Benzydamine HCl for Prophylaxis of Radiation-Induced Oral Mucositis

Results from a Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Joel B. Epstein, D.M.D., M.S.D.[1,2]
Sol Silverman, Jr., D.D.S.[3]
Dario A. Paggiarino, M.D.[4]
Steve Crockett, Ph.D.[5]
Mark M. Schubert, D.D.S., M.S.D.[2]
Neil N. Senzer, M.D.[6]
Peter B. Lockhart, D.D.S.[7]
Michael J. Gallagher, M.D.[8]
Douglas E. Peterson, D.M.D., Ph.D.[9]
Francis G. Leveque, D.D.S.[10]

[1] British Columbia Cancer Agency, Vancouver Hospital and Health Sciences Centre, University of British Columbia, Vancouver, British Columbia, Canada.

[2] Department of Oral Medicine, University of Washington, Seattle, Washington.

[3] School of Dentistry, University of California, San Francisco, California.

[4] Angelini Pharmaceuticals, Inc., River Edge, New Jersey.

[5] D.A.T.A. Inc., Bayou La Batre, Alabama.

[6] Department of Radiation Oncology, Baylor-Sammons Cancer Center, Dallas, Texas.

[7] Department of Oral Medicine, Carolinas Medical Center, Charlotte, North Carolina.

[8] Department of Radiation Oncology, Mercy Hospital, Scranton, Pennsylvania

[9] School of Oral Medicine, Department of Oral Diagnosis, University of Connecticut Health Center, Farmington, Connecticut.

[10] Division of Oral Medicine and Oncology, Harper Hospital, Detroit, Michigan.

Presented in part at the 5th International Congress on Oral Cancer, London, June 5, 1997 and in part at the 11th Multinational Association of Supportive Care in Cancer International Symposium, Nice, France, February 18–20, 1999.

Supported by Angelini Pharmaceuticals, Inc., River Edge, NJ and 3M Pharmaceuticals, St. Paul, MN.

The authors are indebted to Mark Calcamuggio of Quality Network, Inc., and Barbara A. Regan for editorial assistance in the preparation of the article.

BACKGROUND. Benzydamine was evaluated in patients with head and neck carcinoma for treatment of radiation-induced oral mucositis, a frequent complication of radiation therapy (RT) for which there is no predictable therapy or preventive treatment currently available.

METHODS. The safety and efficacy of 0.15% benzydamine oral rinse in preventing or decreasing erythema, ulceration, and pain associated with oral mucositis during RT were evaluated in a randomized, placebo-controlled trial conducted in patients with head and neck carcinoma. Subjects were to rinse with 15 mL for 2 minutes, 4–8 times daily before and during RT, and for 2 weeks after completion of RT; study evaluations were conducted before RT and routinely thereafter up to 3 weeks after RT.

RESULTS. During conventional RT, regimens up to cumulative doses of 5000 centigrays (cGy) benzydamine ($n = 69$) significantly ($P = 0.006$) reduced erythema and ulceration by approximately 30% compared with the placebo ($n = 76$); greater than 33% of benzydamine subjects remained ulcer free compared with 18% of placebo subjects ($P = 0.037$), and benzydamine significantly delayed the use of systemic analgesics compared with placebo ($P < 0.05$). Benzydamine was not effective in subjects ($n = 20$) receiving accelerated RT doses ($\geq$ 220 cGy/day). The incidence of adverse events between treatment groups was comparable without significant differences. Early discontinuation because of adverse events occurred in 6% of benzydamine subjects and 5% of placebo subjects, and there was 1 death (related to the primary diagnosis) in a placebo subject.

CONCLUSIONS. Benzydamine oral rinse was effective, safe, and well tolerated for prophylactic treatment of radiation-induced oral mucositis. ***Cancer* 2001;92: 875–85.** *© 2001 American Cancer Society.*

KEYWORDS: benzydamine oral rinse, radiation therapy, head and neck carcinoma, placebo-controlled clinical trial.

Other study investigators include the following: Pusha M. Patel, M.D., and Gerald A. Ferretti, D.D.S. (Markey Cancer Center, Department of Radiation Medicine, University of Kentucky, Lexington, KY); Adam S. Garden, M.D. (M. D. Anderson Cancer Center, Department of Radiotherapy, Houston, TX); Jonas T. Johnson, M.D. (University of Pittsburgh, Department of Otolaryngology, Pittsburgh, PA); Lauren L. Patton, D.D.S. (University of North Carolina, School of Dentistry, Department of Dental Ecology, Chapel Hill, NC); Jadranka Dragovic, M.D. (Henry Ford Hospital, Department of Radiation Therapy, Detroit, MI); Ramin Razavi, D.M.D. (Georgetown University Medical Center, Department of Otolaryngology, Washington, DC); Carl W. Haveman, D.D.S. (Health Science Center, University of Texas, Department of General Practice, San Antonio, TX); Charles W. Scarantino, M.D. (Rex Cancer Center, Department of Radiation Oncology, Raleigh, NC).

Michael J. Gallagher's current address: 113 Pocono Drive, Milford, PA 18337.

Address for reprints: Joel B. Epstein, D.M.D., M.S.D., British Columbia Health Center, 600 West 10th Avenue, Vancouver, BC V5Z-4E6, Canada; Fax: (604) 872-4596; E-mail: jepstein@bcccancer.bc.ca

Received December 18, 2000; accepted April 20, 2001.

Oral mucositis is a frequent complication of radiation therapy (RT) for head and neck carcinoma, and its severity is directly related to the type of radiation and to the total dosage, fractionation, and duration of treatment.[1–6] Oral mucositis can occur with cumulative RT doses as low as 1000–2000 centigrays (cGy) with therapy administered at a rate of 200 cGy per day.[1] In greater than half of patients with mucositis, the condition is of such severity as to require parenteral analgesia, interruption of RT and/or hospitalization, and the need for parenteral or tube feeding, all of which increase the cost of cancer therapy and have a negative impact on quality of life.[7] Mucositis-associated morbidity can lead to interruption in RT treatments and/or prevent delivery of the total planned dose of RT, both of which likely have a negative impact on survival rates.[8]

Currently, because there is no predictable prevention or therapy for RT mucositis available, treatment is essentially palliative. A recent review of more than 100 studies in patients undergoing cancer therapy indicated that there is no agent or method that is uniformly effective in preventing or treating the resulting oral mucositis.[9] Current management of oral mucositis consists of the use of topical anesthetics and/or anti-inflammatory drugs (e.g., lidocaine, diphenhydramine) and agents such as colloidal silver solutions, salt and soda rinses, or hydrogen peroxide rinses.[1,2,5–7] However, there is no unequivocal evidence that these agents have any significant effect on mucositis, although they may improve patient comfort. These palliative regimens do not address the problems of tissue breakdown, secondary infection (primarily candidal), or impaired healing.

