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Review Article

TETRACYCLINE: A USEFUL CLASS OF ANTIBIOTICS FOR SUCCESSFUL ENDODONTICS

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ABSTRACT

Antibiotics have been used frequently in treatment of odontogenic infections. However in endodontic diseases, the source of infection is rarely eliminated by the use of antimicrobial drugs alone. The mainstay of treating pulpal and periapical infections remains the cleaning and debridement of root canal system. Topical antibacterial agents can be used as an adjunct in the form of an irrigant or intracanal medicament during endodontic therapy. Most often employed antibiotic in endodontics is tetracycline class of drugs. Research has shown that tetracycline agents have various beneficial properties apart from bacteriostatic action, including antiresorptive activity, ability to remove smear layer from canal surface after cleaning and shaping. They also show the property of substantivity which prolongs their effect by allowing slow gradual release over time. Therefore, the present paper aims to outline the possible applications of tetracycline drugs in endodontics.

KEYWORDS: Antibiotics, endodontics, tetracycline.

INTRODUCTION

Microorganisms continue to be the most common causative agents in etiology of pulpal diseases [1]. Hence it is of paramount importance to achieve a root canal space free of pathogenic microbes during endodontic procedures, in order to achieve a predictable treatment outcome. Cleaning and shaping techniques seldom achieve complete cleaning of canal space due to the failure of endodontic instruments in reaching the complex canal intricacies especially in the apical region[2,3]. Therefore, canal disinfection protocols assume a prime role during root canal treatment.

Antimicrobial drugs have been frequently employed in dentistry to eradicate orodental infections. Pulpal diseases however represent a tough environment for the action of systemically administered antibiotics. Due to the presence of compromised blood supply during pulpal inflammation or in pulpal necrosis, the systemically delivered antimicrobial agents fail to reach their site of action, hence proving ineffective. However, a more logical approach has been to use antibiotic agents topically inside the root canal space to maximise their beneficial effects [4]. Although several antibiotic agents have been used in endodontics with varying success, the role of tetracycline appears to be the most interesting with numerous reports in literature elaborating its advantageous role in endodontic treatment procedures.

ANTIBACTERIAL SPECTRUM AND MECHANISM OF ACTION (FIGURE 1)

The initial tetracycline class of drugs that were introduced included chlortetracycline and oxytetracycline, which was discovered during late 1940s. Later other members were identified including semi synthetic forms like doxycycline and minocycline. They produce antimicrobial action by inhibiting protein synthesis in microorganisms. They have a broad spectrum of bacteriostatic activity[5].

Their antimicrobial activity is beneficial during inter-appointment time period for canal disinfection. Additionally, tetracycline analogues have also demonstrated antiresorptive property in treatment of traumatised or replanted teeth [6].Their ability to remove smear layer is a valuable adjunct when used as an irrigant during root canal therapy.

ROLE OF TETRACYCLINE DURING CANAL IRRIGATION

When used as an irrigating agent, tetracycline preparations have shown effective antimicrobial activity against resistant microbes including E faecalis along with the ability to remove smear layer from canal walls [7,8]. Two

commercial preparations of tetracycline analogues are available for irrigation including MTAD (Dentsply, Tulsa, OK) and Tetraclean (Ogna Laboratori Farmaceutici, Muggiò (Mi), Italy).

MTAD

It is a mixture of 3% doxycycline, citric acid and a detergent, polysorbate 80[9]. MTAD removes smear layer from instrumented canal surfaces without significantly altering the structure of dentinal tubules [10]. Torabinejad reported marked cleaning efficacy of BioPure MTAD even in the apical third of root canal and recommended the use of MTAD as a final rinse after irrigating the canal with low concentration of sodium hypochlorite (NaOCl). This finding was however contradicted by another study where the antimicrobial activity of MTAD was compromised when used in root canals that have been previously irrigated with 1.3% NaOCl. The reduced efficacy was speculated to be due to the oxidation of MTAD by NaOCl[11]. An invitro study carried out by Newberry et al demonstrated the antimicrobial efficacy of MTAD against 8 strains of E faecalis. Here MTAD was used as a final rinse for 5 minutes after irrigating the canals initially with 1.3% NaOCl. The results showed complete elimination of 7 out of 8 strains of bacteria [12].

