Local Applications of Tetracyclines in Endodontics and Dental Trauma: A Review

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LEARNING OBJECTIVES:

After reading this article, the individual will learn:

- The rationale for the local applications of antibiotics in endodontic therapy and dental trauma.
- Indications for the local applications of tetracycline-containing root canal irrigants and medicaments.

ABOUT THE AUTHORS

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INTRODUCTION

Antibiotics were first discovered in 1928 but were not routinely used clinically until the Second World War. Prior to this, most wartime deaths were due to bacterial infections of wounds, rather than the wounds themselves. The value of antibiotics was seen with the rapid recovery of wounded military personnel, and the use of these drugs increased dramatically after the end of the war. In endodontics and cases of dental trauma, antibiotics may be applied systemically (orally and parenterally) and locally. The first reported local use of an antibiotic in endodontic treatment was in 1951 when Grossman used a poly-antibiotic paste known as PBSC (penicillin, bacitracin, streptomycin, and caprylate sodium). PBSC contained penicillin to target Gram-positive organisms, bacitracin for penicillin-resistant strains, streptomycin for Gram-negative organisms, and caprylate sodium to target yeasts; these compounds were all suspended in a silicone vehicle. Later, nystatin replaced caprylate sodium as an antifungal agent in a similar medicament (PBSN).

While systemic antibiotics appear to be clinically effective as an adjunct in certain surgical and nonsurgical endodontic cases, their administration is not without the potential risk of adverse systemic side effects, particularly allergic reactions, toxicity, and development of resistant strains of microbes. Further, systemic administration of antibiotics relies on the circulation to bring the active drug to an infected site. That site may no longer have a normal vasculature. Included here are teeth with a necrotic pulp and associated periradicular tissues. Therefore, local application of antibiotics may be a more effective method of delivering antibiotics.

This article reviews the literature regarding the local application of antibiotics in endodontic therapy and cases of dental trauma.

ANTIBIOTICS

Tetracyclines

Tetracyclines, including tetracycline hydro-chloride (HCl), minocycline, demeclocycline, and doxycycline, are a group of broad-spectrum antibiotics that are effective against a wide range of bacteria. This property may be advantageous because in the absence of bacterial cell lysis, antigenic by-products such as endotoxin are not released. Tetracyclines have unique properties other than their antimicrobial effect, such as the inhibition of mammalian collagenases, which prevents tissue breakdown and the inhibition of clastic cells, which...
results in anti-resorptive activity.¹⁰

Inflammatory diseases such as periodontitis include a pathological excess of tissue collagenases, which may be blocked by tetracyclines resulting in enhanced formation of collagen and bone.⁶ In periodontal therapy, tetracyclines have been used to remove the smear layer (ie, dentin conditioning) and tooth/root surface contaminants such as endotoxin. Surface demineralization widens the orifices of the dentinal tubules and exposes the cementum collagen matrix, which stimulates fibroblast attachment and growth.⁵ In endodontics, tetracyclines have been used to remove the smear layer from instrumented root canal walls⁶,¹¹ for irrigation of retrograde cavities during periapical surgery¹², and as an intracanal medicament.¹³

Barkhordar, et al⁶ evaluated the effect of doxycycline HCL on the smear layer of instrumented root canal walls. Their findings showed that doxycycline HCL eliminated the smear layer in a concentration-dependent manner. Results showed that 100 mg/ml doxycycline HCL was more effective than lower concentrations in removing the smear layer. In another investigation Haznedaroglu and Ersev¹¹ used scanning electron microscopy to assess the effectiveness of tetracycline HCL as an endodontic irrigant as a means of removing the smear layer. Their results revealed that tetracycline HCL was as effective as citric acid in removing the smear layer. Barkhordar and Russel¹² evaluated the effect of doxycycline on the apical seal of retrograde filling materials. Their findings were that teeth with retrograde intermediate restorative material or amalgam fillings placed following doxycycline irrigation had significantly less dye penetration.

Carson, et al¹⁴ compared the antimicrobial activities of 6% and 3% sodium hypochlorite (NAOCl), 2% and 0.12% chlorhexidine (CHX) gluconate, and 0.01% and 0.005% doxycycline on 4 microorganisms associated with primary endodontic infections. The agar diffusion test was used to measure antimicrobial activities of these agents against Pepto-streptococcus micros, Prevotella intermedia, Streptococcus sanguis, and Lactobacillus acidophilus. For 3 of the 4 microorganisms, the order of antimicrobial effectiveness was 0.01% Doxy > 0.005% Doxy > 6% > 3% NAOCl > 2% CHX > 0.12% CHX. For L acidophilus, the order of effectiveness was 6% NAOCl > 3% NAOCl > 2% CHX > 0.01% Doxy > 0.005% Doxy > 0.12% CHX.

