Epilepsy & Behavior 19 (2010) 176–181

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Review

Effect of antiepileptic drugs on the postictal state. A critical overview

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ARTICLE INFO

Article history:
Received 17 June 2010
Accepted 17 June 2010
Available online 7 August 2010

Keywords:
Epilepsy
Postictal dysfunction
Postictal state
Antiepileptic drugs
Modern antiepileptic drugs
Lamotrigine
Levetiracetam
Topiramate
Valproate
Zonisamide

ABSTRACT

Although postictal events contribute to seizure severity and thus affect quality of life, the effect of antiepileptic drugs (AEDs) on the postictal state is not well known. This review assesses the available evidence from randomized controlled trials on the effect of AEDs on postictal events. The instruments used in AED trials include postictal items of The Liverpool Seizure Severity Scale (LSSS) and Seizure Severity Scale (SSQ) and postictal recovery of electroencephalography (EEG) background activity. The effect of AEDs on postictal components of LSSS, if documented separately or at all, was either too small to be clinically significant (for lamotrigine) or not different from that of controls (topiramate, valproate). However, lacosamide showed improvement on the SSQ over placebo, and levetiracetam was associated with a speedier postictal recovery of EEG background activity compared with placebo. Although measuring the effect of AEDs on postictal state is of great clinical interest, the limited evidence found in this review suggests that further work is needed to evaluate current instruments used to assess AED-associated changes in postictal events.

1. Introduction

Even for patients with refractory epilepsy, seizures occupy only a tiny fraction of their lives compared with postictal events or interictal morbidity. Emotional sequelae of seizures contribute significantly to clinical depression [1]. Kwan and Brodie [2] suggested that postictal effects may explain, at least in part, persistent cognitive changes in some patients with epilepsy. It is thus of considerable clinical interest to evaluate the efficacy of antiepileptic drugs (AEDs) on postictal events. AEDs may be useful in the management of postictal events in several ways. Ideally, AEDs may prevent postictal events by rendering patients seizure free. But even in patients with uncontrolled seizures, AEDs may attenuate or shorten the postictal period. If the postictal period is shortened or less severe, the patients can resume activities rapidly and might consider the treatment successful, even though seizures do not cease altogether. Finally, AEDs may provide relief for psychiatric postictal dysfunction, for example, aggression, irritability, and depression [3]. It is therefore of great clinical interest to assess the effect of AEDs on postictal events. Any review on the effect of AEDs on the postictal state is, however, fraught with several difficulties. Postictal dysfunction is, by definition, self-limiting in most patients and resolves usually within hours or, at most, within a few days of a seizure [4]. As a consequence, studies of postictal outcome following AED treatment need to be timely and well controlled. Given the subjective nature of postictal dysfunction in many patients, objective tools for measurement are needed. The short duration of postictal dysfunction in most patients and its occurrence in only a minority of patients provide further challenges for trial design. Possible confounding factors for evaluation of postictal events by interviews are postictal memory deficits [5] and depression, which may influence reports of postictal outcome [1]. These caveats in mind, we briefly review the evidence available from well-controlled efficacy trials of AEDs to determine if AEDs affect the postictal state. We do not discuss here results of animal experiments on AED effects on postictal events or the use of AEDs for postictal psychosis and depression, which are covered separately in this issue [3,6]. For an extensive discussion of AEDs in general, see recent reviews (e.g., [7]).

2. Methods

We performed a literature search for studies separately reporting postictal outcome in randomized AED trials in epilepsy published from 1990 to 2009 in English, French, and German. In addition, we searched reviews, textbooks, and monographs for eligible publications.

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doi:10.1016/j.yebeh.2010.06.019

2.1. Instruments for quantification of AED effects on postictal dysfunction

In most studies on the effect of AEDs on postictal events, structured interviews were used to examine a change in perception of the postictal period as reported by patients, parents/guardians, or neurologists. Postictal events and duration are itemized in several scales for measuring outcome in AED trials [8]. In current use are several scales that assess postictal events in adults and in children. The items covered in the scales overlap [9].

2.1.1. The Liverpool Seizure Severity Scale

The Liverpool Seizure Severity Scale (LSSS) [10–12] is based on patients' perceptions of how seizures occur and an overview of the frequency of ictal and postictal phenomena. The scale is completed by patients as a self-rating of aspects of altered consciousness, aspects of recovery (e.g., cognition, falls, urinary incontinence, tongue biting, sleepiness), and time to recovery. The ictal scale has been reevaluated with a new scoring system [13]. The LSSS was developed on the premise that seizure severity comprises two main factors: patients' perceptions of control over their seizures (Percept Subscale, 12 items) and severity of ictal and postictal phenomena (Ictal Subscale, 6 items).

