Journal of Dental Sciences (2015) 10, 28—35

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jds.com

ORIGINAL ARTICLE

Effect of concomitant administration of nifedipine and tacrolimus on the development of gingival overgrowth in rats

Sheng-Yi Chen [a,b,c], Cheng-Yang Chiang [a], Yu-Wen Yeh [d,e], Hsiao-Pei Tu [a,f], Hsien-Chung Chiu [a], Shin Nieh [g], Earl Fu [a*]

[a] *Department of Periodontology, School of Dentistry, National Defense Medical Center and Tri-Service General Hospital, Taipei, Taiwan, ROC*
[b] *Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan, ROC*
[c] *Division of Periodontics, Dentistry Department, Taipei Medical University-Shuang Ho Hospital, Taipei, Taiwan, ROC*
[d] *Department of Internal Medicine, Tri-Service General Hospital Songshan Branch, Taipei, Taiwan, ROC*
[e] *Department of Dermatology, National Defense Medical Center and Tri-Service General Hospital, Taipei, Taiwan, ROC*
[f] *Department of Dental Hygiene, China Medical University, Taichung, Taiwan, ROC*
[g] *Department of Pathology, National Defense Medical Center and Tri-Service General Hospital, Taipei, Taiwan, ROC*

Received 19 April 2013; Final revision received 26 May 2013
Available online 19 October 2013

KEYWORDS
gingival;
nifedipine;
overgrowth;
rat;
tacrolimus

Abstract *Background/purpose:* It is still controversial whether tacrolimus can induce gingival overgrowth. Calcium channel blockers of nifedipine are commonly used for lessening the side effect of high blood pressure induced by tacrolimus; however, nifedipine can also induce gingival overgrowth. This study was conducted to evaluate the effect of concomitant administration of nifedipine and tacrolimus on gingival overgrowth in rats.
Materials and methods: Thirty-six Sprague-Dawley rats were assigned into four groups, including a control group. In drug groups, either tacrolimus (1.5 mg/kg) or nifedipine (30 mg/kg), or both drugs together were administrated daily for 6 weeks. The gingival morphology was examined macroscopically on the mandibular central papilla from cast models biweekly, and analyzed by measuring the sulcular probing depth and the keratinized gingival width around the first mandibular molars immediately after sacrificing. By histology, changes of papillae, including the connective tissue, and the epithelial and total tissue areas, were

* Corresponding author. Department of Periodontology, School of Dentistry, National Defense Medical Center and Tri-Service General Hospital, PO Box 90048-507, Taipei, Taiwan, ROC.
E-mail address: ndmcearl@ndmctsgh.edu.tw (E. Fu).

http://dx.doi.org/10.1016/j.jds.2013.06.003

measured at two different tissue levels.
Results: Significant increases in papillary dimensions, including depth, width, and height, were observed across all groups after Week 1, with the control group showing less changes than experimental drug groups. Among drug groups, significantly increased papillary dimensions were noted in the nifedipine group when compared with groups treated with tacrolimus and both drugs. Changes in keratinized gingival width were found to be similar in the tacrolimus and combined-drug groups but greater in the nifedipine group. For probing depth, experimental groups showed greater changes than the control group, but no difference was observed among the experimental groups. Similar trends were presented for the total and connective tissue areas; however, the epithelial tissue areas did not show any difference among the four treatment groups.
Conclusion: Gingival overgrowth could be induced either by nifedipine or by tacrolimus, although the extent of gingival overgrowth induced by tacrolimus would be less than that by nifedipine. However, a concomitant administration of nifedipine and tacrolimus did not aggravate the induced gingival overgrowth.

Introduction

Gingival overgrowth is one of the adverse effects induced by various groups of drugs, including cyclosporin A, nifedipine, and phenytoin. Tacrolimus (FK506) is an immunosuppressant that was first isolated from *Streptomyces tsukubaensis* in 1984. Tacrolimus has been used successfully as an alternative to cyclosporin A for preventing graft rejection and treating autoimmune diseases.[1] It shares similar pharmacodynamics to cyclosporin A, but has nephrotoxicity, neurotoxicity, and disturbances in glucose metabolism. By contrast, tacrolimus has advantages over cyclosporin A; unlike cyclosporin A, tacrolimus does not cause hyperlipidemia, hypertension, and hirsutism.[1] Many clinical researches have demonstrated the benefit of tacrolimus in terms of reduced gingival overgrowth,[2–5] and recommended the use of tacrolimus over cyclosporin A to lower the risk of developing gingival overgrowth.[4–8]

To attenuate side effects such as nephrotoxicity and hypertension, it is a common practice to administer nifedipine, which may also induce gingival overgrowth,[9] along with tacrolimus.[10] Several clinical studies have evaluated the development of gingival overgrowth after concomitant administration of nifedipine and tacrolimus[2,4,5,8,11,12] and postulated a synergistic relationship between calcium channel blockers and tacrolimus in producing gingival overgrowth.[4,5] Despite former attempts to prove the existence of such a relationship, the effects of coadministration of nifedipine and tacrolimus on gingival overgrowth remain elusive due to the lack of an organized experimental design and randomized control trials. Most previous studies were based on single case reports or case-series reports without an appropriate control variable of each treatment drug. Therefore, the present study aims to evaluate the hypothesis that concomitant treatment of nifedipine and tacrolimus can aggravate gingival overgrowth in an animal model through an experimental design using different drug combinations as variables.

Materials and methods

Experimental design

Thirty-six male Sprague-Dawley rats, 5-week old and weighing 150—200 g, were assigned randomly into four groups treated with different drug combinations: control, tacrolimus, nifedipine, and combined drug (tacrolimus + nifedipine) groups. Animals in the tacrolimus group received tacrolimus dissolved in mineral oil at a daily dose of 1.5 mg/kg body weight via gastric feeding, whereas the control group received the mineral oil solvent alone. Animals in the nifedipinegroup received a daily dose of nifedipine of 30 mg/kg body weight (Sigma, St Louis, MO, USA) dissolved in dimethyl sulfoxide (Sigma-Aldrich, St Louis, MO, USA), whereas those in the tacrolimus + nifedipine group received both tacrolimus and nifedipine, as mentioned above. All the drugs and oil solvent were delivered daily for 6 weeks. The protocol was approved by the Institutional Animal Care Committee of the National Defense Medical Center, Taipei, Taiwan, prior to the commencement of this study.

Macroscopic evaluation of gingival morphology

From the cast models obtained from dental impressions (Coltène/Whaledent, Altstätten, Switzerland), morphological changes of the central mandibular papilla, including the mesiodistal width, buccolingual depth, and vertical height, were measured and evaluated biweekly (Fig. 1A), as described previously.[13] In addition, depths of the gingival sulci at the distobuccal sites of the maxillary and first mandibular molars were recorded using a stereomicroscope (Olympus-SZH, Olympus, Tokyo, Japan) via the insertion of a specially designed plastic gingival probe after sacrificing the animals by carbon dioxide inhalation at the end of the experiment.[14] Widths of keratinized gingiva at the mesio-, mid-, and distobuccal sites of the right and left first mandibular molars were also measured directly using the methods modified in our previous study.[15]