Enteric-coated, pH-dependent peppermint oil capsules for the treatment of irritable bowel syndrome in children

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In a randomized, double-blind controlled trial, 42 children with irritable bowel syndrome (IBS) were given pH-dependent, enteric-coated peppermint oil capsules or placebo. After 2 weeks, 75% of those receiving peppermint oil had reduced severity of pain associated with IBS. Peppermint oil may be used as a therapeutic agent during the symptomatic phase of IBS. (J Pediatr 2001;138:125-8)

In their 1958 classic study of abdominal pain in children, Apley and Naish[1] reported that more than 10% of all school aged children have recurrent abdominal pain severe enough to interfere with their daily living. The terminology of RAP is going through conceptual changes, leading some authors to suggest several types of RAP.[2-4] *RAP* is a generic term and does not specify etiology. This study investigated patients with irritable bowel syndrome found within a broader RAP syndrome. In the last 3 years, IBS has been clarified as a neurobiologic disorder affecting the autonomic, neuroendocrine, and pain mechanisms. Symptoms can be sporadically severe or can be manifested as nagging abdominal pain, virtually on a daily basis. IBS is characterized by altered bowel habits with specific symptoms of diarrhea, constipation, abdominal distension, bloating, and urgency to defecate.[5]

Peppermint oil, the concentrated oil of the herb "Mentha Paprika L," has been claimed to have medicinal value for more than 4000 years. *The London Pharmacopoeia* in 1721 published a treatise on what was believed to be the oil's medicinal property. In the early 1800s, *The English Dictionary of Medical and Surgical Knowledge* described this essential oil as "an aromatic stimulant to allay nausea, relieve spasmodic pain to the stomach and bowels, expel flatus or cover the taste or the quality of gripping effects of other medicine."[6]

Recent literature has documented that peppermint oil both relaxes the lower esophageal sphincter and relieves symptoms of dyspepsia.[7] Peppermint oil may lead to a measurable reduction in colonic spasms during colonoscopy and barium enema examinations.[8-11] Peppermint oil acts as a calcium channel blocker in human and guinea pig intestinal smooth muscle.[12] The primary active ingredient of peppermint oil, the menthol component, is known to block the Ca^{2+} channels.[13,14] Westphal et al[15] reported that peppermint oil extracts, along with other herbs, demonstrated efficacy in relieving flatulence and colon spasms.

GSRS	Gastrointestinal Symptom Rating Scale
IBS	Irritable bowel syndrome
RAP	Recurrent abdominal pain

Several studies have demonstrated the variable efficacy of peppermint oil in adults with IBS.[16-20] A meta-analysis concluded that the "role of peppermint oil [in IBS] has not been established beyond a reasonable doubt."[21]

Delayed releasing mechanisms, such as paraffin capsules, have partially overcome esophageal reflux resulting from relaxation effects of peppermint oil on the lower esophageal sphincter. pH-dependent capsules that release the peppermint oil in the small bowel reduce IBS symptoms more effectively than other releasing mechanisms, suggesting a local effect on the small bowel.[16,22]

This study investigated the efficacy and clinical usefulness of pH-dependent, enteric-coated, peppermint oil

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capsules in the treatment of IBS symptoms in children.

METHODS

Patient Selection

The study initially enrolled 50 children previously diagnosed with IBS from 3 different study centers. All children met the Manning or Rome criteria for IBS.[5] Specific inclusion criteria included frequency of symptoms and regular pain through the preceding 2 weeks. Additional presenting symptoms included headache, vomiting, constipation, dizziness, pallor, nausea, and poor appetite. Children were excluded if they: (1) were <8 years of age, (2) weighed <30 kg, (3) were receiving medication for the treatment of IBS, (4) were receiving other medication that could affect abdominal symptoms, or (5) had other chronic diseases (eg, cystic fibrosis, Crohn's disease, Hirschsprung's disease).

The University Institutional Review Board and the Food and Drug Administration approved the study protocol. The study centers were the Pediatric Gastrointestinal Service at the University of Missouri-Columbia, the Pediatric Gastrointestinal Service at Georgetown University, and a private-practice pediatric gastrointestinal clinic in Charleston, South Carolina.