Pinheiro, et al¹⁵ evaluated the susceptibility to different antibiotics of Enterococcus faecalis isolates from canals of root-filled teeth with periapical lesions. The following antibiotics were used: benzylpenicillin, amoxicillin, amoxicillin-clavulanic acid, erythromycin, azithromycin, vancomycin, chloramphenicol, tetracycline, doxycycline, ciprofloxacin and moxifloxacin; 85.7% of the isolates were susceptible to tetracycline and doxycycline. Chai, et al¹⁶ investigated the antimicrobial efficacy of 6 groups of antibiotics (ampicillin, cotrimoxazole, erythromycin, oxytetracycline, vanco-mycin, and vancomycin followed by gentamicin) and calcium hydroxide against E faecalis biofilm in a membrane filter model, and concluded that erythromycin, oxytetracycline and calcium hydroxide (Ca[OH]2) were 100% effective in eliminating E faecalis biofilm, whereas ampicillin, cotrimoxazole, vancomycin, and vancomycin followed by gentamicin were ineffective.

Based on the hypothesis that microorganisms reach the apical area of a recently replanted tooth from the oral cavity (or from contamination when the tooth is outside the socket), Cvek, et al¹⁷ developed a new protocol for topical treatment of the exposed root with doxycycline before replantation. The objective was to eliminate microorganisms from the root surface of an avulsed tooth in order to reduce the inflammatory response. These authors showed that topical doxycycline significantly increased the chances of successful pulp revascularization. Yanpisat and Trope¹⁸ recently confirmed the beneficial effect of soaking a tooth in doxycycline.

In an animal (dog) study, Ritter, et al¹⁹ investigated the effect of topical antibiotic treatment on pulp revascularization in replanted teeth using laser Doppler flowmetry (LDF), radiography, and histology. After being extracted, teeth were kept dry for 5 minutes, and either covered with minocycline mixture, soaked in doxycycline, or soaked in saline, and then replanted. Teeth in the positive control group were not extracted. Post-operative radiographs and LDF readings were obtained for 2 months after replantation. After sacrifice, the jaws were collected and processed for light microscopy. Pre and postreplantation LDF readings and radiographs, and histologic findings were analyzed to assess revascularization. Pulp
revascularization occurred in 91% (minocycline), 73% (doxycycline), and 33% (saline) of the specimens. In contrast, Bryson, et al\textsuperscript{20} evaluated the effect of minocycline on healing of replanted dog teeth after 60 minutes of drying. Results showed that the roots with and without minocycline treatment showed no significant differences between the remaining root mass or the percentage of favorably healed root surfaces, and no benefit was found from the use of topically applied minocycline in the attenuation or prevention of external root resorption.

\textbf{Substantivity of Tetracyclines}

Tetracyclines readily attach to dentin and are subsequently released without losing antibacterial activity.\textsuperscript{5} This property creates a reservoir of active antibacterial agent, which is then released from the dentin surface in a slow and sustained manner. In periodontics, studies have been conducted on the antibacterial substantivity of tetracyclines. In an in vivo study, Stabholz, et al\textsuperscript{21} compared the antibacterial substantivity of 2 concentrations of tetracycline HCl (50 mg/ml and 10 mg/ml) and 0.12% CHX. Their findings were that both concentrations of tetracycline demonstrated residual antibacterial activity, and the antibacterial substantivity of the 3 solutions in descending order was: 50 mg/ml tetracycline > 10 mg/ml tetracycline > 0.12% CHX.

