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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. 00.093.154
Solicitud de patente a nombre de **NOVARTIS AG**

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 94-76, Of. 305, obrando como apoderada de la sociedad **NOVARTIS AG** domiciliada en Basilea Suiza, solicitante de la patente de la referencia, en respuesta al oficio No. 3113 notificado por fijación en lista el 16 de Marzo de 2006, relacionado con el concepto técnico de fondo No. 0365, me permito manifestar:

1. Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto con este memorial nuevo capítulo reivindicatorio que reemplaza al presentado originalmente, el cual se caracteriza por lo siguiente:

1.1 La materia objeto reivindicada en la presente invención se limitó de manera drástica a una combinación que comprende tegaserod o una sal farmacéuticamente aceptable y omeprazol o una sal farmacéuticamente aceptable y a la participación de los mismos componentes en la fabricación de un medicamento para tratar la enfermedad de reflujo gastro-esofágico.

El sustento para este capítulo reivindicatorio se encuentra a lo largo de la memoria descriptiva y en el antiguo capítulo reivindicatorio de la presente invención. Así pues el examinador notará que el nuevo juego de reivindicaciones no amplía la materia objeto de la presente invención, que por el contrario la limita y la hace mucho más precisa y

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020/
Bogotá, D.C.,

Doctor(a)
Jimena Escobar Uribe
Apoderado(a)
NOVARTIS AG

Oficio N° 9401

REFERENCIA	Radicación	00 93154
	Trámite	002
	Evento	001
	Actuación	430
	Folios	002

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 00 93154, realizado según el artículo 46 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

SOLICITUD DE SUMINISTRO DE INFORMACIÓN

El art. 46 de la Decisión 486 establece que *"La Oficina Nacional competente podrá requerir el informe de expertos o de organismos científicos o tecnológicos que se consideren idóneos para que emitan opinión sobre la patentabilidad de la invención. Asimismo, cuando lo estime conveniente, podrá requerir informes de otras oficinas de propiedad industrial. De ser necesario, a efectos del examen de patentabilidad y a requerimiento de la oficina nacional competente, el solicitante proporcionará, en un plazo que no excederá de 3 meses, uno o más documentos relativos a una o más solicitudes extranjeras referidas total o parcialmente a la misma invención que se examina: ...b) copia de los resultados de exámenes de novedad o de patentabilidad efectuados respecto a esa solicitud extranjera... Si el solicitante no presentara los documentos requeridos dentro del plazo señalado en el presente artículo la oficina nacional competente denegará la patente"*

Como consecuencia de la búsqueda de anterioridades de materia relacionada con la de la presente solicitud, se determinó que existe en el estado de la técnica los siguientes documentos que eventualmente afectarían los requisitos de patentabilidad de esta solicitud:

- 1) SCOTT & PERRY: "Tegaserod" drugs. At, ADIS INTERNATIONAL LTD, vol. 58, no. 3, 1999, pages 492 -496, XP000874675. ISSN: 0012-6667.
- 2) STEADMAN C J ET AL: "Selective 5-Hydroxytryptamine Type 3 Receptor Antagonism With Ondasetron as Treatment for Diarrhea-Predominant Irritable Bowel Syndrome: A Pilot Study". MAYO CLINIC PROCEEDINGS, MAYO MEDICAL VENTURES, ROCHESTER, MN, US, vol. 67, no. 8, August 1992 (1992-08), pages 732-738, XP002098638. ISSN: 0025-6196.

SDZ HTF 919 Stimulates Canine Colonic Motility and Transit *In Vivo*¹

→ Tegaserod.

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ABSTRACT

Effects of the nonbenzamide 5-hydroxytryptamine₄ agonist SDZ HTF 919 on gastrointestinal motility are unclear. Our aim was to assess the *in vivo* effects on gastrointestinal and colonic transit of radiolabeled residue and on colonic phasic contractility. In six female dogs, transit was measured over a period of 2 days by radioscintigraphy and colonic motility was measured by pneumohydraulic perfusion manometry of the proximal and distal colon. SDZ HTF 919 was administered initially by bolus i.v. infusion, followed by s.c. injection 8 and 16 hr later. Doses tested were 0.03, 0.1 and 0.3 mg/kg, and isotonic saline and vehicle served as controls in each dog. Stomach and small bowel transit was not significantly altered by SDZ HTF 919. Overall, i.v. SDZ HTF 919 accelerated colonic transit during the

first 1 hr, compared with controls. These effects were significant even with the lowest dose of SDZ HTF 919. Responses to higher infusion doses were more variable. SDZ HTF 919 did not cause significant changes in quantitative pressure indices, such as amplitude or motor index, in the small bowel or colon. Prolonged postprandial colonic contractions, each lasting >30 sec, were noted after each i.v. agent and were significantly more frequent with the 0.03 mg/kg dose than with control (vehicle) treatment. Thus, SDZ HTF 919 accelerates canine colonic transit *in vivo* during the first 1 hr after i.v. administration. SDZ HTF 919 appears to be a promising agent for stimulation of mammalian colonic transit.

Motor activity of the colon has several major functions, i.e., mixing of contents to facilitate exchange and absorption of water and electrolytes, transportation of colonic contents caudally, maintenance of colonic bacterial population and defecation (Sarna, 1991). Because of its relative inaccessibility, the colon remains one of the least understood organs of the gastrointestinal tract. However, recent advances in intraluminal recording techniques as well as simultaneous scintigraphic measurement of contents within regions of the colon have allowed a better understanding of colonic function (Karaus and Wienbeck, 1991). Migrating and nonmigrating complexes of electrical and contractile activity during fasting were recognized in the canine colon by some authors (Sarna *et al.*, 1984). Others showed that the colonic interdigestive motor complexes in dogs did not "migrate" and were not related to small bowel migrating motor complexes (Schuurkes and Tukker, 1980). Postprandially, contractile activity is more irregular, and the interval between cyclic motor complexes is prolonged, relative to fasting (Sarna and Lang, 1989). Colonic contractions in dogs show two dominant

frequencies, i.e., 0.5 to 2 contractions/min and 4 to 6 contractions/min (Schuurkes and Tukker, 1980; Sarna, 1991) or 7 to 9 contractions/min (Fioramonti *et al.*, 1980).

Several neurotransmitters, including acetylcholine, peptides, amines and other chemicals such as fatty acid-derived substances, modulate colonic contractile activity. Serotonin is thought to play a role in several intestinal functions, including secretion (Beubler *et al.*, 1989), modulation of peristalsis (Buchheit and Buhl, 1993; Briejer *et al.*, 1995) and mediation of visceral afferent signaling, as in the emesis associated with chemotherapy (Cubeddu, 1992). 5-HT-containing neurons are found in the colon of several species, such as rodents and mammals, and four distinct receptor subtypes as well as two less well-characterized categories are recognized, based on operational (agonist and antagonist rank order), transductional (second messenger coupling) and structural (gene and amino acid sequence) criteria (Schmidt and Peroutka, 1989; Saxena, 1994). 5-HT₃ and 5-HT₄ mechanisms have been more thoroughly characterized in recent years (Schmidt and Peroutka 1989), and their potential applications to the treatment of human disease have been reviewed elsewhere (Camilleri and von der Ohe, 1994). The substituted benzamide cisapride is predominantly a 5-HT₄ agonist, with some 5-HT₃ antagonist activity; this drug ap-

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ABBREVIATION: 5-HT, 5-hydroxytryptamine.

appears to have relatively weak effects on motor function in the human colon (Krevsky *et al.*, 1987), but it has proven efficacious in the treatment of disorders of upper gastrointestinal motility (Wiseman and Fauld, 1994).

SDZ HTF 919 (fig. 1) is a nonbenzamide, potent, partial agonist at 5-HT₄ receptors (Pfannkuche *et al.*, 1995). The compound has negligible affinity for 5-HT₃ receptors. SDZ HTF 919 potently stimulated the peristaltic reflex in isolated guinea pig ileum and colon, through 5-HT₄ receptors (Grider and Foxx-Orenstein, 1996). The time to achieve maximum drug concentration after i.v. or oral administration of SDZ HTF 919 in dogs is 1 to 2 hr; the absolute bioavailability in dogs is 22 to 27%. The mean terminal half-life of SDZ HTF 919 in dogs is 7 hr, but there is extensive first-pass hepatic metabolism (41–63% in dogs) (de Bruijn, 1993).

Preliminary comparative studies with the benzamide 5-HT₄ agonist cisapride suggested that the latter was less potent than SDZ HTF 919 (Pfannkuche *et al.*, 1995). Animal studies have revealed stimulatory effects of SDZ HTF 919 on motor functions throughout the gastrointestinal tract. Gastric emptying of solids was stimulated in rats. In the canine small bowel, migrating motor complexes were replaced by intense irregular activity consistent with phase II contractions; in mice, impaired colonic transit was restored to normal (Pfannkuche *et al.*, 1995). However, dose-related effects of SDZ HTF 919 on *in vivo* measurement of gastrointestinal and, in particular, colonic transit, as well as the phasic contractile responses in the postprandial period, are unclear. The aim of our study was to evaluate the dose-related *in vivo* effects of SDZ HTF 919 on gastrointestinal and colonic transit and colonic motility in dogs, after their ingestion of a standard meal.

Materials and Methods

Canine model. Experiments were performed on six healthy, conscious, female dogs, each weighing 18 to 22 kg. Access to the abdominal cavity was achieved by a mini-laparotomy under general anesthesia with Brevital (Eli Lilly, Indianapolis, IN). Atropine (0.6–0.9 mg) was given i.m. preoperatively to minimize shortening of the colon due to handling during the celiotomy. Six manometric catheters were secured in the small bowel and colon (one 1 meter distal to the angle of Treitz, one 1 meter proximal to the ileocecal valve and the rest evenly distributed in the colon). A cecal cannula was placed in the dependent portion of the cecum. During surgery, 500 ml of lactate Ringer solution with 5% dextrose was given i.v. The dogs were allowed 7 to 10 days to recover after surgery.

- 5 Methoxy indol-3-carboxaldehyde amino(pentylamino) methylenehydrazone hydrogenmaleate

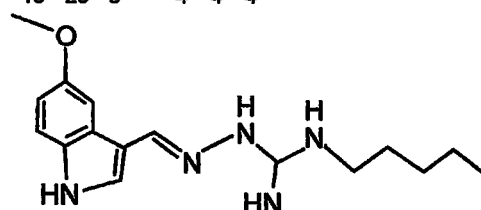
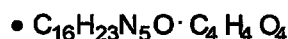


Fig. 1. Chemical structure and formula of SDZ HTF 919.

