Effect of the α2δ ligand, pregabalin, on colonic sensory and motor functions in healthy adults

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Submitted 4 March 2011; accepted in final form 18 May 2011

Iturrino J, Camilleri M, Busciglio I, Burton D, Zinsmeister AR. Effect of the α2δ ligand, pregabalin, on colonic sensory and motor functions in healthy adults. Am J Physiol Gastrointest Liver Physiol 301: G377–G384, 2011. First published May 19, 2011; doi:10.1152/ajpgi.00085.2011.—Pregabalin, an α2δ ligand, is used clinically to treat somatic pain. A prior study suggested that pregabalin reduces distension-induced pain while increasing rectal compliance. We aimed to quantify effects of pregabalin on colonic sensory and motor functions and assess relationships between sensory effects and colonic compliance. We conducted a randomized, double-blind, placebo-controlled, parallel-group study of a single oral administration of 75 or 200 mg of pregabalin in 62 healthy adults (aged 18–75 yr). Subjects underwent left colon intubation. We assessed “stress-arousal symptoms”, compliance, sensation thresholds, sensation ratings averaged over four levels of distension, fasting and postprandial colonic tone, and phasic motility index (MI). Analysis of covariance (adjusted for age, sex, body mass index, and corresponding predrug response) and proportional hazard models were used. There were no clinically important differences among treatment groups for demographics, predrug compliance, tone, MI, and sensation. Treatment was associated with reduced energy and increased drowsiness but no change in tension or relaxation. Sensation ratings averaged over the four distension levels were lower for gas sensation [overall effect P = 0.14, P = 0.05 (pregabalin 200 mg vs. placebo)] and for pain sensation [overall effect P = 0.12, P = 0.04 (pregabalin 200 mg vs. placebo)]. The magnitude of the effect of 200 mg of pregabalin relative to placebo is on average a 25% reduction of both gas and pain sensation ratings. Pregabalin did not significantly affect colonic compliance, sensation thresholds, colonic fasting tone, and MI. Thus 200 mg of pregabalin reduces gas and pain sensation and should be tested in patients with colonic pain.

colic compliance; gas sensation; pain sensation

THE HETEROMULTIMERIC voltage-sensitive calcium (Ca2+) channel is involved in the function of excitable tissues including sensory nerves. It comprises a primary α1 subunit and auxiliary α2δ, β, and γ subunits, and the associated α2δ ligand-binding site (26). Pregabalin binds potently to the α2δ auxiliary protein associated with voltage-gated calcium channels (12), reducing depolarization-induced calcium influx at the nerve terminals. Consequently, pregabalin may reduce the release of several excitatory neurotransmitters, including glutamate, noradrenaline, substance P, and calcitonin gene-related peptide, which have been involved in pain mechanisms (1, 4). Recently, Needham et al. (21) showed that intrinsic primary afferent neurons in the small bowel of guinea pigs express functional N (α1B) channel-forming subunits that are associated with α2δ1 modulatory subunits and are inhibited by pregabalin.

Pregabalin, a second generation α2δ ligand, has been shown to be effective in several animal models of visceral pain including trinitrobenzene sulfonic acid colitis (10), septic shock-induced rectal hypersensitivity (11), and a repeated colonic distension model in normal rat colon (20). These studies led to pregabalin being proposed as a treatment for visceral pain on the basis of its pharmacological actions as a potent anticonvulsant, analgesic, and anxiolytic (1) and its efficacy in neuropathic pain (5). Pregabalin is approved for the management of neuropathic pain associated with diabetic peripheral neuropathy, or postherpetic neuralgia, in addition to fibromyalgia, and as adjunctive therapy for adults with partial seizures. There are no approved or effective centrally or peripherally acting visceral analgesics for irritable bowel syndrome (IBS) and chronic abdominal pain. Therefore, there is a need for effective approaches to treat the chronic visceral pain disorders including IBS.

