Vagal Nerve Stimulation: A Case Report

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Despite numerous medications designed to eliminate or decrease seizures, an estimated 20% of epileptic patients in the United States remain refractory to these agents. Vagal nerve stimulation can decrease the number of seizure episodes. In 1997, the US Food and Drug Administration approved the first implantable stimulation device for the treatment of medically refractory epilepsy.

This case report describes the anesthetic management of a patient for placement of a vagal nerve stimulator. A review is presented of the current literature regarding long-term antiepileptic drug therapy and its effect on anesthetic management, pathophysiology of epilepsy and seizure propagation, and the effects of commonly used anesthetic agents on the seizure threshold. Also discussed are the physiology of vagal nerve stimulation, benefits and potential complications that may occur with its implantation, and device mechanics as it relates to future surgical procedures.

As the use of vagal nerve stimulators increases, knowledge of these processes is important to ensure safe and effective anesthetic management.

Keywords: Antiepileptic drug therapy, medically refractory epilepsy, vagal nerve stimulator.

Epilepsy is defined as a clinical paroxysmal disorder of recurring seizures and is estimated to be present in 0.5% to 2% of the world's population.[1] Despite numerous drugs on the market designed to eliminate or decrease seizure events, it is estimated that 20% of epileptic patients in the United States remain refractory to these agents.[1] Uncontrolled epilepsy is highly devastating and affects numerous aspects of life. Traditionally, resection of the epileptogenic focus has been used as end-stage treatment; however, some patients are not candidates for surgery or are unwilling to accept the potential neurologic deficits that may accompany this procedure.[2] For these reasons, other modalities to treat medically refractory epilepsy have been explored.

For many years, scientists have recognized the effect of vagal nerve stimulation on cerebral function, and in 1985 the first suggestion of using it for epilepsy treatment was put forth.[1] In 1997, the US Food and Drug Administration approved the first implantable device for the treatment of medically refractory epilepsy, and since then more than 15,000 patients have undergone this procedure.[2] This case report describes a patient with lifelong epilepsy undergoing vagal nerve stimulator (VNS) placement under general anesthesia.

Case Summary

A 31-year-old woman weighing 52 kg and with an ASA physical status III presented for VNS placement for treatment of medically refractory epilepsy. Diagnosed with epilepsy at the age of 7 years, she had been receiving antiepileptic drug therapy for 24 years, with levetiracetam as her current medication. In addition to her medical therapy, she had undergone a left temporal lobe resection 3 years ago without a major reduction in frequency of seizures. She has continued to have 1 primarily focal seizure progressing to a secondarily generalized focal seizure each week. She does lose consciousness, and it is not preceded by any substantial aura. History revealed no other past medical disease processes. She had no anesthetic complications from her previous surgery. Her laboratory values were within normal limits, and there were no significant abnormal findings upon physical examination. She had a Mallampati I classification and a thyromental distance of 6 cm with full range of motion in the neck.

Premedication with 5 mg of midazolam was given in the preoperative holding room. The patient was then transported to the operating room, where standard monitors were applied.

The patient was given 100% oxygen through the anesthesia circuit, and general anesthesia was induced with 100 µg of fentanyl and 200 mg of propofol. Vecuronium, 7 mg, was given for endotracheal intubation. Anesthesia was maintained with desflurane and oxygen.

The operative approach was as described in the Discussion section. No major problems were encountered during the procedure, with a total time of 65 minutes and estimated blood loss of 25 mL. One liter of lactated Ringer's solution was infused during the procedure, and ondansetron, 4 mg, was given 30 minutes before emergence. Device activation was not performed intraoperatively. The patient was extubated without complication.

The postoperative course was uneventful, and the patient was discharged home after 1 hour in the recovery room.

Discussion

The brain exists in a dynamic equilibrium between depression and excitation and any pathology that disrupts this equilibrium can produce seizures.[1] Epilepsy is only one type of pathology that results in seizures, and whereas every person with epilepsy has seizure activity, not everyone displaying seizure activity has epilepsy. Furthermore, the classification of epilepsy or other seizure disorder is highly complex and requires vigilant observation, which tends to make treatment with medication difficult.

