Inhibitory effects of desvenlafaxine on gastric slow waves, antral contractions, and gastric accommodation mediated via the sympathetic mechanism in dogs

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Dai F, Lei Y, Chen JD. Inhibitory effects of desvenlafaxine on gastric slow waves, antral contractions, and gastric accommodation mediated via the sympathetic mechanism in dogs. Am J Physiol Gastrointest Liver Physiol 301: G707–G712, 2011. First published July 14, 2011; doi:10.1152/ajpgi.00044.2011.—Desvenlafaxine succinate (DVS; Pristiq) is a new antidepressant, serotonin-norepinephrine reuptake inhibitor. Antidepressants have been widely used for the treatment of functional gastrointestinal disorders. Possible roles of DVS on gastrointestinal motility have not been studied. The aim of this study was to investigate the effects of DVS on gastric slow waves (GSW), antral contractions, and gastric accommodation in dogs. Fifteen healthy dogs implanted with gastric serosal electrodes and a gastric cannula were studied in four separate sessions: control, DVS (50 mg), propranolol (1 mg·kg⁻¹·h⁻¹), and propranolol + DVS. GSW were measured via the gastric serosal electrodes. Antral contractions were assessed via an intraluminal manometric catheter inserted via the gastric cannula. The sympathtovagal activity was assessed from the spectral analysis of the heart rate variability signal. Gastric tone was measured by barostat via an intragastric balloon inserted into the fundus via the gastric cannula. In the postprandial period, in comparison with the control, DVS reduced the percentage of normal GSW (P = 0.001) and increased the percentage of tachygastria (P = 0.005) and bradygastria (P = 0.002). Simultaneously, DVS increased the sympathetic activity (P = 0.006) and the sympathovagal ratio (low frequency/high frequency; P = 0.044). These effects were blocked by propranolol. DVS attenuated postprandial antral contractions and gastric accommodation. The postprandial antral contractile index (area under the curve) was decreased by 26% with DVS (P = 0.013), and gastric accommodation was decreased by about 50% with DVS (P < 0.001). The inhibitory effect of DVS on gastric accommodation was blocked by propranolol. DVS inhibits gastric contractions, slow waves, and accommodation in the fed state. These inhibitory effects are associated with an increased sympathetic modulation in the gastrointestinal system. Cautions should be made when DVS is used for treating patients with depression and gastric motility disorders.

Antidepressants are widely used for the treatment of functional gastrointestinal disorders, such as functional dyspepsia and irritable bowel syndrome (17, 20, 55). The rationale for the use of antidepressants in functional gastrointestinal disorders is based on the following potential effects. First, antidepressants may improve psychiatric and psychological symptoms, particularly anxiety and depression (11, 18, 47). Second, antidepressants have central analgesic actions and alter central processing of visceral pain stimuli (10, 27). Third, antidepressants may have local pharmacological actions on the gut and modulate gut sensorimotor functions (3, 8, 9).

Desvenlafaxine succinate (DVS; Pristiq) is a new antidepressant, the third serotonin-norepinephrine reuptake inhibitor (SNRI) approved by the U.S. Food and Drug Administration for the treatment of major depressive disorders in 2008 (26, 35). It is a novel salt form of the isolated major active metabolite of the antidepressant venlafaxine. A preclinical study using competitive radioligand binding assays indicates that DVS exhibits selective inhibitory activity of neurotransmitter uptake at the human serotonin (5-HT) and norepinephrine transporters and has weak binding affinity at the human dopamine transporter (13). DVS shows virtually no affinity for muscarinic, cholinergic, H1-histaminergic, or α1-adrenergic receptors in vitro (13).

Studies have supported the potential utility of DVS in the treatment of vasomotor symptoms of menopause, anxiety symptoms, and painful physical symptoms (2, 33, 34). To date, there are no published studies elucidating the possible role of DVS on gastrointestinal motility. Because patients with functional gastrointestinal disorders often have impaired gastric motility, it is therefore important to study possible effects of DVS on gastric motility. The aim of this study was to investigate possible effects of DVS on gastric slow waves (GSW), antral contractions, gastric tone, and accommodation in healthy dogs.

