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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref: Expediente No. 00.093.154

Solicitud de patente titulada: "COMBINACIÓN FARMACÉUTICA ÚTIL
PARA EL TRATAMIENTO DE LA MOVILIDAD
GASTROINTESTINAL ALTERADA, SENSIBILIDAD DE
SECRECIÓN, O DESÓRDENES ABDOMINALES".

Solicitante: NOVARTIS AG.

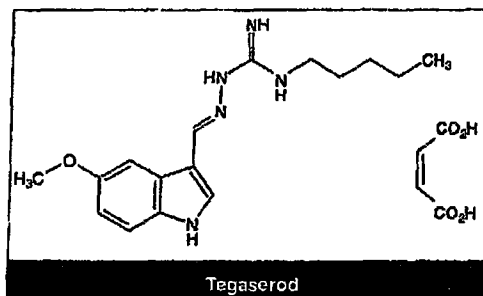
RESPUESTA AL AUTO NOTIFICADO POR ESTADO No. 293,
DE FECHA 24 DE AGOSTO DE 2006, OFICIO No. 9400
(EXAMEN DE BÚSQUEDA DE ANTERIORIDADES)

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal previsto en el artículo 46 de la Decisión 486, en los siguientes términos:

1. Me permito presentar los siguientes documentos exigidos por el Examinador en el examen de búsqueda de anterioridades realizado, según lo previsto en el Artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina:

i)

SCOTT & PERRY: "TEGASEROD"
DRUGS, AT, ADIS INTERNATIONAL LTD,
vol. 58, no. 3, 1999, pages 492-496,
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the whole document



Irritable bowel syndrome (IBS) is a common disorder in Western countries.^[1] Symptoms, which occur in the absence of any detectable biochemical or structural changes, involve a complex of gastrointestinal (GI) changes including disturbed defecation, bloating and abdominal pain.^[2-4] Although the pathophysiology of IBS is not fully understood, it is suggested that dysregulation of intestinal motor, sensory and CNS functions plays a key role; patients with IBS frequently have enhanced visceral sensitivity and hyperalgesia.^[2,4,5]

Several neurotransmitters, including substance P, calcitonin gene-related peptide (CGRP) and serotonin (5-hydroxytryptamine; 5-HT), are reported to be involved in the regulation of motility and pain in the GI tract.^[4,6] The presence of 5-HT receptors, including subtypes 5-HT₁, 5-HT₂, 5-HT₃ and 5-HT₄, throughout the GI tract and the high concentration of serotonin in gut enterochromaffin cells suggests that serotonin plays an important role in several physiological functions.^[4,6] Recent investigations^[4,7] have shown that 5-HT₄ receptors, which are also present in cardiovascular tissue, mediate the release of other neurotransmitters (e.g. CGRP and substance P) in the GI tract. In turn, these neurotransmitters are involved in the overall maintenance of gut motility and modulation of visceral nociceptive neural pathways.^[6] Thus, agonists acting at 5-HT₄ receptors have the potential to alter GI motility, modulate visceral sensitivity and potentially improve symptoms of IBS. Tegaserod, the focus of this profile, is an indole carboxaldehyde derivative [3-(5-methoxy-1H-indole-3-yl)methylene]-N-pentylcarbazimidamide

hydrogen maleate] and acts as a partial agonist at the 5-HT₄ receptor.^[8,9]

1. Pharmacodynamic Profile

In Vitro and *In Vivo* Studies

- Tegaserod bound with high affinity to 5-HT₄ receptors in sections of human brain tissue in a radioligand binding study.^[10] The mean binding affinity of tegaserod (pK_d values) for human 5-HT₄ receptors was 7.74 compared with 7.23 for cisapride, 6.0 for metoclopramide and 7.16 for serotonin. The distribution of tegaserod binding in human brain sections was similar to that observed with [¹²⁵I]SB 207,710 (a 5-HT₄ receptor ligand). Specificity of tegaserod binding was confirmed autoradiographically by displacement of [¹²⁵I]SB 207,710; this displacement was similar to that observed with serotonin.

- Tegaserod 0.1 to 10 µmol/L and its glucuronide metabolite 0.1 to 100 µmol/L had no effect on the QT interval in isolated rabbit hearts; tegaserod 50 µmol/L (500- to 1000-fold higher than therapeutic concentrations) increased the QT interval by 12% compared with the baseline value ($p < 0.01$ vs baseline; $n = 4$).^[11] In contrast, cisapride increased the QT interval by 13% at 0.1 µmol/L and >70% at 50 µmol/L. Alterations in the QT interval may cause slower repolarisation and lead to cardiac arrhythmias.

- Tegaserod increased the release of neurotransmitters *in vitro* from human jejunal segments and stimulated the peristaltic reflex.^[17] Tegaserod 1 µmol/L applied to the intestinal mucosa of isolated jejunal segments increased basal release of CGRP by 348%, of substance P by 216% and of vasoactive intestinal peptide (VIP) by 191%.

