Seizure detection and automatic magnet mode performance study

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The primary study objective is to evaluate the Model 106 VNS Therapy® System cardiac-based seizure detection and Automated Magnet Mode (AMM) stimulation in epilepsy patients. These two new features will be evaluated using continuous observational...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cranial nerve disorders (excl neoplasms)
Study type	Interventional

Summary

ID

NL-OMON38335

Source
ToetsingOnline

Brief title
E-36

Condition

- Cranial nerve disorders (excl neoplasms)

Synonym
convulsion, epilepsy

Research involving
Human

Sponsors and support

Primary sponsor: Cyberonics, Inc.
Source(s) of monetary or material Support: Cyberonics;Inc.

Intervention

Keyword: automatic magnet mode, medical device

Outcome measures

Primary outcome

The purpose of this study is to confirm R-wave detection and to determine whether the SDA and AMM perform in vivo as predicted in silico (i.e. software performance tested by using a library of vEEG/ECG data from multiple patients). Performance analyses are conducted as described below.

Primary Performance Objective

Sensitivity and potential false positive rate per hour * Using vEEG and ECG recordings from the EMU stay, sensitivity and potential false positive rate per hour will be estimated to confirm the performance of the algorithm*s ability to detect seizures at different SDA settings.

Secondary outcome

Secondary Performance Objectives

1. R-Wave ECG Detection * During the implant procedure, patient heart rates will be calculated using detected R-waves from the Implantable Pulse Generator (IPG) and from a standard ECG monitor during a pre-specified time interval. R-wave detection will also be evaluated postoperatively when the patient awakens, at each titration visit, at the beginning and end of the EMU stay, and at the 12 month visit.

2. Latency * Difference between the time of seizure onset and the time of seizure detection by the IPG based on vEEG and ECG recordings collected during the EMU stay and adjudicated by qualified personnel such as neurologists.

3. Post-Stimulation Heart Rate Changes * Heart rate changes during and after stimulation.

4. Seizure Frequency * Baseline measurements of seizure frequency will be collected and compared to patient diary data collected at specific time points post-baseline.

5. Seizure Severity * Baseline measurements of patient and physician rated seizure severity will be collected at baseline and compared to patient rated seizure severity at specific time point*s post-baseline.

6. Seizure Duration and Intensity * Pre-study EEG/ECG recordings will be collected from study patients and used for comparison of seizure duration and intensity during similar recordings during the study EMU stay.

7. Post-Ictal Duration * Pre-study EEG/ECG recordings will be collected from study patients and used for comparison of post-ictal during similar recordings during the study EMU stay.

8. Quality of Life * Baseline measurements of patient rated quality of life will be collected at baseline and compared to patient rated quality of life at specific time points post-baseline.

Study description

Background summary

In 1994 and 1997, Cyberonics* VNS Therapy was approved by KEMA and FDA, respectively, as an adjunctive therapy for the treatment of epilepsy. VNS Therapy is available both as a scheduled stimulation, for example, a 30-second burst every 5 minutes, and as on-demand stimulation, for example, when a magnet is introduced briefly over the implanted device.

Some VNS patients find that magnet-initiated stimulation delivered during an aura or at the beginning of a seizure serves to terminate or dissipate the effects of the seizure. (Boon 2001, Morris 2003, Murphy 2003) However, it is not always possible for patients to use the magnet mode feature immediately before a seizure due to multiple reasons including cognitive impairment, sleep, or the effects of the seizure itself. Cyberonics has developed an algorithm to identify seizure onset based on cardiac rhythm disturbances. The advantage of such an algorithm would not only be the potential to deliver stimulation at the onset of a seizure, but also to provide a consistent assessment of the patient*s seizures. Patient seizure diaries are notoriously inaccurate (Poochikian-Sarkissian 2009), having been documented as inaccurate due to many different issues including cognitive impairment, memory alteration due to the seizure itself, and not taking time to record the seizures every day as they occur. As patient diaries are frequently used when adjusting patients* treatment including titrating antiepileptic drug (AED) doses, an accurate assessment of patients* seizure activity can be an invaluable tool for the neurologist.