Pregabalin attenuated both the viscerosomatic (contractions of the abdominal musculature) and cardiovascular autonomic responses associated with noxious mechanical distension of the colon in rats; in these studies, there was increased colonic compliance (23). These observations on sensation and compliance reflect the results of Houghton et al. (16) in patients with IBS and rectal hypersensitivity (rectal pain sensation threshold <28 mmHg), in whom pregabalin treatment increased pain threshold (suggesting a visceral analgesic effect) and concomitantly increased rectal compliance although there was a limited range of intrarectal balloon distention pressures tested. In that study, pregabalin was administered in a dose-escalation manner over several days (16); this approach may be directed to the central effects of the drug.

Given these promising data (16), we aimed to assess the effects of pregabalin on colon sensation, compliance, and motility in healthy adult individuals to identify the most promising dose to use in patients with functional bowel disease for short-term relief of abdominal pain and to assess relationships between sensory effects and colonic compliance.

The specific study hypotheses were as follows: 1) pregabalin increases sensation thresholds, decreases sensation ratings, and increases compliance in response to balloon distension in the colon; 2) pregabalin reduces colonic phasic and tonic motility in response to a standardized meal; and 3) sensation ratings are lower with higher colonic compliance.

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MATERIALS AND METHODS

Study Design, Randomization, and Allocation to Treatment

A randomized, double-blind, placebo-controlled, two-dose (75 and 200 mg), parallel-group study of the effects of a single oral administration of pregabalin was conducted at a single center in 62 healthy adults, aged between 18 and 75 yr. The randomization schedule was generated before the start of the study in the Division of Biomedical Statistics and Informatics, Mayo Clinic and was given to the research pharmacist. The study medications were prepared and dispensed by the Mayo Research Pharmacy, and the three treatments were identical in appearance. The clinical investigators, study personnel, and volunteers were blinded to the treatment assignments until after the data were finalized for analysis. Allocation was concealed, and medication was administered in double-blinded fashion.

Participants

Participants were enrolled by one study coordinator between April 2010 and January 19, 2011. The study was approved by the Mayo Clinic Institutional Review Board and was registered on the ClinicalTrials.gov website (NCT01094808). All data were collected in the Clinical Research Unit at Mayo Clinic in Rochester, MN.

Healthy volunteers were recruited from a preexisting database of 200 healthy volunteers residing within 150 miles of Rochester, MN, or through local advertisement. All participants gave signed, informed consent. Candidates who met the eligibility criteria for the study underwent a complete history and physical examination before enrollment. Volunteers were screened by means of an abridged Bowel Disease Questionnaire (24) to ensure they had no present or chronic gastrointestinal symptoms and by the Hospital Anxiety and Depression Questionnaire (28), which was used to screen all volunteers for psychiatric comorbidities. Standard criteria excluded those with prior abdominal surgery (other than appendectomy, laparoscopic cholecystectomy, cesarean section, vaginal or laparoscopic hysterectomy, or tubal ligation); chronic gastrointestinal or systemic illnesses and use of medications that could affect gastrointestinal motility; history of tubal ligation; chronic gastrointestinal or systemic illnesses and use of medications that could affect gastrointestinal motility; history of uncontrolled hypertension, chronic renal insufficiency (serum creatinine >1.5 mg/dl), and psychiatric or psychological dysfunction. In all women of childbearing potential, a urine pregnancy test was performed within 48 h of the administration of study administration and conduct of the colonic intubation.

Pregabalin Pharmacokinetics Relative to Colonic Measurements

Pregabalin demonstrates highly predictable and linear pharmacokinetics. Absorption is extensive, rapid, and proportional to dose. Time to maximal plasma concentration ($T_{\text{max}}$) is $\sim1$ h. Pregabalin has high bioavailability, does not bind to plasma proteins, has a mean elimination half life of 6.3 h, and is excreted virtually unchanged (2% metabolism) by the kidneys. It is not subject to hepatic metabolism. In clinical practice in which it is most frequently prescribed for somatic rather than visceral pain, an effective starting dose of pregabalin is 150 mg/day without need for dose escalation (1).

Given these pharmacokinetic characteristics, we conducted measurements before drug administration, and, starting 1 h after oral drug administration, we completed all fasting and postprandial measurements of compliance, sensation, and tone measurements within 5 h (Fig. 1). We also assessed the “stress-arousal” symptoms pre- and posttreatment before conducting the sensation evaluations.