The antifungal activity of MTAD has been questionable since doxycycline is primarily active against gram positive and gram negative bacteria and not against fungi [13]. Ruff et al reported superior antifungal activity of 6% NaOCl and 2% chlorhexidine compared to BioPure MTAD and 17% EDTA [14].

TETRACLEAN

Tetraclean also consists of doxycycline along with an acid and a detergent. The difference from MTAD lies in concentration of doxycycline (50 mg/ml) and the type of detergent (polypropylene glycol)[15]. A comparative study evaluating the effectiveness of NaOCl, MTAD and Tetraclean against E faecalis demonstrated better antimicrobial activity of NaOCl and Tetraclean compared to MTAD [16].

SUBSTANTIVITY

Tetracycline class of drugs (including doxycycline) have a unique property of substantivity, whereby they attach to the surface of dentin and act as a reservoir of antibacterial activity over prolonged time interval [10]. The substantivity of MTAD was reported to be greater than chlorhexidine and NaOCl by Mohammadi and Yazdizadeh [17].

ROLE OF TETRACYCLINE AS INTRACANAL MEDICAMENT

Tetracycline is routinely employed as intracanal medicament during root canal treatment to achieve complete disinfection, especially in treatment of non vital immature teeth where revascularisation procedures may be employed. Apart from the antimicrobial effect, these drugs (including doxycycline, minocycline) also have antiresorptive activity by inhibition of clastic cells [6,18,19]. Such a property is favourable during replantation of teeth to prevent replantation resorption and promote healing of attachment apparatus of teeth.

LEDERMIX

Ledermix paste (Lederle Pharmaceuticals) is a combination of 3.2% demeclocycline HCl and a corticosteroid (1% triamcinolone acetonide) in polyethylene glycol base The function of corticosteroid was to reduce inflammation and antibiotic agent was added to counteract the reduced immune response and limit the possibility of infection [20]. The concentration of antibiotic is sufficient to limit the growth of bacteria in immediate vicinity of the applied medicament inside the canal space. Although the components of paste are able to diffuse through dentinal tubules and cementum and reach the periodontal ligament space and periradicular tissues, still the levels of demeclocycline are inadequate to suppress the bacterial growth[21,22].

A modification of ledermix paste is available in cement form consisting of 0.7% triamcinolone, 3% demeclocycline and calcium salts. It has been used for pulp capping, pulpotomy and as a liner[23]. Ledermix has also shown favourable result in management of cracked teeth with irreversible pulpitis [20]. When used as an intracanal medicament, it also appears to reduce the incidence of postoperative pain in patients with preoperative pain [24]. Research has shown absence of any systemic adverse effects or any detrimental changes in periodontal tissues after application of ledermix paste [19,25].

Ledermix plays a significant role in treatment of traumatically injured teeth. In a study carried out by Bryson, ledermix medicament was placed in the canals of replanted dog teeth after a drying period of 60 minutes. Ledermix treated teeth displayed significantly more healing and less root resorption compared to the teeth treated with calcium hydroxide intracanal medicament[6]. Similar findings were reported by Thong et al, where the incidence of replacement resorption was found to be lowest in

ledermix treated teeth along with more normal histomorphology of periodontal ligament compared with calcium hydroxide treated samples[26]. Chen et al had stated that corticosteroid and tetracycline lower the inflammatory response in replanted teeth including inhibition of clastic-cell mediated resorption and promoting periodontal healing. They even proposed the placement of corticosteroids after pulp extirpation during the emergency visit itself, in cases of tooth injuries involving a wider area of periodontal ligament [27].

Ledermix paste has also been used in combination with calcium hydroxide as intracanal medicament for management of immature necrotic teeth, inflammatory resorption and perforations. A 50:50 mixture of ledermix and calcium hydroxide paste prolongs the effect of medicament in the canal due to slower release and diffusion of components of ledermix [20].

