REVIEWS

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Overview of Compounds that may be Carriers of Metronidazole Used in Topical Treatment of Chronic Periodontitis

Przegląd związków mogących być nośnikami metronidazolu stosowanego w miejscowym leczeniu przewlekłego zapalenia przyzębia

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A – koncepcja i projekt badania; **B** – gromadzenie i/lub zestawianie danych; **C** – opracowanie statystyczne; **D** – interpretacja danych; **E** – przygotowanie tekstu; **F** – zebranie piśmiennictwa

Abstract

Periodontal diseases are now one of the greatest challenges for modern dentistry. Tooth loss impacts on systemic diseases in many patients. It seems therefore that the treatment of chronic periodontitis is beneficial not only for overall dental health but also for overall general health. Currently, the treatment of periodontal diseases emphasizes a maximum of local treatment without systemic complications. The creation of local drug carriers is of great importance and is very useful in periodontic practice. Elimination of side effects from overall treatment creates a good basis for long-term treatment especially in patients with systemic diseases. However, the oral environment does not create favorable conditions for topical pharmacotherapy. The continuous flow of saliva, cheek movement, mealtimes, talking – all these factors make it difficult to maintain medicine long enough on the mucosa or in the periodontal pocket. The application of the medicine itself to the periodontal pocket is difficult; additionally, both the ability to control the amount of medicine released and the medicine continuation time in the pocket is often unpredictable. Modern pharmacology and biotechnology are in search of new solutions and ways to deliver medicines topically. The popular carriers of the past have now been abandoned due to the fact that they required removal from the treated site after a few days. They caused a number of disadvantages, e.g. periodontal tissue damage during application. Modern mucoadhesive medicine carriers produced on the basis of hydrophilic compounds are of particular interest. Several studies have demonstrated ease of application and good retention in the pocket (**Dent. Med. Probl. 2012, 49, 4, 583–587**).

Key words: chronic periodontitis, metronidazol, topical treatment.

Streszczenie

Choroby przyzębia są obecnie jednym z największych wyzwań współczesnej stomatologii. Utrata zębów rzutuje u chorych na wiele schorzeń ogólnoustrojowych. Wydaje się więc, że leczenie przewlekłego zapalenia przyzębia przynosi korzyść nie tylko dla zdrowia jamy ustnej, ale też dla zdrowia ogólnego. Obecnie w leczeniu chorób periodontologicznych dąży się do miejscowego leczenia bez powikłań ogólnoustrojowych. Stworzenie nośników leków działających miejscowo ma duże znaczenie i jest bardzo przydatne w praktyce periodontologicznej. Eliminacja skutków ubocznych leczenia ogólnego stwarza dobre podstawy do leczenia długoterminowego, szczególnie u pacjentów obciążonych chorobami ogólnoustrojowymi. Środowisko jamy ustnej nie stwarza dogodnych warunków do prowadzenia farmakoterapii miejscowej. Ciągły przepływ śliny, ruch policzków, przyjmowanie posiłków, mówienie utrudniają wystarczająco długie utrzymanie leku na błonie śluzowej lub w kieszonce przyzębnej. Samo podanie leku do kieszonki przyzębnej jest trudne, dodatkowo możliwość kontroli ilości uwalnianego leku i długość utrzymania się leku w kieszonce jest często nieprzewidywalna. Współczesna farmakologia i biotechnologia szukają nowych rozwiązań i sposobów dostarczania miejscowego leków. Odchodzi się od popularnych jeszcze kilka lat temu nośników stałych, które wymagały usunięcia z miejsca leczonego po kilku dniach. Niosły one ze sobą wiele niedogodności, np. uszkodzenie tkanek przyzębia podczas aplikacji. Na szczególne zainteresowanie zasługują nowoczesne mukoadhezyjne nośniki leków na bazie związków hydrofilowych. W wielu badaniach udowodniono łatwość podawania i dobrą retencję w kieszonce (**Dent. Med. Probl. 2012, 49, 4, 583–587**).

Słowa kluczowe: przewlekłe zapalenie przyzębia, metronidazol, leczenie miejscowe.

