¿Por qué no reevaluar el tinidazol como tratamiento potencial de infecciones odontogénicas?

El tinidazol es un 5-nitroimidazol que se introdujo en 1969 en la clínica para el tratamiento de infestaciones por parásitos unicelulares. El tinidazol ofrece una actividad bactericida selectiva, no influida por el tamaño del inóculo, frente a bacterias anaerobias, por lo que presenta un interés teórico en infecciones producidas por odontopatógenos. Este artículo revisa las características que requiere un antibiótico dirigido al tratamiento de infecciones odontogénicas por bacterias anaerobias, así como las carencias farmacodinámicas de los antibióticos habitualmente utilizados en este tipo de infecciones. Asimismo se revisan las propiedades in vitro, farmacocinéticas y farmacodinámicas de tinidazol, valorándose el grado de adhesión de este compuesto a las características requeridas para un antibiótico dirigido a este tipo de infecciones. También se identifican las lagunas de conocimiento sobre tinidazol que deben resolverse antes de su utilización en este campo. Tinidazol ofrece unas características interesantes que posibilitan realizar investigaciones como candidato al tratamiento de infecciones odontogénicas anaerobias.


INTRODUCTION

Periodontal disease is the most prevalent infectious disease in the community (50% and 30% of adult population present gingivitis and periodontitis, respectively) and it can be considered as a subacute or chronic disease with acute reactivations along the individual life time. The subgingival plaque is the basis of periodontal disease, and three hypotheses (that physiopathologically can be concomitant) have been postulated.

a) The specific plaque hypothesis: specific bacteria are the etiological agents of the disease.

b) The non-specific plaque hypothesis: the periodontal disease is an inflammatory disease, and the inflammatory process is a response to the bacterial biomass present in the plaque.

c) The environmental plaque hypothesis: the subgingival environment, when including in high amount some specific bacterial species, is responsible for the disease. This hypothesis may be considered a combination of the other two hypotheses.
Regardless the responsibility of one of these three hypotheses on the disease, the therapeutic consequences are the same since therapeutic strategies (mechanical, pharmacological, or both) in periodontitis are directed to reduce the bacterial load, whether to preclude direct damage of periodontopathogens or to decrease the inflammatory stimuli.

While early odontogenic infections are usually produced by aerobic streptococci, subacute, chronic or late infections are produced by anaerobes; thus the first treatment approach is to differentiate early from late infections. Gingivitis and chronic periodontitis are subacute or chronic infections and, when antibiotic therapy is needed, amoxicillin/clavulanic acid or clindamycin are recommended based on the high susceptibility rates of most anaerobic species, despite the non-susceptibility rates of some streptococci species.

An etiological based treatment should consider two types of periodontopathogens:

a) Odontopathogens as Treponema denticola (and other non-cultivable anaerobic spirochetes) whose prevalence increases as severity increases (greater gingival pocket depth), as basis of the consideration of periodontitis as an infectious disease.

b) Bacteria responsible for the non-specific bacterial growth and the subsequent inflammatory disease, being Prevotella spp. the most prevalent anaerobe isolate.

Anaerobic treatment should be directed against both types of bacteria. In early and acute infections, as periodontal abscess, coverage against facultative microorganisms (Streptococcus viridans species) should be added.

TARGET BACTERIA FOR ANTIBIOTIC TREATMENT

Different bacterial species are associated with health or disease in relation to odontogenic infections. With respect to anaerobes, Veillonella spp. is the most common anaerobe in healthy individuals while Prevotella intermedia and Fusobacterium nucleatum are present in gingivitis. In addition to these three periodontopathogens, Treponema denticola, Porphyromonas gingivalis and Tannerella forsythensis are found in chronic periodontitis. In juvenile periodontitis, Actinobacillus actinomycetemcomitans is also present.

While the responsibility of streptococci has been clearly identified in focal systemic infections after odontological procedures in patients at risk, (as endocarditis in patients with endocardic alterations) and in acute local infections as the periodontal abscess, their responsibility in subacute/chronic periodontal disease is not so evident since Streptococcus spp. (mainly S. sanguis and S. mitis) are found in healthy individuals as well as in patients with gingivitis and chronic periodontitis.