Several underlying mechanisms are common to seizure disorder and epilepsy. A nerve cell transmits signals to neighboring cells in 2 ways: (1) altering ionic concentration and (2) releasing neurotransmitters. The change in ionic concentration (sodium, potassium, calcium) conducts an impulse from one end of the nerve cell to the other. At the end, a neurotransmitter is released, carrying the impulse to the next cell. The type of neurotransmitter can either inhibit (eg, γ-aminobutyric acid, or GABA) or excite (eg, glutamate) this process. Improper ionic concentration or an imbalance in the appropriate neurotransmitter can disrupt orderly transmission, triggering seizures.[3]

Numerous drugs are now available to treat epilepsy; however, therapy is often challenging because of the difficulty in classifying seizures. Furthermore, antiepileptic drugs are not classified into categories based on their mechanisms of action.[4] This is because their actions at the molecular level are not completely understood. Most have more than one mechanism of action, and the knowledge of the mechanism of action has limited value in predicting therapeutic and adverse effects of these drugs in the clinical arena.[4] However, there are broad mechanisms emerging whereby specific actions can be linked to specific activity profiles.[4]

Blockade of voltage-gated sodium channels is the primary action of phenytoin, carbamazepine, oxcarbazepine, lamotrigine, topiramate, zonisamide, and felbamate.[4] The spread of seizure impulses is inhibited by preventing nerve terminal depolarization and the release of the excitatory neurotransmitter glutamate.[4] These drugs are particularly useful against partial and secondarily tonic-clonic seizures.[4] Phenytoin is considered the prototypical antiepileptic drug. Unfortunately, phenytoin is fraught with side effects, including neuropathy, ataxia, and most notably gingival hyperplasia.[3] The newer drugs such as zonisamide, first introduced in 2000, and lamotrigine, have many fewer side effects, lack hepatic enzyme induction, and have not been shown to interact with other hepatically metabolized medications.[5]

The main inhibitory neurotransmitter in the brain is GABA, and many antiepileptic drugs suppress epileptic firing by potentiating GABAergic inhibition.[4] Vigabatrin inhibits GABA transaminase and thereby increases the concentration of GABA at presynaptic nerve terminals.[4] Tiagabine, in contrast, blocks the reuptake of GABA at the nerve terminal.[4] Other drugs that work to increase GABAergic inhibition are benzodiazepines, topiramate, and felbamate.[4]

Blockade of specific calcium channels are yet another way in which antiepileptic drugs suppress epileptic activity in the brain. Ethosuximide, valproic acid, and lamotrigine block T-type calcium channels.[4] Carbamazepine blocks L-type channels, and gabapentin and pregabalin block N and P/Q-type channels.[4]

A novel antiepileptic drug, levetiracetam, has been shown to have a distinct mechanism of action. It is primarily used for partial-onset seizures, as in the case of this patient, and generally causes a median reduction in seizure frequency of 26% to 30% within the first 2 weeks of use.[5] Although the exact mechanism is unknown, the binding site for levetiracetam has recently been discovered and may offer clues as to its exact molecular action.[6] Levetiracetam binds to the SV2 integral membrane protein present on all synaptic vesicles, specifically the type A isoform.[6] The exact action of SV2A is unknown, but it has been shown that SV2A knockout mice exhibit severe seizure phenotype.[6] SV2A is ubiquitous in synaptic vesicle physiology and many hypotheses have been proposed. SV2A may transport a component of the vesicle, such as adenosine triphosphate (ATP) or calcium. It also may interact with synaptotagmin, which is considered to be the primary calcium sensor for regulating calcium-dependent exocytosis of synaptic vesicles.[6] The SV2A may potentially inhibit the release of neurotransmitters such as glutamate and aspartate responsible for producing epileptogenic activity.[6] It is interesting to note that levetiracetam has no effect on normal electrophysiology; it does not affect SV2A functions that are critical to normal physiology but rather modulates SV2A present in only pathologic states such as epileptic foci.[6]

Levetiracetam also has a favorable pharmacokinetic profile, which makes it a widely prescribed drug. It has excellent oral absorption, displays linear kinetics, and is not dependent on the cytochrome p450 system for metabolism, but rather is enzymatically hydrolyzed to an inactive carboxylic acid metabolite.[7] It is less than 10% protein bound, so it does not compete with other highly protein-bound drugs and does not have major drug-drug interactions.[7] In addition, it has the highest safety margin in animal models compared with all the other antiepileptic drugs and has minimal side effects, the most common being insomnia, headache, and infection.[5] The major route of elimination is the urine, and dosing is adjusted for patients with concomitant renal disease.[7]

Despite the numerous antiepileptic drugs available, there still remains a population that does not respond to this type of therapy. In these patients, surgical resection of epileptogenic foci may correct the pathology. Unfortunately, epilepsy surgery is only most beneficial in patients with partial epilepsy secondary to a structural

lesion most commonly located in the temporal lobe.[8] In patents with extratemporal lesions, surgery is not usually successful. In addition, surgery is not without potential complications. Regional resection can be associated with substantial neurologic deficits, and some patients are unwilling to accept these risks. It is in these patients that the use of vagal nerve stimulators may be the answer.

