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The relationship between seizures, interictal spikes and antiepileptic drugs

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HIGHLIGHTS

- Interictal EEG spikes demonstrate a considerable diurnal variation with a night-time peak and day-time trough.
- Spike rate decreases with AED taper, increases after seizures and is higher during longer seizure-free periods.
- Interictal EEG spikes may reflect a process that contributes to the prevention and not occurrence of seizures.

ABSTRACT

Objective: A considerable decrease in spike rate accompanies antiepileptic drug (AED) taper during intracranial EEG (icEEG) monitoring. Since spike rate during icEEG monitoring can be influenced by surgery to place intracranial electrodes, we studied spike rate during long-term scalp EEG monitoring to further test this observation.
Methods: We analyzed spike rate, seizure occurrence and AED taper in 130 consecutive patients over an average of 8.9 days (range 5–17 days).
Results: We observed a significant relationship between time to the first seizure, spike rate, AED taper and seizure occurrence ($F(3,126) = 19.77$, $p < 0.0001$). A high spike rate was related to a longer time to the first seizure. Further, in a subset of 79 patients who experienced seizures on or after day 4 of monitoring, spike rate decreased initially from an on- to off-AEDs epoch (from 505.0 to 382.3 spikes per hour, $p < 0.00001$), and increased thereafter with the occurrence of seizures.
Conclusions: There is an interplay between seizures, spikes and AEDs such that spike rate decreases with AED taper and increases after seizure occurrence.
Significance: The direct relationship between spike rate and AEDs and between spike rate and time to the first seizure suggests that spikes are a marker of inhibition rather than excitation.

1. Introduction

Interictal EEG spikes are known to be highly correlated with the presence of epilepsy (Carreño and Lüders, 2001; Bautista, 2013; Staba et al., 2014). However, the relationship between interictal spikes and seizure occurrence is not clear. We previously reported a decrease in spike rate accompanies antiepileptic drug (AED) taper during intracranial EEG (icEEG) monitoring (Spencer et al., 2008; Goncharova et al., 2013). This observation suggests that interictal spikes reflect inhibitory and not excitatory mechanisms (Spencer et al., 2008). There is concern, however, that the spike rate we documented at the beginning of icEEG monitoring could have been influenced by the acute effect of the surgery to place icEEG electrodes. To further clarify the relationship between spikes, seizures and AEDs we studied the effect of AED taper on spike rate during long-term scalp EEG monitoring of patients with epilepsy. By con-

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ducting the current study during scalp EEG monitoring we sought to avoid the possibly deleterious effects of surgery to place intracranial EEG electrodes.

2. Methods

We studied scalp-recorded EEGs in consecutive patients admitted for presurgical evaluation for medically intractable epilepsy. This study was approved by the Human Investigation Committee at Yale University School of Medicine and written informed consent was obtained from all patients. We included patients who were monitored at Yale New Haven Hospital between January 2007 and July 2012. Patients were included in the study if (1) they did not have a seizure during the first day of monitoring; this selection criteria allowed us to compare subsequent days of the study to the first, seizure-free, day; (2) their AEDs were tapered or stopped during monitoring; (3) the duration of monitoring was at least 5 days long to allow sufficient time to observe the effect of AED taper; and (4) the EEG did not contain EKG artifacts. A total of 130 patients (average age 36.9 years, age range 9–72, 63 women) were included in this study. The continuous video-EEG recordings were acquired with standard clinical equipment (Natus/Bio-logic Systems Incorporated, San Carlos, CA), from standard 10–20 sites, in a referential montage, and digitized at 256 Hz. The reference electrode was placed at the Fz–Cz site; that is midway between the Fz and Cz sites.