Epileptic seizures are often accompanied by changes in autonomic function including heart rate, respiratory rate, gastrointestinal/abdominal function, cutaneous appearance, and secretory function, among others. Research supports the occurrence of ictal tachycardia using electroencephalogram (EEG) and electrocardiogram (ECG) recordings in 64-93% of complex partial seizures, primarily of temporal lobe origin (Van Buren 1967, Marshall 1983, Keilson 1989, Smith 1989, O*Donovan 1995, Schernthaner 1999, Leutmezer 2003, DiGennaro 2004).

Time frequency analysis of R-R intervals revealed that autonomic activation may precede clinical seizure onset by several minutes (Novak, 1999). Heart rate changes were observed by Schernthanaer et al. (1999) by an average of 18.7 seconds prior to EEG seizure onset on scalp-EEG in 76.1% of focal seizures. Similarly, sinus tachycardia preceded EEG seizure onset in 75.9% of all seizures by 0.7-49.3 seconds in patients with focal epilepsy in results reported by Leutmezer et al. (2003). The time lag between changes in heart rate and seizure onset was longer in patients with mesial temporal lobe epilepsy compared to those with extratemporal epilepsy (Leutmezer, 2003). Presence or absence of heart rate changes are dependent upon the site of seizure origin as well as the volume of cerebral structures that were recruited into the seizure (Epstein, 1992).

In a study including both focal and generalized epilepsies, although increases in heart rate were reported in 73% of seizures, the rate increase preceded electrographic and clinical onset of seizure in only 23% of seizures (Zijlmans, 2002). Moreover, heart rate increases are observed earlier in mesial versus lateral temporal lobe seizures. Mesial seizures had ictal heart rate changes before both EEG and clinical ictal onset, whereas in lateral temporal lobe seizures, the start of the heart rate increase coincided with the EEG ictal onset (DiGennaro, 2004). Finally, it has been reported that small myoclonic seizures may not manifest in heart rate

changes (van Elmpt, 2006). This indicates that differences in ECG patterns may exist by origin of the epileptic focus, seizure type, as well as the volume of cerebral structures that were recruited into the
seizure. Return to baseline may also be complicated by a number of swings into bradycardia (van Elmpt, 2006). Note additional information regarding preclinical device testing is available in the E-36 Investigator Brochure.
Cyberonics has developed an algorithm designed to detect changes in heart rate that may be indicative of a seizure. The algorithm has been implemented in a VNS device capable of detecting heart rate, and when a potential seizure is detected, the device is capable of delivering
VNS stimulation, much the same way that VNS devices currently deliver stimulation when a magnet is passed over the device.

Study objective

The primary study objective is to evaluate the Model 106 VNS Therapy® System cardiac-based seizure detection and Automated Magnet Mode (AMM) stimulation in epilepsy patients. These two new features will be evaluated using continuous observational video electroencephalogram (vEEG) and electrocardiogram (ECG) data in ictal and non-ictal events during an Epilepsy Monitoring Unit (EMU) stay.
Secondary objectives include:
1. Validation of cardiac R-wave detection by the Model 106 device.
2. Assess stimulation-related adverse event rates to outline the tolerability profile of Model 106 device.
3. Characterization of latency period.
4. Characterization of post-stimulation heart rate changes.
5. Evaluation of human factors and usability of the system.
6. Assess changes from baseline in seizure frequency.
7. Assess changes from baseline in seizure severity.
8. Assess changes from baseline in seizure duration.
9. Assess changes from baseline in seizure intensity.
10. Assess changes from baseline in post-ictal duration.
11. Assess changes from baseline in quality of life.

Study design

Prospective, observational, unblinded, multi-site study designed to collect data on up to 35 patients implanted with a Model 106 VNS Therapy System from baseline through an EMU stay of up to 5 days. Good Clinical Practices shall be followed during the study including the Declaration of Helsinki, ISO 14155:2011, WMO, and MEDDEV 2.7.1. Note that each patient undergoes activation of the Seizure Detection Algorithm (SDA)
feature during implantation of the device for intra-operative evaluation (detection only) and throughout the EMU stay (detection and automated stimulation). After the EMU stay, patients continue follow-up for safety until

final regulatory approval of the product.

