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Effect of Leuprolide Acetate in Patients with Moderate to Severe Functional Bowel Disease

Double-Blind, Placebo-Controlled Study

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Moderate to severe functional bowel disease results in debilitating abdominal pain, nausea, intermittent vomiting, early satiety, bloating, abdominal distension, and/or altered bowel habits. Because it occurs ~20–30 times more frequently in women than in men and its symptoms often coincide with the menstrual cycle, we hypothesized that reproductive steroids may antagonize diseased nerves of the gastrointestinal tract, enhancing the expression of symptoms. No effective or consistent therapy has existed for these patients. We prospectively investigated the effect of a gonadotropin-releasing hormone analog, leuprolide acetate, in 30 women with symptoms of moderate to severe functional bowel disease. The study was phase II, randomized, double blind, and placebo controlled. Lupron Depot 3.75 mg (which delivers a continuous low dose of drug for one month) or placebo were given intramuscularly monthly for three months. Symptom scores were assessed at each four-week visit. Follicle-stimulating hormone, luteinizing hormone, estradiol, and progesterone levels were assessed before and after therapy. Patients treated with low-dose leuprolide improved progressively and significantly in scores for nausea, vomiting, bloating, abdominal pain, and early satiety, and for overall symptoms ($P < 0.01$–0.05). All hormone levels decreased significantly ($P < 0.05$) except luteinizing hormone ($P = 0.054$).

KEY WORDS: functional bowel disease; irritable bowel syndrome; leuprolide acetate; gonadotropin-releasing hormone; migrating motor complex.

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Chronic unexplained abdominal pain, nausea, intermittent vomiting, early satiety, abdominal distension and bloating, and altered bowel habits are common gastrointestinal symptoms of functional bowel disease (neuromuscular disease of the gastrointestinal tract, also called irritable bowel syndrome) (1–3). Functional bowel disease has been estimated to affect ~12–14% of the United States population (~31–33 million Americans) and constitutes almost one half of the practice of gastroenterology (4). These neuromuscular disorders have been termed "functional" because the patients of-

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ten complain of disabling symptoms in the absence of objective evidence from conventional laboratory, radiographic, and endoscopic testing. Specialized manometric and radiographic testing and transit studies now allow better definition of these diseases as malfunctions of the motility of the gastrointestinal system (5–9).

We have reported significant improvement in five women with severe and disabling symptoms secondary to severe functional bowel disease who were treated with leuprolide acetate on an open-label basis for one year (10). Before initiating this therapy, we had hypothesized that ovarian sex hormones, especially progesterone (11, 12), which is produced and secreted in the postovulatory phase of the menstrual cycle, act as endogenous antagonists of enteric nerve function. Thus, because the symptoms in these patients had been exacerbated during this phase of the reproductive cycle, we believed that they might benefit from therapy with a gonadotropin-releasing hormone (GnRH) analog such as leuprolide acetate.

Leuprolide acetate is a nonapeptide GnRH analog agonist with mechanisms of action similar to those of native GnRH. Native GnRH is a decapeptide (**pGlu^1-His^2-Try^3-Ser^4-Tyr^5-Gly^6-Leu^7-Arg^8-Pro^9-Gly^{10}-NH$_2$**) (13, 14) that is synthesized and stored in the neurosecretory cells of the medial basal eminence of the hypothalamus and then secreted into the hypothalamic–pituitary portal circulation (15). GnRH binds to specific receptors (16) on the gonadotrophs in the anterior pituitary to initiate secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (15, 16). FSH stimulates ovarian follicle growth and maturation in females and spermatogenesis in males, whereas LH stimulates ovulation and corpus luteum formation in females and testosterone secretion in males (16). In turn, these steroid hormones regulate GnRH secretion through closed-loop feedback mechanisms (17).

In women, native GnRH is secreted in a pulsatile manner, its peak occurring in the middle of the menstrual cycle (18). However, if GnRH is administered in a continuous dose, as in a daily injection or depot form, there is an initial rise in LH and FSH levels, followed about 7–10 days later by a gradual decrease in secretion of both hormones, which then remain at low levels thereafter (19, 20). This phenomenon, referred to as "down-modulation" or "desensitization," results in significant decrease or complete inhibition of sex hormones (19, 20). Desensitization has been applied clinically in various conditions (eg, hormone-dependent prostatic carcinoma in men, central precocious puberty, and endometriosis) and is currently being investigated for hypogonadism, uterine fibroid tumors, and polycystic ovary syndrome (21).