Gastrointestinal transit. The procedures for radiolabeling the meal and colon residue have been previously described in detail (Camilleri *et al.*, 1989). One millicurie of [^{99m}Tc]pertechnetate was used to radiolabel 10 g of Amberlite 410 pellets (Sigma Chemical Co., St. Louis, MO), which were subsequently mixed with the standard dog meal (2 cans of I/D; Hill's Pet Nutrition, Inc., Topeka, KS). To label colonic residue, 10 g of Amberlite 120 pellets (Sigma) were radiolabeled with 0.05 mCi of ¹¹¹InCl₃ and suspended in 10 ml of saline. This slurry was infused into the fasting dog's cecum over 5 min, by means of a syringe that was fitted into the cecal cannula. An anteriorly positioned, large-field-of-view, gamma camera with a medium-energy collimator was used to localize pellets in the digestive tract and thereby allow assessment of gastric, small bowel and colonic transit [as previously performed in humans (von der Ohe *et al.*, 1993) and dogs (Wen *et al.*, 1995)]. Windows of 147 keV and 240 keV (±10%) were used to detect and quantitate ^{99m}Tc and ¹¹¹In, respectively. A standardized protocol for scanning times was followed in all experiments (fig. 2). Corrections were applied for isotope decay and time-activity curves generated for gastric, small bowel and colonic regions.

Manometry of small bowel and colon. A manometric perfusion system under air pressure control (*i.e.*, pneumohydraulic infusion) (Arndorfer *et al.*, 1977) was used to measure phasic contractility of the small bowel and colon. During these studies, dogs were placed in a Pavlov sling and were allowed to rest on a gamma camera, to facilitate simultaneous measurements of both intestinal phasic pressure activity and transit through the gastrointestinal tract.

Experimental design (fig. 2). A Latin-square design was used to randomize the delivery of saline, vehicle and three doses of the drug SDZ HTF 919 (0.03, 0.1 and 0.3 mg/kg). SDZ HTF 919 was kindly supplied by Sandoz Pharma Ltd. (Basel, Switzerland); the vehicle for SDZ HTF 919 contained 1-methyl-2-pyrrolidinone. The first dose of the drug was given i.v. and was followed by s.c. injections at 8-hr intervals until all isotope was shown by scintigraphy to have emptied from the dog's colon.

Each experiment started after a 24-hr period of fasting. Before the ingestion of the radiolabeled meal, the ¹¹¹In-labeled pellets were infused *via* the cecal cannula over a period of 5 min. Thirty minutes later the medication was infused i.v., and after an additional 30 min the dog was allowed to ingest the ^{99m}Tc-containing standardized dog meal. Scans were taken immediately after infusion of the ¹¹¹In-labeled pellets into the cecum, as well as at the time of medication infusion and ingestion of the meal. Thereafter, a standardized protocol of scanning every 15 min for the first 2 hr and every 30 min for the next 4 hr facilitated measurements of gastrointestinal transit. Additional scans were taken at 7, 8, 25, 35 and 49 hr after the infusion of medication or until the isotope was completely emptied from the colon. The study was approved by Mayo's Institutional Animal Care and Use Committee.

Data analysis of gastrointestinal and colonic transit. The percentage of isotope remaining in the stomach was plotted against

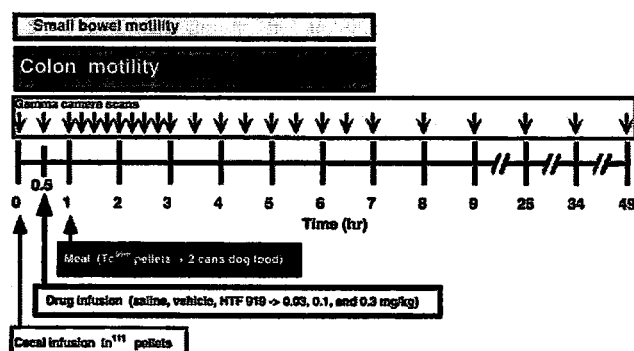


Fig. 2. Experimental design.

time, and the lag time (time for 10% of the isotope to be emptied from the stomach) and the slope (or fractional emptying rate) of the gastric emptying curve were calculated as in previous studies, using a linear model (Camilleri *et al.*, 1989). The slope was estimated by linear regression analysis of all data points beyond the lag time. The gastric emptying data over the first 8 hr were also analyzed using a power exponential model (Elashoff *et al.*, 1982; Camilleri *et al.*, 1989) and summarized as k (or the slope from power exponential analysis), β (or the initial shape of the curve) and time for 50% emptying ($T_{1/2}$). The formula used was as follows: $\text{prop } t = \exp[-(k \cdot t)^\beta]$. Small bowel transit was estimated by subtracting the time for 10% of the isotope to empty from the stomach from the time taken for 10% of the ^{99m}Tc to reach the colon (Greydanus *et al.*, 1990).

Colonic transit was summarized as the geometric center (or weighted average) of counts at each hour during the first 6 hr of the experiment and at 24 hr. The geometric center was calculated as recently suggested by Wen *et al.* (1995), by dividing the colon into three segments, *i.e.*, proximal colon, left colon and rectosigmoid colon. The stool radioactivity content constituted the fourth region of interest for the purpose of calculating the geometric center. The rectosigmoid colon was identified as that portion of the left colon located below the level of the most proximal point of the colon on the right side of the abdomen. The geometric center was calculated by multiplying the proportion of isotope in each of the four colonic regions by factors of 1, 2, 3 and 4, respectively.

Manometric recordings were analyzed using a peak-finding program that has been adapted in our laboratory from a commercially available program (Vaxlab; Digital Equipment, Boston, MA). Recordings were filtered for respiratory and motion artifacts. After visual analysis of the colonic manometric tracings, two types of phasic pressure activities were analyzed, 1) all phasic contractile activity that had a frequency of >1 contraction/min and 2) contractions of >30 -sec duration (*i.e.*, up to 0.5 contraction/min). The average amplitude of contraction and the motility index per hour for each of these two types of contractile activity were calculated, and the mean data for the colonic recordings in each dog were estimated for the 2-hr postprandial period in each experiment. The motility index was calculated by using the following formula: $\text{motility index} = \log(\text{sum of amplitudes} \times \text{number of contractions} + 1)$.

Statistical analysis. For each dog under each condition (saline, vehicle and dose of SDZ HTF 919), a summary of the measured responses was computed (*e.g.*, lag duration and $T_{1/2}$ for gastric emptying and geometric center at 1, 2, 3, 4, 5 and 6 hr for colonic transit). These summary values were then analyzed using a univariate, repeated-measures, analysis of variance to assess the overall effects of vehicle and drug. Pairwise comparisons among treatments were based on the paired t test; corresponding two-sided P values are reported in the text. Significant values were declared for $P < .05$; values that were $<.1$ were included in the text or tables. Because SDZ HTF 919 was administered as a bolus *i.v.* injection and its pharmacokinetics show a relatively rapid time to achieve maximum drug concentration and metabolism, we were particularly interested in the initial effects of the agent and we analyzed the colonic transit data during the first 2 hr as a primary efficacy parameter. Geometric centers of colonic isotope were also compared during 2 to 6 hr and at 24 hr, to determine whether there were delayed effects of the agent. Data in this manuscript are expressed as mean $\pm$ S.E.M.

Results

Effects of SDZ HTF 919 on gastrointestinal transit. There were no differences between transit profiles during saline and vehicle treatment and no overall effects of the medication on gastric emptying (fig. 3, which shows median data derived from k and β of power exponential analysis for each group, and tables 1 and 2) or small bowel transit (table 1). The gastric emptying data appeared to show acceleration

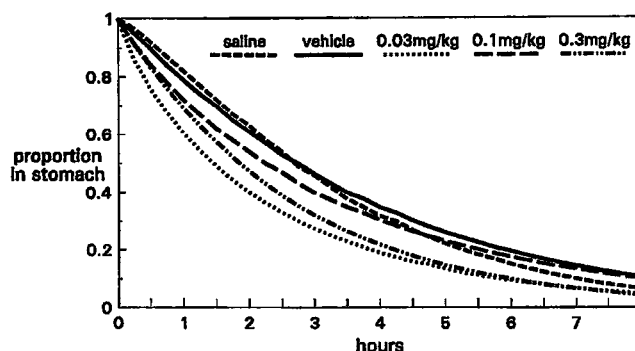


Fig. 3. Summary plots of gastric emptying data in five treatment groups; the plots were derived from the group's median k and β estimated by power exponential analysis. There was no significant drug effect, compared with saline or vehicle.

with the 0.03 and 0.3 mg/kg doses, but the large variability in the 0.1 mg/kg group reduced the significance of the overall drug effects. The similarity of gastric emptying with 0.03 and 0.3 mg/kg suggested that there was no dose-related effect of the agent.

Effects of SDZ HTF 919 on colonic transit. There were no differences in colonic transit between saline and vehicle treatments. When we compared colonic transit over the first 1 hr (*i.e.*, from time of instillation of isotope into the colon at 0 hr through the time of the *i.v.* bolus medication at 30 min and the time of meal ingestion at 1 hr) during treatment with vehicle and each of the three doses of SDZ HTF 919 individually, we were unable to show significant effects of the drug. However, because the effects on colonic transit profiles of the three drug doses were not different by analysis of linear or quadratic trends, we grouped all three doses of the SDZ HTF 919 to assess whether there was an overall drug effect, compared with saline control. This analysis showed a significant drug-time interaction ($P = .03$) over the first 1 hr after administration of SDZ HTF 919, which was associated with some acceleration ($P = .07$) of transit during the first 0.5 hr and a significant effect ($P = .006$) for the whole 1 hr.

The distribution of isotope in the different regions of the colon during the earlier part of the study, 30 min after *i.v.* infusion of SDZ HTF 919, is shown graphically in figure 4. To evaluate the colonic profiles at subsequent time points, we assessed the paired differences in colonic geometric center at each of the first 6 hr, compared with base line (0 hr), for the experiments performed with vehicle treatment and the three individual doses of SDZ HTF 919. Profiles of colonic transit for one dog and the mean time-activity curves for the six dogs are shown in figure 5. Table 3 indicates the P values of the pairwise comparisons of each drug dose and vehicle at different time points. The two higher doses of SDZ HTF 919 appeared to have effects qualitatively similar to those of the lowest dose, 0.03 mg/kg. However, there was a high degree of variation in the early effects, particularly that of 0.3 mg/kg in two of the six dogs. Indeed, from 3 hr onward, the transit profile was significantly faster with 0.3 mg/kg, compared with vehicle.

The second acceleration of colonic transit noted in figure 6 coincides with images taken immediately after the second *s.c.* administration of the agent at 8 hr. However, there were no significant differences in the colonic geometric center at 8 hr in the different groups.

TABLE 1

Effect of SDZ HTF 919 on gastric emptying (by linear analysis) and small bowel transit time (SBTT)

Data show mean $\pm$ S.E.M.

	Gastric Emptying		SBTT
	Lag Duration	Post-Lag Fractional Emptying Rate	
	min	%/min	min
Saline	65 $\pm$ 15	0.36 $\pm$ 0.05	67 $\pm$ 8
Vehicle	64 $\pm$ 28	0.27 $\pm$ 0.02	75 $\pm$ 22
SDZ HTF 919, 0.03 mg/kg	32 $\pm$ 6	0.55 $\pm$ 0.16	52 $\pm$ 12
SDZ HTF 919, 0.10 mg/kg	36 $\pm$ 6	0.32 $\pm$ 0.04	69 $\pm$ 13
SDZ HTF 919, 0.30 mg/kg	35 $\pm$ 7	0.53 $\pm$ 0.16	45 $\pm$ 9*

* $P < .1$ vs. vehicle.† $P < .05$ vs. .1 mg/kg dose.