- In animals, tegaserod reduced the firing rate of spinal rectal afferents following rectal distension in a dose-dependent manner.^[12] The effective dose range with intravenous tegaserod was 0.3 to 1.2 mg/kg; half-maximal reduction in the firing rate was observed at a dose of 0.7 mg/kg. The reduction in firing rate was mediated via 5-HT₄ receptor stimulation; furthermore, it was not secondary to mod-

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ifications of the mechanical properties (compliance) of the rectal wall.^[12]

Healthy Volunteers and Patients with Constipation-Predominant Irritable Bowel Syndrome

- In a small double-blind trial, tegaserod 2mg twice daily accelerated small bowel transit (increased colonic filling at 6 hours; $p = 0.015$) and colonic transit time compared with placebo in patients with constipation-predominant IBS.^[13] Although the mean colonic transit time (measured using radiopaque markers) was similar in both treatment groups, there was a mean 20% increase in proximal colonic emptying (measured scintigraphically) with tegaserod compared with baseline values ($p = 0.05$; fig. 1). In this study, 24 patients (mean baseline colonic transit time of >40 hours) were randomised after a 1-week washout period to receive tegaserod or placebo for 1 week.

- In an exploratory pharmacodynamic study in which colonic transit was prolonged by dietary means, oral tegaserod 5mg twice daily significantly ($p < 0.05$) shortened total colonic transit time in 11 healthy male volunteers given fibre supplementation.^[14] Tegaserod 1 ($n = 12$), 5 ($n = 11$), 25 ($n = 12$) and 100mg ($n = 12$) twice daily reduced median total colonic transit time by 10, 22, 26 and 8 hours, respectively, compared with 16 hours in those receiving placebo ($n = 12$). In this randomised double-blind trial, total colonic transit time was assessed at the end of each of three 7-day intervention periods: a self-selected diet; followed by a liquid formula diet with fibre supplementation (FD); and then concurrent tegaserod with FD. It was suggested that the lack of significant effect at lower (1mg) and higher (25 and 100mg) doses of tegaserod may indicate a biphasic dose-response relationship to colonic transit time.^[14]

- In 24 healthy volunteers tegaserod 12mg reduced both the early [0.65 vs 0.44 (fraction of fasting volume); $p \leq 0.05$ vs placebo] and late (0.70 vs 0.84; $p \leq 0.05$ vs placebo) postprandial decrease in colonic tone.^[15]

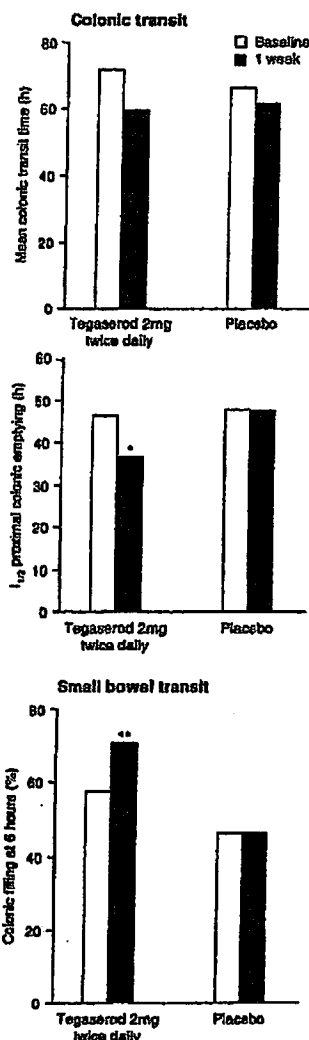


Fig. 1. Effects of tegaserod 2mg twice daily on small bowel transit and proximal colonic emptying in patients with constipation-predominant irritable bowel syndrome. Mean baseline colonic transit time was >40 hours. * $p < 0.05$ vs baseline; ** $p < 0.01$ vs baseline. Data are mean $\pm$ SD. The study was a randomised, double-blind, placebo-controlled trial. Patients received tegaserod or placebo for 1 week following a 1-week washout period. Proximal colonic emptying was measured scintigraphically and total colonic transit time was measured using radiopaque markers. Data are mean $\pm$ SD, adjusted for baseline.

• When compared with baseline, a single oral dose of tegaserod 12mg significantly increased ($p \leq 0.05$) colonic phasic motility in both fasting and fed healthy volunteers (12.3 and 12.8, respectively; $n = 18$); in contrast, placebo significantly increased ($p \leq 0.05$) colonic phasic motility only in fed volunteers (11.8 and 12.6; $n = 6$).^[15] Colonic phasic motility was measured by manometry and expressed as a motility index [$MI = \ln(\text{Amplitude} \times \text{number of contractions})$].

Patients with Gastro-Oesophageal Reflux Disease

• Exposure to oesophageal acid was reduced with tegaserod 1 ($p = 0.05$ vs placebo) and 4 mg/day in patients with gastro-oesophageal reflux disease.^[16] The percentage of time during the 3 hour postprandial period when distal oesophageal pH exceeded 4 was 5, 8, 13, 10 and 13% with tegaserod 1, 4, 12 and 24 mg/day and placebo, respectively. This reduction in acid exposure was not due to changes in lower oesophageal sphincter pressure (LES_p; measured by manometry); LES_p values with tegaserod 1, 4, 12 and 24 mg/day and placebo were 13, 10, 13, 13 and 14 mmHg, respectively.