Abbott, et al\textsuperscript{22} demonstrated that tetracyclines form a strong reversible bond with hard tissues and that they exhibit slow release over an extended period of time. Khademi, et al\textsuperscript{23} compared the antibacterial substantivity of 2% CHX, 100 mg/ml doxycycline HCL, and 2.6% NAOCI in bovine root dentin over 5 experimental periods of 0, 7, 14, 21, and 28 days in vitro. Their findings revealed that after 7 days, the NAOCI and doxycycline HCl groups showed the lowest and the highest number of colony forming units (CFU), respectively. However, at the other evaluations, the CHX group showed the lowest number of CFUs. In another study, Mohammadi, et al\textsuperscript{24} evaluated the antibacterial substantivity of 3 concentrations of doxycycline HCL (100 mg/ml, 50 mg/ml, and 10 mg/ml) in bovine root dentin at 5 time points (0, 7, 14, 21, and 28 days). Results showed that the numbers of CFUs in all 3 experimental groups were minimum in first cultures (at 7 days), and the results were significantly different from each other at all time periods. In first culture the 100 mg/ml group and the 10 mg/ml group showed the lowest and highest numbers of CFUs, respectively. In each group the numbers of CFUs increased significantly over time.

\textbf{BioPure MTAD}

BioPure (DENTSPLY/Tulsa), otherwise known as MTAD, is a relatively new root canal irrigant which was introduced by Torabinejad, et al in 2003.\textsuperscript{5} This solution is a mixture of 3% doxycycline, 4.25% citric acid, and a detergent (0.5% Polysorbate 80).\textsuperscript{25} Several studies have evaluated the effectiveness of MTAD for disinfection of root canals. Torabinejad, et al have showed that MTAD is able to remove the smear layer\textsuperscript{5} and is effective against \textit{E faecalis}.\textsuperscript{26-28} Shabahang, et al\textsuperscript{27} cleaned and shaped root canals of extracted human teeth and exposed them to human saliva. They then compared the antibacterial efficacy of a combination of 1.3% NAOCI as a root canal irrigant and MTAD as a final rinse with that of 5.25% NAOCI. Their findings showed that the use of MTAD was more effective than 5.25% NAOCI in disinfecting root canals. However, Tay, et al\textsuperscript{29} found that when MTAD is applied to 1.3% NAOCI-irrigated dentin, its antimicrobial substantivity is reduced. They attributed this phenomenon to the oxidation of MTAD by NAOCI in a manner similar to the peroxidation of tetracycline by reactive oxygen species.

In another study, Shabahang and Torabinejad\textsuperscript{28} compared the anti-bacterial effects of MTAD with that of NAOCI and ethylenediaminetetraacetic acid (EDTA). They used standard in vitro microbiological techniques, and reported that MTAD was significantly more effective than the other 2 agents against \textit{E faecalis}.\textsuperscript{26-28} Kho and Baumgartner\textsuperscript{30} compared the antimicrobial efficacy against \textit{E faecalis} of 1.3% NAOCI/BioPure MTAD with that of the combined use of 5.25% NAOCI and 15% EDTA when used for root canal irrigation. Bacterial samples taken early in the canal cleaning process revealed no growth in any of the 20 samples with 5.25% NAOCI/15% EDTA irrigation and growth in 8 of 20 samples with 1.3% NAOCI/BioPure MTAD irrigation. Further samples taken after additional canal enlargement revealed growth in none of 20 samples when 5.25% NAOCI/15% EDTA were used, but there was growth in 10 of the 20 samples when 1.3% NAOCI/ BioPure MTAD was used. This investigation showed a
consistent disinfection of infected root canals with a combination of 5.25% NAOCl/ 15% EDTA. However, the combination of 1.3% NAOCl/BioPure MTAD left nearly 50% of the canals contaminated with \( E\ faecalis \).

Krause, et al\(^{31}\) compared the antimicrobial effect against \( E\ faecalis \) of MTAD, 2 of its components (doxycycline and citric acid), and sodium hypochlorite in 2 in vitro models using 2 different methods. In the tooth model, NAOCl and doxycycline were more effective than the control in killing \( E\ faecalis \) at shallow bur depths into dentin, but at deeper bur depths the NAOCl was superior. In the agar diffusion model, NAOCl produced less inhibition of bacteria than MTAD or doxycycline. Ghoddusi, et al\(^{32}\) evaluated the effect of MTAD as a final irrigant on bacterial leakage of the root canal, and its interaction with 2 conventional root canal sealers (AH-Plus or Rickert). The results revealed that it took longer for bacteria to penetrate when either EDTA or MTAD was used for smear layer removal. Further, the root canals obturated with AH-Plus showed significantly longer duration of resistance to bacterial penetration than canals obturated with Rickert. Davis, et al\(^{33}\) investigated the antimicrobial action of Dermacyn (a super-oxidized, pH-neutral solution containing minimal chlorine) (Oculus Innovative Sciences), BioPure MTAD, 2% CHX, and 5.25% NAOCl against \( E\ faecalis \) using the zone of inhibition test. BioPure MTAD showed significantly larger zones of microbial inhibition than 5.25% NAOCl, 2% CHX, and Dermacyn. Newberry, et al\(^{34}\) determined the in vitro antimicrobial effect of MTAD as a final irrigant on 8 strains of \( E\ faecalis \) and measured the minimum inhibitory concentration (MIC) and the minimum lethal concentration (MLC) of MTAD. After irrigating with 1.3% NAOCl, the root canal and the external surfaces were exposed to MTAD for 5 minutes. This treatment regimen was effective in completely eliminating growth of 7 of 8 strains of \( E\ faecalis \). The MIC/MLC tests showed that MTAD inhibited most strains of \( E\ faecalis \) growth when diluted 1:8192, and killed most strains of \( E\ faecalis \) when diluted 1:512.