TABLE 2

Effect of SDZ HTF 919 on gastric emptying (power exponential analysis)

Data show median (interquartile range).

	β	k	$T_{1/2}$
			min
Saline	1.26 (1.17–1.32)	0.28 (0.25–0.30)	159 (152–161)
Vehicle	1.09 (0.90–1.20)	0.26 (0.22–0.38)	160 (104–203)
SDZ HTF 919, 0.03 mg/kg	0.86 (0.78–1.42)	0.45 (0.27–0.73)	90 (67–170)
SDZ HTF 919, 0.10 mg/kg	0.94 (0.87–1.00)	0.30 (0.19–0.37)	139 (118–210)
SDZ HTF 919, 0.30 mg/kg	1.03 (0.80–1.16)	0.38 (0.30–0.48)	116 (78–134)

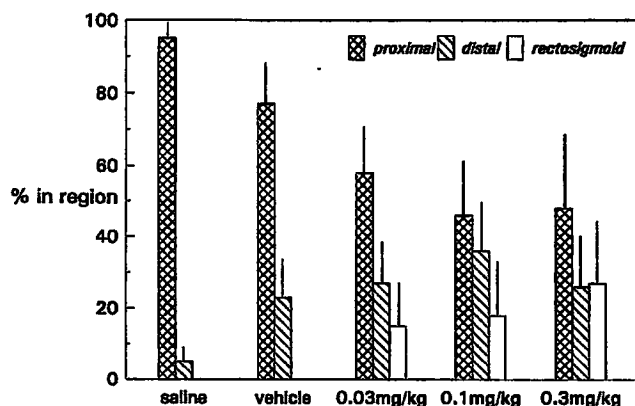


Fig. 4. Distribution of radioactivity in proximal, distal and rectosigmoid colon at 30 min after i.v. SDZ HTF 919. Note the trend toward more distal distribution of isotope with medication but no significant trends related to the dose of medication used.

Effect of SDZ HTF 919 on small intestinal phasic pressure activity. Phasic pressure responses of the small intestine during the first 2 hr postprandially were characterized by irregular contractile activity, typical of the "fed" response, that replaced the fasting migrating motor complexes observed before meal ingestion. Quantitation of phasic contractility showed no drug effects on contraction amplitude (data not shown) or motility indices (table 4).

Effect of SDZ HTF 919 on colonic phasic pressure activity. Table 5 shows a summary of the effects of saline, vehicle and SDZ HTF 919 on average proximal and distal colonic motility indices. There was an overall increase in the phasic motility index induced by meal ingestion ($P = .0006$, by paired t test for all groups); however, the increase in the colonic motility index postprandially was no different between the groups, suggesting that the meal rather than the drug led to an increase in the motility index and the drug did not increase this index further.

There were phasic contractions lasting >30 sec (fig. 6) after drug and in the postprandial period. The postprandial increase in the number of waves lasting >30 sec over the fasting period was significant ($P < .05$) for treatment with SDZ HTF 919 at 0.03 mg/kg, compared with vehicle (table 6).

Discussion

This study demonstrates that the nonbenzamide 5-HT₄ agonist SDZ HTF 919 significantly stimulates transit of solid residue in the colon. Our study suggests that the higher doses (0.1 and 0.3 mg/kg) are not more efficacious than the lower dose (0.03 mg/kg) of SDZ HTF 919. Our data are generally consistent with many of the previous observations on the effects of this agent on the motor function of the gut in animals. The reason for the lack of a demonstrable dose-related effect of the drug on colonic motility is unclear. Several possibilities should be considered. First, the dose range used may have been at the upper end of the dose-response curve. Second, the drug may act at sites other than 5-HT₄ receptors at higher doses, thereby inhibiting its potential to stimulate colonic motility or obscuring its pro-transit effects. There is evidence that SDZ HTF 919 is an agonist at 5-HT_{1D} receptors (Buchheit and Pfannkuche, 1992), an action that has been shown to reduce tone in the mammalian gastrointestinal tract (Coulie, 1996), including feline stomach and human colon (B. Coulie and J. Tak, University of Leuven, Belgium, personal communication). Third, the drug may not act *via* a receptor-mediated mechanism to stimulate transit. Finally, the drug may not affect colonic transit consistently; this was particularly evident in the large variance of the transit measurements with the 0.1 mg/kg dose in this study.

SDZ HTF 919 stimulated gastric emptying of solids in conscious rats, but it exhibited a bell-shaped dose-response curve when given orally or i.p. in doses similar to those used in our study (de Bruijn, 1993). The ED₅₀ for SDZ HTF 919 in acceleration of liquid emptying from the stomach in conscious

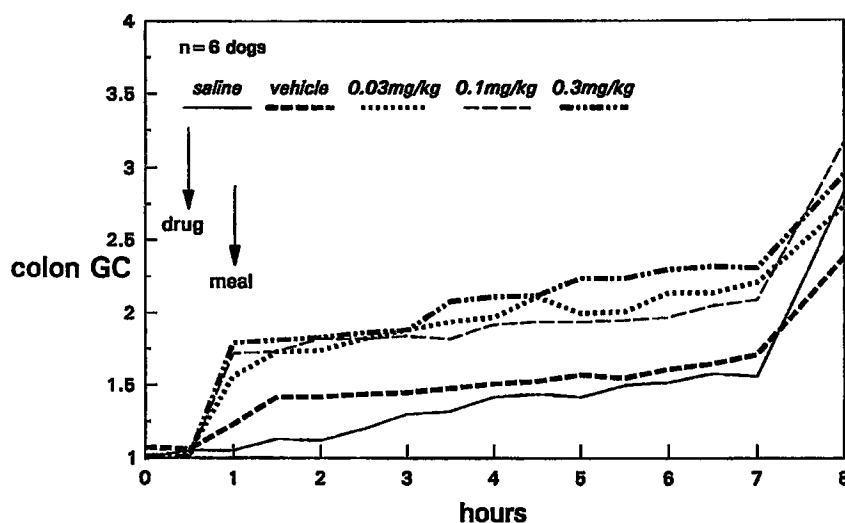


Fig. 5. Mean colonic transit time-activity curves in six dogs. Note that the effect of medication is seen almost immediately and precedes the ingestion of the meal. There is a trend toward a second increment in the aboral movement of chyme at about 7 to 8 hr, when the second s.c. injection of SDZ HTF 919 was administered. GC, geometric center.

TABLE 3

Results (P values) of paired *t* tests for Δ values (geometric center at specified time minus geometric center at base line) comparing vehicle vs. dose of SDZ HTF 919

	Paired <i>t</i> Test P Values for Δ Values (Compared with Vehicle)					
	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr
Saline	.08	.09	>.2	>.2	>.2	>.2
SDZ HTF 919, 0.03 mg/kg	.10	.13	.04	.04	.04	.02
SDZ HTF 919, 0.10 mg/kg	.10	>.2	>.2	.18	>.2	.19
SDZ HTF 919, 0.30 mg/kg	.11	.13	.08	.006	.002	.007

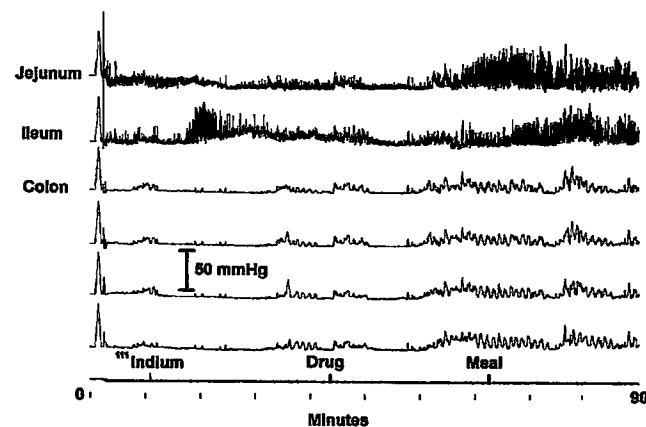


Fig. 6. Examples of jejunal, ileal and colonic phasic pressure activity recorded by manometry. Note the contractions of relatively long duration observed at all levels in the colon, particularly after the meal was administered. There appear to be no immediate effects of the drug on overall phasic pressure activity before the ingestion of the meal.

guinea pigs was 0.1 $\mu\text{g}/\text{kg}$ i.p. (de Bruijn, 1993). In conscious dogs, we were unable to replicate the bell-shaped dose-response curve shown previously.

SDZ HTF 919 stimulated small intestinal motility in guinea pigs, and it induced a phase II-like motility pattern in the upper and lower part of the small intestine of conscious dogs. The functional significance of such contractile activity is unclear; however, we did not observe a significant acceleration in small bowel transit with SDZ HTF 919.

In a pharmacological model of impaired large intestinal motility in mice treated with the α -2 adrenergic agonist

TABLE 4

Effect of SDZ HTF 919 on small bowel phasic pressure activity (mean $\pm$ S.E.M.)

	Motility Index/hr		
	Fasting	After Drug	Postprandial
Saline	10.3 $\pm$ 1.4	11.9 $\pm$ 0.6	13.2 $\pm$ 0.3
Vehicle	11.1 $\pm$ 0.7	12.4 $\pm$ 0.5	12.6 $\pm$ 0.3
SDZ HTF 919, 0.03 mg/kg	11.1 $\pm$ 0.8	13.6 $\pm$ 0.6	12.5 $\pm$ 0.8
SDZ HTF 919, 0.10 mg/kg	11.2 $\pm$ 0.9	13.3 $\pm$ 0.2	12.9 $\pm$ 0.3
SDZ HTF 919, 0.30 mg/kg	11.2 $\pm$ 0.7	13.0 $\pm$ 1.1	12.3 $\pm$ 1.1

TABLE 5

Effect of SDZ HTF 919 on colonic phasic pressure activity (mean $\pm$ S.E.M.)

	Motility Index/hr		
	Fasting	After Drug	Postprandial
Saline	8.4 $\pm$ 1.0	8.8 $\pm$ 1.1	8.9 $\pm$ 0.9
Vehicle	8.2 $\pm$ 1.1	9.4 $\pm$ 0.7	9.6 $\pm$ 0.7
SDZ HTF 919, 0.03 mg/kg	8.0 $\pm$ 0.7	9.0 $\pm$ 0.5	9.2 $\pm$ 0.7
SDZ HTF 919, 0.10 mg/kg	8.6 $\pm$ 0.1	10.0 $\pm$ 0.3	9.7 $\pm$ 0.5
SDZ HTF 919, 0.30 mg/kg	8.0 $\pm$ 0.8	8.6 $\pm$ 0.6	8.5 $\pm$ 0.8

lidamidine, i.p. administration of 0.01 mg/kg SDZ HTF 919 restored colonic motility to control levels. Similarly, after the i.p. administration of SDZ HTF 919 at doses of 1.0 $\mu\text{g}/\text{kg}$ to 1.0 mg/kg, mice developed soft stools (K. H. Buchheit, per-

TABLE 6

Effect of SDZ HTF 919 on colonic contractions of >30-sec duration (mean $\pm$ S.E.M.)

