Epilepsy Research 140 (2018) 171–176

Contents lists available at ScienceDirect

Epilepsy Research

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

Fosphenytoin pre-medication for pediatric extra-operative electrical stimulation brain mapping

Ravindra Arya[a,*], Gewalin Aungaroon[a], Alonso Zea Vera[a], Paul S. Horn[a], Anna W. Byars[a], Hansel M. Greiner[a], Francesco T. Mangano[b], Katherine D. Holland[a]

[a] Comprehensive Epilepsy Center, Division of Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[b] Division of Pediatric Neurosurgery, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

ARTICLE INFO

Keywords:
Functional brain mapping
Intracranial EEG
Electrocorticography (ECoG)

ABSTRACT

Purpose: We studied the effect of fosphenytoin (FOS) pre-medication on the incidence and thresholds of after-discharges (ADs), seizures, and functional responses during electrical stimulation mapping (ESM).

Methods: As individualized by the attending epileptologist, FOS was given intravenously at 2 mg-phenytoin-equivalents (PE)/kg/min or 150 mg-PE/min (whichever slower). Patients who received and did not receive FOS were compared for the incidence and thresholds of ADs, seizures, and functional responses.

Results: Before ESM, 40 and 82 patients respectively were pre-medicated/not pre-medicated with FOS. The incidence of ESM-induced seizures was significantly lower in FOS pre-medicated patients (22.5% vs. 42.7%, $p = 0.044$), whereas temporal language threshold was higher (9.2 vs. 6.5 mA, $p = 0.032$). FOS was more efficacious in preventing ESM-induced seizures in patients with symptomatogenic zone ipsilateral to the side of ESM.

Although FOS dose had no significant effect on minimum language, minimum motor, or AD thresholds; seizure and temporal language thresholds showed trends approaching significance, intersecting at 12.2 mg-PE/kg. The incidence of ESM-induced seizures was significantly lower in those who received FOS at a dose of ≤12 mg/kg (9.1%) compared to those who did not receive any FOS (42.7%, $p = 0.046$), while the temporal language thresholds were not significantly different (6.3 vs. 6.5 mA, $p = 0.897$).

Conclusions: This study provides class III evidence that FOS pre-medication before ESM decreases the incidence of ESM-induced seizures, but increases temporal language threshold. FOS pre-medication may thus be considered before ESM. Future studies should prospectively verify these observations and characterize dose-response relationships.

1. Introduction

The conventional method to localize brain function with subdural electrodes involves assessment of behavioral response during electrical stimulation of pairs of adjacent electrodes. This electrical stimulation mapping (ESM) is associated with after-discharges (ADs) and risk of iatrogenic seizures, which undermine its safety and neurophysiologic validity. A recent large study reported ESM-induced seizures in 43/122 (35.2%) patients and showed that occurrence of ADs on ESM is a significant risk factor for ESM-induced seizure(s) (Aungaroon et al., 2017). Occurrence of a seizure during ESM precludes continuation of the procedure and potentially exposes the patient to additional risks, even though the patient is in a controlled environment. Thus, some physicians administer an anti-epileptic drug (AED) before the ESM. However, there is lack of data about safety or efficacy of this approach, and the effect of such pre-medication on AD, seizure, and functional thresholds. In this retrospective study, we compared the incidence and thresholds of ESM-induced ADs, seizures, and functional responses between groups of patients who received and did not receive fosphenytoin (FOS) before ESM. We also examined the relationship between the dose of FOS pre-medication and the incidence and thresholds for ADs, seizures and functional responses.

2. Methods

2.1. Patient sample

All patients who underwent ESM at Cincinnati Children's Hospital

* Corresponding author at: Comprehensive Epilepsy Center, Division of Neurology, Cincinnati Children's Hospital Medical Center, E4-145, MLC 2015, 3333 Burnet Avenue, Cincinnati, Ohio, 45229, USA.
E-mail address: Ravindra.Arya@cchmc.org (R. Arya).

https://doi.org/10.1016/j.eplepsyres.2018.01.017
Received 3 November 2017; Received in revised form 9 January 2018; Accepted 16 January 2018
Available online 03 February 2018
0920-1211/

between January 2007 and December 2014 were included. ESM was performed during pre-surgical evaluation of patients with drug-resistant epilepsy with concern for potential overlap between motor and/or language cortices and the planned resection. Patients who were unable to complete the testing for reason(s) other than ESM-induced seizure(s) were excluded. The study protocol was approved by the institutional review board (IRB 2015–6342).

2.2. Extra-operative electrocorticography (ECoG)

Extra-operative ECoG was recorded with subdural electrodes consisting of 4.75 mm platinum/iridium discs embedded in silicone elastomer, with 2.5 mm exposed surface and 1 cm inter-electrode distance (Integra Neurosciences, Plainsboro, NJ). Reference and ground were provided by a 2-contact strip facing the dura, placed away from the region of interest. The configuration of grids/strips were individualized for each patient. Electrode position was confirmed intra-operatively by visualization and post-operatively by co-registration of pre-implantation volumetric brain magnetic resonance imaging (MRI) with post-implantation head computed tomography scan. ECoG was recorded using Bio-Logic Ceegraph XL-II amplifiers (Bio-Logic System Inc., Mundelein, IL) at 0.1–400 Hz until April 2008 (n = 17) and Stellate eAM (Stellate Systems Inc., Montreal, Canada) at 0.1–667 Hz afterwards.