Analysis of the subgingival plaque has demonstrated that oral microflora can be defined as color-coded complexes (purple, yellow, green, orange and red) since bacteria in different health/disease/odonto flora niches are present in different specific aggregations. This color sequence represents progression from health (purple complex) to disease, with orange (Prevotella spp., Fusobacterium spp.) and red (where Porphyromonas spp., Tannerella spp. and Treponema spp. are added) complexes associated with periodontitis. Thus, there is a progression of microflora from health (characterized by a predominantly gram-positive, aerobic, non-motive microflora) to disease (characterized by a gram-negative, anaerobic, mobile microflora).

In a study carried out in our country, PCR detection yielded positive results for Tannerella forsythensis in approximately 71 %, T. denticola in 63 %, Porphyromonas gingivalis in 58 %, and Prevotella intermedia in 36 % patients with periodontitis. Interestingly, detection of T. denticola (p = 0.01), P. gingivalis (p = 0.08) and T. forsythensis (p = 0.1) was associated (significantly higher detected, chi-square) with pocket depth > 4 mm. Isolation rates (frequency per 100 patients) of the different species were approx. 60% for Prevotella buccae, 40% for Prevotella denticola, 38% for Fusobacterium nucleatum, 35% for Prevotella intermedia, and 23% for Veillonella spp. and Prevotella melaninogenica, with respect to anaerobes. β-lactamase production, rendering amoxicillin inactive, was positive in 54 % Prevotella spp., 39% F. nucleatum, and 10% Veillonella spp. Nearly 100% anaerobes were susceptible to metronidazole and amoxicillin/clavulanic acid, while resistance rates for clindamycin ranged from 9% to 21% in Prevotella species.

With respect to aerobes and facultatives, isolation rate was approx. 71% for S. oralis and S. mitis and 25% for Capnocytophaga (30% of them were β-lactamase producers). Amoxicillin and clindamycin were the most active compounds against S. mitis and S. oralis, and this should be taken into account if aerobic/facultative coverage is needed.

PITFALLS OF APPROVED ANTIBIOTIC TREATMENTS/PHARMACODYNAMIA

Clinical trials in odontogenic infections are scarce and usually include a low number of patients; for this reason pharmacodynamic principles have been used to evaluate the degree of periodontopathogen coverage with different compounds. Pharmacodynamics explores the relation between systemic antibiotic concentrations along the dosing interval and in vitro susceptibility, defining parameters that predict efficacy. The pharmacodynamic parameter predicting efficacy for antibiotics with time-dependent action (β-lactams, macrolides, clindamycin) is the time (expressed as % dosing interval) that concentrations exceed the minimal inhibitory concentration (MIC) (T>MIC), while in the case of concentration-dependent antibiotics (azalides, metronida-
zole), the parameter predicting efficacy is the relation between the area under the serum concentration-time curve (AUC) and MIC (AUC/MIC). Classically it has been considered that T > MIC values > 40 % and AUC/MIC values > 25 are associated to efficacy 16.

Given the prevalence of β-lactamase producing anaerobes among periodontopathogens, amoxicillin given as monotherapy cannot be considered an adequate antibiotic in the treatment of infections caused by these bacteria, due to its low T > MIC values consequence of the enzymatic hydrolysis by the β-lactamase produced.

Taking Prevotella intermedia, Porphyromonas gingivalis, Fusobacterium spp and Tannerella forsythensis as anaerobic index bacteria, only three-times daily (tid) amoxicillin/clavulanic acid regimens and clindamycin, but not spiramycin, obtain adequate T > MIC values against them 16. In the case of concentration-dependent antibiotics, twice daily (bid) regimens of metronidazole, but not of quinolones or azalides, obtain adequate AUC/MIC values 16.

