ORIGINAL ARTICLE

The Effect of Supraphysiologic Levels of Iodine on Patients with Cyclic Mastalgia

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■ **Abstract:** A randomized, double-blind, placebo-controlled, multicenter clinical trial was conducted with 111 otherwise healthy euthyroid women with a history of breast pain. Patients had to document moderate or severe breast pain by recording a score ≥5 on a visual analog scale (VAS) of pain for ≥6 days per cycle and had to present with fibrosis involving at least 25% of both breast surfaces. Subjects could not be effectively treated with more conservative measures such as local heat or nonprescription analgesics. There was not a statistically significant difference in the dropout rate for patients on placebo (11.8%), 1.5 mg/day (31.3%), 3.0 mg/day (18.4%), or 6.0 mg/day (25%) of molecular iodine for 6 months. Physicians assessed breast pain, tenderness, and nodularity each cycle; patients assessed breast pain and tenderness with the Lewin breast pain scale at 3-month intervals and with a VAS at each cycle. A statistically significant improvement ($p < 0.01$) associated with dose was observed in the Lewin overall pain scale for all treated groups compared to placebo. Reductions in all three physician assessments were observed in patients after 5 months of therapy in the 3.0 mg/day (7/28; 25%) and 6.0 mg/day (15/27; 18.5%) treatment groups, but not the 1.5 mg/day or placebo group. Patients recorded statistically significant decreases in pain by month 3 in the 3.0 and 6.0 mg/day treatment groups, but not the 1.5 mg/day or placebo group; more than 50% of the 6.0 mg/day treatment group recorded a clinically significant reduction in overall pain. All doses were associated with an acceptable safety profile. No dose-related increase in any adverse event was observed. ■

Key Words: breast pain, cyclic mastalgia, iodine, Lewin breast pain scale, mastalgia, molecular iodine

The literature contains numerous studies investigating the interaction of iodine with breast tissue that suggest iodine is important for development and maintenance of the well-differentiated adult mammary gland. An iodine deficiency in rat causes tissue hyperplasia and areas of atypia in mammary tissue (1,2). Epidemiologic data suggest a relationship between regions of known endemic goiter (3,4) and breast health. Kato et al. (5) and Funahashi et al. (6) have reported a suppressive effect of iodine on induced mammary tumors in rats. Vishnyakova and Mura'yeva (7) treated 167 patients with daily doses of potassium iodide for 18 to 36 months and observed changes in breast pain and fibrosis. A positive effect, pain reduction, and disappearance of diffuse indurations and nodularity occurred in 120 patients and no effect was noted in 47 patients. Between 1975 and 1989 Ghent and Eskin (8) treated more than 1300 patients with a variety of iodine compositions and observed an improvement rate of 40 to 70% in subjective (pain) and objective (fibrosis) symptoms. While these studies strongly suggest that iodine can have an impact on breast tissue, there is no agreement on the mechanism of action for this effect.

The literature suggests that daily administration of supraphysiologic levels of iodine for 6 months can remediate breast pain in a majority of women with clinical cyclic mastalgia associated with fibrocystic breasts. However, to date, there has not been a controlled multicenter trial with a well-characterized dosage form of iodine to determine whether there are benefits to patients over and above placebo effects. In addition, if iodine is shown to be beneficial, there are no clinical studies that provide information concerning the optimal dose of iodine for treating breast pain. Patients selected for previous iodine-based trials exhibited some degree of palpable fibrosis, and in each of these studies, reductions in nodularity were correlated with pain reduction, although the duration of treatment required to reduce nodularity was significantly longer than that for pain.

