International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

International Journal of Pharmacology 2 (4): 467-470, 2006
ISSN 1811-7775

Evaluation of Long-Term Usage of Low Dose Doxycycline after Periodontal Surgery in Patients with Chronic Periodontitis

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Abstract: The major aim of periodontal treatment is reconstruction of broken tissues and maintenance of periodontal health. Different chemotherapeutic agents are used to change the host response to bacterial irritants along with nonsurgical and surgical periodontal therapies. Doxycycline is one of these agents used widely due to its anticollagenolytic and antibacterial properties. The aim of this study was to evaluate the effect of long-term usage of low dose doxycycline after periodontal surgery in the treatment of chronic periodontitis. In this study, 30 patients with chronic periodontitis were selected. After initial therapy and periodontal surgery, all patients were recalled and Probing Depth (PD), Attachment Level (AL) and Bleeding on Probing (BOP) indices were measured. Then they randomly allocated to test and control groups. In the test group (15 patients) all patients received 90 capsules (20 mg doxycycline) to use one cap per day for the following 3 month. The controls received the same shape and color placebo capsules. All the patients were recalled after one and 3 month and the above mentioned parameters were recorded again. The results showed significant reduction in PD and AL in the test group. Bop did not change significantly in both groups. PD and CAL increased in the control group but these increases were significant only for PD. The results of this study showed that the use of low dose doxycycline along with supportive periodontal treatment and oral hygiene during maintenance period can improve the clinical parameters.

Key words: Low dose doxycycline, chronic periodontitis, periodontal surgery, maintenance, antibiotic therapy, supportive treatment

INTRODUCTION

The main aim of periodontal treatment is establishment of periodontal health. Preservation of periodontal health requires a good maintenance program to prevent recurrence of the disease (Merin, 2002).

More recently biologic actions affecting inflammation, proteolysis, angiogenesis, apoptosis, metal chelation, iontophoresis and bone metabolism have been researched (Sapadin and Fleischmajer, 2006). Tetracyclines have recently been shown to inhibit the activity of some not all matrix metalloproteinases (MMPs), believed to mediate periodontal destruction (Ingman *et al*., 1993). Elevation in the levels of MMPs, is believed to account for the majority of the connective tissue destruction which occurs in periodontitis and the severity of human periodontal disease is positively correlated with the levels and activity of MMP-8 and other MMPS (Sorsa and Golub, 2005).

Doxycycline hyclate was originally used as a broad spectrum antibiotic that acts as such at the ribosomal level where they interfere with protein synthesis (Sapadin and Fleischmajer, 2006).

A previous study showed that Subantimicrobial Dose Doxycycline (SDD) has not any effect upon subgingival bacterial flora and has been clearly shown that SDD exerts no detectable effect on the normal oral bacterium, intestinal and vaginal flora or on the antibiotic susceptibilities of these bacteria (Thomas *et al*., 1998, 2000; Walker *et al*., 2000, 2005).

Substantial evidence indicates that the adjunctive use of Subantimicrobial Dose Doxycycline (SDD)

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consisting of 20 mg doxycycline hyclate provides a significant benefit to scaling and root planning in the treatment of periodontitis because of the anticollagenase and anti-inflammatory activities (Golub *et al*., 1990, 1985; Ingman *et al*., 1993). This formulation is the only MMP inhibitor which has been accepted by US Food and Drug Administration (FDA) (Sorsa *et al*., 2004).

However the specificity of above effect's in maintenance phase of surgically treated patients has not been examined in detail so the purpose of this study was to monitor the effects of a 3 month regimen of 20 mg doxycycline relative to a placebo control on the periodontal condition in maintenance phase.

MATERIALS AND METHODS

Study population: A total of 30 volunteers (12 male and 18 female, mean age 42 years) were selected for this study. Patients were referred to the Department of Periodontology in Mashhad Faculty of Dentistry, Mashhad, Iran for treatment of chronic periodontitis. For inclusion to the study they must have: Moderate to severe chronic periodontitis and need periodontal surgery for treatment. Exclusion criteria were: 1- Systemic or topical periodontal antibiotic therapy 6 month period to initiation of the study. 2- Pregnancy, lactating or planning a pregnancy. 3- Systemic diseases such as diabetes, Kidney or liver diseases. 4- Known HIV infection. 5- Use of non steroid anti-inflammatory drugs. 6- Acute systemic infection and 7- Smoking.

Study design: This clinical trial was a randomized, double blind; Placebo controlled study and extended between baseline (one month after surgery) and the trial over a 3 month period in Mashhad Faculty of Dentistry and Dental Research Center, Iran in 2004-2005. This study was carried out with the approval of the methodology and ethical committee of the University of Mashhad. Prior to participation, the purpose and procedures were fully explained to all patients, patients were entered in to the study only after having given written consent.