Intervention

Not applicable

Study burden and risks

Surgery and treatment with VNS Therapy have possible risks, complications, and side effects. Most of these are known from previous clinical studies. However, there may be side effects from surgery and stimulation by the VNS Therapy System that are unknown at this time.

Stimulation may cause some health problems to get worse. Asthma and bronchitis may get worse with stimulation. Swallowing problems, hoarseness, and lung conditions also may get worse with stimulation. Stimulation may also irritate the windpipe (larynx), especially in case of smokers. It is not known how safe or effective the VNS Therapy System is in patients with:

* History of previous therapeutic brain surgery or brain injury
* Progressive neurological diseases other than epilepsy
* Irregular heartbeats or other heart abnormalities
* History of dysautonomias (problems caused by the autonomic nervous system)
* History of lung diseases or disorders, including shortness of breath and asthma
* History of ulcers (gastric, duodenal, or other)
* History of fainting
* Other forms of brain stimulation
* Preexisting hoarseness
* Difficulty swallowing
* Shortness of breath
* Episodes where breathing stops for short periods of time while sleeping.

Because of the vagus nerve*s effect on the stomach, duodenal or gastric ulcers could develop. If the patient has stomach problems already, treatment could make them worse. However, these stomach problems have not yet been reported in clinical studies of VNS Therapy.

Surgery that requires general anesthesia may carry the risk of death. Surgery to implant VNS Therapy requires local, regional, or general anesthetic. Rarely, heart rate slowing occurs during a short stimulation of the vagus nerve that is done in the operating room. All patients have recovered from this slowing of heart rate. Vagus nerve damage, if it occurs, can cause vocal cord paralysis. It can also cause Horner*s syndrome. Horner*s syndrome has symptoms that involve the eye and eyelid, and an absence of sweating on one side of the face. Nerve damage during surgery may also occur. It could result in permanent hoarseness, difficulty in swallowing, or gastrointestinal problems

Mechanical problems:

The following problems could occur:
* The Pulse Generator could malfunction and not deliver stimulation or deliver too much stimulation.
* The Pulse Generator or Bipolar Lead could move or push through the skin.
* The Bipolar Lead could break or become corroded, disconnected, or dislodged.
* The battery in the Pulse Generator could become depleted (reach its end-of-life).
Any mechanical problems could require surgery. Surgery could cause the nerve to swell because of the Lead placement around the vagus nerve. If the Pulse Generator and Lead are removed, it is possible the nerve may swell due to the handling of the nerve. Moving the VNS Therapy System could cause damage to the vagus nerve or other parts of the body.
A malfunction of the Pulse Generator could damage the vagus nerve. This malfunction could lead to permanent hoarseness or other complications. A malfunction could cause the Pulse Generator battery to last a shorter time period than expected.

In addition, there are risks specific to the Model 106 VNS Therapy System, which is designed to detect an increase in heart rate associated with some seizures. These include:
* The device might stimulate too often because it is not accurately sensing the heart rate. The device is programmed to ignore heart rates that are too high or too unlikely to be real, and therefore, will not trigger the stimulation. To further guard against excessive stimulation, each stimulation is followed by a waiting period that lasts at least as long as the period of stimulation. Also, the device cannot be programmed to give stimulation at a higher frequency than what is given with the currently approved VNS Therapy System.
* Stimulation can sometimes cause a temporary increase in heart rate which could trigger AMM. The device is programmed to wait for a minimum period after stimulation before it can again sense increases in heart rate and trigger another stimulation.
* If the device is set to be too sensitive, it might trigger stimulation too often. Cyberonics has instructed the physician on how to choose initial settings to avoid having the device be too sensitive.
* If the device is set to have too little sensitivity, it might not trigger stimulation often enough. Cyberonics has instructed the physician on how to choose initial settings to avoid having the device have too little sensitivity. In addition, if the patient begins to experience a seizure and the device does not trigger stimulation, he/she can manually trigger the stimulation by passing the magnet over the generator (Magnet Mode Stimulation).
* If the heart rate does not increase at the beginning of a seizure, or if the device does not detect an increase in the heart rate at the beginning of a seizure, the patient will not receive AMM. He/she will still be receiving Normal Mode VNS therapy at the programmed settings and will also be able to