MATERIALS AND METHODS

Animal Preparation

A total of 15 healthy female hound dogs (20–25 kg) were used in the study. After an overnight fast, the dogs were anesthetized with intravenous sodium thiopental (Pentothal; 5 mg/kg; Abbott Laboratories, North Chicago, IL) and maintained on IsoFlo (isoflurane, 1.5%; inhalation anesthesia; Abbott Laboratories) in oxygen-nitrous oxide (1:1) carrier gases delivered from a ventilator following endotracheal intubation. Laparotomy was performed with the vital sign monitoring of mucosal color, pulse rate, and breath rate. One pair of 28-gauge cardiac pacing electrodes (A&E Medical, Farmingdale, NJ) was implanted on the serosal surface of the distal antrum (6 cm proximal to pylorus) near the greater curvature. The connecting wires of the electrodes were tunneled through the anterior abdominal wall subcutaneously along the right side of the trunk and placed outside the skin around the right hypochondrium for the attachment to an electromyographic recorder. In addition, a cannula was placed in the stomach 10 cm proximal to the pylorus for the assessment of gastric tone and antral motility. After the placement of the electrodes and cannula, the abdomen was closed and the anesthetics were stopped. Once consciousness was regained, the dog was transferred to a recovery cage after receiving medications for postoperative pain control. The experiments described below were performed after the dog had completely recovered from surgery (14 days later). The experimental protocol
was approved by the Institutional Animal Care and Use Committees at the Veterans Affairs Medical Center (Oklahoma City, OK).

Experimental Protocols

Two experiments were performed to simultaneously assess the effects of DVS on antral contractions, GSW, and heart rate variability (HRV) and possible sympathetic mechanisms and to assess the effects of DVS on gastric tone and accommodation.

Experiment 1: effects of DVS on GSW, HRV, and antral motility and possible sympathetic mechanisms. The experiment was performed in four randomized sessions on separate days: control session (1 placebo tablet given orally, 6 h before the study), DVS session (50 mg DVS given orally, 6 h before the study), propranolol session (1 mg·kg\(^{-1}\)·h\(^{-1}\) iv, immediately before the study), and propranolol + DVS session (50 mg DVS given orally, 6 h before the study and 1 mg·kg\(^{-1}\)·h\(^{-1}\) iv propranolol, immediately before the study). The dose of 50 mg for DVS was based on a previous study (16). We chose to give DVS 6 h before the study (or about 7 h before the actual recordings) because the maximum plasma concentration of DVS was reported to be 7 to 8 h after oral administration (35). Propranolol was used to block the β-adrenergic pathway, and the dose was chosen according to one of our previous studies (31). Antral contractions, GSW, and ECG were recorded simultaneously for 30 min at baseline in the fasting state (overnight fasted) and 60 min after one can of solid dog food (413 kcal; 13.2 ounces; crude protein, 8.0%; crude fat, 6.0%; crude fiber, 1.5%; moisture, 78.0%; Pedigree; Masterfoods, Vernon, CA). The animal was standing on an experimental table loosely restrained during the recordings and was trained to get acclimated to the experimental environment before the experiment.

GSW were recorded by connecting the gastric serosal electrodes to a multiplex recorder. The ECG was recorded via a special one-channel amplifier with two separate leads and one ground electrode. The two leads were attached to the left and right supraventricular fossas of the subjects and the ground to the left leg. A manometry catheter was inserted through the gastric cannula into the distal stomach to measure antral contractions. Detailed descriptions of these measurements are given below.

Experiment 2: effects of DVS on gastric tone and accommodation. Each dog was studied in the same four sessions as in Experiment 1 on separate days: control, DVS, propranolol, and propranolol + DVS with the same dosage and administration timing and route as in Experiment 1. A polyethylene bag (CTBP800; H&AMUI Enterprise, Mississauga, ON, Canada) was inserted and positioned in the proximal stomach through the gastric cannula for the measurement of gastric tone for 30 min in the fasting state (overnight fasted) and 60 min after one can of Boost was given orally (a liquid meal; 237 ml, 240 kcal; total fat, 4.0 grams; protein, 10.0 grams; total carbohydrate, 41.0 grams; Novartis Medical Nutrition, Fremont, MI). Similarly, the animal was standing on an experimental table loosely restrained during the recording period and was acclimated to the experimental environment before the experiment.

Measurements and Analyses

Recording and analysis of GSW. A biosignal recorder (Acknowledge III, EOG 100A; Biopac Systems, Santa Barbara, CA) was used to record GSW. The signal was displayed on a computer monitor and saved to the computer’s hard disk. The low and high cutoff frequencies of the amplifiers were 0.05 and 35 Hz, respectively. The signal was initially sampled at a frequency of 100 Hz and then downsampled at 2 Hz after low-pass filtering with a cutoff frequency of 1 Hz. The parameters assessed from the GSW were dominant frequency, dominant power, and the percentages of normal GSW, tachygastria, and bradygastria.

