Published in final edited form as:

J Clin Neurophysiol. 2014 June ; 31(3): 194–198. doi:10.1097/WNP.000000000000051.

De novo generalized periodic discharges (GPDs) related to anesthetic withdrawal (GAWs) resolve spontaneously

Amar B. Bhatt¹, Alexandra Popescu², Elizabeth Waterhouse³, and Bassel W. Abou-Khalil¹

¹Vanderbilt University Medical Center, Dept. of Neurology, Nashville, TN

²University of Pittsburgh Medical Center, Dept. of Neurology, Pittsburgh, PA

³Virginia Commonwealth University School of Medicine, Richmond, VA

Abstract

Pentobarbital and propofol are used for the treatment of refractory status epilepticus and elevated intracranial pressure, typically with continuous EEG monitoring. We report a series of patients who developed generalized periodic discharges (GPDs) related to anesthetic withdrawal (GAWs), different from prior seizure activity. At times, this pattern was misinterpreted as recurrent seizure activity, leading to reinstitution of drug-induced coma, but resolved spontaneously without additional treatment.

We identified five patients who developed GAWs during pentobarbital or propofol withdrawal. Two patients received pentobarbital for increased intracranial pressure. One patient received pentobarbital and propofol for encephalopathy accompanied by a rhythmic EEG pattern erroneously thought to be ictal. Two patients received pentobarbital for refractory partial status epilepticus. In all cases, anesthetic agents were withdrawn after 24-48 hours of burst-suppression on EEG. We analyzed the course of GAWs on EEG and the associated clinical outcomes.

All five patients developed GAWs, consisting of periodic 1-4 Hz GPDs, not previously seen on EEG. In all cases, the pattern eventually resolved spontaneously, over 12-120 hours. However, in three cases the pattern was initially thought to represent ictal activity, and drug-induced coma was reinitiated. The pattern recurred during repeated anesthetic withdrawal, was then recognized as non-ictal, and then resolved without further treatment. In all cases but one, the patients exhibited improvement to near baseline mentation.

Corresponding Author Bassel W. Abou-Khalil Vanderbilt University Medical Center, Dept. of Neurology 1161 21st Avenue South, A-0118 Medical Center North Nashville, TN 37232-2551 615-936-0060 (phone) 615-936-0223 (fax) bassel.abou-khalil@vanderbilt.edu.

Disclosures, Conflicts of Interest, and Sources of Funding

1. The project (notably the use of the REDCap database at Vanderbilt University) was supported by the National Center for Research Resources, Grant UL1 RR024975-01, and is now at the National Center for Advancing Translational Sciences, Grant 2 UL1 TR000445-06. (The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.)
2. No additional sources of funding to disclose for any of the authors.
3. The authors have no conflicts of interest to disclose.
4. These data were presented as a poster presentation at the American Epilepsy Society Annual Meeting in San Diego, California in December 2012.

GRAWs may occur de novo after pentobarbital or propofol withdrawal. GRAWs should resolve spontaneously without treatment, and without recurrence of clinical seizure activity. GRAWs are not likely to represent status epilepticus and should not prompt resumption of drug-induced coma, unless there is reappearance of original electrographic seizure activity.

Keywords

Drug-induced coma; Periodic discharges; Triphasic waves; Non-convulsive status epilepticus; Critical illness; Continuous EEG monitoring

Introduction

Anesthetic medications such as pentobarbital (PTB) and propofol (PRO) are widely used for the treatment of refractory status epilepticus or refractory elevated intracranial pressure (ICP) (Bratton et al., 2007; Brophy et al., 2012). Continuous EEG monitoring is essential in determining the depth of anesthesia and guiding treatment in the ICU (Brophy et al., 2012). In most cases, the decision to withdraw anesthetics is dependent on whether the EEG shows adequate suppression of seizure activity (Krishnamurthy & Drislane, 1996; Krishnamurthy & Drislane, 1999; Claassen et al., 2001) or adequate lowering of ICP (Winer et al., 1991). Often the appearance of alarming EEG patterns that could possibly be ictal prompts re-initiation of anesthesia.