The pharmacodynamic relationship of antibiotics and odontopathogens has also been described 3 using crevicular fluid concentrations (36.7 µg/ml for metronidazole, 14 µg/ml for amoxicillin  and 0.40 µg/ml for clavulanic acid—, 5 µg/ml for spiramycin, and 2 µg/ml for clindamycin, after standard doses) 17-19. Mean gingival crevicular concentrations of amoxicillin/clavulanic acid and metronidazole cover MIC90 (MIC value inhibiting 90 % isolates) of anaerobic isolates, but this is not the case of clindamycin that pharmacodynamically does not cover resistant strains and several susceptible strains 8. Spiramycin crevicular fluid concentrations are below MIC90 values for Fusobacterium nucleatum 16,17.

TINIDAZOLE AND ODONTOGENIC INFECTIONS

Tinidazole and metronidazole are the only nitroimidazoles available in the United States 20.

Tinidazole is a 5-nitroimidazole initially introduced into clinical medicine in 1969 for antiparasitic treatment of Trichomonas vaginalis infections and later on for the treatment of infections by Entamoeba histolytica and Giardia lamblia 21. There is a common feature for these three unicellular parasites: they are anaerobic microorganisms. Tinidazole is intracellularly released (mediated by a ferredoxin system and a low oxidation-reduction potential) to active intermediates 21. Most aerobic microorganisms do not generate low oxidation-reduction potential, explaining the selective activity of tinidazole against anaerobic microorganisms 21.

a) In vitro activity

Scarce (occasional reports) and old data are available regarding tinidazole activity against anaerobic bacteria of odontological interest. It has been reported that tinidazole is in vitro active against most anaerobic bacteria including Tannerella (previously Bacteroides) and Fusobacterium species 21, and that Bacteroides and Fusobacteria are regularly inhibited by 0.5 µg/ml nitroimidazoles 22. Minimal bactericidal concentration (MBC) values for nitroimidazoles are equal to MIC values 23. Tinidazole is rapidly bactericidal, its activity is not affected by the inoculum size, and emergence of resistance during treatment is rare 23.

b) Pharmacokinetics

Tinidazole in daily doses up to 2 g is free of toxicity, exhibiting a half-life of 12–14 h (doubling that of metronidazole) allowing once daily regimens 24. Tinidazole is almost complete absorbed after oral administration and a single 2 g dose provides peak serum concentrations of 40 µg/ml at 24 h and 2.5 µg/ml at 48 h 42. Daily maintenance doses of 1 g maintain drug concentrations above 8 µg/ml throughout the treatment period 23. Six hours after administration of 1 g single dose, mean serum concentrations are 19.3 µg/ml 22. AUC values range from approx. 600 µg x h/ml with the 1 g dose to 1,000 µg x h/ml with the 2 g dose 41.

Tinidazole is secreted in saliva with concentrations in mixed, parotid and submandibular saliva similar to those in serum at the same time 22,24. Concentrations are detectable in saliva up to 7 days after a 1 g single dose administration when serum concentrations are not found 25. After 1 g single dose administration, concentrations in mixed, parotid and submandibular saliva were approximately 10 µg/ml at 1 h, 20 µg/ml from 3 h to 6 h, and 10 µg/ml at 24 h 22. Three hours after 1 g single dose administration, crevicular fluid concentrations are per-patient similar to those in serum (mean 18.5 µg/ml; range 14.6–24.6), and in alveolar bone, mean ± SD concentrations are 1.9 ± 0.5 µg/ml 22,26.

When measuring in vivo effects (quantitative counting of anaerobic bacteria in saliva) after 1 g single dose administration to 10 subjects, salivary anaerobic flora suffered a marked decrease in all subjects, with completely disappearance after 6 h of Fusobacteria in 8 subjects and Veillonella spp. in 4 subjects 25.

c) Theoretical pharmacodynamics and in vivo antibacterial activity

Resistance to metronidazole is 0 % in Veillonella, Fusobacterium, and most species of Prevotella (melaninogenica, denticola, oralis...), and <6 % in Prevotella intermedia and buccae 9. MIC90 of metronidazole is 2–6 µg/ml for Prevotella intermedia, 2 µg/ml for Porphyromonas gingivalis, 1–8 µg/ml for Fusobacterium nucleatum and 0.25 µg/ml for Tannerella forsythensis 9,16. Assuming the same intrinsic activity for both nitroimidazoles (tinidazole and metronidazole), MIC
values of tinidazole against most anaerobic periodontopathogens would be far below concentrations in serum, saliva and crevicular fluid.

