



## The Use of Individual Mouthpiece with Tinidazole and Doripenem in Complex Treatment of Periodontal Diseases

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**ABSTRACT:** The proposed method of therapy may be considered as a method of choice and an alternative to other methods of treatment of chronic generalized periodontitis. In the complex treatment of chronic generalized periodontitis, the authors used a combination of antimicrobial agents tinidazole and doripenem with a 1:1 ratio as a system for local delivery. For adjunctive fixation, an individual mouthpiece was made with a depot for drugs, which provided long exposure periods. Analysis of the data from clinical studies allows the authors to conclude that the use of this method is viable, promising and requires further research.

**Keywords:** Dentistry, periodontitis, microorganisms, antimicrobial therapy, complex periodontal index, curettage, mouthpiece.

### I. INTRODUCTION

Inflammatory periodontal diseases are one of the most pressing problems in dentistry. They have social significance because they are widespread, cause severe changes in the periodontal tissues and in the entire patient's body, and affect young people. Periods of remission and exacerbation occur during the course of inflammatory diseases of periodontal tissues, which often significantly disrupt the function of the dental system due to bone resorption and damage of the dental apparatus [1-3].

Different types of bacteria that grow on teeth and gums form complex associations. Associative flora usually contributes to the chronic course of inflammatory diseases with occasional exacerbations or leads to abscess formation.

Pathogenic bacteria produce a number of substances that have an extremely pronounced damaging effect on tissue structures. Most bacteria secrete short-chain fatty acids that inhibit leukocyte chemotaxis and phagocytosis. In this regard, they have certain toxicity. Anaerobes and spirochetes secrete a number of substances that are highly toxic to the cells of most tissues (butyric and propionic acids, indole). Several anaerobes are able to secrete mercaptans and H<sub>2</sub>S, which increase the permeability of the gum epithelial layer, inhibit T-lymphocytes and inhibit collagen synthesis by fibroblasts.

Having a toxic effect on fibroblasts, the waste products of microorganisms suppress reparative processes in the connective and bone tissues of the periodontium, causing severe dystrophic changes in them.

The accumulation of pathogenic microorganisms, as well as the products of their vital activity and decay over and under epithelial attachment to the tooth is accompanied by the formation of a primary focus of damage.

Enzymes secreted by pathogenic bacteria play a key role in the initiation of the primary damaging process in periodontal tissues. As a result of damage to tissue components, proserine esterase, thrombin, kinin, fibrinogen, and activated complement fractions. These

substances together with the bacterial waste products play the role of chemotactic factors for polymorphonuclear leukocytes, macrophages, and other cellular elements involved in the organization and development of the inflammatory process and have destructive effects.

As a result of the effect of these factors in the connective tissue basis of the gums, the dissociation of the protein-glycosamino-glycan complexes and accumulation of free amino acids, uronic acids, amino sugars, low-molecular polysaccharides, and polypeptides occurs. Osmotic pressure increases, swelling and water retention occurs, acidosis and hypoxia develops, accompanied by accumulation of lactic acid and fatty acids. A high level of lipid peroxidation leads to the destruction of cell membranes.

Structural and functional damage of the elements of the gum connective tissue is associated with a pronounced vasomotor reaction – prolonged dilation of the blood vessels. Persistent hyperemia is associated with impaired permeability of the vascular walls and migration of polymorphonuclear leukocytes and macrophages into the intercellular spaces. This is the beginning of the inflammation in the gums [2, 4].

According to several studies, only a small number of strains are associated with the development of periodontitis. The most likely pathogens are permanent members of the oral flora. However, microorganisms (enterobacteria, pseudomonads, staphylococci, fungi) that do not normally live in the oral cavity may also be present and cause superinfection. Periodontal damage is often caused by concurrent forms and not by monoculture. The most common periodontal pathogens are gram-negative anaerobic bacilli. However, in certain cases, facultative and anaerobic gram-positive cocci and bacilli, as well as facultative gram-negative bacilli, can be pathogenic. Facultative periodontal pathogens vary considerably in their sensitivity to various antimicrobial drugs, which creates certain difficulties in the selection of antimicrobial therapy [5].

