Review Article

Overview on the Current Antibiotic Containing Agents Used in Endodontics

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Abstract

Antibiotics are systemically and locally used extensively in endodontics. However, local antibiotic application mode is considered more effective than systemic administration. The local mode enables the dentist to target bacteria in every nook and corner of root canal system, which is otherwise beyond reach if targeted by instrumentation or conventional root canal treatment protocols. Therefore, they are an important adjunct to conventional treatment of root canal. The present study reviews the various antibiotic containing dental agents used in endodontics. A web-based research on MedLine was performed with terms Review Articles published in the last 10 year's dental journals in English for literature researching, extracting, and synthesizing data. Relevant articles were shortlisted. Important cross-reference articles were also reviewed.

Keywords: Antibiotics, Intracanal medicaments, Irrigants, Obturation, Regeneration

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Introduction

Antibiotics have revolutionized the entire health-care system, since the discovery of penicillin in 1928 by Fleming. For many decades, antibiotics are prescribed in numerous disciplines of medicine and dentistry.[1] During endodontic treatment, antibiotics may be given systemically or regionally (i.e., intra-dental use). Systemic antibiotics should be used to treat dental infections on the basis of a defined indication.[2] The local application of antibiotics is an effective mode of disinfection in endodontics[3], as systemic antibiotics fail to reach the necrotic pulpless teeth due to absence of blood supply.

The purpose of this article is to review the antibiotic compounds used during endodontic treatment. A web-based research on MedLine was done to collect relevant articles by using term Review published in the last 10 year's dental journals in English language papers. The keywords searched on MedLine were "Antibiotics and Endodontics," "Intracanal medicaments," "Antibiotics and Root Canal Irrigation," "Antibiotics and Obturation," "Root Canal Sealers," "Tooth Reimplantation," and "Root Canal Revascularization." In addition, important cross-reference articles were reviewed. The present review screened about 100 articles, relevant articles were shortlisted and facts were compiled.

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History

Mixtures with antimicrobial properties utilized in the treatment of infections were described over 2,000 years ago.[4] Traditionally, plant materials and extracts[5], honey[6], moldy soybean curd, warm earth rich in molds and fungi were used to treat infections. These folk remedies tell the tale of inadvertent use of antibiotics since ages, although the concept of antibiotics is relatively recent. Physician Paul Ehrlich laid down the foundation of idea of antibiotics by introducing the term "magic bullets" for a chemical that would attach itself to the germ and kill it. Jean Paul Vuillemin used the term "antibiosis" that means "against life" for early antibacterial drugs.[7] Antibiosis was first described in 1877 by Louis Pasteur and Robert Koch.[8]

In 1942, Selman Waksman referred antibacterial drugs as antibiotics to describe any substance produced by a micro-organism that is antagonistic to the growth of other micro-organisms in a high dilution.[9] Grossman, known as father of endodontics, in 1951 proposed PBSC (polyantibiotic paste which suspended in a silicone vehicle, and was a combination of penicillin, bacitracin, streptomycin and caprylate sodium), that was the firstly reported local use of an antibiotic in endodontics.[10] Polyantibiotic paste showed therapeutic potential, but owing to the drawbacks including ineffectiveness against anaerobic species and allergic reactions, the Food and Drug Administration (FDA) prohibited PBSC for endodontic use in 1975. Later, an antifungal version of PBSC named with PBSN, in which Nystatin substituted caprylate sodium, was released.[11]

Discussion

The various modalities, which contain antibiotic compounds for the treatment in Endodontics, are discussed below:

Pulp capping

Several topical antibiotic-containing preparations have been evaluated for their use as pulp capping agents but without a precise efficacy.

Ledermix containing both triamcinolone (a steroid) and demethylchlortetracycline (an antibiotic)[12] is a topical preparation that is used as pulp capping agent. It is available in kits containing dental paste, dental cement powder, hardener "F" dental liquid (fast setting time) and hardener "S" dental liquid (slow setting time). The paste form is preferred in the treatment of exposed pulp, as it contains one third more steroid than the cement form. Thus, it is effective in the control of inflammation after tooth preparation, and reduces the need to rely on analgesics for pain relief. For emergency management of irreversible pulpitis, the paste relieves pain till definitive root canal therapy is carried out. The cement can be used as a pulp-capping agent in case of small pulp exposure and as an excellent subliner for deep cavities where no exposure has occurred but hypersensitive dentine is present. Although Ledermix has shown to be an efficacious pulp capping agent[13], since it is a pulp irritant[14], its use as a pulp capping agent is not recommended.[15]

Pulpomixine is composed of dexamethasone acetate, polymyxin B sulfate and framycetin sulfate. Its use is contraindicated in patients allergic to any of its ingredients. Pulpoximine is applied to the floor of the cavity in deep cavities without pulp exposure, acute pulpitis and recent pulp exposure with recent pulpitis.