2. Pharmacokinetic Profile

The pharmacokinetic properties of oral tegaserod have been investigated in healthy volunteers in single-dose^[17,18] and multiple-dose^[18] studies and in patients with renal insufficiency requiring haemodialysis^[19] or with hepatic cirrhosis^[20] in single dose, placebo-controlled studies. Volunteers received tegaserod twice daily for 5 days in the multiple-dose study.^[18]

Healthy Volunteers

- Maximum steady-state concentrations of tegaserod in plasma ($C_{\text{max,ss}}$) with 2, 6 and 12mg twice daily doses were 0.7, 2.7 and 5.6 $\mu\text{g/L}$, respectively.^[18] After single and multiple doses of the drug, C_{max} values were similar (data not presented).
- Areas under the plasma concentration-time curve over a 12-hour dosage period at steady state (AUC_{τ})

for tegaserod 2, 6 and 12mg twice daily were 2.4, 8.9 and 20.4 $\mu\text{g/L} \cdot \text{h}$.^[18]

• Dose-normalised AUC_{τ} and $C_{\text{max,ss}}$ values indicate that 2, 6, and 12mg doses of tegaserod demonstrate dose-proportionality and that there is no accumulation of the drug.^[18]

• Mean times to reach maximum plasma concentration of tegaserod over a 12-hour dosage period at steady state ($t_{\text{max,ss}}$) for 2, 6 and 12mg twice daily oral doses were 1.1, 1.0 and 1.3 hours, respectively.^[18]

• Oral tegaserod 12mg had a mean absolute bioavailability of 11%, a terminal elimination half-life of 11 hours, an apparent oral clearance (clearance/bioavailability) of 77 L/h, and an apparent volume of distribution at steady state of 368L.^[17]

Patients with Liver and Renal Dysfunction

• There were no significant changes in the pharmacokinetic parameters (C_{max} , t_{max} and AUC) of tegaserod 12mg in patients with severe renal insufficiency requiring haemodialysis^[19] or in patients with hepatic cirrhosis^[20] compared with healthy volunteers.

3. Therapeutic Trials

The clinical efficacy of oral tegaserod was assessed in patients with constipation-predominant IBS in double blind, dose-escalating^[21] (1 to 24 mg/day; discontinued prematurely for administrative reasons) and a dose-ranging trial.^[22-24] In the dose-ranging trial, patients received tegaserod 0.5, 2, 6 or 12 mg twice daily or placebo for 12 weeks. The primary end-points measured were considerable or complete relief from baseline in overall symptoms, abdominal discomfort (pain and bloating) and constipation.^[21,22,24] These were assessed using a 5-point ordinal Subject's Global Assessment (SGA) scale. The appropriateness of the SGA as a measure of efficacy was recently tested and validated versus other subjective measures (diary score of symptoms and SF-36 subscales).^[24]

• Tegaserod 2 ($p < 0.05$) or 6mg twice daily improved symptoms of abdominal discomfort, consti-

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pation and bloating in patients compared with placebo.^[22,23] In addition, tegaserod 2mg twice daily reduced the number of days per month that patients had significant pain from 14.6 to 10 days ($p < 0.05$ vs placebo). The clinical efficacy of tegaserod after 12 weeks of treatment is shown in figure 2.

- Tegaserod 0.5 and 2mg twice daily reduced the number of days per month with significant pain by 4.4 and 4.6 days, respectively, compared with placebo (reduced by 2.3 days), decreased the number of days per month with significant bloating by 3.3, 4.9 and 2.4 days, and decreased the number of days per month without bowel movement (median % change) by 29.8, 26.5 and 16.1%.^[24]

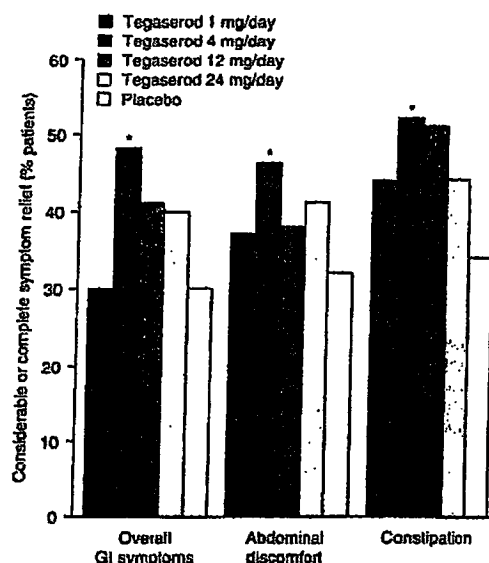


Fig. 2. Effects of oral tegaserod versus placebo on gastrointestinal symptoms after 12 weeks in patients with constipation-predominant irritable bowel syndrome.^[22] Patients received oral tegaserod 0.5 (n = 89), 2 (n = 87), 6 (n = 91) or 12mg (n = 90) twice daily or placebo (n = 93) in a double-blind, dose-ranging trial. Efficacy was assessed at monthly intervals using a 5-point ordinal Subject's Global Assessment scale for overall gastrointestinal symptoms, abdominal discomfort and constipation. The definition of considerable or complete symptom relief was not stated. * $p < 0.05$ vs placebo.

