Effects of a κ-opioid agonist, asimadoline, on satiation and GI motor and sensory functions in humans

Silvia Delgado-Aros,1 Heather J. Chial,1 Michael Camilleri,1 Lawrence A. Szarka,1 Frank T. Weber,3 Jutta Jacob,3 Irene Ferber,1 Sanna McKinzie,1 Duane D. Burton,1 and Alan R. Zinsmeister2

1Clinical Enteric Neuroscience Translational and Epidemiological Research Program and 2Division of Biostatistics, Mayo Clinic, Rochester, Minnesota 55905; and 3Merck KGaA, Darmstadt, Germany

Submitted 23 August 2002; accepted in final form 19 November 2002

Effects of a κ-opioid agonist, asimadoline, on satiation and GI motor and sensory functions in humans, 91 healthy participants were randomized in a double-blind fashion to 0.15, 0.5, or 1.5 mg of asimadoline or placebo orally twice a day for 9 days. We assessed satiation (nutrient drink test), colonic compliance, tone, perception of colonic distension (barostat), and whole gut transit (scintigraphy). Treatment effect was assessed by analysis of covariance. Asimadoline increased nutrient drink intake (P = 0.03). Asimadoline decreased colonic tone during fasting (P = 0.03) without affecting postprandial colonic contraction, compliance, or transit. Gas scores in response to colonic distension were decreased with 0.5 mg of asimadoline at low levels (8 mmHg above operating pressure) of distension (P = 0.04) but not at higher levels of distension. Asimadoline at 1.5 mg increased gas scores at 16 mmHg of distension (P = 0.03) and pain scores at distensions of 8 and 16 mmHg (P = 0.003 and 0.03, respectively) but not at higher levels of distension. Further studies of this compound in diseases with altered satiation or visceral sensation are warranted.

VISCERAL PAIN AND DISCOMFORT are relevant clinical features of many medical processes, including functional gastrointestinal (GI) disorders (57). These are frequent and chronic-relapsing conditions with a great impact on quality of life (23), yet no satisfactory treatment is available for treatment of pain in these highly prevalent conditions.

The three major opioid receptors, μ, δ, and κ, are distributed in the peripheral and central nervous systems (45, 53) and are known to modulate visceral nociception (16, 22, 29). Available opioid agonists relieve pain, but they usually result in many adverse effects, such as constipation and central side effects (13), including opioid dependence (51). Such adverse effects preclude their general use in clinical practice. In contrast, peripheral κ-opioid receptor agonists seem to be devoid of these side effects, and preliminary clinical evidence suggests that this class of compound can reduce visceral sensation in human studies (14, 17, 20, 44).

Asimadoline (EMD-61753) is a compound with high affinity and selectivity for the κ-opioid receptor (27) and does not cross the blood-brain barrier (3, 4). Asimadoline has been shown to reduce sensation responses to gastric and colonic distension (8, 41, 48) and to heat (54) in animal models. In previous human phase I and phase IIa studies, asimadoline has shown high oral bioavailability and a good safety profile with single doses up to 10 mg and multiple doses up to 5 mg (2). No withdrawal symptoms have been reported in animals or humans (2).

The aims of this study were to determine the safety and effects of 9 days of treatment with three different doses of asimadoline compared with placebo on visceral sensation and GI motor functions in healthy volunteers. Such in-depth studies are essential for the translation of basic physiological insights on κ-opioid receptor agonists to potential therapies for patients with illnesses associated with altered visceral sensation.

MATERIALS AND METHODS

Study Population

The study was conducted between February 2001 and March 2002. Volunteers between 18 and 60 yr of age were recruited from the local community by public advertisement. Pregnant or breast-feeding women and those with child-bearing potential who were not using reliable methods of contraception were excluded. Other exclusion criteria included known hypersensitivity to asimadoline or opioid agonists; known substance abuse; significant affective or anxiety disorder (with the Hospital Anxiety and Depression Scale used for screening purposes), systemic disease, prior abdominal surgery other than appendectomy, laparoscopic cholecystectomy, or tubal ligation; present or previous chronic GI illness, including functional GI disorders (with the Bowel...
Disease Questionnaire used for this purpose); and use of medications that may alter GI motility or induce cytochrome P-3A4 and -2D6 or analgesic drugs, including opioids, non-steroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors. The protocol was approved by the Mayo Institutional Review Board, and written informed consent was obtained from all participants before enrollment in the study.

