Digestive Diseases and Sciences, Vol. 36, No. 8 (August 1991), pp. 1029–1033

Transcutaneous Electrical Nerve Stimulation Decreases Lower Esophageal Sphincter Pressure in Patients with Achalasia

MOISES GUELRUD, MD, ALICIA ROSSITER, MD, PAUL F. SOUNEY, MS, and MARYSELIS SULBARAN, MD

Vasoactive intestinal peptide (VIP) is believed to be an inhibitory neurotransmitter responsible for lower esophageal sphincter (LES) relaxation. In patients with achalasia the concentration of VIP and the number of VIP-containing nerve fibers are reduced or absent. It has been suggested that the response to low-frequency transcutaneous electrical nerve stimulation (TENS) may be mediated by a nonadrenergic noncholinergic pathway in which the release of VIP is responsible for the smooth muscle relaxation. The present study was designed to evaluate the effect of TENS on LES pressure and on VIP plasma concentrations in six patients with achalasia (five female, one male). TENS was performed daily during one week for 45-min sessions with a pocket stimulator that delivered low-frequency pulses (6.5 Hz), at 10 pulses/sec of 0.1-msec duration at intensities of 10–20 mA until rhythmic flexion of the fingers was obtained without producing pain. LES pressure and VIP levels were obtained before TENS, after the first 45-min session, and after a week of daily stimulation. After 45-min, TENS produced a significant reduction ($P < 0.01$) in LES resting pressure from the mean value 56 ± 6.4 mm Hg to 42.3 ± 6.4 mm Hg; with LES relaxation improvement from 50.6 ± 3% to 63.1 ± 3.2% ($P < 0.01$). After one week of daily TENS, an additional reduction in LES resting pressure (40.3 ± 4 mm Hg) was observed ($P < 0.01$). The mean basal values of VIP in five patients showed a significant increase after 45 min of TENS from 19.8 ± 2.1 pg/ml to 25.3 ± 2 pg/ml ($P < 0.02$); with a mean increase of 30%. After one week, the mean plasma values (26.3 ± 1.5 pg/ml) remained still significantly increased compared to basal values ($P < 0.002$). In conclusion, in patients with achalasia, TENS decreases LES pressure, improves LES relaxation, and increases the VIP plasma concentration.

KEY WORDS: vasoactive intestinal polypeptide; esophageal manometry; humans; achalasia; transcutaneous electrical nerve stimulation.

Lower esophageal sphincter (LES) relaxation is mediated by intramural neurons that release nonadrenergic, noncholinergic neurotransmitters, mainly vasoactive intestinal polypeptide (VIP) (1–8). In achalasia, the concentration of VIP and the number of VIP-containing fibers are reduced or absent (7, 9, 10).

Successful treatment of dysphagia in two patients with achalasia, by low-frequency transcutaneous nerve stimulation (TENS) has been recently reported (11). The response to TENS was accompa-

Manuscript received July 23, 1990; revised manuscript received November 2, 1990; accepted December 27, 1990.

From the Gastroenterology Department, Hospital General del Oeste, Caracas, Venezuela; Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts; and Pharmacy Department, Brigham and Women's Hospital, Boston, Massachusetts.

Address for reprint requests: Dr. Moises Guelrud, Policlinica Metropolitana, Urb. Caurimare, Caracas, Venezuela.

0163-2116/91/0800-1029$06.50/0

nied by elevated plasma levels of VIP, suggesting the release of the peptide. However, esophageal manometry was not performed to objectively assess the LES motor function. It has been shown recently that TENS significantly reduced the LES pressure in healthy volunteers (12).

The purpose of this study was to evaluate the effect of TENS on LES resting pressure and on VIP plasma concentrations in patients with achalasia.

MATERIALS AND METHODS

Six patients (five female and one male) ages 14–49 years, mean 29 years, with previously untreated achalasia; diagnosed by clinical, radiographic, and manometric criteria, gave written informed consent to take part in the study. Prior to entry all patients were fully informed regarding risk, limitations, possible side effects, and the investigative nature of the treatment approach. All the study procedures and treatments were done on an outpatient basis. The study was approved by the ethical committee of the hospital.