The vagus nerve (cranial nerve X) derives its name from the Latin word for wanderer, and as its name suggests, travels extensively throughout the head, thorax, and abdominopelvic regions.[9] The vagus nerve carries both somatic and visceral afferent and efferent nerve fibers, and in the cervical region where a VNS is placed, 80% of them are afferent in nature.[9] Vagal afferents carry information concerning visceral sensation from the pharynx, larynx, trachea, and thoracoabdominal organs, from somatic sensation from the skin near the external ear, and from taste. They traverse the brain stem in the solitary tract and synapse in several structures in the brain, most notably the nucleus of the tractus solitarius (NTS).[9] The NTS receives a wide range of somatic and visceral sensory afferents, receives projections from other brain regions, performs extensive information processing, and produces motor and autonomic efferent outputs. The NTS projects most densely to the parabrachial nucleus of the pons and can influence activities of respiration and pain modulation.[9] In addition, the NTS projects to the noradrenergic and serotonergic neuromodulatory systems of the brain and spinal cord, including the locus coeruleus (the major source of norepinephrine) and the raphe nuclei (the major source of serotonin).[9] These interactions may partially explain the mechanism for VNS, because norepinephrine and serotonin exert antiseizure effects.[9]

In the cerebrum, the NTS projects to several structures, including the thalamus, hypothalamus, and amygdala. It is in the amygdala where the limbic system has been implicated as sites that most often generate complex partial seizures; stimulation of these regions through vagal-mediated processes may decrease spontaneous seizure activity.[9]

The exact mechanism is unknown. It is postulated that the actions of the NTS on many structures of the brain contributes to the efficacy of VNS, and these effects will have an impact on anesthetic management for VNS placement or management of patients in whom a VNS has been placed previously.

Placement of a VNS is most commonly performed as an outpatient procedure under general anesthesia with endotracheal intubation. Antiepileptic drug therapy is most often continued through the day of surgery.[10] Important preoperative considerations include type and dosing regimen of antiepileptics, type and frequency of seizures, the presence of any auras preceding seizure activity, preexisting neurologic deficits, known cardiac conduction disturbances, and any other concomitant disease. It is interesting to note that approximately one-third of patients in a small study population with medically refractory epilepsy displayed symptoms of obstructive sleep apnea (OSA).[11] Several mechanisms have been proposed, including chronic antiepileptic drug–induced hypoventilation, obesity associated with antiepileptic drug therapy, and sleep apnea–induced seizure activity, in addition to direct effects on specific brain regions.[11] The presence of OSA in these patients will influence anesthetic management, especially in the postoperative recovery area.

Anesthetic management requires a comprehensive knowledge of the effects of commonly used inhaled anesthetics, intravenous anesthetics, and opioids on the seizure threshold. It is important to recognize that long-term antiepileptic drug therapy, with the exception of some of the newer drugs such as levetiracetam, may alter the metabolism of many anesthetic drugs with the inducement of the cytochrome p450 system[12] and may require larger doses. Benzodiazepines are potent anticonvulsants and suppress electroencephalographic (EEG) activity by abolishing interictal spikes, the brief, periodic burst of neuronal activity thought to initiate seizures.[12] They are also effective in controlling status epilepticus and as such are important in the armamentarium of the anesthesia provider. Propofol clinically appears to possess anticonvulsant properties as well; however, there are some reports of activation of epileptogenic foci after a bolus dose.[12] No excitatory motor effects were seen, but EEG patterns suggested frequent discharges of spikes.[12] In contrast, however, propofol has been used in the suppression of seizure activity in a patient with refractory status epilepticus.[12] Overall, propofol appears to be safe to use clinically in patients with epilepsy.