Protocol

The primary investigators obtained a standardized history and performed a physical examination concentrating on IBS and associated symptoms. Each potential participant and parent(s) were extensively interviewed. All recent medications were recorded. Attending clinicians used standardized treatment methods for patients who did not meet protocol criteria. The interview included history of gastrointestinal symptoms, food intolerances, and associated complaints. The clinicians also obtained a urinalysis, stool sample for occult blood and ova/parasites, and hematology profile; serum *Helicobacter pylori* screen, liver function tests, thyroid function tests, and radiography were also performed. Endoscopy and lactose hydrogen breath tests were performed depending on clinical need. Furthermore, the study design included socioeconomic status and life events for control purposes. Pre-trial and post-trial measures were recorded by the same investigator on day 1 and day 14. The measures included the following: (1) detailed neurologic examination, (2) the 15-item Gastrointestinal Symptom Rating Scale[23]; (3) a severity of symptom scale; (4) a change of symptom scale; and (5) questions to monitor other variables that may have affected study results (eg, intercurrent infections, life events). The primary investigator performed the neurologic examinations, which included evaluation of the sensorium, deep-tendon reflexes, cranial nerves, and cerebellar function. The GSRS is an interview-based 4-point rating scale with descriptive anchors. These anchors addressed duration and frequency of symptoms and impact on daily functioning. Typical symptoms in this 15-item scale included heartburn, nausea, vomiting, and urgency for defecation. The inter-rater reliability ranged from 0.92 to 0.94 for adult patients with IBS in prior studies.[23] The primary investigators piloted the GSRS in a group of 16 children, which paralleled our study group, and found a 0.84 inter-rater reliability coefficient.

Using a model derived from prior studies, the clinicians ranked the severity of pain on a scale of 1 to 5 (1 = excellent, 2 = good, 3 = fair, 4 = bad, and 5 = terrible) on day 1 and day 14 of the trial. Clinicians also ranked the change in symptoms (1 = much better, 2 = better, 3 = no effect, 4 = worse, and 5 = much worse) on day 1 and day 14.[16,17,20] The patients filled out a daily diary to report changes in severity of symptoms (modeled after the severity of symptoms scale), headaches, heartburn, flu-like symptoms, other side effects, worries, and compliance issues. The clinicians rehearsed these questionnaires with the patients and parent(s) on day 1. The clinicians taught the parent(s) to help in the completion of the diary. However, the parent(s) refrained from giving personal perceptions concerning the ranking of the symptoms.

Design

The study was a randomized, double-blind control trial of 2 weeks. Peppermint oil and placebo (arachis oil) treatments were prescribed provided under the trademark Colpermin, manufactured by Tillotts of Switzerland (dosage 0.2 mL or 0.1 mL 3 times daily). Each dose of Colpermin consisted of 187 mg of peppermint oil in a pH-dependent, enteric-coated, hard gelatin capsule that resists disintegration and release until it passes through the stomach and encounters an intestinal pH of 6.8 or higher.[22] Patients weighing more than 45 kg received 2 peppermint oil or placebo capsules 3 times a day. The smaller children, who weighed between 30 kg and 45 kg, received 1 capsule 3 times a day.

Statistical Analysis

SAS software (SAS Institute, Cary, NC) was used for the categorical data analysis; the Cochran-Armitage test was used to analyze the data.[24] The Cochran-Armitage test, a type of χ^2 test, factors in the amount of change that occurs from pre-trial to post-trial periods. The χ^2 test was used to determine the independence of the severity of pain and change of symptom scales. Typical χ^2 tables were treatment (peppermint oil vs placebo) by change in symptoms. The analysis performed on the GSRS and patient diaries was done with the Wilcoxon sum of squares (T) for non-parametric data because normality was not assumed in the study. All significance levels were set at $P < .05$.

RESULTS

We studied 42 patients; 8 patients of the original 50 withdrew from the study.

Reasons for withdrawing included long travel distances to the clinic (2 patients), the use of antibiotics such as erythromycin (2 patients), and inability to swallow pills (4 patients). These children were between the ages of 8 and 10 years. We analyzed data on socioeconomic status and other demographic variables obtained from these 8 patients. No significant differences were found between the patients who withdrew from the study and those who remained in the study.