One of us (BAK) had previously consulted on a patient treated with PTB coma for status epilepticus and noted generalized periodic discharges (GPDs) concerning for ictal activity that had appeared with PTB taper. Reinstitution of PTB was recommended. The recommendation was not followed, but the patient woke up the next day. This observation raised awareness to the possibility that periodic patterns during PTB withdrawal may not be ictal in nature. We report a series of patients with de novo GPDs in the setting of PTB or PRO withdrawal, an EEG pattern different from prior seizure activity. At times, this pattern was misinterpreted as recurrent seizure activity, leading to reinstitution of drug-induced coma. This pattern was identified as GPDs related to anesthetic withdrawal (GRAWs) and had a unique course of spontaneous resolution. We report our experience with GRAWs and their relationship to clinical outcome.

Methods

We identified patients who underwent continuous EEG monitoring while on PTB or PRO at Vanderbilt University Medical Center between January 1, 2000 and January 31, 2012. We included patients who were at least 10 years old, in whom anesthesia was used for treatment of seizures or elevated ICP, who developed GRAWs immediately after withdrawal of PTB or PRO. We excluded patients who, prior to anesthetic use, had generalized convulsive status epilepticus or GPDs. We also excluded patients with anoxic brain injury, cardiopulmonary arrest, or suspected prion disease.

A total of five patients were appropriate for inclusion in the final analysis. After approval by the appropriate institutional review board, we reviewed historical data, imaging, EEG data,

and clinical course for each case. The REDCap database was used for data collection and analysis. In our institution, the usual PTB doses range from 1-3 mg/kg/hr. We treat both seizures and elevated ICP to a goal of a burst-suppression pattern on EEG, with deeper anesthesia if prior seizure patterns persist during EEG bursts. In ICP treatment, we withdraw anesthetics based on the ICP itself; in treatment of seizures, we discontinue anesthetics after 24-48 hours of burst-suppression on EEG. In both settings, our practice is to stop PRO and PTB without gradual tapering.

Results

The clinical and EEG data for the five cases are summarized in Table 1.

Case 1

A 12-year-old boy with no prior history of seizures was admitted after a gunshot wound to the head. Brain CT revealed right **fronto**-parietal hemorrhage with edema. He was given prophylactic phenytoin. He initially did have encephalopathy with right sided (ipsilateral) arm twitching, but EEG was negative for ictal activity and revealed generalized irregular-arrhythmic delta activity.

He developed refractory elevated ICP and a PTB infusion was initiated. Burst-suppression was maintained for 48 hours. Upon withdrawal of PTB, GPDs were noted and PTB was restarted. Over the next 10 days, multiple attempts to withdraw PTB led to recurrence of GPDs at 2-3 Hz. On the sixteenth day of hospitalization, GPDs again recurred but anesthetics were held. The pattern resolved spontaneously within 12 hours, and the patient gradually awakened (Figure 1). Despite a persistent left hemiparesis that was commensurate with the patient's right parietal injury, he had a complete recovery of mental status.

Case 2

A 59-year-old man with no prior seizure history remained unresponsive after thoracic aortic aneurysm repair, despite withdrawal of sedation. One day postoperatively he had a witnessed generalized tonic-clonic seizure and was started on phenytoin. Neuroimaging revealed acute infarcts in the bilateral posterior fronto-parietal regions and the left posterior temporal lobe, as well as multiple diffuse punctate microhemorrhages.

EEG monitoring revealed frequent independent left frontal and right occipital seizures, which progressed into persistent right occipital electrographic partial status epilepticus. Seizure activity persisted even after addition of levetiracetam, and PTB infusion was then initiated. A burst-suppression pattern was maintained for 48 hours.