- In a dose-escalating study, tegaserod (mean dose 15.5 mg/day) significantly reduced discomfort compared with placebo at 20 weeks in 65 evaluable patients (50 vs 24%; $p = 0.05$); it also improved the SGA of overall symptoms (52 vs 29%; $p < 0.1$) and constipation (57 and 33%; $p < 0.1$).^[21] Increasing the dose of tegaserod from 12 to 24 mg/kg did not enhance efficacy (data not provided).

4. Tolerability

- The incidence of transient diarrhoea in patients with constipation-predominant IBS receiving tegaserod 2, 6 and 12mg twice daily was 26.2, 30.7 and 26.5%, respectively, compared with 12.8% for those receiving placebo (no data given for 0.5mg dose).^[22,23] The diarrhoea was transient and resolved spontaneously after a few days. Flatulence was also a common, but less frequent, adverse event. The incidence of nausea, abdominal pain and headache was reported to be similar to that with placebo.

- Tegaserod administered at dosages of 25, 50 and 100mg twice daily for 14 days caused no clinically relevant changes in blood pressure, pulse rate, QRS or QT_c interval in 24 healthy volunteers.^[25]

5. Tegaserod: Current Status

Tegaserod is a 5-HT₄ receptor partial agonist that stimulates the peristaltic reflex *in vitro* and shortens small bowel and colonic transit time in patients with constipation-predominant IBS. Tegaserod, which is in clinical development, effectively improves GI symptoms (including abdominal discomfort, bloating and constipation) in patients with constipation-predominant IBS.

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Selective 5-Hydroxytryptamine Type 3 Receptor Antagonism With Ondansetron as Treatment for Diarrhea-Predominant Irritable Bowel Syndrome: A Pilot Study

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Serotonergic innervation may contribute to the control of colonic motility and to visceral sensation from the large bowel. Indeed, ondansetron hydrochloride, a selective 5-hydroxytryptamine type 3 receptor antagonist, has been shown to slow colonic transit in healthy volunteers. Thus, we wished to determine whether 5-hydroxytryptamine type 3 receptor blockade slows colonic and small bowel transit in patients with diarrhea-predominant irritable bowel syndrome (IBS) and whether symptoms would be ameliorated with drug therapy. Of 14 patients with well-established IBS who entered a randomized, double-blind, placebo-controlled crossover pilot trial of 4 weeks of treatment with ondansetron, 16 mg three times daily, 11 completed the study. A minimal "washout period" of 4 weeks (median, 7 weeks) separated the two phases of the trial because patients were required to have similar symptoms before both periods of the study. Colonic transit tended to be longer during drug therapy than during the placebo trial, but this difference was not significant. Small intestinal transit and orocecal transit were unchanged by the drug. The integrated and peak postprandial increases in neurotensin, peptide YY, and human pancreatic polypeptide in serum were not significantly different in the drug and placebo periods. After treatment with ondansetron, stool consistency improved significantly; however, stool frequency, stool weight, abdominal pain, and the symptom criteria for IBS were not significantly altered by the drug. The results of this pilot study suggest that the motor effects expected with 5-hydroxytryptamine type 3 receptor blockade (namely, slowed colonic transit) may be diminished in some patients with IBS. The subjective improvement in stool consistency may reflect changes in the perception of defecation. Therefore, 5-hydroxytryptamine type 3 receptor blockade warrants further study in diarrhea-predominant IBS.

Irritable bowel syndrome (IBS) is a common disorder^{1,2} for which little selective therapy is available.³ Clinically, patients with IBS experience fluctuations in bowel habit, abdominal pain, and other symptoms^{2,4} in the absence of

an identifiable organic disease. Although a variable bowel habit is characteristic, subgroups of patients with IBS can be identified, including those with predominant diarrhea or constipation and also those with alternating bowel habits.^{2,4}

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Because the pathophysiologic features of IBS are poorly understood,^{2,7} most therapy is empirical. Abnormal contraction of intestinal smooth muscle may have an important role in producing the symptoms; thus, drug therapy is often aimed at modifying contractile activity. The efficacy of anticholinergic agents and tricyclic antidepressants (which have anticholinergic actions), however, has not been verified, and their side effects remain a problem.³ Intestinal

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smooth muscle is also under noncholinergic control, and 5-hydroxytryptamine is one of the putative alternative control systems.⁸⁻¹⁰ Drugs that interact with subclasses of the 5-hydroxytryptamine receptor and that affect the function of the gut have been developed. Previously, we reported that ondansetron hydrochloride, a new agent that selectively blocks 5-hydroxytryptamine type 3 receptors, prolonged colonic transit in healthy volunteers,¹¹ and this observation has been confirmed by other investigators.¹² Other 5-hydroxytryptamine type 3 receptor blockers have been shown to reduce visceral pain responses in the gut.¹³ We also observed in healthy volunteers that ondansetron decreased the postprandial integrated response and peak release of peptide YY^{11,14} and tended to reduce the peak release of neurotensin,¹⁴ but the clinical significance of these findings is unknown.

