Effects of Cilomilast, a Selective Phosphodiesterase 4 Inhibitor, on Esophageal Motility and pH, and Orocecal and Colonic Transit: Two Single-Center, Randomized, Double-Blind, Placebo-Controlled, Two-Part Crossover Studies in Healthy Volunteers

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ABSTRACT

Background: Phase IIb studies have reported that cilomilast, a selective phosphodiesterase 4 inhibitor being developed for the treatment of chronic obstructive pulmonary disease, is associated with gastrointestinal (GI) adverse effects (AEs) in a small proportion (~5%) of individuals.

Objectives: The aims of these 2 studies were to investigate the effects of cilomilast 15 mg BID on: (1) lower esophageal sphincter pressure (LESP) and esophageal body motility and pH (study 1); and (2) orocecal and whole-gut transit times (OCTT and WGTT, respectively) (study 2) in healthy volunteers.

Methods: These 2 randomized, double-blind, placebo-controlled, 2-part crossover studies were conducted at the Neurogastroenterology Unit, Wythenshawe Hospital, Manchester, United Kingdom (study 1) and GlaxoSmithKline, Harlow, United Kingdom (study 2). In study 1, subjects were randomly assigned to receive either cilomilast (15 mg BID) or matched placebo (control) for 7 days (13 doses; subjects were not given the evening dose on day 7), and in study 2, cilomilast (15 mg BID) or matched placebo (control) for 9 days (18 doses) in each of 2 treatment periods. After study drug administration, combined esophageal motility and pH were recorded for 2 hours before and 4 hours after the administration of a standardized meal (2400 kJ [573 kcal]). Sequences of 6 consecutive 5-mL water swallows (separated by 20 seconds) were carried out 60 and 90 minutes (fasting) and 150, 180, 210, 240, 300, and 360 minutes (fed) after study drug administration. OCTT was determined from the increase in breath hydrogen after the meal. WGTT was determined from the time taken to excrete at least 16 of 20 ingested radiopaque markers, ingested as 2 capsules, each containing 10 radiopaque markers, with 240 mL of water. AEs were elicited at specified times throughout each session using nonleading questions, spontaneously reported AEs, and diary cards.

Results: Study 1 enrolled 20 subjects (11 men, 9 women; age range, 20–52 years). Study 2 enrolled 16 subjects (10 men, 6 women; age range, 19–48 years). No clinically significant differences in the amplitude (mean difference in postprandial–preprandial AUC_{0-t}/t, 6.09 mm Hg; 95% CI, –10.66 to 22.84), duration (difference, –0.08 second; 95% CI, –0.54 to 0.37), or velocity of propagation (difference, 0.90 cm/s; 95% CI, –0.66 to 2.46) of esophageal contractions, LESP (difference, –0.39 mm Hg; 95% CI, –5.23 to 4.45), or preprandial or postprandial percentage time pH <4 (median differences: preprandial, 0.47% [95% CI, –0.45 to 1.27]; postprandial, –0.005% [95% CI, –1.30 to 6.27]) were found with cilomilast compared with placebo. No significant differences in OCTT (difference, –0.37 hour; 95% CI, –1.59 to 0.84) or WGTT (difference, –2.96 hours; 95% CI, –20.76 to 14.84) were found with cilomilast compared with controls. In both studies, the most frequently reported AEs with

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cilomilast use were nausea (8/18 in study 1 and 3/16 in study 2) and headache (8/18 in study 1 and 6/16 in study 2); however, these were generally of mild to moderate intensity. Overall, GI AEs did not correlate with changes in GI motility.

Conclusion: The results of these 2 studies suggest that cilomilast was not associated with significant changes in esophageal motility and pH or GI transit in these healthy volunteers. (*Clin Ther.* 2006;28:569–581)

Key words: phosphodiesterase 4 inhibitor, cilomilast, esophageal motility, esophageal pH, transit.

INTRODUCTION

Phosphodiesterase 4 (PDE-4), a key regulator of cyclic adenosine monophosphate (cAMP) metabolism, has become an important molecular target in the development of novel therapies for chronic lung disorders, such as chronic obstructive pulmonary disease (COPD). By increasing cAMP accumulation in proinflammatory and immune cells, as well as in airway smooth muscle, inhibitors of PDE-4 have been shown to exert significant anti-inflammatory effects.[1,2]

A major limitation in the use of first-generation PDE-4 inhibitors, such as rolipram, was their propensity to cause significant gastrointestinal (GI) disturbance,[3,4] which led to their eventual withdrawal from development. With a median inhibitory concentration of 71 nmol/L at the receptor, cilomilast is a potent and selective PDE-4B inhibitor that retains the anti-inflammatory activity of earlier compounds, such as rolipram, but with a reduced potency for GI upset.[5–8] In Phase IIb and III studies, the prevalence of GI disturbance in patients with COPD receiving cilomilast was between 5% and 10%.[9]

GI disturbances associated with cilomilast include nausea, vomiting, dyspepsia/heartburn, and diarrhea, but, based on a MEDLINE search for literature concerning the pharmacodynamic properties of cilomilast (key terms: *cilomilast*, *esophagus*, *motility*, *pH*, and *gastrointestinal transit*; years: 2000–2006), the mechanisms underlying these effects remain unknown. Two early studies found that several PDE-4 isozymes are expressed in the gut musculature, where their selective inhibition results in increased cAMP levels and, consequently, relaxation of GI smooth muscle and lower esophageal sphincter (LES) muscle.[10,11] Another study found that PDE-4 inhibitors are inducers of gastric acid secretion.[5] These effects could theoretically contribute to the tolerability of cilomilast, but based on our literature search, to date, no studies of this investigational drug have examined its effects on GI motility or gastroesophageal reflux (GER) in humans (GlaxoSmithKline [GSK], unpublished data, 2005).