Etomidate has both proconvulsant and anticonvulsant effects, as shown on the EEG.[12] It does produce myoclonic behavior in many patients, but whether this is epileptogenic in nature is unclear.[12] Higher doses suppress low-dose induced motor activity, so it appears that the dose and rate of administration determines which effect etomidate will have on the seizure threshold.[12] Ketamine activates epileptogenic foci in patients with known seizure disorders in large intubating doses and should be avoided.[12] In low doses, evidence does not support seizure inducement.[12]

Of the muscle relaxants used currently, none have been reported to cause seizure activity.[12] At high concentrations, the metabolite of atracurium, laudanosine, has been implicated in producing EEG and seizure activity in animals, but this has not been seen in humans, even in patients with liver or renal failure.[12] Similarly, none of the anticholinesterases or anticholinergics frequently used has been reported to cause seizure activity.[12]

Although not as commonly used today as in years past, enflurane has long been known to produce epileptiform activity in both epileptic and nonepileptic patients.[13] The ability to produce seizure activity depends

on 2 factors: the inspired concentration of enflurane and the arterial partial pressure of carbon dioxide ($PaCO_2$) of the blood.[13] These factors share an inverse relationship. At a normal $PaCO_2$ level, seizure activity is maximal at an inspired concentration of 2% to 3%. As the concentration of carbon dioxide increases, seizure activity decreases, whereas during periods of hyperventilation, seizure activity increases.[13] Of the volatile anesthetics used routinely today, only sevoflurane has been reported to produce epileptiform EEG activity during inhalational induction in both adults and pediatric patients.[13] It has also been implicated in producing EEG changes during surgical levels of anesthesia in patients with epilepsy.[13]

Opioids are equivocal with regard to their potential to induce seizure activity. Large doses of fentanyl and sufentanil, such as those used in bypass surgery, have been shown to produce EEG patterns consistent with cortical seizure activity in animal models.[10] At doses needed for VNS placement, opioids have not been shown to produce seizure activity. Meperidine may be the one exception. With repeated or continuous administration, the metabolite normeperidine accumulates and can cause neurotoxicity leading to convulsions.[13] This is further exacerbated with concomitant renal failure. Overall, VNS placement is not usually associated with a high level of pain postoperatively and as such the use of high-dose opioids is not indicated.

• *Description of Surgical Procedure.* The vagus nerve is approached via a left lateral neck dissection in the region near the anterior border of the sternocleidomastoid muscle at the level of the sixth cervical vertebrae.[6] The left nerve is chosen because of the greater number of cardiac efferent fibers from the right vagus nerve.[10] The nerve is exposed within the carotid sheath between the jugular vein and the carotid artery.[10] Because of the proximity to these major vessels, it is important to have at least one functioning large-bore intravenous (IV) catheter in case rapid volume or blood replacement is needed. Once the nerve is exposed, a pocket is created in the left anterior pectoral fascia for generator placement.[10] With the use of a tunneling approach, the connector lead from the vagus electrodes is pulled into the chest and connected to the generator.[10] The device is interrogated in a similar manner to a pacemaker, using a programming wand.

The surgeon will choose whether to activate the device in the operating room, recovery room, or at a future follow-up appointment. If stimulation is performed intraoperatively, it is important to recognize the effects that stimulation may have on the conduction system. Although quite infrequent, bradycardia, complete atrial-ventricular block, and asystole have been reported.[10] As such, epinephrine, atropine, and perhaps transcutaneous pacing ability should be available in case of emergency.

• *Postoperative Complications.* Postoperative complications can be divided into immediate and long term. In the immediate postoperative recovery period, several potential complications, although rare, must be anticipated. These include laryngeal dysfunction resulting from direct trauma and hematoma formation, all of which can potentially lead to airway compromise.[10] Additionally, seizure precautions must be taken in all patients with a seizure disorder. If stimulation has been activated, monitoring for electrocardiographic changes, especially in patients with a known conduction abnormality, is warranted. These patients may necessitate an overnight stay if changes are apparent.