The biology of ulcerative mucositis involves the sequential interaction of cells, cytokines, and the oral microflora.[10] The initial tissue response to radiation appears to be the release of a number of proinflammatory cytokines, including interleukin (IL)-1 and IL-6 and tumor necrosis factor (TNF)-α). With respect to TNF-α, sequential polymerase chain reaction tissue analysis of radiated mucosal tissue has shown increasing levels of cytokines that peak just before the development of ulcerative lesions.[11] Similarly, immunohistochemical analysis for IL-11 shows increasing local tissue levels in irradiated mucosa compared with controls.[11] In addition, as a consequence of the cytotoxic effects of RT on normal cells of the basal epithelium, the literature suggests that renewal of the oral mucosa is impaired, leading to atrophy and subsequent ulceration.[12] It is likely that this process is accelerated by a surge in apoptotic cell death. It has been proposed that another frequent radiation-induced effect, xerostomia (decreased salivation), results in changes in the oral microbial flora as well, and the resulting pathogens can colonize these altered mucosal surfaces.[5,7,13] Bacterial cell wall products such as peptidoglycans and teichoic acid then can stimulate connective tissue borne histiocyte cytokine and nitric oxide production that potentially amplify mucosal damage.[14]

Benzydamine hydrochloride is a nonsteroidal drug that has shown topical anti-inflammatory, analgesic, anesthetic, and antimicrobial activities.[15–22] Results from several clinical studies suggest that topically applied benzydamine is effective in attenuating a variety of inflammatory conditions including oral mucositis induced by antineoplastic radiation or chemotherapy.[2–4,23–28] A literature review of oral mucositis studies using a variety of topical and systemic agents in patients undergoing anticancer therapy listed 15 randomized, placebo-controlled, double-blind RT trials, and benzydamine was tested in 3 of them; the 7 studies reporting significant reductions in mucositis included all 3 of the benzydamine studies.[9] Recent studies have suggested that benzydamine is a particularly effective inhibitor of TNF-α production, which may explain its anti-inflammatory effects.[29–31] These studies have shown that benzydamine inhibits production of inflammatory cytokines by human and murine mononuclear phagocytes exposed to various inducers. Production of TNF-α and, to a lesser extent, IL-1 were consistently inhibited.[28–30] In addition, benzydamine was shown to reduce lethality in the mouse model of lipopolysaccharide-induced shock with a concomitant reduction of peak plasma levels of both TNF-α and IL-1 whereas IL-6 and IL-8 were unaffected.[31] The potential clinical applicability of these findings was suggested by Sironi et al. who found that the therapeutic benefit observed with the topical use of benzydamine in the treatment of candidal vaginitis was likely because of suppression of TNF-α.[30] The mechanism by which benzydamine reduces radiation-induced mucosal toxicity may be its ability to suppress selected proinflammatory cytokine production.

METHODS

This study was conducted with identical protocols at 16 centers in North America (15 in the U.S. and 1 in Canada), following all experimental procedures in accord with international ethical standards. The study was conducted in compliance with principles of Good Clinical Practice, and all subjects provided written institutional approved informed consent. Clinical staging of tumor involvement for diagnostic purposes was based on American Joint Committee on Cancer recommendations.[32]

Male and nonpregnant female subjects 18–80 years old with diagnoses of head and neck carcinoma

who were scheduled to receive a total external beam RT dose of at least 5000 cGy via a megavoltage treatment with either a cobalt-60 teletherapy unit or a linear accelerator were eligible for the study if they had at least 2 oral sites included in the planned RT treatment volume.

Subjects were excluded from the study if they had a Karnofsky performance status less than 80%, a known hypersensitivity to benzydamine or typical nonsteroidal anti-inflammatory drugs (NSAIDs), or residual oral or pharyngeal mucositis from previous RT or chemotherapy or if they were already on RT, had taken experimental drugs within 30 days of study start, or chronically took steroids, NSAIDs, or other analgesics for other medical conditions (low-dose aspirin for thromboembolic prophylaxis was permitted). Prison inmates and women who were pregnant or of childbearing potential not using adequate contraception also were excluded. Concomitant use of drugs such as antibiotics, oral antifungals, and antivirals was allowed.

Standard oral care protocols at each institution were permitted, and consistency in use of institution protocols was emphasized. Subjects were encouraged to brush their teeth at least twice daily, floss once daily, rinse as necessary with bland oral rinses (e.g., normal saline, sodium bicarbonate), apply fluoride daily (neutral pH sodium fluoride), and use remineralizing solutions if deemed appropriate. Commercial mouthwashes (over the counter or prescription), chlorhexidine, or other agents to aid in oral hygiene were prohibited.

The objectives of this multicenter, randomized, parallel-group, placebo-controlled clinical trial were to establish the safety and tolerability of benzydamine oral rinse in patients with head and neck carcinoma undergoing RT and to investigate the efficacy of the prophylactic use of benzydamine in preventing or decreasing erythema, ulceration, and pain associated with oral mucositis.

All subjects received external beam RT treatments to the head and neck, using either single or twice daily treatment regimens for 5 days a week to total planned cumulative RT doses of at least 5000 cGy. The relation between RT and mucositis is quantitative and well characterized,[33] and therefore the planned RT regimen provided an important pretreatment stratification. Subjects were stratified within investigative sites according to one of the RT regimens listed below and then randomized to treatment with either benzydamine oral rinse or placebo. The RT dosage of stratum B represented an accelerated aggressive regimen limited to some subjects in the Canadian study site. The following is a list of the RT regimens per stratum: stratum A,single daily tumor dose of 180 to less than220 cGy; B, single daily tumor dose of 220–250 cGy; C, twice daily tumor dose of 110–150 cGy (total daily tumor dose of 220–300 cGy); D, single daily tumor dose of 180 to less than 220 cGy plus chemotherapy.

Oral rinsing with study treatments was initiated before RT and continued for 2 weeks after the end of RT. Subjects were evaluated before RT; twice weekly during RT; at the end of RT; and at 2 and 3 weeks after RT. Radiation source, modality, field size, treatment areas, total planned dose, number of fractions, days of irradiation, and suspensions or discontinuations of RT (including reason) were recorded. Initiation and duration of tube feeding were noted.