VIP Determinations. VIP plasma analysis was performed by a specific radioimmunoassay (Nichols Institute, California), which has a detection limit of 12.5 pg/ml and a 95% of confidence. Measurements were performed blinded in duplicate and the mean value was used; all samples were assessed in the same assay. Results are expressed as mean ± SEM. A total of three blood samples were drawn for VIP plasma determinations in fasting patients: The first day, two samples were obtained, one prior to the initiation of the study procedures (basal values), and the second sample 45 min after TENS. The third sample was drawn one week after daily 45-min sessions of TENS. In each patient 8 ml of blood were drawn from the cubital vein of the nonstimulated arm, and collected in chilled glass tubes previously filled with 0.5 ml aprotinin (10.000 IUK Trasylol, Bayer) added in order to prevent proteolytic degradation of VIP and 25 units/ml blood of heparin (Elkins-Sinn). The samples were immediately centrifuged at 2500 rpm at 4°C for 30 min. The separate plasma was frozen at −20°C until the radioimmunoassay was done.

Esophageal Motility Testing. Esophageal motility was evaluated using an intraluminal perfused catheter system with a Dent sleeve. The sleeve was positioned at the level of the LES and was continuously perfused at a rate of 0.5 ml/min by means of a low-compliance pneumohydraulic capillary infusion system (Arndorfer Specialities, Greendale, Wisconsin) connected to external pressure transducers, Cobe CDX-2 (Cobe Laboratories, Lakewood, Colorado) and to a four-channel recorder, Sandhill DMS-A (Sandhill, Littleton, Colorado). All subjects were studied after an overnight fast.

In order to avoid artifacts after the Dent sleeve placement, the first 15 min of the tracing were not used for interpretation. LES pressures were measured in the semirecumbent position. LES pressures were determined as the difference between the mean midrespiratory fundic pressure and the mean midrespiratory pressure recorded by the sleeve. The degree of LES relaxation was calculated as the maximal reduction in sphincter pressure after six wet swallows (5 ml water) given at 30-sec intervals and was expressed as a percentage of the resting pressure. LES pressures were obtained before and after the first 45 min of the TENS session and after one week of daily stimulation. All manometric traces were coded and read by two reviewers who were blinded to the investigation.

Transcutaneous Electrical Nerve Stimulation. TENS was performed daily for 45-min sessions before breakfast during one week. The procedure was done with a pocket stimulator Uni-tens XL. (Agar Electronics, Israel), which delivered low-frequency pulses (6 Hz) of 0.1-msec duration at intensities of 10–20 mA until rhythmic flexion of the fingers were obtained without producing pain. A negative electrode was placed on the dorsal web between the first and the second metacarpal bones and a positive electrode was placed at the ulnar border of the same hand.

Statistical Analysis. For statistical evaluation of LES pressures, absolute values and percentages of variation from basal values were compared using paired Student's *t* test. Results are expressed as mean ± SEM. VIP values were compared by means of Student's *t* test for paired samples. Results are expressed as mean ± SEM.

TABLE 1. EFFECT OF TENS ON LES BASAL PRESSURE IN SIX PATIENTS WITH ACHALASIA

N	*Pre-TENS (mm Hg)*	*Post-45 min (mm Hg)*	*1 week (mm Hg)*
1	78	60	50
2	50	52	50
3	72	52	46
4	44	32	36
5	40	18	26
6	52	40	34
X ± SEM	56.0 ± 6.4	42.3 ± 6.4*	40.3 ± 4.0*

*$P < 0.01$.

RESULTS

Effect of TENS on LES Pressure. The average resting basal LES pressure in the six patients with achalasia was 56.0 ± 6.4 mm Hg. After 45 min of TENS, a significant decrease ($P < 0.01$) on LES basal pressure to 42.3 ± 6.4 mm Hg was observed (Table 1). This represents a 24% reduction on LES pressure. After one week of daily stimulation, the LES basal pressure showed a moderate additional significant reduction to 40.3 ± 4.0 mm Hg ($P < 0.01$), representing 28% reduction of LES pressure with respect to basal levels. One patient did not respond to TENS, with LES pressure values 50, 52, and 50 mm Hg in the three phases of study respectively.

TABLE 2. EFFECT OF TENS ON LES RELAXATION IN SIX PATIENTS WITH ACHALASIA

N	*Pre-TENS (% relaxation)*	*Post-45 min (% relaxation)*	*1 week (% relaxation)*
1	59	77	68
2	60	61	56
3	41	56	50
4	54	60	53
5	45	67	54
6	45	58	61
$X \pm$ SEM	50.6 ± 3.3	63.1 ± 3.2*	57.0 ± 2.7*

*$P < 0.01$.

Effect of TENS on LES Relaxation. The mean LES relaxation for the six patients with achalasia was 50.6 ± 3%. After 45 min of TENS, there was a moderate but significant ($P < 0.01$) improvement of LES relaxation to 63.1 ± 3.2%. One week after daily TENS, the mean of LES relaxation was 57 ± 2.7% (Table 2). One patient had no improvement on LES relaxation, presenting values of 60, 61, and 61% in the three phases of the study, respectively.

