Alteration of the threshold stimulus for intraoperative brain mapping via use of antiepileptic medications

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Abstract

Intraoperative seizures during awake craniotomy with cortical and subcortical mapping are a common occurrence. Patients are routinely treated preoperatively with anti-convulsive medications to reduce seizure occurrence. Historically these drugs have not been believed to significantly affect awake craniotomy procedures. We report a patient undergoing intraoperative mapping with differential response and seizure occurrence based upon antiepileptic drug usage. A 43 year old female presented with history of seizures, right sided hemiparesis, electrical sensations, and difficulty with language function. She was determined to have a mass lesion involving the left frontal and temporal lobes and subsequently elected to undergo resection by awake craniotomy with intraoperative mapping. A first attempt at lesion resection was performed after a missed dose of anti-convulsant medication (levetiracetam) and was subsequently aborted because of repeated seizure activity. The threshold for seizure generation (1.75 mA) was observed to be significantly lower than expected. Therapy was begun with both levetiracetam and phenytoin prior to a second attempted resection one week later. Thresholds for cortical motor response in the second operation were significantly higher than expected (> 9.0 mA), and no intraoperative seizure activity was observed. To our knowledge this is the first quantitative example of antiepileptic drugs affecting the current required for intraoperative mapping. This case highlights the potential for higher current requirements in patients preoperatively treated with high doses of antiepileptic drugs, as well as the importance of confirming adequate dosage of antiepileptic drugs in patients at an increased risk of seizure generation.

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Introduction

The increasing availability of functional magnetic resonance imaging, cortical magnetoencephalography, and Diffusion Tensor Imaging (DTI) has offered additional methods to pre-operatively map brain function and the associated functional white matter tracts. Despite these novel imaging techniques, awake craniotomy with direct cortical and subcortical stimulation remains the gold standard for brain mapping in order to identify which lesions or portions thereof may be removed with minimal clinical sequelae. However, unlike the aforementioned non-invasive imaging modalities, intraoperative seizures during an awake craniotomy with brain mapping are a relatively common complication of the procedure, with reported incidence as high as 32% [1,2]. From our experience seizures are more commonly observed with higher levels of stimulation, although there is no established threshold for seizure generation. Most seizures are sporadic and quickly aborted, and prior studies show that these intraoperative seizures rarely evolve into generalized seizures [1,3,4].

Research into this procedure has found the strongest correlation for intraoperative seizures in patients with a history of epilepsy, as well as patients taking multiple antiepileptic drugs [4,5]. In order to reduce the occurrence and severity of intraoperative seizures, antiepileptic drugs (AEDs) are routinely given preoperatively even to patients who have not had seizures. Historically these drugs have not been believed to have a significant negative effect on awake craniotomy procedures, although a recent review of 424 awake craniotomy procedures reported that phenytoin was significantly associated with communication failures during cortical mapping [6]. Although it is commonly understood that abrupt discontinuation of AEDs can lead to a transient period with a reduced seizure threshold, to our knowledge there have been no reports detailing the effects of antiepileptic drugs on the amount of current required to map eloquent cortex in awake craniotomies. We describe a case where antiepileptic use/disuse was thought to be directly related to both the amount of current required to elicit a motor response and the current needed to produce a seizure.

Case

We present the case of a 43 year old right-handed white female who presented to us with a 3 month history of electrical sensations in her right hand and right leg in addition to difficulty with word finding.
comprehension, and memory. The patient had a right hemiparesis and was noted to have anxiety. The patient denied any history of seizure activity. MRI demonstrated a ring-enhancing mass lesion in the posterior aspect of the left frontal lobe with extension into the superior posterior left temporal lobe and insula with surrounding vasogenic edema. There was mass effect with mild effacement of the lateral ventricle. Pre-operative MRI images are shown in Fig. 1. This mass was biopsied stereotactically. The pathology specimen was determined to be a glioblastoma multiforme (GBM). DTI was performed and this demonstrated that the corticospinal tracts were likely to be anteromedial to the lesion. The arcuate fasciculus, however, appeared to be pushed superiorly via mass effect and was in much closer proximity to and possibly invaded by the lesion. Due to the proximity of eloquent cortex affecting language, motor, and sensory tracts, the patient was advised to undergo an awake craniotomy with intraoperative brain mapping and stealth guidance and this was arranged for the fifth day following her biopsy. She was discharged on lorazepam 1 mg TID PRN for anxiety, dexamethasone 4 mg QID, and levetiracetam 500 mg BID four days prior to her awake craniotomy. The levetiracetam was started on postoperative day 1 of the stereotactic biopsy, so this discharge regimen would allow the patient to take eight doses of levetiracetam before the surgery.