Study medications were 0.15% benzydamine oral rinse (1.5 mg/mL benzydamine) and a placebo identical in appearance and taste consisting of the vehicle only (excipients included approximately 10% alcohol by volume, menthol, peppermint oil, clove oil, and other flavoring agents). Subjects were to rinse with 15 mL for 2 minutes, 4–8 times daily before and during RT, and for 2 weeks after completion of RT. If burning or stinging occurred, dilution of the rinse with water at 1:1 or 1:2 was allowed. All dosing information was recorded daily by the subject and weekly at the study site; all bottles of study rinse were returned each week and the amount returned recorded.

Systemic analgesics for oropharyngeal pain were prescribed as needed according to the following analgesic ladder[34]: level 1, NSAIDs (except ketorolac) and other nonopioid and nonopiate analgesics; level 2, weak opioids or opiates with or without level 1 drugs; level 3: strong opioids or opiates with or without level 1 drugs.

The amount of time a subject was treated at any level of analgesic was not determined by the principal investigator and was considered to be at least 6 hours. If a higher level analgesic was used, subjects were considered to have failed the lower analgesic level. All concomitant medications were recorded.

A complete oral examination was performed within 24 hours of the first dose of study medication and at each clinic visit. Oral areas at risk were scored for the major signs of oral mucositis (i.e., erythema, pseudomembrane, and ulceration) using a 4-point scale: 0 = within normal limits or healed; 1 = erythema; 2 = single ulcer/pseudomembrane less than 1 cm; 3 = single ulcer/pseudomembrane greater than 1 cm or multiple ulcers/pseudomembranes. Fourteen anatomic oral sites were evaluated and scored separately for mucositis: buccal mucosa (right and left), labial mucosa (upper and lower), tongue (ventral and dorsal), gingiva (upper and lower), hard palate, soft palate, lips (upper and lower), floor of the mouth, and

oropharynx. The mean mucositis score was obtained by adding the single scores for each anatomic area at risk (defined as areas receiving a cumulative radiation dose of at least 4000 cGy) and dividing by the number of areas included in the RT field. If RT or use of study medication terminated before the accumulation of 4000 cGy to the reduced volume, all areas receiving radiation that were normal at baseline were considered at risk. Limiting the inclusion of scores to those areas at risk of developing mucositis was intended to prevent dilution of an overall efficacy score by areas outside the treatment volume in which no mucositis would be expected to occur. In addition, because head and neck carcinoma constitutes several anatomic sites in which the volume of radiation exposure oropharyngeal mucous membrane varies substantially, dividing the sum of the single mucositis scores of each area at risk by the number of areas included in the RT field provided an objective, meaningful measure of response to radiation irrespective of the number of areas at risk or specific sites affected. Mouth pain, throat pain, and pain during meals also were assessed at each clinic visit and scored using a 7-point categoric self-rating scale (0 = none; 1 = slight; 2 = mild; 3 = moderate; 4 = considerable; 5 = severe; 6 = intolerable).

General physical examinations, vital signs, and laboratory tests (blood chemistry, hematology, and urinalysis) were completed at baseline and at the end of the study; body weight was recorded at each clinic visit. Volunteered and observed adverse events were recorded and graded as mild, moderate, or severe; relation to study drug was noted; and subjects were followed until resolution of the event.

The primary efficacy variable was area under the curve (AUC) for the mean mucositis scores over cumulative RT dose. The secondary efficacy variables were 1) distribution of mean mucositis scores over 4, equal, sequential intervals of radiation: 0–1250 cGy, 1250–2500 cGy, 2500–3750 cGy, and 3750–5000 cGy; 2) use of concomitant systemic analgesic medications; 3) evaluations of 3 pain scores; and 4) subject body weights, RT suspension/discontinuation, and use of enteral supportive nutrition initiated during RT because of severe oral mucositis.

Statistical Analysis

No information concerning the primary efficacy variable defined for this study (AUC of mucositis scores) was available in the literature; consequently, the sample size chosen was based on results of clinical trials in which mucositis scores,[5] occurrence of ulcers,[6] and time to first use of analgesics[4] were reported. It was estimated that a minimum sample size of 40 subjects per treatment group would enable detection of clinically significant differences between treatment groups at an α-level of 0.05 with a power of 0.80. Therefore, 80 subjects per treatment arm was expected to provide more than adequate power to detect clinically significant differences. The study was not designed to detect statistically significant differences in efficacy between treatments within each RT stratum.

Demographics and tumor-related data were compared between groups and investigative sites using a two-factor analysis of variance (ANOVA) for continuous variables and Cochran-Mantel-Haenzel tests of association for categoric variables. The treated population (subjects who received at least one dose of study medication) was used for demographic and safety analyses. In addition, the intent-to-treat (ITT) population was defined for purposes of analysis of efficacy as all randomized subjects who had taken study medication at least once *and* had at least one on-radiation evaluation.

The primary efficacy analysis was AUC computed on the mean mucositis scores over the cumulative radiation exposure interval of 0–5000 cGy and over intervals of 1250 cGy. If either RT or study medication was terminated before the final interval, the last mean mucositis score was carried forward. If more than one evaluation occurred for a cumulative exposure dose as a consequence of interruptions in RT, the score of the first evaluation at that dose was used. The analysis of treatment effect was a repeated-measures ANOVA on mean AUC over RT intervals. The consistency of response to treatment based on the AUC measure was examined for age, gender, race, and RT strata of the ITT population. Response to radiation was defined as a mucositis score of 2 (ulceration) or higher in any oral area at risk, and a secondary endpoint for mucositis included the cumulative RT dose for onset of the first ulcer in any area at risk. Analysis of radiation response was conducted by comparing the distribution of cumulative dose from 0 to 5000 cGy at the onset of response. Survival curves were compared by using the log-rank test. The proportion of subjects remaining ulcer free at RT doses up to 5000 cGy was determined, as was distribution of mucositis scores in the two treatment groups. For descriptive purposes only, the distribution of mucositis scores over all oral areas at risk for all subjects was described for each treatment group using the last observation in each cumulative dose interval of 1250 cGy up to 5000 cGy (this distribution indicates the number of areas at risk that remained ulcer free at specified RT intervals).

