Epilepsy & Behavior 83 (2018) 192–200

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Clinical and electrocorticographic response to antiepileptic drugs in patients treated with responsive stimulation

Tara L. Skarpaas [a,*], Thomas K. Tcheng [a], Martha J. Morrell [a,b]

[a] NeuroPace, Inc., Mountain View, CA, Clinical and Research Departments, United States
[b] Stanford University School of Medicine, Stanford, CA, Neurology Department, United States

ARTICLE INFO

Article history:
Received 17 February 2018
Revised 7 April 2018
Accepted 7 April 2018
Available online xxxx

Keywords:
Closed-loop
Responsive stimulation
Neuromodulation
Partial seizures
Medically intractable epilepsy
Antiepileptic drug

ABSTRACT

Objective: The objective of this study was to explore whether chronic electrocorticographic (ECoG) data recorded by a responsive neurostimulation system could be used to assess clinical responses to antiepileptic drugs (AEDs).
Methods: Antiepileptic drugs initiated and maintained for ≥3 months by patients participating in clinical trials of the RNS® System were identified. Such "AED Starts" that produced an additional ≥50% reduction in patient-reported clinical seizure frequency were categorized as clinically beneficial, and the remaining as not beneficial. Electrocorticographic features recorded by the RNS® Neurostimulator were analyzed during three periods: 3 months before the AED Start, first month after the AED Start, and the first 3 months after the AED Start.
Results: The most commonly added medications were clobazam (n = 41), lacosamide (n = 96), levetiracetam (n = 31), and pregabalin (n = 25). Across all four medications, there were sufficient clinical data for 193 AED Starts to be included in the analyses, and 59 AED Starts were considered clinically beneficial. The proportion of AED Starts that qualified as clinically beneficial was higher for clobazam (53.7%) and levetiracetam (51.6%) than for lacosamide (18.8%) and pregabalin (12%). Across all AED Starts for which RNS ECoG detection settings were held constant, the clinically beneficial AED Starts were associated with a significantly greater reduction in the detection of epileptiform activity ($p < 0.001$) at 1 (n = 33) and 3 months (n = 30) compared with AED Starts that were not beneficial at 1 (n = 71) and 3 months (n = 60). Furthermore, there was a significant reduction in interictal spike rate and spectral power (1–125 Hz) associated with a clinically beneficial response to an AED Start at 1 (n = 32) and 3 months (n = 35) ($p < 0.001$). These reductions were not observed at either 1 (n = 59) or 3 months (n = 60) for AED Starts that were not clinically beneficial.
Conclusions: Significant quantitative changes in ECoG data recorded by the RNS System were observed in patients who experienced an additional clinical response to a new AED. While there was variability across patients in the changes observed, the results suggest that quantitative ECoG data may provide useful information when assessing whether a patient may have a favorable clinical response to an AED.

1. Introduction

Establishing whether an antiepileptic drug (AED) is effective for an individual patient with epilepsy generally relies on patient self-reported seizures over time. However, patient and caregiver seizure reports may be inaccurate [1–5]. Also, depending on a patient's seizure frequency, it may take months to detect a response, and this process must be repeated with each dose adjustment. A physiological biomarker that provides a rapid assessment of a medication's effect on cortical excitability could quickly and objectively establish whether a given medication and dose are likely to be clinically effective. Chronic electrocorticographic (ECoG) sensing and recording devices could provide such information.

Pathologically increased cortical excitability is a hallmark of epilepsy [6,7], and AEDs measurably decrease cortical excitability. For instance, Badawy et al. [8] demonstrated that AED induced changes in transcranial magnetic stimulation-evoked measures of cortical excitability could predict seizure-freedom. This was observed regardless of the AED used. Further, Meisel et al. [9] demonstrated that the effect of AEDs could be quantified in a graded manner using intrinsic measures of cortical excitability recorded during intracranial monitoring. However, neither evoked nor intrinsic measures of cortical excitability have been available outside of the clinic or hospital.

The aim of this retrospective study was to explore whether chronic ambulatory ECoG data recorded by a closed-loop neurostimulation system (the RNS® System, NeuroPace Inc.) could reveal potential biomarkers

* Corresponding author at: 455 N. Bernardo Ave, Mountain View, CA 94043, United States.
E-mail addresses: tskarpaas@neuropace.com, (T.L. Skarpaas), ttcheng@neuropace.com, (T.K. Tcheng), mmorrell@neuropace.com. (M.J. Morrell).

https://doi.org/10.1016/j.yebeh.2018.04.003

of cortical excitability that could be used to assess a patient's clinical response to AED changes.

2. Methods

The RNS® System (NeuroPace, Mountain View CA) is a chronically implanted responsive neurostimulation system used for the adjunctive treatment of adults with medically refractory partial onset seizures arising from ≤2 seizure foci. The neurostimulator is placed within the cranium and connected to 2 leads that are placed according to that patient's seizure focus. Each lead contains 4 sensing and stimulating electrodes. The neurostimulator continually senses ECoG activity through the electrodes and is programed by the physician to detect specific patterns in the ECoG, such as epileptiform discharges or patterns characteristic of the onset of an electrographic seizure. When the neurostimulator detects one of these patterns, it responds by providing short bursts of electrical stimulation. In addition to providing responsive stimulation, the RNS System records multiple 1- to 3-minute segments of ECoG activity and provides hourly counts of physician-prespecified epileptiform events that are specific to that patient. These data are obtained as patients go about their normal routines.

