

ABSTRACT

Development of gingivitis and periodontitis have been hypothesized to be associated with a localized dysfunction of the immune response in the gingival tissues. Since mast cells are present in inflamed gingiva and histamine has been shown to inhibit immune and inflammatory cell function via interaction with H₂-receptors, local histamine release might mediate this dysfunction. **Objectives:** Determine whether H₂ antagonists (H₂'s) can inhibit development of gingivitis. **Methods:** A series of studies were conducted in the canine gingivitis model to evaluate the H₂'s, cimetidine, ranitidine and famotidine, for their efficacy in preventing development of gingivitis. Nine animals per leg were used in each of the 30 Day gingivitis studies along with the appropriate controls. Both topical (rinse) and systemic treatments were evaluated. Following baseline prophylaxis, and 30 days of twice a day treatments, they were graded for changes in gingivitis to assess the inflammation index (II), Loe-Silness GI, plaque and stain. **Results:** Topical application (concentrations ≥ 0.05%) of cimetidine rinses provided significant reductions (P<0.05) in gingival inflammation (II) in 9 out of 10 studies. Statistically significant reductions were also obtained with ranitidine in 5 out of 5 studies and with famotidine in 2 out of 3 studies. The H₂'s did not cause an increase in tooth stain. H₂'s provided benefits vs. gingival bleeding in selected studies, however, the H₂'s had no effect on plaque accumulation. **Conclusions: These studies demonstrate that H₂'s exhibit a benefit in the reduction of gingival inflammation without an increase in tooth staining.**

INTRODUCTION

The immunology literature report that histamine can activate T-suppressor cells and that this activation is mediated by H₂-receptors on T-lymphocytes. H₂ antagonists can inhibit this histamine-mediated immune suppression. Eleven canine experimental gingivitis studies (randomized, parallel groups) were conducted to evaluate H₂ antagonists for their effect on gingivitis.

MATERIALS AND METHODS

Nine animals per treatment group were used in each of the 30 Day gingivitis studies. One week after prophylaxis, a baseline gingivitis grading was performed consisting of the inflammation index (II) and the Loe-Silness GI index. This was followed by a polishing of the teeth to remove any buildup since the prophylaxis. The dogs were then balanced on baseline gingivitis scores and randomly allocated into treatment groups, or the appropriate controls: buffered placebo (negative control) or 0.12% chlorhexidine (positive control).

Treatments were applied topically (or where indicated systemically), twice daily for thirty days. At the end of thirty days, the final grading for gingivitis, plaque and stain was made.

Table 1 contains the range of the H₂ treatments for these studies both topical and systemic

Table 1. H ₂ Treatments			
Treatments	Rinse (concentration)	Treatments	Tablets
Cimetidine	0.05% - 1%	Cimetidine (Tagamet)	200, 300, and 800 mg
Ranitidine	0.05% - 0.5%	Ranitidine (Zantac)	75, 150, and 300 mg
Famotidine	0.048% - 0.48%		

Grading: The buccal surfaces of the following teeth in all four quadrants are measured for a total of twenty teeth: first molar, fourth, third and second premolars and first canine. Two different assessments for gingivitis are made.

Inflammation index (II): Measures the extent (in mm) of the inflammation taken from the reddened gingival margin to the end of a row of continuous red dots.

Modified Loe-Silness GI: Gingival index is a 0-3 scale. 0 = no inflammation, 1 = inflammation present, gingiva is red, 2 = bleeding upon probing, 3 = spontaneous bleeding. A perio probe is gently inserted below the gingiva at the distal end of the tooth and gently swept around the tooth.

Stain: Measured as percent coverage of each tooth. Yellowish plaque is not counted.

Plaque: Measured by percent coverage of each tooth. The teeth are disclosed with 1% basic fuchsin solution applied with a cotton tipped applicator. Water is sprayed to remove excessive staining solution.

Statistical Analysis: Analysis of variance was used to compare treatments with respect to plaque and stain. Treatments were compared with respect to gingivitis endpoints with analysis of covariance, where the baseline score was used as a covariate.