Preparations containing erythromycin estolate[16] and vancomycin[17] have also been used, but they are proved to be ineffective with some side effects.

Intracanal medicaments

Intracanal medicaments are defined as antiseptic agents in the chemical form applied to the walls of the root canals with the objective of eliminating microorganisms present before or even after cleaning and irrigating the root canal system. Various polyantibiotic intracanal pastes that have been in use are discussed below:

Ledermix paste

Schroeder and Triadan developed Ledermix in 1960, which was made commercially available by Lederle Pharmaceuticals in 1962.[18] Ledermix paste contains an antibiotic demeclocycline—HCl (3.2%) and a corticosteroid, triamcinolone acetonide (1%), in a polyethylene glycol base.[18] The paste utilizes corticosteroids to control pain and inflammation related with pulp and periapical diseases.[18] Antibiotic is added to Ledermix to compensate for the perceived corticoid-induced reduction in the host immune response. Both triamcinolone and demeclocycline are capable of diffusing through dentinal tubules and cementum to reach the periradicular and periapical tissues.[19] Various studies have confirmed the effectiveness of Ledermix as intracanal medicament.[20-22] Perfect for use in endodontic therapy and between appointments, Ledermix is water soluble, well rinsed out easily, and does not result in any systemic side effect in the intradental use.[23]

Odontopaste

Released in February 2008, odontopaste is a zinc oxide-based root canal paste with 5% clindamycin hydrochloride and 1% triamcinolone acetonide. Clindamycin is effective against many endodontic pathogens including *Streptococci*, *Peptostreptococcus*, *Actinomyces*, *Fusobacterium, Eubacterium, Propionobacterium, Microaerophilic, Peptococcus, Porphyromonas, Veillonella* and *Prevotella*. Clindamycin paste as an intracanal dressing has good antibacterial effect[24,25], however, it does not have the anti-resorptive properties.[25] This antibiotic provides a bacteriostatic activity, and acts as interim dressing material preventing bacterial repopulation within the root canal. Additionally, the steroid part, triamcinolone acetonide, can temporarily reduce inflammation and postoperative pain. No bleaching is required following the use of odontopaste, as it does not stain teeth.[26] Mixing of additional calcium hydroxide in a 50:50 combination with Odontopaste is not recommended because the steroid component gets destroyed immediately by increased alkalinity. Odontopaste contains calcium hydroxide at 0.5% level, which has been proven to be optimal for the preservation of the steroid component.[27]

Septomixine forte

Septomixine Forte paste contains dexamethasone, halethazole tartrate, neomycin sulfate, polymyxin B sulfate, and tyrothricin. Septomixine Forte paste, however, is no longer recommended because the antibiotics (neomycin and polymyxin B sulfate) are unsuitable for use against endodontic bacteria due to their inappropriate spectra of activity.[19]

Sulfonamides

Sulfanilamide and sulfathiazole were initially used as root canal medicaments,[28] but now are no longer used as they tend to cause a yellowish discoloration of the teeth.[29]

Irrigants Containing Antibiotics

Irrigation is an indispensable part of root canal treatment as it cleans much better than root canal instrumentation alone does.[30] A variety of chemicals has been used as root canal irrigants, including citric and phosphoric acids, chelating agent (EDTA), proteolytic enzymes, alkaline solutions (sodium hypochlorite, sodium hydroxide, urea and potassium hydroxide), oxidative agents (hydrogen peroxide and Gly-Oxide), local anaesthetic solutions and normal saline.[31] Two new root canal irrigants, Mixture of Tetracycline, Citric Acid and Detergent (MTAD) and Tetraclean, containing antibiotics have recently been introduced.

BioPure MTAD

Root canal irrigant MTAD commercialized as BioPure MTAD was introduced by Torabinejad and Johnson[32] in 2003.