Shabahang, et al\(^{35}\) evaluated the effect of the addition of, or substitution by, CHX for doxycycline in MTAD and compared the 3 formulations for their ability to disinfect extracted human teeth infected with \( E\ faecalis \). None of the samples treated with MTAD or MTAD + CHX demonstrated residual bacteria. In contrast, 7 of 10 samples treated with MCAD (CHX substituted for doxycycline) showed positive cultures of \( E\ faecalis \). The results clearly demonstrated that although the addition of CHX did not negatively impact the efficacy of MTAD, the substitution of this antimicrobial agent for doxycycline significantly reduced the antibacterial efficacy of the solution.

**Substantivity of MTAD**

As stated previously, tetracyclines (including doxycycline) readily attach to dentin and are subsequently released over time without losing their antibacterial activity.\(^{11}\) The presence of doxycycline in MTAD suggests that MTAD may have some substantive antimicrobial action.\(^{5}\) In an in vitro study, Mohammadi and Yazdizadeh\(^{36}\) evaluated the substantivity of NAOCl, CHX, and MTAD using a bovine dentin tube model. Dentin chips were removed from the canals with sequential sterile low-speed round burs with increasing ISO sizes of 025, 027, 029, 031, and 033 at 0, 7, 14, 21, and 28 days following irrigation with the test solution. In the first culture, the NAOCl group and the CHX group showed the lowest and highest number of CFUs, respectively. In each group, the number of CFUs increased significantly over time. It was concluded that the substantivity of MTAD was significantly greater than CHX and NAOCl. These findings were confirmed in a human model.\(^{37}\)

In another study, Mohammadi\(^{38}\) assessed the substantivity of 3 concentrations (100%, 10%, and 1%) of MTAD using a bovine dentin tube model. As described, dentin chips were removed from the canals with sequential sterile low-speed round burs with increasing ISO sizes of 025, 027, 029, 031, and 033 at 0, 7, 14, 21, and 28 days. Results showed that in the first culture, MTAD 100% and MTAD 1% showed the lowest and highest number of CFUs, respectively. In each group, the number of CFUs increased significantly over time. It was concluded that the substantivity of MTAD was significantly greater than the 2 lower concentrations of MTAD.

**Tetraclean**

Tetraclean (Ogna Laboratori Farmaceutici, Muggiò (MI), Italy), like MTAD, is a mixture of an antibiotic, an acid, and a detergent. However, the concentration of antibiotic...
(50 mg/ml doxycycline) and the type of detergent (polypropylene glycol) differ from those of MTAD. Giardino, et al.\(^{39}\) compared the surface tension of EDTA 17%, Cetrexidin (a mixture of 0.02 Cetrimyde and CHX in an aqueous base), Smear Clear (a mixture of EDTA 17% and Tween 80), and NAOCl 5.25% with the surface tension of MTAD and Tetraclean. Sodium hypochlorite 5.25% and EDTA 17% had the highest surface tension, whereas those of Cetrexidin and Tetraclean had the lowest surface tensions. In another study, they compared the antimicrobial efficacy of 5.25% NAOCl, BioPure MTAD, and Tetraclean against \(E\ faecalis\) biofilm formed on cellulose nitrate membrane filters. Results showed that only 5.25% NAOCl could consistently disegrate and remove the biofilm; however, as compared with MTAD, treatment with Tetraclean led to a high degree of biofilm disgregation at every time interval.\(^{40}\)

