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Norfloxacin In Dental Practice

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Abstract

Antibiotics are commonly used in dental practice. It has been estimated that 10% of all antibiotic prescriptions are related with dental infections.Periodontal disease is caused by bacteria in dental plaque, the sticky substance that forms on your teeth a couple of hours after you have brushed. Interestingly, it is your body's response to the bacterial infection that causes most of the problems. In an effort to eliminate the bacteria, the cells of your immune system release substances that cause inflammation and destruction of the gums, periodontal ligament or alveolar bone. This leads to swollen, bleeding gums, signs of gingivitis the earliest stage of periodontal disease, and loosening of the teeth, a sign of severe periodontitis the advanced stage of disease. A Method for treating or preventing periodontal disease which comprises administering nor floxacin or salts thereof locally to periodontal tissue are disclosed. The method is excellent on the treatment of periodontal disease in small dose without disturbance of bacterial flora. The rate of progression of periodontal disease in an individual is dependent on the virulence (or strength of attack) of the bacterial plaque and on the efficiency of the local and systemic immune inflammatory responses in the person (host). The overall balance between the bacterial plaque challenge and the body's immune inflammatory responses is critical to periodontal health. The best clinical outcome for a periodontal patient following treatment would be the retention of formerly diseased teeth for a lifetime. The vast majority of gum diseases can be easily prevented by daily thorough plaque removal. However, irregularities around the teeth such as overhanging edges on fillings, poorly contoured fillings, and some types of partial denture designs make tooth cleaning difficult and encourage the accumulation of plaque. The presence of calculus (tartar) – plaque that has calcified and hardened – may also cause plaque to accumulate more readily and requires professional removal (scaling). For the majority of the population, however, periodontal health can be effectively maintained by proper oral hygiene practices as well as avoidance of behavioral and environmental risk factors (e.g., tobacco smoke, stress, poor diet) on the part of the individual. Because periodontal disease is linked to an increased susceptibility to systemic disease (e.g., cardiovascular disease, infective endocarditis, bacterial pneumonia, low birth weight, diabetes), it is important not only for oral health but also for general health to control periodontal disease.

Key Words*: dental practice, odontogenic infections,Periodontal disease, dental caries, gingivitis, periodontits, norfloxacin*

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I. Introduction

Dentist use of antibiotics is characterized by a number of particularities. In effect, antibiotic prescription is empirical, i.e., the clinician does not know what microorganism is responsible for the infection, since pus or exudate cultures are not commonly made. Based on clinical and bacterial epidemiological data, the germs responsible for the infectious process are suspected, and treatment is decided on a presumptive basis, fundamented on probabilistic reasoning.

The tolerability profile of norfloxacin, the first of a new generation of fluoroquinolone carboxylic acid antibacterials, has been defined in numerous laboratory animal and human trials. Whether administered for moderate or protracted periods, norfloxacin has been relatively safe in animals over a wide range of doses. There has been no evidence of a teratogenic effect in any of the animal species tested (rat, rabbit, mouse, monkey) at six to 50 times the human dose (400 mg twice daily). However, norfloxacin has been shown to produce embryonic loss in monkeys when given in doses 10 times the maximal human dose, resulting in peak plasma levels that are two to three times those obtained in humans. Although there are no adequate and well-controlled studies in pregnant women, norfloxacin is not recommended for use in this population because it, like other drugs in this class, causes arthropathy in immature animals. In animals, norfloxacin is neither mutagenic nor carcinogenic, and, in clinical trials, norfloxacin-related adverse experiences have been uncommon.[1]

Periodontal or gum disease is a pathological inflammatory condition of the gum and bone support (periodontal tissues) surrounding the teeth.
Many of the adults affects from this kind of periodontal disease based on the most advance national oral health survey only 20% of 15–23 year olds and 6% of 34–43 year olds and 5% of older people aged 64 years and above have healthy gingiva.[2]

The two most common periodontal diseases are:

- Gingivitis – inflammation of the gum at the necks of the teeth, and
- Periodontitis – inflammation affecting the bone and tissues of the teeth.

