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Impact of withdrawal of antiepileptic medication on the duration of focal onset seizures

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ABSTRACT

Purpose: To systematically evaluate the duration of focal onset seizures under medication withdrawal as a function of drug half-life.
Methods: Adults with drug resistant focal epilepsy and invasive electroencephalographic (iEEG) recording between 01/2006 and 06/2016 (n = 128) were identified. Patients with multifocal or unknown epileptic foci were excluded, as well as subclinical seizures, isolated auras, or status epileptic. Antiepileptic drugs (AEDs) were withdrawn upon admission. The seizure duration was determined based on the invasive EEG data, and the latency since start of the monitoring was noted in hours. A negative binomial mixed model was used to compare the seizure durations before and after a cut-off, which was set at 2.5 half-lives of the individual anticonvulsive medication as this is thought to separate therapeutic and ineffective drug levels.
Results: In total, 70 patients were included in the study and the duration of 672 seizures analyzed. On average, the patients were treated with 2.36 ± 0.78 AEDs. The individual cut-off of 2.5 half-lives was on average reached after 95.02 ± 80.18 h. The seizure frequency (321 vs. 351) and the rate of generalization (15.6% vs. 16.8%) was comparable before and after the individual cut-off point. The mean seizure duration was not statistically significantly prolonged after 2.5 half-lives by a factor of 1.168 for focal onset seizures (p = 0.090) and a factor of 1.091 for secondary generalized seizures (p = 0.545).
Conclusions: Although AED withdrawal increases the likelihood for epileptic seizures, it did not prolong the seizure duration, nor did it increase the rate of secondary generalization in our study.

1. Introduction

Presurgical evaluation in the epilepsy monitoring unit (EMU) is challenged by the need to record enough seizures in a limited number of days. Thus, it is well accepted to partially or totally withdraw AEDs in the EMU to precipitate seizures, more so as it is unlikely to influence the localizing significance of the recorded seizures [1–5]. AED withdrawal is typically associated with an increase in seizure frequency and generalization rate [6–9]. The increase in seizure frequency and generalized seizures correlates with the taper rate and is more pronounced for carbamazepine and oxcarbazepine than for other AEDs like phenytoin, valproate or lamotrigine [6,7,10]. Furthermore, the highest seizure frequencies are typically observed during the first days of EEG-video monitoring [6,7]. Thus, it was speculated that the quick change in AED dosage rather than the AED dosage itself is causal [5,11].

However, most withdrawal studies were performed nearly two decades ago, focusing on classical AEDs [2,3,11–14]. In the last years, there was a rapid development of new AEDs with different pharmacokinetics and mechanisms of action [15–19]. Those AEDs, though, were not available and thus not considered in former AED withdrawal studies. Further, the patient population admitted to EMUs changed in the meanwhile encompassing more and more non-lesional, multi-drug resistant epilepsy patients. And although parameters like seizure duration co-determine the seizure related health risk [20,21], the aspect of seizure prolongation under AED withdrawal was not systematically evaluated yet. Updated empiric data would be needed for a thorough risk appraisal but is as yet missing. Our study thus aimed to systematically evaluate the duration of focal onset seizures under medication withdrawal as a function of drug half-life in drug-resistant epilepsy patients admitted to invasive EEG-evaluation.

Abbreviations: AED, antiepileptic drug; ECoG, electrocorticography; EEG, electroencephalography; EMU, epilepsy monitoring unit; MRI, Magnet-Resonance-Imaging

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2. Methods

This study complies with the institutional review board-approved ethical guidelines of the University of Munich and all patients gave written informed consent to the scientific use of their clinically acquired, anonymized data.