2.3. Electrical stimulation mapping

ESM was performed after having captured a sufficient numbers of habitual seizures, using OCS2 Ojemann cortical stimulator in 96 patients (Integra Life Sciences, Plainsboro, NJ), and Natus Cortical Stimulator (Natus Medical Inc., Middleton, WI) in 26 patients. Pairs of adjacent electrodes were stimulated with biphasic 0.3 ms, 50 Hz, square-wave pulses for 2 s (motor mapping) and 5 s (language mapping), with an initial current of 1 mA. The current strength was increased by 1–2 mA until: a functional response was obtained, an evolving burst of ADs/seizure was triggered, or the maximal instrument current limit was achieved (10 mA for Ojemann stimulator and 15 mA for Natus stimulator). In some cases with ADs, the current intensity was reduced by ~25%, pulse duration was increased to 0.5–1 ms, and the stimulation was repeated, in accordance with the dual-increment paradigm (Jayakar et al., 1992).

A picture naming task was used for language mapping, due to relatively better evidence for external validity among the available language tasks, and the assumption that salvaging cortical naming sites is protective against any type of post-operative aphasia (Hamberger, 2007). During motor mapping, stimulation-induced movements were ascertained by direct visualization.

2.4. FOS administration

The decision to pre-medicate with FOS before ESM and the prescribed dose were at the discretion of the attending epileptologist, due to lack of a standard practice. This decision was irrespective of the patient characteristics including seizure frequency or history of prolonged seizures. When used, FOS (50 mg phenytoin equivalents (PE)/ml) solution was intravenously infused at 2 mg-PE/kg/min or 150 mg-PE/min, whichever was slower, under cardio-respiratory monitoring.

2.5. Data extraction

Medical records of patients were reviewed to extract the following data: demographic (gender, handedness); pre-surgical (age of onset of seizures, AEDs, seizure frequency, full-scale intelligence quotient (FSIQ), presence and location of brain MRI lesion, language lateralization by verb generation paradigm on functional MRI, lateralization of seizure semiology, interictal and ictal scalp video EEG, interictal FDG positron emission tomography (PET), subtraction ictal single photon emission computed tomography (SPECT) co-registered to MRI (SISCOM), magnetoencephalography (MEG); surgical (cortical areas covered by subdural electrodes); and ESM information (age at the time of ESM, brain lobes stimulated, current thresholds for language inhibition and/or motor response). Whether the patient was re-started on regular AEDs before ESM was also documented. The histology of resected brain tissue was noted. Lateralization concordance of a pre-surgical modality was classified based on correspondence to the side of ESM. Extra-operative ECoG during ESM were reviewed again for study purposes.

2.6. Outcomes

Outcomes include proportion of patients with, and thresholds for, ESM-induced ADs, seizures, and functional responses. ADs were defined as rhythmic discharges (spikes, poly-spikes, sharp waves, or spike-waves) which were clearly distinct from pre-stimulation electrographic activity and occurred for ≥3 s immediately following stimulation (Aungaroon et al., 2017; Blume et al., 2004). ESM-induced seizures were defined as trains of ADs that evolved in terms of distribution, morphology, and/or frequency, and were accompanied by clinical manifestations.

Current thresholds were defined as the minimum stimulation current (mA) that resulted in a pre-defined endpoint including occurrence of a ≥3 s AD train, an ESM-induced seizure, or functional response. Specifically, the highest current which failed to elicit the response, was not used to define AD/seizure threshold. Language responses included semantic or phonemic paraphasic errors, aphasia, or anomia during the picture naming. It is known that speech difficulties during language ESM can be due to interference with cognitive and/or motor aspects of naming, and it may be difficult to distinguish the relative contributions of aphasia, dysarthria, and amnestic anomia. Hence, we regarded any of the above responses as suggestive of ESM language localization (Zea Vera et al., 2017). Motor responses were defined by occurrence of a clearly visible involuntary movement of facial, upper, or lower extremity (UE/LE) muscles. We documented language thresholds for frontal and temporal lobes; motor thresholds for face, UE, and LE; as well as an overall minimum language and motor threshold for each patient. Minimum threshold was defined as the lowest current that produced language inhibition or motor response in a given patient irrespective of the lobar location.

2.7. Statistical analysis

The groups of patients who were and were not pre-medicated with FOS were compared for the incidence and thresholds of ADs, ESM-induced seizures, and functional responses. These groups were also compared for baseline characteristics including demographic profile, relevant clinical features, lateralization and concordance of pre-surgical functional imaging modalities, presence of a lesion on pre-operative brain MRI, whether regular AEDs were restarted before ESM, and presence of a malformation of cortical development on post-operative tissue histology. Odds ratios (OR) and standardized mean differences (Hedge's "g") along with 95% confidence intervals (CI) were calculated respectively for categorical and continuous variables for each comparison. Statistical significance was determined by Fisher's exact test (categorical variables) and *t*-test for independent samples (continuous variables). Due to exploratory nature of the analysis, adjustment for multiple comparisons was not performed. Instead, we considered doing principal component analysis to come up with summary score(s) using linear combinations of outcome variables, which could be compared between groups. However, the non-random nature of the missing data (for example, patients who did not have an ESM-induced seizure were missing a value for seizure threshold) precluded clinically meaningful imputation, and hence, we could not use this approach. Univariate