Gingivitis

Many of the children below 15 yrs have conditions of different inflammation of the gingival tissue layers at the edges of the teeth among adult and the primary level of gingival disease is prevented. This type of formation is called as gingivitis and it is differentiated by the redness of the gingival margins, swelling and bleeding during brushing. And Gingivitis can be both the chronic and acute forms. The Acute gingivitis is commonly accommodated with particular infections, micro-organisms, and the trauma. Chronic inflammation of the gum tissue surrounding the teeth is associated with the bacterial bio film (plaque) that covers the teeth and gums. The Gingivitis is primarily during the initial level in the chronic degenerative mechanism that is concluded in the loss of both gum and bone tissue surrounding the teeth. It is identified that gingivitis can be reversed by efficient personal oral hygiene practices. The proper form of tooth brushing as sign of daily activities seems to have concluded in oral cavity and being generally eliminating and showing low signals of inflammation especially among young adults, though gingivitis and it is spreading in the population.[3]

Periodontitis

The periodontal diseases affect on the bony layer and its supporting tissue which is known as periodontitis and is differentiated by the development of pockets and spaces between the tooth and gingival region. The important thing is the progression and produces chronic periodontal elimination that moves to loosening of teeth and loss of teeth. The characterization of the disease is such that the affected person can experience different conditions of frequent periodontal disease activity in a considerably limited period of time and followed by episodes of remission. The main majority of adults are caused by the gingivitis and gingivitis considerably does not frequently develop into periodontal disease. The transformation of gingival disease is produced by the number of conditions in which oral hygiene and genetic predisposition included. One of the factors for early identification of periodontal disease is its silent nature where the disease does not provide pain and can transforms unnoticed. In its initial stages the bleeding gingival during tooth brushing may be the sign detected and as the disease progresses and the gingival deteriorate and the bleeding may be stopped and there can be no transfer obvious signs till the teeth starts to feel loosely. In many cases, the periodontal diseases may respond to treatment and although the elimination is widely irreversible its transformation can be altred.

Norfloxacin on Periodontal Diseases

Norfloxacin is used to treat a variety of bacterial infections. This medication belongs to a class of drugs known as quinolone antibiotics. It works by stopping the growth of bacteria. This antibiotic treats only bacterial infections. It will not work for viral infections (such as common cold, flu). Using any antibiotic when it is not needed can cause it to not work for future infections.[4]

II. Description of Norfloxacin in periodontal diseases

Field of the Invention

The present invention relates to a method for treating or preventing locally periodontal disease. In particular, the present invention relates to a method for treating or preventing periodontal disease which comprises administering ofloxacin (9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid) or salts thereof to periodontal tissue of a patient having periodontal disease.

Description of the Disease

Periodontal disease and dental caries are the two most common diseases in the dental field. In most cases, tooth loss in adults is caused by periodontal disease. Periodontal disease is an inflammatory disease on periodontal tissue such as the gingival, and includes various types which vary depending on the progress degree of the disease or the age of the patient. Generally, those types can be mainly classified into gingivitis and periodontitis. Further, periodontitis can be classified into adult periodontitis and juvenile periodontitis. Previously, it was hypothesized that periodontal disease was caused by non-specific stimulation derived from dental calculus or dental plaque. However, recent intensive bacteriological and immunochemical investigation have made it apparent that some specific bacteria among more than 200 kinds of bacteria, which exist in the dental plaque, relate to the occurrence of periodontal disease. Particularly, as those bacteria, Actionmyces group,

Spirochetes group, and gram negative bacteria such as Bacteroides group, Actinobacillus group, Fusobacterium group, Capnocytophaga group, Eikenella group are noted.Further, relationships between some bacteria and some periodontal diseases have been reported. For example, Bacteroidesgingivalis is supposed to relate to occurrence of adult periodontitis and Actinobacillusactinomycetemcomitans is supposed to relate to occurrence of juvenile periodontitis.[5]

Periodontal disease has been treated by the following methods;

(1) Scaling for the purpose of removing sub-gingival plaque and dental calculus from periodontal pockets,

(2) Gingivectomy for the purpose of removing the inflammatory tissue or periodontal pocket, and,

(3) Root planning for the purpose of mechanically grinding the surface of the dental roots to accelerate the adhesion of the gingiva on the dental roots.