Upon PTB withdrawal, the EEG revealed GPDs occurring at 2-3 per second, and the patient remained comatose. This pattern was treated with PRO infusion (again to burst-suppression) for 48 hours. The pattern was again seen after PRO withdrawal, and resolved without treatment over 24 hours (Figure 2). The patient became progressively more alert and interactive over the next five days. He underwent rehabilitation over the next ten days and made a complete neurologic recovery.

Case 3

A 50-year-old woman with no prior seizure history was admitted to the hospital for confusion. On examination she was nonverbal and could not follow commands, though she moved all limbs spontaneously against gravity. She was on tiagabine for back pain related to lumbar spine disease. She was also on alprazolam and amitriptyline.

EEG revealed high voltage generalized rhythmic alpha and theta activity. It was not clear if this represented an ictal pattern or encephalopathy. Routine laboratory studies, including ammonia level, were unremarkable. Tiagabine was stopped. She was treated with lorazepam (12 mg total), valproic acid, and levetiracetam, without EEG or clinical improvement. Subsequently, PRO infusion was initiated, and this was switched to PTB after 24 hours. Burst-suppression was maintained for a total of 48 hours.

Upon PTB withdrawal, EEG revealed high voltage 3-4 Hz GPDs. This activity spontaneously resolved within 24 hours (see Figure 3), without further treatment. Over the next three days, the patient returned to normal **both clinically and electrographically**.

Case 4

A 58-year-old woman underwent angiogram for embolization of a right frontal premotor arteriovenous malformation (AVM). She had a history of right basal ganglia hemorrhage eight months prior, but no history of seizures. She developed a transient left sided weakness intraoperatively and embolization was deferred. Head CT revealed scattered right frontoparietal subarachnoid and intraparenchymal hemorrhage. The next day, she underwent craniotomy for resection of the AVM. Due to intraoperative concerns for brain edema and elevated ICP, PRO was continued post-operatively, and PTB was added upon transfer to the intensive care unit.

EEG monitoring was initiated at the time of transfer. Burst-suppression pattern was maintained for 24 hours. Upon PTB and PRO withdrawal, 1-2 Hz GPDs were noted on EEG. This pattern resolved spontaneously over 48 hours, and EEG showed generalized arrhythmic slow activity. Five days later, there were two brief subclinical right frontal ictal discharges, and levetiracetam was added. The patient's mentation gradually improved over that time period. Despite a persistent left hemiparesis commensurate with the patient's hemorrhage, she had a complete recovery of mental status.

Case 5

A 56-year-old woman developed new-onset seizures and a right mesial temporal hemorrhage. She was treated with levetiracetam and eventually transferred to inpatient rehabilitation. However, she was re-admitted the hospital for confusion. She would only speak a few words, would not follow commands, and would occasionally pick at her face with the right hand. MRI was negative for any acute lesions; lumbar puncture revealed a mild lymphocytic pleocytosis (WBC 171) with negative HSV-1 and HSV-2 PCR.

EEG revealed waxing and waning focal right frontal delta activity, which was not clearly ictal. She was empirically treated with lorazepam and phenytoin for presumed partial status

epilepticus, and SPECT showed prominent right temporal hyperperfusion, supporting this diagnosis. However, the patient did not improve clinically despite addition of oxcarbazepine and topiramate. Therefore, PTB was initiated to achieve seizure control. Burst-suppression was maintained for 48 hours.

Upon PTB withdrawal, the EEG revealed waxing and waning GPDs occurring at 1-2 Hz. Due to concern that this pattern represented nonconvulsive status epilepticus, PTB was re-initiated, and burst-suppression was once again maintained for 48 hours. The GPDs did recur after the second PTB withdrawal, but anesthetic was not restarted. The EEG pattern was gradually replaced by progressively more continuous delta and theta activity over a five day period. The patient did awaken but did not follow commands and had a persistent left sided spasticity. However, at this point, in accordance with the family's wishes, the decision was made to withdraw care.