The aims of these 2 studies were to investigate the effects of cilomilast on: (1) esophageal and LES motor function and esophageal pH (study 1); and (2) orocecal and whole-gut transit times (OCTT and WGTT, respectively) (study 2) in healthy volunteers.

SUBJECTS AND METHODS

Subjects

Study 1 (SB-207499/112)

Subjects with a history or presence of abnormalities in esophageal body and/or LES motor function were excluded.

Study 2 (SB-207499/113)

Patients with regular bowel movements (~1 a day) were enrolled in the study.

These 2 studies were conducted in accordance with Good Clinical Practice guidelines[12] and the Declaration of Helsinki (as amended in 1996).[13] The protocols of both studies were reviewed and approved by the appropriate ethics committees at the study centers: the South Manchester Research Ethics Committee, Manchester, United Kingdom (study 1), and SmithKline Beecham Pharmaceuticals Independent Ethics Committee, Harlow, United Kingdom (study 2).

For both studies, male and female healthy volunteers aged ≥18 years were recruited from volunteer panels at each site, using advertising media approved by the local ethics committees. Subjects enrolled in both studies were required to be aged between 18 and 55 years; have no abnormalities on biochemistry or hematology examinations on the prestudy medical examination; and have a body weight >50 kg, but within 25% of ideal weight for sex, height, frame, and age according to 1983 Metropolitan Height/Weight Tables.[14] This homogeneous population was chosen to allow the pharmacology of cilomilast to be manifested without the confounding factors of age and comorbid disease. Female subjects who were surgically sterilized or had undergone a hysterectomy were included in the studies. Women of childbearing potential were included provided they used adequate

contraceptive precautions (ie, oral contraceptive and/or at least 1 barrier method). Subjects who had received a prescribed medication in the 7 days before the first dosing day or over-the-counter medication in the 48 hours before the first study dosing day, which might have interfered with the study procedures and/or compromised the integrity of the tolerability results, were excluded. All subjects provided written informed consent. Volunteers were paid a small honorarium for their time and travel expenses in accordance with ethics committee guidelines.

Study Design and Procedures

Both studies were single center, randomized, double-blind, placebo-controlled, and 2-part crossover in design. In study 1, subjects were randomly assigned to receive either cilomilast (15 mg BID) or matched placebo (control) for 7 days (13 doses; subjects were not given the evening dose on day 7), and in study 2, cilomilast (15 mg BID) or matched placebo (control) for 9 days (18 doses) in each of 2 treatment periods. Tablets were self-administered every 12 hours, immediately after meals. Within each study, assessments were performed at the same times of day and treatment periods were separated by at least 7 days.

In both studies, subjects were randomly allocated to 1 of 2 dosing sequences: cilomilast, placebo or placebo, cilomilast. The randomization schedule was prepared by Clinical Pharmacology Statistics, GSK, and sent to Clinical Trial Supplies, GSK, for the packaging of double-blind (identical) supplies for individual study subjects, before dispatch to the investigational sites. Subjects were enrolled in sequential fashion, using the next available subject number, once deemed eligible for enrollment and having signed the informed-consent form. All study participants, investigational staff, GSK monitoring staff, and GSK data-management staff remained blinded to treatment allocation throughout the study. No other medications were allowed throughout the studies, and compliance was assessed using pill counts at each study visit or by monitored study drug administration in the clinic.

Study 1

On the morning of day 7 of each treatment period, subjects were required to report to the study site, having fasted from food and fluids for at least 6 hours. After completion of predose assessments (adverse effects [AEs], electrocardiography, urine tests for drug and pregnancy screening for female subjects of childbearing potential), subjects self-administered the last single 15-mg tablet of cilomilast or placebo with 100 mL mineral water. A sleeve manometric/pH assembly was passed via a lightly anesthetized nostril and maneuvered into position such that the sleeve sensor straddled the LES, as described by Foster et al.[15] The subjects then rested in a sitting position for 10 minutes. With the subjects still in a sitting position, 2 sequences of six 5-mL water swallows (with each swallow separated by at least 20 seconds) were performed at 60 and 90 minutes after study drug administration. If a subject swallowed twice, or took a dry swallow during the 20-second interval between water swallows, the water swallow was repeated after an additional 20 seconds. Two hours after study drug administration, the subjects consumed a standardized meal consisting of 335 g shepherd's pie (117 g minced beef, 33 g onions, 60 g carrots, 167 g boiled potatoes, 7 g butter, 17 mL milk, 50 mL beef stock), 75 g vanilla ice cream, and 142 mL whole milk (total energy intake, 2400 kJ [573 kcal]) within 15 minutes. Additional sequences of six 5-mL water swallows were then carried out 30, 60, 90, 120, 180, and 240 minutes after the start of the ingestion of the meal (ie, 150, 180, 210, 240, 300, and 360 minutes after study drug administration). The subjects were prohibited from sleeping during the assessments and were allowed to move from the sitting position only to void their bladders. AEs were elicited at specified times throughout each session using nonleading questions, spontaneously reported AEs, and diary cards.