Several synthetic analogs/agonists of native GnRH have been made, most with changes at three positions of the molecule: at position 6, substitution of a D-amino acid (22), which decreases the analog's susceptibility to enzymatic degradation by peptidases in the hypothalamus (23, 24) and pituitary (25, 26); at position 10, a desgly-NH_2 deletion; and at position 9, addition of an ethylamide to the proline, which increases the binding affinity to gonadotropin receptors (27). Because these analogs are more potent than native GnRH, they are employed in various clinical situations (21, 28). Leuprolide acetate is one such analog agonist, with a substitution of D-leucine at position 6 and of an ethylamide at position 9 (29, 30); it is 15 times more potent than native GnRH and causes down-modulation of pituitary gonadotropins with inhibition of sex hormone production in humans and laboratory animals (16).

We report here the results of the first double-blind, placebo-controlled study using low-dose leuprolide acetate in depot form in 30 patients with moderate to severe functional bowel disease.

MATERIALS AND METHODS

Subjects. Thirty women between the ages of 20 and 52 were enrolled into the study; all had an intact reproductive system (one patient had had a unilateral oophorectomy with hysterectomy) and symptoms of chronic nausea, intermittent vomiting, chronic abdominal pain, and/or altered bowel habits. Informed consent was obtained from all subjects, and the study protocol was approved by the Institutional Human Research Review Committee of The University of Texas Medical Branch at Galveston on July 31, 1989. The patients were recruited from the Gastroenterology Clinic at the university, where they had been referred for evaluation of irritable bowel syndrome or functional bowel disease that was unresponsive to conventional medications; none had been previously treated with leuprolide. Each patient in the pretreatment phase was examined with a detailed history and physical examination; she was also examined by a board-certified gynecologist and found to lack any indication of endometriosis.

Study Design. The study was a phase-II, randomized, double-blind, placebo-controlled study of leuprolide acetate (Lupron Depot 3.75 mg, TAP Pharmaceuticals, Deerfield, Illinois) versus placebo in 30 patients with moderate to severe functional bowel disease. That each patient had a motility disorder was documented by duodenal–jejunal

TABLE 1. CLINICAL CHARACTERISTICS OF STUDY PATIENTS*

	Total patients (N = 29)	*Leuprolide (N = 14)*	*Placebo (N = 15)*
Sex, female	29	14	15
Race			
White	28	14	14
Black	1	0	1
Age (yr), mean ± SD	34.5 ± 7.4	33.0 ± 7.7	35.9 ± 7.0
Height (m), mean	1.63 ± 0.06	1.63 ± 0.05	1.62 ± 0.06
Weight (kg), mean	64.0 ± 18.3	57.9 ± 8.7	70.1 ± 23.2

*No differences between leuprolide-treated and placebo-treated patients were significant (P = 0.1–0.9).

manometry with an ultraminiature force-transducer probe (Millar Instruments, Houston, Texas) (31). The study began with a two-week, no-treatment lead-in period, during which the patient's gastrointestinal symptoms were evaluated. All patients were required to have had, for ≥6 months, symptoms of unexplained nausea, intermittent vomiting, early satiety or anorexia or both, bloating and distension, and (especially) unexplained abdominal pain before and after eating. On the entrance questionnaire, the patients had to have a total symptom score of ≥15 when each of the six symptoms was scored on a scale of 0 (no symptoms) to 10 (serious symptoms) and summed. The patients also assessed their own overall symptoms on the same scale at entrance and each subsequent visit. At entrance, each patient was required to have either esophagogastroduodenoscopy or an upper gastrointestinal x-ray series performed within six months before the first study visit, and either test must have been negative for active peptic ulcer disease, anatomical obstruction, esophageal stricture, or other gastrointestinal disease such as gastric or esophageal cancer or inflammatory bowel disease (Crohn's disease). Because we realized that leuprolide acetate would suppress a patient's gonadal hormones and thus affect her menstrual cycle, in order to keep the investigators "blinded," each patient was instructed from the beginning never to comment to us (the symptom assessors—J.R.M., P.H.R., and L.L.S.) about the status of her menstrual cycle. If a problem arose, she was to consult the gynecologist (N.J.S.), who was not involved in the assessment of patient symptoms. At no time during the study period was a patient's menstrual cycle discussed with or by us until the study was unblinded.