Ader and Shriver have gathered comprehensive prevalence data on mastalgia (9) in a U.S.-based obstetrics/gynecology (OB/GYN) clinic setting. Moderate or severe breast pain for at least 7 days per cycle was reported by 11% of subjects, and fibrosis was present in 35% of this population. The overwhelming majority of these patients

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are successfully treated by reassurance, but approximately 5% of these patients experience breast pain that is severe enough to cause relationship problems within the family (10). The average duration of severe mastalgia is more than 8 years (11), and a recent review (12) concluded that the needs of these patients are not addressed in the United States. Clinicians in the United Kingdom have derived a structured treatment algorithm from a series of clinical studies spanning more than 30 years (10,13). Unfortunately the U.S. standard of care for this condition is undetermined, and Mansel (14) has speculated that this is because of a difference in attitude between physicians in Europe and the United States as opposed to any medical considerations.

This study was conducted to determine if daily administration of supraphysiologic levels of iodine have an effect on patients with clinical cyclic mastalgia, as previously suggested in the literature. The primary hypotheses for this study are (a) patients treated with iodine will exhibit a greater decrease in breast pain than women treated with placebo; (b) there will be a dose-related effect for iodine, such that patients treated with lower doses will report less benefit than those treated with higher doses; and (c) any reductions in nodularity will be associated with pain relief and require at least 3 mg/day of iodine. In addition to testing the above hypotheses, this study determined the specific dose of iodine that produces the largest decrease in breast pain severity, as well as the safety of iodine as a treatment for breast pain.

MATERIALS AND METHODS

Subject Selection

Subjects needed to have a history of at least 6 months of moderate or severe breast pain and had to document a score ≥5 out of 10 on a visual analog scale (VAS) in a daily pain dairy at least 6 days per cycle. All potential participants had to present with at least several diffuse nodules or increased thickness of breast tissue involving at least 25% of both breast surfaces. The subjects ranged in age from 18 to 50 years and the women were otherwise healthy. Subjects could not be effectively treated with more conservative measures such as local heat, nonprescription analgesics, and/or nonsteroidal anti-inflammatory drugs (NSAIDs); subjects could continue to take nonprescription analgesics throughout the trial as needed. Subjects with a history of thyroid disease or out-of-range thyroid function tests (T_3, T_4, thyroid-stimulating hormone [TSH], positive thyroid peroxidase antibodies) were excluded, as well as those who were receiving treatment with any hormonal therapy (oral contraceptives, hormone replacement therapy, or progestin) that was started or changed within 6 months of enrollment. Subjects were also excluded for prior treatment with gonadotropin-releasing hormone (Gn-RH) agonists, danazol, tamoxifen, raloxifene, or bromocriptine within 3 months of starting the study. Of the 364 women who were screened, 253 failed to meet one or more of the criteria required for enrollment. Of the 111 patients enrolled and randomized, 24 participants discontinued early: 2 (11.8%) were in the placebo group, 5 (31.3%) in the 1.5 mg/day group, 7 (18.4%) in the 3.0 mg/day group, and 10 (25.0%) in the 6.0 mg/day group.

One hundred seven subjects had assessments by physicians at baseline and at least one postbaseline time point. The percentage of subjects who were assessed by physicians at baseline as either moderate or severe in all three categories of pain, tenderness, and nodularity ranged from 56.3% (9/16) for the 1.5 mg/day group to 70.6% (12/17) for placebo (Table 1). It was not possible to ensure that the monthly physician assessments were made during the luteal phase in every instance, and this probably contributed to the number of patients who were scored by physicians as none or mild for breast pain at baseline.

Study Drug

The active study drug (IoGen) is a novel iodine formulation based on sodium iodide and sodium iodate; these two food additives are generally regarded as safe for general consumption. The test article generates molecular iodine (I_2) in the stomach upon dissolution in gastric fluid. Molecular iodine was selected as the active iodine species since several studies (15,16) have demonstrated that molecular iodine is less thyrotoxic than iodide due to a different tissue distribution in mammals. The placebo and study drug were prepared with identical excipients, manufacturing process, and tooling. The study drug did not lose any activity when stored at 40°C at a relative humidity of 75% for 6 months or 25°C at a relative humidity of 60% for 24 months.