TRIPLE ANTIBIOTIC PASTE

Endodontic infections are often polymicrobial, necessitating the use of multiple antimicrobial agents to achieve thorough canal disinfection and sterilisation. A combination of triple antibiotics including metronidazole, ciprofloxacin and minocycline has been tried for management of immature necrotic teeth and teeth with large periapical lesions. These antibacterial medicaments have also been employed under the concept of "lesion sterilization and tissue repair therapy" for treating immature teeth with endodontic infections [28]. The efficacy of this combination was demonstrated by Hoshino et al who tested the antibacterial activity on these drugs alone as well in combination. He concluded that although none of the antibiotics were able to remove all pathogens completely, however the combination of the same resulted in consistent sterilization of all teeth [29].

Triple antibiotic paste has gained popularity during revascularization of non vital young permanent teeth by creating a sterile canal space due to the presence of both bactericidal (metronidazole, ciprofloxacin) and bacteriostatic agents (minocycline)[30]. Previous studies have revealed improved radiographic and histological architecture of immature teeth in which revascularization has been attempted after using doxycycline and minocycline[31,32]. Various tetracycline preparations are enlisted in table 1.

Table 1: Various Tetracycline Preparations Used In Dentistry

Irrigating agents	Intracanal medicaments	Antibacterial Agents (Used in management of Endo-Perio lesion)
• TETRACLEAN (50mg/ml Doxycycline) • MTAD (3% Doxycycline)	• LEDERMIX PASTE (3.2% Doxycycline HCl) • TRIPLE ANTIBIOTIC PASTE (Minocycline)	• ATRIDOX (Doxycycline) • ARESTIN (Minocycline) • ACTISITE (Tetracycline HCl) • PERIOSTAT (Doxycycline)

SYSTEMIC USE OF TETRACYCLINE

Burke investigated the ability of systemically delivered tetracycline to inhibit the growth of endodontic bacteria. Endodontic cultures were evaluated to assess the concentration of tetracycline absorbed in root canals of teeth. He observed that tetracycline was detected only in one of ten patients after 48 hours and its concentration was insignificant to hamper microbial growth [33]. Sae-Lim et al compared the effect of systemically administered tetracycline and amoxicillin in limiting root resorption after replantation of avulsed teeth. Results revealed that tetracycline enhanced healing significantly in more number of teeth compared to amoxicillin [34]. He further stated that absorption and distribution of drug from the oral route might be highly variable, thus making the treatment outcome unpredictable.

ADVERSE EFFECTS OF TETRACYCLINE

Unfortunately, the use of tetracycline drugs as intracanal medicament has been associated with staining of teeth. Research has shown that yellowish to dark grey staining of teeth occurs on prolonged exposure to sunlight [35,36]. Discoloration occurs due to the property of tetracycline to chelate with calcium ions forming an insoluble complex[37]. The incidence of staining appears to be more in immature teeth than in mature teeth. Discoloration of teeth is less severe when the medicament is limited to below the level of cementoenamel junction (CEJ)[35,36].

CONCLUSION

Antibiotic agents have been tried with varying success in management of pulpal and periapical lesions. Since systemic administration of antibiotic have little value due to compromised pulpal blood flow during inflammatory condition, local or topical placement of these drugs inside the root canal appears to be more judicious. One

of the most successfully employed drug is tetracycline class of drugs that have several unique properties other than bacteriostatic action, such as inhibition of clastic cells and matrix metalloproteinases. Doxycycline is a part of commercial irrigating preparations such as Tetraclean and MTAD. They have the ability to remove smear layer from instrumented root surfaces, thus promoting close adaptation of obturation materials with root canal walls. As an intracanal medicament, tetracycline members are included in Ledermix paste and triple antibiotic paste. Both these combinations have yielded successful results in treatment of traumatized permanent teeth while attempting replantation of revascularisation procedures. The only concern with the use of intracanal tetracycline paste seems to be the discoloration of teeth on sunlight exposure. This however, can be minimized by restricting the medicament to below the level of CEJ.

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Figure 1: **Mechanism of action of tetracycline drugs in management of endodontic infection**