Dominant frequency and power of the GSW. The smoothed power spectral analysis method was applied to the fasting or postprandial recording of the GSW to derive a power spectrum. From the power spectrum, the peak power and its corresponding frequency were identified and defined as the dominant power and dominant frequency of the GSW.

Percentages of normal GSW and dysrhythmia. A special running spectral analysis method, called adaptive spectral analysis method, was applied to the GSW recording (6). One power spectrum was generated for every 1 min of data. The peak power in each spectrum was identified. If the peak power was within the normal range \([4–6 \text{ cycles/min counts per min (cpm)}]\), that minute was considered as normal; otherwise, it was defined as tachygastria (if the peak is at a frequency higher than 6 cpm), bradygastria (the peak is at a frequency lower than 4 cpm), or arrhythmia (no obvious peak). The definition of normal slow waves from 4 to 6 cpm was based on a previous study (36, 42).

Recording and analysis of the ECG. The ECG was recorded via a UFI amplifier (UFI, model 2283 16-bit Fetrode Amplifier; Morro Bay, CA) and digitized with a sampling frequency of 6,000 Hz using the sound card on the personal computer. The signal was downsampled to 500 Hz before analysis. The HRV signal was derived from the ECG signal by detection and interpolation of R-R intervals. Power spectral analysis was then performed on the segmental HRV data to derive sympathetic and vagal activities (32).

The spectral analysis of the HRV was calculated by a previously validated method (32). The power in the low frequency (LF) band (0.04–0.15 Hz) was calculated, and it primarily represents sympathetic activity. The power in the high frequency (HF) band (0.15–0.50 Hz) representing solely vagal activity was also computed. The LF (sympathetic component) was obtained by calculating the area under the curve in the frequency range of 0.04–0.15 Hz, and the HF was determined by computing the area under the curve in the frequency range of 0.15–0.50 Hz. The ratio of LF to HF represents the balance between sympathetic and vagal activity.

Recording of Antral Contractions

Antral contractile activities were recorded from four pressure sensors (1 cm apart from each other) attached to a manometric catheter by using a PC polygraph HR system (Synectics Medical, Stockholm, Sweden) and a microcapillary infusion system (Medtronic Synectics, Stockholm, Sweden) (31). All recordings were displayed on a computer monitor. A contractile index was used to represent antral contractions, defined as the mean amplitude of all contractile samples over the baseline and computed using the Polygram Function Testing Software (Medtronic, Shoreview, MN). To be consistent among different animals, the data presented in this study were obtained from Channel 3 in all animals that was about 7 cm from the pylorus. The quality of antral contractile signal was good in all channels; however, Channel 3 consistently showed higher amplitude in antral contractions. Because the purpose of this study was to investigate the effect of DVS on antral contractions in the fed state, the fasting recording was made only for 30 min (long enough to get reliable electrogastrogram data) and the phase of migrating motor complex was not controlled.

Measurement of Gastric Tone and Accommodation

The barostat bag used for the measurement of gastric tone was noncompliant, had a maximal volume of 700 ml, and was attached to the distal end of a double-lumen catheter. The orientation of the gastric cannula was marked during surgery, when the abdomen was open, to ensure accurate placement of the barostat bag into the fundus. The catheter was connected to a computer-controlled electrical barostat device (Distender Series III; G & J Electronics, Willowdale, ON, Canada) (57). After its placement in the fundus, the bag was briefly inflated with 300 ml air and then completely deflated. After a brief rest period, the minimal distending pressure was determined by inflating the bag in 1 mmHg increments until a pressure at which evident respiratory excursions were recorded and the bag volume was
equal to or larger than 30 ml (40). Gastric tone, reflected by gastric volume, was recorded at an operating pressure of 2 mmHg higher than the minimal distending pressure during the entire experiment. At a constant operating pressure, an increase in gastric volume reflects a decrease in gastric tone, and vice versa. Gastric accommodation was calculated as the difference in gastric volume between postprandial and fasting recordings.

**Statistical Analysis**

All values are expressed as means ± SE. Paired Student’s t-test was used to investigate the differences between two sessions. One-way ANOVA followed by Fisher’s protected least-significant difference test (PLSD) was used to compare the data among three sessions or more. P < 0.05 was considered statistically significant.