Measures

Physician Measures. Investigators performed categorical assessments of pain, tenderness, and nodularity within 10 days of menses using previously validated tools from the trials that led to U.S. Food and Drug Administration (FDA) approval of danazol for treatment of fibrocystic breast disease. Physicians scored pain and tenderness as

none, mild, moderate, or severe based on a discrete set of observations. Nodularity was scored as none (no nodules), few (one nodule), several, or numerous. Changes in clinical measures were assessed according to whether there was elimination, a decrease, no change, or an increase from baseline. Each symptom or finding was assessed separately for each breast. In subjects whose symptom intensity differed between breasts, symptoms were graded on the basis of the breast having the greatest degree of involvement. Physicians scored patients as improved if they exhibited a reduction in all three of the following variables: breast pain, breast tenderness, and nodularity. Physicians scored subjects as worsened if they exhibited an increase in one of these variables without an offsetting improvement (reduction) in another variable or if they exhibited an increase in two or three of the variables.

Self-Reported Measures of Breast Pain. The Lewin group's validated health-related quality of life (HRQoL) questionnaire was previously developed using the SF-12 Health Survey as a generic measure (17); specific breast pain-targeted scales were developed as part of this instrument. The Lewin HRQoL was self-administered at randomization (pretreatment) and after 3 and 6 months of double-blind therapy. The breast pain assessment in this HRQoL instrument was developed to provide a more comprehensive assessment of breast pain than that offered with a simple VAS.

The frequency and bothersomeness of four different breast pain symptoms were assessed in this instrument: dull aching pain, sharp shooting pain, pain from movement, and pain from pressure. Patients rated the frequency of these four symptoms as 1, never; 2, once or twice; 3, a few times; 4, fairly often; or 5, very often. Patients rated the bothersomeness of these four symptoms as 1, not at all bothersome; 2, slightly bothersome; 3, moderately bothersome; 4, fairly often bothersome; or 5, very often bothersome. The combined frequency and bothersomeness scores for each symptom have 25 possible outcomes that are scaled to yield a score that ranges from 0 to 100. An overall pain score is computed that is the mean composite score of the four individual pain symptom scores.

Study Procedures

The study was reviewed and approved by the Western Institutional Review Board, Olympia, Washington, for all 19 study sites. Subjects were recruited by media and were randomized to receive one tablet per day that delivered 0, 1.5, 3.0, or 6.0 mg of molecular iodine, according to a computer-generated randomization list in blocks of six in a dosing ratio of 1:1:2:2. The study period included an observational pretreatment menstrual cycle, a run-in menstrual cycle (cycle 1) during which all subjects received placebo tablets, six menstrual cycles of daily dosing with randomized drug (months 1–6), and a follow-up safety assessment 2 months after the last dose of study drug. Physician assessments were scheduled according to the menstrual cycle and performed monthly, within 10 days of menses, from cycle 1 through 7, and 2 months after administration of the last dose of study drug, and included a physical examination, breast evaluation, a chemistry profile, hematology analysis, urinalysis, serum α-HCG (human chorionic gonadotropin), and thyroid function tests (T_3, T_4, TSH, FT_3).

Laboratory Methods

Separate blood samples were drawn for chemistry profiles, thyroid function tests (TFTs), hematology analysis, urinalysis, serum α-HCG, and thyroid peroxidase antibodies (TPOAb); the medical monitor was the only person who reviewed the results of the TFTs. With the exception of TPOAb, samples were analyzed by Covance Classic Laboratory Services, Indianapolis, Indiana. TPOAb samples were analyzed at the Rochester Clinic, Rochester, Minnesota. Analysis of iodine in urine was performed with a validated method (18) by Sam Pino in the laboratory of Dr. Lewis Braverman at the Boston Medical Center, Boston, Massachusetts.