Our laboratory studies have shown that most patients with diarrhea-predominant IBS have accelerated transit through the proximal colon, and some patients have accelerated left colonic transit.¹⁵ Other investigators have demonstrated that many patients with IBS have an excessively sensitive colon.¹⁶ We hypothesized that ondansetron would not only slow colonic transit and thus decrease diarrhea but also block visceral hypersensitivity and thereby diminish pain in patients who experience diarrhea and pain as the main symptoms of IBS. Therefore, in this study our primary objective was to determine whether 5-hydroxytryptamine type 3 receptor blockade altered colonic and small intestinal transit and gastrointestinal release of peptide hormones in patients with diarrhea-predominant IBS. A secondary objective was to explore whether ondansetron altered symptoms in IBS.

STUDY SUBJECTS AND METHODS

Selection of Patients.—Patients with diarrhea-predominant IBS diagnosed at the Mayo Clinic were sought from the medical records. Those patients considered likely to fulfill the entry criteria were contacted by mail and, if they still were experiencing symptoms, were invited to participate in an interview. All candidates for the study had diarrhea (more than three stools/day when symptomatic) and abdominal pain. Patients were also required to have at least three of the following six specific symptom criteria for IBS:¹⁷ pain that was relieved by defecation, more frequent stools at the onset of pain, looser stools at the onset of pain, abdominal distention, passage of mucus per rectum, and a feeling of incomplete evacuation. Patients with a history of any gastrointestinal surgical procedure, organic gastrointestinal disease detected on prior investigation of bowel symptoms, other major medical conditions, psychiatric disease, salicylate or sulfonamide allergy, or notable abnormalities on physical examination were excluded from participation. Written in-

formed consent was obtained from all participants in the study.

Experimental Design.—The experimental protocol was approved by the Institutional Review Board and the Radiation Safety Committee of the Mayo Clinic. Ondansetron was administered in a dosage of 16 mg three times per day in a randomized, placebo-controlled, double-blind crossover trial, which consisted of two 28-day periods of therapy separated by a minimal "washout period" of 4 weeks. The second period of therapy was delayed for as long as was necessary to ensure comparable symptoms at the start of both phases. In each of the two therapeutic phases, patients ceased taking all medication for IBS 8 days before commencing the trial therapy and were counseled to standardize their diets by including 20 to 25 g of indigestible fiber per day.

Monitoring of Patients.—Seven days before the onset of therapy and on days 1, 14, and 28 of each phase of the study, patients were interviewed. All study participants completed a modified version of a self-report, standardized, previously validated bowel disease questionnaire that inquired about stool frequency, stool consistency, and abdominal pain during the prior week.¹⁸ In addition, they were questioned about any adverse events that might be related to therapy, underwent a brief physical examination, and were assessed for compliance by a tablet count of medication. Blood samples were withdrawn for hematologic and biochemical profiles. From day 1 to day 28 of therapy, a daily diary of symptoms—including the number of bowel movements, number of episodes of pain, severity of pain (from mild to very severe), and presence of symptom criteria for the diagnosis of IBS¹⁷—was completed. All patients were telephoned each week for assessment of compliance with diet and medications. Stools were collected for 24 hours before treatment was begun and on day 26 of each treatment period, and the stool weight was determined.

Gastrointestinal Physiologic Studies.—Each phase of therapy was terminated with physiologic studies of gastrointestinal function. On the final day of treatment (day 28), patients fasted and were admitted to the Clinical Research Center at 7:30 a.m. Colonic transit time was measured, by using the single abdominal x-ray technique after 20 radiopaque plastic markers had been taken at the same time on each morning of days 25 to 27 of therapy.^{11,19} After completion of the previously described monitoring procedures, the patients underwent fluoroscopically assisted duodenal intubation with a fine-bore tube (Keofeed II, 8-F diameter); a large vein in the arm was cannulated for sampling of blood. The study subjects then consumed 16 mg of ondansetron or placebo and, 10 minutes later, a standardized 378-kcal meal of beans, pork, toast, skim milk, and 7.5 g of lactulose. Immediately after the meal was consumed, 2 g of sulfasala-

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zine suspension was introduced into the duodenum through the oroduodenal tube, after which the tube was removed. After sulfasalazine is hydrolyzed by colonic bacterial enzymes, sulfapyridine is absorbed into the blood, where it can be detected spectrophotometrically.

In accordance with an established schedule, blood samples were obtained during fasting before the meal, every 10 minutes for 30 minutes, and thereafter every 20 minutes for 180 minutes. Subsequently, levels of gastrointestinal peptide hormones were measured. During fasting and after the meal, blood samples were obtained every 10 minutes for 420 minutes to measure serum levels of sulfapyridine. Paired breath samples were also taken every 10 minutes to measure the concentration of hydrogen.¹⁴

Previously described methods^{14,20} were used for measuring sulfapyridine levels, and a microlyzer (Quintron model 12) was used for determining breath hydrogen. The gastrointestinal peptide hormones neurotensin, peptide YY, and human pancreatic polypeptide were measured by specific radioimmunoassay (these peptide hormones had previously been evaluated in healthy volunteers).^{11,14} The time of first appearance of sulfapyridine in plasma was recorded as the small intestinal transit time,^{14,20} and the first sustained increase in breath hydrogen (more than 1-ppm concentration) was used to indicate the orocecal transit time.^{14,21}