Study Design

This was a randomized, double-blind, placebo-controlled study conducted in two parts. Part 2 was added to test a higher dose of asimadoline than those tested in part 1 and was planned and nested in the study before part 1 was finished. Eligible volunteers were randomized (using random permuted blocks stratified on age and gender) to receive a 9-day oral treatment with 0.15 or 0.5 mg of asimadoline (EMD-61753, Merck, Darmstadt, Germany) or identical-appearing placebo twice a day during part 1 and with 1.5 mg of asimadoline or placebo twice a day during part 2.

Study Protocol

Satiation and postprandial symptoms were assessed at baseline (day 0) before initiation of the treatment period. On day 1, participants underwent colonic motor and sensory function measurements before the treatment and 1 h after the first dose of the assigned treatment. Satiation and postprandial symptoms were assessed on treatment day 6, and gastric emptying and small bowel and colonic transit were measured from day 7 to day 9 of treatment (Fig. 1).

Medication was administered at the study site, except from day 2 to day 5 of treatment. Compliance with treatment was assessed by means of tablet counts and review of subjects’ diaries.

Safety Monitoring

Adverse effects were monitored at the study site daily from day 6 to day 9, and patients were given a telephone number to contact study investigators to report any side effect. An electrocardiogram and routine laboratory tests were performed during the last 2 days of treatment and at the follow-up visit, scheduled within 1 wk of the end of active treatment, to follow any abnormality observed in the previous visit.

Assessment of Satiation and Postprandial Symptoms: Nutrient Drink Test

To measure satiation [i.e., the final signal during ingestion that contributes to meal termination (37)] and postprandial symptoms, we used the nutrient drink test as described in the literature (19, 55). Briefly, after an overnight fast, participants drank a nutrient liquid meal (Ensure; 1 kcal/ml, 11% fat, 73% carbohydrate, and 16% protein) at a constant rate (30 ml/min). At 5-min intervals, participants scored their level of fullness or satiation using a scale from 0 (no symptoms) to 5 (maximum or unbearable fullness/satiation). Participants were asked to stop meal intake when they reached the score of 5, and the total volume ingested was recorded as the maximum tolerated volume (MTV). At 30 min after reaching the point of maximum satiation, participants used 100-mm visual analog scales (VAS), with the words “none” and “worst ever” anchored at the left and right ends of the lines, to score their symptoms of nausea, fullness, bloating, and pain.

Assessment of GI Transit by Scintigraphy

We measured gastric emptying and small bowel and colonic transit of solids using scintigraphy as described in previous studies (5, 7, 9). Briefly, after an overnight fast, participants ingested an 111In-charcoal capsule coated with a pH-sensitive methacrylate that dissolves when it reaches the stomach (9), allowing colonic transit measurement with a gamma camera. After the capsule was emptied from the stomach, participants ingested two scrambled eggs labeled with 99mTc-sulfur colloid with one slice of whole-wheat bread and one glass of whole milk (total 300 kcal) to measure gastric emptying and the colonic filling at 6 h after the meal as a measurement of small bowel transit. Subjects ingested standardized meals for lunch and dinner at 4 and 8 h after the radiolabeled meal. Anterior and posterior abdominal images of 2-min duration were obtained at 1-h intervals for the first 8 h and at 24, 32, and 48 h.

Assessment of Colonic Motor and Sensory Function

To measure colonic tone and compliance and to perform colonic distensions, a barostat-balloon assembly was used as described in previous studies (52, 59). An “infinitely” compli-

---

**Fig. 1. Study protocol.** Participants performed a baseline nutrient drink test (for measurement of satiation and postprandial symptoms) before treatment period. On a different day, colonic motor and sensory function were measured before the drug and 1 h after the first dose. Participants performed a second nutrient drink test after 6 days of treatment. Gastric emptying and small bowel and colonic transit were measured from day 7 to day 9 of treatment.
ant balloon, 10 cm long and with a maximum volume of 600 ml (Hefty Baggies, Mobil Chemical, Pittsford, NY), was placed into the descending colon using flexible colonoscopy and fluoroscopy.