Overview of Data Analyses

Analyses were performed using data from all randomly assigned subjects who received at least one dose of study drug and had at least one postbaseline assessment and were considered evaluable. Missing postbaseline data were imputed with the last observation carried forward (LOCF). Patients who left the study prematurely were not replaced. Physician-assessed measures of efficacy were compared among the treatment groups and an analysis of patients who completed at least the month 5 physician assessment was performed using the Mantel-Haenszel chi-squared statistical test. The 5-month time point was selected because the literature suggests that this is the minimum treatment duration required to observe a reduction in nodularity. Data obtained from the HRQoL questionnaire were analyzed by using (a) *t*-tests to compare mean scale scores between the pooled treatment groups and the placebo group at baseline and at months 3 and 6, (b) the *t*-distribution with $n - 1$ degrees of freedom were used to compute confidence intervals, (c) the Student's *t*-test was used for pairwise comparison of regression slopes, and

Table 1. Demographic and Baseline Data for Randomized Subjects

	Placebo ($n = 17$)	1.5 mg ($n = 16$)	3.0 mg ($n = 38$)	6.0 mg ($n = 40$)
Age (years ± SD)	39.1 ± 8.0	38.9 ± 5.5	40.3 ± 7.5	38.4 ± 6.6
Body mass index (kg/m^2 ± SD)	23.8 ± 3.2	24.9 ± 4.4	24.2 ± 3.1	24.3 ± 3.6
Race				
Caucasian	16 (94.1%)	15 (93.8%)	34 (89.5%)	37 (92.5%)
Black	1 (5.9%)	0	1 (2.6%)	1 (2.5%)
Asian	0	0	1 (2.6%)	0
Hispanic	0	1 (6.3%)	2 (5.3%)	2 (5.0%)
Moderate/severe pain, tenderness, and nodularity at baseline	12 (70.6%)	9 (56.3%)	22 (57.9%)	27 (67.5%)

(d) an *F*-test to compare changes in mean scale scores among the different treatment groups. For each thyroid function test, an analysis of change from baseline to the minimum extreme value observed at any time point was conducted, as well as an analysis of change from baseline to the maximum extreme value observed at any time point.

RESULTS

Physician Assessments of Pain, Tenderness, and Nodularity

Ghent and Eskin (8) report that 6 months of therapy with iodine is minimally required to effectively reduce nodularity and that the optimum response requires 18 months of treatment. Table 2 shows the number of subjects that were scored by physicians as improved in all three categorical assessments after 5 months of therapy. Twelve subjects (seven who received 3.0 mg/day and five who received 6.0 mg/day) improved in all three of the physician-assessed categories (pain, tenderness, and nodularity) at the 5-month assessment point, although the difference in the frequency of improvement across groups was not statistically significant. None of the subjects in the placebo or 1.5 mg/day groups had such improvement. Of the 80 subjects who had all three clinical findings at baseline and who completed at least 5 months of double-blind therapy, 7 of 28 in the 3.0 mg group and 5 of 27 in the 6.0 mg group exhibited a reduction in all three physician-assessed variables compared to no subjects in either the placebo or 1.5 mg groups. This observation is consistent with prior observations that indicate 3.0 to 6.0 mg/day is the effective dose range for treating pain and fibrosis. When the placebo and 1.5 mg/day groups were combined and compared to the pooled 3.0 mg/day and 6.0 mg/day groups, a statistically significant difference was observed ($p < 0.02$) based on the physician's assessments.