Vocal cord dysfunction can be divided into 2 categories: those that occur due to surgery and those attributed to vagal stimulation.[14] In the former, direct trauma or manipulation of the vagus nerve, inadvertent clamping, heating, or traction, or disruption to the blood supply can lead to temporary paresis or permanent paralysis of the vocal fold.[14] Patients with varying degrees of glottic closure will display symptoms of mild dysphonia and dysphagia, to aphonia and aspiration.[14] Episodic complaints of voice change, dysphagia, paresthesias, pain, and occasional aspiration have been reported.[14] The goal is to find a balance between maximal seizure control and minimization, or at least toleration, of side effects.[14]

• *Outcomes.* Although VNS therapy is not curative, the efficacy is substantial for many patients. In the largest, prospective, randomized, double-blinded study on long-term VNS efficacy, a statistically significant reduction in frequency of seizures at 3 and 12 months was observed.[15] At 3 months there was a 34% median reduction in total seizures compared with preimplantation baseline.[15] This improved to 45% at 12 months.[15] Furthermore, the data also strongly supported a cumulative effect, in that as stimulation settings increased over time, seizure activity decreased further.[15] The most common adverse events reported were hoarseness, paresthesias, and cough.[15] These symptoms were reported as mild to moderate by subjects and generally diminished with decreasing current.[15]

Several recent studies, although smaller and retrospective, have also demonstrated the efficacy of VNS therapy. In a follow-up to a small prospective study, Ardesch and colleagues[16] demonstrated increased efficacy of VNS therapy at intervals of 1 to 6 years after implantation. At year 1 after implantation, participants had a 14% mean seizure reduction; this percentage improved every year and climbed to 50% by year 6.[16] Similarly, You et al[17] demonstrated the efficacy of VNS placement in children with refractory epilepsy. Of the 28 children in whom the device had been implanted, 15 showed a greater than 50% reduction in seizure frequency and 9 had a greater than 75% reduction.[17] The authors went on to measure not only seizure reduction but also important quality of life measurements. Of the participants, 32% had increased memory, 43% had improved mood, 40% had improved behavior, 43% had increased alertness, and 25% improved in their verbal and achievement skills.[17]

• *Future Surgery.* As the frequency of VNS placement

increases, there will be times when patients with these devices will present for other types of surgery. It is therefore important to consider the impact of anesthetic management on these patients.

One of the most important aspects of VNS therapy and anesthesia is the impact that VNS therapy may have on respiration. As mentioned previously, approximately one-third of patients in a small study population with medically refractory epilepsy displayed symptoms of OSA.[11] It has also been suggested that VNS may worsen OSA symptoms during stimulation intervals.[10] Proposed mechanisms include effects on the central respiratory centers and peripheral stimulation of vagal afferents activating motor efferents, resulting in altered neuromuscular transmission to laryngeal and pharyngeal muscles.[10] Combining both the respiratory depressant effects of opioids and VNS may lead to severe postoperative apneic episodes.[10] It is therefore prudent to obtain a thorough history regarding sleep and respiratory patterns and to adjust anesthetic technique based on abnormal findings.

Although not specifically recommended by the manufacturer, in cases of severe OSA, the device may be turned off before an elective procedure to help mitigate the effects on respiratory patterns.[10] If this is the case, discussion with a neurologist beforehand is warranted. Turning the device off requires the use of a magnet, which is supplied by the manufacturer and delivers 50 G at 1 inch (2.5 cm).[18] Application of the magnet for at least 1 second and then its immediate removal produces an on-demand stimulation for a preprogrammed amount of time.[18] This can be done as an attempt to abort or deintensify an oncoming seizure. Placing the magnet over the device for more than 65 seconds temporarily inhibits the device.[18] Once the magnet is removed, the device will return to its normal programmed mode.[18] Patients are supplied the magnets as a watch or pager by the manufacturer and usually carry it with them at all times. They should be instructed to bring it with them on the day of surgery. Again, any discussion regarding device manipulation should be in conjunction with a neurologist.

Similar to a pacemaker, the pulse generator of a VNS may be damaged by electrocautery and cardioversion/defibrillation.[10] If defibrillation is required, the lowest setting should be used and the pads placed as far away from the generator as possible. In addition, the grounding pad from the electrocautery unit should be placed so that current does not travel through the device.

Conclusion

Medically refractory epilepsy is a highly debilitating disease. Although not curative, vagal nerve stimulation is a relatively safe and effective choice that generally provides a decrease in frequency and number of seizure episodes. Anesthetic management requires knowledge of the disease process, the effects of antiepileptic therapy on anesthetic pharmacokinetics and dynamics, effects of anesthetics on seizure threshold, and potential complications from the surgery itself. In addition, as the use of vagal nerve stimulators increases, knowledge of device mechanics is important in patients who are undergoing surgery for different reasons in whom a stimulator has been placed previously.

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