The balloon was linked to an electronic, rigid-piston barostat (Engineering Department, Mayo Clinic) by means of a double-lumen tube for balloon distension and intraballoon pressure measurement (56).

The operating pressure was set at 2 mmHg above the minimum distending pressure, defined as the pressure at which respiratory excursions during deep inspiration were accompanied by a noticeable deflection in the balloon volume. Intraballoon volumes were monitored throughout the study. A pneumobelt was applied to the abdominal wall at the level of the low costal margin to exclude artifact during movement and coughing.

After a conditioning distension (28) and an equilibration period at the operating pressure, we measured colonic compliance by increasing intraballoon pressure from 0 to 44 mmHg in 4-mmHg steps at 30-s intervals. During assessment of colonic compliance, participants were asked to report first perception of gas and pain. After compliance measurement, fasting colonic tone was assessed at the operating pressure and then at phasic balloon distensions of 8, 16, 24, and 32 mmHg above the operating pressure, performed in random order. During distensions, participants rated the intensity of gas and pain perception using a 100-mm VAS with the words “unnoticeable” and “unbearable” anchored at the left and right ends of the lines. This has been shown to be an adequate model of visceral sensation in humans (25, 40).

Colonic wall compliance and fasting tone, thresholds for first perception of gas and pain, and the intensity of perception during phasic distensions were measured before the subjects received the drug and 1 h after the first dose of the drug. The timing of postdrug measurements was based on the known pharmacokinetic profile of asimadoline (2). After the drug was administered, we also assessed postprandial colonic volume during 60 min after ingestion of a 750-ml milkshake containing 1,000 kcal (53% fat, 35% carbohydrate, and 12% protein; Fig. 2).

Data Analysis

MTV and postprandial symptoms. The total volume ingested (MTV) was recorded. The aggregate postprandial symptoms score (30 min after ingestion of Ensure) was calculated as the sum (0–400 mm) of VAS scores for each postprandial symptom (0–100 mm each).

GI transit. Gastric emptying was summarized as the proportion of 99mTc emptied from the stomach at 2 and 4 h and orocecal transit as the colonic filling with 99mTc at 6 h. Colonic transit was summarized by means of the geometric center (GC) at any given time, which is calculated by multiplying the proportion of 111In in each colonic region (ascending (AC), transverse (TC), descending (DC), rectosigmoid (RS), and stool) by its weighting factor as indicated in the following formula: GC = (%AC × 1 + %TC × 2 + %DC × 3 + %RS × 4 + %stool × 5)/100. A low GC, therefore, means slow transit, and a high GC indicates rapid colonic transit.

Colonic tone and compliance. Colonic tone, i.e., intraballoon volume at the operating pressure, was calculated by averaging the colonic volume throughout the period of tone assessment during fasting and postprandially, as in previous studies (5, 6, 58). Changes in colonic tone were calculated as proportional changes during fasting ([fasting colonic tone postdrug – predrug] × 100/fasting colonic tone predrug) and postprandially (postprandial colonic tone – fasting colonic tone) (58). Because colonic pressure-volume relations are not linear but sigmoidal, compliance was summarized by a power exponential model by plotting observed volume at each pressure divided by the maximum observed volume as a function of 1/pressure as follows: Vol/Vol$_{max}$ = $r$ + $\exp(- (\kappa \times 1/Pr)^\beta)$, as in previous studies (5, 6, 34, 58), where $r$ represents the minimum observed volume divided by the maximum observed volume (Vol$_{max}$), Pr is pressure, and $\kappa$ and $\beta$ are constants that describe the compliance curve.