MTAD is commercially available as Powder-Liquid system. Part A is a liquid containing 4.25% citric acid and 0.5% polysorbate 80 detergent (Tween 80). Citric acid removes organic and inorganic materials from the surfaces of roots. Tween 80 (polyoxyethylene sorbitan mono-oleate) is a non-ionic surfactant, which helps reducing the surface tension thereby enhancing the flow and penetration of irrigating solutions. Part B is a powder containing 3% doxycycline hyclate, which is a broad spectrum antibiotic, and is supplied in bottles. Doxycycline hyclate is used to increase the water solubility, instead of its free-base doxycycline monohydrate.[33] It disinfects the internal surface of root, is bacteriostatic and shows the property of substantivity and anticollagenase activity. The powder and liquid are mixed by following the manufacturer's instructions to obtain the final ready to use MTAD.

MTAD is clinically effective and biocompatible, and has proved its antimicrobial effectiveness against E. faecalis[34,35] and over standard irrigants.[36,37] The bacteriostatic property of doxycycline is advantageous, because in the absence of bacterial cell lysis, endotoxins are not released[38] and the substantivity of doxycycline provides a prolonged antibacterial effect.[38] Doxycycline additionally helps MTAD to get rid of smear layer by acting as a calcium chelator, thereby, resulting in root surface demineralization.[39] The exact mechanism of antimicrobial action of citric acid is not known yet, however, it is known to extend the antibacterial impact of varied substances.[40]

Tetraclean

Tetraclean is a mixture of an antibiotic, acid and detergent like MTAD, but differs in the concentration of doxycycline (50 mg/ml) and type of detergent (polypropylene glycol).[41] It shows a high action against strict anaerobic as well as facultative anaerobic bacteria, and also removes the smear layer. Giardino *et al*.[41] showed that both cetrexedin and tetraclean had the lowest value of surface tension when compared to 17% EDTA, Smear Clear, 5.25% NaOCl and MTAD. Tetraclean is more effective than MTAD against *E. faecalis* in the planktonic culture and the mixed species *in vitro* biofilm.[42] The another study by Giardino *et al*. again proved a higher antimicrobial efficacy of tetraclean, as it resulted a high degree of biofilm disaggregation on cellulose nitrate membrane filters when compared to MTAD and 5.25% NaOCl.[43]

Obturation with medicated gutta percha points

If root-canal obturation material possesses some antimicrobial activity, it can assist eliminate microbes residing in anatomical complexities of root canals such as cementum crypts, secondary canals, isthmus, and dentin tubules, and survives biomechanical preparation of root canal space.

Howard Martin developed medicated gutta-percha (MGP)[44] containing 10% iodoform and tetracycline-impregnated gutta percha (TGP) containing 10% tetracycline[45], which intent to retard the growth of bacteria inside the obturated root canal. TGP acts as an antimicrobial reservoir with a capability of diffusing onto the surface of the gutta percha, inhibiting colonization of bacteria on the gutta percha points and within the root canals.[46] TGP has been advocated as an inter-appointment intracanal medicament and final obturating material.[47] Gutta Percha points containing metronidazole for root canal disinfection have been investigated, and may be considered as an ideal method for clinical application.[48,49] This concept needs in-vivo studies to evaluate the toxicity and antibacterial and antifungal effects.

Medicated Sealers

The addition of antibiotics to the root canal sealer is beneficial to prevent re-infection and impart antimicrobial property for an extended period of time. Hoelscher *et al*. found that, except for metronidazole, amoxicillin, penicillin, clindamycin and doxycycline enhanced the antimicrobial efficacy of Kerr Pulp Canal Sealer (PCS) against *E. faecalis*.[50] Another study showed that addition of amoxicillin, doxycycline and metronidazole to Kerr PCS (extended working time) improves both the antibacterial property and apical sealing ability.[51] Hasan R *et al*. found that AH26 sealer in combination with amoxicillin and doxycycline individually was effective in killing *E.faecalis* in dentinal tubules.[52]