Discussion

In our series of five patients, this de novo pattern of GRAWs was seen after cessation of PTB or PRO. This pattern of generalized 1-4 per second periodic sharp activity occurred immediately after anesthetic withdrawal (after the burst-suppression pattern). Although at times having an appearance on EEG that was concerning for ictal activity, GRAWs were transient and resolved spontaneously as the anesthesia cleared, in association with clinical improvement (Table 2). Time to resolution is usually 12-48 hours, though resolution may be slower as a result of accumulation of PTB in adipose tissue (as may have occurred in patient 5).

Such new-onset patterns have only previously been described in single case reports. A pattern of periodic discharges in association with PTB withdrawal was first reported in a 54-year-old woman who underwent PTB induced coma for six days after complications during surgery for ophthalmic artery aneurysm (Lancman et al., 1997). "Generalized periodic triphasic waves" appeared one day after PTB withdrawal, while the patient was still comatose. Anesthesia was not reinstituted, and the patient had no clinical seizures and made a complete recovery. We suggest that the pattern of GRAWs is common though not universal. However, a larger study of consecutive patients undergoing EEG monitoring during withdrawal of PTB or PRO will be important to confirm this impression and provide the true incidence of GRAWs in this setting.

Though GPDs themselves are nonspecific, anesthetic withdrawal is a likely explanation for this pattern, for several reasons. First, none of the patients had a generalized periodic pattern prior to initiation or withdrawal of anesthetics; therefore anesthetic withdrawal was not unmasking a previously established EEG pattern. Second, the pattern resolved spontaneously, without additional anti-seizure treatment. Third, when anesthesia was re-initiated and re-titrated to burst-suppression on EEG, GRAWs recurred again after anesthetic withdrawal. Fourth, our patients did not have any other clear causes of de novo GPDs (e.g., metabolic derangements, toxins, or medications other than anesthetic withdrawal). Finally, none of our patients had generalized convulsive status epilepticus, a condition known to progress to generalized periodic patterns (Treiman et al., 1990). Overall,

these factors lead to anesthetic withdrawal as the common denominator in all of our cases. The pathophysiology of GRAWs is unclear. GPDs appear to be a nonspecific pattern with multiple underlying mechanisms. GPDs may occur in association with reversible encephalopathies such as hepatic encephalopathy, nonconvulsive status epilepticus, as well as diffuse cortical injury as may be seen with anoxic brain injury and prion disease (Gloor et al., 1968, Brenner & Schaul, 1990). In the current series, GRAWs were a reversible phenomenon related to withdrawal of two drugs with similar mechanisms of action on GABA receptors. It is not clear if our practice of abrupt withdrawal of anesthesia could be a potential cause of GRAWs, or if GRAWs would be less likely with a slower taper.

The classification of generalized periodic patterns remains controversial (Brenner & Schaul, 1990; Husain et al., 1999; Brenner, 2002; Kaplan, 2004). Published proposed criteria for the diagnosis of NCSE or definite ictal discharges can be helpful. For some equivocal patterns, clinical response to a benzodiazepine can help support or refute the NCSE diagnosis (Young et al., 1996; Chong & Hirsch, 2005; Kaplan, 2007). However, the use of a benzodiazepine trial to support a diagnosis of NCSE may not necessarily make clinical sense in patients who remain comatose after recent withdrawal of high dose anesthetics. There are a number of arguments against an ictal nature for GRAWs in our patients. GRAWs resolved spontaneously regardless of whether the pattern exceeded 2.5 Hz. GRAWs were also different from the EEG findings prior to initiation of anesthesia. Furthermore, none of our patients had any clinical correlation to GRAWs, **other than coma**.

There are important implications regarding the management of GRAWs. In three of five cases, GRAWs were thought to represent ictal activity, which led to re-initiation of anesthesia. This practice could lead to anesthesia-related morbidity and mortality, prolonged ICU and overall hospital stays, or possibly even worse neurologic outcomes. GRAWs are unlikely to represent status epilepticus and should not prompt resumption of drug-induced coma, unless there is recurrence of clinical seizures, reappearance of original electrographic ictal activity, or presence of definite ictal discharges. The overall clinical picture should guide management, regardless of the presence or absence of a given EEG pattern.