Study 2

On the morning of day 5 of each treatment period, fasted subjects were required to report to the clinical unit where, 30 minutes after the scheduled morning study drug administration, subjects consumed a standardized breakfast, and OCTT for the head of the meal was assessed using a method similar to that described by Levitt.[16] On day 6 of each treatment period, after fasting and administration of the scheduled morning study drug and standardized breakfast, WGTT of 20 radiopaque markers was assessed. The markers were swallowed with the meal with the fluids provided. AEs were elicited at specified times throughout each session using nonleading questions, spontaneously reported AEs, and diary cards.

Study 1

Esophageal Manometry/pH

Manometric recordings were performed using an 8-lumen catheter that incorporated a 6-cm sleeve sensor at the distal end to monitor the LES pressure (LESP) (part no. A-E1-LOSS-1, Dentsleeve International Ltd., Bowden, Australia; external diameter, 4.5 mm), as described by Foster et al.[15] Swallowing was recorded via a side hole in the pharynx, 25 cm superior to the proximal margin of the sleeve. Esophageal contractions were measured via side holes located 0, 5, 10, and 15 cm superior to the proximal margin of the sleeve, and gastric pressure via a side hole 1 cm inferior to the distal margin of the sleeve. The esophageal and pharyngeal side holes were perfused with degassed distilled water at 0.3 mL/min and the sleeve sensor, and the gastric side hole at 0.5 mL/min, by a pneumohydraulic capillary infusion system (Arndorfer Inc., Greendale, Wisconsin). Pressures were sensed by external water-filled pressure transducers connected to an analog–digital converter (Polygraph HR, Synectics Medical Ltd., Stockholm, Sweden) and then displayed and recorded on a personal computer using Polygram software (Synectics Medical Ltd.). The system was calibrated at 0 and 50 mm Hg at the beginning of each assessment and checked again at the end of each study to confirm it was still recording these pressures accurately.

Esophageal pH was monitored using a pediatric antimony electrode (2-mm diameter) with an external cutaneous reference electrode (Synectics Medical Ltd.). The pH electrode was positioned 3 cm superior to the proximal margin of the sleeve, as described by Mittal and McCallum,[17] corresponding to 5 cm superior to the LES, as described by Johnson,[18] and attached to the manometric catheter by small bands (external diameter, 3.7 mm; internal diameter, 3.1 mm; length, 4 mm) of silicone rubber tubing (Altec Products Ltd., Alton, United Kingdom) spaced at 5-cm intervals along the catheter. The pH data recorded by the electrode was digitized by the analog–digital converter and then displayed and recorded on the computer. The pH electrode was calibrated at 1.07 and 7.01 pH units before each study and checked at the end of the recording to ensure that it was still accurately registering pH.

Study 2

Orocecal Transit Time

After subjects rinsed their mouths with a 1% chlorhexidine mouthwash (Corsodyl, GSK Consumer Healthcare, United Kingdom), 3 end-expiratory breath samples were drawn as baseline samples. The mean of the 3 samples was calculated. Subjects then ingested 250 g baked beans on 2 pieces of bread or toast, and immediately after consumption rinsed their mouths again with mouthwash. Thirty minutes after breakfast, end-expiratory breath samples were collected at 10-minute intervals for a maximum of 10 hours after the meal. Arrival of the head of the meal in the cecum defined the *first time breath hydrogen increased to 15 ppm above the mean baseline value* and was sustained for 3 consecutive readings. Breath hydrogen was measured using a breath hydrogen monitor (model 81HP, Gas Measurement Instruments Ltd., Renfrew, United Kingdom).

Whole-Gut Transit Time

Immediately after breakfast, 2 capsules, each containing 10 radiopaque markers, were ingested with 240 mL water. Feces were then collected after each bowel movement into separate containers until a total of at least 16 (80%) of the markers had been recovered. The time of the last bowel movement that yielded the total of at least 16 markers was recorded as the WGTT.

Data Measurements

Study 1

Esophageal Motility

The esophageal contractions produced by water swallows were assessed under blinded conditions by the same observer (W.A.) for all assessments. The observer manually positioned cursors on the computer monitor and then used the software to calculate the various parameters listed below. Baseline values were set automatically by the computer program. The amplitude was measured (in mm Hg) from the baseline to the peak of esophageal contraction. The *contraction duration* was defined as the time interval (in seconds) between the onset of the sharp increase in the esophageal pressure wave and the return of pressure to baseline, as described by Richter et al.[19] The velocity of propagation was calculated (in cm/s) by dividing the time interval between the peaks of the esophageal contractions into the distance between adjacent side holes (ie, 5 cm), as described by Dooley et al.[20]

After esophageal manometry, motility was arbitrarily defined as *clinically abnormal* if >15% of the total number of esophageal contractions exhibited 1 or more of the following: amplitude >180 mm Hg; dura-

tion >7 seconds; and/or >2 repetitive contractions occurred, as described by Castell.[21]

Lower Esophageal Sphincter Pressure

LESP was measured visually by placing a mean line over the end-expiratory pressures recorded in the 1-minute period preceding each sequence of 6 water swallows and referenced to intragastric pressure, as described by Dent et al.[22] The baseline LESP before each water swallow and the nadir LESP during sphincter relaxation were measured and referenced to intragastric pressure to determine the extent of relaxation of the LES, as described by Murray et al.[23] Extent of relaxation of the LES was represented as the *percentage relaxation*, calculated as follows:

$$\% \text{ Relaxation} = (\text{Baseline LESP} - [\text{Relaxed LESP/Baseline LESP}]) \times 100$$

Esophageal pH

The pH recording was used to identify *GER episodes*, defined as periods during which the esophageal pH was <4 for at least 4 seconds. The method employed in analyzing these data has been described previously.[22] Briefly, the *duration of GER episode* was defined as the time period between the onset of the pH decrease to <4 and when the pH returned to 4. The *esophageal acid exposure time* was calculated as the sum of the durations of all reflux episodes, divided by the total recording period, multiplied by 100, to give the total percentage time esophageal pH was <4 (%t pH <4).