initiate Magnet Mode stimulation by passing the magnet over the generator.
* MRI or other sources of electromagnetic interference might make the device trigger unwanted stimulation. The patient should avoid MRI and other sources of electromagnetic interference. The physician has been instructed to re-program the device for medical procedures that may involve MRI or may involve other equipment that could involve electromagnetic interference.
* With standard VNS therapy, stimulation always happens at regular intervals. However with AMM, the stimulation does not happen at regular intervals, and can therefore seem to be unpredictable.

BENEFITS:

Each patient has different results from using the magnet. Some patients say that the magnet stops all or most seizures, shortens them, or lessens their intensity or their recovery period. For other people, the magnet has little or no effect. This study is not powered to confirm any benefits of magnet mode; however, it has been shown that for some patients, magnet use may terminate or shorten seizures or post-ictal symptoms. (Morris, 2003)
Many patients and caregivers desire to use the magnet mode to trigger stimulation at the beginning of an aura or seizure but are unable to do so, for example because of the patient*s physical or cognitive disabilities or because the seizure occurs during the patient*s or caregiver*s sleep. The potential benefit of the Model 106 VNS Therapy System is that the AMM feature has the ability to detect seizures and respond automatically with VNS stimulation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patients with a clinical diagnosis of medically refractory epilepsy dominated by partial seizures suitable for implantation with the Model 106 VNS Therapy System.
2. Patients with a history of increased heart rate (tachycardia) associated with seizure onset based on clinical data obtained from medical history, admission/hospital charts, or prior neurophysiologic evaluations.
3. Patients willing to undergo an EMU evaluation for a period of at least three days with activation of the AMM feature during that time.
4. Patients having an average of * 6 seizures per month based upon diary or patient reporting for the 3 months prior to enrolling.
5. Patients must have peak-peak R-wave amplitude greater than or equal to 0.25 mV on ECG measured from the proposed electrode location in the neck to the proposed generator location in the chest via surface ECG electrodes.
6. Patients must be at least 18 years old.
7. Patients must be in good general health and ambulatory.
8. Patient or guardian must be willing and able to complete informed consent.

Exclusion criteria

1. Patients have had a bilateral or left cervical vagotomy.
2. Patients currently use, or are expected to use, short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy.
3. A VNS Therapy System implant would (in the investigator*s judgment) pose an unacceptable surgical or medical risk for the patient.
4. Patients expected to require full body magnetic resonance imaging.
5. Patients have a history of VNS Therapy.
6. Patients have a documented history of clinically meaningful bradycardia

(heart rate less than 50 bpm) associated with seizures.
7. Patients with a significant psychiatric disorder, history of depression, or suicidality as defined by DSM IV-TR that in the investigator*s judgment would pose an unacceptable risk for the patient or prevent the patient*s successful completion of the study.
8. Patients with a history of status epilepticus within 3 months of study enrollment.
9. Patients prescribed drugs specifically for a cardiac or autonomic disorder that in the investigator*s opinion would affect heart rate response unless the patient has ictal tachycardia while taking said drugs. These include, but are not limited to, beta adrenergic antagonists (*beta blockers*).
10. Patients with known clinically meaningful cardiovascular arrhythmias as well as patients with clinically meaningful cardiovascular arrhythmias determined by a 24-hour Holter recording obtained at the baseline visit.
11. Patients dependent on alcohol or narcotic drugs as defined by DSM IV-TR within the past 2 years.
12. Patients with a history of only psychogenic or pseudo seizures.
13. Women who are pregnant. Women of childbearing age must take a pregnancy test.
14. Patients currently enrolled in another investigational study.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-01-2013
Enrollment:	3
Type:	Actual

Medical products/devices used

Generic name:	Model 106 Pulse Generator & Model 250 Version 9.0 Programming Software
Registration:	No

Ethics review

Approved WMO Date:	07-12-2011
Application type:	First submission
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	07-03-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	24-09-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	Aanmelding bij clinicaltrials.gov is pending
CCMO	NL35548.068.11