Colonic Tube Placement

We elected to study colonic rather than rectal sensation to avoid potential confounding of measurements of compliance or sensation by surrounding organs such as the uterus and the bony pelvis and potential individual variations. On the study day, colonic motility and sensation were assessed as in previous studies conducted in our laboratory (14). The bowel was prepared overnight with an oral colonic lavage solution (GoLYTELY; Braintree Laboratories, Brain-tree, MA). Flexible colonoscopy to the splenic flexure was performed without sedation by one investigator (M. Camilleri). The barostat catheter incorporating six manometric point sensors 5 cm apart was introduced into the colon over a guidewire, and the polyethylene balloon [10 cm long, cylindrical shape with a maximum volume of 600 ml (Hefty Baggies; Mobil Chemical, Pittsford, NY)] was placed in the middescending or junction of the sigmoid and descending colon. A rigid-piston barostat was used (Mayo Rigid Barostat; Engineering Department, Mayo Clinic, Rochester, MN) to measure intra-balloon pressure and volume throughout the study.

After an initial inflation to a volume of 75 ml to ensure unfolding of the balloon, the operating pressure was identified as the distention pressure at which respiratory excursions were recorded clearly from the barostat tracing, and the intra-balloon pressure was set 2 mmHg above the minimal. This pressure was defined as the balloon-operating pressure.

Experimental Protocol to Assess Colonic Motor and Sensory Function

The experimental protocol is summarized in Fig. 1. A conditioning distention from 0 to 36 mmHg in increments of 4 mmHg every 15 s was performed over a period of 3 min. After an equilibration period of 10 min, colonic compliance was assessed by the ascending methods of limit (ramp-like increases of 4 mmHg at 30-s intervals). During the assessment of colonic compliance, participants reported their thresholds for first perception, gas, and pain. After the assessment of compliance and a 10-min equilibration period, fasting colonic tone was measured at the operating pressure for a period of 10 min (14, 22).

Randomized-order phasic distentions were then applied at 16, 24, 30, and 36 mmHg above the operating pressure to measure the sensations of gas and pain. Each distention lasted 1 min and was followed by an equilibration period at the operating pressure for 2 min. A 100-mm visual analog scale (VAS) was used to assess the rating of arousal and stress experienced by each subject before performing the phasic distentions (2, 3, 15, 18, 22). Levels of stress were also assessed using two similar scales anchored with the terms

![Fig. 1. Experimental protocol.](http://ajpgi.physiology.org/)
“peaceful” and “tense” and “worried” and “relaxed”, respectively. During the distentions, participants also used the 100-mm VAS to rate the intensity of gas and pain perception at 30 s from the start of the distention.

Colonic compliance, fasting tone, pressure thresholds for first perception, gas, and pain, and VAS scores of gas and pain during phasic distentions were measured before administering the study medication and 1 h after drug administration. After the postdrug assessment of sensation with phasic distentions, a 30-min assessment of fasting colonic tone was measured in each subject; this provided a baseline to compare the effect of a standard 750-ml chocolate milkshake (1,000 kcal, 53% fat, 35% carbohydrate, 12% protein) meal across treatment groups. Postprandial tone was measured over 60 min, with the main focus on the first 30 min (14, 22). When the recording was completed, the balloon was deflated and the tube removed by gentle traction.

Data Analysis

Compliance. Compliance was measured by a computer-based linear interpolation method as previously validated by Floyd et al. (13). This estimated the pressure corresponding to specific volumes at 10% and 50% of maximum distention.

Colonic motor function. Colonic tone was assessed operationally, as in the prior literature, as the intracolonic balloon volume measured at the operating pressure (25). A computer program separated baseline volume from phasic volume events. Tone was calculated by averaging the colonic volumes measured throughout the period of interest during fasting or after the meal. Changes in colonic tone were calculated as absolute volume changes during fasting in response to the study medication and as the symmetric percent change in volume postprandially.

High-amplitude propagating contractions were defined as 75-mmHg increases in pressure that propagated across a minimum of three leads (10 cm) in the left colon (8, 18).

Colonic sensation. Sensation was assessed as the pressure thresholds at which participants reported first perception, gas, and pain during the assessment of colonic compliance (ramp-like distention) and the intensity ratings recorded for gas and pain on 100-mm VAS scales during phasic distentions.