Perception of colonic distension. The pressures at which participants reported first perception for gas and pain, during stepwise distensions, were recorded as the pressure thresholds for gas and pain perception. Gas and pain VAS intensity scores at each distension pressure, during random phasic distensions, were also recorded.

Statistical Analysis

The primary outcomes for satiation and postprandial symptoms were the MTV and the aggregate postprandial symptoms score. These have been shown in previous studies to be the most robust end-point variables measured by the nutrient drink test (18). Primary outcomes for GI transit were the proportion emptied from the stomach at 4 h and colonic filling at 6 h. The primary outcomes for colonic motor

Fig. 2. Colonic barostat protocol. Colonic wall compliance, fasting tone, and perception in response to random pressure distensions were measured before participants received the drug and 1 h after the first dose of the drug. Postprandial colonic volume was also assessed after the drug. OP, operating pressure; VAS, visual analog scale.
function and transit were postprandial change in colonic tone and the colonic GC at 24 h. Primary outcomes for perception of colonic distension were the VAS scores for gas and pain at each distension pressure, because physiological evidence suggests that different neuronal populations respond to different ranges of colonic distension (35, 39, 40, 47).

An analysis of covariance (ANCOVA) was used to assess treatment effects on the satiation, transit, tone, and compliance outcome responses. The covariates in these analyses included gender, body mass index, and baseline (pretreatment) response values for those outcomes measured before and after drug administration. Because the study was conducted in two parts, a main effect term for study phase (part 1 vs. part 2) was included in these ANCOVA models. The two-part study design resulted in the highest dose of drug only being used in part 2; thus the treatment effect was incorporated as a “nested factor” (within-study phase). Specific contrasts were then used to test for an overall drug effect (combined doses vs. respective placebos) and a treatment effect (simultaneous comparison of each dose vs. respective placebo). The results (P values) for this latter contrast are reported for each outcome variable. A multivariate ANCOVA model was used to assess treatment effects on the VAS perception scores at 8, 16, 24, and 32 mmHg. The results for the multivariate (4 pressure distension levels) version of the treatment effect contrast and the results for the individual pressure levels are reported below. The analysis of pressure thresholds for first perception of gas and pain was based on a proportional hazards regression model to account for censored values (i.e., maximum pressure level attained without specific type of sensation reported). The above specific contrast for treatment effect was also examined in these analyses.

Because treatment was nested within the separate study parts, data are displayed separately for parts 1 and 2. Values are means ± SE.

RESULTS

Study Conduct and Participants

Sixty healthy subjects were randomized in part 1 of the study: 20 were assigned to receive placebo, 21 to receive 0.15 mg of asimadoline, and 19 to receive 0.5 mg of asimadoline. Thirty-one subjects were randomized in part 2: 10 were assigned to receive placebo and 21 to receive asimadoline at 1.5 mg. Participants’ demographic characteristics are presented in Table 1. There was only one drop-out during part 2 of the study, in the group assigned to 1.5 mg of asimadoline; the participant withdrew because of severe abdominal pain after endoscopic tube placement before receiving the first dose of the assigned treatment. This participant was replaced as planned in the study protocol. Compliance was 100% for all participants, except for three subjects in the group that received 1.5 mg of asimadoline: two subjects missed 1 dose of a total of 18 (5%), and one subject did not take the last 9 doses (50%) and did not attend scheduled visits for transit measurements. None of the missed doses were due to adverse effects. Data on postprandial symptoms after maximum satiation were missing in three participants who departed from the study site without completing the VAS for symptoms. Data on transit were missing for the participant who did not attend the scheduled visits for transit measurement. The missing data for postdrug values of postprandial symptoms after maximum satiation (3 patients) were imputed on the basis of an overall patients regression of postdrug values on predrug data. Missing data for transit (only 1 patient) were imputed using an overall (patients) mean value of nonmissing values.

Satiation and Postprandial Symptoms

Asimadoline significantly augmented the volume of Ensure that was ingested to reach satiation (P = 0.03). Figure 3 shows the change in ingested volume after treatment relative to before treatment.