These methods are effective to some extent. However, some patients with specific internal diseases, for example a circulatory disease cannot undergo those surgical operations. Further, as treating agents for periodontal disease, dentifrices containing a germicide or anti inflammatory agent, and pastes for massaging the gingiva have been used. However, these agents are not yet satisfactory for the treatment of periodontal disease. Under these circumstances, a method for treating periodontal disease, which is more effective than hose mechanical or surgical methods, is strongly desired. As described above, specific bacteria relate to the occurrence of periodontal disease. Therefore, it is supposed to be effective for the treatment of periodontal disease to apply an antibacterial agent such as antibiotics in a suitable form to treat at an effective concentration the lesions of periodontal disease. However, this method has not been conducted for the following reasons:

(i) The bacteria which cause periodontal disease have not been identified.

(ii) Periodontal disease is usually classified into a chronic inflammatory disease and, it takes a long time to treat that disease. Therefore, when an antibacterial agent is given over a long period, a side effect of the agent may appear, or an opportunistic infection may appear by a disturbance of normal bacterial flora in the oral cavity and intestines.

(iii) No suitable administration method has been proposed. The bacteria which cause periodontal disease exists in the periodontal pockets between the teeth and the gingiva. Since the pockets are anatomically outer parts of the body, antibacterial agents are not delivered effectively to them when it is administered orally or by injection. Furthermore, even when they are administered in the form of a dentifrice, mouth wash or gingival massaging agent, they are not substantially delivered to the periodontal pockets and further, they are removed rapidly by the washing effect of saliva. Therefore, an effective concentration of antibacterial agents in the lesions of periodontal disease cannot be maintained.[6]

After intensive investigations to solve these problems, the inventors have found that nor floxacin or salts thereof exhibit strong antibacterial effects against those bacteria and that when they are administered locally to lesions of periodontal disease, specifically to the periodontal pockets, remarkable effects on the treatment of periodontal disease are obtained. This invention relates to a method for treating or preventing periodontal disease which comprises administering nor floxacin or salts thereof locally to periodontal tissue.[7]

Description of the preferred embodiments

Examples of the salts of nor floxacin include acid addition salts thereof with an inorganic acid such as hydrochloric and sulfuric acid or an organic acid, and carboxylate with alkali metals or alkaline earth metals such as sodium, potassium and calcium. Typical examples of the pharmaceutical preparations for administering nor floxacin or salts thereof locally to periodontal tissue include gels for the oral cavity, ointments adhesive to the membrane of the oral cavity, preparations to be inserted into periodontal pockets and tapes to be adhered to the gingiva. The preparations for local administration can be prepared by mixing an active ingredient, that is, nor floxacin or salts thereof with excipients or vehicles used for preparations to the oral cavity by using conventional methods. The preferred excipients and vehicles for those preparations include hydroxypropylcellulose, methylcellulose, hydroxymethylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, liquid paraffin, white petrolatum, plastibase, Eudragit L, sodium alginate, propylene glycol alginate, pullulan, tragantha, xanthane gum, chitosan, polyvinyl pyrrolidone, polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, ethyl methacrylate, dimethylamino acetate, cellulose acetate, polyethyleneglycol, collagen and atelocollagen. These substances can be used either respectively or as a combination of two or more kinds thereof. The combination is suitably selected depending on the preparation form. Those preparations may contain a coloring agent or a perfume as an additive. Typical examples of those preparations are shown below.