	Motility Index/hr		
	Fasting	After Drug	Postprandial
Saline	5.3 $\pm$ 1.9	6.4 $\pm$ 2.2	6.4 $\pm$ 2.0
Vehicle	7.1 $\pm$ 2.5	7.8 $\pm$ 2.5	5.9 $\pm$ 1.8
SDZ HTF 919, 0.03 mg/kg	3.8 $\pm$ 1.5	4.9 $\pm$ 1.0	7.8 $\pm$ 2.4*
SDZ HTF 919, 0.10 mg/kg	2.2 $\pm$ 0.3	7.1 $\pm$ 2.2	5.6 $\pm$ 1.7
SDZ HTF 919, 0.30 mg/kg	4.3 $\pm$ 1.2	2.8 $\pm$ 0.7	3.9 $\pm$ 1.0

* Ratio of postprandial/fasting motility index/hr significantly greater ($P < .05$) than vehicle control group by Dunnett's test.

sonal communication). Our data suggest that this effect on stool consistency may result at least partly from acceleration of colonic transit.

Our data also confirmed the importance of 5-HT₄ receptors in the control of canine colonic motor function. Fink and Friedman (1960) previously demonstrated the differential effects of serotonin on proximal and distal colon. Sleisenger *et al.* (1959) demonstrated that intra-arterial administration of serotonin stimulated the colon of intact anesthetized dogs. Subsequently, identification of receptor subtypes for serotonin suggested the existence of a type 4 receptor subtype in the digestive tract, chiefly on cholinergic nerves (Elswood *et al.*, 1991). The *in vitro* work of several groups using circular muscle strips from guinea pig ascending colon (Elswood *et al.*, 1991; Briejer *et al.*, 1993; Kojima and Shimo, 1995) or human colon (Tam *et al.*, 1994) and *in vivo* studies in the dog colon (Kadowaki *et al.*, 1993) confirm the stimulation of colonic contractility with 5-HT₄ agonists. Recently, Grider and Fox-Orenstein (1996) showed that SDZ HTF 919 can trigger the peristaltic reflex in rat and guinea pig colon via 5-HT₄ receptor activation. In humans, the substituted benzamide cisapride appears to predominantly stimulate proximal colonic emptying in health (Krevsky *et al.*, 1987) and in the disease colonic inertia (Krevsky *et al.*, 1989), which is characterized most frequently by delayed proximal colonic transit (Stivland *et al.*, 1991). We have confirmed the stimulation of canine colonic transit, in a chronic *in vivo* dog model, by the non-benzamide 5-HT₄ agonist SDZ HTF 919.

The motor mechanisms responsible for colonic propulsion are unclear; high-amplitude propagated phasic contractions are thought to be responsible for mass movements, but they are relatively infrequent and were not observed during the 2 hr after SDZ HTF 919 infusions. Contraction, amplitude and motility indices were not different postprandially among treatment groups. Hence, the motor parameters, including possible effects of SDZ HTF 919 on colonic tone, which may influence colonic propulsion, require further evaluation. Thus, colonic tone is clearly increased in human models of accelerated transit, such as carcinoid diarrhea (von der Ohe *et al.*, 1993), and decreased in chronic colonic megacolon (von der Ohe *et al.*, 1994) and in some patients with slow-transit constipation (O'Brien *et al.*, 1996).

In summary, SDZ HTF 919 appears to be a promising agent to stimulate motility and transit in the colon and may also stimulate gastric emptying, although the latter effects are not as consistent as are effects on colonic transit. Future

studies are needed to further elucidate the motor mechanisms resulting in the accelerated transit. Ultimately, the therapeutic use of this agent will require similar dose-response pharmacodynamic studies in humans and appropriate placebo-controlled trials in carefully selected patients with objectively delayed transit, particularly those with delays in proximal colonic emptying, which are quantifiable using radioscinigraphy and a delayed-release capsule that delivers isotopically labeled solid residue to the ileocolonic junction (Proano *et al.*, 1990; Stivland *et al.*, 1991).

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Effect of gastric acid suppressants on human gastric motility

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Abstract

Background—The effect of histamine H_2 receptor antagonists on gastric emptying is controversial.

Aims—To determine the effects of ranitidine, famotidine, and omeprazole on gastric motility and emptying.

Patients and methods—Fifteen normal subjects underwent simultaneous antroduodenal manometry, electrogastrography (EGG), and gastric emptying with dynamic antral scintigraphy (DAS). After 30 minutes of fasting manometry and EGG recording, subjects received either intravenous saline, ranitidine, or famotidine, followed by another 30 minutes recording and then three hours of postprandial recording after ingestion of a radiolabelled meal. Images were obtained every 10–15 minutes for three hours to measure gastric emptying and assess antral contractility. Similar testing was performed after omeprazole 20 mg daily for one week.

Results—Fasting antral phase III migrating motor complexes (MMCs) were more common after ranitidine (9/15 subjects, 60%), famotidine (12/15, 80%), and omeprazole (8/12, 67%) compared with placebo (4/14, 29%; $p < 0.05$). Postprandially, ranitidine, famotidine, and omeprazole slowed gastric emptying, increased the amplitude of DAS contractions, increased the EGG power, and increased the antral manometric motility index.

Conclusions—Suppression of gastric acid secretion with therapeutic doses of gastric acid suppressants is associated with delayed gastric emptying but increased antral motility.

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Keywords: gastric motility; gastric emptying; histamine H_2 receptor antagonists; proton pump inhibitors; gastric acid secretion; scintigraphy

Gastric acid suppression with histamine H_2 receptor antagonists has been reported to have variable effects on gastric motility and emptying. Studies have suggested an increase,^{1,2} no change,^{3,4} or a decrease in overall gastric emptying.^{5–7} Theoretically, gastric acid suppression may affect gastric emptying by several mechanisms. Diminished hydrolysis of solids because of acid suppression may delay solid phase gastric emptying.^{7,8} Acid suppression may increase serum levels of gastrin,⁹ a peptide known to slow gastric emptying.¹⁰ Removal of

the normal braking action of acid in the duodenum could lead to an increase in gastric emptying.^{11–13} In addition, specific H_2 receptor antagonists may also directly affect gastric motility.^{5,6,14,15} In vitro, ranitidine, but not famotidine, has been reported to increase antral contractility by a cholinergic mechanism.^{16,17}

The aims of this study were twofold: to determine the effect of gastric acid suppression on gastric motility both in the fasting and postprandial periods; and to compare the effects of three different gastric acid suppressants (ranitidine, an H_2 receptor antagonist with cholinergic properties; famotidine, an H_2 receptor antagonist with minimal cholinergic effects; and omeprazole, a proton pump inhibitor without H_2 receptor antagonist or cholinergic effects) on gastric motor function and emptying. Based on previous in vitro studies,¹⁶ we hypothesised that ranitidine, but not famotidine or omeprazole, would increase gastric motility and might accelerate gastric emptying.

Materials and methods

Fifteen normal volunteers were studied using a four way crossover design comparing the effects of placebo, ranitidine, famotidine, and omeprazole on gastric motility. On each study day, subjects underwent simultaneous antroduodenal manometry (ADM), cutaneous electrogastrography (EGG), and gastric emptying (GE) with dynamic antral scintigraphy (DAS). This protocol was approved by the Institutional Review Board and Radiation Protection Committee of Temple University.

STUDY SUBJECTS

Normal subjects were recruited for this project (10 men and five women, mean age 26.2 years, range 18–38 years). They were initially screened by telephone, and potential subjects underwent a medical history and physical examination. Exclusion criteria included prior gastrointestinal surgery (except appendectomy), the presence or history of gastro-oesophageal reflux, peptic ulcer disease, irritable bowel syndrome, chronic gastrointestinal symptoms, or the use of any medications that might affect gastrointestinal motility. Women were studied only during the follicular phase (days 1–10) of the menstrual cycle. Pregnancy screening with serum β human chorionic gonadotropin was performed on women on the morning prior to the start of each study.

STUDY PROTOCOL

Enrolled subjects were instructed to begin fasting at 10 pm on the night prior to the study and

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arrive at the research facility at 7 30 am. An antroduodenal manometry catheter was advanced transnasally to the ligament of Treitz (see below). Cutaneous EGG electrodes were placed (see below). The study day protocol included an initial 30 minute recording of fasting antroduodenal manometry and EGG prior to intravenous infusion of study drug. During the first three sessions, each subject received in random order: placebo (normal saline 5 ml intravenous bolus then 50 ml/hour intravenously), ranitidine (50 mg intravenous bolus then 6.25 mg/hour intravenously), or famotidine (20 mg intravenous bolus then 1.67 mg/hour intravenously). These doses of H_2 receptor antagonists are those recommended for therapeutic dosing by intravenous infusion.^{18 19} The continuous infusion of study drug continued for the rest of the four hour recording period for that day. For the fourth session, each subject had been taking omeprazole, 20 mg daily for one week; the last dose of omeprazole was taken just prior to placement of the antroduodenal catheter (approximately 2.5 hours prior to meal ingestion). For the omeprazole sessions, subjects received an intravenous infusion of saline, similar to the placebo studies.

After infusion of the bolus doses of test agents, fasting antroduodenal manometry and EGG recordings were continued for another 30 minutes. Longer recording times in the fasting period were not possible with the time constraints for the entire study. Each subject then ingested a technetium-99m sulphur colloid labelled solid meal with 300 ml unlabelled water (see below). Three hours of postprandial recordings were then obtained using simultaneous ADM, cutaneous EGG, and GE with DAS. Static gamma camera images were obtained every 10–15 minutes to measure solid phase gastric emptying. Each static image was followed by dynamic, one second images for 256 seconds, for DAS which was synchronised with antral manometry and EGG recording.

At the end of the study day, a repeat fluoroscopic verification of manometry tube position was obtained, followed by removal of the manometry tube and EGG electrodes.

Antroduodenal manometry

An antroduodenal manometry catheter containing six solid state pressure transducers was used for these studies (Königsberg Instruments, Inc., Pasadena, California). The three proximal transducers were 2 cm apart and the distal three transducers were 10 cm apart.²⁰ The catheter was passed by nasal intubation into the stomach and positioned fluoroscopically through the pylorus into the duodenum so that the three proximal transducers were located in the distal antrum and the distal tip of the catheter usually at the ligament of Treitz. Antral and small bowel motility were recorded with a microDigitrapper (Synectics Medical, Inc., Irving, Texas).