The distribution of cumulative dose of RT to the first use of the three levels of analgesics was determined using a survival analysis model over the cumu-

TABLE 1
Subject Disposition for Each Treatment Group

Characteristic	Benzydamine (%)	Placebo (%)
No. of subjects		
Screened	456	
Randomized	84	89
Treated	84	88
Completed	62 (74)	66 (75)
No. of subjects discontinued		
Total	22 (26)	22 (25)
Deaths	0 (0)	1 (1)
Adverse events	5 (6)	4 (5)
Lack of efficacy	5 (6)	6 (7)
RT terminated early	1 (1)	0 (0)
Subject withdrew consent (or unrelated to treatment)	10 (12)	11 (13)
Lost to follow-up	1 (1)	0 (0)
Intent-to-treat study population[a]		
Included	79 (94)	86 (98)
Excluded	5 (6)	2 (2)

RT: radiation therapy.
[a] Subjects who had a least one dose of study medication and at least one on-radiation evaluation.

lative radiation interval from 0 to 5000 cGy, and survival curves were compared by the log-rank test. Subjects who discontinued RT or study medication or who never used a given level of analgesic before 5000 cGy were right-censored at 5000 cGy.

Mouth pain at rest was identified as the primary pain measure. Areas under the curve of pain intensity for all 3 measures versus cumulative radiation dose over the 4 intervals of 1250 cGy up to 5000 cGy were analyzed by a repeated-measures ANOVA. Subjects who received nasogastric or percutaneous gastrostomy tubes either before or during the trial were eliminated from the analysis of functional pain (i.e., pain during meals).

The comparability of treatment groups with regard to baseline body weight was tested by ANOVA. The association between RT suspension and treatment group was evaluated with Fisher exact test. Safety variables were analyzed using Fisher exact test, ANOVA, Student *t* test, or survival curves as appropriate.

RESULTS

Subject disposition data are summarized in Table 1. The treated population included 172 subjects (84 benzydamine, 88 placebo) enrolled at the 16 study sites, randomized to treatment, and receiving at least 1 dose of study medication. The ITT population comprised a total of 165 of these subjects (79 benzydamine, 86 placebo) who also had at least one on-radiation evaluation.

TABLE 2
Demographics and Patient Characteristics for the Treated Population (*n* = 172)

Parameter	Benzydamine (*n* = 84) (%)	Placebo (*n* = 88) (%)
Age (mean ±SD, yrs)	55.9 ± 11.6	56.5 ± 11.1
Range (yrs)	20–78	26–79
Gender		
Male	64 (76)	68 (77)
Female	20 (24)	20 (23)
Race		
White	67 (80)	65 (74)
Nonwhite	17 (20)	23 (26)
Karnofsky performance status		
80	12 (14)	12 (14)
90	38 (45)	38 (43)
100	34 (40)	38 (43)
Length of diagnosis (mean ±SD, wks)	9.2 ± 12.6	10.8 ± 20.9
Range (wks)	1–102	0–143
Tumor stage		
I	10 (12)	8 (9)
II	16 (19)	15 (17)
III	18 (21)	15 (17)
IV	36 (43)	44 (50)
Missing	4 (5)	6 (7)
Tumor grade		
Well differentiated (G1)	8 (10)	10 (11)
Moderately differentiated (G2)	38 (45)	35 (40)
Poorly differentiated (G3,4)	28 (33)	36 (41)
Missing	10 (12)	7 (8)
Primary tumor site		
Lip and oral cavity	29 (35)	27 (31)
Pharynx	25 (30)	28 (32)
Larynx	8 (10)	6 (7)
Salivary glands	8 (10)	4 (5)
Paranasal sinuses	0 (0)	1 (1)
Other site	3 (4)	3 (3)
Multiple oral sites	11 (13)	19 (22)
RT dose stratum and final tumor dose (mean ± SD, cGy)		
A: single daily dose of 180 to < 220 cGy	61 (73) 6368 ± 687	62 (70) 6230 ± 887
B: single daily dose of 220–250 cGy	10 (12) 5799 ± 421	10 (11) 5735 ± 515
C: 110–150 cGy twice daily	8 (9) 7363 ± 613	11 (13) 7190 ± 670
D: conventional RT + chemotherapy	5 (6) 7160 ± 89	5 (6) 7014 ± 233

SD: standard deviation; G: Grade; RT: radiation therapy; cGy: centigray.

Table 2 summarizes demographics and subject characteristics for the treated population. Most patients' disease was diagnosed as Stage III or IV, and most were moderately or poorly differentiated. Overall, no significant differences were observed between treatment groups for any of the baseline subject characteristics, and the study population provided a good clinical representation of patients with carcinoma of

TABLE 3
Study Populations: Number of Subjects per Treatment Group Stratified by Radiation Exposure Rates

	Study populations							
	Randomized (n = 173)		Treated (n = 172)		Intent-to-treat (n = 165)		Conventional US RT[a] (n = 145)	
RT stratum	B	P	B	P	B	P	B	P
A (single daily dose of 180 to < 220 cGy)	61	63	61	62	56	60	56	60
B[b] (single daily dose of 220–250 cGy)	10	10	10	10	10	10	NA	NA
C (110–150 cGy twice daily)	8	11	8	11	8	11	8	11
D[c] (conventional RT + chemotherapy)	5	5	5	5	5	5	5	5
Totals	84	89	84	88	79	86	69	76

RT: radiation therapy; B: benzydamine treatment group; P: placebo treatment group; cGy: centigray; NA: not applicable.

[a] Strata A + B + C combined.

[b] No patients enrolled in any of the U.S. sites were stratified to this aggressive, nonconventional RT regimen, which was limited to some patients in the only Canadian site.

[c] Chemotherapy regimens included single-dose cisplatin at or near the beginning of RT (5 subjects), cisplatin at the beginning of RT and again 3 weeks later (1 subject), cisplatin at the beginning of RT and again 1 and 2 mos later (1 subject), cisplatin 3 and 7 wks after initiation of RT (1 subject), cisplatin at the beginning of RT and 5-fluorouracil (FU) 5 days later (1 subject), course of cisplatin followed by 5-FU at the beginning of RT and again 1 mo (1 subject).

the head and neck intended for treatment with radiation.

Subject exposure to study medication was similar in both treatment groups: the mean number of days of dosing plus or minus standard error was 52.2 ± 2.6 in the benzydamine group compared with 54.5 ± 2.1 days in the placebo group. There were no differences between treatment groups in number of doses taken (in both treatment groups, the median number of doses per day across the entire RT interval was between 3 and 7, averaging 4–5 doses/day), dilution of the oral rinses, or the number of subjects using study medication for at least 2 weeks after the end of RT (39 [46%] in the benzydamine group and 43 [49%] in the placebo group).