Self-Assessment of Breast Pain

The Lewin overall breast pain scale ranges from 0 to 100, and a wide distribution skewed toward the lower values was observed at baseline. The lowest recorded Lewin overall pain score was 3 pain units and the highest score was 95; 42% of subjects scored 30 or less in Lewin overall breast pain; 25% scored 60 or more. This wide distribution in self-assessed pain at baseline was observed in a patient population that meets the traditional diagnostic criteria for clinical mastalgia based on VAS scores recorded in a daily diary. This apparent anomaly may be a consequence of the multicomponent nature of the Lewin overall breast pain scale. Subjects who do not experience a particular type of pain or who suffer primarily from one

Table 2. Number and Percent of Subjects Scored by Physicians as Showing Improvement in All Three Monthly Assessments[a]

	Placebo	1.5 mg	3.0 mg	6.0 mg	*p*
All randomized subjects who received at least one dose of study drug	0/17 (0%)	0/16 (0%)	7/38 (18.9%)	5/40 (13.2%)	0.145
All randomized subjects who completed the month 5 assessment	0/15 (0%)	0/11 (0%)	7/34 (20.6%)	5/31 (16.1%)	0.123
All randomized subjects who had pain, tenderness, and nodularity at baseline and completed the month 5 assessment	0/15 (0%)	0/10 (0%)	7/28 (25.0%)	5/27 (18.5%)	0.047
All randomized subjects who had moderate or severe pain, tenderness, and nodularity at baseline and completed the month 5 assessment	0/12 (0%)	0/9 (0%)	6/22 (27.3%)	5/27 (18.5%)	0.108

[a]Breast pain, tenderness, and nodularity.

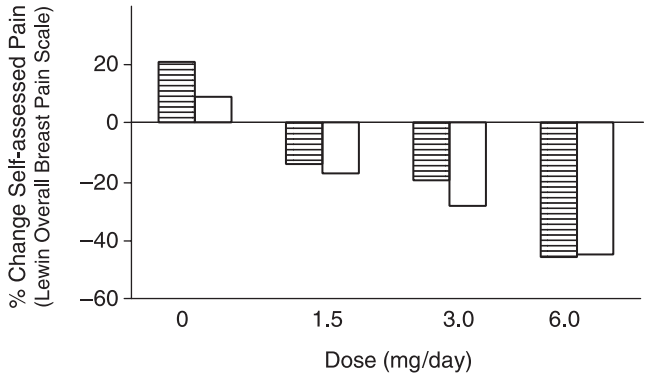

Figure 1. Mean percent reduction in self-assessed breast pain (Lewin overall pain scale) as a function of dose at 3 and 6 months.

or two of these symptoms cannot score as highly as those who are more severely affected.

At baseline, the placebo (mean overall pain 37.7) and pooled treatment group (mean overall pain 38.4) reported scores that were not significantly different across all four pain scales (data not shown). After 3 months of double-blind therapy, the pooled treatment group differed significantly from the placebo group with respect to dull aching pain ($p < 0.02$), sharp shooting pain ($p < 0.05$), pain during movement ($p < 0.02$), pain from pressure ($p < 0.05$), and overall pain ($p < 0.02$). Similar results were observed after 6 months of double-blind therapy, except that dull aching pain did not achieve statistical significance ($p > 0.10$).

After 3 and 6 months of double-blind therapy, subjects on placebo reported a slight increase, 20% and 8%, respectively, in Lewin overall breast pain as compared to a reduction reported in all treatments groups (see Fig. 1). The largest mean reduction in Lewin overall pain was reported by the 6.0 mg/day group and the magnitude of pain reduction increased with dose in a statistically significant manner at both month 3 ($p < 0.01$) and month 6 ($p < 0.01$). The majority of change in the Lewin overall pain scale occurred by month 3 for the three treatment groups, and all of the benefit in the 6.0 mg/day group was observed by month 3 (i.e., 45.4% and 45.0%, respectively).

Studies indicate that more than 95% of subjects would be satisfied with a 50% reduction in pain (19); Table 3 shows the percentage of each dose group that reported a reduction in overall breast pain of at least 50%. These values ranged from a low of 8.3% for the placebo group to a high of 51.7% for the 6.0 mg/day group at month 6. The percentage of responders increased with dose at months 3 and 6, and all treatment groups except placebo demonstrated an increase in this variable at month 6 as compared to month 3.