In summary, new-onset GRAWs may be seen on EEG, when PTB or PRO are discontinued. GRAWs are a subset of GPDs not ictal in nature. This pattern is expected to resolve spontaneously without treatment.

Acknowledgments

The project (notably the use of the REDCap database at Vanderbilt University) was supported by the National Center for Research Resources, Grant UL1 RR024975-01, and is now at the National Center for Advancing Translational Sciences, Grant 2 UL1 TR000445-06. (The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.)

References

- Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J, Shutter L, Timmons SD, Ullman JS, Videtta W, Wilberger JE, Wright DW. Guidelines for the Management of Severe Traumatic Brain Injury. Brain Trauma Foundation and AANS/CNS Joint Section on Neurotrauma and Critical Care. J Neurotrauma. 2007; 24(Suppl. 1):S71–S76. [PubMed: 17511550]

- Brenner RP, Schaul N. Periodic EEG patterns: classification, clinical correlation and pathophysiology. *J Clin Neurophysiol.* 1990; 7:249–67. [PubMed: 2187023]
- Brenner RP. Is it status? *Epilepsia.* 2002; 43(Suppl. 1):3103–13.
- Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, Laroche SM, Riviello JJ Jr. Shutter L, Sperling MR, Treiman DM, Vespa PM. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care.* 2012; 17:3–23. [PubMed: 22528274]
- Chong DJ, Hirsch LJ. Which EEG patterns warrant treatment in the critically ill? Reviewing the evidence for treatment of periodic epileptiform discharges and related patterns. *J Clin Neurophysiol.* 2005; 22:79–91. [PubMed: 15805807]
- Claassen J, Hirsch LJ, Emerson RG, Bates JE, Thompson TB, Mayer SA. Continuous EEG monitoring and midazolam infusion for refractory nonconvulsive status epilepticus. *Neurology.* 2001; 57(6): 1036–42. [PubMed: 11571331]
- Gloor P, Kalabay O, Giard N. The electroencephalogram in diffuse encephalopathies: electroencephalographic correlates of grey and white matter lesions. *Brain.* 1968; 91:779–802.
- Husain AM, Mebust KA, Radtke RA. Generalized periodic epileptiform discharges; etiologies, relationship to status epilepticus, and prognosis. *J Clin Neurophysiol.* 1999; 16:51–8. [PubMed: 10082092]
- Kaplan PW. EEG criteria for nonconvulsive status epilepticus. *Epilepsia.* 2007; 48(Suppl. 8):39–41. [PubMed: 18329995]
- Kaplan PW. EEG in metabolic encephalopathy and coma. *J Clin Neurophysiol.* 2004; 21:307–18. [PubMed: 15592005]
- Krishnamurthy KB, Drislane FW. Relapse and survival after barbiturate anesthetic treatment of refractory status epilepticus. *Epilepsia.* 1996; 37(9):863–7. [PubMed: 8814099]
- Krishnamurthy KB, Drislane FW. Depth of EEG suppression and outcome in barbiturate anesthetic treatment for refractory status epilepticus. *Epilepsia.* 1996; 40(6):759–62. [PubMed: 10368075]
- Lancman ME, Marks S, Mahmood K, Lansen T. Atypical triphasic waves associated with the use of pentobarbital. *Electroencephalogr Clin Neurophysiol.* 1997; 102:175–7. [PubMed: 9129572]
- Treiman DM, Walton NY, Kendrick C. A progressive sequence of electroencephalographic changes during generalized convulsive status epilepticus. *Epilepsy Res.* 1990; 5:49–60. [PubMed: 2303022]
- Winer JW, Rosenwasser RH, Jimenez F. Electroencephalographic activity and serum and cerebrospinal fluid pentobarbital levels in determining the therapeutic end point during barbiturate coma. *Neurosurgery.* 1991; 29:739–742. [PubMed: 1961405]
- Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. *Neurology.* 1996; 47:83–9. [PubMed: 8710130]

Figure 1.