The postictal subscale of the LSSS includes several variables. Degree of postictal confusion is assessed as: very confused, fairly confused, slightly confused, and not at all confused. Duration of postictal confusion is quantified as <1 minute, 1–2 minutes, 2–5 minutes, and >5 minutes. Postictal headache and postictal sleepiness are categorized as always, usually, sometimes, or never. Time to full recovery is quantified as <1 minute, 1–5 minutes, 6–60 minutes, or >60 minutes [12]. Patients are asked for their perceptions of each item. It should be noted that the LSSS has been evaluated only for patients who have had at least one seizure in the 4 weeks preceding the interview [13]. More recently, the LSSS was revised to include the following postictal events after the most severe seizures: degree and duration of confusion, postictal headache, and postictal sleepiness (Table 1).

Most postictal items on the LSSS (except the time to recovery) were significantly associated with QOLIE-10 scores, as well as the various scales of the QOLIE-10. Likewise, all QOLIE-10 scales were significantly associated with overall LSSS scores. The correlation between seizure severity and frequency was insignificant. On multiple linear regression, both seizure severity and frequency were independently associated with QOLIE-10 scores. Although the study had methodological issues—many patients did not have a seizure in the 4 weeks preceding the LSSS interview as required for the LSSS—the authors concluded that seizure severity, including a number of postictal variables, is associated with quality of life and this association exists independent of seizure frequency [14].

Table 1
Postictal variables in the revised Liverpool Seizure Severity Scale (LSSS) [13].

4. After my most severe seizures:
I feel very confused (0)
I feel fairly confused (1)
I feel slightly confused (2)
I do not feel confused at all (3)
5. After my most severe seizures my confusion lasts for:
<1 minute (1),
1–5 minutes (2)
6 minutes–1 hour (3)
1–2 hours (4)
>2 hours (5)
I never feel confused (0)
7. After my most severe seizures:
I always have headache (0)
I usually have a headache (1)
I sometimes have a headache (2)
I never have a headache (3)
8. After my most severe seizures:
I always feel sleepy (0)
I usually feel sleepy (1)
I sometimes feel sleepy (2)
I never feel sleepy (3)

2.1.2. The National Hospital Seizure Severity Scale

The National Hospital Seizure Severity Scale (NHS-3) [15], formerly The Chalfont Scale [16], like the LSSS, is a structured interview in which the clinician rater assigns a score to seizures based on interference with patient function. Information is gathered from the patient and witnesses, if available. Eight questions are asked about: tonic–clonic movements, falling, injury, incontinence, altered consciousness, postictal impairment, and disruptive automatisms. The NHS3 includes one question on time to recovery after a seizure, that is, until the patient feels fully functional. It reads: "How long is it until the patient is really back to normal, i.e., feels fully functional, after the seizure? The response categories are: between 10 minutes and 1 hour, between 1 and 3 hours, and more than 3 hours" [8,15].

An adaptation of the NHS3 is being used in a multicenter study of epilepsy surgery [17]. In that well-defined group of patients with drug-resistant seizures, the NHS3 did not correlate well with health-related quality-of-life (HRQOL) scores. Analyses revealed, however, that the single item of recovery time broadly related to HRQOL domains, but the correlations were not strong ($r = -0.16$ to -0.30). This report highlights the importance of evaluating the postictal recovery period.

2.1.3. The Seizure Severity Questionnaire

Cramer et al. [1,9] recently developed the Seizure Severity Questionnaire (SSQ), a 22-item scale that categorizes seizures in the aura, ictal, and postictal phases, based on patient or other (usually family) interviews. The SSQ includes elements that may change with treatment effect and was developed to assess change in clinical trials. Patient-reported assessment of seizures is made both as (1) categories of seizure frequency based on whether seizures had occurred recently (<1 week ago, 1–3 weeks ago, 1–3 months ago) or not recently (4–12 months ago, 1–2 years ago, >2 years ago); and (2) as a patient-rated assessment [9]. The SSQ categorizes seizures into three phases: warning (aura), ictal activity, and postictal recovery. The recovery phase was further subdivided into three components: cognitive, emotional, and physical aspects of recovery, each rated for frequency, severity, and bothersomeness. Items were rated on a 7-point Likert scale: frequency—never (1) to always (7); severity—very mild (1) to very severe (7); bothersome— no bother (1) to very bothersome (7), with lower scores representing lesser impact. Severity and bothersomeness components had good cross-sectional reliability (rtt = 0.75 and 0.89, respectively). The Overall Score, which represented the subject's overall impression of the severity and bothersomeness of all seizures (cross-sectional reliability rtt = 0.69; test–retest rtt = 0.65), also was reliable as assessed with the κ statistic. These analyses used the "Seizure Recovery" score as the main variable describing recovery from the predominant type of seizure experienced by the respondent. Other SSQ subscale scores used in these analyses included individual scores for Cognition, Emotional, and Physical recovery components, encompassing frequency, severity, and bother. Seizure Recovery was an average of the Cognition, Emotional, and Physical scores. Overall Frequency, Overall Severity, and Overall Bother were averages of recovery components for cognitive, emotional, and physical aspects of seizures. Global Severity and Global Bother were individual items that were averaged to create the Global Impact score [9].

Prompted by comments from patients and families that the recovery period was the most problematic aspect of seizures, the SSQ expanded inquiries into recovery from cognitive, emotional, and