![Graph showing satiation and postprandial symptoms](Fig. 3. Satiation: maximum tolerated volume. Volume of Ensure ingested after treatment is compared with that ingested before treatment. After treatment, volume intake was decreased in participants treated with placebo, whereas intake of the liquid nutrient was not decreased, and even augmented, in participants treated with asimadoline.)
Treatment did not significantly affect aggregate (P = 0.18) or individual postprandial symptom scores. Table 2 shows data on individual postprandial symptoms scores.

**GI and Colonic Transit**

No significant treatment effect was observed for any of the primary or secondary outcomes for GI transit: gastric emptying at 2 h (P = 0.60), colonic filling at 6 h (P = 0.14), and GC at 24 h (P = 0.95; Table 2).

**Colonic Tone and Compliance**

Asimadoline increased colonic volume (relaxation) during fasting (P = 0.03; Figure 4A). However, the colonic volume response (contraction) to the standard meal was preserved in all treatment groups (P = 0.32; Fig. 4B). No treatment effects were observed on colonic wall compliance (Fig. 5).

**Gas Perception of Phasic Colonic Distension**

Significant treatment effects (overall multivariate test) were observed for gas scores (P = 0.002). Treatment effects were significant at the specific distension pressure of 8 mmHg (P = 0.04) but did not reach statistical significance at 16 mmHg (P = 0.09). When higher distension pressures were applied, no significant treatment effects were observed (P = 0.78 and 0.26 for 24 and 32 mmHg above operating pressure distensions, respectively; Fig. 6A).

Post hoc analysis of pairwise comparisons between each specific dose and corresponding placebo suggested that 0.5 mg of asimadoline reduced gas perception related to placebo at 8 mmHg of distension (P = 0.11) to increase, rather than decrease, gas perception at 8 mmHg of distension, and a significant (P = 0.03) increase of gas perception was observed at 16 mmHg of distension.

### Table 2. Postprandial symptoms and transit data

<table>
<thead>
<tr>
<th></th>
<th>Placebo 1 (n = 20)</th>
<th>0.15 mg bid (n = 21)</th>
<th>0.5 mg bid (n = 19)</th>
<th>Placebo 2 (n = 10)</th>
<th>1.5 mg bid (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Postprandial symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>37.0 ± 4.7</td>
<td>38.0 ± 4.7</td>
<td>34.5 ± 4.9</td>
<td>25.0 ± 6.6</td>
<td>36.0 ± 4.6</td>
</tr>
<tr>
<td>Bloating</td>
<td>50.5 ± 4.3</td>
<td>57.5 ± 4.3</td>
<td>48.2 ± 4.4</td>
<td>42.1 ± 6.1</td>
<td>57.0 ± 4.1</td>
</tr>
<tr>
<td>Fullness</td>
<td>73.5 ± 2.7</td>
<td>74.1 ± 2.6</td>
<td>70.5 ± 2.7</td>
<td>63.6 ± 3.7</td>
<td>74.4 ± 2.6</td>
</tr>
<tr>
<td>Pain</td>
<td>21.7 ± 3.8</td>
<td>23.3 ± 3.7</td>
<td>23.1 ± 3.9</td>
<td>18.9 ± 5.3</td>
<td>27.8 ± 3.6</td>
</tr>
<tr>
<td><strong>GI transit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GE2h, %</td>
<td>62.1 ± 3.7</td>
<td>61.0 ± 3.7</td>
<td>55.5 ± 3.8</td>
<td>54.3 ± 5.3</td>
<td>57.1 ± 3.9</td>
</tr>
<tr>
<td>CF6h, %</td>
<td>71.4 ± 6.4</td>
<td>60.4 ± 6.3</td>
<td>58.5 ± 6.6</td>
<td>46.5 ± 9.2</td>
<td>67.0 ± 3.7</td>
</tr>
<tr>
<td>GC24h</td>
<td>2.4 ± 0.2</td>
<td>2.4 ± 0.2</td>
<td>2.3 ± 0.2</td>
<td>2.5 ± 0.3</td>
<td>2.6 ± 0.2</td>
</tr>
</tbody>
</table>