Statistical Analysis.—The results were assessed for possible treatment (drug versus placebo) and order effects. For assessment of order, a two-sample *t* test or a signed rank test was used, whereas treatment effects were assessed by using a paired *t* test, signed rank test, or McNemar's test as appropriate. The complete sulfapyridine and hydrogen time curves were summarized by accumulating these values over time for each subject. These data were then proportionally scaled, with use of cumulative curves for both drug and placebo studies. A nonlinear model was used to summarize the cumulative appearance times; the estimated parameters were used to compute the time until 5% (± 0.05) and 15% (± 0.15) of the cumulative total were reached.¹⁴ The colonic transit times in drug and placebo phases were analyzed by using a paired *t* test.

We used a log transformation to combat skewness in the peptide hormone data. The hormone values were first adjusted to the overall (drug and placebo) mean baseline value, and then the mean (log) postprandial response and peak postprandial response in each study subject were computed. The mean (log) values were compared (drug versus placebo) by using a paired *t* test.

Symptoms recorded in the diary during the week before each treatment period and during the last week of each treatment period were summarized for each patient by totaling the number of occurrences of a particular symptom

(number of bowel movements, number of episodes of pain, and score for severity of pain) or combination of symptoms¹⁷ for the complete week. The weekly totals for symptoms were then transformed by calculating the square roots. A regression analysis (treatment score on baseline score) of these values compared the slope and the intercept estimates (drug versus placebo), accounting for the paired nature of the regressions.

All calculated probability values were two-tailed; the α -level of significance was 0.05.

RESULTS

All 14 patients (8 men and 6 women; 28 to 61 years of age) who entered the study had previously been diagnosed as having diarrhea-predominant IBS for more than 6 months and had no evidence of major organic disease on prior clinical assessment. Of the 14 patients, 11 completed the study; the median time to crossover in the experimental protocol was 7 weeks (range, 4 to 13 weeks).

Of the three patients who failed to complete the protocol, the first (a 32-year-old woman) was withdrawn from the study because she became pregnant during the ondansetron trial. Before onset of the drug therapy, contraceptives were being used, and a serum pregnancy test yielded negative results. A healthy male baby was born, who later was found to have congenital pyloric stenosis and underwent successful surgical treatment. The second patient withdrawn from the study was a 61-year-old woman in whom a small intestinal obstruction developed during the placebo trial; ondansetron therapy had been completed approximately 4 months previously. Laparotomy showed no pathologic changes except a large bolus of intact (unchewed) vegetable material impacted in the small intestine. The third patient, a 36-year-old woman, was withdrawn from the study because of multiple somatic complaints, including headache, dry mouth, and tiredness, that occurred soon after therapy with placebo was commenced.

Compliance.—On the basis of tablet counts, patients were compliant with the prescribed therapy. Only one man stopped taking trial medication for 1 week after his symptoms resolved on drug therapy, but he resumed his scheduled medications after counseling. A second man requested a decrease in dose after diarrhea changed to mild constipation (hard stools), but he remained compliant after counseling. No changes in results of routine laboratory tests could be attributed to ondansetron.

Colonic Transit.—We noted only a tendency for colonic transit to be delayed by ondansetron ($0.05 < P < 0.1$); the median total colonic transit time during administration of the drug was 25 hours and of placebo was 24 hours (Fig. 1). No significant order effects were detected. With 11 patients, the

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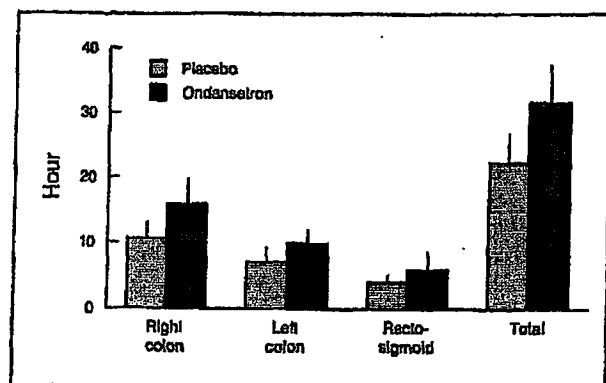


Fig. 1. Colonic transit times (mean + SEM) during ondansetron and placebo trials in 11 patients with irritable bowel syndrome. Although total colonic transit time tended to be prolonged during drug therapy ($0.05 < P < 0.1$), median total colonic transit times were 25 and 24 hours during drug and placebo trials, respectively.

power of the study to detect a 12-hour difference in colonic transit was greater than 80%.

Small Intestinal and Orocecal Transit.—The sulfapyridine and breath hydrogen appearances are summarized in standardized time curves in Figures 2 and 3. No significant order effects were detected, and the overall comparison failed to detect any differences in small intestinal or orocecal transit after treatment with ondansetron.

Responses of Peptide Hormones.—No significant differences were observed in circulating levels of neurotensin,

peptide YY, or human pancreatic polypeptide between drug and placebo trials (Table 1). No significant order effects were detected.