Statistical Considerations

Study endpoints. The study primary endpoints for analysis were 1) sensation thresholds of pain, 2) mean sensation ratings of pain and gas over the four distention pressures, 3) compliance estimated as Pr50%, 4) postprandial colonic tone as the symmetric percent reduction in baseline colonic barostat balloon volume during the first 30 min postprandially corrected for the preprandial (30 min) tone [symmetric percent change = 100 \ \cdot \log_{10} \text{(Fasting/PP)}], and 5) phasic motor function as the first 30-min postprandial motility index [MI = \log_{10} \text{(Sum of amplitudes } \# \text{ of contractions) } + 1] \text{ and the preprandial MI.}

Secondary study endpoints were compliance Pr10%, threshold for gas sensation, and the VAS ratings of pain and gas sensation at 30- and 36-mmHg distentions.

Statistical analysis. Analysis of covariance (ANCOVA) models were used to assess overall treatment effects (differences among the 3 treatment groups) on colonic tone, compliance, sensation VAS ratings at 36 mmHg, phasic motor function, and stress-arousal scores in all randomized subjects [intent to treat (ITT) analysis]. The covariates considered for inclusion in these analyses were sex, body mass index (BMI), and the corresponding baseline (pretreatment) response values. ANCOVA was also used to assess overall treatment effects on the sensation ratings averaged over distensions at 16, 24, 30, and 36 mmHg above the baseline operating pressure. Sex, mean pretreatment sensation ratings, and pretreatment compliance (Pr50%) were included as covariates in this analysis. The association between compliance, sensation (VAS) ratings, and stress-arousal scores were estimated using (Pearson) correlation coefficients. Two specific pairwise comparisons (each dose vs. placebo) were also examined. We did not adjust the \( \alpha \)-level to 0.025 for the pairwise comparisons despite testing the two doses of pregabalin because there are no prior human dose-response data to identify effects on visceral sensation. Our study addressed each dose of pregabalin (75 and 200 mg) separately vs. placebo, and a dose-response relationship was not considered in the study hypothesis.

The analyses of pressure thresholds for first perception, gas, and pain utilized Cox proportional hazards regression models to account for the potential censored values in those instances when the maximum pressure level of 60 mmHg was reached without pain or gas being reported. The stress-arousal scores and corresponding pretreatment threshold level were included as covariates in these models.

Imputation for missing data. Because the ITT analysis included all subjects randomized and on-treatment data were not available from two participants who withdrew because they were unable to tolerate the bowel preparation, the following method was used for data imputation of missing compliance, tone, and phasic motor function endpoints. Missing values for a specific endpoint were replaced by the corresponding mean value over all participants who completed the studies. To adjust the residual error variance, the number of error degrees of freedom was reduced by one for each data value imputed.

Sample-size assessment. Before the study, the effect size demonstrable, based on 20 participants per group, was estimated on the basis of the previously observed coefficients of variation for the main endpoints of interest (Table 1). In addition, the variation observed in this study was also used to estimate the effect sizes that could have been detected (Table 2).

Table 1. Estimated effect sizes predicted to be demonstrable in primary sensory, compliance, and motility endpoints with 20 participants per group

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>COV, %</th>
<th>Effect Size, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain threshold</td>
<td>46</td>
<td>42</td>
</tr>
<tr>
<td>Pain sensation at 30 mmHg distension</td>
<td>59</td>
<td>54</td>
</tr>
<tr>
<td>Compliance Pr50</td>
<td>41</td>
<td>37</td>
</tr>
<tr>
<td>PP colon tone, symmetric % change</td>
<td>47</td>
<td>43</td>
</tr>
<tr>
<td>PP colon MI</td>
<td>24</td>
<td>22</td>
</tr>
</tbody>
</table>

Effect size is the difference in group means as a result of the treatment that could be detected using 20 participants per group with the coefficients of variation (COV)% (SD/mean) calculated from prior studies using the same methods in our laboratory. Pr50, pretreatment compliance at 50%; PP, postprandial; MI, motility index.