Oral medicine is a concept used in the English literature, corresponding to the Polish medical dentistry which deals with diseases occurring in the oral cavity and periodontal structures, and particularly with irregularities in the mucous membranes, and the manifestation of systemic diseases [1]. The term correlates with the abundance of medical diseases observed in the oral mucosa. However, despite this abundance, the number of drugs that can be applied here is not large. This is due to the lack of good systems to maintain therapeutic drug concentrations in the mucous membrane or in the periodontal pocket. The lack of these systems is associated with numerous disadvantages in therapy for both patient and doctor. A lack of control over the maintenance of treatment of pathologically-affected areas is often associated with failure of local therapy.

Local chemotherapy conducted in the oral cavity is very difficult due to the specific environment in which it is used. The mouth with the numerous recesses and continuous muscle, cheek and tongue movement is constantly moistened by saliva which creates an environment in which it is difficult to maintain drugs. In addition, it fulfills the role of the first section of the gastrointestinal tract and the consumption of food and beverages is associated with constant changes in the pH of the environment.

All the above factors negatively affect the treatment of oral diseases, which are usually chronic and require prolonged treatment.

Medicine delivery systems in periodontal diseases are divided into subgingival irrigation methods and medicine-soaked solid carriers. Contradictory research results have been reported, some have confirmed the significant value of local therapy, while others have shown no justification for this type of therapy. Accurate selection of patients, the quality of medicine administration, initial pocket depth, and time of use are key factors in the evaluation of the use of topical medications. New meta-analyses have shown that topical metronidazole application, as an additive in conventional mechanical treatment, provides a better effect than in other comparable therapies in terms of reduction of pocket depth [2].

Periodontal disease is a chronic disease caused by bacteria in periodontal pockets. It occurs at the appropriate genotype of the patient and with the participation of modifying factors. Mechanotherapy is the mainstay of treatment and consists mainly of scaling and root planning aimed at smoothing the tooth root and the elimination of iatrogenic recesses. Chemotherapy is, in many cases, a support for mechanotherapy. The use of antibiotics does not improve overall treatment outcomes of chronic periodontitis. They should be used only in specific cases because their side effects seem to outweigh the benefits.

The American Academy of Periodontology has begun to discourage the routine use of antibiotics in general in order to avoid side effects. The use of topical antimicrobial medicines is a subject of clinical trials, where their effectiveness as support or alternative methods to traditional mechanical methods is being tested [2].

Local chemotherapy as an adjunct, always after the initial phase of hygienization, is considered to be a good supplement, but requires the use of a carrier that would maintain optimal therapeutic concentrations of the active substance in the periodontal pocket for a prolonged period of time. The use of modern carriers for drugs administered into a pocket gives more control over drug delivery and its extended action.

Conditions for maintaining the drug in the pocket are especially difficult because it is still an open reservoir, exposed to reinfection from supragingival plaque and intracellular sources (epithelium gums, cheek). In addition, a continuous flow of fluid out of the pockets makes it difficult to obtain the MIC (minimal inhibitory concentration), and the half-life of an unbound drug in the pocket is estimated at about 1 minute. However, the possibility of drug delivery locally into the pocket (with the minimization of overall adverse events) has resulted in several forms of topically administered drugs called LDD (local drug delivery). They are based on different carriers and different active ingredients (Atridox, Actisite, Periochip). However, now in Poland, these drugs are difficult to obtain, and the therapy is very expensive [3].

It seems that the search for new forms of drug stability and new methods of its delivery directly into the pockets noticeably facilitate the healing process.

There is a need for methods of more effective drug delivery to enable the maintenance of constant therapeutic concentrations in the tissue to be treated in the long term, with minimal risk to the body [4] (Table 1).

Polyacrylic acid, called CARBOPOL (carboxypolymethylene, carboxyvinyl polymer, carbomer), is used as a universal excipient in modern pharmaceutical confections. Carbopol is used in cosmetics and pharmaceuticals to thicken solutions, to stabilize the suspensions and emulsions and the manufacture of tablets and capsules. Due to its bioadhesive properties, it is included in the production of nasal, buccal, intra-uterine and rectal dosage drug forms. Carbopols are used in the formulation of dermatological preparations such

Table 1. The three main advantages that characterize drug delivering polymer compositions [4]

Tabela 1. Trzy podstawowe zalety, jakie charakteryzują polimerowe kompozycje dostarczające lek [4]

Local drug delivery	the product can be delivered directly at the point where the drug is required, and thus systemic effects of the drug will be reduced. This is particularly important in the case of toxic drugs associated with a variety of effects in the body
Flower drug delivery	the drug is released over an extended period of time
Drug stabilization	the product can be delivered directly at the point where the drug is required, and thus systemic effects of the drug will be reduced. This is particularly important in the case of toxic drugs associated with a variety of effects in the body

as ointments and gels. Preparations marked P, e.g. CARBOPOL 974P and CARBOPOL 971P, are allowed for oral use, and contact with mucous membranes [5].