Randomized patients received either: (1) Lupron Depot 3.75 mg (a depot formulation that would continuously release a low dose of leuprolide acetate suspended in 1 ml of diluent over a period of one month) or (2) placebo-matching Lupron Depot (in 1 ml of diluent) by intramuscular injection monthly. An injection was given during treatment visit 1 and at weeks 4 and 8 of the study period. All subjects were required to use a barrier method for birth control during the 12-week study.

Biochemical Measurements. Clinical laboratory tests included a complete blood count, biochemical profile, and urinalysis (SmithKline Laboratory, Van Nuys, California). Gonadotropins (FSH and LH) and sex hormones (estradiol and progesterone) were measured by Endocrine Sciences (Calabasas Hills, California). The blood and urine tests were repeated at each treatment period (initial, 4, 8, and 12 weeks). During each visit, patient and investigator assessments of the patient's symptoms during the previous four weeks were made. A beta-human chorionic gonadotropin level for pregnancy, was performed at the pretreatment visit and at the end of the 12-week study. A hydrogen breath test (Quintron, Milwaukee, Wisconsin) was also performed to assess oral-to-cecal transit time and a Sitzmarks test (Lafayette Pharmacal, Fort Worth, Texas) was conducted to assess colonic transit time before starting the treatment phase and at the end of the 12 weeks. In the Sitzmarks test, a subject ingested a capsule containing radiopaque markers and then was given an abdominal x-ray every other day until all the markers had passed (or until day 9).

Statistical Analysis. Statistical analysis of the data was conducted by a professional statistician (P.H.H.) at Abbott Laboratories. Data from the symptom scores were analyzed with nonparametric techniques, using the Wilcoxon two-sample test and Wilcoxon signed-rank test. Data from the hydrogen breath test and Sitzmarks test were analyzed with ANOVA using the Kruskal-Wallis test. The global assessments of the patient and investigator symptom evaluations were analyzed by chi-square. For all tests, values of $P < 0.05$ were considered as statistically significant.

RESULTS

Clinical Characteristics. The clinical characteristics of the patient population are shown in Table 1. Thirty women were randomized to either leuprolide acetate therapy (N = 15) or placebo (N = 15); the two groups were not statistically significantly different in any of their characteristics. Data from one patient in the leuprolide group were excluded due to noncompliance. Another patient (placebo group), in whom cervical dysplasia was later found on pelvic examination, was also excluded from efficacy analysis. The age range of subjects was between 20 and 52 years; the mean ages, heights, and weights in both groups were similar.

Duodenal–Jejunal Manometry. Table 2 summarizes the results of the duodenal–jejunal manometry