Table 2. Effect sizes that could have been detected with 80% power (2-sided \( \alpha \) of 0.05) based on a 2-sample \( t \)-test

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Observed COV, %</th>
<th>Effect Size, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain threshold</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>Pain sensation average over 4 distensions</td>
<td>56</td>
<td>51</td>
</tr>
<tr>
<td>Compliance Pr50</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>PP colon tone, symmetric % change</td>
<td>74</td>
<td>67</td>
</tr>
<tr>
<td>PP colon MI (proximal)</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>PP colon MI (distal)</td>
<td>29</td>
<td>26</td>
</tr>
</tbody>
</table>

The effect size is the difference in group mean values as a percentage of the overall subject mean value; \( n = 20 \) per group using the COV actually observed in this study.
RESULTS

Demographics

Sixty-two healthy adults were recruited (Fig. 2). Two participants dropped out after randomization (1 on 75 mg, 1 on 200 mg pregabalin) because they were unable to tolerate the bowel preparation the day before the barostat placement. The demographic data from all 62 and the other baseline data in the 60 healthy adult participants are summarized by randomization group (pregabalin 75 mg, pregabalin 200 mg, or placebo) in Fig. 2. There were no clinically important differences among treatment groups for demographics, BMI, or baseline operating pressure of the intracolonic balloon.

Colonic Sensation Ratings for Gas and Pain During Random-Order Phasic Distensions

Adjusting for predrug compliance, sensation ratings, and sex, there were overall (among the 3 treatment groups) numerical differences in colonic sensation ratings for gas ($P = 0.14$) and pain ($P = 0.12$) averaged over the four distension levels (Fig. 3, A and B). The differences for placebo were attributable to pregabalin 200 mg (gas, $P = 0.05$; pain, $P = 0.04$ compared with placebo; both comparisons unadjusted for 2 doses tested), but not the 75 mg dose, the latter showing virtually no difference in ratings compared with placebo. The magnitude of the effect of 200 mg of pregabalin relative to placebo is on average a 25% reduction of both gas and pain sensation ratings. There was a relationship of effects on sensation with stress-arousal scores (see below).

Colonic Compliance

There was no significant effect of pregabalin on colonic compliance (Table 3).

Colonic Sensation Thresholds, Colonic Motility, and Tone

There were no treatment effects of pregabalin on sensory thresholds for gas or pain, even after adjusting for sex and baseline values (Table 3). Similarly, there were no treatment effects on colonic fasting or postprandial tone or motility index (colonic phasic pressure activity).

Effects of Treatment on Stress-Arousal Symptoms and Relationships to Sensation Ratings

The scores of energy and drowsiness were highly (inverse) correlated ($r = -0.79$, $P < 0.001$); similarly, tenseness and relaxation were highly (inverse) correlated ($r = -0.81$, $P < 0.001$) although correlations between other pairs were not significant. Given this pattern of correlation, we considered that there were two stress-arousal domains.

No significant relationships were observed between pretreatment stress-arousal symptoms and pre- or posttreatment sensation ratings for gas and pain.

There were overall treatment effects on energy and drowsiness ($P = 0.044$ and $P = 0.050$, respectively; both unadjusted for 4 overall assessments of stress arousal measures) but no treatment effects on tenseness and relaxation scores. Figure 4A shows pre- and posttreatment scores for these symptoms. Because the pretreatment stress-arousal scores were strongly correlated with the posttreatment scores, we also plotted the least-square means for the posttreatment scores (Fig. 4B).

Fig. 2. Study design and participant demographics and baseline features. BOP, balloon operating pressure; BMI, body mass index.
adapting for the modest differences in pretreatment scores among the groups.

There were significant positive associations between posttreatment mean gas and pain sensory ratings with posttreatment tenseness (gas $r = 0.496$, $P < 0.001$; pain $r = 0.464$, $P = 0.0002$) and inverse correlations with posttreatment relaxation (gas $r = -0.490$, $P < .0001$; pain $r = -0.467$, $P = 0.0002$), but not with posttreatment drowsiness or energy scores.

**Adverse Events**

The most common adverse event was tachycardia in 40% of the participants: 7/19 with pregabalin 200 mg, 9/20 with pregabalin 75 mg, 8/21 with placebo ($P = 0.89$). The second most common adverse event was dizziness, observed in 20% of participants: 7/19 with pregabalin 200 mg, 4/20 pregabalin 75 mg, and 1/21 with placebo ($P = 0.04$). Dizziness occurred in 13%: 7/19 with pregabalin 200 mg, 1/20 with pregabalin 75 mg, and 0/21 with placebo ($P = 0.001$).