The microbial etiology of inflammatory periodontal diseases explains the need for the use of antimicrobial

agents during complex periodontal treatment [4, 5, 6]. Antibiotics and other drugs were prescribed to patients suffering from periodontal diseases that were not curable using traditional mechanical therapy, to patients with acute inflammatory periodontal diseases associated with systemic symptoms, and for prevention and as an additional therapy for surgical and non-surgical periodontal treatment [7].

Therefore, the effectiveness of the periodontal treatment depends on the antimicrobial spectrum and pharmacokinetic characteristics of the drug and on local factors. These include: the accumulation of the drug in the tissues; resistance of pathogens – binding, consumption or destruction of the drug by microorganisms that are not included in the antibiotic spectrum; the formation of biofilm that protects pathogens in the dental plaque; the number of microorganisms at which the antibiotic concentration will be sufficient to ensure a suppressive effect; the effectiveness of the protection mechanisms of microorganisms; the presence of pathogens in the periodontal pockets, on the surfaces of the roots, and in other areas of the oral cavity that are not undergoing treatment [5, 8, 9].

The constantly increasing resistance of microorganisms to antimicrobial agents makes the use of new drugs in the treatment of periodontal diseases relevant. Suggested drugs must meet the following requirements: have the ability to completely cover the entire spectrum; have the ability to mix; have the ability to act synergistically; have the lowest possible toxicity.

In our opinion, most of the above requirements are met by the following drugs: tinidazole and doripenem.

Tinidazole (second generation 5-nitromidazol) is equal in effectiveness to metronidazole and has better tolerability. Tinidazole is an antiprotozoal and antimicrobial agent active against anaerobic pathogens (*Bacteroides* spp., including *Bacteroides fragilis*, *Bacteroides melaninogenicus*, *Clostridium* spp., *Eubacter* spp., *Fusobacterium* spp., *Peptococcus* spp., *Peptostreptococcus* spp.). Being highly lipophilic, it penetrates anaerobic microorganisms, where it is reduced by nitroreductase and inhibits the synthesis and damages the DNA structure [1, 10].

Doripenem is a new carbapenem antibiotic with broad-spectrum antimicrobial activity. Doripenem has a number of advantages compared to previously known carbapenems and other classes of antimicrobial drugs used for this indication. It has a broad antimicrobial spectrum against gram-positive and gram-negative aerobic and anaerobic microorganisms, including gram-negative polyresistant bacteria. Compared to other antibiotics, it has slightly higher in vitro activity against a number of gram-negative bacteria (including *Pseudomonas aeruginosa*) [11, 12].

When several strains with different sensitivity to antibiotics are involved in the pathological process, it may be useful to use a combination of antimicrobial agents. The combination should include drugs that act synergistically or have an additive effect in vitro. We used a mixture of doripenem and tinidazole.

## II. MATERIAL AND METHODS

This study was supported by the “Project of

competitiveness of leading Russian universities among the world's leading research and educational centers”.

We studied 108 people (64 women – 59.3%, and 44 men – 40.7%, ages 18-65) with chronic generalized periodontitis of varying severity. A comprehensive examination of each patient who subsequently underwent a course of treatment according to the indications was carried out according to the generally accepted scheme, which allows establishing both general and dental status. All 108 patients received periodontal treatment.

We used the following general polyclinic methods of the dental status analysis: survey, external examination, evaluation of the condition of teeth, dentitions, oral mucosa. During the study of the dental status, particular attention was given to the determination of the state of periodontal tissues. Assessment of the clinical condition of the periodontal part of the gums was performed at the examination stage and during the treatment process.

Periodontal status was assessed using the complex periodontal index (CPI). The probing depth of periodontal pockets was determined as in the case of classical manual probing.