Stool Weight.—The mean stool weight was 191 g (SD 81) during ondansetron treatment but 286 g (SD 147) at the end of the placebo trial; this difference was not statistically significant. The stool weights were similar in the drug and placebo groups at the beginning of the study (mean values, 259 and 252 g, respectively).

Symptoms.—On the basis of the self-report questionnaire, the symptom responses at entry into the study and at the end of the drug and placebo trials were evaluated. During the week before the trial commenced, 8 of 11 patients who received ondansetron and 7 of 11 who received placebo reported loose or watery stools more than 25% of the time; during the last week of treatment, 1 of 11 patients who received the drug and 8 of 11 who received placebo reported this symptom. Thus, stool consistency improved more during drug therapy than during placebo treatment (McNemar's test, $P < 0.05$), and no significant order effect was detected for stool consistency. The median number of episodes of pain was decreased by ondansetron, but this difference was not statistically significant. An order effect was detected for abdominal pain; on analysis of data for the first period only, no significant difference was noted between drug and placebo.

The analysis of diary data for weekly total symptoms of IBS¹⁷ is summarized in Figure 4. Plotted on the y-axis is the square root of the weekly score for the treatment period and on the x-axis is the corresponding subjects' value for

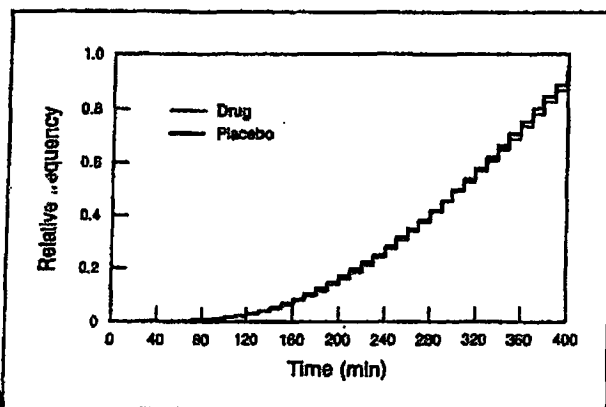


Fig. 2. Cumulative curves of concentration of sulfapyridine in serum after sulfasalazine was instilled into the duodenum in 11 patients with irritable bowel syndrome. Curve to the left represents results after ondansetron treatment; curve to the right represents results after placebo trial. No differences in time to 5% or 15% appearance were detected.

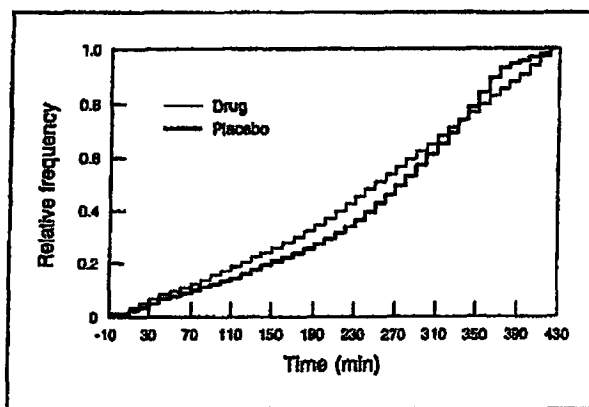


Fig. 3. Cumulative curves of concentration of hydrogen in expired air after an oral load of carbohydrate in 11 patients with irritable bowel syndrome. Curve to the left represents results after ondansetron treatment; curve to the right represents results after placebo trial. No differences in time to 5% or 15% appearance were detected.

Table 1.—Postprandial Responses* of Gastrointestinal Peptides After Administration of Ondansetron or Placebo

Peptide	Geometric mean responses, ng/ml over 210 min (95% CI)†		Median peak responses, pg/ml (interquartile range)	
	Drug	Placebo	Drug	Placebo
Neurotensin	48 (40-57)	48 (40-57)	80 (63-81)	71 (62-92)
Peptide YY	84 (72-98)	78 (63-95)	95 (81-127)	97 (74-128)
Human pancreatic polypeptide	164 (129-209)	162 (133-198)	268 (222-342)	270 (223-342)

*Response values at each sampling point were first adjusted to overall (drug and placebo) baseline values by using a linear regression analysis.

†CI = confidence interval.

the baseline week (before treatment). The equiangular line ($y = x$) and the estimated regression lines for drug and placebo periods are also plotted. Both regression lines were significantly different from the $y = x$ line ($P < 0.05$), an indication that "treatment" decreased the symptom scores. Ondansetron tended to reduce this symptom score somewhat more than did placebo, but no significant difference between the regression lines was detected ($P > 0.15$). By incorporating a dummy regression variable in the analysis, a test for order effects was obtained, but no significant order effect was detected for the symptom score. Essentially similar results were obtained for episodes of pain, severity of pain, and number of bowel movements, although an order effect was detected for the pain score (the "placebo effect" seemed to depend on the order of administration).