Spontaneous resolution of GAWs over 12 hours in Case 1. **The first panel showed persistent GAWs, which progressively attenuated in the third and fourth panels, and resolved in the last panel.**

Figure 2.

Spontaneous resolution of GRAWs over 24 hours in Case 2. **The first panel shows persistent GRAWs that just started attenuating in the second panel. The time difference between the first and third panels is 15 hours.**

Figure 3.
Spontaneous resolution of GRAWs over 24 hours in Case 3. **The time difference between the first and third panels is 10 hours.**

Table 1

Summary of clinical and EEG case data from five cases with GRAWs.

	Case 1	Case 2	Case 3	Case 4	Case 5
age/gender	12-year-old male	59-year-old male	50-year-old female	58-year-old female	56-year-old female
reason for admission	gunshot wound to the head (right hemisphere)	thoracic aortic aneurysm repair	confusion (on amitriptyline and tiagabine for pain)	right frontal AVM resection (prior right basal ganglia bleed)	new onset seizures and confusion
pre-anesthetic exam	encephalopathy with left sided weakness	unresponsive and nonfocal (postoperatively)	encephalopathic, nonverbal, not following commands	comatose (continued on PRO postoperatively)	encephalopathy, intermittent right-handed face picking
pre-anesthetic imaging	right parietal hemorrhage/edema	acute bi-frontoparietal & left temporal infarcts; diffuse microhemorrhages	Unremarkable	right frontoparietal subarachnoid and intra-parenchymal hemorrhage	right mesial temporal hemorrhage
pre-anesthetic EEG	generalized irregular arrhythmic delta	left frontal seizures; right occipital partial status	high voltage generalized rhythmic alpha-theta	EEG started after anesthetic	right temporal delta; SPECT confirmed ictal nature
reason for anesthetic	refractory elevated ICP	refractory partial status epilepticus	suspected nonconvulsive status epilepticus	elevated ICP and brain edema	refractory partial status epilepticus
anesthetic(s) used	PTB	PTB	PRO, then PTB	PRO and PTB	PTB
EEG pattern after anesthetic withdrawal	GRAWs: 2-3 Hz GPDs (recurred with multiple PTB withdrawal trials)	GRAWs: 2-3 Hz GPDs	GRAWs: 3-4 Hz GPDs	GRAWs: 1-2 Hz GPDs	GRAWs: 1-2 Hz GPDs (recurred with second PTB withdrawal trial)
time to GRAWs resolution	12 hours	24 hours	24 hours	48 hours	120 hours
post-anesthetic clinical course	recovery of mentation, expected left hemiparesis	complete neurologic recovery	complete neurologic recovery	recovery of mentation; expected left hemiparesis	patient awoke from coma; withdrawal of care

AVM, arteriovenous malformation; PTB, pentobarbital; PRO, propofol; ICP, intracranial pressure; GPDs, generalized periodic discharges; GRAWs, GPDs related to anesthetic withdrawal

Table 2

Electro-clinical features which may identify GRAWs.

Electro-clinical features which may identify GRAWs
New-onset GPDs after anesthetic withdrawal, especially after drug-induced burst-suppression
No GPDs prior to anesthetic use
GPDs differ from pre-anesthetic EEG pattern (e.g., pre-anesthetic EEG with focal ictal discharges)
Spontaneous electrographic and clinical improvement without treatment
Recurrence of pattern with repeated anesthetic withdrawal
Absence of confounding conditions (e.g., generalized convulsive status epilepticus, prion disease, anoxic brain injury, or diffuse toxic/metabolic processes)
Absence of clinical ictal signs, other than coma
GRAWs, GPDs related to anesthetic withdrawal; GPDs, generalized periodic discharges