The advantages of hydrophilic foundations based on Carbopol are its mucoadhesive properties, which mean that they are used as preparations for skin and more frequently mucous membranes. The use of hydrogels is recommended in acute inflammation, in cases of lyophilic base intolerance, mucosal diseases, and diseases of the scalp. It has also been observed that many of the active substances are released faster from hydrophilic bases than lyophilic ones [6].

Metronidazole is an antimicrobial drug often used in local chemotherapy of chronic periodontitis. It is a drug of nitroimidazole derivatives. It exhibits bactericidal activity against protozoonicidal and anaerobic microorganisms. It can be delivered either orally – 250 mg tablets, and localized mostly in the form of a gel, 1%, 5% and 10%, 25% metronidazole gel Elyzol, and often clinically in the form of pocket irrigation – 0.5% solution for injection.

Metronidazole gel Elyzol® 25% – the preparation is in a syringe with a dispenser, which allows quick and accurate application. Immediately after administration into the pocket the drug is a sol, and contact with saliva or gingival fluid causes its transformation into a gel, which then undergoes crystallization, thus securing its long-term therapeutic effect. Metronidazole acts primarily on anaerobic flora and its mechanism of action is inhibition of DNA synthesis in the bacterial cell [7].

Numerous studies have confirmed the additional therapeutic effects of Elyzol when combined with root planning treatment and metronidazole 25% (Elyzol) [7–10]. The largest percentage of shallow pockets was observed in groups using the combination therapy. However, it was noticed that only long-term studies may indicate good non-surgical treatment efficacy in combination with metronidazole. Short-term results of treatment with metronidazole and placebos were similar, but four months after gel application, the level of PD increased fourfold in pockets treated with placebos while in pockets treated with metronidazole it remained unchanged. While comparing the effectiveness of the application of 1% and 25% gel, comparable results were seen and the conclusion is that most important in local application is not only the same active substance (the percentages), but also the form of medicine that would guarantee its longest presence in the pocket [8–10].

In 2010 Antonietta Rizzo et al. [11] conducted a series of experiments, the purpose of which was to investigate the *in vitro* effect of metronidazole on periodontal ligament cell viability; however, the impact of metronidazole to modulate the release of interleukin IL 1-beta, IL-6, IL-8, IL-12, and tumor necrosis factor (TNF-alpha) was also evaluated.

Continuous stimulation of immune cells and periodontal cells by pathogens and their virulence factors, such as LPS liposaccharide, results in uncontrolled production of cytokines. They directly and indirectly cause bone destruction and local periodontal structure destruction. Periodontal ligament cells are involved in the immune response in the oral cavity. They can produce cytokines which enhance the inflammatory response.

The results showed that metronidazole has no cytotoxic effect on periodontal ligament cells and is able to inhibit the production of proinflammatory cytokines, which provides more therapeutic application possibilities.

It now seems that the quantitative and qualitative analysis of the specific components of gingival pocket fluid (GCF) could be useful in assessing the health of periodontal tissues.

Jaleh Varshosaz [12] used the production of gel based on metronidazole and Carbopol in his research. In its assumptions he focused on exploring the following parameters: the hardness and efficiency of the product, the ability to compress and distribute, the ability for syringe applications, the ability to adhere.

In order to develop a locally acting drug that provides a prolonged duration of action in the gingival pocket, he prepared the following bioadhesive polymers containing 5% metronidazole: car-

boxymethylcellulose, methylcellulose, hydroxyethylcellulose, polyvinylpyrrolidone, carbopol.

Increased polymer concentrations decrease the release of the drug and facilitate delivery with a syringe, improve efficiency value and adhesion, but decrease the ability to spread. PH and the concentration of Ca2 + had an impact on gel bioadhesion.

The viscosity of the products was increased via greater polymer concentration. In this way reduction in the values of the drug deposit was caused by reduced values of penetration and dissolution in the more viscous products.

Newer methods of obtaining such medicine carriers guaranteeing the best treatment results are used in biotechnology.