The final study group had an age range of 8 to 17 years, with a mean age of 12 years. Congruent with previous studies, the results indicated a sex ratio of 60% females and 40% males[3,25]; 83% of the patients were white, and the remainder were African American. Socioeconomic status, sex, and severity of IBS symptoms showed no significant differences between the drug and placebo groups. Table I displays the percentage of patients who experienced IBS symptoms at the beginning of the study. Three patients in the peppermint oil group and 5 patients in the placebo group had endoscopy procedures; all showed no organic disease. Four patients in the peppermint oil group and 7 patients in the placebo group had a lactose breath hydrogen test; all results were negative.

At the conclusion of the 2-week trial, the peppermint oil group showed significant improvement; 76% of the patients receiving peppermint oil reported changes in the severity of symptom scale at the end of the 2-week trial compared with 19% receiving placebo (χ^2 [6, n = 42] = 12.6, $P < .001$) (Table II). Improvements in the change of symptom scale were reported in 71% of the patients receiving peppermint oil compared with 43% receiving placebo across the 2-week study period (χ^2 [6, n = 42] = 9.5, $P < .002$) (Table II).

The GSRS showed no significant differences between groups when summed across the 15 items. Symptoms such as changes in abdominal rumbling, abdominal distention, belching, gas, and heartburn exhibited no changes when peppermint oil was compared with placebo. The daily diary entries recorded by the patients indicated that the mean severity of pain symptoms in the peppermint oil condition was significantly lower than that in the placebo group (T [60] = 1.99, $P < .03$). This result demonstrated that peppermint oil reduced the severity of pain over the 2-week period as reported by the patients. The patient diary measures such as headaches, nose bleeds, and sinus problems showed no significant differences between the peppermint oil and placebo groups. No side effects were reported by either the investigator or patients during the 2-week study period. Lastly, the neurologic examinations on day 1 and day 14 showed no abnormalities in either of the study groups.

Table I. Clinical symptoms of all patients: Day 1

Symptom	No.	%
Abdominal pain	42	100
Changes in stool pattern (from diarrhea to constipation)	37	90
Abdominal rumbling	36	86
Gas	36	86
Nausea	26	62
Pellet stools	25	60
Belching	21	50
Urgency for defecation	21	50
Heartburn	14	33
Abdominal distention	10	24

Table II. Change in symptoms from day 1 to day 14*

Treatment		Much worse	Worse	No effect	Better	Much better
Peppermint oil	Frequency	0	0	6	6	9
	Percent	0	0	29	29	42
Placebo	Frequency	2	4	6	9	0
	Percent	10	19	28	43	0

*$P < .002$.

DISCUSSION

In this investigation, a pH-dependent peppermint oil capsule reduced the pain children experienced during acute phases of IBS as measured by the symptom scales and the daily diary. Peppermint oil did not reduce other symptoms of IBS in this short-term study. The total score of the GSRS showed no differences between the groups (ie, all 15 questions analyzed together). The analysis showed that peppermint oil did not alter heartburn, gas, urgency of stools, belching, stool pattern, or stool consistency. Peppermint oil blocks Ca^{2+} channels and reduces colonic spasms and associated pain. Because peppermint oil is also a mild topical analgesic, the releasing mechanism spreads the oil through the bowel, thus reducing pain. Long-term changes in motility, diarrhea, or fecal retention were not studied.

A larger multicenter study with peppermint oil is indicated, particularly in light of the complex factors potentially involved in studying IBS. Analysis of the data from our 3 varied participating sites indicated similar results from

each site as compared with the overall study. The smaller sample sizes from these 3 groups did not differ from the data from the overall study. Results of this study are also in agreement with other IBS research regarding the placebo response rate of approximately 40%.[17,19,22]

With regard to the safety or side effects of peppermint oil, this study found no adverse events. Previous studies have demonstrated a few side effects, including mild rectal burning, esophagitis, and allergic reactions.[16,17] Clinicians have proposed that these side effects were due to the menthol component of peppermint oil (ie, causing rectal burning) and to the capsules dissolving in the upper stomach causing local esophageal reflux.[16] Continued studies need to be done because safety of any treatment warrants persistent examination, especially in children.

In conclusion, peppermint oil reduced the pain associated with IBS. Other associated symptoms were not altered. Peppermint oil should be considered for the treatment of moderate levels of pain in children with IBS.

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