Values are mean ± SE. Postprandial symptoms are expressed in mm on visual analog scale. GE2h, gastric emptying at 2 h; CF6h, colonic filling at 6 h; GC, geometric center at 24 h.
Pain Perception of Phasic Colonic Distension

The simultaneous test (overall distension levels) indicated borderline statistically significant treatment effects ($P = 0.096$) for pain scores. The pain scores were also significantly affected by treatment at low distension pressures ($P = 0.01$ and $0.09$ for 8 and 16 mmHg, respectively). This effect was not observed at higher distension pressures ($P = 0.29$ and $0.46$ for 24 and 32 mmHg, respectively; Fig. 6B).

Post hoc analysis of pairwise comparisons between each specific dose and corresponding placebo suggested that 1.5 mg of asimadoline was associated with increased pain perception at 8 and 16 mmHg of distension ($P = 0.003$ and $0.03$, respectively).

Thresholds for Perception During Stepwise Distensions

We did not observe any significant effect of treatment on the thresholds for perception of gas ($P = 0.36$) or pain ($P = 0.30$). Figure 7 shows the Kaplan-Meier curves with the proportion of subjects reporting first perception for gas and pain at each distension pressure in each study group. The shift to the right in the curve of pain thresholds with 1.5 mg of asimadoline suggested a decrease in pain threshold for this group, but a post hoc pairwise comparison of 1.5 mg of asimadoline vs. placebo (log-rank test) did not detect a significant difference ($P = 0.27$).

Adverse Events

Adverse events are described in Table 3. No serious adverse events were reported. The most commonly reported adverse events were those related to the central nervous system, such as dizziness and headache, and the GI system, such as abdominal complaints related to endoscopic tube placement, nausea, anorexia, or heartburn. All adverse events were equally prevalent in the placebo and active treatment groups.

DISCUSSION

In this phase I study, oral administration of the selective κ-opioid agonist asimadoline modulated nutrient liquid intake and perception of colonic distension. This occurred without significant alteration of GI motor reflexes and transit.

Visceral pain is a common clinical problem for which there is no satisfactory or universally effective treatment. The role of the opiate system in the modulation of visceral pain has been long recognized, yet the widespread use of opioid receptor agonists to treat chronic visceral pain is avoided because of the associated high rate of central side effects (13). Side effects include tolerance and physical dependence (51) and the inhibition of GI motor reflexes (1) that result in transit delay (30) and severe constipation (13).

Asimadoline is a diarylacetamide κ-opioid receptor agonist that binds preferentially to κ-opioid receptors (27), which are involved in the perception of visceral pain (50). This compound has a very low distribution to the brain (3, 4). In animal studies, central nervous system-mediated adverse reactions were seen at doses 50–600 times higher than analgesic doses, and no opiate-like physical dependence has been observed after 8 wk of treatment with asimadoline in humans (2).

Asimadoline has been tested in animals and was shown to reduce sensation in response to gastric and colorectal distension (8, 41, 48). These properties suggest that asimadoline is a suitable medication to be tested for the treatment of visceral pain in humans.

In this study, we have also shown that oral administration of 0.15–1.5 mg of asimadoline twice a day over 9 days is well tolerated, with no serious adverse effects.
Our evaluation of gastric visceral nociception was not based on gastric distension stimuli. Instead, we tested the effects of the drug in a situation that mimics the common clinical presentation of early satiation and postprandial complaints, such as abdominal pain, nausea, fullness, and bloating. Asimadoline delayed the onset of satiation at constant rates of ingestion, allowing greater ingestion of a nutrient liquid meal than placebo without affecting postprandial symptoms. This is consistent with a specific effect of asimadoline on regulation of food intake, which is shared with other opioid agonists (21, 32). In all participants who received placebo, there was a decrease in the volume ingested during the nutrient drink test repeated after randomization. Interestingly, asimadoline appeared to prevent this decrease in MTV. Although we did not specifically question study participants about palatability or taste aversion of Ensure, these results suggest that asimadoline’s effect on food intake may be, at least in part, related to its regulation of orosensory reward, perhaps increasing palatability of the ingested nutrient meal, as suggested with other opioid agonists (42, 61).