Two participants withdrew from the study because of intolerance to bowel preparation (before receiving treatment). No participant withdrew form the study as a result of a treatment-related adverse event.

**DISCUSSION**

This study evaluated the effects of a single dose of pregabalin on colonic sensation and motor function in healthy adults and demonstrated that 200 mg of pregabalin reduces mean gas and pain sensation ratings in response to four random-order phasic distensions over the range of pressures, with the highest pressures reaching around 50 mmHg. These significant reductions in sensation ratings of gas and pain were observed in the absence of any significant effects on relaxation and only small effects on energy and drowsiness, the latter being significant on unadjusted comparison. These data suggest that the effect of pregabalin is mediated by a decrease in peripheral or spinal afferent functions. In our study, the two doses of pregabalin tested did not significantly affect sensation thresholds, colonic compliance, colonic fasting tone, or phasic MI.

A reduction in rectal pain sensation in response to distension was also reported by Houghton et al. (16) in patients with IBS. Human and rodent studies had suggested that the effect of pregabalin on pain sensation in the bowel was explained in part by the increased viscus compliance in response to the drug (16, 23). Ravnefjord et al. (23) also described an increase in colonic compliance with pregabalin. Our study did not find a significant effect of pregabalin on colonic compliance on the basis of the calculated Pr50%, which reflects the estimated pressure for half the maximum balloon volume, and the calculated Pr10%, which would reflect a left shift (signifying increased compliance) as observed with clonidine (3) in the pressure-volume curve. A careful review of the compliance curves in the studies from Ravnefjord et al. and Houghton et al. (16, 23) demonstrates that the increase in compliance with pregabalin over placebo was relatively small in the main range of pressures tested, including the region close to Pr50%. Compliance measured above the Pr50% may reflect the elasticity of the viscus rather than the neuromuscular function and may be less relevant to the assessment of the role of viscus compliance in sensation ratings. Despite the observation of increased compli-

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**Table 3. Effects of treatment on compliance, sensation thresholds, motility, and tone**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Pregabalin, 75 mg</th>
<th>Pregabalin, 200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance Pr10%, mmHg</td>
<td>5.7 ± 1.8</td>
<td>5.9 ± 2.0</td>
<td>6.4 ± 1.9</td>
</tr>
<tr>
<td>Compliance Pr50%, mmHg</td>
<td>17.4 ± 4.8</td>
<td>17.6 ± 5.1</td>
<td>19.1 ± 4.6</td>
</tr>
<tr>
<td>Gas threshold, mmHg†</td>
<td>34.5 ± 16.8</td>
<td>27.6 ± 18.3</td>
<td>34.3 ± 11.1</td>
</tr>
<tr>
<td>Pain threshold, mmHg‡</td>
<td>45.0 ± 14.0</td>
<td>45.8 ± 14.9</td>
<td>46.7 ± 13.9</td>
</tr>
<tr>
<td>Gas sensation ratings at 30 mmHg</td>
<td>46.6 ± 22.3</td>
<td>53.4 ± 27.9</td>
<td>33.2 ± 19.6</td>
</tr>
<tr>
<td>Gas sensation ratings at 36 mmHg</td>
<td>46.2 ± 22.4</td>
<td>49.6 ± 25.0</td>
<td>36.6 ± 22.4</td>
</tr>
<tr>
<td>Pain sensation ratings at 30 mmHg</td>
<td>46.0 ± 28.7</td>
<td>47.4 ± 28.3</td>
<td>36.1 ± 28.4</td>
</tr>
<tr>
<td>Pain sensation ratings at 36 mmHg</td>
<td>47.6 ± 30.4</td>
<td>44.3 ± 24.0</td>
<td>43.4 ± 26.9</td>
</tr>
<tr>
<td>Colon tone fasting, ml</td>
<td>100.2 ± 27.2</td>
<td>100.8 ± 24.0</td>
<td>100.3 ± 26.7</td>
</tr>
<tr>
<td>Colon tone fed, ml</td>
<td>75.9 ± 30.0</td>
<td>84.5 ± 23.4</td>
<td>74.1 ± 25.4</td>
</tr>
<tr>
<td>Postprandial % Δ colonic tone, first 30 min PP/ fasting 30 min*</td>
<td>27.8 ± 21.8</td>
<td>21.9 ± 12.4</td>
<td>35.3 ± 25.2</td>
</tr>
<tr>
<td>Colon MI fasting</td>
<td>10.6 ± 1.5</td>
<td>9.9 ± 2.1</td>
<td>9.9 ± 2.4</td>
</tr>
<tr>
<td>Colon MI fed</td>
<td>11.5 ± 1.3</td>
<td>11.3 ± 1.6</td>
<td>11.4 ± 1.4</td>
</tr>
</tbody>
</table>