2.1. Participants

A retrospective database search was performed at the Epilepsy Center of the University Hospital Munich to identify all adult patients with drug resistant focal epilepsy syndrome, who underwent presurgical evaluation including intracranial EEG-recording between 01/2006 and 06/2016 (n = 128). Only patients with available Magnetic-Resonance-Imaging (MRI) data and at least one clinical seizure recorded with video- and EEG were included in the study. Patients who experienced only subclinical seizures or isolated auras during the invasive presurgical evaluation were excluded (n = 5). Further exclusion criteria were multifocality (n = 44), unknown epileptic focus (n = 3), status epilepticus with undeterminable seizure pattern onset and/or ending, missing relevant clinical or electroencephalographic data (n = 2), and missing consent (n = 4). Seizures that occurred during electrical intracranial stimulation were not analyzed.

Epilepsy syndromes were classified in an interdisciplinary patient management conference based on the available EEG data, seizure semiology, electrical stimulation, neuropsychological test results, as well as functional and structural imaging data. Besides the epilepsy syndrome, we documented demographical data and the antiepileptic drugs (AEDs) used.

2.2. Half-life determination and AED withdrawal

All patients were on antiepileptic treatment upon admission. AEDs were withdrawn at the beginning of the EEG-video monitoring (EMU), i.e. after implantation of the intracranial EEG-electrodes and post-operative computed tomography (CT). Medication tapering followed three main principles: in patients with up to two AEDs, the medication was completely withdrawn within one day. In patients with three or more AEDs or history of status epilepticus, all but one AED were stopped on the first day and the remaining AED was tapered during the following one to three days. Lorazepam 2.5 mg was administered sublingually after each generalized convulsive seizure or a series of three or more focal onset seizures.

Medication half-life was assessed based on the respective summary of product characteristics. Of note, always the given upper limit was used in our study, i.e. 2.3 h for oxcarbazepine, 6.3 h for pregabalin, 7 h for gabapentin, 8 h for levetiracetam, 13 h for lacosamide, 15.2 h for primidone, 16 h for valproic acid, 20 h for carbamazepine as well as eslicarbazepine acetate, 21 h for topiramate, 33 h for lamotrigine, 36 h for clobazam, 40 h for clonazepam, 60 h for zonisamide and phenytoin, 105 h for perampanel, and 150 h for phenobarbital. If lamotrigine was given in combination with enzyme inducing AEDs like carbamazepine, phenytoin, phenobarbital, or primidon, its half-life was halved [22,23], whereas it was duplicated in case of combination with valproate. The half-lives of the individual AED combinations were set at the maximum half-life of the single AEDs used. For example, the half-life for the combination of levetiracetam (8 h) and zonisamide (60 h) was set at 60 h. To analyze the changes in seizure duration under AED withdrawal, we set a cut-off at 2.5 half-lives of the individual AED combination. After 2.5 half-lives, the AED concentration has theoretically dropped by more than 80% [24] and should thus differentiate between therapeutic and ineffective drug levels.

2.3. Electroencephalographic seizure duration

The seizure duration was determined based on the intracranial EEG-recordings, i.e. electrocorticography (EcoG) and stereo-EEG (sEEG). The EEG signal from the intracranial electrodes (AD-Tech Medical Instrument corporation, Racine, WI, USA) was recorded using XLTEK Neuroworks software and a XLTEK EMU128FS amplifier (Natus Medical Incorporated, San Carlos, CA, USA) with a sampling rate of 1024 Hz and 12–16 bit A–D conversion. In addition to the seizure duration, i.e. the time difference between EEG seizure pattern onset and cessation, the latency since start of the EEG-video-monitoring was noted in hours. Seizures with undeterminable seizure duration, like status epilepticus or seizures with transition to periodic lateralized epileptiform discharges (PLEDs), were not analyzed.