TABLE 2. RESULTS OF DUODENAL-JEJUNAL MANOMETRY

Patient	Dysfunction		MMC characteristics			Fed-state conversion	Peristaltic rush frequency (0–3)
	Antral	Duodenal	Period (min)	Duration (min)	Propagation velocity (cm/min)		
1	yes	yes	58	4.5	*	yes	1
2	yes	yes	0	*	*	no	3
3	yes	yes	107	5.3	16.4	yes	1
4	yes	yes	108	8.1	8.7	yes	2
5	yes	yes	95	4.0	18.0	yes	1
6	yes	yes	133	5.4	*	no	2
7	yes	yes	240	4.3	*	no	0
8	yes	yes	81	7.9	14.2	yes	2
9	yes	yes	126	7.4	34.8	yes	3
10	yes	yes	127	4.7	10.5	yes	1
11	yes	yes	78	8.0	6.5	yes	1
12	yes	yes	95	2.7	22.2	yes	3
13	yes	yes	75	4.2	15.7	yes	3
14	no	yes	185	5.6	11.8	yes	3
15	yes	yes	69	3.3	*	no	3
16	yes	yes	100	3.6	14.3	yes	2
17	yes	yes	112	6.5	27.1	yes	3
18	yes	yes	778	3.5	*	no	3
19	yes	yes	155	5.9	37.3	no	1
20	yes	yes	128	5.7	11.0	no	1
21	yes	yes	134	8.6	11.1	yes	3
22	yes	yes	89	5.9	6.5	yes	1
23	yes	yes	157	5.9	*	yes	3
24	yes	yes	91	4.3	67.5	yes	1
25	yes	yes	249	6.5	17.9	yes	3
26	yes	yes	135	8.2	14.5	yes	2
27	yes	yes	0	*	*	no	0
28	yes	yes	162	7.5	31.1	yes	2
29	yes	yes	58	4.0	11.2	yes	3
Controls	no	no	94	6.4	8.2	yes	0

*Not measurable.

that was conducted for all subjects before the study began. Recordings were performed for 12 hr while patients were fasting (5, 31); a 3-hr recording then followed immediately after the patients had been fed a liquid meal (Ensure). The 15-hr records were assessed for dysfunctional motility patterns, the characteristics and numbers of migrating motor complexes (MMCs), whether or not the patient converted to a fed-state motility pattern after the meal, and the frequency of peristaltic rushes (rapidly propagating ring contractions). All patients showed signs of duodenal dysfunction, such as irregular contraction rhythms during the activity front of the MMC and contractions of >100 mm Hg in amplitude. Antral dysfunction [contractions <100 mm Hg and irregular (not 3/min) contractions at the beginning of an MMC activity front] was apparent in 28 of 29 patients. There was a wide difference from patient to patient in the number of MMC cycles that occurred per 12 hr, ranging from two subjects who had no MMCs to two who had 12 MMCs (period = 58 min); the mean for normal controls is 7.6 MMCs/12 hr. Eight of 29 subjects failed to convert to the fed state after the test meal. Gastrointestinal motor disease was diagnosed in all patients.

Symptom and Global Assessment Scores. Table 3 shows the symptom scores derived from the questionnaire at baseline and at weeks 4, 8, and 12. In contrast to the minimal change in the placebo-treated group, reductions in individual symptom scores for nausea, vomiting, bloating, abdominal pain, and early satiety were all statistically significant in the leuprolide-treated group ($P < 0.05$), as were the total symptom scores ($P < 0.01$). Even though the between-group difference was not statistically significant, the reductions in symptom severity showed progressive improvement with length of treatment (median change of −3.5, −12.0, and −14.5, respectively, at weeks 4, 8, and 12) in the leuprolide group. The placebo group showed no such increase in effectiveness (median changes of −2.0, −4.0, and −4.0, respectively, at weeks 4, 8,

TABLE 3. MEDIAN SCORES IN INDIVIDUAL CLINICAL SYMPTOMS AND TOTAL SYMPTOM SCORES

			Week		
		Baseline	*4*	*8*	*12*
Individual symptom scores (0–10)					
Nausea	Placebo	6	5	4.5	5
	Leuprolide	8	6	4.5a*	3b
Vomiting	Placebo	3	0	0	0
	Leuprolide	3	0	0	0*
Bloating	Placebo	7	8	7	7
	Leuprolide	7	6	4.5b	4.5a
Pain	Placebo	7	7	7	6
	Leuprolide	10	7a	7.5a	6b
Anorexia	Placebo	5	5	5	6
	Leuprolide	7	6.5	5.5	5
Early satiety	Placebo	7	7	6	5a
	Leuprolide	6.5	5	5	4.5a
Overall visit score	Placebo	8	7a	7	7
	Leuprolide	9	7b	6.5a	5b
Total symptom score (0–60):					
Placebo		34	36	31.5	31
Leuprolide		40	32	28b	21.5b

*a, $P < 0.05$, b, $P < 0.01$; Wilcoxon signed-rank test for absolute change from baseline equal to zero.

and 12) with length of treatment. The level of anorexia did not change significantly in either group.