**Ledermix**

Ledermix is a glucocorticosteroid-antibiotic compound. Ledermix paste was developed by Schroeder and Triadan in 1960, and became available in Europe (Lederle Pharmaceuticals) in 1962.\(^{41}\) The development of Ledermix paste was based on the use of corticosteroid to control pain and inflammation,\(^{41}\) and the antibiotic component was added to compensate for what was perceived to be a possible corticoid-induced reduction in the host immune response. Schroeder and Triadan initially incorporated chloramphenicol in their first trials, but when Lederle Pharmaceuticals became the manufacturer, the antibiotic was changed to demeclocycline HCl. Today, Leder-mix paste remains a combination of the same tetracycline antibiotic (demeclocycline HCl at a concentration of 3.2%) and a corticosteroid (triamcinolone acetonide, concentration 1%) in a polyethylene glycol base.\(^{41}\)

The 2 therapeutic components of Ledermix (ie, triamcinolone and demeclocycline) are capable of diffusing through dentinal tubules and cementum to reach the periodontal and periapical tissues.\(^{42}\) Abbott, et al.\(^{22}\) demonstrated that dentinal tubules were the major supply route of the active components to the periradicular tissues, and the apical foramen was not as significant a supply route. Various factors can affect the supply of the active components to the periradicular tissues, including the presence or absence of the smear layer, the presence or absence of cementum, and the presence of other materials within the canal, for example, Ca(OH)\(_2\). The concentration of demeclocycline within Ledermix paste itself is high enough to be effective against susceptible species of bacteria. However, within the peripheral parts of the dentin and in the periradicular tissues the concentration achieved through diffusion is insufficient to inactivate bacteria, especially over time.\(^{43}\) Immediately adjacent to the root canal, inhibitory levels of demeclocycline are achieved for all studied bacteria for the first day following application, but the concentration drops to about one-tenth of the original concentration after one week in both the mid-root and the apical one-third of the canal. Further, away from the root canal towards the cementum, the concentration of demeclocycline after one day is not high enough to inhibit growth of 12 of the 13 strains of commonly reported endodontic bacteria.\(^{43}\) Heling and Pecht\(^{44}\) evaluated the efficacy of Ledermix paste in the disinfection of dentinal tubules. Ledermix and 3% tetracycline in a hydrous base were effective in reducing the amount of \(S\) aureus in dentinal tubules after 7 days of incubation and also after recontamination. Neither were effective after 24 hours.

The use of Ledermix has been studied in other ways. Abbott\(^{45}\) showed that the intradental use of Ledermix paste and Ledermix cement is unlikely to result in any systemic side effects. Pierce, et al.\(^{9}\) demonstrated histologically that Ledermix eliminated experimentally induced external inflammatory root resorption in vivo. They also found that Ledermix paste had no damaging effects on the periodontal membrane, and that this paste was an effective medication for the treatment of progressive root resorption in traumatically injured teeth. Taylor, et al.\(^{46}\) evaluated the effects of Ledermix paste and Pulpdent paste (Pulpdent) on mouse fibroblasts and bacteria in vitro. Dilutions of Ledermix paste, Pulpdent paste, and a mixture of equal parts by weight of Ledermix paste and Pulpdent paste were added to in vitro cultures of mouse fibroblasts or bacteria for 24 hours, and various cell functions were then examined: mitosis by and survival of fibroblasts, and survival of \(Lacto-bacillus casei\) or \(S\) mutans. Ledermix was found to reversibly inhibit mitosis in the concentration range
of $10^{-3}$ to $10^{-6}$ mg/ml. Mixing with Pulpdent did not modify this antimitotic effect. Ledermix killed mouse fibroblasts at $10^{-3}$ mg/ml and above, while Pulpdent killed these cells at 1 mg/ml and above. The toxic effect of Ledermix was slightly inhibited by mixing it with Pulpdent. Ledermix killed *S mutans* at about the same concentration at which it killed the mammalian cells, but required a one thousand-fold greater concentration to kill *L casei*. Pulpdent killed both *L casei* and *S mutans* at approximately one-fifth of the concentration at which it killed the mammalian cells.