When considering the value of the pharmacodynamic parameter predicting efficacy for nitroimidazoles (AUC/MIC >25\textsuperscript{19}), this value is exceeded with tinidazole for MIC\textsubscript{90} values against all Prevotella spp., Veillonella spp., Fusobacterium nucleatum, Tannerella forsythensis and Porphyromonas gingivalis with the 1 g dose if we assume that tinidazole MIC\textsubscript{90} values are lower or equal to metronidazole MIC\textsubscript{90} values.

**GAPS IN THE KNOWLEDGE OF TINIDAZOLE FOR THE TREATMENT OF ODONTOGENIC INFECTIONS**

Scarc data on tinidazole is available from investigations in the specific field of odontogenic infections, whether from the in vitro susceptibility, pharmacokinetics, pharmacodynamics, or clinical points of view, but previous data on tinidazole point it as a promising agent in this field. Compared with metronidazole, tinidazole has the potential of improving the pharmacodynamic coverage and/or the dosing regimen of the principal nitroimidazole.

From the in vitro perspective, susceptibility data obtained with panels of recent periodontopathogens isolates would be desirable. From the pharmacokinetic perspective, lower doses can be explored because the serum and crevicular fluid concentrations after 1 g dose administration are highly above the expected MIC. From the pharmacodynamic and clinical points of view it would be necessary to relate isolates (and the tinidazole MICs against them), crevicular fluid concentrations and outcome in patients with periodontitis.

On the other hand, treatments in Odontology are usually directed to both aerobic and anaerobic bacteria, and for this reason antibiotic combinations are usually prescribed\textsuperscript{27,28}: a) spiramycin + metronidazole, despite the fact of high resistance rates to macrolides (frequently associated to resistance to tetracyclines, clindamycin and azithromycin) in Streptococcus viridans in our country\textsuperscript{29-31}, and b) amoxicillin + clavulanic acid to cover β-lactamase producing isolates from Prevotella, Fusobacterium and Veillonella species. From this perspective, an association of tinidazole and amoxicillin seems an interesting possibility to be explored because it could improve the coverage of the whole bacterial spectrum in odontogenic infections. To this end, in vitro killing curves studies against antibacterial inocula (simulating a periodontal pathogen multibacterial niche) with both aerobic/facultative and anaerobic microorganisms, comparing amoxicillin, tinidazole and amoxicillin + tinidazole would be the first step to explore the potential of this possible association: the most potent drug against the aerobic/facultative component (amoxicillin) and the anaerobic candidate tinidazole.

From the pharmacokinetic point of view this possible association needs to be synchronized because of the different half-life values of amoxicillin and tinidazole. Again, pharmacodynamic studies with lower doses of tinidazole are desirable. A possibility to be explored is bid regimens with high amoxicillin concentrations and tinidazole doses lower than those previously studied (1 and 2 g).

Tinidazole has been evaluated in the prevention of postoperative complications after surgical removal of the third molar\textsuperscript{32-34} as well as in the treatment of adult periodontal disease with or without adjunctive scaling\textsuperscript{35}.

**CONCLUSION**

Tinidazole may offer interesting characteristics making worthy investigations as a candidate for the treatment of anaerobic odontogenic infections. Maybe it is time to revise a classic antibiotic considered mainly as an antiparasitic agent that may help to counter some pitfalls of previous antibiotic treatments in an area where 80 % of success of mechanical treatment is inexplicably accepted by clinicians\textsuperscript{36}, and where only in the 20 % cases of failure of mechanical treatment the antibiotic treatment is mandatory\textsuperscript{37}.

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