On the administration of those preparations, the gels or ointments are spread to the gingiva, the tapes are adhered to the gingiva and the preparations to be inserted into the pockets are inserted therein.The dose varies depending on the degree of periodontal disease. Usually, a suitable amount of the preparation containing at least 0.01 wt % of Norfloxacin is applied to the lesions of periodontal disease. Nor floxacin has already been used clinically as an excellent synthetic antibacterial agent by oral administration. [8][9]

According to the present invention, a method for treating or preventing periodontal disease, which exhibits very excellent effects without disturbance of bacterial flora even in a small dose, can be obtained. Also, according to the present invention, the excellent effective concentrations of nor floxacin or salts thereof in periodontal tissue are kept compared to that obtained by administering those compounds orally or in the form of injections.[10][11][12]

The following examples will further illustrate the present invention, but by no means limit the invention.

Example 1 [Gels for the oral cavity]:

945 g of water was added to 50 g of high molecular weight hydroxypropylcellulose to prepare a gel. 5 g of nor floxacin was added to the gel to produce a homogeneous mixture to be used as the gels for the oral cavity.[13]

Example 2 [Ointments adhesive to the mucous membrane of the oral cavity]:

313 g of liquid paraffin was added in small portions to 30 g of ofloxacin to obtain a mixture. 115 g of white petrolatum and 229 g of plastibase were added to the mixture and the obtained mixture was needed.

Further, 313 g of sodium carboxymethylcellulose was added thereto and the mixture was thoroughly needed to obtain a homogeneous ointment.[14]

Example 3 [Preparations to be inserted into the periodontal pockets]:

250 g of Eudragit L30D-55 (30% dispersion), 5 g of nor floxacin and 20 g of Tween 80 were mixed together. By using a casting method a film having a thickness of 300 μm was prepared from the mixture. The film was cut into strips having a width of 1 mm and a length of 10 mm to be inserted into the periodontal pockets.[15]

Example 4 [Tapes to be adhered to the gingival]:

85 g of a low molecular weight hydroxypropylcellulose was dissolved in 1,000 ml of water to form a gel. 5 g of nor floxacin and 10 g of polyethylene glycol 400 were mixed therein. The mixture was formed into a film having a thickness of 300 μm by the casting method. The film was cut into strips having a width of 10 mm and a length of 100 mm to be used as tapes to be adhered to the gingiva.[16]

Effects of the neither gels containing nor floxacin on experimental periodontitis:

The effects of the gel preparation containing nor floxacin on experimental periodontitis of hamsters infected with Actinomycesviscosus (hereinafter referred to as A. viscosus) were examined. 18 male golden Syrian hamsters (3-week-old) were fed with an ordinary solid diet, CE-2 (CLEA Japan Co.) for two weeks, and were given penicillin G solution (4000 U/ml) freely for three days before the infection so as to control the indigenous bacterial flora and to facilitate the infection. The hamsters were then randomly assigned to one of the following three groups: an infected group to be treated, an infected group not to be treated and a non-infected group, each group comprising six hamsters. The oral cavity of each animal of the infected groups was inoculated with 0.25 ml of culture broth (2.5×10^8 colonyl forming unit/ml; hereinafter CFU/ml) of A. viscosus ATCC 15987. The bacterial inoculation was performed daily for five days. From the first day of the infection, all animals were fed with Diet 2050 in place of feed CE-2. Diet 2050 was a powdery periodontitis-inducing feed comprising 28% of sucrose, 28% of corn starch, 28% of skim milk powder, 6% of flour, 4% of beer yeast, 3% of alfalfa powder, 1% of liver powder and 2% of common salt. After two weeks, 0.1 ml/day of the gels prepared in and was spread to the gingiva of each hamster every day. Eleven weeks after the first bacterial inoculation, the salivary occult blood degree of each animal was evaluated with occult blood test papers under anesthesia, and the results were classified into five ranks of 0 to 4 according to the color standard. The gingival index was evaluated and assigned into 4 ranks of 0 to 3 macroscopically according to the criteria of Rosenberg et al.[17] Then, all the hamsters were decapitated. Dental plaque was scratched off thoroughly from the first molar of the left maxilla of each hamster, and was immediately suspended in an anaerobic Ringer's solution. A 10 fold dilution series was prepared in an anaerobic glove box. The total number of the bacteria was enumerated on a GAM agar culture medium, the number of A. viscosus was enumerated on a selective medium for A. viscosus and the number of black-pigmented Bactericides was enumerated on Kanamycin- Vancomycinmenadion-blood agar medium. The plaque index was evaluated by the method of Regolati and Hotz after staining the teeth with a colorant. After evaluation of the plaque index, the jawbones were taken out. The soft tissue and debris were removed from the left jawbone to make a bone specimen. A macrograph of the each jaw was taken with a stereomicroscope along the lingual aspect. Measurements of the distances from the cement-enamel junction to