Electrospinning is a process that involves the use of electricity for pumping semi-liquid substances and the production of very thin thread. The final effect is achieved through the use of specially-designed very narrow nozzles. The resulting fibers are then woven like a classic fabric, but their strength is incomparably greater [13].

This process was used to synthesize absorbed, polylactide fibers with metronidazole used in the topical treatment of periodontitis [14]. In the quoted experiment, such fibers were loaded with 0.1––40% metronidazole and the metronidazole-release profiles from the fibers were analyzed. Antibacterial effectiveness (*Fusobacterium nucleatum, Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis*) was determined by measuring zones of growth inhibition on agar. Cytotoxicity was tested on human fibroblasts. As a result of the experiment, it turned out that metronidazole was freed the fastest from the fiber of 20% content for the first 3 days. All fibers released 32–48% of the total medicine. Portions of the medicine obtained from fibers inhibited the growth of all three bacteria. Metronidazole was released for up to 28 days from fibers containing 40% of the substance. All fibers and portions of the medicine showed no toxicity in relation to the tissues. Such fibers are an interesting alternative to previously used non-absorbed fibers (tetracycline fibers, ATRIDOX®), which had to be removed after a few days, which was a risk of periodontal tissue damage and was time consuming [15]. Polylactide fiber core has proven itself as a carrier of medicines because it is biodegradable, stable and allowed for medical purposes, and the metronidazole amount released from it is able to inhibit even the *Aggregatibacter actinomycetemcomitans*.

In the search for the perfect, modern medicine carriers it has been observed that materials with similar chemical compositions to the bone containing calcium and phosphorus have excellent bioactivity, biodegradability and the ability to form chemical bonding with tissues [16]. Silicide can be used as a component which improves the mechanical properties of calcium-phosphate materials. Xerogels are non-toxic derivatives of silicide and in vivo biocompatible.

Due to weak bone vascularization and poor medicine penetration to the bones, their topical application is a very desirable solution [17].

Medicines used in the topical treatment of periodontitis chronica could also be applied not only to the periodontal pocket, but also for example be attached to the buccal mucosa, from where the treating substance would be released. Chitosan has antibacterial properties and is a promising bioadhesive material at physiological pH. The downside is that hyperhydration (saliva) can cause gel transformation into slippery mucus. For this reason other types of biodegradable polymers were added to hitozan which enabled adhesion failures to be avoided. Biodegradable polymers are biocompatible, easy to form and have good mechanical properties. The main aim of the experiment conducted by El-Kamel et al. [18] was the invention of local, oral, mucoadhesive, metronidazole benzoate with controlled release, which could be applied to the buccal mucosa and removed by the patient. Mucoadhesive films from chitosan and chitowan in conjunction with the polymer were prepared in order to achieve the aim. Fourteen healthy patients aged 20–30 years were instructed to rinse their mouths with water, and then stick films on the mucosa of both buccals. Each film contained 20 mg of metronidazole. During the study, patients could not eat or drink. Every 15 minutes, saliva was collected from them to determine the concentration of released medicine. Patients did not complain of discomfort, they had no taste disorders, and could talk freely. The amount of metronidazole released from films ranged from 5–15 mg. The developed mucoadhesive membrane met the conditions for both medicine release, and mechanical and bioadhesive properties. In addition, it allows delivery of medicine of a greater amount than the minimum concentration required to act against anaerobes for 6 hours. The proposed solution does not require application by the physician providing the patient with the possibility of home application [18].

Mucoadhesive drug delivery systems have several advantages, e.g. ease of application, and good retention in the gingival pocket. They draw water locally and form strong secondary chemical bonds on the dehydrated mucosa. In summary, the continuous improvement of pharmaceutical procedures, using increasing numbers of new biodegradable carriers, does not preclude the use of metronida-

zole as a locally used antibiotic in periodontal diseases and offers hope of achieving the aim of producing a proven drug for everyday clinical work.

Currently researchers at the Department of Periodontology, Wroclaw Medical University are examining hydrophilic compounds produced on the basis of Carbopol 971P with active-metronidazole which are administered into the pocket in chronic periodontitis. The main objective of the research is to determine whether modern mucoadhesive drug carriers have the potential to increase the effectiveness of local chemotherapy in the treatment of periodontitis. The answer to this question is hoped to be known soon, because the research has already entered the clinical trial phase. The research is being conducted in cooperation with the Department of Pharmaceutical Technology, Wroclaw Medical University.

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