**RESULTS**

**Effects of DVS on GSW and Sympathetic Mechanisms (n = 8)**

There were no significant differences in dominant frequency (ANOVA; P = 0.577), dominant power (P = 0.059), percentage of normal GSW (P = 0.336), percentage of tachygastria (P = 0.061), the percentage of bradygastria (P = 0.571), or the percentage of arrhythmia (P = 0.181) in the fasting state among the four sessions of control, DVS, propranolol, and propranolol plus DVS, suggesting that DVS or propranolol had no effects on GSW in the fasting state. During the postprandial period, however, DVS reduced the percentage of normal GSW (48.6 ± 7.3% vs. 76.6 ± 5.7%; P = 0.001) and increased the percentage of tachygastria (15.7 ± 3.0% vs. 6.1 ± 1.6; P = 0.005) and bradygastria (14.2 ± 2.2% vs. 5.4 ± 1.4; P = 0.002) but did not affect the dominant frequency or dominant power of the slow waves. Although administrated alone, propranolol did not alter GSW; however, it completely blocked the inhibitory effects of DVS on GSW. The percentages of normal GSW, tachygastria, and bradygastria with propranolol plus DVS were 70.3 ± 9.3 (P = 0.377), 8.7 ± 2.2 (P = 0.399), and 6.9 ± 2.5 (P = 0.509), respectively, which were not significantly different from those in the control session (Fig. 1).

**Effects of DVS on HRV and Sympathetic mechanisms (n = 8)**

No differences were noted in sympathetic activity (LF; P = 0.333), vagal activity (HF; P = 0.434), or the sympathovagal ratio (LF/HF; P = 0.557) in the fasting state among the four sessions of control, DVS, propranolol, and propranolol + DVS. In the postprandial period, however, DVS increased sympathetic activity (LF; 1.02 ± 0.19 vs. 0.66 ± 0.19; P = 0.006) and the sympathovagal ratio (LF/HF; 0.48 ± 0.09 vs. 0.33 ± 0.10; P = 0.044). These effects were blocked by propranolol. The sympathetic activity (LF) and the sympathovagal ratio (LF/HF) in the session of propranolol + DVS were 0.76 ± 0.16 (vs. control; P = 0.381) and 0.22 ± 0.04 (vs. control; P = 0.105), respectively (Fig. 2). DVS showed no effects on vagal activity (HF).

**Effects of DVS on Antral Contractions (n = 8)**

DVS attenuated postprandial antral contractions. The postprandial antral contractile index was 9.4 ± 1.4 mmHg in the DVS session and 12.7 ± 1.1 mmHg in the control session (P = 0.013; Fig. 3). The contractile index of antral contractions in the fasting state was not altered with DVS (7.5 ± 1.0 mmHg vs. 7.5 ± 0.9 mmHg; P = 0.99); however, it should be noted that these values were not conclusive because the fasting antral contractions are associated with a phase of the migrating motor complex and the 30-min recording made in this study was not controlled for the phase of migrating motor complex since the experiment was not designed to study the effect of DVS on fasting antral contractions.

**Effects of DVS on Gastric Tone and Accommodation and Sympathetic Mechanisms (n = 7)**

No differences were found in gastric volume in the fasting state among the four sessions of control, DVS, propranolol, and propranolol + DVS (ANOVA; P = 0.51). However, DVS decreased gastric accommodation (125.8 ± 32.9 ml in DVS session vs. 246.4 ± 29.2 ml in the control session; P < 0.001; Fig. 4). Propranolol alone did not alter gastric accommodation (225.7 ± 30.7 ml in propranolol session; P = 0.4, vs. control session); it however, blocked the inhibitory effects of DVS on gastric accommodation (214.6 ± 30.0 ml, in the DVS + propranolol session, P = 0.2, vs. control session).
DISCUSSION