All subjects received external beam radiation with tumor doses ranging from 2020 to 8160 cGy. While the patients were taking the study medication, the mean tumor RT dose delivered (± standard deviation) was 5499 ± 1709 cGy in the benzydamine group and 5568 ± 1503 cGy in the placebo group (P = 0.783). In addition, no subject was excluded from the efficacy analyses because all subjects had at least two oral areas at risk. Thus, the mean AUC of the mean mucositis score across oral areas at risk provided a single value reflective of the severity of a subject's mucositis.

Table 3 presents the number of subjects stratified by radiation exposure rates per treatment group within the treated, ITT, and conventional RT subgroup populations. For the conventional RT subgroups, obtained by excluding the RT stratum B subjects (10 benzydamine, 10 placebo), 145 subjects (69 benzydamine, 76 placebo) were included in the efficacy analyses.

Primary Efficacy Results

For all patients across the 4 RT strata who received at least 1 dose of both study drug and radiation (n = 165), benzydamine produced a 26.3% reduction in mean mucositis AUC compared with placebo for the overall 0–5000-cGy interval (P = 0.009). As described above, subjects were stratified within investigative sites according to four RT regimens (strata A–D) with sequential randomization to treatment group. Enrollment into stratum B, the aggressive RT regimen of high single daily doses of at least 220 cGy was limited to 20 patients in only 1 of the 16 centers. Overall mean mucositis AUCs of placebo subjects in strata A (964.4), C (915.7), and D (748.4) were substantially lower than AUCs of placebo patients in stratum B (1169.0) indicating that mucositis produced by the high single daily RT doses was more severe than effects produced by the conventional RT regimens. Moreover, benzydamine produced substantial reductions in AUCs of subjects in strata A (32.2%), C (33.8%), and D (57.7%) compared with a slight increase in patients in strata B (9.5%).

Because RT effects in stratum B were more severe than those occurring in the other strata, and benzydamine was not effective in reducing the more severe mucositis in those patients receiving the high single daily RT regimen, an RT subgroup analysis (which excluded the stratum B subjects) was performed to describe the effects of benzydamine in patients receiving conventional RT regimens.

In the efficacy analyses of subjects receiving conventional RT with or without chemotherapy, the AUC of mean mucositis scores showed a 30% reduction in

TABLE 4
Mean AUCs of Mean Mucositis Scores by RT Interval for Patients Receiving Conventional RT (n = 145)

RT interval (cGy)	Benzydamine mean AUCs	Placebo mean AUCs	Benzydamine-placebo	Reduction (%)	P value
0–5000	663.3	945.1	−281.8	29.8	0.006
0–1250	83.6	145.9	−62.3	42.7	0.627
1250–2500	620.4	823.4	−202.9	24.6	0.114
2500–3750	902.7	1410.3	−507.6	36.0	<0.001
3750–5000	1046.4	1400.7	−354.3	25.3	0.006

AUC: area under the curve; RT: radiation therapy; cGy: centigray.

erythema and ulceration with benzydamine over the cumulative RT interval of 0–5000 cGy compared with placebo (P = 0.006). Table 4 summarizes the mean AUCs of the mean mucositis score results over the RT intervals for subjects receiving conventional RT regimens. Benzydamine produced statistically significant reductions in mucositis in the highest two RT intervals compared with placebo: 36% in the 2500–3750-cGy interval ($P < 0.001$) and 25.3% in the 3750–5000-cGy interval (P = 0.006). Overall, as would be expected, mucositis scores increased rapidly in severity between the 2500- and 5000-cGy cumulative RT intervals (corresponding approximately to the second and fourth week of treatment) and appeared to plateau approaching the end of treatment.

Secondary Efficacy Results

The results of the secondary efficacy parameters in the ITT population subgroups receiving conventional RT also provided evidence of the superiority of benzydamine treatment over placebo and showed a prophylactic effect of benzydamine on oral mucositis. Most mucositis scores in oropharyngeal areas at risk for ulceration in both treatment groups remained in the 0–1 range (no ulceration) at cumulative RT exposures of 3750 and 5000 cGy; however, more areas at risk treated with benzydamine remained ulcer free than those treated with placebo (85.5% benzydamine vs. 72.9% placebo at 3750 cGy; 79.5% benzydamine vs. 70.9% placebo at 5000 cGy). The percentage of oropharyngeal areas at risk that actually developed ulceration (i.e., mucositis score of ≥2) at specific RT exposures is noteworthy. From 1250 to 2500 cGy, the percentage of oropharyngeal areas at risk in which ulceration occurred increased by approximately 13% in both treatment groups; from 2500 to 3750 cGy, the percentage in the benzydamine group increased only another 1% in contrast with the 11% increase in the placebo group; and at 5000 cGy, the percentage of oropharyngeal areas at risk that developed ulceration increased to 20% in the benzydamine group compared with 29% in the placebo group (Fig. 1). Thus, from 0 to 5000 cGy, the extent of mucosal ulceration in the benzydamine group never reached the severity observed in the placebo group. Notably, greater than 33% of benzydamine-treated subjects did not develop any mucosal ulceration compared with approximately 18% of placebo-treated subjects (P = 0.037).

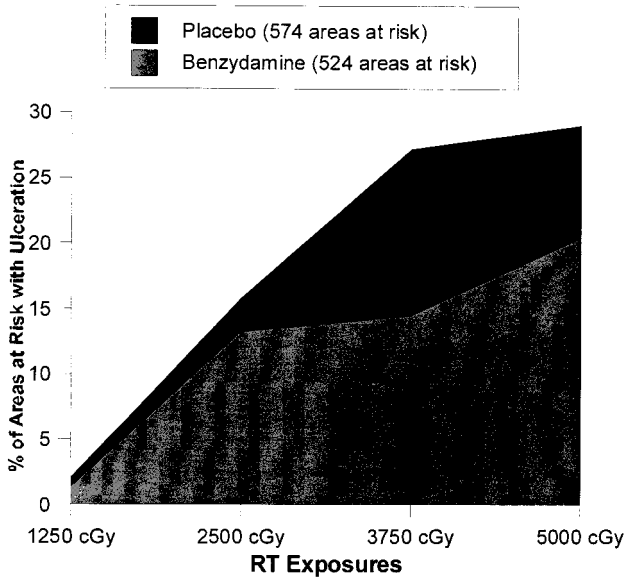

FIGURE 1. Percentage of areas at risk with ulceration per treatment group at specific cumulative radiation exposures. Conventional RT subgroup (n = 145; 56 benzydamine, 60 placebo). RT: radiation therapy; cGy: centigray.