Tooth reimplantation

Avulsed teeth with immature roots are subject to root resorption, but also possess the potential for pulpal revascularization.[53] Bacterial contamination of root surfaces may occur during the extra-oral time that could inhibit healing of the recently replanted teeth, therefore, a protocol for the topical treatment of exposed roots with doxycycline before reimplantation was developed.[54] Avulsed teeth with an open apex should be soaked for 5 minutes in a 1 mg/20 mL doxycycline solution, and then reimplanted.[55] This resulted in up to 40% to 60% increase in pulp revascularization of the reimplantation cases along with decrease in frequency of external replacement resorption, ankylosis, and external inflammatory resorption.[54] The beneficial effect of soaking a tooth in doxycycline has been confirmed by Yanpiset *et al*.[56] Along with this it is recommended to prescribe oral antibiotic therapy to avoid infection and external root resorption.[57] The antibiotic choice is amoxicillin,[57] although doxycycline is advantageous.[58]

Antibiotics in regenerative endodontics

Sterile environment is the prerequisite for success of any regenerative endodontic procedures. To achieve this, triple antibiotic paste (TAP) based on lesion sterilization and tissue repair therapy concept is most commonly used. The lesion sterilization and tissue repair therapy utilizes a combination of antibacterial drugs for the disinfection of pulpal lesions.[59] TAP, first used by Sato *et al*.[60], contains metronidazole, ciprofloxacin, and minocycline, and is commercially available as 3 MIX MP. Hoshino *et al*. recommended metronidazole (500 mg), minocycline (100 mg) and ciprofloxacin (200 mg) at a ratio of 1:1:1 for the 3Mix formulation.[61] The carrier (MP) recommended was propylene glycol and macrogol ointment[61] at the ratio of 1:1. The formulation was modified by Takushige *et al*., and recommended metronidazole, minocycline and ciprofloxacin antibiotics mixed in the ratio at 3:3:1. This can be mixed with MP or root canal sealers, although the mixture with sealers is presently not recommended.[62]

A recent study showed that the administration of single antibiotic augmentin paste for 5 weeks as an intracanal medicament resulted in excellent infection control, and gave complete osseous healing of the periapical lesion and formation of the root apex.[63]

Antibiotic-containing scaffolds

Although TAP is established antibiotic paste, but it has its own drawbacks. TAP is radiolucent[61], propylene glycol as a vehicle of TAP may be difficult to remove from the dentin surface, an additional appointment is required to remove TAP and re-opening the tooth to remove TAP introduces a risk of recontamination. Antibiotic containing scaffolds can solve the problems.

Bottino MC *et al*.[64] have suggested that the polymer-based antibiotic-containing electrospun scaffolds may act as a biologically safe antimicrobial drug delivery system for regenerative endodontics. This can improve drug delivery due to high surface area fibers arranged in an interconnecting structure that allows controlled drug release[65] and improve drug adaptation to the canal wall in the regeneration procedure. As the scaffold degrades over time[66], it does not required to be removed, thus, reduces appointments and a subsequent risk of bacterial contamination. In addition, the drug release can be manipulated in a mode-rapid, intermediate or delayed, depending on the polymer used.[67] The effectiveness of an electrospun scaffold capable of drug release has been reported in the literature.[65,68] Bottino MC *et al*.[69] suggested the electrospun nanocomposite fibrous material to act as a scaffold for regenerative endodontics, and a drug-delivery device to aid in root maturogenesis and the regeneration of the pulp-dentine complex. Various other synthetic electrospun polymeric nanofibers are under investigation for use as drug delivery devices in the medicine and other applications for tissue engineering.[65]

Demerits of Local Antibiotic Application

Although a local antibiotic medication in endodontics offers advantages including an efficient and predictable disinfection, and a high drug concentration at the local site, reducing systemic complications of antibiotic medication, this mode has some drawbacks, including development of bacterial resistant strains[70], allergic reactions[71,72], inhibition of angiogenesis[73], and tooth staining or discoloration.[74,75] In addition to these drawbacks, the development of antibiotic resistance is alarming, and should be checked. One major cause contributing to antibiotic resistance is the use of antibiotics in an improper manner, which leads to

resistant microorganisms and increases transfer of resistance genes from antibiotic-resistant to antibiotic-susceptible microorganisms.[76] Antibiotics should be used very selectively, but, dentists unfortunately prescribe antibiotics for dental conditions which should be managed by analgesics and local measures. The profession needs to realize the importance of using antibiotics correctly, and routine prescribing antibiotics for endodontic procedure must be discouraged. Antibiotic resistance threatens mankind with the prospect of a return to the pre-antibiotic era.[77] It is strongly suggested that bacterial resistance to antibacterial agents is reversed by avoiding the use of antibiotics until extremely necessary.[78]

Can Intracanal Antibiotics be Substituted?

