverse groups of obligate and facultative gram-positive and gram-negative bacteria, providing an environment for healing. In regeneration protocol cases, this allows the development, disinfection, and possible sterilization of the root canal system, so that new tissue can infiltrate and grow into the radicular area.

Introduction

Antibiotic therapy has become an inseparable part of diverse medical and medical-related treatments and acts because it the one among the most fronts against microorganisms[1]. Various antibiotics with divergent formulas are used, for prevention and prophylaxis; to cure active and acute infections and diseases[2,3]. TAP is a combination of ciprofloxacin, metronidazole, and minocycline[4]. Was introduced in dentistry, especially for the regeneration and revascularization protocol and the treatment of open apex teeth with necrotic pulp. This material has also shown other applications in endodontics [5]. Initially, TAP was largely developed by Hoshino and colleagues[6], who investigated the effectiveness of the paste on the removal of microorganisms from the root canals. Researchers have also used TAP in vitro to disinfect Escherichia coli-infected dentine[7]. Later, particular attention was given to the antibiotic paste and its effect against microorganisms present in carious dentin and infected pulp. The outcome showed excellent results in the eradication of the bacteria from the radicular system[8]. Rationales in combining the antibiotics Considering the polymicrobial nature of tooth infection, single empirical antibiotics aren't ready to provide a bacteria-free zone within the canal. In addition, using non-specific antibiotic therapy could end in the destruction of normal bacterial flora which allows residual virulent microorganisms to repopulate the canal. As a result, it's essential to use a mixture of antibiotics against all endodontic pathogens to stop microbial resistance[9]. Therefore, TAP can affect gram-negative, gram-positive, and anaerobic bacteria, and this mix is often effective against odontogenic microorganisms[10].

Ciprofloxacin

Ciprofloxacin is that the most potent fluoroquinolone, active against a broad range of bacteria[11], the foremost susceptible being the aerobic Gram-negative bacilli, especially the Enterobacteriaceae and Neisseria[12]. It is a second-generation fluoroquinolone and has depicted a substantial and myriad spectrum of activity for several infectious conditions. Ciprofloxacin may be a very promising and efficacious drug, having potent antibacterial activity alongside well-established safety aspects[13]. It has also attracted significant interest in the scientific community due to its antiproliferative and apoptotic activities in several cancer cell lines. It was observed that it can induce time- and dose-dependent growth inhibition and apoptosis of varied carcinoma, osteosarcoma, and leukemia cell lines[14]. The mechanism of action of fluoroquinolones is inhibit the bacterial enzyme DNA gyrase, which nicks double-stranded DNA, introduces negative

supercoils, then reseals the nicked end. This is necessary to prevent excessive positive supercoiling of the strands when they separate to permit replication and transcription. [15,16] The DNA gyrase consists of two A and two B subunits, The A subunit carries out nicking of DNA, the B subunit introduces negative supercoil and then the A subunit reveals the strands. Fluoroquinolone binds to A subunit with high affinity and interferes with its strand cutting and resealing function. In gram-positive bacteria, the major target of fluoroquinolone action is a similar enzyme topoisomerase Ⅳ which nicks and separates daughter DNA replication. Greater affinity for topoisomerase Ⅳ may confer higher potency against gram-positive bacteria. The bactericidal action probably results from the digestion of DNA by exonucleases whose production is signaled by the damaged DNA. Ciprofloxacin inhibits the activity of DNA gyrase, an important adenosine triphosphate-hydrolyzing topoisomerase II enzyme, or it prevents the detachment of gyrase from DNA. The topoisomerases exert their bactericidal activity by interacting with the DNA. [17] During the processes of replication and transcription, an enzyme called helicase unwinds the DNA double helix. The uncoiling process creates tension because of excess supercoiling of the remaining DNA helix. This tension needs to be relieved if the process is to continue. The topoisomerase II enzyme allows the relaxation of supercoiled DNA by breaking both strands of the DNA chain, crossing them over, and finally resealing them.[18]