Traditional treatment included hygiene training and professional hygiene (removal of supra- and subgingival dental plaque, polishing of the teeth surfaces). Depending on the depth of the periodontal pockets, appropriate surgical treatment (curettage, open curettage) and, if necessary, removal of teeth, the preservation of which became impossible, was performed. Local anti-inflammatory treatment included washing of periodontal pockets with a 0.06% chlorhexidine digluconate solution.

Based on the objectives of the study, patients were divided into four groups:

The first group (18) included patients who underwent only professional oral hygienic treatment.

The second group (28) included patients who, in addition to professional hygienic treatment, were treated using tinidazole in the form of periodontal dressings.

The third group included 26 patients, who, in addition to the professional hygienic treatment of the oral cavity, received an injection of doripenem into periodontal pockets.

The fourth group included 36 patients, who, in addition to professional hygienic treatment, received an injection of a combination of tinidazole + doripenem (1:1) into periodontal pockets.

In all four groups, an individual mouthpiece with a drug depot was used as a fixator.

The mouthpiece was made according to the following procedure: individual imprints were used to create models; using an electric spatula, a wax groove was made on the model 0.5 mm above the gum level; an individual mouthpiece was manufactured using a Pro-Form apparatus; the resulting cavity served as a depot for the drug and prevented it from splashing during the first 3-5 days after surgery.

## III. RESULTS AND DISCUSSION

As a result of the study, we found that the use of tinidazole and doripenem in the treatment of periodontal tissue diseases gives a positive effect.

**Table 1: Comparative characteristics of the control and second groups based on CPI.**

I control group			CPI		II group tinidazole solution			CPI	
Mild generalized chronic periodontitis	Moderately severe chronic generalized periodontitis	Severe chronic generalized periodontitis	Before research	After research	Mild generalized chronic periodontitis	Moderately severe chronic generalized periodontitis	Severe chronic generalized periodontitis	Before research	After research
5	10	3	4.23±0.08	1.83±0.04	8	14	6	4.23±0.08	1.45±0.04
18					28				

Among the patients from the first group: five people had mild generalized chronic periodontitis; ten people had moderately severe chronic generalized periodontitis and three had severe chronic generalized periodontitis. Improvement of dental status and positive dynamics of the CPI were observed in these patients after traditional

treatment and a period of wearing mouthpieces. We observed a decrease in teeth mobility, induration of the gingival margin, and reduction (in several cases – disappearance) of periodontal pockets in patients with mild and moderate severity. CPI decreased from 4.23 ± 0.08 to 1.83 ± 0.04 (Table 1).

**Table 2. Comparative characteristics of the control and third groups based on CPI.**

I control group			CPI		III group doripenem solution			CPI	
Mild generalized chronic periodontitis	Moderately severe chronic generalized periodontitis	Severe chronic generalized periodontitis	Before research	After research	Mild generalized chronic periodontitis	Moderately severe chronic generalized periodontitis	Severe chronic generalized periodontitis	Before research	After research
5	10	3	4.23±0.08	1.83±0.04	6	13	7	4.23±0.08	1.25±0.04

Among the patients from the second group (28), for which the tinidazole solution (1:1 – powder: liquid, applications using an individual mouthpiece) was used in addition to the traditional treatment: eight patients had mild chronic generalized periodontitis, 14 patients had moderately severe chronic generalized periodontitis, and six patients had severe chronic generalized periodontitis. One month after the treatment, induration of the gingival margin and reduction of periodontal pockets was observed. CPI decreased from 4.23 ± 0.08 to 1.45 ± 0.04 (Table 2).

One month after the treatment, induration of the gingival margin and reduction of periodontal pockets was observed. CPI decreased from 4.23 ± 0.08 to 1.25 ± 0.04 (Table 3). The analysis of the depth of periodontal pockets using probing after one month showed a statistically significant decrease of about 1.7 times. Upon the discussion of the obtained data, we established that the tinidazol+doripenem complex has the highest therapeutic effect (Fig.1). The results of complex treatment of chronic generalized periodontitis in 36 patients using tinidazole + doripenem complex (periodontal dressings – individual caps) demonstrated a significant improvement in dental status after one month. CPI decreased to 0.45 ± 0.04 points. Probing analysis of the periodontal pockets' depth after one month showed a statistically significant decrease – approximately 1.7 times.