Surgical procedure and clinical course

An incision was fashioned based upon the location of the tumor. An adequate cortical surface was exposed to map the frontal cortex and associated language cortex. The location of the tumor was confirmed with the Stealth system and the proposed mapping sites were reconfirmed. Intraoperative mapping was undertaken using 4–5 s square wave pulses at a frequency of 60 Hz. The area of anticipated motor cortex was initially stimulated with 1 mA with no response. Two milliamperes then was used over the motor cortex and this elicited no response. The current was then increased and no motor response was seen until stimulation with 9.0 mA. This current was observed to be the threshold stimulation to elicit repetitive arm response. This same current was then used to complete speech and motor mapping.

Discussion

This case demonstrates the unique findings of a patient undergoing intraoperative cortical stimulation on two different AED regimens only one week apart. Although exact levetiracetam levels are not known, during the first surgery the patient’s levels were likely lower after missing her dose the morning of the procedure, while the second surgery was performed with the patient on high dosage levetiracetam and a therapeutic phenytoin level. The threshold for motor stimulation was observed to increase from 1.75 mA during the first procedure to 9.0 mA in the second procedure. Additionally, seizure activity was initiated at 1.75 mA in the first procedure, while stimulation at levels up to 9.0 mA did not evoke seizure activity in the second procedure.

Although this effect might be taken for granted by those who routinely pretreat their patients with AED’s prior to intraoperative brain mapping, this is the first report of a quantitative increase in seizure and motor stimulation thresholds as a result of varying preoperative AED dosages in a single patient.

Phenytoin is a well-established anti-convulsant drug used to prevent repetitive firing of neurons and resulting generation and spread of seizure activity. Although phenytoin’s mechanism of action is not completely understood, it is proposed to inhibit sodium flux through voltage dependent sodium channels on the neuronal membrane. This inhibition serves to stabilize membrane potential by her preoperative instructions. It was determined that the patient had taken her scheduled dose the evening prior to surgery, but had omitted her dose the morning of surgery. The patient remained neurologically stable, although she did experience some worsening of her expressive aphasia as a result of the seizure activity. The patient was transferred to the floor the next day, and discharged home on the 2nd postoperative day.

The patient returned to the hospital on the 7th postoperative day for another attempt at resection; however, this time she had a phenytoin level of 15.4 μg/ml and was taking an increased dosage of levetiracetam. This awake craniotomy proceeded as anticipated with a very different response to stimulation. As before, the motor cortex was stimulated with 1 mA and this elicited no response. The current was slowly increased and no motor response was seen until stimulation with 9.0 mA. This current was observed to be the threshold stimulation to elicit repetitive arm response. This same current was then used to complete speech and motor mapping. The procedure was successful in removing the vast majority of the tumor with only a small residual that was adherent to the middle cerebral artery. No intraoperative seizures were observed during this second craniotomy for resection.

Fig. 1. Pre-operative MRI images: axial T2 flair (left), axial T1 post-contrast (center), and coronal T1 post-contrast (right). MRI illustrates edema, necrosis, and contrast enhancement characteristic of glioblastoma multiforme. Due to the proximity of the tumor to the temporal and insular lobes of the patient’s dominant hemisphere, an awake craniotomy with intraoperative mapping was recommended for resection of the lesion.
and prevent repetitive and inappropriate firing. By stabilizing individual neurons against excessive firing, phenytoin is able to inhibit the spread of neuronal electrical activity, preventing localized seizure foci from evolving into generalized seizures as seen in this case. The antiepileptic effects of levetiracetam are believed to be due to the drug’s ability to bind synaptic vesicle protein 2A. This protein plays a role in exocytosis of neurotransmitter containing vesicles, although the details of these interactions are not completely understood. By modulating the axonal release of neurotransmitter, levetiracetam has been shown to be protective against seizure activity in a variety of epilepsy models, as well as effective in reducing development of seizure kindling [7].

