Vagus nerve stimulation for epilepsy: Randomized comparison of three stimulation paradigms

C. DeGiorgio, C. Heck, S. Bunch, et al.

Neurology 2005;65;317-319
DOI 10.1212/01.wnl.0000168899.11598.00

Vagus nerve stimulation for epilepsy: Randomized comparison of three stimulation paradigms

Abstract—Vagus nerve stimulation (VNS) is an effective adjunctive treatment for intractable epilepsy. However, the optimal range of device duty-cycles [on/(on + off times)] is poorly understood. The authors performed a multicenter, randomized trial of three unique modes of VNS, which varied primarily by duty-cycle. The results indicate that the three duty-cycles were equally effective. The data support the use of standard duty-cycles as initial therapy.

NEUROLOGY 2005;65:317–319

C. DeGiorgio, MD; C. Heck, MD; S. Bunch; J. Britton, MD; P. Green, MD; M. Lancman, MD; J. Murphy, MD; P. Olejniczak, MD; J. Shih, MD; S. Arrambide, PhD; and J. Soss, MD

Vagus nerve stimulation (VNS) is an effective adjunctive treatment for intractable seizures. Stimulation is delivered via a programmable generator, allowing variation in current, pulse, frequency, and duty-cycle [on ÷ (on + off time)]. The optimal device settings are poorly understood.[1] Acute studies show that duty-cycles of 30 seconds on/5 minutes off are more effective than control settings (30 seconds on/180 minutes off).[2,3] Long-term data suggest that off-times less than 1.1 minute (duty cycle > 20%) improve response in some patients where initial response to standard on/off times was suboptimal.[4,5] However, the long-term studies were uncontrolled and open-label.[5-7] Confounding variables such as duration of therapy and changes in current may have contributed to efficacy.[5-7] To better address the issue of alternative device settings, we conducted a multicenter, randomized comparison of three distinct duty-cycles: 7 seconds on and 18 seconds off (rapid cycle); 30 seconds on and 30 seconds off; and 30 seconds on and 3 minutes off. We compared the safety and efficacy of three alternative duty-cycles in the initial treatment with VNS.

Methods. Patients with intractable localization related seizures were enrolled in a multicenter, randomized trial. Inclusion criteria were ages 12 years and older, one or more antiepileptic medications (AEDs), and at least one seizure/30 days with alteration of consciousness. Exclusion criteria included active cardiac, pulmonary, or peptic ulcer disease, vagotomy, general anesthesia within 30 days, concomitant investigational drug or device, or unstable medical condition. Only subjects who could document one or more seizures with loss of consciousness per 30 days for the 3 months prior to enrollment were included.

Upon study entry, a 4-week prospective baseline was initiated. At completion of the 4-week baseline, patients who met the following additional eligibility criteria for implantation were surgically implanted: at least one seizure that involved a loss or alteration of consciousness over the 4-week baseline period, and no change, addition, or discontinuation of AEDs since enrollment. Patients failing to meet criteria for implantation exited the study.

Patients who qualified underwent implantation with VNS within 14 days of completion of baseline. Subjects were randomized into one of three treatment groups (A, B, or C; table 1). As part of the study design, the parameters of Group C were chosen as 30 seconds on, and 3 minutes off, rather than the traditional 30 seconds on, 5 minutes off. These parameters were selected since they are commonly used by ours and many other centers, and had up until now not been studied in a prospective fashion. Randomization occurred in blocks of six (two for each group), with a unique predetermined randomization schedule for each site. Stimulation was initiated prior to discharge from the hospital following implantation. Output current was initiated at 0.25 mAs, and ramped as tolerated to a maximum of 0.75 mAs at the end of the initial titration visit. Subjects were followed as outpatients every 4 weeks for the 3-month treatment period. Output current was adjusted as tolerated up to 1.5 mAs at each subsequent follow-up visit. Other than current, no changes in pulse duration, frequency, or duty-cycle were allowed during the 3-month treatment period.

Statistical analysis. The primary outcome variables were within-group and between-group percentage changes in seizure frequency. Within-group and between-group comparisons were performed using parametric and nonparametric statistics, including Student *t*-test, Sign test, Kruskal Wallis test, and analysis of variance (ANOVA), with a level of significance of 0.05.