Among the patients from the third group (26), for which the doripenem solution (1:1 – powder: liquid, applications using an individual mouthpiece) was used in addition to the traditional treatment: six patients had mild chronic generalized periodontitis, 11 patients had moderately severe chronic generalized periodontitis, and seven patients had severe chronic generalized periodontitis.

**Table 3: Comparative characteristics of the control and fourth groups based on CPI.**

I control group			CPI		IV group tinidazol+doripenem solution			CPI	
Mild generalized chronic periodontitis	Moderately severe chronic generalized periodontitis	Severe chronic generalized periodontitis	Before research	After research	Mild generalized chronic periodontitis	Moderately severe chronic generalized periodontitis	Severe chronic generalized periodontitis	Before research	After research
5	10	3	4.23±0.08	1.83±0.04	11	14	11	4.23±0.08	0.45±0.04

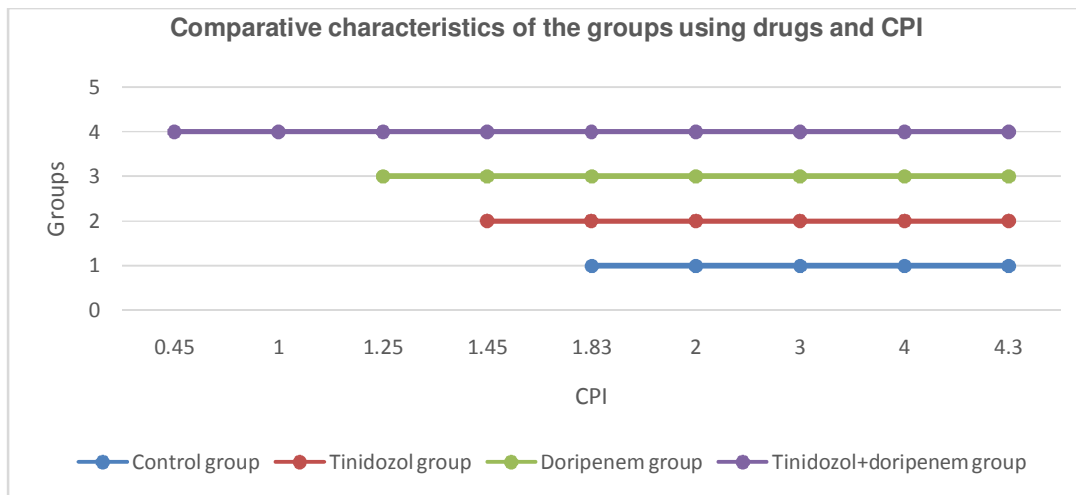


Fig. 1. Comparative characteristics of the groups using drugs and CPI.

#### IV. CONCLUSION

The results of the study demonstrated a high activity of tinidazole and doripenem against potential pathogens associated with periodontitis. The proposed method of minimally invasive therapy can be considered as a method of choice and an alternative to other methods of treatment of chronic generalized periodontitis.

In the complex treatment of chronic generalized periodontitis, it is necessary to use a combination of antimicrobial drugs tinidazole and doripenem in a 1:1 ratio as a local delivery system. The biocomposition should be prepared *ex tempore* by mixing the antibacterial preparations in powder and liquid forms and injected as a single dose into the periodontal pocket using a syringe with a blunt needle.

Individual mouthpiece with a depot for drugs, which provides a longer exposure, should be made for additional fixation. The exposure time in the oral cavity is 25-30 minutes, after which the mouthpiece is removed by the patient, followed by rinsing the oral cavity with warm water.

The treatment of chronic generalized periodontitis, supplemented by the use of tinidazole + doripenem in an individual mouthpiece, demonstrated high efficiency compared to the traditional method of treating patients. Analysis of the data from clinical studies allows us to conclude that the use of this method is appropriate, promising and requires further research.

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