Values are means ± SD. *Overall $P = 0.10$; all $P > 0.05$, †ignores censoring.
Pregabalin and Colonic Sensation in Healthy Humans

Fig. 4. A: symptoms used to evaluate effects of treatment on measures of stress. B: comparisons of posttreatment stress-arousal scores (least-square means adjusted for minor differences in groups observed at baseline) show significant effect of treatment on energy and drowsiness levels. *Overall differences among the 3 groups observed at baseline) show significant effect of treatment on energy and drowsiness levels. Dunnett’s test, but not 75 mg of pregabalin for energy scores, whereas, for the drowsiness scores, both 75 mg and 200 mg of pregabalin were borderline (P = 0.062 for both, Dunnett’s test).

Pregabalin did not significantly affect sensation thresholds, colonic fasting tone, or MI. We used two different methods for assessment of colonic sensation; sensory thresholds for gas and pain were assessed by using ascending methods of limits, which may predispose participants to response bias because participants report their sensation at each of 13 pressure levels. In addition, we have shown that sensation thresholds in human rectum and colon are associated with relatively larger coefficients of variation (6, 22). On the other hand, phasic random distensions with assessment of sensation ratings are expected to be less prone to bias because the distensions are delivered in random order and the coefficient of variation is smaller.

In our experience, sensation ratings using random colonic distensions are more sensitive to assess effects on sensation because the ratings are less prone to sequence effects from one distension level to the next, as the stepwise increase in pressures in the distending balloon may be predictable to participants after the first sensation is achieved. In contrast, random-order pressure distensions used to assess sensation ratings avoid this potential sequence effect. Moreover, with sensation ratings, there is wide range of response over the range of distensions, and therefore it was possible to identify a ~25% difference when ratings were averaged over four distensions. In contrast, sensation thresholds are more narrowly distributed, and the magnitude of difference in pain sensation threshold between health (~32 to 36 mmHg) and IBS (~28 to 32 mmHg) is only ~4 mmHg. For such an effect size of 13%, the sample size required to demonstrate group differences is much greater than the 20 participants per group, on the basis of the data previously published (6).

The lack of effect of pregabalin on colonic motor responses (tone, phasic motility, and compliance) suggests that pregabalin affects afferent nerve pathways. This is supported by the studies of Needham et al. (21), who showed that intrinsic primary afferent neurons are associated with α2δ1 modulatory subunits, which are inhibited by pregabalin. We conducted a post hoc assessment of statistical power based on the sample studied and the observed coefficient of variation. Table 2 shows the results and illustrates that the study had sufficient power to identify an effect on sensation ratings and sensory thresholds although the coefficient of variation in the postprandial change in colonic tone (symmetric % change) was greater than in the prestudy analysis, and therefore we cannot exclude a type II error in the assessment of effects of pregabalin on postprandial change in colonic tone.

As we had previously reported that higher BMI was associated with decreased pain rating during distensions and a higher threshold for pain (9), we compared the BMI of the pregabalin and placebo groups and found they were not significantly different. Therefore, BMI does not explain the differences in sensation observed with 200 mg of pregabalin compared with placebo.