Table 3. Percent of Subjects with ≥50% Reduction in Self-Assessed Breast Pain in the Lewin Overall Pain Scale

	Placebo	1.5 mg	3.0 mg	6.0 mg
Month 3	8.3 (1/12)	23.0 (3/13)	30.0 (9/30)	37.9 (11/29)
Month 6	8.3 (1/12)	38.5 (5/13)	37.9 (11/29)	51.7 (15/29)

Comparison of Breast Pain Assessment by Physicians and Patients

Twelve subjects demonstrated a reduction in all three physician-assessed variables (pain, tenderness, and nodularity), 58 were scored as unchanged, and 27 as worsened. In all four of the Lewin breast pain symptom categories, the magnitude of the decrease (i.e., improvement) of the mean change was greatest for those subjects who were scored by the physician as a clinical success and smallest for those who were scored as worsening. This correlation was statistically significant for dull aching pain ($p < 0.002$), pain during movement ($p < 0.05$), pain from pressure ($p < 0.02$), and for the composite score of overall pain ($p < 0.01$). There was a statistically significant ($p < 0.001$) correlation at baseline between the categorical pain assessments made by physicians and patient self-assessment for the four individual pain scales in addition to the overall Lewin pain scale; this relationship was maintained even as subjects moved between categorical rankings, month 3 ($p < 0.001$), and month 6 ($p < 0.001$).

A cohort analysis comparing the physician-assessed change in a patient's breast pain status (e.g., severe to mild, moderate to none) to the change in Lewin overall breast pain is shown in Table 4. The largest change in Lewin overall breast pain for those subjects who started the

Table 4. Cohort Analysis: Comparison of the Categorical Change in Physician Assessment versus the Quantitative Change in Self-Assessment with the Lewin Overall Pain Scale

Cohort ($n = 99$)	Sample size	Average change	Category change	Point change per category
Severe to moderate	8	–26.19	1	26
Severe to mild	3	–23.61	2	12
Severe to none	3	–54.17	3	18
Moderate to mild	24	–17.63	1	18
Moderate to none	8	–35.52	2	18
Mild to none	3	4.51	1	5
No change	29	1.88	—	—
Worsened	15	4.24	—	—

trial in either the moderate or severe pain category was observed for those who finished the trial with a pain assessment of none. Similar results were observed when this analysis was conducted based on physician-assessed tenderness (data not shown). These data from the cohort analysis suggest that the minimally clinically significant change in Lewin overall breast pain is about 15 pain units; 15.4% (2/13), 35.7% (5/14), 45.1% (14/31), and 51.6% (15/31) of subjects reported a change of at least 15 pain units from baseline to month 6 in the placebo, 1.5, 3.0, and 6.0 mg/day treatment groups, respectively. A change of five Lewin overall pain units in the region between 15 and 60 pain units corresponded to a change of 1 in a patient's VAS score.

Safety

The doses of molecular iodine administered in this study were not associated with increases in incidence, severity, and causality of treatment-emergent adverse events or clinically significant changes in laboratory parameters or vital signs compared to placebo. The 10 most frequently reported treatment-emergent adverse events were upper respiratory tract infection ($n = 29$; 26%), headache ($n = 23$; 20%), sinusitis ($n = 14$; 12%), nausea ($n = 11$; 9.9%), acne ($n = 10$; 9.0%), back pain ($n = 10$; 9.0%), diarrhea ($n = 10$; 9.0%), dyspepsia ($n = 9$; 8.1%), rash ($n = 9$; 8.1%), and abdominal pain ($n = 7$; 6.3%). Headaches were the only adverse event that occurred in a different proportion among the treatment groups; 41% of the placebo group reported headaches as compared to 6.3% of 1.5 mg/day group, 26% of the 3.0 mg/day group, and 12% of the 6.0 mg/day group ($p < 0.05$). There was not a statistically significant difference in the dropout rate for patients on placebo (11.8%), 1.5 mg/day (31.3%), 3.0 mg/day (18.4%), or 6.0 mg/day (25%).