Thong, et al\(^47\) compared the effect of Ca(OH)\(_2\) (Pulpdent) and Ledermix paste on periodontal healing and root resorption following replantation. Histomorphometrically, they found that periodontal ligament inflammation and inflammatory root resorption were markedly inhibited by both Ca(OH)\(_2\) and the corticosteroid-antibiotic relative to untreated controls. Replacement resorption was lowest in the corticosteroid-antibiotic group, and significantly more normal periodontal ligament was present in this group than in the Ca(OH)\(_2\) and control groups. Wong and Sae-Lim\(^48\) evaluated the effect of immediate intracanal Ledermix on root resorption of delayed replanted monkey teeth. For the experimental group, intracanal Ledermix was placed prior to extraction and replantation after 1-hour bench dry. The positive control group was root filled and replanted after 1 hour while the negative control group was root filled and replanted immediately. The negative control group produced more favorable healing as compared to the Ledermix group. The Ledermix group showed significantly higher occurrence of complete healing (35.46%) compared to the positive control group (16.58%) but there were no significant differences in the inflammatory root resorption and replacement resorption. Nevertheless, when the latter 2 unfavorable healing patterns were combined, there was significantly lower unfavorable healing in the Ledermix group (64.54%) when compared to the positive control group (83.43%). This unfavorable healing outcome in the Leder-mix group, however, was not significantly different from the favorable healing outcome with the same treatment modality.

Bryson, et al\(^10\) evaluated the effect of immediate intracanal placement of Ledermix Paste on healing of replanted dog teeth after an extended drying time (60 min). The Ledermix Paste-treated roots had statistically significantly more healing and less resorption than the roots treated with Ca(OH)\(_2\). Root filling with Ledermix Paste also resulted in significantly less loss of root mass due to resorption compared to roots filled with Ca(OH)\(_2\). Chen, et al\(^49\) evaluated the individual influence of triamcinolone and demeclocycline on external root resorption after an extended extraoral drying time (60 minutes). The groups treated with Ledermix, triamcinolone, and demeclocycline had significantly more favorable healing than the group filled with gutta-percha and replanted after 60 minutes drying time (positive control). There was no statistically significant difference between the Ledermix group and the triamcinolone group, while the tetracycline group showed less favorable healing as compared to the other groups. They concluded that corticosteroid and tetracycline, as anti-inflammatory and antiresorptive agents, stopped or minimized the inflammatory response including clastic-cell mediated resorption, thus promoting more favorable healing than the positive control group, which had no intracanal medicaments. Further-more, they proposed that in severe traumatic injuries, where a large surface area of periodontal inflammation is expected, removing the pulp and placing corticosteroids into the canal at the emergency visit should become a standard protocol.

Trope\(^50\) evaluated the relationship of intracanal medicaments to endodontic flare-ups. Formocresol, Ledermix, and Ca(OH)\(_2\) were placed in a specific sequence irrespective of the presence or absence of symptoms or radiographic signs of apical periodontitis. He found no significant difference in the flare-up rate among the 3 intracanal medicaments. Ehrmann, et al\(^51\) investigated the relationship of postoperative pain to 3 different medicaments placed in the root canal after complete biomechanical debridement in emergency patients. They found that painful teeth with acute apical periodontitis that had been dressed with Leder-mix paste were associated with less pain as compared to teeth dressed with Ca(OH)\(_2\) or no dressing at all.

Kim, et al\(^52\) investigated the effects of Ledermix paste as an intracanal medicament on discoloration of mature teeth, whether the discoloring was related to the method of
application, as well as the effects of sunlight upon discoloration of these teeth. After 12 weeks of sunlight exposure dark grey-brown staining of the teeth occurred in the Leder-mix groups, but not when the teeth were kept in darkness. More severe staining was noted when Ledermix paste filled the pulp chamber than when the paste was restricted to below the CEJ. It was suggested that if placement of the Ledermix is restricted to the canal below the gingival margin, staining effects could be minimized. In another study, they investigated the effects of Ledermix paste as an intracanal medicament on discoloration of immature teeth, whether the discoloring effects were related to the method of application, and the effects of sunlight upon discoloration of immature teeth. After 12 weeks, sunlight exposure again caused dark grey-brown staining in the Ledermix groups, but this did not occur when the teeth were kept in darkness. More severe staining was noted when Ledermix paste filled the pulp chamber than when Ledermix paste was restricted to below the cementoenamel junction and when teeth were exposed to sunlight.

When compared to the results of a similar study using mature teeth, the immature teeth were more severely stained than the mature teeth. The Ca(OH)$_2$ paste caused an increase in whiteness and yellowness in immature teeth.