EGG recording

Electrogastrography was performed as previously described.²¹ After placement of the

antroduodenal manometry catheter, the abdominal skin surface for each recording site was carefully abraded until slightly erythematous (Buf-Puf Regular; 3M Personal Care Products, St Paul, Minnesota). If abdominal hair was present, this was removed with a razor. Three surface electrodes (Cleartrace electrodes; Medtronic Andover Medical, Inc., Haverhill, Massachusetts) were placed on the abdominal surface overlying the stomach. Two active electrodes were used: one electrode was placed on the midline of the abdomen, halfway between the umbilicus and the xyphoid process; the other was placed on the subject's left side, 1 cm below the bottom rib and a quarter of the distance towards the ventral midline. A reference electrode was placed on the left lower abdomen, below the umbilicus equidistant between each active electrode. Gastric myoelectric activity was recorded using the same Synectics microDigitrapper as used for antroduodenal manometry, thus data were acquired simultaneously. The sampling frequency for digital EGG recording was set at 4 Hz.

Gastric and dynamic antral scintigraphy

Gastric scintigraphy was performed as previously reported^{22 23} with several modifications. Solid phase gastric emptying was evaluated after ingestion of a standardised test meal consisting of a ^{99m}Tc sulphur colloid labelled egg sandwich (two large beaten eggs mixed with 74 MBq (2 mCi) ^{99m}Tc sulphur colloid, cooked on a Teflon non-stick griddle until firm and served between two pieces of toasted bread) with 300 ml of unlabelled water. This meal contains 1.18 MJ; 32% protein, 46% carbohydrate, 22% fat. Imaging for technetium counts (128 × 128 pixel matrix) using a 140 Kev photopeak with a 20% window was performed with the subjects in both the anterior and posterior standing positions for 30 seconds each every 10 minutes for one hour, then every 15 minutes for another two hours using a large field of view gamma camera (GE535, General Electric Medical Systems, Milwaukee, Wisconsin). In addition, after each static acquisition, dynamic acquisition (256 consecutive one second images; 64 × 64 pixel matrix) in the anterior standing position was recorded to characterise antral contractions.^{22 24} The event marker on the microDigitrapper was used to record a time signal at the start of DAS recording to facilitate timing for later analysis of simultaneously acquired DAS, EGG, and ADM.

DATA ANALYSIS

Antroduodenal manometry

After the study was completed, the manometric and EGG data were downloaded from the microDigitrapper to a computer (NEC Powermate SX/25i). The fasting manometric tracings were inspected for the presence of phase III migrating motor complexes (MMCs) during both 30 minute periods before and after beginning study drug infusion. An antral phase III MMC was defined as the presence of at least two minutes of regular antral contractions at a frequency of 1–3 per minute, and associated in

252
250

temporal sequence with phase III activity in the duodenum.^{20, 25} For postprandial recordings, the most distal lead showing an antral pattern of contractility—that is, high amplitude pressure waves with frequencies of 0–4 cycles per minute, was analysed.²⁰ The distal small bowel pressure transducer was used for distal duodenal contractility. Postprandial antral and duodenal contractility were quantified as motility indexes calculated using computer software (Multigram 6.31B2H4, Gastrosoft, Irving, Texas).^{20, 23} Distal antral and duodenal motility indexes were calculated for each of the 256 second time periods corresponding to the DAS recordings. This motility index expresses the contractile activity as the natural logarithm of the area under the manometric pressure peaks above a threshold pressure of 9 mm Hg. The motility indexes (MI) were calculated using the formula: $MI = \ln [\text{area under the curve/duration of recording}]$. An overall mean postprandial motility index was obtained by averaging the individual 4 minute 16 second MIs from the time period 0 to 180 minutes.

Electrogastrography

EKGs were analysed using computer software (Multigram 6.31B2H4, Synectics Medical, Inc., Irving, Texas) which employed fast Fourier transform (FFT) and running spectral analysis, as previously described²¹ with modifications to analyse smaller time periods throughout the study. Running spectral analysis was used for 15 minutes before drug infusion and 15 minutes after drug infusion. Each running spectrum was 4 minutes 16 seconds long, with the next spectrum advancing one minute, giving 3 minutes 16 seconds overlap between consecutive spectra. For the postprandial period, the FFT used a 4 minute 16 second spectrum of data starting at the time stamp entered to indicate the simultaneous acquisition of the DAS images. Use of 4 Hz sampling frequency and 4 minute 16 second spectra for the FFT gives a frequency resolution of 0.23 cpm.

The FFT results were expressed as power as a function of frequency, with the dominant frequency defined as the frequency with the highest power.^{21, 26} The dominant slow wave frequency and its power were determined for the fasting period, both before and after study drug infusion, and for each 256 second DAS acquisition time interval. In addition, the postprandial to fasting power ratio—that is, the ratio between the postprandial and fasting (prior to drug infusion) power of the dominant frequency, was computed for each DAS acquisition time interval. An overall mean postprandial EGG power ratio was obtained by averaging the individual power ratios from the time period 0 to 180 minutes.

Gastric and dynamic antral scintigraphy

Gastric emptying was analysed using conventional techniques.²² A region of interest was manually created to outline the entire stomach. Radioactive counts in the gastric region of interest were summed and corrected for isotope decay. The geometric mean of anterior

and posterior counts was used to correct for attenuation (geometric mean counts = square root [anterior counts × posterior counts]). Geometric mean counts were then expressed as a percentage of the maximal counts. Residual percent ^{99m}Tc counts in the gastric region of interest were plotted against time to obtain time activity curves. The time to reach 50% retention ($t_{1/2}$), the lag phase of the solid meal, and the emptying rate were determined by using computerised curve fitting techniques of the per cent retention versus time using a modified power exponential function $y(t) = 100 - 100(1 - e^{-kt})^\beta$ ²⁷ (Kaleidagraph 3.04, Synergy Software, Malvern, Pennsylvania) on Power Macintosh Computer (8100/80AV, Apple Computer, Cupertino, California). The parameters k and β were determined by a non-linear least squares fitting algorithm. Using this modified power exponential function, the lag phase is equal to $[\ln \beta]/k$ and the slope of the terminal portion of the emptying curve is k .²⁷ Using this mathematical definition, the lag phase corresponds to the inflection point of the emptying curve at which the slope becomes constant.²⁷

Regional gastric emptying of the proximal stomach was performed by drawing regions encompassing the proximal and distal portions of the stomach as previously described.²⁸ The proximal stomach was taken as the upper third of the stomach. The distal stomach was taken as the area of the stomach excluding the proximal stomach. Each region was outlined manually and decay corrected geometric mean counts for the proximal and distal stomach were expressed as a percentage of the maximum geometric mean counts in the total stomach and plotted versus time.

Dynamic antral scintigraphy was analysed by previously reported techniques.^{24, 29} In order to allow for precise outlining of the antrum, each set of dynamic images was first reframed in a single composite image. Three equal size regions of interest were drawn on the horizontal portion of the stomach between the incisura angularis and the pylorus to delineate the proximal, middle, and distal antrum. The time activity curves generated from proximal, middle, and distal regions of interest in the antrum were then analysed from the dynamic images using a refined Fourier transform to determine the dominant frequency and the amplitude of the antral contractile activity. A baseline restoration and normalisation of the raw antral time activity curves was first performed using a third degree polynomial fit.²⁴ This helps eliminate artefacts due to patient or stomach translational movement and transforms the data in per cent change to the respective antral mean counts. An autocorrelation function was then applied to the normalised antral time activity curves.²⁴ This function helps eliminate background noise and non-periodic events in the defined time interval. The fast Fourier transform of the autocorrelated data was obtained to determine the dominant frequency (in contractions per minute) and the amplitude of the dominant frequency in each of the proximal, mid, and distal antral regions of interest. This

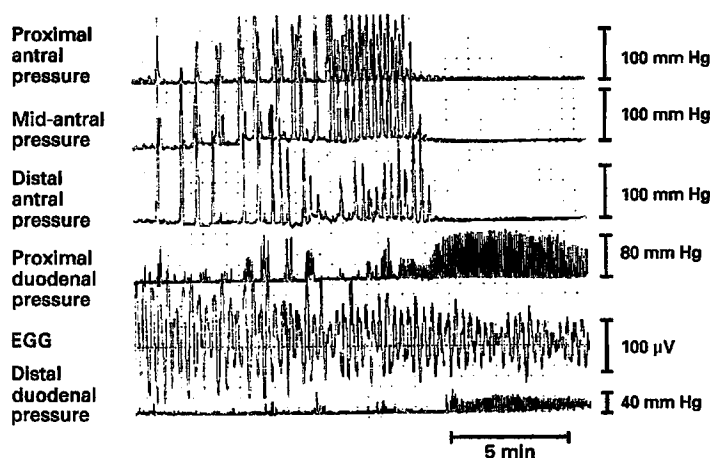


Figure 1 Fasting antroduodenal manometry and EGG recording. This tracing, taken during the fasting pattern, depicts a phase III MMC starting in the antrum and progressing distally into the duodenum.

Table 1 Effect of gastric acid suppressants on postprandial antroduodenal motility

	DAS amplitude (%)	EGG power ratio motility index	Antral manometric motility index	Duodenal motility index
Placebo	14.3 (0.4)	4.0 (0.4)	3.3 (0.1)	4.9 (0.1)
Ranitidine	15.8 (0.4)*	12.5 (1.4)*	4.3 (0.1)*	4.8 (0.1)
Famotidine	16.2 (0.4)*	22.8 (3.8)*	4.4 (0.1)*	4.7 (0.1)
Omeprazole	16.4 (0.5)*	18.2 (1.8)*	4.2 (0.1)*	4.9 (0.1)

Results are expressed as mean (SEM).

* $p < 0.05$ v placebo.

DAS amplitude represents the per cent variation of the normalised counts at the dominant frequency of antral contractions, and has been used as a non-invasive assessment of antral contractions.^{22-24, 29} The overall DAS frequency and amplitude of antral contractions were taken as the average value of the proximal, mid, and distal antrum for each of the 256 second acquisition periods. An overall mean postprandial DAS contractile amplitude was obtained by averaging the individual DAS contractile amplitude from the time period 20 to 150 minutes.

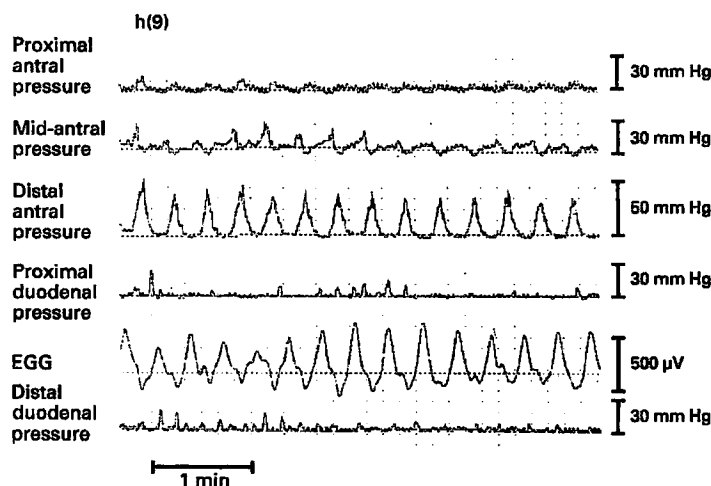


Figure 2 Postprandial antroduodenal manometry and EGG recording. In this tracing, prominent three cycle per minute antral contractile activity and three cycle per minute EGG activity are shown.