In the benzydamine group receiving conventional RT, there was also a statistically significant delay in the use of concomitant systemic analgesics (Fig. 2). At a cumulative RT dose of 5000 cGy, at all 3 levels of analgesics, statistically significantly fewer benzydamine-treated subjects required concomitant systemic analgesics compared with the placebo-treated subjects. For mouth pain at rest in patients receiving conventional RT, benzydamine produced a 25.8% reduction in AUC (P = 0.064) versus placebo over the RT

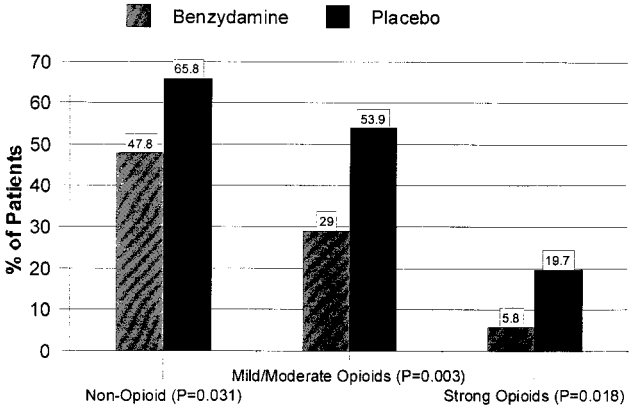

FIGURE 2. Percentage of subjects using systemic analgesics to 5000 centigrays. Conventional radiation therapy subgroup (n = 145; 56 benzydamine, 60 placebo). Log-rank test comparisons between treatment groups.

interval of 0–5000 cGy; for throat pain, a 22.5% reduction in AUC (P = 0.064) was noted. Pain during meals was not effectively reduced by the use of benzydamine compared with placebo.

In the treated population, overall mean weight loss from baseline in both treatment groups at 5000 cGy was approximately 3.0 kg, with no significant difference between the groups. Fewer subjects treated with benzydamine suspended RT because of the complications of oral mucositis compared with placebo (7.6% vs. 10.5%, respectively; P = 0.595). Also, during the study fewer benzydamine-treated subjects required either nasogastric or percutaneous endoscopic gastrostomy tube feeding because of effects of oral mucositis (12.7% benzydamine vs. 18.6% placebo).

Safety Results

As shown in Table 1, 44 subjects (22 [26%] in the benzydamine group and 22 [25%] in the placebo group) did not complete the study. There was no significant difference between treatment groups for early discontinuations. One death occurred during the study in a placebo-treated subject, and cause of death was related to the primary diagnosis (i.e., head and neck carcinoma).

Most subjects in both treatment groups experienced at least one adverse event (AE), the highest percentages being in the digestive system, in which 87% of benzydamine subjects and 91% of placebo subjects experienced an AE. Of the 125 AEs possibly and probably related to the study medication (benzydamine or placebo), most (73; 58%) could be attributed to the expected local pharmacologic actions of the study drug and vehicle on inflamed mucous membranes (i.e., oropharyngeal burning, numbness/tingling, taste loss, and taste alteration), whereas approximately half of the remaining possibly and probably related AEs (24, or 19%) were nausea and vomiting, which are commonly associated with RT. Most (> 85%) of AEs reported for the treated population were either mild or moderate in severity. There was no evidence of a differential effect on the treatment groups with respect to salivary production: the incidences of dry mouth in the benzydamine (60%) and placebo (52%) groups were not statistically significantly different (P = 0.360), and the severity and number of reports were comparable.

Comparisons of the clinical laboratory results showed no differences in hematology, serum chemistry, urinalysis, or endocrine (i.e., thyroid-stimulating hormone) values.

DISCUSSION

Assessing mucositis in subjects treated with head and neck RT requires consideration of the areas included in the irradiation fields that are at risk of tissue reaction. In this randomized study, the 145 subjects receiving conventional RT presented a total of 1098 areas at risk for developing radiation-induced mucositis (524 in the benzydamine group, 574 in the placebo group).

The four-point mucositis scale, which has been used in other studies of a variety of ulcerative conditions of the mouth,[35] was used here because of its simplicity, because it scored ulcerative lesions and inflammation (erythema) separately, and because it was restricted to objective anatomic-pathologic findings and excluded concomitant evaluation of functional symptoms. By comparison, the World Health Organization Index[36] scores signs (oral lesions) and symptoms (eating behavior) concurrently. In addition, the primary symptom of mucositis, pain, was assessed separately in the present trial using a variety of pain scales and through monitoring the use of systemic analgesics. Use of AUCs to evaluate mucositis, taking into account the cumulative RT dose and the course of development of mucositis with increasing RT exposure, allowed comparison of the incidence, onset, and severity of radiation-induced effects between the treatment groups.

Recognizing that fewer patients were stratified to the accelerated RT (20 patients) or to conventional RT regimens with concurrent chemotherapy (10 patients), benzydamine oral rinse was effective in a variety of RT regimens except single daily doses greater than 220 cGy. These data suggest the existence of a threshold beyond which the oral rinse did not control the cascade of inflammatory events associated with high single daily RT doses.

The radiation exposure at which mucosal ulceration first developed was similar in both treatment groups up to 2500 cGy; however, beyond 2500 cGy exposure, the distributions diverged in favor of benzydamine. At the last 2 RT intervals, treatment with benzydamine produced statistically significant reductions in mucositis compared with placebo of 36% (2500–3750 cGy) and 25% (3750–5000 cGy). This differential effect with increasing cumulative RT doses is of clinical significance because it is during these final two cumulative radiation intervals that mucositis reached peak severity in the placebo group (i.e., AUCs of >1400). In addition, from 0 to 5000 cGy, the extent of mucosal ulceration in the benzydamine group never reached the severity observed in the placebo group. This effect can be described as a true "preventive" (although incomplete) effect of benzydamine compared with placebo. In fact, greater than a third of the benzydamine-treated subjects did not develop mucosal ulceration compared with approximately 18% of placebo-treated subjects ($P = 0.037$).

In addition, the results showed that treatment with benzydamine produced statistically significant reductions in the use of systemic analgesics during RT at all three levels of analgesics. The reduction in the number of oropharyngeal areas affected by ulceration may explain the reduced use of analgesics in the benzydamine group. Also, the topical analgesic effect of benzydamine may have affected the pain experience.