Effect of TENS on VIP Plasma Concentrations. As seen in Table 3, on the first day of study one patient with basal VIP below the sensitivity of the assay experienced a marked increase in the VIP level to 61.7 pg/ml (more than 300% if 12 pg/ml is taken as basal value). As we do not know the actual VIP basal value for this patient, we decided to exclude him from the statistical analysis to avoid misleading results. The mean basal value of VIP plasma concentrations in the remaining five patients was 19.8 ± 2.1 pg/ml. After 45 min of TENS, there was a significant ($P < 0.02$) increase in the VIP plasma concentrations to 25.3 ± 2 pg/ml. After one week of daily TENS, the mean VIP plasma concentrations of 26.3 ± 1.5 pg/ml still remained significantly increased ($P < 0.002$) compared to the basal values.

TABLE 3. VARIATIONS ON VIP PLASMA VALUES AFTER TENS IN SIX PATIENTS WITH ACHALASIA

N	*Pre-TENS (pg/ml)*	*Post-45 min (pg/ml)*	*1 week (pg/ml)*
1	16.0	20.9	24.6
2	27.9	30.2	30.9
3	20.4	26.5	27.7
4	17.1	20.5	21.4
5	below sensitivity of the assay	61.7	29.3
6	17.9	28.8	27.1
X ± SEM*	19.8 ± 2.1	25.3 ± 2†	26.3 ± 1.5‡

*Patient 5 not included.
†$P < 0.02$.
‡$P < 0.002$.

The VIP plasma concentration in five patients showed a mean increase of 30% the first day and 35% after one week of daily stimulation. The patient with no improvement on basal LES pressure or LES relaxation showed a minimal (NS) increase of VIP plasma levels from 27.9 pg/ml to 30.2 and 30.9 pg/ml after 45 min and one week of daily TENS, respectively.

Side Effects. No side effects to TENS were seen in this group of patients after one week of therapy.

DISCUSSION

In the gut, VIP is especially rich in the gastrointestinal sphincters (13, 14) and in the neurons of the myenteric plexus in the region of the LES where it exerts a relaxing effect by acting directly on circular muscle cells (3, 15–17).

In patients with achalasia, the most consistent manometric finding is incomplete LES relaxation. Degeneration in nerve cell bodies at the myenteric plexus and a reduction in the number in conjunction with a defect of VIPergic neurons has been demonstrated (18). The concentration of VIP and the number of VIP-containing nerve fibers are reduced or absent (7, 9, 10). Recently, TENS has been used successfully in the treatment of achalasia (11) with improvement of clinical symptoms as well as radiological findings of improved esophageal emptying time. These findings were correlated to increases of VIP plasma levels up to 30% from basal levels. However, this study was performed in two patients in whom only radiographic monitoring was done, lacking more objective information such as the esophageal manometry.

In the present study we found that low-frequency TENS produced a moderate but significant fall in the LES pressure with improvement on LES relaxation. These responses were accompanied by an increase of VIP in the systemic circulation, which is viewed as an overflow of the neuronal release (5), probably reflecting the sum of neuronal activities in a number of different tissues. These results are consistent with our recent observations in patients with biliary dyskinesia (19), as well as with other studies that have shown an increase on the VIP plasma concentration in response to TENS in some pathologic stages as well as in healthy volunteers (11, 20, 21).

The mechanism by which TENS decreases LES pressure in patients with achalasia is probably by activation of nonadrenergic noncholinergic path-

ways, which implies the release of VIP responsible for LES relaxation. The marked increase (more than 300%) of the VIP plasma concentration observed in one of our patients who had a basal level below the detection limit of the assay was coincidental with one of the better responses to TENS on the first day of therapy, manifested by the greatest reduction (55%) of LES resting pressure from 40 to 18 mm Hg. The possibility that the release of VIP in response to TENS is inversely proportional to its basal level remains to be assessed.

TENS may result in stimulation of a multiplicity of neurons and may cause the release not only of VIP, but also other neurotransmitters contained in VIPergic neurons (22), such as peptide histidine isoleucine (PHI) (23–25), neuropeptide Y (NPY) (26, 27), and galanin (28). PHI is cosynthesized and coreleased with VIP, but is about 10 times less potent than VIP in causing smooth muscle relaxation in the gut (29). A specific PHI antiserum partially blocks the neurally induced relaxation of LES (5). A possible role of PHI in achalasia cannot be excluded.