At the end of the study each patient was asked to make an overall (global) evaluation about whether she thought she had improved, had deteriorated, or was unchanged (Table 4). Thirteen of the 14 evaluable patients (93%) treated with leuprolide improved ($P = 0.005$), compared with only five of 12 evaluable patients (42%) treated with placebo. The global evaluation independently assessed by the investigator was almost identical to the patient's evaluation (also yielded $P = 0.005$ for differences between treatments). Similar analysis of all 28 intent-to-treat subjects yielded virtually the same results (Table 4).

Adverse Effects. Table 5 shows the adverse side effects experienced by patients during the study. In general, the side effects were relatively few and similar for the two groups.

Gonadotropin, Estradiol, and Progesterone Levels. Table 6 shows the hormonal evaluation for the treatment groups at baseline and at the end of the 12th week. Serum FSH, estradiol, and progesterone levels significantly decreased ($P < 0.05$) in the leuprolide-treated group. LH also decreased and neared significance ($P = 0.054$). There were no

TABLE 4. GLOBAL EVALUATIONS

			Improvement			
	Deteriorated	*Unchanged*	*Minimal*	*Moderate*	*Marked*	*Percent improved*
Analysis of evaluable patients						
By patient						
Leuprolide	1	0	4	4	5	93*
Placebo	2	5	3	1	1	42
By investigator						
Leuprolide	0	1	4	4	5	93
Placebo	1	5	2	2	1	45
Intent-to-treat analysis						
By patient						
Leuprolide	1	0	4	4	5	93*
Placebo	2	6	3	2	1	43
By investigator						
Leuprolide	0	1	4	4	5	93*
Placebo	1	7	2	3	1	43

*$P = 0.005$, leuprolide-treated compared with placebo-treated; chi-square with $df = 1$.

TABLE 5. NUMBER OF PATIENTS WITH ADVERSE EFFECTS

Event	*Placebo*	*Leuprolide*
Backpain/headache	1	1
Migraine/hot flashes	2	3
Edema	1	0
Bone pain/tenosynovitis	2	0
Emotional lability	1	0
Insomnia/nervousness	2	0
Respiratory symptoms	1	3
Cystitis/hematuria/menorrhagia	1	2
No. patients with any signs or symptoms	7/15	7/14

significant changes in the placebo-treated group. Only the change in estradiol level was significantly different between the two treatment groups.

Hydrogen Breath and Sitzmarks Tests. The results of the hydrogen breath tests, in general, showed no statistically significant changes in oral-to-cecal transit in either group. The value for the leuprolide-treated group before therapy was 121.0 ± 6.8 min (mean ± SEM), which was reduced to 108.0 ± 7.8 min at the end of the 12th week; in the placebo-treated group the baseline value was 93.0 ± 7.2 min and increased to 103.0 ± 7.6 minutes at the end of the study. However, in the leuprolide-treated group, 38% became faster, 38% remained unchanged, and 23% became prolonged. These values were in contrast to the placebo-treated group where 54% remained unchanged, 38% became prolonged, and 8% became faster. Among those with values out of the normal range (90 ± 15 min), 50% converted to normal in the leuprolide-treated group and 29% converted to normal in the placebo-treated group.

The Sitzmarks tests showed shortened transit time among the leuprolide-treated patients compared with the placebo-treated subjects (64% vs 31%, $P < 0.107$). The test proved to be an unsatisfactory way to compare colon transit because multiple x-rays were required over a period of nine days.

Although not formally assessed by symptom score, bowel habits changed toward normal.

TABLE 6. HORMONE EVALUATION BEFORE AND AFTER 12 WEEKS OF THERAPY

Hormone	*Treatment*	*Week 0*	*Week 12*
Basal FSH	Leuprolide	6.8 ± 2.2	4.9 ± 1.4*
(mIU/ml)	Placebo	8.9 ± 1.9	6.6 ± 1.2
Basal LH	Leuprolide	8.6 ± 1.9	5.6 ± 1.3†
(mIU/ml)	Placebo	7.9 ± 1.7	7.9 ± 1.2
Estradiol	Leuprolide	5.3 ± 1.2	2.1 ± 1.4*
(ng/dl)	Placebo	4.8 ± 1.2	7.2 ± 1.3
Progesterone	Leuprolide	377.3 ± 145.9	28.0 ± 89.5*
(ng/dl)	Placebo	130.8 ± 132.0	243.0 ± 80.7

*$P < 0.05$.
†$P = 0.054$.