2.4. Statistical analysis

Mean and standard deviation were calculated for quantitative parameters. Mann-Whitney-U test was performed for group comparison of continuous data and two-tailed Fisher´s exact test was applied on categorical data. To analyze the length of epileptic seizures, a negative binomial mixed model was used. Age, lobe and the cut-off of 2.5 half-lives were used as fixed effects for calculations on focal onset seizures without generalization, as these parameters affect the duration of focal onset seizures (unpublished data). Similarly, for focal onset seizures with secondary generalization, age at disease onset, sign of four, and the cut-off of 2.5 half-lives were used as fixed effects. To account for the fact that multiple seizures per patient were recorded, a random intercept per patient was also part of the model. A p-value below 0.05 was considered statistically significant.

3. Results

3.1. Demographics and clinical characteristics

In total, 70 adult patients with unifocal epilepsy were included in the study. The cohort was characterized by an equal distribution between sexes. An identical percentage of patients was diagnosed with frontal or temporal lobe epilepsy, and a minority had a parieto-occipital lobe epilepsy. Left and right hemispheric epilepsy syndromes were similarly frequent. Mean age at monitoring was 36.47 ± 12.00 years. Further, patients reported a disease onset at the age of 16.03 ± 11.01 years, resulting in a disease duration of 20.31 ± 12.98 years with a minimum of two years and a maximum of 56 years. The majority was evaluated with stereo-EEG, whereas 21.4% had subdural electrodes (ECoG). A summary of the demographic and clinical data is given in Table 1.

On average, the patients were treated with 2.36 ± 0.78 AEDs, with the majority taking two (n = 36/70; 51.4%) or three (n = 23/70; 32.9%) AEDs. Only single patients had one (n = 7/70; 9.7%), four (n = 3/70; 4.3%), or five (n = 1/70; 1.4%) AEDs. Levetiracetam was most commonly used (51.4%), followed by lacosamide (31.4%) and valproic acid (24.3%). A complete list and frequency of AEDs used is given in Fig. 1.

Table 1
Demographics and clinical characteristics of the study cohort (n = 70).

Age at monitoring [years]	mean or n 36.47	stddv or % 12.00
Sex (male:female)	34:36	48.6%:51.4%
Epilepsy syndrome:	31	43.1%
FLE	31	43.1%
TLE	8	11.1%
POE	36:34	51.4%:48.6%
Hemisphere (right:left)		
Age at disease onset [years]	16.03	11.01
Disease duration [years]	20.31	12.98
Invasive EEG-evaluation (sEEG:ECoG)	41:29	3.33
Number of AEDs at admission	2.36	0.78