Processing of the static and dynamic data was performed on an 8200 Apple Power PC computer (Apple, Cupertino, California) with applications developed using Kaleidagraph (Abelbeck Software, Pennsylvania) and LabVIEW (National Instruments, Texas) software programs.

STATISTICAL ANALYSIS

Data are expressed as mean (SEM). The effects of each study drug on each motility parameter were assessed using χ^2 analysis, Wilcoxon signed rank test, analysis of variance, or paired Student's t test with Bonferroni adjustment for repeated measures.³⁰ These statistical calculations were performed on a Macintosh Classic II computer using statistical software (Stat Works; Cricket Software, Inc., Philadelphia, Pennsylvania). Differences were considered statistically significant when the p value was less than 0.05.

Results

All 15 subjects entered into the protocol underwent the first three studies investigating the effects of placebo, ranitidine, and famotidine. During the placebo session in one subject, the microDigitrapper malfunctioned, not allowing the data from the antroduodenal manometry and EGG to be recovered. Twelve of the 15 subjects successfully completed the omeprazole session; three subjects voluntarily withdrew.

EFFECTS OF GASTRIC ACID SUPPRESSANTS ON FASTING ANTRODUODENAL MANOMETRY

Figure 1 shows an example of antroduodenal manometry and EGG recording taken during the fasting period. The antroduodenal tracings in the fasting period for the 30 minute periods before and after study drug infusions were analysed for the presence of antral phase III MMCs. Antral phase III MMCs were significantly more common during ranitidine (9/15 subjects, 60%), famotidine (12/15, 80%), and omeprazole (8/12, 67%) administration compared with placebo (4/14, 29%; $p < 0.05$ by χ^2 analysis).

EFFECTS OF GASTRIC ACID SUPPRESSANTS ON POSTPRANDIAL ANTRODUODENAL MOTILITY

Antroduodenal manometry
Figure 2 shows recordings of postprandial antroduodenal manometry and electrogastrography. Figure 3 shows the postprandial antral motility indexes over time for each of the treatment groups. There was a significant ($p < 0.01$) increase in the mean overall three hour postprandial antral motility index with each of the three acid suppressants: ranitidine (4.3 (0.1)), famotidine (4.4 (0.1)), and omeprazole (4.2 (0.1)), compared with placebo (3.4 (0.1)) (table 1). There was no significant difference in the postprandial duodenal motility index for any of the drug regimens compared with placebo (table 1).

Electrogastrography

The EGG signals (lead 5 in figs 1 and 2) were analysed for fasting and postprandial time

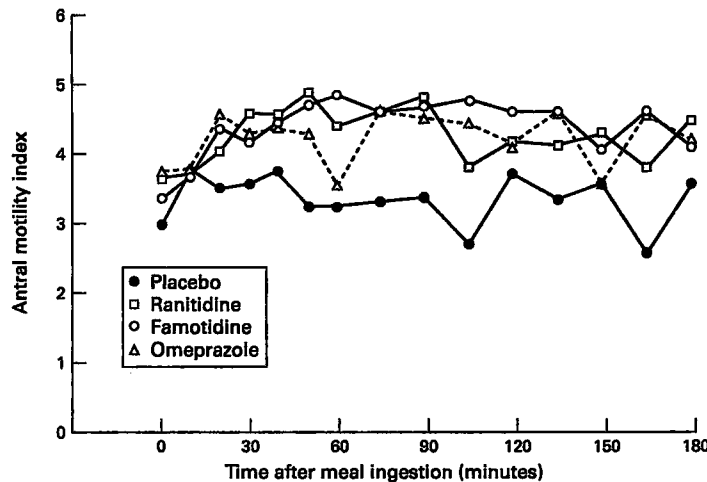


Figure 3 Effects of gastric acid suppressants on postprandial antral motility indexes.

periods by fast Fourier transform analysis to obtain a dominant frequency and power of the dominant frequency. There was an initial decrease in EGG dominant frequency after meal ingestion for all treatment groups. In the placebo study the initial fasting dominant frequency of 2.94 (0.05) cpm transiently decreased to 2.70 (0.10) cpm ($p < 0.01$) after meal ingestion and rapidly returned to a three cycle per minute pattern for the rest of the postprandial recording. The frequency of the EGG during administration of the three gastric acid suppressants was no different from placebo.

EGG power increased significantly after meal ingestion with each of the four treatment arms of the study. The ratio of the power of the postprandial dominant frequency to the power of the fasting dominant frequency (the EGG power ratio) increased significantly for each of the three gastric acid suppressants compared with placebo (table 1). There was no statistically significant difference among the three gastric acid suppressants.

Gastric emptying scintigraphy

Gastric emptying curves, expressed as per cent retention over time, were similar for the initial part of the study for placebo, ranitidine, famotidine, and omeprazole (fig 4A). After 60 minutes, the curves diverged; there was significantly more retention for ranitidine, famotidine, and omeprazole compared with placebo. At two hours after meal ingestion, gastric retention was 46 (4)% for ranitidine, 41 (5)% for famotidine, and 46 (13)% for omeprazole compared with 27 (4)% for placebo ($p < 0.01$; table 2). Similarly, the half emptying times for ranitidine, famotidine, and

omeprazole were significantly greater than for placebo (table 2). This delay was associated with similar lag phases for the four groups, whereas the slopes of the emptying curves were significantly less for ranitidine, famotidine, and omeprazole than for placebo (table 2).

The delay in gastric emptying was further evaluated using regional gastric emptying analysis. The emptying of the proximal stomach was similar for the four study groups (fig 4B). In contrast, meal retention in the distal stomach was increased for ranitidine, famotidine, and omeprazole compared with placebo (fig 4C). At 120 minutes, the values for ranitidine (39.1 (2.6)% retention), famotidine (35.6 (3.5)%), and omeprazole (40.6 (3.1)% retention) were greater than that for placebo (20.2 (2.7)% retention). Using analysis of variance, these numbers are significantly different ($p < 0.01$).

Dynamic antral scintigraphy

For analysis of antral contractility using dynamic acquisition, three regions of interest from the proximal, mid, and distal antral regions were designated, and the counts over time were quantified for each region. The results of the DAS are interpreted only for the 20 to 150 minute postprandial periods due to low counts in the antrum at other times. In the early portion (times 0 and 10 minutes), not enough counts had arrived in the antrum; and in the later phase (times 165 and 180 minutes), there were too few counts in the antrum as a result of gastric emptying. Figures 5A and 5B show examples of these time activity curves from the mid-antral region of interest. The phasic counts represent the contracting antrum. Using fast Fourier transform analysis expressing amplitude as a function of frequency, the dominant frequency is represented by the peak with the highest amplitude (figs 5C and 5D). This DAS amplitude represents the per cent variation of the normalised counts at the dominant frequency of antral contractions. There were no differences in the DAS dominant frequency observed over time with the three acid suppression agents, compared with placebo. In contrast, the DAS amplitude of contractions increased significantly for each of the three gastric acid suppressants corresponding to the increase in EGG power and antral manometric motility index (table 1).

Discussion

This study has shown that therapeutic doses of ranitidine, famotidine, and omeprazole, which suppress gastric acid secretion, affect both gastric motility and gastric emptying. All significantly delayed gastric emptying despite an increase in postprandial antral contractility as assessed using antral manometry, electrogastrography, and dynamic antral scintigraphy. Interestingly, these agents also significantly stimulated antral phase III MMCs in the fasting state.

The observation that during fasting, gastric acid suppression with each of the agents, ranitidine, famotidine, and omeprazole, was associated with an increased occurrence of antral phase III MMCs suggests that gastric acid

Table 2 Effect of gastric acid suppressants on gastric emptying scintigraphy

	Per cent remaining at 2 hours	$t_{1/2}$ (min)	Lag phase (min)	Slope (k) (min ⁻¹)
Placebo	27 (4)	78 (5)	46 (4)	0.017 (0.002)
Ranitidine	46 (4)*	113 (10)*	57 (6)	0.012 (0.001)*
Famotidine	41 (5)*	103 (8)*	47 (7)	0.012 (0.001)*
Omeprazole	46 (4)*	107 (8)*	48 (10)	0.011 (0.001)*

Results are expressed as mean (SEM).

* $p < 0.05$ v placebo.

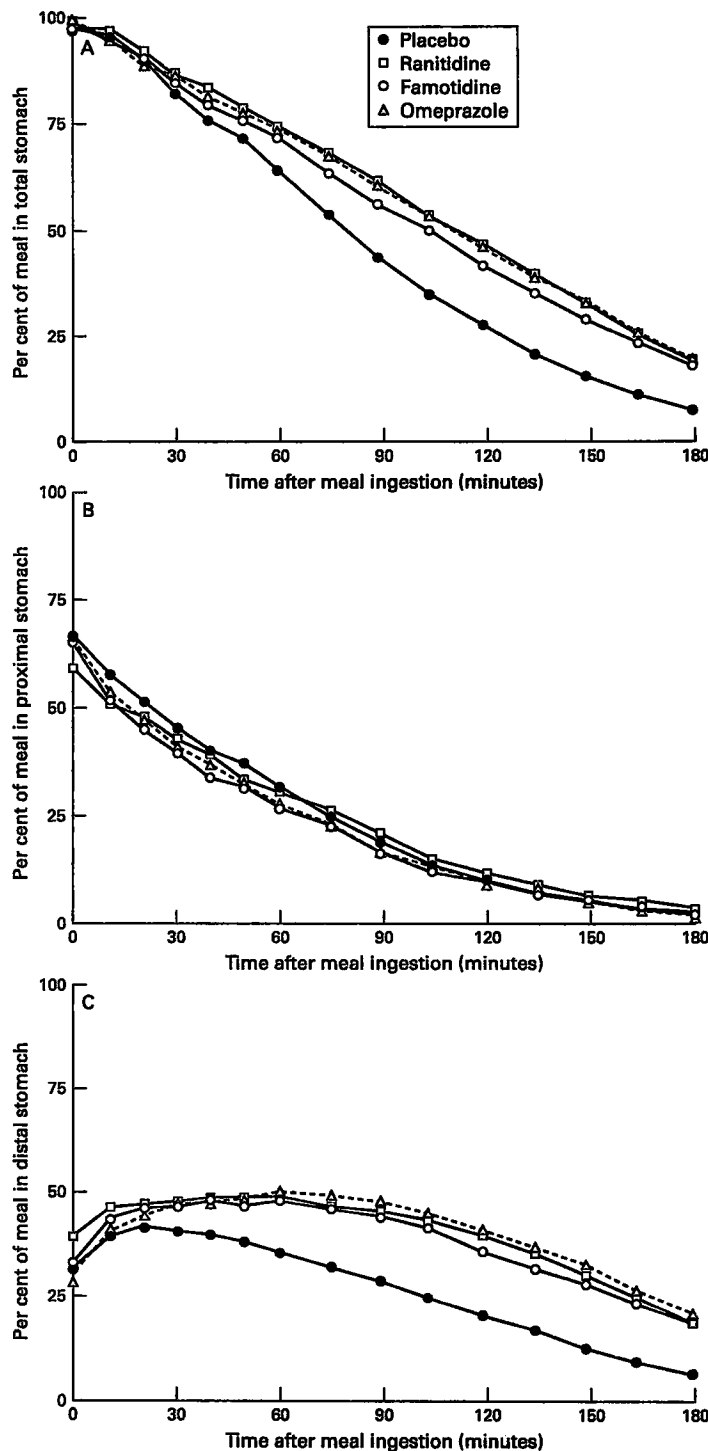
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Figure 4 Effects of gastric acid suppressants on gastric emptying. (A) Total gastric emptying; (B) proximal gastric emptying; (C) distal gastric emptying.