2.1. Subjects

Two hundred thirty patients participated in a long-term treatment (LTT) study of the RNS System. The study protocol was approved by the institutional review boards of participating investigation sites. All patients gave written informed consent. The study was registered on www.clinicaltrials.gov (NCT00079781, NCT00264810, NCT00572195).

The study protocol has been described in detail elsewhere [10–12]. In brief, adults with medically intractable partial onset seizures with ≤2 seizure foci were initially enrolled in either an open-label feasibility or a subsequent randomized-controlled pivotal study. Safety and efficacy data were collected in each study to 2 years postimplant. Patients were then invited to continue in the open-label 7-year follow-on LTT study. The LTT study was ongoing as of the data cut-off on November 1, 2016.

During the open-label periods of the trials, any adjustments in AEDs were documented including the AED name, dosage, date, and type of change (e.g., new medication, dose adjustment, or discontinuation). Any time patients initiated a new medication, the event was marked as an "AED Start". To be included in further analyses, AED Starts had to meet the following criteria: (1) the new AED had to be maintained for at least 3 months; and (2) the specific AED had to be started in at least 30 patients in order to provide enough data for further analysis. The AED Starts that corresponded to a resumption of a previously used medication were excluded from the analysis. Thus, individual patients could have multiple nonoverlapping AED Starts but not for the same AED.

Clinical seizure data were collected prospectively in seizure diaries. Seizure frequency was calculated based on the total number of disabling seizures, which included simple partial motor, complex partial, and secondarily generalized tonic–clonic seizures. At least 70 days of valid seizure diary data during each of the 3-month analysis periods were required for an AED Start to be included in the analyses.

2.2. Analysis timeline

Analyses were conducted over the timeframes shown in Fig. 1. The "Before AED" period was defined as the 3 months immediately prior to initiating an AED (AED Start), the "After AED_{1M}" period as the first month after the AED Start, and the "After AED_{3M}" period as the first 3 months after the AED Start.

For all data types, comparisons were made between After AED_{1M} and Before AED periods (abbreviated "After AED_{1M}:Before AED") and between After AED_{3M} and Before AED periods (After AED_{3M}:Before AED). For clinical seizure frequency data only, comparisons were also made between After AED_{3M} and a 3-month baseline (Preimplant Baseline) obtained prior to implantation of the neurostimulator and leads (After AED_{3M}:Preimplant Baseline) and Before AED and the Preimplant Baseline (Before AED:Preimplant Baseline).

2.3. Clinical seizure frequency

For assessing the effect of the individual AEDs, each patient's clinical seizure frequency was normalized to their Preimplant Baseline seizure frequency. The changes were quantified as follows: ((After AED_{3M} or Before AED − Preimplant Baseline) / Preimplant Baseline) * 100.

2.3.1. Clinically beneficial AED Starts

For changes in seizure frequency associated with AED Starts, each patient's clinical seizure frequency was normalized to their Before AED seizure frequency. The changes in seizure frequency associated with AED Starts were quantified as follows: ((After AED_{3M} − Before AED) / Before AED) * 100. Antiepileptic drug Starts were classified as being "clinically beneficial" when the medication change was followed by an additional ≥50% reduction in clinical seizure frequency, and as "not beneficial" when the medication change was followed by a <50% reduction in clinical seizure frequency.

2.4. RNS System data

2.4.1. Electrocorticographic events

Two types of neurostimulator hourly count data were analyzed: the number of "Detections" and of "Long Episodes". Detections consisted of times that the neurostimulator detected activity prespecified by the physician as abnormal. The Detections were mostly composed of brief interictal epileptiform events but also included a smaller number of electrographic seizure onsets. Long Episodes were abnormal events detected by the neurostimulator that did not return to baseline ECoG

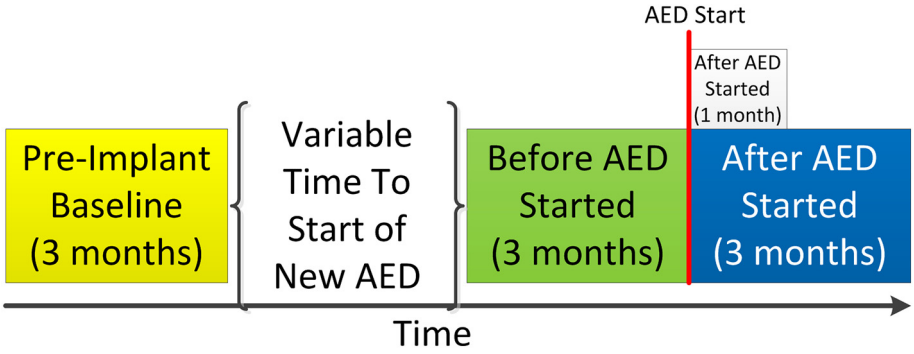

Fig. 1. Schematic illustrating the timeframes included in the analyses.