alveolar crest were done for all lingual roots of molars on the macrograph. The sum of these distances in each hamster was calculated to determine the alveolar bone loss vale. On the other hand, the right jaw was fixed in formalin, dehydrated, decalcified and embedded in paraffin. It was then sectioned and stained with haematoxylin and eosin. Histological observation of the samples was conducted with a microscope. [18]

The degree of the periodontitis in the treated group was lower than that in the untreated, infected group with respect to the salivary occult blood which indicated hemorrhage from the gingival crevice, gingival index indicating the degree of inflammation of the gingival, the plaque index indicating the quantity of the plaque, and the alveolar bone loss which is especially peculiar to periodontitis. The condition of the periodontal tissue in the treated group was similar to that of the non-infected group. The counts of bacteria in the plaque in the respective groups. In the treated group, the counts of A. viscosus used for the infection and black-pigmented Bacteroides, whose pathogenicity in periodontitis has been noted, were quite small, though the total counts of bacteria was only slightly lower than that in the infected group.[19]

Histological Observation

In the histological observation, the deposition of a large amount of the plaque and emigration of poly morpho nuclear leucocytes were observed in the infected group, proving presence of periodontitis, though these are not shown in the tables. On the contrary, they were only slight in the treated group and the degrees thereof were similar to those of the non-infected group.

These results indicate that the local administration of nor floxacin gel is effective on periodontal disease, particularly, periodontitis.[20]

Odontogenic infections

Odontogenic infections are among the most common infections of the oral cavity. They can be caused by dental caries, deep restorations that approximate the pulp chamber, pulpitis, periapical abscess, periodontitis, periodontal abscess, and pericoronitis.[21]. Odontogenic infections may develop into osteoperiostitis of the jaw, osteomyelitis, and deep fascial space infections. In normal hosts, acute odontogenic infections usually do not occur without some type of predisposing condition, such as periodontal accumulations, necrotic pulp tissue, or tissue damage associated with trauma or surgery.[22]

The increasing rates of antimicrobial resistance are well recognized and described in the literature. However, there is some evidence to suggest that virulence has also changed in some bacteria The epidemic of Brazilian purpuric fever in 1990, which was associated with a new clonal variation of Haemophilusinfluenzae, and the more recent devastating invasive infections caused by group A Streptococcus provide convincing evidence of this.[23]

There has also been a notable change in the behavior of odontogenic infections at our institutions. The inappropriate and increased use of resin restorations in the pediatric population has caused severe odontogenic infections to become an apparent and growing problem in this group.[4] Furthermore, the severity of these infections in the adult population is far greater than in the past, with a more rapid and dramatic spread through the fascial planes surrounding the airways. This change has necessitated the use of CT scans to diagnose and determine the extent of severe odontogenic infections, as well as the more frequent use of a lifesaving surgical

airway such as a tracheotomy, and broader incision and drainage techniques. The length of hospitalization for patients with these infections has also increased. Late referral makes the treatment of such patients more precarious. Dentists must therefore be prepared to refer their patients in a timely and appropriate manner.[24]