The sole purpose behind a local application of antibiotic compounds is to eliminate microbes. If this motive is achieved by some other means, then antibiotics can be avoided. The EndoVac apical negative-pressure system of irrigation can be one of such ways, in which the irrigating agents are safely delivered to the full

Table 1: Antibiotics containing agents used in endodontics

Antibiotic compound	Antibiotics present	Effectiveness against bacteria (Gram+/-)	Usage	References
Ledermix	Demethylchlor-tetracycline	+/-	Pulp capping agent	Cowan A 1966[12], Shovelton DS *et al.* 1971[13], Paterson RC 1976[14,15]
			Intracanal medicament	Athanassiadis B *et al.* 2007[19], Abbott PV 1990[20], Heling I, Pecht M 1991[21], Ehrmann EH *et al.*[22], Abbott PV 1992[23]
Pulpomixine	Polymyxin B Sulfate	-, except the Proteus group	Pulp capping agent	Czarnocka K 1977[85], Ruszyńska H 1980[86]
	Framycetin Sulfate	Aerobic -/some aerobic +		
Odontopaste	Clindamycin hydrochloride 5%	+/ some -	Intracanal medicament	Molander A, Dahlen G 2003[24], Lin S *et al.* 2003[25]
Septomixine Forte	Neomycin	-/some +	Intracanal medicament	Athanassiadis B *et al.* 2007[19]
	Polymyxin B sulfate	-, except the Proteus group		
BioPure MTAD	3% Doxycycline hyclate	+/-	Irrigant	Shabahang S, Torabinejad M 2003[34], Torabinejad M *et al.* 2003[35], Bansal R *et al.* 2013[36], Blerim K *et al.* 2012[37]
Tetraclean	Doxycycline	+/-	Irrigant	Pappen FG *et al.*2010[42], Giardino L *et al.* 2007[43]
Tetracycline-impregnated gutta percha (TGP)	10% tetracycline	+/-	Intracanal medicament, Final obturating material	Emre B *et al.* 2008[46], Vijay R *et al.* 2010[47]
Sustained release delivery Gutta Percha point containing metronidazole (SRDGM)	Metronidazole	Anaerobic+/-	Intracanal medicament, Final obturating material	Gao J *et al.* 2004[48]
Controlled-release delivery gutta-percha points containing metronidazole compound (CDGMC)	Metronidazole	Anaerobic +/-	Intracanal medicament, Final obturating material	Wang D *et al.* 2003[49]
Triple antibiotic paste (TAP)	Metronidazole,	Anaerobic +/-	Canal disinfection for pulp revascularization	Sato I *et al.* 1996[60], Hoshino E *et al.* 1996[61], Takushige T *et al.* 2004[62]
	Ciprofloxacin,	+/-		
	Minocycline	+/-		
Antibiotic-Containing Scaffolds	Metronidazole or	Anaerobic +/-	Canal disinfection for pulp revascularization	Kim K *et al* 2004[67], Tabata Y 2005[68], Thakur RA *et al.* 2008[65], Bottino MC *et al* 2013[69,87]
	Ciprofloxacin	+/-		

extent of the root-canal terminus, resulting in a better removal of organic tissue, microbial contaminants[79] and a better cleaning of the isthmus area.[80] Thus, optimum conditions are created to promote healing without the use of antibiotics. Hockett *et al*.[81] showed that the apical negative pressure eradicated biofilms of *Enterococcus faecalis* within 48 hours, not only from the walls of the root canal system, but also from the dentinal tubules. Various other studies have also shown that apical negative pressure with sodium hypochlorite irrigation results in similar bacterial reductions, as with use of apical positive pressure irrigation and a triple antibiotic in immature teeth[82] and equivalent repair process resulted.[83] Thus, the use of intracanal antibiotics is not necessary.[83] Additionally, using negative apical pressure and sodium hypochlorite also avoids the risk of drug resistance, tooth discoloration, and allergic reactions.[74,84]

Various antibiotic containing agents, applications, and bacterial spectrum along with the literature are given in Table 1.

Conclusion

Use of antibiotics both systemic and topical is common in the endodontic treatment, particularly for patients with pain or swelling. The antibiotic containing dental agents are used to eliminate bacteria from the root canal system, and provide a favorable healing environment. The use of antibiotic containing dental agents should be carefully justified, in order to avoid a bacterial resistance.

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