**Combination of Ledermix and Calcium Hydroxide**

The combination of Ledermix paste with Ca(OH)$_2$ has been advocated by Schroeder, initially for the treatment of necrotic teeth with incomplete root formation. A 50:50 mixture of Ledermix paste and Ca(OH)$_2$ has also been advocated as an intracanal dressing for infected root canals, pulp necrosis, infection with incomplete root formation (as an initial dressing prior to using Ca(OH)$_2$ alone for apexification), perforations, inflammatory root resorption, inflammatory periapical bone resorption, and for treatment of large periapical radiolucent lesions. It has been shown that the 50:50 mixture results in slower release and diffusion of the active components of Ledermix paste, which makes the medicament last longer in the canal. This in turn helps to maintain the sterility of the canal for a longer period of time and also maintains a higher concentration of all components within the canal.

The 50:50 mixture of Ledermix paste and Ca(OH)$_2$ paste does not alter the pH to any noticeable degree and therefore it is expected that the mixture will act in a similar manner to when Ca(OH)$_2$ is used alone. Taylor, et al also showed that for 2 indicator microorganisms, L casei and S mutans (which are cariogenic), the 50:50 mixture was marginally more effective than either paste used alone. However, Seow showed that for S sanguis and S aureus, the addition of only 25% by volume of Calyxl (a Ca(OH)$_2$ in saline paste; Otto and Company, Frankfurt, Germany) to Ledermix converted the zone of complete inhibition originally seen in Ledermix to one of only partial inhibition. This study suggested that some medicaments should not be used in combination, and that when 2 medicaments with strong antimicrobial activity are combined there may be no additive or synergistic effects.

Chu, et al compared the efficacy of disinfection of root canals with periapical radiolucencies when treated with either antibiotics/steroid medicaments (Ledermix or Septomixine [10 million IU neomycin + 20 million IU polymixine B sulfate]) or a Ca(OH)$_2$ paste (Calasept). In the Ledermix group, 38 strains of bacteria were recovered, the Septomixine group had 25 strains, and the Calasept group had 25 strains. In all cases, Gram-positive facultative anaerobic cocci (including staphylococci and streptococci) were more prevalent than the Gram-negative obligate anaerobic rods after treatment.

**SUMMARY**

Local application of antibiotics within the root canal system may be a more effective mode for delivering the drug. Tetracyclines have been used to remove the smear layer from instrumented root canal walls, for irrigation of retrograde cavities during periapical surgical procedures, and as an intracanal medicament. Substantivity of tetracyclines has been shown for up to at least 12 weeks. BioPure MTAD is effective in removing the smear layer. However, the antimicrobial efficacy against E faecalis of 1.3% NAOCl/MTAD compared with that of the combined alternate use of 5.25% NAOCl and 15% EDTA is still controversial. Substantivity of MTAD has been shown for up to 4 weeks. Further-more, application of MTAD to 1.3% NAOCl-irrigated dentin may reduce its substantivity.
Local Applications of Tetracyclines in Endodontics and Dental Trauma: A Review

Tetraclean is a mixture of an antibiotic (doxycycline), an acid, and a detergent (like MTAD), with a very low surface tension and high degree efficacy against bacterial biofilms. Ledermix, a glucocorticosteroid-antibiotic compound, due to anti-inflammatory and antiresorptive properties, reduces the inflammatory reaction including clastic-cell mediated resorption, significantly lowers the incidence of replacement resorption, and thus prompts more favorable healing in replanted teeth. A 50:50 mixture of Ledermix paste and Ca(OH)2 has been advocated as an intracanal dressing in cases of infected root canals, pulp necrosis and infection with incomplete root formation (apexification), perforations, inflammatory root resorption, inflammatory periapical bone resorption, and for the treatment of large perforations, inflammatory root resorption, and for the treatment of large perforations, inflammatory infection with incomplete root formation (apexification), dressing in cases of infected root canals, pulp necrosis and infection with incomplete root formation (apexification), perforations, inflammatory root resorption, inflammatory periapical bone resorption, and for the treatment of large periapical radiolucent lesions.