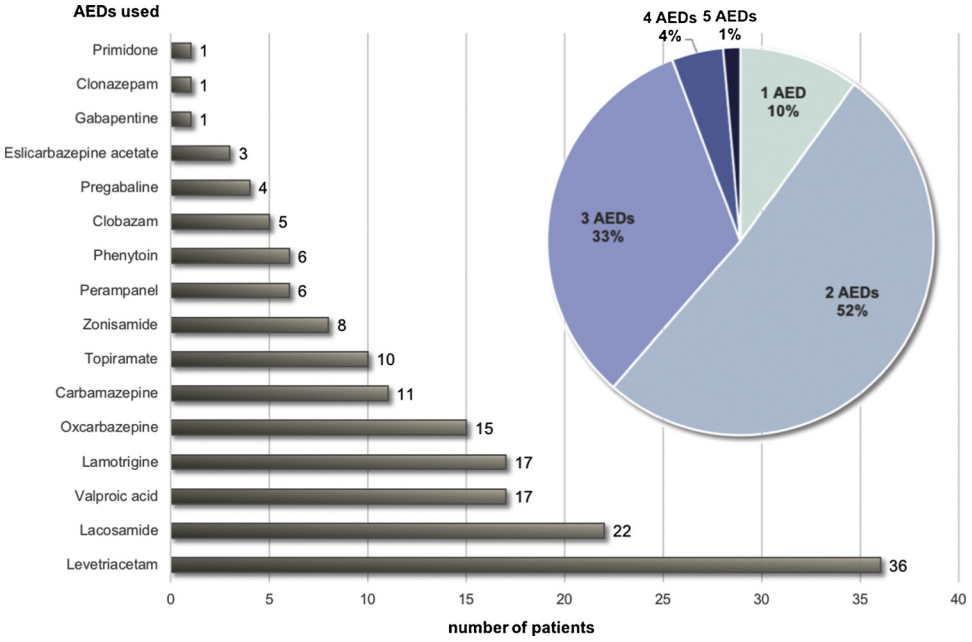

Fig. 1. Antiepileptic drugs (AEDs) at admission. The histogram gives an overview on the different AEDs used in study cohort at admission, whereby the length of the bar represents the number of patients taking the respective AED. The circle diagram visualizes the percentage of patients with mono- (1 AED) or combination therapy (2–5 AEDs).

3.2. AED half-life and seizure duration

The theoretical cut-off of 2.5 half-lives was on average reached after 95.02 ± 80.18 h (median 52.50 h)., i.e. after the fourth day of EEG-video monitoring. The shortest cut-off time of 5.75 h was calculated for oxcarbazepine monotherapy, whereas the longest of 375 h was given in one patient with a combination therapy of phenobarbital and lacosamide.

A total of 672 focal onset seizures were analyzed, whereof 16.2% (109/672) had a secondary generalization. Most of the seizures (405/672; 60.3%) occurred within the first four days of monitoring, whereof 41/672 (6.1%) occurred on the very first day, i.e. monitoring start (Fig. 2). A comparable amount of seizures manifested before (321/672; 47.8%) and after (351/672; 52.2%) the individual cut-off point of 2.5 half-lives. Although the evaluation of the rate of secondary generalization by day of monitoring suggested a gradual increase with maximum rates of 62.5% (5/8 seizures) on day 9 and 100% (4/4) on day 11 (Fig. 2), the rate of secondary generalization did not change before (50/321; 15.6%) versus after (59/351; 16.8%) the individual cut-off ($p = 0.677$). The 321 seizures that occurred before the cut-off point of 2.5 half-lives had an average duration of 78.79 ± 85.99 s, whereas a mean duration of 81.11 ± 75.93 s was measured for the 351 seizures that occurred after the cut-off point. In detail, focal seizures had an average duration of 78.38 ± 92.53 s ($n = 271$) before and 75.47 ± 73.95 s ($n = 292$) after the cut-off point, whereas seizures with secondary generalization had an average duration of 80.96 ± 33.34 s before and 109.07 ± 79.95 s after the calculate 2.5 half-lives (Fig. 3). Of note, 27/70 (38.6%) patients had seizures only after their individual cut-off point. In the multivariate model and adjusted for age and lobe or age at disease onset and sign of four the mean seizure duration was non-significantly prolonged after 2.5 half-lives by a factor of 1.168 for focal onset seizures ($p = 0.090$) and a factor of 1.091 for secondary generalized seizures ($p = 0.545$).