No statistically significant change was observed in any of the five thyroid function tests (T_3, T_4, T uptake, TSH, and FT_3) for any treatment group, as the mean changes were all within the normal range and considered not clinically significant. No significant shifts either up or down in change from baseline to minimum or maximum were observed. No statistically significant differences among treatment groups were observed for mean change from baseline to minimum except for T_4 ($p < 0.05$). The largest mean change from baseline to the maximum value in TSH at any time point was 1.2 mU/ml for the 6.0 mg/day treatment group. Low TSH values were observed for eight subjects receiving molecular iodine; these returned to normal in all but one of the subjects within several months after discontinuation of therapy.

DISCUSSION

Several aspects of the current study are consistent with previously reported iodine-based trials. Ghent and Eskin (8) concluded (a) 3.0 to 6.0 mg/day of iodine are needed to provide relief from cyclic mastalgia; (b) the majority of pain relief is observed by month 6; and (c) the maximum reduction in nodularity requires 18 months of therapy, but some improvement is observable after 6 months. In the current study, more than 50% of the 6.0 mg/day subjects reported a ≥50% reduction in pain as compared to 8.3% in the placebo group. The observed reduction in breast pain demonstrated a dose-dependent trend when assessed by either descriptive (Fig. 1) or binomial (Table 3) statistics. In addition, improvement in physician-assessed nodularity and breast pain was not observed in this study at a dose less than 3.0 mg/day, as previously suggested. A direct comparison between this study and earlier trials is not possible because the duration of treatment in this study (6 months) was substantially less than that used in earlier trials (1.5–5 years). Nevertheless, assessments from both physicians and patients in this study are consistent with previously published reports that indicate iodine provides relief in the majority of women who experience chronic cyclic mastalgia associated with fibrocystic breasts. The 6.0 mg/day regimen provided the greatest relief and was not associated with any statistically significant increases in adverse events or statistically significant alterations in clinical chemistry parameters as compared to any other treatment group.

Cycle length in this patient population is believed to be more variable than normal, and a major difficulty in this study was ensuring that patient evaluations were performed during the luteal phase of their cycle. Approximately 11% of physician assessments were made after menses and it is likely that these protocol violations effected the evaluations, as relief is frequently felt following menses. Daily pain diaries are the standard means to diagnose and monitor breast pain patients, and such data would have provided additional assistance in the evaluation of patient responses. In addition, the assessment tool used for nodularity, while suitable for danazol, proved to be too insensitive to identify meaningful patient improvement in many instances. A nodularity assessment instrument that allows physicians to document improvements other than elimination of nodules to two or less would provide more meaningful data.

In contrast to prior trials with iodine, this study used validated instruments to gather data from both physicians and patients. Pain reduction was dose dependent, and a

clinically significant reduction in pain was observed in a statistically significant percentage (more than 50%) of the 6.0 mg/day treatment group. In addition, there was a statistically significant correlation between physician assessments and patient self-assessments. The data from this study are consistent with previous observations in more than 1300 patients and provide support for the efficacy of iodine in the treatment of chronic cyclic mastalgia. Additional iodine-based studies in women with clinically significant cyclic mastalgia associated with fibrocystic breast tissue may lead to a realistic treatment option (12) for these patients in the United States.