The extended duration of EEG recordings studied (average 8.9 days, range 5–17 days) precluded manual scoring, and spikes were thus identified and tabulated automatically with commercially available software (Reveal, Persyst Development Corp., Prescott, AZ). This algorithm detects spikes using a neural network-based algorithm according to a "perception" index that does not necessarily correspond to the highest spike amplitude, but rather to the extent to which a spike is distinct from the EEG background (Wilson et al., 1999). In instances when a spike is visible in several EEG channels simultaneously this algorithm assigns spike detection to the single location where the spike is most prominent; thus the reported spikes are presumably independent. In this study we report only the spike rate and not any of the other characteristics of spikes. The spike rate was calculated as the number of spikes per hour. Spike detection was performed with the same version of the program and the same parameter settings for all patients. We used recommended parameter settings to detect the spikes (Wilson et al., 1999). In our preliminary evaluation of these parameter settings we found that they resulted in spike detections which reasonably coincided with expert detection. EMG artifacts were never falsely detected as EEG spikes. However, EEG spikes were underestimated if the EEG recordings were obscured by EMG contamination. Such contamination resulted from movement and activity such as chewing and was typically observed in the daytime. False positive detections occurred when lambda waves, sharp waves, and EKG were falsely detected as EEG spikes. False positive detections stemming from lambda waves were infrequent because lambda waves are rare EEG phenomenon. This study was focused solely on EEG spikes and sharp waves were thus considered to be false positive detections. Sharp waves formed a relatively small fraction of the detections, however, constituting between 2% and 10% of all detections in some patients. False positive detections stemming from EKG artifacts, on the other hand, increased the number of detections tremendously. We, thus, excluded all patients with EKG contamination of the EEG from the study.

The AEDs prescribed to the patients and the observed spike rates were compared between an on-AEDs epoch, selected from days 1 or 2 (average day 1.2), and an off-AEDs epoch, selected from days 3–11 (average day 5.4). Both the on- and off-AEDs epochs, each 24 h in duration, were selected from days when the patient did not have seizures, and the start and end of these epochs were at least 6 h away in time from a seizure. The on-AEDs epoch was usually selected as day 1. At times it was selected as day 2 if there was evidence of patient discomfort on day 1. Most of the patients were on full dose of AEDs during the on-AEDs epoch. The off-AEDs epoch was selected as the day when a patient received the lowest dose of AEDs. In patients who had several days over which their AEDs were completely stopped, we selected the first day which was free of seizures for the off-AEDs epoch. The average duration of the on- and off-AEDs epochs were 23.7 and 23.8 h, respectively. These values are slightly lower than 24 h due to the occurrence of seizures, in 8 and 4 patients, proximal in time to the on- and off-AEDs epochs, respectively. In these patients we selected a study duration shorter than 24 h to respect the condition that the epochs be at least 6 h removed from seizure onset or offset.

The patients received between 1 and 5 AEDs. Since the initial dose and taper were individualized, we employed a simple surrogate measure, AED%, to index AED taper. AED% was calculated as the daily average percentage of the initial AED dose. On average, patients were on 97.1% (range 50–100%) of the full dose during the on-AEDs epoch, and 21.8% during the off-AEDs epoch (range 0–50%). The average AED% in the transition period (calculated as the daily average value during the time between the on- and off-AED epochs) was 52.9%. In 79 patients (Group A), the first seizure occurred on or after day 4. This was after the point in time when the AEDs had been tapered to the minimal dose. In this group the off-AEDs epoch was selected before seizure occurrence. In the remaining 51 patients (Group B), the first seizure occurred on or shortly after day 2. That is, in Group B at least one seizure occurred before AEDs had been tapered to the minimal dose. In Group B the off-AEDs epoch was selected after at least one seizure had already occurred.

We calculated the average spike rate over the entire monitoring period for all patients. We then calculated the average spike rate during the on-and off-AEDs epochs. We also calculated the average spike rate from the total number of spikes which were detected both over the time before the first seizure and over the entire monitoring period. For this analysis the first two hours of monitoring was excluded to allow the patients time to adjust to the epilepsy monitoring unit (EMU). Furthermore, seven hours centered on each seizure were also excluded from the analysis to preclude the inclusion of acute seizure related changes.

We performed two types of analysis. A cross-sectional analysis was performed either for the full cohort of patients or separately for each of the two patient groups, Groups A and B, studied. This analysis was performed to test the relationship between different parameters, where the values of the parameters were averaged for each patient over the duration of monitoring. For example, we performed Pearson's test to assess the relationship between the average spike rate and average AED%, with each averaged over the duration of study, for the entire cohort of patients ($n = 130$, $df = 128$). Second, we performed longitudinal analysis to evaluate and compare the time course of different parameters through the multiple days of the study. In contrast to the cross-sectional analysis, here, we averaged parameters across all patients for each day of monitoring. For example, we performed Pearson's test to assess the relationship, evaluated daily over the first ten days of monitoring, between the spike rate and AED% ($n = 10$, $df = 8$). As patients were discharged from the hospital at the completion of their monitoring, the number of patients in the study decreased with the day of monitoring (see Table 1 and Supplementary Table S1). Due to this reason, we selected the off-AEDs epoch from the first 14 days of monitoring, limited the cross-sectional analyses to the same time-period, and limited longitudinal analyses to the first 10 days of monitoring.