Possible factors to explain only a 28% reduction on LES pressure include the methodology employed to produce TENS, which might have produced submaximal stimulation. It is possible that a different technique could produce higher release of VIP. However, further increase of VIP may not mean better LES relaxation. It might be expected that high concentrations of VIP should be sufficiently potent to produce complete relaxation of *in vitro* preparations of LES muscle strips, thus preventing further relaxation. However, the inability to obtain further relaxation in response to electrical field stimulation might argue against the VIP as the only inhibitory neurotransmitter (30). It is also possible that some patients with achalasia have more severely damaged neurons than others. This may explain varying results; the patients with less damaged neurons may have better responses. After TENS, we have observed a statistical but moderate decrease on LES resting pressure, and five patients reported relief of retrosternal pain and better tolerance to solid meals manifested as a reduction in the time needed to complete a meal. Intraindividual variations on LES resting pressures in healthy volunteers are well recognized. However, we cannot predict if these variations are also present and have a similar pattern in patients with achalasia. The fact that manometric traces were performed blindly makes unlikely that the LES changes reported in this study are the result of such variations.

Our results resemble those obtained in several studies performed using nifedipine in patients with achalasia (31–33), in which the average decrease in LES pressure after therapy was between 28 and 34%. Similar to our study, this reduction on LES resting pressure on the order of 30% was accompanied by improvement of the symptoms. However, this type of reduction is substantially less than what is observed with successful dilatation. Patients having 30% reduction in LES pressure after TENS may not have as good a result as with dilatation.

The possibility that an increase in plasma VIP concentration after TENS is causally related to the induced reduction on LES resting pressure would suggest a direct effect of circulating VIP on the sphincter smooth muscle. This has been demonstrated previously by Rattan et al (15), who reported that the intravenous administration of VIP in the anesthetized opossum produced a dose-dependent decrease on LES pressure. In order to corroborate these findings in human beings, we recently have performed intravenous administration of VIP in patients with achalasia, which resulted in a dose-dependent relaxation of the LES similar to that obtained in this study (data recently submitted for publication).

The results of this study should be considered as preliminary physiologic observations that need to be further evaluated in a placebo-controlled study with the objective assessment of other parameters such as dysphagia and esophageal emptying times. In conclusion, low-frequency transcutaneous nerve stimulation decreases LES resting pressure and improves LES relaxation, possibly by a direct effect of the released VIP in the systemic circulation.

REFERENCES

1. Feldman M: Southwestern Internal Medicine Conference: Esophageal achalasia syndromes. Am J Med Sci 295(1):60–81, 1988
2. Rattan S, Moummi C: Influence of stimulators and inhibitors of cyclic nucleotides on lower esophageal sphincter. J Pharmacol Exp Ther 248(2):703–709, 1989
3. Goyal RK, Rattan S: VIP as a possible neurotransmitter of non-cholinergic non-adrenergic inhibitory neurones. Nature 288:378–379, 1980
4. Rattan S: The non-adrenergic non-cholinergic innervation of the esophagus and the lower esophageal sphincter. Arch Int Pharmacodyn Ther 280(2 suppl):62–83, 1986
5. Biancani P, Beinfeld MC, Coy DH, Hillemeier JH, Walsh JH, Behar J: Dysfunction of the gastrointestinal tract. Va-