In addition, the total number of postdose transient LES relaxations (TLESRs) was recorded. As described elsewhere,[24] the event associated with each episode of GER was recorded as TLESR only; TLESR plus a strain (defined as a brief and sharp increase in gastric and esophageal pressure >2-fold the normal respiratory excursions in gastric pressure observed in the individual); swallow-induced LES relaxation (pharyngeal contraction between 4 seconds before and 2 seconds after LES relaxation); strain only; absent baseline LESP (pressure drift to 0 mm Hg at a rate of ≤1 mm Hg/s); or spontaneous GER if no pressure activity preceded the decrease in pH.

Study 2
Orocecal and Whole-Gut Transit Times

OCTT was defined as the time (in hours) of the first of 3 consecutive breath hydrogen readings of ≥15 ppm higher than the baseline value. Patients who did not achieve 3 consecutive breath hydrogen readings of ≥15 ppm higher than baseline were assigned a transit time of 10 hours (GSK, unpublished data, 1997).

WGTT was determined as the time (in hours) when the fecal samples yielded a total count of at least 16 of the 20 (at least 80%) radiopaque markers.

Statistical Analysis
Study 1

The following measurements were derived: (1) analysis of variance (ANOVA)-derived preprandial and postprandial area under the plasma cilomilast concentration–time curve from time 0 to the last measurable plasma cilomilast concentration, averaged over time (AUC_{0-t}/t); (2) the difference between postprandial and preprandial AUC_{0-t}/t values; and (3) the maximum preprandial and postprandial values of amplitude, duration, and velocity of propagation of esophageal contraction and LESP. In addition, preprandial and postprandial %t pH <4 values were calculated.

The primary end point was amplitude of contraction. Secondary end points were duration, velocity of propagation, and LESP. All end points (except %t pH <4), including the effects of sequence, subject within sequence, period, and regimen, were analyzed using ANOVA. All results were adjusted for these factors. The %t pH <4 was analyzed using a nonparametric test using the method described by Hauschke et al.[25] Point estimates and 95% CI for the cilomilast–placebo difference were constructed using the residual variance from the ANOVA. There were no adjustments for multiple comparisons.

Based on a within-subject SD of 10 mm Hg, it was estimated that a sample size of 12 subjects was required to complete the study to establish 90% power to show a difference between cilomilast and control groups in terms of AUC_{0-t}/t (the weighted mean) for the amplitude of esophageal contraction, based on an underlying difference of 20%, type I error rate of 5%, 2-sided hypothesis test, and control amplitude contraction of 72 mm Hg.[25]

Study 2

The end points were OCTT and WGTT, which were analyzed using ANOVA, including the effects of sequence, subject within sequence, period, and regimen. All results presented are adjusted for these factors. Point estimates and 95% CIs for the between-group

differences were constructed from the residual variances from the ANOVA. There were no adjustments for multiple comparisons.

We recruited 16 subjects to ensure assessable data from at least 12 subjects. Based on previous similar studies (GSK, unpublished data, 1997), within-subject variation, expressed as an SD, was estimated to be ~1.27 hours for OCTT and 21.88 hours for WGTT. Based on these estimates of within-subject variability and a sample size of 12 subjects, the lower and upper 95% confidence limits for the between-group difference should be no more than 1.16 hours from the point estimate for OCTT and 19.90 hours from the point estimate for WGTT.

RESULTS

Study Populations

Study 1

A total of 20 healthy subjects (11 men, 9 women; age range, 20–52 years; 17 white, 2 Asian, 1 mixed) were enrolled in the study. Of the 20 subjects enrolled, 12 were included in the intrasubject pharmacodynamic analysis. Nine subjects were prematurely withdrawn from the study (4 due to AEs and 5 for other reasons, mainly intolerance of intubation of the esophageal catheter). In the 4 subjects who withdrew due to AEs, 1 AE was GI (severe nausea inducing vomiting when the esophageal catheter was intubated, leading to removal of the catheter). The other 3 AEs leading to withdrawal were migraine, headache (with nausea), and trigeminal neuralgia, all of which led to removal of the catheter and study withdrawal. One subject, although lost to follow-up, was included in the analysis due to having complete manometry/pH data available from both treatment periods.

Study 2

A total of 16 healthy subjects (10 men, 6 women; age range, 19–48 years; 13 white, 2 Asian, 1 mixed) were enrolled in the study. Of the 16 subjects enrolled, 15 were included in the analysis. One subject was prematurely withdrawn due to an AE unrelated to study medication (prolapsed vertebral disc leading to prescription of co-proxamol and diclofenac, which, because of their potential effects on GI transit, required the subject to be withdrawn from the study).