Because pain scale assessment is affected by the effectiveness of pain management provided, we anticipated that despite differences in the use of analgesics between treatment groups, pain control could be achieved to the same extent in the overall study population. However, the reduction in mouth pain at rest observed with benzydamine compared with placebo (25.8%; $P = 0.064$)—despite a delayed use of analgesics in the benzydamine group compared with the placebo group—is important because it signifies that during the RT interval up to 5000 cGy the benzydamine subjects experienced less intense pain and used less analgesic medication. Mouth pain was expected to be more likely affected by the topical analgesic and anti-inflammatory effects of benzydamine because of greater exposure of the oral cavity during rinsing compared with the oropharynx. Nevertheless, throat pain also was reduced with benzydamine compared with placebo from up to 5000 cGy (22.5%; $P = 0.064$). Pain on swallowing was not different between treatment groups, an expected finding because benzydamine was not likely to reach the esophagus in sufficient concentrations. The current study supports the findings of prior study of benzydamine in prophylaxis of mucositis during RT[2–4] and pain.[4]

Weight loss, RT suspension or discontinuation, and the need for enteral supportive nutrition have been used as outcome measures in the assessment of topical treatments such as chlorhexidine[37] and sucralfate[38] mouthwashes. On-study weight loss of 10% or more is generally considered of clinical significance,[37] although in our study this did not occur in either treatment group. Nearly 50% of patients may require suspension of RT because of severe mucositis,[38] and nasogastric tube placement during RT has been reported in up to 20% of patients receiving 6000 cGy.[38] Although our results of reduced incidence of RT suspension and enteral nutrition in the benzydamine group were not statistically significant, the trend in favor of benzydamine treatment despite low incidence in both groups has a potentially significant impact on quality of life and cost of care. Study outcomes (i.e., minimal weight loss, small percentage of RT suspensions, and small percentage of subjects requiring enteral supportive nutrition, all irrespective of study treatment) may support the hypothesis formulated by Feber[39] that frequent use of saline solutions, or "inactive" medications, alone can account for a beneficial therapeutic effect in patients experiencing oral mucositis. It therefore is reasonable to question whether the placebo formulation used in this trial could be considered as truly inactive. Thus, it is possible that the benzydamine group was compared with an "active" placebo group and not to a true "placebo" population. Despite the plausible therapeutic activity of the control, benzydamine was still superior to placebo in terms of both prevention of ulceration and control of pain.

Benzydamine 0.15% oral rinse was safe and well tolerated in this study. No drug-related trends were apparent in the incidence of AEs, and incidence rates between treatment groups were highly comparable without statistically significant differences. Diagnoses of oral candidiasis were included in AE reports. Twenty-one percent of benzydamine-treated subjects developed oral candidiasis compared with 31% using placebo (based on AE data; finding not statistically significant), suggesting that benzydamine may provide an antifungal effect as has been suggested in the literature.[40–42] A potential reduction in infection due to *Candida* may have implications for patients receiving head and neck irradiation in whom oral colonization and clinical infection increases throughout the course of RT and continues after therapy if xerostomia persists.[43–45] Although systemic pilocarpine has no known direct effect on oral infections,[46] a recent report indicates that in patients with impaired salivary flow, long-term use of pilocarpine doubled salivary flow rate and was associated with reduced *Candida*

albicans levels and reduced clinical manifestations of infection.[47]

The results of this study support routine prophylactic use of benzydamine 0.15% oral rinse in patients with head and neck carcinoma receiving a variety of RT regimens. In this study, benzydamine was not effective at single daily RT doses beyond 220 cGy.