The quantitative difference in current required for cortical mapping and initiation of seizure activity between the two attempted resections one week apart suggests a difference in cortex excitability potentially due to the presence of phenytoin and levetiracetam. Missing a dosage of antiepileptic medication in a patient with potential seizure foci may have resulted in a decreased seizure threshold in the first attempted resection, as evidenced by the repeated induction of seizure activity at 1.75 mA of stimulation. The presence of both phenytoin and levetiracetam in higher levels for the second attempted resection may have significantly reduced the excitability of the neurons to electrical stimulation and resulted in much higher current (9.0 mA) requirement to elicit motor response. From our experience using this pattern of intraoperative electrical stimulation, patients normally exhibit motor response in the range of 2–6 mA. This patient’s response threshold was observed to increase from a lower than expected level of 1.75 mA to a higher than usual value of 9.0 mA in the time of one week concurrent with increasing dosages of antiepileptic medications. One possible explanation may be that the differing mechanisms of seizure blockade for phenytoin and levetiracetam led to even greater depression of neuronal excitability than would be seen with either drug independently.

The lack of intraoperative seizures in the second attempt at tumor resection can potentially be explained by the presence therapeutic serum levels of antiepileptic drugs. The modulatory effects of phenytoin on membrane sodium channels and levetiracetam on synaptic vesicle protein 2A have a dampening effect on abnormal firing similar to that seen during

Fig. 2. After stimulation with 2 mA, the patient produced tonic–clonic movement that progressed to generalized seizure. Iced lactated Ringer’s solution was used and the seizure was aborted.

Fig. 3. The current was reduced to 1.75 mA and electrical stimulation was applied and again the patient developed an electrographic and clinical seizure that started as focal tonic–clonic movements that later generalized. Iced lactated Ringer’s solution was used and the seizure was aborted.
a seizure. During the first attempted resection, excitation was provided by the current used for mapping of the cortex and this caused the firing of neurons to become excessive leading to a generalized seizure. Under the modulation of antiepileptic drugs, the same degree of stimulation and increasingly higher levels of stimulation may have failed to generate action potentials required to initiate seizure activity.

The use of perioperative dexamethasone in this patient represents the current standard of care in patients with high grade gliomas and brain metastases. Glucocorticoid use has been shown to decrease pain, nausea, and vomiting and improve overall outcomes by relieving intracranial pressure in the perioperative period. This pressure reduction is due to modulation of vasogenic edema that is seen in intracranial tumors due to increased permeability of the blood brain barrier [8]. Glucocorticoids reduce expression of inflammatory cytokines and chemokines responsible for escalating the inflammatory response and increasing the fluid permeability of the blood brain barrier. In addition, glucocorticoids may protect neurons against glutamate toxicity that has been shown to induce seizure activity in patients with high grade gliomas [9]. Dexamethasone is the most commonly used glucocorticoid by neuro-oncologists and neurosurgeons owing to its comparatively minimal mineralocorticoid activity and possibly lower risk of infection or cognitive impairment. There have been no previous reports of glucocorticoids influencing the current required for intraoperative brain mapping, and current understanding of glucocorticoid mechanisms does not predict the existence of such interactions.

For both the initial resection attempt and follow up surgery, propofol was used in anesthetic management. The rate of propofol administration in each procedure ranged from 0 μg/kg/min (during awake stimulation) to 125 μg/kg/min for a total dose of 1590 mg in the first procedure and 1475 mg in the second. Propofol is recognized as having uniform depressant activity on the central nervous system. As a result propofol may suppress neuronal firing and seizure generation by inhibiting release of excitatory neurotransmitters [10]. Because similar doses of propofol were given in both surgical attempts and because propofol is not administered during stimulation, the observed difference in cortical response thresholds seen cannot be attributed to the actions of propofol. To date there have been no reports of propofol altering seizure and motor thresholds in awake cortical and subcortical mapping procedures to the degree observed in this case.

The findings in this case confer that the antiepileptic drugs phenytoin and levetiracetam do impact the awake craniotomy procedure. In repeated resection attempts only 7 days apart, our patient was observed to have increased seizure and motor stimulation thresholds with intraoperative cortical stimulation on the higher dose regimen, as would be expected. The significance of this report is in the quantification of a specific and reproducible increase in the motor stimulus and seizure threshold that can be attributed to a defined intervention, that is the institution of high dose levetiracetam and phenytoin administration. The findings in this case indicate the need for awareness of the potential for higher current requirements in patients preoperatively treated with high doses of antiepileptic drugs prior to awake craniotomy procedures. In addition, this case emphasizes the importance of confirming adequate dosage of antiepileptic drugs in patients undergoing awake craniotomies, especially those believed to be at an increased risk of seizure generation.

**Conflict of Interest**

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property. We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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