None of the subjects missed any medication in either of the studies.

Esophageal Motility/pH

Cilomilast had no statistically significant effect on the amplitude, duration, and velocity of propagation of esophageal contractions, or on baseline LESP (ANOVA-derived mean preprandial AUC_{0-t}/t, postprandial AUC_{0-t}/t, postprandial–preprandial AUC_{0-t}/t difference, or preprandial and postprandial maximum amplitude) compared with controls (**Figure 1** and **Table I**).

No clinically significant abnormal contractile activity was observed throughout the study, and no difference in esophageal motor and pH patterns could be seen between subjects who experienced GI disturbance and those who did not.

No significant effects on the preprandial %t pH <4 (median difference, 0.47%; 95% CI, –0.45 to 1.27) or postprandial %t pH <4 (median difference, –0.005%; 95% CI, –1.30 to 6.27) were found with cilomilast. Furthermore, no statistically significant differences in %t pH <4 with meal ingestion were found between cilomilast (preprandial, 0.52% [95% CI, 0%–4.35%]; postprandial, 1.08% [95% CI, 0.05%–15.6%]) and placebo (preprandial, 0.16% [95% CI, 0%–5.64%]; postprandial, 1.49% [95% CI, 0%– 6.50%]).

Most GER events were associated with either swallow-induced or TLESR, and there appeared to be no significant difference in their prevalences between cilomilast and controls. Although other events associated with GER were relatively uncommon, there were numerically more postprandial spontaneous GER events. No clinically significant differences in the prevalences of GER events were found between the cilomilast and control groups (**Table II**).

Orocecal Transit Time

No statistically significant differences in OCTT were found between the 2 groups, with the adjusted mean OCTTs of 5.04 and 5.41 hours after administration of cilomilast and placebo, respectively (**Figure 2A**). Inclusion or exclusion of patients with assigned 10-hour OCTTs made no significant difference in the analysis (data not shown).

Whole-Gut Transit Time

No statistically significant differences in WGTTs were found between the 2 groups, with the adjusted mean WGTTs of 50.74 and 53.70 hours after administration of cilomilast and placebo, respectively (**Figure 2B**). Including or excluding the 2 subjects

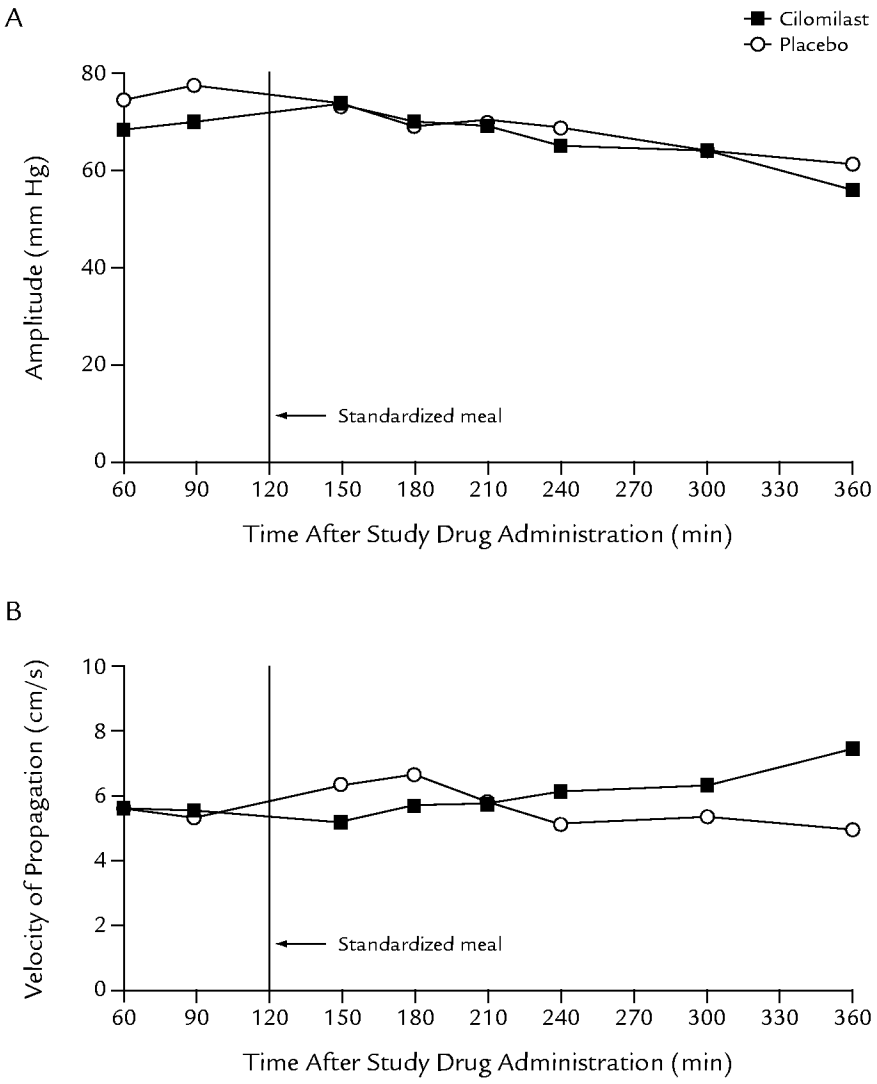

Figure 1. Effects of 7-day self-administration of cilomilast 15 mg BID on esophageal motility in healthy volunteers (N = 12). Mean (A) amplitude and (B) velocity.