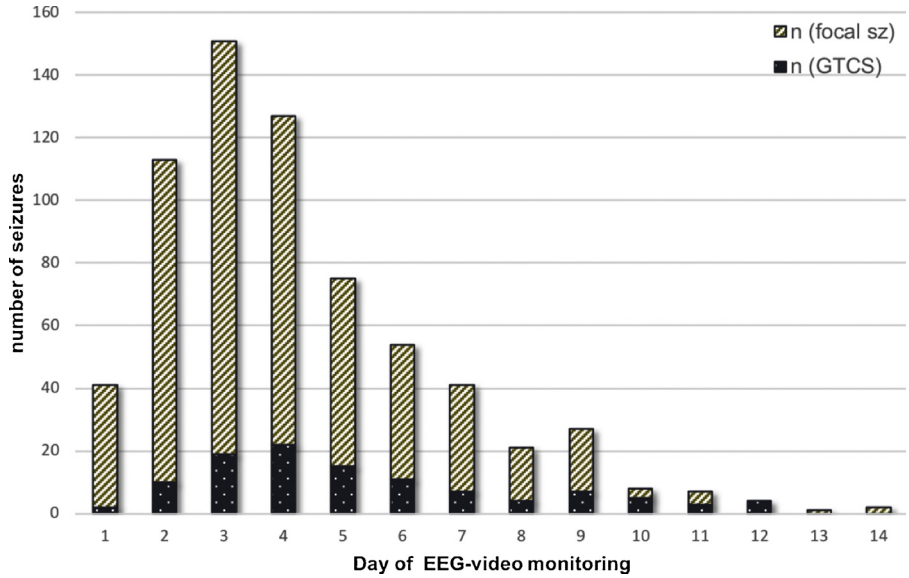

Fig. 2. Seizure frequency distribution. The stacked bars represent the number of focal onset seizures with (dotted bars) and without (striped bars) generalization per day of EEG-video monitoring. GTCS: generalized tonic-clonic seizure; sz: seizure.

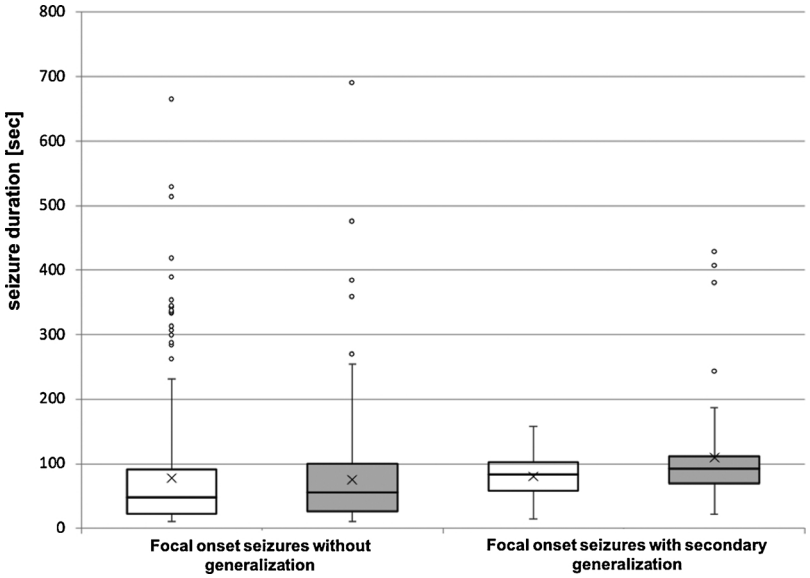

Fig. 3. Change of seizure duration under AED withdrawal. The boxplot diagrams represent the respective minimum value, the median, the mean (indicated with an x), the first and third quartile, as well as the upper 1.5 interquartile range and single outliers (circles). The transparent plots represent the duration before the individual cut-off of 2.5 half-lives, whereas the grey plots represent the seizure duration after this cut-off. In total, 271 or 292 focal onset seizures without generalization were analyzed before and after the cut-off, as well as 50 and 59 focal onset seizures with secondary generalization. No significant seizure prolongation was observed after the cut-off, using a multivariate model adjusted for age and lobe or age at disease onset and sign of four. AED: antiepileptic drugs.

4. Discussion

Although the likelihood of seizure occurrence increases upon AED withdrawal [6,7,14], we did not observe a seizure prolongation after a cut-off of 2.5 half-lives nor an increase in the generalization rate.