REFERENCES

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1. The first reported local use of an antibiotic in endodontics was by________.
   a. Seltzer
   b. Grossman
   c. Weine
   d. Ingle

2. Tetracyclines are a group of _______ and ________ antibiotics.
   a. narrow spectrum-bactericidal
   b. broad spectrum-bactericidal
   c. broad spectrum-bacteriostatic
   d. narrow spectrum-bacteriostatic

3. Substantivity of BioPure MTAD lasts for up to____ weeks.
   a. 2
   b. 4
   c. 12
   d. 24

4. BioPure MTAD is a mixture of __________.
   a. tetracycline, nitric acid, and Tween 80
   b. doxycycline, citric acid, and Cetrimyde
   c. minocycline, citric acid, and Tween 80
   d. doxycycline, citric acid, and Tween 80

5. The components of ________ are similar to MTAD.
   a. Tetraclean
   b. EDTA
   c. Cetrexidin
   d. Smear Clear

6. Dentin pre-treatment with_______ reduces the substantivity of MTAD.
   a. sodium hypochlorite
   b. EDTA
   c. Smear Clear
   d. Dermacyn

7. Ledermix is a ________ - ________ compound.
   a. antibiotic-antibiotic
   b. antibiotic-corticosteroid
   c. corticosteroid-corticosteroid
   d. antibiotic-mineral corticoid
8. The type of detergent in Tetraclean is__________.
   a. Tween 80  
   b. Polypropylene glycol  
   c. Polysorbate 80  
   d. Cetrexidin

9. The bacteriostaticity of tetracyclines may be considered as an advantage because:
   a. by-products such as endotoxin are not released.  
   b. it has anti-resorptive activity.  
   c. bacterial cell is not lysed.  
   d. a and c.

10. Presence of the antibiotic component in Ledermix is to:
    a. control pain.  
    b. prevent root resorption.  
    c. compensate possible reduction in the immune response.  
    d. control inflammation.

11. Ledermix reversibly inhibits mitosis in the concentration range of ______ mg/mL.
    a. 10-1 to 10-3  
    b. 10-6 to 10-9  
    c. 10-3 to 10-6  
    d. 1

12. Currently, Ledermix paste is a combination of ______ and _______.
    a. triamcinolone acetonide-doxycline  
    b. dexamethasone-tetracycline  
    c. hydrocortisone-demeclocycline  
    d. triamcinolone acetonide-demeclocycline

13. The concentrations of antibiotic in Tetraclean and BioPure MTAD are_____ and_____ mg/ mL, respectively.
    a. 100 and 50  
    b. 50 and 100  
    c. 100 and 200  
    d. 25 and 50

14. The accurate formula of BioPure MTAD is as follows:
    a. 3% doxycycline, 4.25% citric acid, and 0.5% Tween 80.  
    b. 3% tetracycline, 4.25% citric acid, and 0.5% Polysorbate 80.  
    c. 4.25% doxycycline, 3% citric acid, and 0.5% Tween 80.  
    d. 3% minocycline, 4.25% citric acid, 0.5% polypropylene glycol

15. Ledermix paste, after_____ weeks of sunlight exposure, causes staining of teeth.
    a. 12  
    b. 4  
    c. 24  
    d. 2

16. _______ slightly reduces the toxicity of Ledermix.
    a. Chlorhexidine  
    b. Calcium hydroxide  
    c. Septomixine  
    d. Streptomycin
Local Applications of Tetracyclines in Endodontics and Dental Trauma: A Review

PROGRAM COMPLETION INFORMATION

If you wish to purchase and complete this activity traditionally (mail or fax) rather than Online, you must provide the information requested below. Please be sure to select your answers carefully and complete the evaluation information. To receive credit you must answer at least six of the eight questions correctly.

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ANSWER FORM: COURSE #: 109
Please check the correct box for each question below.

1. ☐ a  ☐ b  ☐ c  ☐ d
2. ☐ a  ☐ b  ☐ c  ☐ d
3. ☐ a  ☐ b  ☐ c  ☐ d
4. ☐ a  ☐ b  ☐ c  ☐ d
5. ☐ a  ☐ b  ☐ c  ☐ d
6. ☐ a  ☐ b  ☐ c  ☐ d
7. ☐ a  ☐ b  ☐ c  ☐ d
8. ☐ a  ☐ b  ☐ c  ☐ d
9. ☐ a  ☐ b  ☐ c  ☐ d
10. ☐ a  ☐ b  ☐ c  ☐ d
11. ☐ a  ☐ b  ☐ c  ☐ d
12. ☐ a  ☐ b  ☐ c  ☐ d
13. ☐ a  ☐ b  ☐ c  ☐ d
14. ☐ a  ☐ b  ☐ c  ☐ d
15. ☐ a  ☐ b  ☐ c  ☐ d
16. ☐ a  ☐ b  ☐ c  ☐ d

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Please complete the following activity evaluation questions.

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