Asimadoline at 0.5 mg decreased perception of gas in response to low levels of colonic distension. This is in accordance with animal studies (8, 48). No effect was observed at higher levels of distension. At least two types of receptors in the colon encode nociception: intensity-encoding receptors, which have a low threshold to natural stimuli, and high-threshold receptors, which are evoked by stimuli within the noxious range (10, 26). Therefore, it is conceivable that oral asimadoline may act at the periphery, altering the function of the low-threshold receptor at the doses used in this study. This concurs with the different effects of asimadoline on pelvic afferent fibers stimulated by colorectal distension (54).

In contrast, the highest dose of asimadoline tested (1.5 mg) was associated with increased gas and pain perception at low levels of colonic distension. The hyperalgesia associated with high doses of asimadoline

Table 3. Adverse events

<table>
<thead>
<tr>
<th>Body System</th>
<th>Placebo (n = 30)</th>
<th>0.15 mg bid (n = 21)</th>
<th>0.5 mg bid (n = 19)</th>
<th>1.5 mg bid (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal</td>
<td>2(2)</td>
<td>0</td>
<td>0</td>
<td>1(1)</td>
</tr>
<tr>
<td>Central and peripheral nervous system</td>
<td>4(4)</td>
<td>1(1)</td>
<td>4(4)</td>
<td>4(4)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>3(3)</td>
<td>2(2)</td>
<td>0</td>
<td>1(1)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>4(2)</td>
<td>2(2)</td>
<td>2(1)</td>
<td>4(3)</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>2(2)</td>
<td>0</td>
<td>1(1)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory</td>
<td>5(3)</td>
<td>0</td>
<td>0</td>
<td>3(2)</td>
</tr>
<tr>
<td>Application site</td>
<td>1(1)</td>
<td>1(1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Body as a whole</td>
<td>0</td>
<td>0</td>
<td>1(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>Vision</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1(1)</td>
</tr>
</tbody>
</table>

Values represent number of events, with number of subjects in parentheses (participants may have had >1 event).
has been previously observed in animals and humans (36) and is consistent with the dual modulatory mechanisms of opioids proposed by Crain and Shen (15). Their proposed dual modulatory mechanisms were based on electrophysiological studies on sensory dorsal root ganglion neurons that show that κ-opioid agonists can evoke prolongation (12, 49) or shortening (11, 24, 38, 60) of the action potential of these cells when applied at low and high concentrations, respectively.

Whether the hyperalgesic effects observed with the higher dose of asimadoline in our study involve excitatory opioid receptors (15) or nonopioid receptors, such as the N-methyl-D-aspartic acid receptor (31, 33, 46), is beyond the scope of this study. However, several lines of evidence suggest that κ-opioid agonists exert hyperalgesia through activation of the N-methyl-D-aspartic acid receptor (31, 33, 46).

One of the significant deleterious effects associated with the use of opioid agonists is the inhibition of intestinal motor reflexes (1), which results in transit delay (30, 43) and severe constipation (13). At the doses used in this study, asimadoline modulates perception without altering compliance of the colon, the physiologic postprandial colonic contraction, or GI or colonic transit.

In conclusion, in this phase I study, we have demonstrated that asimadoline appears to be safe and is capable of increasing acute nutrient intake and that low doses of asimadoline (0.5 mg) can decrease visceral perception in humans without deleterious effects on gut motor functions. Higher doses of asimadoline may increase visceral perception. Clinical studies of this compound in illnesses associated with altered satiation or visceral sensation are warranted.

We thank Mary Lempke, George M. Thomforde, and Cindy Stanislav for pharmacy, technical, and secretarial support, respectively.

This study was supported by a grant from Merck (Darmstadt, Germany) and in part by National Institutes of Health General Clinical Research Center Grant RR-00585 (Physiology Core) and National Institute of Diabetes and Digestive and Kidney Diseases Grants R01-DK-54681 (M. Camilleri) and K24-DK-02638 (M. Camilleri).

REFERENCES