The only uncontested hormonal imbalance observed in these patients is an elevated prolactin (PRL) responsiveness to thyrotropin-releasing hormone (TRH), which is expressed in about 50% of subjects (20–22). The status of a patient's dynamic PRL release predicts their response to endocrine therapy (23,24), and normalization of this variable is correlated with pain relief (25,26). Measurement of basal PRL levels has yielded contradictory findings, but circulating hormone levels may not reflect activity at a target tissue as comparisons of PRL in sera and breast duct fluid indicate (27). Rose (28) demonstrated that lactogenic activity in breast ducts is significantly higher in cystic breast disease patients than in normal controls, in contrast to PRL measurements made on sera. Vizoso (29) observed that the PRL response to TRH is significantly higher in women whose breast secretions contain milk proteins for both normal and fibrocystic breast tissue, suggesting that increased lactogenic activity is associated with this imbalance. The exaggerated PRL response to TRH may be an epiphenomenon, but the data suggest that cyclic mastalgia patients may well experience an elevated level of mammary stimulation from PRL. Active transport of iodide is under control of PRL in breast tissue (30) and atypical PRL stimulation of breast tissue would be expected to result in elevated levels of iodine in mammary tissue, as Kilbane et al. have observed (31).

Mammary and thyroid peroxidase oxidize iodide by transferring reducing equivalents from iodide to hydrogen peroxide. The mechanism of this reaction is uncertain, but it is clear that reactive intermediates are formed in the active site. Kinetic analysis (32,33) indicates that the initial concentration of iodide in these reactions largely determines if the reaction products will be directed toward iodination or coupling. Under elevated iodide concentrations, molecular iodine is formed and can diffuse from the active site. Model systems have been devised that rely on this extraenzymatic aspect of peroxidase chemistry to generate and control the concentration of molecular iodine (34). Inactivation of glucose oxidase (35) at elevated iodide concentrations has been attributed to molecular iodine or a reactive by-product. An increase in mammary iodide concentrations would be expected to result in increased iodination reactions in mammary tissue.

Molecular iodine, the putative iodinating species generated by lactoperoxidase, is a highly polarizable and hydrophobic molecule that is 50 to 100 times more soluble in organic solvents that water. Lactoperoxidase, like thyroid peroxidase, is a membrane-bound protein, and any molecular iodine that diffused from the active site could partition in the adjacent lipid layer; molecular iodine iodinates unsaturated double bonds of these lipids, leading to the formation of several different iodinated lipids. Boeynaems et al. (36) demonstrated the transformation of arachidonic acid into several different iodolactones by lactoperoxidase in a model system. Studies in thyroid tissue over the past 30 years (37–39) indicate that elevated iodide concentrations in the thyroid lead to the formation of multiple classes of iodolipids. Alpha-iodohexadecanol is believed to be involved in the autoregulation of specific thyroid functions mediated by the cyclic adenosine-3′,5′-monophosphate (cAMP) pathway (40). 6-iodo-5-hydroxy-8,11,14-eicosatrienoic acid δ-lactone has been identified in human thyroid tissue and has been shown to inhibit signal transduction pathways (39) induced by local growth factors such as epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF). Iodinated lipids appear to play a central role in regulating metabolic activity under high iodine loads in the thyroid.

The mammary tissue of women with clinical cyclic mastalgia may actively sequester iodine as a consequence of a subtle imbalance in the dynamic control of PRL. Increased levels of iodine, in turn, may lead to formation of iodolipids. The antiproliferative activity of iodolactones could be the basis for the reported effects of iodine on breast tissue and the effects observed in this trial, as previously suggested (3). The association of breast cancer with iodine intake or thyroid disorder has long been a topic of discussion (41–43). Stadel (43) first suggested chemoprevention trials with iodine in 1967. Venturi developed an evolutionary rationale relating iodine intake to cancer (44,45). Cann et al. (3,46) first suggested that iodolipids may be the basis for iodine-induced suppression of mammary hyperplasia and tumor growth that has been observed in animal models.

In contrast to prior suggestions, the concept proposed here is potentially relevant only to nonlactating women whose mammary tissue may be capable of concentrating iodine due to a subtle imbalance in PRL control. The use

of iodine in a patient population with cyclic mastalgia and clinically significant fibrocystic breast tissue could provide clinicians with a new tool to address the question of whether this combination of symptoms predisposes certain women to breast cancer as some believe (47–49).

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