RESULTS

Overview of all H₂ Studies

Figure 1. Inflammation Index

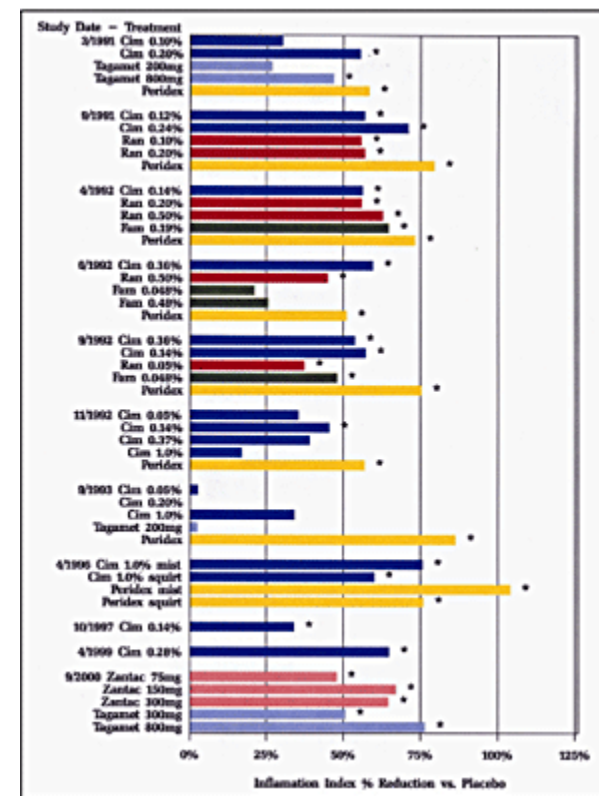


Figure 2. Löe-Silness Gingival Index (GI)

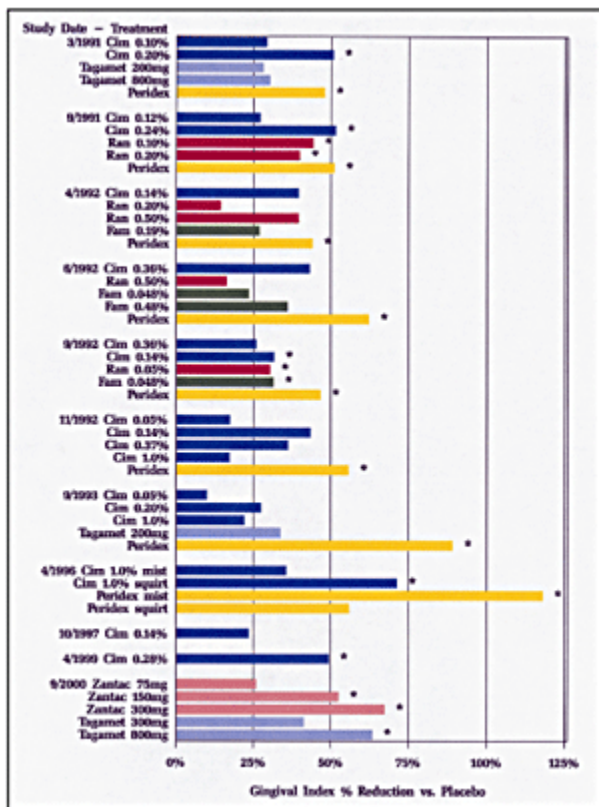


Table 2. Summary of Results

Actives	# of Studies / # Trt Groups	Mean % Reduction vs Placebo ¹	% Groups w/ p<0.05 vs. Placebo ¹
		(II / GI)	(II / GI)
Cimetidine			
- Rinses	10 / 19	65% / 35%	63% / 26%
- Tagamet	3 / 5	75% / 37%	60% / 20%
Ranitidine			
- Rinses	4 / 6	74% / 42%	100% / 50%
- Zantac	1 / 3	52% / 29%	100% / 67%
Famotidine			
- Rinses	3 / 4	79% / 41%	50% / 25%

¹ Across all treatment groups

CONCLUSION

These studies demonstrate that H₂'s exhibit a benefit in the reduction of gingival inflammation without an increase in tooth staining.

The H₂'s had no significant effect on plaque formation.

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DISCUSSION

The H₂ greatest benefit is primarily in the reduction of gingival inflammation (Figure 1) and secondarily in GI (Figure 2). The H₂'s did not cause an increase in tooth stain and had no significant effect on plaque accumulation, therefore, no data is present.

All treatments had similar mean percent reductions versus placebo with respect to II and GI. Ranitidine demonstrated higher percentage of significant groups (100%) versus placebo followed by cimetidine (63% & 60%) and then famotidine (50%).

In most studies, an increase in the concentration of the H₂'s led to an increase in antingivitis efficacy with regards to II and GI.

Results were mixed in comparison of rinses versus tablets. Neither dosage form demonstrated clear superiority over the other for either II or GI.