To the best of our knowledge, this was the first comprehensive study investigating the effects of DVS on gastric motility, including GSW, antral contractions, gastric tone, and gastric accommodation. It was found that DVS had inhibitory effects on gastric motility in the postprandial state but not in the fasting state. In the fed state, DVS at a single dose of 50 mg impaired GSW, inhibited antral contractions and attenuated gastric accommodations. These effects were mediated via the \( \beta \)-adrenergic mechanisms. DVS decreased the percentage of normal GSW and increased the percentages of tachygastria and bradygastria in the fed state, and these effects were completely blocked by a \( \beta \)-adrenergic blocker, propranolol. Simultaneously, DVS increased the sympathetic activity and sympathovagal balance, assessed by the spectral analysis of HRV. These findings suggested that the DVS-induced impairment in postprandial GSW was attributed to the activation of the sympathetic pathways, particularly the \( \beta \)-adrenergic mechanism. Gastric dysrhythmia includes three types: tachygastria, bradygastria, and arrhythmia. The earlier studies investigated the origins of the three types of gastric dysrhythmia in a canine model (23, 36). Tachygastria was found to originate from an ectopic pacemaker in the antrum and to propagate retrogradely. Both tachygastria and arrhythmia were associated with gastric hypomotility. Bradygastria was originated in the normal pacemaker and propagated distally and was associated with gastric contractions with a reduced frequency (4, 43). Gastric dysrhythmia has been reported to be associated with nausea and vomiting (5). It remains to be studied whether nausea and vomiting observed in clinical use of DVS might be associated with DVS-induced gastric dysrhythmia (14, 25). However, during this study, no nausea or vomiting was observed in the dogs.

HRV, more specifically the spectral analysis of HRV, has been used to assess cardiac autonomic balance due to its noninvasive measurement and high reproducibility (30) and has been studied as a marker for predicting the risk of cardiac arrhythmias (19). A number of studies showed that antidepressant treatment impacted on HRV. Tricyclic antidepressants (TCAs) reduced parasympathetic tone and decreased HRV (22, 24, 56, 58). Nortriptyline was reported to decrease sympathetic activity in patients under awake and sleeping conditions and decreased vagal activity in the awakening condition (58). A reduction in HRV associated with the TCA treatment was attributed to anticholinergic and \( \alpha_1 \)-adrenergic properties (21, 38). The effect of selective serotonin reuptake inhibitor anti-
depressants (SSRIs) on HRV was much less clear. Some studies reported increased HRV during SSRI treatment (28, 39, 53), whereas others found no difference or a reduction (1, 12, 37). SNRIs were reported to reduce HRV in most of studies (41, 54, 56). In the present study, DVS increased the sympathovagal ratio (LF/HF) and sympathetic activity in the fed state. These effects were blocked by propranolol. These findings suggested that excessive norepinephrine induced by DVS might be an important mechanism mediating sympathovagal cardiac imbalance, characterized by excessive sympathetic cardiac activity. Accordingly, more attention should be paid when selecting antidepressant medications in clinical practice, especially for patients at risk for cardiac arrhythmia or an otherwise increased cardiovascular risk.

Similar to its effects on GSW, DVS also decreased antral contractions in the fed state. It is well known that the autonomic nervous system plays an important role in the regulation of gastrointestinal motility (48, 50). Norepinephrine has been reported to inhibit gastric motility (51) and small intestinal motility (52). The inhibitory effect of DVS on postprandial antral contractions is therefore believed to be attributed to increased postprandial sympathetic activity. Accordingly, based on the findings of the current study, cautions should be made when DVS is to be used for treating patients with depression and gastric hypomotility, such as functional dyspepsia.

Studies in animals and humans have established that the accommodation reflex is mediated via a vagovagal reflex pathway, resulting in activation of nitricergic neurons in the gastric wall (15, 45). Animal studies demonstrated the involvement of 5-HT in vagally mediated gastric relaxation via the release of nitric oxide (29). In this study, DVS was found to exert no influence on gastric tone in the fasting state; this was in agreement with a previous study in which an SSRI, paroxetine, was found to have no effects on gastric tone in humans (44). However, it is interesting to note that DVS significantly reduced gastric accommodation, and these effects were blocked by propranolol. These findings suggested that the impairment in gastric accommodation induced by DVS was attributed to the activation of the sympathetic pathways, particularly the β-adrenergic mechanism. Previously, other antidepressants were reported to alter gastric accommodation as well. The SSRI paroxetine enhanced gastric accommodation in humans although it did not alter fasting gastric tone (44). Another study reported a marked enhancing effect of Venlafaxine-XR, a SNRI, on gastric accommodation (7). Because impaired accommodation is associated with early satiety and weight loss and is one of the contributing factors of functional dyspepsia (46), DVS may not be appropriate for patients with functional dyspepsia.

In conclusion, DVS inhibits gastric contractions, impairs GSW, and attenuates gastric accommodation in the fed state. These inhibitory effects are believed to be associated with the increased sympathetic modulation in the gastrointestinal system. Cautions should be made when DVS is used for treating patients with depression and gastric motility disorders.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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