suppression, rather than a direct effect of the pharmacological agents, caused the increased phase III MMCs. A correlation between gastrointestinal secretion and motility has been described previously with increases in gastric acid secretion occurring when motility increases.³¹ Increased gastric acid secretion has been shown to be temporally related to the

phase III portion of the MMC.³² It has been proposed that the regularity of the MMC may be governed by duodenal acidity; an alkaline duodenal pH is important for initiation of gastric phase III complexes.³³ The short duration of fasting recording performed in this study (30 minutes) is a potential limitation; however, inhibition of gastric acid secretion has been observed to cause an increase in fasting gastric phase III activity in other studies with ranitidine³⁴ and omeprazole³⁵ with more prolonged recording times. Conversely, increased gastric acid secretion has been associated with a decreased occurrence of MMCs.³⁶

Postprandially, gastric emptying of solids was prolonged with ranitidine, an H_2 receptor antagonist with cholinergic properties,^{16,17} famotidine, an H_2 receptor antagonist with minimal cholinergic effects, and omeprazole, a proton pump inhibitor without H_2 receptor antagonist or cholinergic effects. These observations suggest that suppression of gastric acid per se resulted in delayed gastric emptying. There are several potential explanations for this effect. Firstly, decreased acid secretion and consequent pepsin deactivation may decrease hydrolysis of solids^{7,10} resulting in larger food particles that would not pass easily through the pylorus. The delay in solid phase gastric emptying seen with omeprazole as reported here and in other studies,^{9,37,38} is associated with normal liquid phase gastric emptying.³⁸ Secondly, decreased gastric acid secretion is associated with an increase in serum gastrin.^{9,38} Gastrin has been reported to delay gastric emptying despite producing an increase in antral contractility.¹⁰ Gastric acid suppression may affect gastric motility and emptying by other mechanisms also. Decreased acid secretion is accompanied by decreased fluid secretion; this might increase viscosity of the meals and alter gastric emptying. On the other hand, gastric acid per se has been reported to delay gastric emptying by activation of duodenal chemoreceptors.^{11,12} Therefore, decreased gastric acid secretion would be expected to alkalinise the stomach and duodenum and thus lessen the "braking action" of duodenal acid.^{11,12,39} This would be expected to accelerate gastric emptying,^{39,40} but such was not seen in this study.

Interestingly, antral contractility was increased postprandially with each of the gastric acid suppressants despite a slowing of gastric emptying. There are some concerns about catheter migration during meal periods when using ambulatory antral manometry²⁰; with ingestion of the test meal and fundic relaxation, the catheter might be withdrawn so that the recording transducers are temporarily recording from a more proximal area, with less contractility. This potential problem, if it occurred, would be similar for each of the study arms and the change between the study arms in this crossover protocol should not be affected. Furthermore, the results of antral manometry are in agreement with those of DAS and EGG. Duodenal contractility, which potentially could inhibit gastric emptying,^{41,42} was not changed during gastric acid suppression. The inverse

256
254

relationship between antral contractility and gastric emptying has been observed previously with gastrin and the cholinergic agonist, bethanechol.¹⁰ Both of these agents increase antral motility, but do not accelerate gastric emptying. Delayed gastric emptying despite augmented antral contractility may be due to decreased hydrolysis of solids, increased pyloric tone, or uncoupling of antroduodenal contractions.

Dynamic antral scintigraphy images and quantifies the displacement of antral contents induced by antral contractions using rapid scintigraphic imaging. The results obtained with dynamic antral scintigraphy were similar to those obtained using antral manometry and electrogastrography. Correlation between these techniques has been reported previously.¹³⁻¹⁵ The increased antral contractility during gastric acid suppression was due to an increased amplitude, but not frequency, of contractions. This observation is similar to that recorded using antral manometry. Interestingly, although there was an increase in DAS amplitude, gastric emptying was delayed due to retention of the radiolabelled meal in the antrum and not in the proximal stomach.

The EGG power, which measures both amplitude and regularity of the recorded EGG signal, increases postprandially.²⁶ The EGG postprandial power increase was greater with each of the three gastric acid suppressants.

This phenomenon is likely to be due to an increase in contractility (as shown with antral manometry and DAS), but could be affected by prolonged gastric distension due to longer gastric retention of the solid meal.²⁶

H₂ receptor antagonists may have effects on gastric motility independent of H₂ receptor blockade and/or inhibition of gastric acid secretion.^{13-14, 40} We reported previously that ranitidine and nizatidine, but not famotidine or cimetidine, increased the amplitude of antral contractions in vitro.¹⁶ This effect was cholinergically mediated. This cholinergic property of some, but not all, of the H₂ receptor antagonists has been reported in several other studies^{14, 15} and may be due to inhibition of acetylcholinesterase,^{19, 17} direct cholinergic agonist activity,¹⁶ or increased neuronal release of acetylcholine.⁴⁰ Previous in vivo studies have found that ranitidine, but not cimetidine, accelerates gastric emptying.^{1, 14} Other studies have suggested that ranitidine, but not cimetidine, increased antral contractility.⁵ Our study in normal human subjects shows increased antral contractility not only with ranitidine, but also with famotidine which has minimal cholinergic effects and also with the proton pump inhibitor, omeprazole. Thus the changes in gastric motility were seen irrespective of the method of gastric acid suppression, suggesting that the increased antral contractility might not be related to selective cholinergic properties of the compounds,

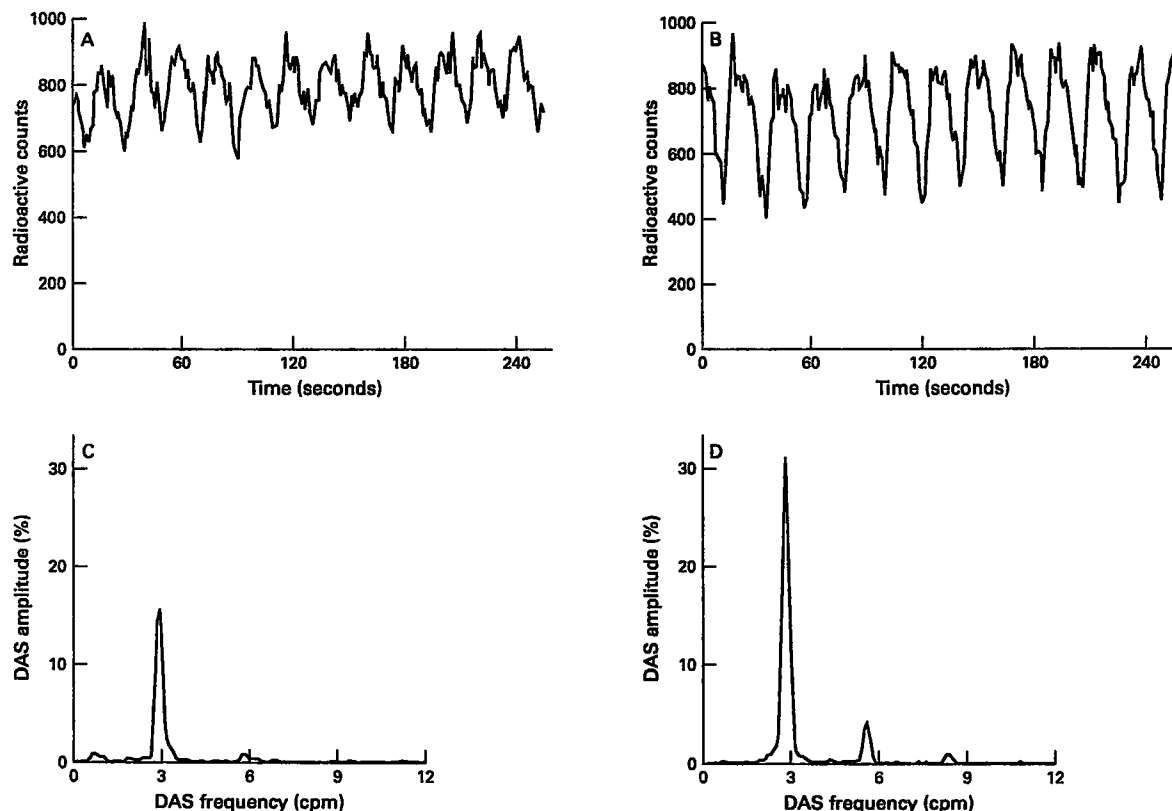


Figure 5 Dynamic antral scintigraphy. The time activity curve (A) depicts radioactive counts in the mid-antral region versus time for the placebo arm for a subject 60 minutes after meal ingestion. The phasic counts represent the contracting antrum. (B) represents the same subject at the same time period after omeprazole therapy. There were increased phasic excursions of the radioactive counts in the omeprazole period as compared with placebo. With the fast Fourier transform analysis, the dominant frequency is represented by the peak with the highest amplitude (C and D).

2875

but rather, to the inhibitory effects of these compounds on gastric acid secretion.

These studies show that therapeutic doses of histamine H_2 receptor antagonists administered intravenously and proton pump inhibitors administered orally delay gastric emptying. We cannot specifically address the degree of acid suppression achieved by these drug treatments, since an intragastric pH probe was not used during these studies. The study design used accepted therapeutic doses of the gastric acid suppressants, ones that are used clinically to achieve robust acid suppression. Using our clinical cut off for determining delayed gastric emptying of >50% retention at two hours,⁴⁷ 5/15 of the subjects had delayed gastric emptying while in the ranitidine arm, 6/15 while in the famotidine arm, and 4/12 while in the omeprazole arm, compared with only 1/15 subjects in the placebo arm. Thus, the performance of the gastric emptying test on gastric acid suppressants may cause a clinically significant delay in gastric emptying. From a practical point of view, gastric emptying and motility studies should be interpreted cautiously in patients under treatment with gastric acid suppressants. Whether gastric emptying is slowed by oral administration of H_2 receptor antagonists,⁴ and whether this slowing affects dyspeptic symptoms (early satiety, nausea, abdominal bloating) remains to be determined.