(continued)

whose data were identified as outliers made no significant difference in the final analysis (data not shown).

Tolerability

Study 1

Of the 18 subjects exposed to cilomilast, the most frequently reported AEs were nausea (8 patients), headache (8), abdominal pain (5), diarrhea (3), pharyngitis (3), vomiting (2), dyspepsia (2), dizziness (2), and fatigue (2). The majority of these AEs were of mild or moderate intensity and were considered related to the study procedures, study drug, or both. Of the 15 subjects exposed to placebo, 8 reported AEs, with the most frequently reported being headache (7 patients), pharyngitis (2), and fatigue (2).

Study 2

During this study, a total of 32 AEs were reported, 13 of which occurred with cilomilast, and 19 with placebo. Of the 16 subjects exposed to cilomilast, the most frequently reported AEs were headache (6 pa-

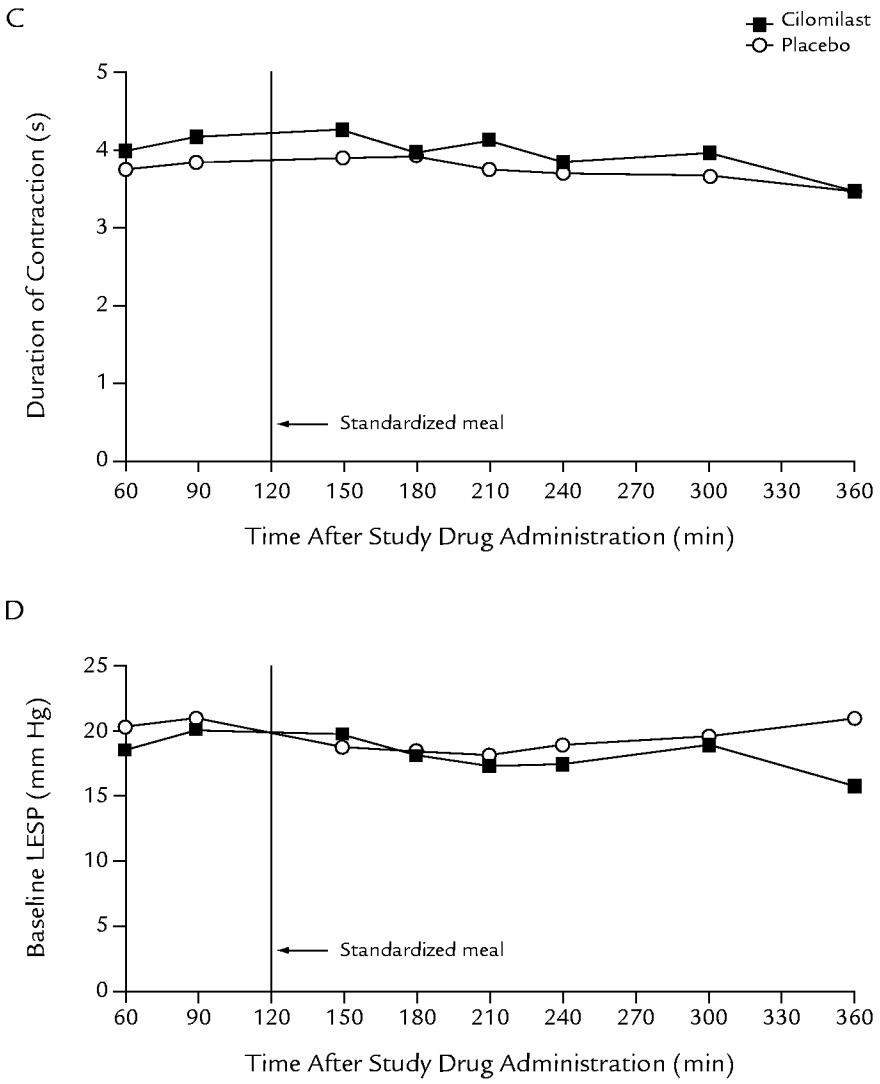

Figure 1. (Continued) Effects of 7-day self-administration of cilomilast 15 mg BID on esophageal motility in healthy volunteers (N = 12). Mean (C) duration of esophageal contractions and (D) mean baseline lower esophageal sphincter pressure (LESP).

tients) and nausea (3). Of the 16 subjects exposed to placebo, the most frequently reported AEs were headache (4 patients), diarrhea (3), abdominal pain (2), and other AEs (7).

In both studies, the pharmacodynamic data from subjects who reported GI AEs appeared similar to those from subjects who did not report them.

DISCUSSION

The results of this study suggest that the PDE-4 inhibitor cilomilast had no significant effects on esophageal motility, resting LESP, TLESR, GER, or gut transit time, even in subjects who reported GI AEs.

Numerous studies,[22,26–35] but not all,[36] have suggested an association between disturbances in GI motility and symptoms. For example, inappropriate TLESR[22,30,33] and dysfunction of the proximal stomach[31] have been found to accompany GER and have been associated with symptoms such as heartburn and dyspepsia; delayed gastric emptying, particularly that of solids, with postprandial fullness and vomiting[32,34]; impaired gastric accommodation with early satiety[35];

Table I. Differences in pharmacodynamic characteristics (esophageal and lower esophageal sphincter motility) (cilomilast 15 mg BID–placebo) after 7-day self-administration in healthy volunteers (N = 20).