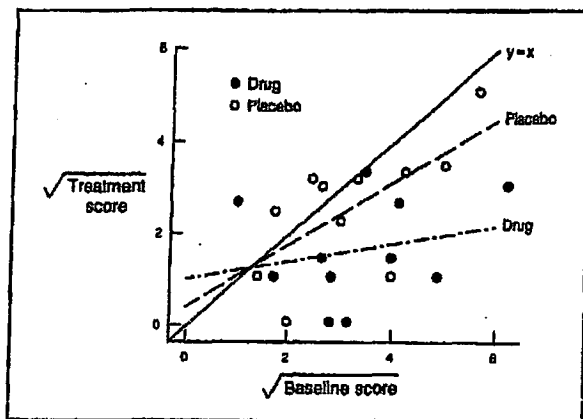


Fig. 4. Regression analysis of the symptom criteria for irritable bowel syndrome, based on daily diary data of 11 patients. Regression lines for drug and placebo periods were significantly different from $y = x$ line. Score = sum of six specific symptoms for a 1-week period. See text for further information.

DISCUSSION

We believe that this study is the first to explore the therapeutic effects of ondansetron on the symptoms of IBS.²² One of the strengths of the study was the use of clear-cut criteria for inclusion of participants; thus, the symptoms of the study group were as uniform as possible. On the basis of our earlier observations,^{11,14} we chose a group of patients with diarrhea-predominant IBS. A standardized questionnaire and diary data were used to measure the efficacy of ondansetron in controlling symptoms, and the symptoms that were assessed (diarrhea and abdominal pain) constituted the major elements of the definition of IBS used for entering patients into the study. The maximal dose of drug thought to be safe for prolonged oral ingestion was administered in this trial; indeed, three study subjects reported having mild constipation (hard stools) during drug therapy, perhaps a reflection of the dose of ondansetron used. In each patient, a subsequent phase of treatment was not commenced until symptoms were comparable to those at the beginning of the study. Although this approach prolonged the study—3 months elapsed between phases in some patients—we believe that this stipulation was necessary for satisfactory comparisons to be made between active treatment and placebo. The effects of variation in the diet were minimized in both phases by actively working with patients to maintain an intake of 20 to 25 g of fiber per day throughout each phase.

Potential limitations of the current pilot study were the crossover design and the duration of the treatment period.³ Because the primary aim was to assess changes in intestinal transit rather than symptoms and because the study included only a small number of patients, we believed that using patients as their own control subjects would prove advantageous by enhancing the statistical power of the findings. Although considerable efforts were invested to ensure that carryover effects from the first phase of the study (that is, alleviation of symptoms due to any factor, drug related or not) did not influence the second phase, we did find an order effect for abdominal pain; however, no significant order ef-

fects were detected for the results of intestinal transit or hormonal studies. Nonetheless, our results suggest that ondansetron provides relief from watery or liquid stools in patients with diarrhea-predominant IBS without causing major adverse reactions. Stool frequency, however, was unaffected. Maxton and associates,²³ who prescribed a smaller dose of ondansetron than we used, also reported firmer stools in patients with diarrhea-predominant IBS and lesser degrees of postprandial discomfort, flatulence, and heartburn, but abdominal pain was similarly unaffected. Of importance, our results were in a highly selected study group; more than 90% of the patients with IBS considered for entry into our study did not have symptoms of sufficient severity or frequency to fulfill the entry criteria. Thus, our results cannot be generalized to all patients with diarrhea-predominant IBS or to patients with other causes of diarrhea.

5-Hydroxytryptamine has been shown to affect human colonic contractile activity;^{10,13} in guinea pig ileum, it activates smooth muscle directly and also stimulates indirectly through the release of acetylcholine.²⁴ Recently, investigators have shown that the actions of 5-hydroxytryptamine are mediated through several receptor subtypes, now known as types 1, 2, 3, and 4 (which replace the previous "D" and "M" classifications).^{13,25-27} The physiologic roles of receptor subtypes can now be analyzed because specific pharmacologic antagonists have been developed.^{13,25,27} One of these antagonists, ondansetron, is selective for 5-hydroxytryptamine type 3 receptors. Its principal application has been to ameliorate the nausea and vomiting associated with use of cytotoxic drugs such as cisplatin, but ondansetron also slows colonic transit in healthy humans while having minimal effect on small intestinal transit.¹¹⁻¹⁴ In this study, we found that colonic transit in patients with IBS was not significantly altered. Perhaps the normal role of 5-hydroxytryptamine type 3 receptors in modulating colonic function is disabled in some patients with IBS so that blockade of these receptors produces no significant functional change. The lack of significant alterations in stool frequency and stool weight supports the colonic transit findings. The improvement in stool consistency is also of interest; this result could reflect alteration of the perception of unsatisfactory defecation by 5-hydroxytryptamine type 3 receptor blockade rather than alteration of transit. If these findings are confirmed, they may provide an unexpected clue to the pathogenesis of diarrhea-predominant IBS.

CONCLUSION

We believe that further studies on the effects of 5-hydroxytryptamine type 3 blockade in IBS are needed. To determine whether this class of antagonists is truly efficacious in IBS will also necessitate studies with use of larger,

parallel groups and randomized, double-blind, placebo-controlled trials of longer duration. Nevertheless, the prospect of more selective agents being available for subgroups of patients with IBS increases optimism about better therapy for these common conditions.

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