III. Discussion

On comparing the concentrations of norfloxacin in the oral cavity by oral administration and local administration: The preparations of Example 3 containing nor floxacin to be inserted into the periodontal pockets were locally administered to the pockets of volunteers and the concentration of nor floxacin in the periodontal fluid in the pockets was determined and compared with that in saliva obtained by oral administration thereof. In the test, the preparations of Example 3 having a thickness of 0.3 mm and width of 1 mm were cut into strips having a length of 4 mm (each neither containing 0.06 mg of nor floxacin). The strip was inserted into a periodontal pocket of each volunteer. The probing depth of the pocket was 5 mm. After a given time, a filter paper having a width of 1 mm was inserted into the pocket to take the periodontal fluid out of the pocket. The amount of nor floxacin in the periodontal fluid was determined from the diameter of an inhibition circle according to an agar plate diffusion method with E. coli K 12. The quantity of the periodontal fluid thus taken out was determined from a calibration curve prepared from the quantity of a previously prepared liquid sample and the wetted area of the filter paper. The concentration of nor floxacin was thus determined. The time profile of the concentrations of norfloxacin in saliva in the oral administration was taken from a report of Morihana et al. The results concludes, when 0.06 mg of nor floxacin was locally inserted into the periodontal pocket, the concentration thereof in the pocket was maintained above 70 μg/ml for longer than 5 h and 16.6 μg/ml even after 24 hours, while the maximum concentration in saliva was 1.8 μg/ml in 3 hours after the oral administration of 200 mg thereof. Namely, when nor floxacin in an amount of less than 1/3,000 of that given by the oral administration was inserted in the periodontal pocket according to the local administration, the concentration thereof in the pocket could be kept higher than that obtained by the oral administration. The concentration of norfloxacin in the periodontal pockets can be maintained for a longer period of time by varying the composition of the high molecular vesicles.Norfloxacin is indicated for traveller's diarrhea, summer diarrhea, shigellosis and urinary tract infections. Norfloxacin is active against aerobic and some anaerobic bacteria. The rationale of combination of norfloxacin is based on the fact that quinolones and imidazole derivatives act synergistically. Combinations of fluoroquinolones with other antimicrobial agents have been extensively investigated. Severe periodontal disease often coexists with severe diabetes mellitus. Diabetes is a risk factor for severe periodontal disease. The converse possibility that periodontal disease either predisposes or exacerbates the diabetic condition has received more and more attention. The periodontitis, are a potential contributing factor to a variety of clinically important systemic diseases. Almost all treatment and prevention techniques have used nonspecific debridement procedures as the primary means of controlling these plaque accumulations. This nonspecific approach to the management of dental infections (the Non-specific Plaque Hypothesis) has been universally applied to all individuals, even though it has been known for many years that a minority of individuals have the majority of the dental morbidity.[25]

IV. Conclusion

Periodontal infections can involve a variety of pathogens with different antimicrobial sensitivities and resistance patterns. In periodontal infections, tissue barriers and bio films should be removed, by mechanical debridement prior to or with antibiotics.Norfloxacin is a fluoroquinolone antimicrobial agent. The periodontal disease status and the antimicrobial regimen must be determined carefully to succeed with antimicrobial periodontal therapy. Unless antimicrobial agents against periodontal disease are used intelligently, we may soon face a new breed of oral microorganisms with heightened defenses that will ensure the survival of the species, allows for greater pathogen city and transfer genetic material coding for increased virulence and antibiotic resistance to other oral and non oral microorganisms. There are many delivery system identified for the administration for anti microbial and anti bacterial on to the periodontal pocket for local and systemic action in treatment of periodontal diseases such as gingivitis and periodontitis etc. The advantages of intra-pocket delivery over systemic delivery in periodontitis are that administration is less time-consuming than mechanical debridement and a lower dose of drug would be required to achieve effective therapeutic concentration at the site of action. The drug delivery system is used to improve the bio availability and to decrease the associated side effects which are harmful. The drug-loaded chitosan films were flexible, possessed good tensile strength and demonstrated satisfactory physicochemical characteristics. The management of periodontal disease by means of a treatment strategy based on the Specific Plaque Hypothesis is easier and less expensive to implement than one based on debridement/surgical intervention, as espoused by the Non-specific Plaque Hypothesis.

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