Our study is generalizable to middle-aged, predominantly female, Caucasian healthy adults; the extent to which these results apply to other populations remains further study. In this study, pregabalin showed a favorable safety profile, with drowsiness as the most common side effect, and there were slightly lower energy and higher drowsiness ratings (~10% on pregabalin 75 and 200 mg doses) relative to placebo. Dizziness had been reported in many previous studies (27) and is consistent with the central actions and ease of crossing the blood-brain barrier of pregabalin. We observed a significant positive correlation between posttreatment tension and gas pain sensations and inverse relationships between posttreatment relaxation and gas and pain sensations, but no such relationship with energy and drowsiness levels (which were the stress-arousal symptoms actually altered by treatment), suggesting that the...
effects of pregabalin on sensation are not mediated centrally and that the likely peripheral or spinal sensory mechanisms may contribute (by calculated $r^2$) to $\sim 25\%$ of the variance in gas and pain sensations. These data contrast with the reported effects on mental function associated with visceral analgesic effects of high dose fentanyl (17).

The strengths of this study include the use of two different doses of pregabalin compared with placebo to identify at least one dose that shows potentially relevant clinical efficacy, the participation of healthy adults not exposed to medications that can alter colon motility or sensation, the use of a standardized barostat distension protocol performed and analyzed by experienced investigators, and known coefficients of variation in the study endpoints.

However, we recognize that the symptoms elicited by mechanical stimuli may be lower in healthy subjects than in patients with IBS. Before our study, the effective dose of pregabalin for somatic pain was recorded as 150 mg. We compared only two doses of pregabalin, 75 mg and 200 mg, to placebo because we wished not to expose healthy participants to unnecessary adverse effects. The effect size for pain at 30 mmHg distension demonstrable with 20 participants per group was 54%; therefore, there may have been lower degrees of pain relief that would only have been detectable with a larger sample size. On the other hand, our post hoc effect size analysis suggests that our study was well powered to assess the effects of pregabalin on sensation thresholds and sensory ratings of gas and pain.

In summary, a single administration of 200 mg of pregabalin is safe and reduces colonic mean sensation ratings for gas and pain, suggesting a reduction of function inafferent pathways; this observation suggests that pregabalin is promising for the treatment of colonic pain. Acute administration of pregabalin demonstrated a 13% prevalence of dizziness, which might be a potential disadvantage if patients with IBS were to receive this treatment. Headache, somnolence, and dizziness occurred in 15–32% of patients with fibromyalgia (30% of whom had IBS) in a randomized, 8-wk, controlled trial of 150 and 300 mg pregabalin/day (7); however, $\sim 80\%$ of participants completed the 8-wk trial despite the presence of these treatment-emergent adverse events. Future studies should assess both the potential role of pregabalin in visceral pain and in the treatment of visceral hypersensitivity in patients with IBS, as well as the relationship of colonic compliance and pain perception, and such studies should demonstrate further insight into the pathophysiology of chronic abdominal pain in IBS.

GRANTS

Dr. Camilleri is supported in part by grants 1RC1-DK-086182, R01-DK-079866, and R01-DK-67071 from National Institutes of Health. The study was conducted in the Clinical Research Unit of the Mayo Clinic CTSA (RR24150). This study is registered in ClinicalTrials.gov with the identifier NCT01948408.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors. Study conceptualization, endoscopic placements, writing of protocol and manuscript were performed by M. Camilleri; research fellowship, recruitment, assisting with measurements, writing protocol and manuscript were performed by J. Turinco; database management and statistical analysis were performed by A. R. Zinsmeister; participant recruitment, sensation and motility studies were performed by I. Busciglio; endoscopic placements were performed by D. Burton.

REFERENCES

and actions of pregabalin on intrinsic primary afferent neurons in the
22. Odunsi ST, Camilleri M, Bharucha AE, Papathanasopoulos A,
Busciglio I, Burton D, Zinsmeister AR. Reproducibility and perfor-
mance characteristics of colonic compliance, tone, and sensory tests in
23. Ravnefjord A, Brusberg M, Larsson H, Lindstrom E, Martinez V.
Effects of pregabalin on visceral pain responses and colonic compliance in
25. von der Ohe MR, Hanson RB, Camilleri M. Serotonergic mediation of
postprandial colonic tonic and phasic responses in humans. Gut 35:
alization of the domain structure of an L-type Ca2+ channel using electron
profile of pregabalin: A systematic review and meta-analysis of random-