REFERENCES

1. Silverman S Jr. Oral cavity toxicity. In: John MJ, Legha SS, Phillips TL, editors. Chemoradiation. Philadelphia: Lea & Febiger, 1993:511–523.
2. Kim JH, Chu F, Lakshmi V, Houde RA. Benzydamine HCl, a new agent for the treatment of radiation mucositis of the oropharynx. *Am J Clin Oncol* 1986;9:132–4.
3. Prada A, Chiesa F. Effects of benzydamine on the oral mucositis during antineoplastic radiotherapy and/or intra-arterial chemotherapy. *Int J Tissue React* 1987;9:115–9.
4. Epstein JB, Stevenson-Moore P, Jackson S, Mohamed JH, Spinelli JJ. Prevention of oral mucositis in radiation therapy: a controlled study with benzydamine hydrochloride rinse. *Int J Radiat Oncol Biol Phys* 1989;16:1571–5.
5. Spijkervet FKL, van Saene HK, Panders AK, Vermey A, van Saene JJ, Mehta DM, et al. Effects of chlorhexidine rinsing on the oropharyngeal ecology in patients with head and neck cancer who have irradiation mucositis. *Oral Surg Oral Med Oral Pathol* 1989;67:154–61.
6. Barker G, Loftus L, Cuddy P, Barker B. The effects of sucralfate suspension and diphenhydramine syrup plus kaolin-pectin on radiotherapy-induced mucositis. *Oral Surg Oral Med Oral Pathol* 1991;71:288–93.
7. Scully C, Epstein JB. Oral health care for cancer patients. *Oral Oncol Eur J Cancer* 1996;32B:281–92.
8. Alden ME, O'Reilly RC, Tophan A, Lowry LD, Brodovsky H, Curran WJ Jr. Elapsed radiation therapy treatment time as a predictor of survival in patients with advanced head and neck cancer who receive chemotherapy and radiation therapy. *Radiology* 1996;201:675–80.
9. Plevova P. Prevention and treatment of chemotherapy- and radiotherapy-induced oral mucositis: a review. *Oral Oncol* 1999;35:453–70.
10. Sonis ST, Peterson RL, Edwards LJ, Lucey CA, Wang L, Mason L, et al. Defining mechanisms of action of interlukin-11 on the progression of radiation-induced oral mucositis in hamsters. *Oral Oncol* 2000;36:373–81.
11. Sonis ST, Login G, Yamakawa M, Dorner A. The biological basis for interleukin-11 attenuation of oral mucositis [abstract 111]. Proceedings of the 11th Symposium Molecular Biology of Hematopoiesis, 1998.
12. Wardley AM, Booth D, Roberts SA, Scarffe JH, Potten CS. A quantitative histometric murine *in vivo* model of radiation-induced oral mucositis. *Arch Oral Biol* 1998;43:567–77.
13. Garg AK, Malo M. Manifestations and treatment of xerostomia and associated effects secondary to head and neck radiation therapy. *J Am Dent Assoc* 1997;128:1128–33.
14. Gifford GE, Lohmann-Matthes ML. Gamma interferon priming of mouse and human macrophages for induction of tumor necrosis factor by bacterial lipopolysaccharides. *J Natl Cancer Inst* 1987;78:121–4.
15. Cioli V, Corradino C, Scorza-Barcellona P. Review of pharmacological data on benzydamine. *Int J Tissue React* 1985; 7:205–13.
16. Hunter KM. A clinical evaluation of benzydamine hydrochloride. *Aust Dent J* 1978;23:164–6.
17. Kataoka S, Nishimura K, Naito T. *In vivo* metabolism and anti-inflammatory activity of benzydamine hydrochloride in rats treated with carrageenin. *Chem Pharm Bull* 1979;27: 2890–3.
18. Lisciani R, Scorza-Barcellona P, Silvestrini B. Research on the topical activity of benzydamine. *Eur J Pharmacol* 1968; 3:157–62.
19. Segre G, Hammarstrom S. Aspects of the mechanisms of action of benzydamine. *Int J Tissue React* 1985;7:187–93.
20. Whiteside MW. A controlled study of benzydamine oral rinse in general practice. *Curr Med Res* 1982;8:188–90.
21. White SK. The pharmacology of benzydamine. *Res Clin Forums* 1989;10:9–23.
22. Runti C, Baiocchi L. The chemistry of benzydamine. *Int J Tissue React* 1985;7:175–86.
23. Schubert MM, Newton RE. The use of benzydamine HCl for the management of cancer therapy-induced mucositis: a preliminary report of a multi-centre study. *Int J Tissue React* 1987;9:99–103.
24. Kim JH, Chu FCH, Lakshmi V, Houde R. Benzydamine HCl, a new agent for the treatment of radiation mucositis of the oropharynx. *Am J Clin Oncol* 1986;9:132–4.
25. Epstein, JB. Benzydamine HCl in the prevention of oropharyngeal mucositis in radiation therapy: literature review and clinical study. In: Dick WC, Bowsher DR, editors. Benzydamine: a topical NSAID. *Res Clin Forums* 1988;10:91–9.
26. Samaranayake LP, Robertson AG, MacFarlane TW, Hunter IP, MacFarlane G, Soutar DS, et al. The effect of chlorhexidine and benzydamine mouthwashes on mucositis induced by therapeutic irradiation. *Clin Radiol* 1988;39:291–4.
27. O'Sullivan B, Kroll B. Benzydamine hydrochloride for symptomatic relief of radiation mucositis in the treatment of advanced larynx cancer. In: Dick WC, Bowsher DR, editors. Benzydamine: a topical NSAID. *Res Clin Forums* 1988;10: 83–9.
28. Sonis ST, Clairmont F, Lockhart PB, Connolly SF. Benzydamine HCl in the management of chemotherapy-induced mucositis. *J Oral Med* 1985;40:67–71.
29. Sironi MK, Pozzi P, Polentarutti N, Benigni F, Coletta I, Guglielmotti A, et al. Inhibition of inflammatory cytokine production and protection against endotoxin toxicity by benzydamine. *Cytokine* 1996;8:710–6.
30. Sironi M, Milanese C, Vecchi A, Polenzani L, Guglielmotti A, Coletta I, et al. Benzydamine inhibits the release of tumor necrosis factor-alpha and monocyte chemotactic protein-1 by *Candida albicans*-stimulated human peripheral blood cells. *Int J Clin Lab Res* 1997;27:118–22.
31. Guglielmotti A, Aquilini L, Rosignoli MT, Landolfi C, Soldo L, Coletta I, et al. Benzydamine protection in a mouse model of endotoxemia. *Inflamm Res* 1997;46:332–5.
32. Beahrs OH, Henson DE, Hutter RVP, Myers MH, editors. American Joint Committee on Cancer manual for staging. 3rd ed. Philadelphia: JB Lippincott, 1988.
33. Million RR, Cassisi NJ, Wittes RE. Cancer of the head and neck (general principles of radiation therapy). In: DeVita VT, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 2nd ed. Philadelphia: J.B. Lippincott, 1985:416–29.
34. Cherny NI. The management of cancer pain. *CA Cancer J Clin* 2000;50:70–116.

35. Silverman S, Lozada-Nur F, Migliorati C. Clinical efficacy of prednisone in the treatment of patients with oral inflammatory ulcerative diseases: a study of fifty-five patients. *Oral Surg Oral Med Oral Pathol* 1985;59:360–3.
36. Dibble SL, Shiba G, MacPhail L, Dodd MJ. MacDibbs mouth assessment. A new tool to evaluate mucositis in the radiation therapy patient. *Cancer Pract* 1996;4:135–40.
37. Foote RL, Loprinzi CL, Frank AR, O'Fallon JR, Gulavita S, Tewfik HH, et al. Randomized trial of a chlorhexidine mouthwash for alleviation of radiation-induced mucositis. *J Clin Oncol* 1994;12:2630–3.
38. Makkonen TA, Bostrom P, Vilja P, Joensuu H. Sucralfate mouth washing in the prevention of radiation-induced mucositis: a placebo-controlled double-blind randomized study. *Int J Radiat Oncol Biol Phys* 1994;30:177–82.
39. Feber T. Management of mucositis in oral irradiation. *Clin Oncol* 1996;8:106–11.
40. Gunter J, Ault K, Dozier D, Faro S. *In vitro* benzydamine susceptibility testing with time kill assays [abstract]. First Annual International Infectious Disease Society of Obstetrics and Gynecology–USA Branch Meeting. Boulder, CO, April 27–28, 1996.
41. Molinari GL, Andreoni S, Fortina G. Bacterial and fungicidal activity *in vitro* of benzydamine hydrochloride. *Microbiol Med* 1993;8:180–3.
42. Zara C, Montanari L, Polatti F. Ultrastructural aspects of *Candida albicans* after benzydamine exposure *in vitro*. *Cervix* 1987;5:13–8.
43. Epstein JB, Chin EA, Jacobson JJ, Rishiraj B, Le ND. The relationship among fluoride, cariogenic oral flora and salivary flow rate during radiation therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998;86:286–92.
44. Epstein JB, Freilich MM, Le ND. Risk factors for oropharyngeal candidiasis in patients who receive radiation therapy for malignant conditions of the head and neck. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1993;76:169–74.
45. Ramirez-Amador V, Silverman S Jr., Mayer P, Tyler M, Quivey J. Candidal colonization and oral candidiasis in patients undergoing oral and pharyngeal radiation therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997;84:149–53.
46. Johnson JT, Ferretti GA, Nethery WJ, Valdez IH, Fox PC, Ng D, et al. Oral pilocarpine for post-irradiation xerostomia in patients with head and neck cancer. *N Engl J Med* 1993;329:390–5.
47. Rhodus NL, Liljemark W, Bloomquist C, Bereuter J. *Candida albicans* levels in patients with Sjogren's syndrome before and after long-term use of pilocarpine hydrochloride: a pilot study. *Quintessence Int* 1998;29:705–10.