soactive intestinal peptide in peristalsis and sphincter function. Ann NY Acad Sci 527:546–567, 1988
6. Biancani P, Walsh JH, Behar J: Vasoactive intestinal polypeptide. A neurotransmitter for lower esophageal sphincter relaxation. J Clin Invest 73:963–967, 1984
7. Aggestrup S, Uddman R, Jensen SL, Sundler F, Schaffalitzky de Muckadell O, Holst JJ, Hakanson R, Ekman R, Sorensen HR: Regulatory peptides in the lower esophageal sphincter of man. Regul Pept 10:167–178, 1985
8. Fahrenkrug J, Emrson PC: Vasoactive intestinal polypeptide: Functional aspects. Br Med Bull 38:265–270, 1982
9. Aggestrup S, Uddman R, Sundler F, Fahrenkrug J, Hakanson R, Sorensen HR, Hambraeus G: Lack of vasoactive intestinal peptide nerves in esophageal achalasia. Gastroenterology 84:924–927, 1983
10. Gridelli B, Buffa R, Salvini P: Lack of VIP-immunoreactive nerves in oesophageal achalasia. Ital J Gastroenterol 14:211–213, 1982
11. Kaada B: Successful treatment of esophageal dysmotility and Raynaud's phenomenon in systemic sclerosis and achalasia by transcutaneous nerve stimulation. Increase in VIP plasma concentration. Scand J Gastroenterol 22(9):1137–1146, 1987
12. Chang FY, Sample M, Ouyang A: Specific changes in esophageal motility result from transcutaneous nerve stimulation of an esophageal acupuncture site in normals. Gastroenterology 98(Pt2):A335, 1990
13. Uddman R, Aluments J, Edvinsson L, Hakason R, Sundler F: Peptidergic (VIP) innervation of the esophagus. Gastroenterology 75:5–8, 1978
14. Aluments J, Fahrenbrug J, Hakason R, Schaffalitzky De Muckadell O, Sunder F, Uddman RA: Rich VIP nerve supply is characteristic of sphincters. Nature 280:155–156, 1979
15. Rattan S, Said SI, Goyal RK: Effect of vasoactive intestinal polypeptide (VIP) on the lower esophageal sphincter pressure (LESP). Proc Soc Exp Biol Med 155:40–43, 1977
16. Behar JS, Field S, Marin C: Effect of glucagon, secretin and vasoactive intestinal polypeptide on the feline lower esophageal sphincter: Mechanism of action. Gastroenterology 77:1001–1007, 1979
17. Domschke W, Lux G, Domschke S, Strunz J, Bloom SR, Wunsch E: Effects of vasoactive intestinal peptide on resting pentagastrin-stimulated lower esophageal sphincter pressure. Gastroenterology 75:9–12, 1978
18. Misiewicz JJ, Waller SJ, Anthony PP, Gummer JWP: Achalasia of the cardia, pharmacology and histopathology of isolated cardia muscle from patients with and without achalasia. Q J Med 149:17–30, 1969
19. Guelrud M, Rossiter A, Mendoza S, Souney PF, Mujica V: Transcutaneous electrical nerve stimulation (TENS) decreases sphincter of Oddi (SO) resting pressure and increases VIP plasma levels in patients with SO dyskinesia. Gastroenterology 98(Pt 2):A248, 1990
20. Kaada B, Helle K: In search of mediators of skin vasodilation induced by transcutaneous nerve stimulation: *In vitro* bioassay of the vasoinhibitory activity of sera from patients suffering from peripheral ischaemia. Gen Pharmacol 15:115–122, 1984
21. Bjrna H, Kaada B: Successful treatment of itching and atopic eczema by transcutaneous nerve stimulation. Acupunct Electrother Res 12(2):101–112, 1987
22. Wattchow DA, Furness JB, Costa M: Distribution and coexistence of peptides in nerve fibers of the external muscle of the human gastrointestinal tract. Gastroenterology 95:32–41, 1988
23. Bishop AE, Polak JM, Yiangou Y, Christofides ND, Bloom SR: The distribution of PHI and VIP in porcine gut and their co-localization to a proportion of intrinsic ganglion cells. Peptides 5:255–259, 1984
24. Christofides ND, Polak JM, Bloom SR: Studies on the distribution of PHI in mammals. Peptides 5:261–266, 1984
25. Ekblad E, Ekelund M, Graffner H, Hakason R, Sundler F: Peptide containing nerve fibers in the stomach wall of rat and mouse. Gastroenterology 89:73–85, 1985
26. Wattchow DA, Furness JB, Costa M, O'Brien PE, Peacock M: Distributions of neuropeptides in the human esophagus. Gastroenterology 93:1363–1371, 1987.
27. Ekbland E, Hakanson R, Sundler F: VIP and PHI coexist with and NPY like peptide in the intramural neurones of the small intestine. Regul Pept 10:47–55, 1984
28. Melander T, Hokfelt T, Rokaeus A, Fahrenkrug J, Tatemoto K, Mutt V: Distribution of galanin-like immunoreactivity in the gastrointestinal tract of several mammalian species. Cell Tissue Res 239:253–270, 1985
29. Grider JR, Makhlouf GM: Prejunctional inhibition of vasoactive intestinal peptide release. Am J Physiol 253:G7–G12, 1987
30. McKerdy HC, Marshall RW: Effect of drugs and electrical field stimulation on circular muscle strips from human lower oesophagus. Q J Exp Physiol 70:591–601, 1985
31. Traube M, Dubivik S, Lange RC, McCallum RW: The role of nifedipine therapy in achalasia: Results of a randomized double-blind, placebo-controlled study. Am J Gastroenterol 84:1259–1262, 1989
32. Hongo M, Traube M, McCallum RW: Comparison of effects of nifedipine, propantheline bromide, and the combination on esophageal motor function in normal volunteers. Dig Dis Sci 29:300–304, 1984
33. Hongo M, Traube M, McAllister RG Jr, McCallum RW: Effects of nifedipine on esophageal motor function in humans: Correlation with plasma nifedipine concentration. Gastroenterology 86:8–12, 1984