After initial therapy, periodontal surgeries were done by two periodontists who were completely calibrated. Full thickness apically positioned flap was done in surgical area. Osteoplasty and ostectomy performed as needed.

All patients got amoxicillin 500 mg tid for one week and acetaminophen codeine qid for two days after surgery. One month after the last surgery, the patients were recalled. The clinical parameters including Pocket Depth (PD), Clinical Attachment Level (CAL) and Bleeding Index (BI) have been recorded. In addition oral hygiene measures were reinforced. On the same day patients were randomly assigned to receive coded study medication of either 20 mg doxycycline or identical placebo capsules (lactose capsules) to be taken one cap per day for the following 3 month. Then all the patients were recalled and above parameters were recorded again.

Statistical analysis: Paired t-test was used to analyze the changes in mean PD and CAL and BOP in each group.

Two sample t-test was used to compare the results between groups. All statistical analysis was done using SPSS software ver. 10.5.

RESULTS AND DISCUSSION

Table 1 shows the results in each group. PD, CAL and BI in the test group (N = 15) at the base line were 1.63±0.38, 2.01±0.43 and 0.86±0.19, respectively. After 3 month they reduced to 0.88±0.49, 1.3±0.75 and 0.6±0.36, respectively. The reductions in PD and CAL were significant (p = 0.00). PD and CAL increased in the control group but these increases were not significant.

The differences between mean changes in PD, CAL and BI in both groups have been shown in Table 2. There were significant differences in PD and CAL between test and control groups.

The principal aim of this clinical trial was to determine if SDD exerted any significant effect on the periodontal condition in maintenance phase. Doxycycline is normally given at a daily dose of 100 mg following a loading dose of 200 mg which yields steady-state levels of 2.1-2.9 μg mL^{-1} in the blood

Table 1: Pocket depth, clinical attachment level and bleeding index (Mean±SD) at baseline and after 3 month in each group

	Case group				Control group			
	Baseline		After 3 month		Base line		After 3 month	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
P.D*	1.63	0.36	0.88	0.49	1.40	0.26	1.76	0.44
	P = 0.00				P = 0.08			
CAL**	2.01	0.43	1.30	0.75	1.55	0.55	1.64	0.57
	P = 0.00				P = 0.42			
BI***	0.86	0.19	0.60	0.36	0.75	0.42	0.50	0.38
	P = 0.19				P = 0.05			

*Pocket depth, **Clinical attachment, ***Bleeding index

Table 2: Changes (Mean±SD) in PD, CAL and BI in each group

	Test			Control	
	Mean	SD		Mean	SD
PD*	0.74	0.39		-0.36	0.45
			p = 0.00		
CAL**	0.67	0.37		-0.09	0.44
			p = 0.00		
BI***	0.3	0.61		0.26	0.33
			p = 0.68		

* Pocket depth, **Clinical attachment level, *** Bleeding index

and 3-5 μg mL^{-1} in the gingival crevicular fluid (Pascale *et al*., 1986). Studies in human volunteers have demonstrated that 20 mg doxycycline bid yields mean steady-state serum concentration of 0.4 μg mL^{-1} which translates to ≈0.04 μg mL^{-1} of free doxycycline (Collagenex Pharmaceutical, 1996).

This level of free doxycycline is considerably below the MIC determined *in vitro* for the vast majority of the bacteria isolated from human normal flora (Sutter *et al*., 1983), even so the possibility exists that levels attached with SDD might be inhibitory for certain bacteria that are sensitive to the tetracycline.

SDD does not inhibit fibroblast-type collagenase, or even MMP-8 up to sub physiologic levels (Owen *et al*., 2004; Ingman *et al*., 1993), which may help explain their lack of effect on normal connective tissue remodeling, thus it is now becoming apparent that leaky MMPI such as tetracycline based MMIS only reduce pathologically-excessive MMPS, not reduce MMP levels/activity below those required for physiologic function (Overall and Lopezootin, 2002).

Periodontitis is induced by host inflammatory-immune response to bacterial antigen. Host response to bacterial activity leads to collagen destruction that released by neutrophil and fibroblast when SDD adds to treatment plan, clinical parameters improve and level of TGF-β in gingival sulcus increases (Gurkan *et al*., 2005).

All of the previous studies used doxycycline two times daily, but in this study it has been used as one 20 mg cap per day. The results of this study are in agreement with Gapski *et al*. (2004).

Pocket depth and attachment loss significantly decreased compared to control group but there was not any significant difference in BI between two groups. BI is related to bacterial plaque and gingival inflammation. Twenty milligram doxycycline does not have antibacterial effect there for It is clear that it will not have any effect on dental plaque, so BI did not differ between two groups.

CONCLUSIONS

The results of this study show that long-term treatment with monodosage doxycycline can improve the periodontal condition during maintenance phase. Further long-term randomized controlled trial studies employing larger study populations are needed to determine the effect of tetracyclines on periodontium during maintenance period.

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