Parameter	Amplitude, mm Hg	Velocity of Propagation, cm/s	Duration, s	Baseline LESP, mm Hg
AUC_{0-t}/t (postprandial)				
Mean	−0.41	0.94	0.17	−1.35
95% CI	−9.98 to 9.17	−0.97 to 2.85	−0.02 to 0.36	−4.50 to 1.79
P	0.92	0.30	0.073	0.36
AUC_{0-t}/t (preprandial)				
Mean	−6.50	0.04	0.25	−0.96
95% CI	−28.81 to 15.81	−1.93 to 2.00	−0.12 to 0.63	−5.76 to 3.84
P	0.53	0.96	0.16	0.66
AUC_{0-t}/(t postprandial) − (t preprandial)				
Mean	6.09	0.90	−0.08	−0.39
95% CI	−10.66 to 22.84	−0.66 to 2.46	−0.54 to 0.37	−5.23 to 4.45
P	0.44	0.23	0.70	0.86
Maximum postprandial				
Mean	1.43	1.80	0.32	−0.92
95% CI	−9.53 to 12.40	−1.66 to 5.25	−0.01 to 0.65	−4.88 to 3.05
P	0.78	0.27	0.059	0.62
Maximum preprandial				
Mean	−10.03	−0.23	0.21	−2.17
95% CI	−32.27 to 12.21	−3.22 to 2.77	−0.24 to 0.67	−6.93 to 2.59
P	0.34	0.87	0.32	0.33

LESP = lower esophageal sphincter pressure.

and accelerated GI transit with diarrhea.[26–29] In the present study, despite numerically but not statistically significantly increased duration of esophageal contraction after cilomilast administration compared with placebo, the increase was <1 second, and the resulting duration was well within the normal range,[37] making it unlikely to be the cause of any of the reported upper GI disturbances. Likewise, all other esophageal motor and pH parameters were unaffected by cilomilast, even in subjects experiencing GI AEs. Similarly, although OCTT decreased numerically but not statistically significantly after cilomilast administration, it remained well within that considered to be normal and was not associated with diarrhea. These results suggest that it is unlikely that the GI disturbances associated with cilomilast were a consequence of motor dysfunction.

Preclinical studies suggest that GI AEs result from PDE-4 pharmacology and are caused primarily by inhibition of PDE-4 in the central nervous system (CNS).[38] The four PDE-4 subtypes—PDE-4A, -4B, -4C, and -4D—share similar catalytic sites, and are similarly affected by a variety of PDE-4 inhibitors.[39,40] It is interesting to speculate that PDE-4 subtype selectivity might mediate these GI events, but based on our literature search, no studies are available to support or dispute this hypothesis.

Evidence of a CNS-mediated effect came from studies assessing the anesthetic reversal effect of PDE-4 inhibitors in animal models,[41–43] in which it was hypothesized that PDE-4 inhibitors could trigger the emetic reflex via a sympathetic pathway by mimicking the pharmacologic actions of α_2-adrenoceptor antagonists. Observations that the α_2-adrenoceptor agonist clonidine prevented emesis induced by PDE-4 inhibitors and that the α_2-adrenoceptor antagonist yohimbine triggered vomiting in ferrets lent further support to this hypothesis.[41–43]

It is known that PDE-4 isozymes can adopt 2 distinct conformations, which can be distinguished by their

Table II. Reflux-related adverse events with 7-day self-administration of cilomilast 15 mg BID or placebo in healthy volunteers (N = 20).*† Values are no. (%) of occurrences.

Event	Cilomilast	Placebo
Preprandial		
Swallow-induced LES relaxation‡	34 (65.4)	18 (62.1)
TLESR only	14 (26.9)	8 (27.6)
Absent baseline LESP§	2 (3.8)	1 (3.4)
Strain only	2 (3.8)	0
Spontaneous reflux‖	0	2 (6.9)
Transient relaxation only accompanied by a strain	0	0
Total events	52 (100)	29 (100)
Postprandial		
Swallow-induced LES relaxation‡	64 (57.1)	66 (60.0)
TLESR only	22 (19.6)	21 (19.1)
Spontaneous reflux‖	17 (15.2)	14 (12.7)
Strain only	5 (4.5)	3 (2.7)
Absent baseline LESP§	3 (2.7)	4 (3.6)
Transient relaxation only accompanied by a strain	1 (0.9)	2 (1.8)
Total events	112 (100)	110 (100)

LES = lower esophageal sphincter; TLESR = transient LES relaxation; LESP = LES pressure.
*No clinically significant differences were found.
† Percentages might not total 100% due to rounding.
‡ Swallow-induced LES relaxation = pharyngeal contraction between 4 seconds before and 2 seconds after sphincter relaxation.
§ Absent baseline LESP = pressure drift to 0 mm Hg at a rate of ≤1 mm Hg/s.
‖ Spontaneous reflux = if no pressure activity preceded the pH decrease.