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- El resumen y el capítulo descriptivo de la solicitud de los folios 63 y 4 a 42 respectivamente.
- Los ejemplos que ilustran la solicitud en los folios 43 a 53.
- Las cláusulas 1 a 10 relacionadas en el capítulo reivindicatorio de la solicitud y que se encuentran en los folios 54 a 62.
- El primer examen de forma realizado a la solicitud con número de oficio 757, que se encuentra en el folio 69.
- Copia de la solicitud original mediante la cual se reivindica prioridad, allegada con motivo del requerimiento formal No. 757 y mediante memorial de fecha 23/01/2001. La prioridad de Estados Unidos US09/458388 de 10/12/1999 se encuentra en los folios 171 a 221, junto con su traducción correspondiente en los folios 89 a 170.
- La solicitud de examen de patentabilidad junto con su correspondiente recibo de pago, que se encuentra en los folios 225 y 226.
- El primer examen de fondo realizado a la solicitud, en virtud del artículo 45 de la Decisión 486, que se encuentra en los folios 228 a 233, notificado por fijación en lista el 16/03/2006.
- El memorial de fecha 17/08/2005 mediante el cual se solicita se atienda el asunto de la patentabilidad de la invención en los folios 234 y 235.
- El memorial de fecha 07/06/2006, mediante el cual se da respuesta al requerimiento técnico de fondo efectuado a la luz del artículo 45 y que contiene un nuevo capítulo reivindicatorio de cuatro cláusulas y se encuentra en los folios 236 a 239.

2. OBJETO DE LA INVENCION:

La solicitud hace referencia a una ***"Combinación farmacéutica útil para el tratamiento de movilidad gastrointestinal alterada, sensibilidad, secreción, o desórdenes abdominales"***.

- **Reivindicaciones 1 a 4:**

Se reivindica una combinación farmacéutica que comprende:

- a) Tegaserod o una sal farmacéuticamente aceptable del mismo; y
- b) Omeprazol o una sal, enantiómero o racemato farmacéuticamente aceptable del mismo; y
- c) Vehículos farmacéuticamente aceptables.

La cual participa en la fabricación de un medicamento para tratar la enfermedad de reflujo gastro-esofágico (GRED).

Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K³¹/404³¹/155** de la **Clasificación Internacional de Patentes**.

3. EXCEPCIONES A LA PATENTABILIDAD:

El artículo 20 en su literal (d) contempla: *"No serán patentables los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*

Al tenor del artículo 20 de la norma Andina, es claro que el alcance de la cláusula 3, que hace referencia a la aptitud de la combinación farmacológica para participar en el tratamiento terapéutico del reflujo gastro-esofágico (GRED) se encuentra contemplada dentro de las excepciones a la patentabilidad que el legislador Andino, señaló de manera taxativa en la Decisión comunitaria; así las cosas, se recomienda eliminar del capítulo reivindicatorio la cláusula señalada.

4. DETERMINACIÓN DEL ESTADO DE LA TÉCNICA:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de presentación de la solicitud en estudio - 10.12.1999-, relacionados con la materia técnica reivindicada:

Nº	Documento	Título	Fecha de Publicación
D1	Artículo 1*	"Effect of gastric acid supressants on human gastric motility"	1998
D2	Artículo 2**	"SDZ HTF 919 Stimulates Canine Colonic Motility and Transit In Vivo"	1997

*Artículo 1: Parkman H P, Urbain J-L C, Knight L C, Brown K L, Trate D M, Miller M A, Maurer A H,

258

260

Fisher R S. "Effect of gastric acid suppressants on human gastric motility". Temple University-USA. 1998. URL: <http://www.bmjjournals.com/subscriptions>

**** Artículo 2:** Nguyen A, Camillero M, Kost L, Metzger A, Sarr M, Hanson R, Fett S y Zinsmeister A R. "SDZ HTF 919 Stimulates Canine Colon Motility and Transit *In Vivo*". The Journal of Pharmacology and Experimental Therapeutics. 1997. Vol. 280, No. 3. pages 1270 – 1276.

5. EVALUACIÓN DE LOS REQUISITOS DE PATENTABILIDAD:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*.

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

5.1 Evaluación de SUFICIENCIA Y NIVEL INVENTIVO:

El artículo 18 de la decisión 486 dispone: *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la Materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica"*

El artículo 28 de la decisión 486 dispone: *"La descripción deberá divulgar la invención de manera suficientemente clara y completa para su comprensión y para que una persona capacitada en la materia técnica correspondiente pueda ejecutarla. La descripción de la invención indicará el nombre de la invención e incluirá la siguiente información:*

(...) c) una descripción de la invención en términos que permitan la comprensión del problema técnico y de la solución aportada por la invención, exponiendo las diferencias y eventuales ventajas con respecto a la tecnología anterior;

Y el artículo 30 de la decisión 486 dispone: *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*.

Una vez efectuado el análisis de la afectación ejercida por las publicaciones médicas D1 y D2 esta Dependencia se permite formular el siguiente concepto:

- Teniendo en cuenta el alcance de la publicación D1 que relaciona los resultados de un estudio clínico que pretendía determinar el efecto causado sobre la motilidad gastrointestinal al utilizar sustancias que presentan actividad supresora de la liberación de ácidos gástricos, tal es el caso de Ranitidina, Famotidina y Omeprazol y que la publicación D2 señala el efecto de Tegaserod, un agonista 5HT, sobre la motilidad gastrointestinal, es posible

afirmar que existe una falta evidente de nivel inventivo de la materia reclamada, por cuanto ya el estado de la técnica a la fecha de presentación de la solicitud en estudio, afirmaba acerca de los efectos benéficos de las sustancias activas en la terapéutica de los síndromes gastrointestinales.

Una vez se estudian a fondo las publicaciones señaladas, es posible determinar que la acción de combinar dos fármacos como Tegaserod y Omeprazol para tratar el síndrome de movilidad intestinal constituye una derivación evidente del estado de la técnica, por cuanto no era inesperada la actividad benéfica que los principios activos ejercían por separado cuando se administraban a pacientes que padecían síndromes gastrointestinales como reflujo gastroesofágico o disfunción en el tránsito y motilidad intestinal.

Es importante enfatizar en el hecho de que la asociación farmacológica reclamada no se encuentra suficientemente sustentada en el aparte descriptivo, porque en el mismo sólo se hace referencia a la caracterización de ciertas enfermedades gastrointestinales asociadas a la actividad disfuncional del músculo liso que inerva estas vías y a la producción exacerbada de los ácidos gástricos e intestinales. Si bien es cierto se presentan ejemplos de asociaciones farmacológicas, en ningún aparte de la descripción se encuentran resultados sorprendentes o inesperados entorno a un efecto acumulativo sinérgico de adición o dualismo que respalde técnicamente las pretensiones del solicitante.

- Entorno a la formulación del problema técnico que se pretendía resolver se mencionan ciertas patologías como el síndrome de intestino irritable, la enfermedad de reflujo gastro-esofágico y la dispepsia, todas ellas caracterizadas por la motilidad alterada, sensibilidad, secreción y/o infecciones como las causadas por *Helicobacter pylori*, así como el estrés.

De acuerdo con la argumentación técnica, existía entonces la necesidad de formular agentes que modularan y normalizaran la movilidad gastrointestinal alterada, la sensibilidad y la secreción, y que interactuaran con los receptores 5-HT que se involucraban en diferentes procesos fisiológicos.

Así las cosas, el aporte que hace la invención al estado de la técnica se deriva de la combinación farmacológica de cuando menos un agente capaz de interactuar con un receptor 5HT – como es el caso de Tegaserod – con un coagente que lo respalde en la terapia, tal es el caso de un inhibidor de la bomba de protones como Omeprazol.

Sin embargo, las publicaciones médicas D1 y D2 ya establecían la posibilidad de formular Omeprazol y Tegaserod, de forma separada, para el tratamiento de disfunciones en la movilidad gastrointestinal. Si bien es cierto que en la solicitud se pretende el privilegio de patente para la asociación farmacológica, las publicaciones médicas ya habían mencionado la actividad beneficiosa que se conseguía al administrar por separado los fármacos Tegaserod y Omeprazol, lo cual constituye un indicio de falta de nivel inventivo por cuanto ya el estado de la técnica hacía alusión a la administración de los fármacos en esta clase de patologías.

De otro lado, si realmente existe una ventaja técnica inesperada y sorprendente derivada de la administración concomitante de los principios activos, cabe preguntarse porqué no se reportan los resultados comparados que evidencien el sinergismo de adición o dualismo entre Tegaserod y Omeprazol; ya que no basta con afirmar que existen ventajas como se presenta en el folio 44 *“La combinación de tegaserod mas un coagente incrementó de una manera significativa la movilidad gastrointestinal y colónica, comparándose con el placebo y cualquiera de los compuestos*

administrados solos”; o como se presenta en el folio 48 “La combinación farmacéutica de Tegaserod y un coagente reduce de una manera significativa el dolor gástrico asociado con la distensión gástrica y los incrementos en el tono gástrico, comparándose con el placebo y cualquiera de los compuestos administrados solos”; o en el folio 50 “La combinación farmacéutica de Tegaserod mas un coagente, reduce de una manera significativa el dolor rectal y colónico asociado con distensión rectal, e incrementa el tono colorrectal, comparándose con el placebo y con cualquiera de los compuestos administrados solos”; e incluso en el folio 52 “La combinación de 1) Tegaserod con Omeprazol y 2) Tegaserod con ranitidina, reduce de una manera significativa los episodios de agruras que se presentan por semana durante e periodo de ocho (8) semanas del periodo doble-ciego controlado con placebo del estudio, comparándose con cualquiera del placebo, Tegaserod, ranitidina y omeprazol solos”; se requieren los resultados comparados de los parámetros farmacocinéticos medidos, una vez se administró concomitantemente la combinación farmacológica.

Bajo este respecto es importante señalar que en ningún aparte de la solicitud se precisa cómo se administra la combinación farmacológica, por cuanto el término “Combinación” es impreciso al momento de definir si los principios activos de administraron de manera independiente, independiente y secuencial o de manera concomitante, y para una persona versada en la materia técnica es bien sabido que estos parámetros en clínica son definitivos al momento de determinar si se produjo un efecto farmacológico acumulativo, sinérgico aditivo o de dualismo. Es por esto que se requiere al interesado para que fije los aspectos característicos de la composición farmacéutica que contiene dicha combinación farmacológica, de tal suerte que sea posible determinar cómo se administran los compuestos de la invención y bajo qué parámetros farmacocinéticos y farmacotécnicos se sustenta la ventaja técnica que se señala en la invención.

- Por otro lado la invención no se describe en términos que permitan la comprensión del problema técnico asociado a la administración independiente de los principios activos y tampoco sustenta la ventaja técnica de la administración concomitante y la solución aportada por la invención al estado de la técnica y tampoco se exponen las diferencias y eventuales ventajas con respecto a la tecnología anterior.

Y bajo este respecto es que se afirma la afectación ejercida por las anterioridades D1 y D2 que si bien es cierto no señalan de forma taxativa la combinación terapéutica, si constituyen indicio de la actividad terapéutica de las moléculas sobre el tránsito y la movilidad intestinal y en este sentido su asociación resulta obvia para una persona versada en farmacología clínica.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	Artículo 1	1 a 4	Nivel Inventivo
D2	Artículo 2	1 a 4	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días