4.1. Seizure frequency and duration

The study cohort was representative for drug-resistant epilepsy patients admitted to invasive EEG-video monitoring, having a median disease duration of 18 years and receiving anticonvulsive polytherapy with up to five AEDs. By definition, anticonvulsive medication has only a limited effect in this group of drug-resistant epilepsy patients. Further, they are suspected to develop drug tolerance under repeated AED admission [6,25–29]. Both might contribute to the non-significant effect of AED withdrawal on seizure frequency and duration observed in our study cohort. The seizure frequency distribution, though, suggests a “rebound” phenomenon after AED withdrawal, as a high number of seizures occurred already within the first two days of monitoring (22.9%; day 1: 41/672 seizures; day 2: 113/672 seizures). Especially carbamazepine and oxcarbazepine have been associated with more severe rebound seizures then other AEDs like phenytoin or valproic acid [6,7]. On the first day of AED withdrawal, 15 patients of the study cohort experienced seizures, whereof 5 had carbamazepine and 3 oxcarbazepine. Thus, similar to the literature [7,12,30,31], a disproportionately high percentage of cabamazepine and oxcarbazepine treated patients, i.e. 33.3% (5/15) and 27.3% (3/11), had seizures already on the first day of monitoring. These rebound seizures might be explained by a reduction of seizure threshold below baseline during carbamazepine withdrawal, which is, of note, independent of carbamazepine plasma levels [32]. Besides the AED class, the AED taper rate is thought to be pivotal for the increase in seizure frequency and severity, whereby rapid withdrawal leads to more pronounced changes [7,8,10,12,14]. It was hypothesized that the increase in seizure frequency is related to change in AED dosage rather than to the dosage itself [11,13]. Accordingly, we observed an increasing seizure frequency within the first three days of monitoring after rapid tapering. Moreover, performing long EMU evaluations of up to 20 days and considering the individual AED half-lives, we did not observe an increase in seizure frequency throughout the monitoring stay.

Our study focused on the impact of AED withdrawal on the seizure duration, which was precisely determined using invasive EEG-recordings. Although commonly assumed, a seizure prolongation was not observed. Thus, AED tapering increases the likelihood of seizures, without influencing their duration or stereotypic evolution.

4.2. Generalization rate

The frequency distribution of secondary generalized seizures was comparable to the one observed for focal onset seizures without generalization. No change in the generalization rate was observed after 2.5 half-lives. Withdrawal of carbamazepine and oxcarbazepine is known to lead to higher generalization rates compared to phenytoin or lamotrigine [4,6,7,12,30]. Thereby, the frequency of generalized convulsive seizures is also related to the taper rate [30]. Cessation of carbamazepine treatment increases the frequency of previous, i.e. habitual seizures, but it does not lead to new seizure types [5]. Similarly, the duration of focal onset seizures with secondary generalization did not change during AED withdrawal.

4.3. Limitations

Our cohort represents real-life conditions in epilepsy-monitoring units with highly selected, drug-resistant patients admitted with combination therapy. To address the question of seizure prolongation under AED withdrawal, a simplified approach was used to estimate the individual cut-off between therapeutic and ineffective drug levels. The half-lives of active metabolites, though, were not considered and the observation duration of up to 20 days might still have been too short to fully capture the effect of dropping AED levels [5]. Administration of rescue medication or individual exceptions in the taper process could not be respected in the mathematical model. Further, serum drug levels were not systematically measured, but they would also not reflect drug efficacy as metabolites and brain-plasma differences would remain undetected and correlation with cortical excitability is missing [32–35]. In addition, the comparability of our finding with the literature is limited, as most patients were on combination therapy, including newer AEDs like zonisamide, eslicarbazepine acetate, perampanel, or lacosamide in 53% (37/70 patients). Those AEDs might have different withdrawal effects and were not available and thus not considered in former analyses which analyzed classical AEDs mainly administered in monotherapy [6,7,11–13].

5. Conclusion

Considering AED combinations and half-lives, AED withdrawal in

the EMU setting did not prolong seizure duration, nor did it increase the rate of secondary generalization in our study. However, we evaluated a selected group of drug-resistant epilepsy patients, thus our finding must be extrapolated with caution to patients with other types of epilepsy and different AED taper procedures.

Declaration of interest

None.

Conflicts of interest

None of the authors has any conflict of interest to disclose.

Ethical publication statement

We confirm that we have read the Journal´s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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