Results. Sixty-four subjects were enrolled. Sixty-one completed the study. Three subjects exited early: one developed a device infection, requiring removal. One could not tolerate stimulation (Group A), requiring conversion to a standard duty-cycle and exit from the study. One was lost to follow-up. Nineteen subjects were enrolled in Group A (7 seconds on, 18 seconds off), 19 subjects enrolled in Group B (30 seconds on, 30 seconds off), and 23 subjects enrolled in Group C (30 seconds on, 3 minutes off).

All three treatment modes were well tolerated. The most common adverse events were postoperative pain at the electrodes or generator (n = 13), throat pain/pharyngitis (n = 6), increased cough (n = 6), and voice alteration (n = 3). Cough and voice alteration were more common among Group A (26%, vs 5% for Group B and 9% for Group C). One subject sustained vocal cord paralysis because of implantation, and one subject was hospitalized due to abdominal pain and diarrhea. Final output current, measured at completion of the study, was similar for the three groups (ANOVA, n/sec) (table 2).

Patients in all three groups experienced a significant

From UCLA-Geffen School of Medicine (Drs. DeGiorgio and Soss, S. Bunch), Los Angeles; USC-Keck School of Medicine (Dr. Heck), Los Angeles, CA; Mayo Clinic Rochester (Dr. Britton), MN; Borgess Medical Center Research Group (Dr. Green), Kalamazoo, MI; Northeast Regional Epilepsy Group (Dr. Lancman), White Plains, NY; Childrens Mercy Hospital (Dr. Murphy), Kansas City, MO; LSU HSC Epilepsy Center of Excellence (Dr. Olejniczak), New Orleans, LA; University of New Mexico School of Medicine (Dr. Shih), Albuquerque; and SYNERGOS Biomedical Consulting (Dr. Arrambide), The Woodlands, TX.

Supported by a grant from Cyberonics, Inc.

Drs. DeGiorgio, Heck, Britton, Green, Lancman, Murphy, Olejniczak, and Shih have received grant support and honoraria from Cyberonics, Inc. Dr. Arrambide has received consulting fees from Cyberonics, Inc. for statistical consultation. Dr. Soss and S. Bunch have nothing to disclose.

Received October 21, 2004. Accepted in final form April 11, 2005.

Address correspondence and reprint requests to Dr. Christopher M. DeGiorgio, Reed Neurological Research Center, 710 Westwood Plaza, C-139 AMDG, Los Angeles, CA 90095; e-mail: cmd@mednet.ucla.edu

Table 1 *Stimulation paradigms for the three groups*

	Treatment A	Treatment B	Treatment C
On/off time	7 s/18 s	30 s/30 s	30 s/3 min
Duty-cycle, %	28	50	14
Output current	Initially 0.25 mAs up to 0.75 mAs at first visit, to a maximum of 1.5 mAs at end of study	Initially 0.25 mAs up to 0.75 mAs at first visit, to a maximum of 1.5 mAs at end of study	Initially 0.25 mAs up to 0.75 mAs at first visit, to a maximum of 1.5 mAs at end of study
Frequency, Hz	20	20	30
Pulse width, sec	500	250	500
Magnet current	Similar to output current	Similar to output current	Similar to output current

reduction in cumulative seizure frequency during the 3-month treatment period. The median reduction in seizure frequency was 22% for Group A ($p = 0.0078$), 26% for Group B ($p = 0.0270$), and 29% for Group C ($p = 0.0004$) (Sign test). For the entire study group, the median reduction in seizures was 40%. Between-group comparisons found no differences in seizure frequency (Kruskal Wallis test). The > 50% responder rate was the same for all three groups. The 75% responder rate was highest in Group C (13%), but this was not significant (see table 2). Table 3 summarizes the response for each group at each treatment visit.

Discussion. The primary finding is that all three duty-cycles were equally effective as initial therapy. Consistent with clinical and animal data, duty-cycles of up to 50% were safe and well tolerated.[1] Side effects of stimulation were mild, more common in Group A, but responded to adjustment of output current. Only one subject (Group A) exited the study as a result of duty-cycle. Efficacy was virtually identical for all three modes of treatment.