different affinities for rolipram: high-affinity rolipram binding sites (HARBSs) and low-affinity rolipram binding sites (LARBSs).[44] Pharmacologic studies have suggested that HARBS inhibition is more closely associated with CNS and GI AEs compared with LARBS,[38,45] whereas interaction of PDE-4 inhibitors with the LARBS correlates with beneficial anti-inflammatory effects, such as the suppression of tumor necrosis factor–α production from monocytes.[46] Research is needed to determine the effects of PDE-4 inhibitors exhibiting a reduced activity to the HARBS conformer on the prevalence of GI-related AEs. Cilomilast has been found to be markedly (100-fold) less potent than rolipram at binding HARBS, and a less potent gastric acid secretagogue (–logEC, 6.1 vs 8.3).[47] Indeed, only 5% to 10% of patients with COPD in Phase IIb clinical trials of cilomilast experienced GI AEs, such as mild to moderate dyspepsia and diarrhea.[48] Because preliminary data concerning another PDE-4–specific inhibitor, roflumilast, have suggested a similar AE profile,[49] it is possible that these GI AEs are inherent to PDE-4 pharmacology. However, age might also be a confounding factor: a study examining the role of cilomilast in a younger (mean age, 45 years), mixed population of 211 asthmatic patients in Europe and South Africa did not report diarrhea to be one of the top 10 most common AEs.[50] Thus, a shortcoming of the present study was that, to define the pharmacology of cilomilast, a young, healthy population was studied, leading to limitations in extrapolating the results to an elderly population with COPD.

CONCLUSION

The results of these 2 studies suggest that cilomilast was not associated with significant changes in esophageal motility and pH or GI transit in these healthy volunteers.

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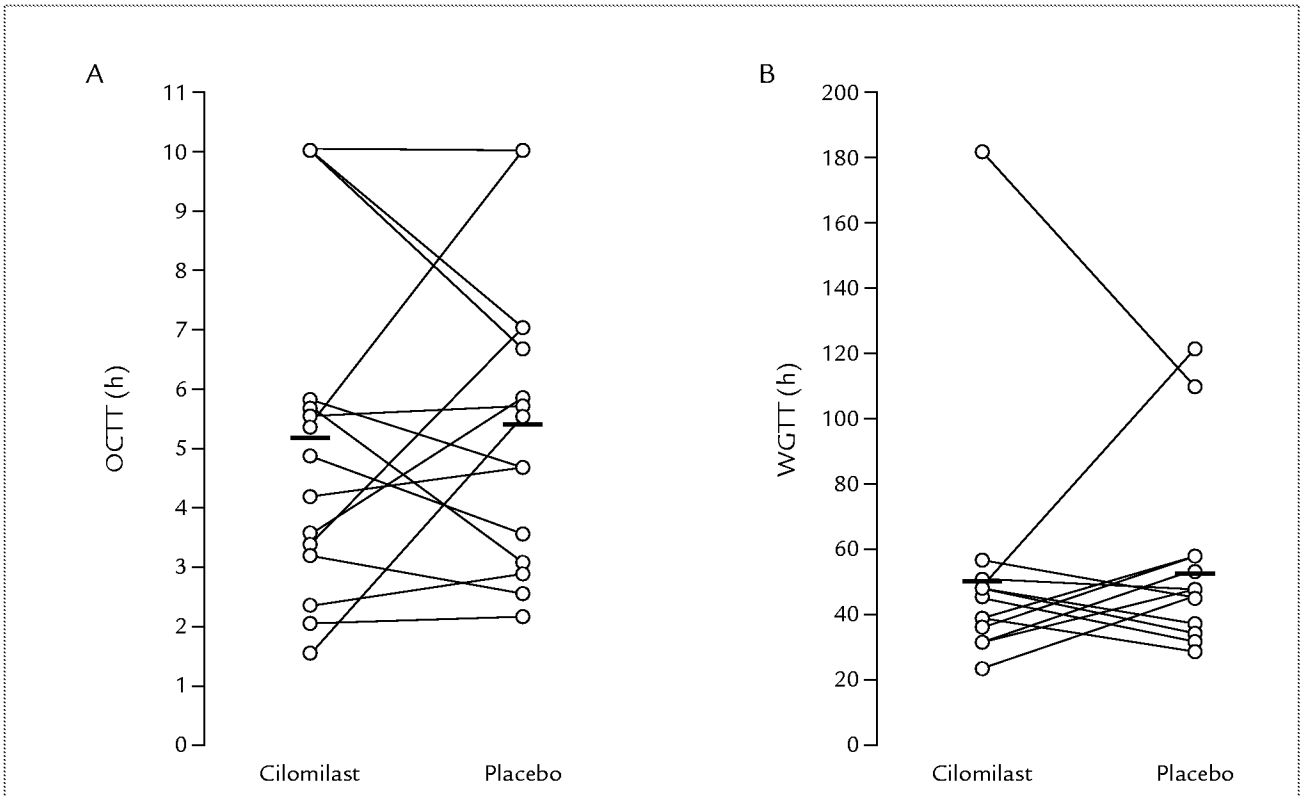

Figure 2. Effects of 7-day self-administration of cilomilast 15 mg BID on (A) orocecal transit time (OCTT) and (B) whole-gut transit time (WGTT) in healthy volunteers (N = 12).

and other physiologic studies from GSK; Novartis Pharmaceuticals Corporation, Basel, Switzerland, and East Hanover, New Jersey; Pfizer Central Research, Sandwich, United Kingdom; Solvay Pharmaceuticals GmbH, Hannover, Germany; Janssen Pharmaceutica N.V., Beerse, Belgium; Rotta Research Laboratorium SpA/Rottapharm Group, Monza, Italy; and Procter and Gamble Pharmaceuticals, Cincinnati, Ohio.

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