Metronidazole

Metronidazole is one of the nitroimidazole compound which exhibits a broad spectrum of activities against protozoa and anaerobic bacteria. Since it is famous for its effective antimicrobial activities against anaerobic cocci as well as gram-negative and gram-positive bacilli, it has been used widely in periodontology in both systemic and local forms. Metronidazole destroys bacteria cells by permeating their membrane then binding to the DNA, disrupting the helix structure and causing rapid death of microbe. Metronidazole is effective against anaerobic bacteria, but not in aerobic bacteria and it prevented the expansion of all obligate anaerobes tested and is more effective against two of the strains in comparison to the calcium hydroxide.[19,20] The mechanism of action of metronidazole occurs through a four-step process. Step one is the entry into the organism by diffusion across the cell membranes of anaerobic and aerobic pathogens. However, antimicrobial effects are limited to anaerobes.[21] Step two involves reductive activation by intracellular transport proteins by altering the chemical structure of pyruvate-ferredoxin oxidoreductase. The reduction

of metronidazole creates a degree gradient within the cell that drives uptake of more drug and promotes radical formation that's cytotoxic.[22] Step three, interactions with intracellular targets, is achieved by cytotoxic particles interacting with host cell DNA leading to DNA strand breakage and fatal destabilization of the DNA helix.[23] Step four is the breakdown of cytotoxic products. Metronidazole isadditionally cytotoxic to facultatively an aerobic bacteria like Helicobacter pylori and Gardnerella vaginalis, but the mechanism of action to those pathogens isn't well understood.[21]

Minocycline

Minocycline is a second-generation, and semi synthetic tetracycline analogue.[24] It was first introduced in the 1960s. Effective against both Gram-positive and Gram-negative bacteria. Minocycline has optimal tissue penetration and a longer half-life in comparison to first-generation tetracyclines it shows more lipophilicity than other tetracyclines.[25] It has a Modification in ring D through carbons 7–9 is the basis for the higher efficacy of minocycline.[26] The main mechanism of action in minocycline is similar to the other tetracycline drug family and acts as an inhibitor of bacterial protein translation (elongation of the peptide chain) via binding reversibly to a helical region (H34) on the 30S subunit of bacterial ribosomes; this blocks the incorporation of aminoalkanoic acid residues into the elongating peptide chains, leading to the loss of peptide formation and bacterial growth[27,28] Tetracycline, including tetracycline-HCl, minocycline, demeclocycline, and doxycycline is a group of broad-spectrum antibiotics effective against a wide range of microorganisms. Tetracycline is in the bacteriostatic subgroup of antibiotics. This could be one of the advantages of this subgroup for its safety because when the bacterial cells are not lysed, there will not be any antigenic by products released in the infected area (such as endotoxins).[29] Also, tetracycline possesses various unique properties apart from their antimicrobial action, including the inhibition of mammalian collagenases, which prevents tissue degeneration, and therefore, the inhibition of clastic cells, which ends up in anti-resorptive activities. Naturally, inflammatory diseases such as periodontitis include numerous tissue collagenases, which could be prevented by the mentioned tetracycline's property, thus leading to enhance formation of the collagen and bone. 30 , 31 specifically tetracyclines inhibit metalloproteinases (MMPs) and suppress hydrolases such as α-amylases and phospholipase A2 (a key enzyme in the biosynthesis of inflammatory mediators such as the prostaglandins).32,33 and tetracyclines also

scavenge reactive oxygen species and thereby prevent or reduce pathological tissue destruction. Another important effect, significantly contributing to the overall immune-regulatory activity of tetracyclines, is the interference with cytokine production from neutrophils and macrophages during inflammatory conditions. Tetracyclines suppress cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin- (IL-) 1β, and IL-6, involved in inflammatory disorders. 32,34

conclusion:

Systemic antibiotic therapy has proven useful in dental surgical and non-surgical procedures, but it also comes with some complications like various side effects (allergic reactions or toxicities) and therefore, the development of resistant strains of microbes. Besides, looking a systemic antibiotic therapy depends on numerous factors, including the patient's compliance in taking a particular dosage regimen, the absorption of those drugs by the gastrointestinal system, the transportation via the blood circulatory system to urge to the infected area which means the medication-required area having a correct blood supply which is not any longer available in teeth with necrotic pulps, a pulpless and infected canal. As a result, local application of antibiotics within the canal may be a more effective mode for delivering the drug. However, the development of resistant bacterial strains and tooth discoloration are some of its disadvantages. Nonetheless, TAP seems to be a successful combination of drugs in root canal disinfection/sterilization and pulp regeneration and revascularization protocol.

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