The effect of duty-cycle on seizure frequency is poorly understood. In two acute trials, a duty-cycle of 30 seconds on/5 minutes off was significantly more effective than control stimulation of 30 seconds on/180 minutes off.[2,3] Further, subjects initially randomized to 30 seconds on/180 minutes off experienced robust reductions in seizure frequency when they were crossed over to 30 seconds on/5 minutes off.[8]

Table 2 *Response by treatment group*

	Treatment A	Treatment B	Treatment C
On/off time	7 s/18 s	30 s/30 s	30 s /3 min
Number of subjects in group	19	19	23
Mean output current at completion of study, mA (SD)	0.87 (0.39)	0.80 (0 .36)	0.93 (0.54)
Number of 50% responders	6	6	6
Number of 75% responders	1	0	3
50% Responder rate, %	31.6	31.7	26.1
75% Responder rate, %	5.3	0.0	13.0

Moreover, nonresponders to standard duty-cycles also experienced significant improvements in seizure frequency when duty-cycle was increased from 9% to greater than 20%.[5] In that study, the 50% responder rate also improved significantly from 19% to 35% with an increase in duty cycle.[5]

As for rapid cycle, Group A, Sherrmann et al. found that initial treatment with rapid cycle was less effective than conventional settings of 30 seconds on/5 minutes off.[6] However, when nonresponders to standard settings were crossed over to rapid cycle, the 50% responder rate improved from 30% to 47%.[6] Similar results have been noted by Ben-Menachem et al.[4] These results are consistent with our study and the other long-term studies—rapid cycle does not confer any advantage as initial treatment,[6] but can be effective later in nonresponders.[4,5]

This study focused on the question of duty cycle. Other parameters, such as current, pulse duration, and frequency, also impact efficacy.[1] There were slight differences between groups for frequency and pulse duration, but these differences were employed to enhance safety. Variations within this range are not known to significantly affect efficacy.[1]

This study has practical implications. In the first 3 months of therapy, initial settings of 30 seconds on/3 minutes off are well tolerated, and produce the most 75% responders. Initially, there is no benefit from a 50% duty-cycle or from rapid cycle. Once patients have been treated for 3 months, long-term studies support conversion to higher duty-cycles for nonresponders.[5,6] This conclusion is consistent with current treatment guidelines, which recommend the initial use of 30 seconds on/5 minutes off for the first 3 months of therapy, followed by shorter off-times and higher duty-cycles for those refractory to VNS.[1]

Table 3 *Median percent reduction (increase) in seizures for each group at each treatment visit.*

Treatment group	Month 1	Month 2	Month 3
Group A	+7.7	−30.2	−25.5
Group B	−4.2	−26.9	−27.3
Group C	−28.6	−28.1	−29

Acknowledgment

The authors thank the following individuals for help with study recruitment, study coordination, and data entry: Pam Behr, Cindy Eversman, Sandra Oviedo, Barbara Riso, Candy Schmoll, and Jennifer West. The authors also thank Clinton Wright, PharmD, and Brent Tarver of Cyberonics, for their assistance.

References

1. Heck C, Helmers SL, DeGiorgio CM. Vagus nerve stimulation therapy, epilepsy, and device parameters: scientific basis and recommendations for use. Neurology 2002;59:S31–S37.
2. Vagus Nerve Stimulation Study Group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. Neurology 1995;45:224–230.
3. Handforth A, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial onset seizures. A randomized active-control study. Neurology 1998;51:48–55.
4. Ben-Menachem E, Hellstrom K, Waldton C, et al. Evaluation of refractory epilepsy treated with vagus nerve stimulation for up to 5 years. Neurology 1999;52:1265–1267.
5. DeGiorgio CM, Thompson J, Lewis P, et al. Vagus nerve stimulation: analysis of device parameters in 154 patients during the long-term XE5 study. Epilepsia 2001;42:1017–1020.
6. Scherrmann J, Hoppe C, Kral T, et al. Vagus nerve stimulation: clinical experience in a large patient series. J Clin Neurophysiol 2001;18:408–414.
7. Labar D. Vagus nerve stimulation for 1 year in 269 patients on unchanged antiepileptic drugs. Seizure 2004;6:392–298.
8. DeGiorgio CM, Schachter SC, Handforth A, et al. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. Epilepsia 2000;41:1195–2000.