DISCUSSION

We originally postulated that the reason for these motility disorders being expressed 20–30 times more commonly in women than in men (10) was most likely their differences in reproductive physiology. Women produce substances in their ovaries, especially during the postovulatory state, that men do not. These substances, such as progesterone and perhaps others like relaxins and LH, antagonize the gastrointestinal tract (11, 12) and perhaps other hollow viscera. If the bowel and other hollow viscera are diseased from a unknown cause, or from such known causes as diabetes or connective tissue disease, symptoms of gastrointestinal and urinary dysfunction, for example, are expressed early in the disease process. Studies assessing intestinal transit by using a hydrogen breath test in women showed prolonged transit in the postovulatory phase of the reproductive cycle compared with the preovulatory period (11). In addition, prolonged transit was also present in women taking oral contraceptives and during pregnancy (12). Recently, Heitkemper and Jarrett (32) demonstrated that the symptoms in women with functional bowel disease occur after ovulation (midluteal phase) and increase up to the onset of the menses and then quickly decrease. In our clinical experience with functional bowel disease, the onset of symptoms or the worsening of symptoms almost always develops in the postovulatory phase of the reproductive cycle. These conditions always occur when progesterone and perhaps other ovarian hormones are at their highest levels of secretion. Ovaries, however, are important endocrine organs, producing substances that interact with other systems and contribute to their normal function or perhaps dysfunction. We believe these endocrine organs should not be removed without very specific reasons.

Progesterone is a potent provocative hormone. When we periodically give it to women on open-label leuprolide therapy to induce shedding of the endometrium, which we routinely do every four to six months, the patients' gastrointestinal symptoms quickly return and continue for the duration of progesterone treatment. In contrast, when we administer estrogen to similar patients to protect

against osteoporosis, their symptoms do not recur as a result of replacing estrogen inhibition. Estrogen is not an antagonist. Thus some, but not all, reproductive hormones in the woman can be potent antagonists of enteric nerve function.

We have also shown in a female rat model that leuprolide acetate restores normal motor function to the gastrointestinal tract through unknown neuromechanisms (33). We appreciate, however, that this mechanism of action is most likely a direct effect on enteric nerves because intraventricular administration of leuprolide in rats had little if any effect (34). Thus far, we have also reported leuprolide to restore normal motor function in a single human patient (35). How leuprolide affects the nerves at the cellular level is unknown, but in gonadotrophs the GnRH analogs are potent modulators of calcium metabolism.

This study is the initial double-blind, placebo-controlled study of the effect of Lupron Depot 3.75 mg on gastrointestinal disease. This formulation delivers a continuous, but low dosage of the drug. In our wide experience with women patients using leuprolide acetate on an open-label basis, 1.0–1.5 mg is needed daily to achieve therapeutic effect. This dosage is considerably greater than that released by Depot 3.75 mg. We therefore limited the participants to women with at least one functional ovary, recognizing from experience with other patients that women without ovaries, postmenopausal women, and men all may require two to three times the 1.0–1.5 mg/day dosage for therapeutic effectiveness. Higher dosages of leuprolide acetate are also needed in male and ovariectomized female rats to affect their intestinal motility (33). The population of patients selected for the double-blind study was therefore fairly homogeneous in age and symptomatic complaints. All patients showed abnormal gastrointestinal motility through duodenal–jejunal manometry. They all had symptom levels that were disabling, and 13 of 14 subjects responded to leuprolide therapy with significant and progressive improvement in their symptom scores.

In summary, low dosages of the GnRH analog leuprolide acetate significantly and progressively improved debilitating symptoms in patients with moderate to severe functional bowel disease. Leuprolide acetate seems not only to inhibit ovarian hormones that act as antagonists on the gastrointestinal tract and urinary bladder, but may also restore normal cycling motor activity by an as-yet-undefined neural mechanism.

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