Seizure 27 (2015) 25–29

Contents lists available at ScienceDirect

Seizure

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

Effect of reduction of antiepileptic drugs in patients with drug-refractory epilepsy☆,☆☆

Deepa Dash [a], Vikas Aggarwal [a], Rupa Joshi [b], Madakasira Vasantha Padma [a], Manjari Tripathi [a,*]

[a] Department of Neurology, All India Institute of Medical Sciences, New Delhi 110029, India
[b] Department of Pharmacology, All India Institute of Medical Sciences, New Delhi 110029, India

ARTICLE INFO

Article history:
Received 11 June 2014
Received in revised form 19 February 2015
Accepted 23 February 2015

Keywords:
Antiepileptic drugs
Reduction
Drug refractory epilepsy
Epilepsy monitoring unit

ABSTRACT

Purpose: The present study was conducted with the aim of evaluating the effects of reducing the number of antiepileptic drugs (AEDs) administered to patients with drug-refractory epilepsy (DRE) during their admission and document any change in seizure frequency in subsequent follow up.
Methods: A total of 962 patients with DRE who were admitted to the neurology wards waiting for connection to video EEG were recruited for this prospective study. After their admission to the neurology ward, modifications in the number and dosage of AEDs were done with a target of a maximum of three AEDs in every patient. Drug tapering was done using a standardized protocol. The primary outcome was the change in seizure frequency in the follow-up period of 6 months. Secondary outcome measures were the adverse event profile (AEP) and the quality of life (QOL).
Results: Of the 1134 patients screened, 962 patients gave consent to participate in the study. The mean number of AEDs received by each patient was 4.24. After the tapering following a standardized protocol each patient received a mean of 2.65 AEDs per patient. In 82.70% patients with DRE, there was either a reduction or no change in seizure frequency in the subsequent 6 months follow up. There was a significant reduction in the AEP score after the reduction in the number of AEDs ($P = 0.001$).
Conclusion: Our study proves that optimization of reduction of the number of AED's in patients with DRE leads to reduction or no change in seizure frequency with a significant decrease in adverse effects.

1. Introduction

Despite recent advances in neuropharmacology, around 20–30% of persons with epilepsy (PWE) have DRE. Most of them are on multiple AEDs with the hope of achieving good seizure control [1]. Although there is evidence that there is a decreased chance of seizure control after failure of an adequate trial of first-line AEDs, polytherapy is rampant in clinical practice.

Polytherapy increases the side effects of medications through drug–drug interactions, impacts cognition, mood, and overall behavior in PWE. It also leads to reduced compliance and makes monitoring more difficult. Moreover, some AEDs are known to aggravate pre-existing seizures and trigger new seizure types [15].

There is evidence from previous studies that reduction of one or more AED is possible without an increase in seizure frequency in patients with DRE [2,3,14].

Uncontrolled epilepsy leads to an increase risk of death, cognitive and behavioral dysfunction and socioeconomic disadvantage. All attempts should be made to make the patient seizure free, but not at the cost of a poor QOL. The present study aims to evaluate the effects of reducing the number of AEDs administered to patients with DRE during their stay in the neurology ward and the likelihood of decrease and non-increase in seizure frequency in subsequent 6 month follow up.

2. Methods

A total of 1134 patients of DRE who were being evaluated in the EMU from 2003 to 2012 were identified and were screened for the study. Out of them 962 were recruited for this prospective study

☆ The abstract was presented as a poster in Neurological Society of India Annual Conference, 2013, Mumbai and a part of the study in the Asian & Oceanian Epilepsy Congress.
☆☆ The source(s) of support in the form of grants, equipment or drugs: Work done by Center of Excellence for epilepsy, funded by the department of biotechnology, BT/01/09/08 India.
* Corresponding author at: Department of Neurology, All India Institute of Medical Sciences, Room No. 705, Neurosciences Centre, New Delhi 110029, India. Tel.: +91 26594494/588248; fax: +91 26588248/166.
E-mail address: manjari.tripathi1@gmail.com (M. Tripathi).

http://dx.doi.org/10.1016/j.seizure.2015.02.025
1059-1311/

after informed written consent. The study was approved by the institute ethical committee. Informed consent was sought from the patient or and caregiver after explaining the details of the study in the language the patient could understand, by an epilepsy fellow. Patients and or their caregivers were also explained the possible risk of increase in seizure frequency during the study. Out of the 172 patients who declined to the study, 124 did so due to their inability to come for a timely follow up (As they were residing in remote rural areas) and 48 declined after they were explained the possible risk of increase in seizure frequency during the study. DRE was defined as failure of adequate trials of two tolerated and appropriately selected and used AED schedules (in combination) to achieve sustained seizure freedom.

Inclusion criteria consisted of patients with DRE being treated with at least three or more AEDs with seizure frequency of at least 1 per month. Frequency of seizures was determined as an average of the previous 6 months. PWE with catastrophic epilepsies like Rasmussen encephalitis, malignant brain tumors and severe central nervous system infections like fungal infections, prion diseases, progressive multifocal leukoencephalopathy were excluded.

Patients were enrolled into the study after admission to neurology wards while they were waiting for connection to VEEG either for characterization of seizure type or as a work up for epilepsy surgery. Clinical, demographic, diagnostic evaluation and treatment-related details were recorded in all patients after an interview in a structured proforma. Details regarding the age of onset of seizures, the semiology of seizures, frequency of seizures, any history of status epilepticus was recorded. Treatment details included the number of AEDs prior to the monitoring, their combinations, dose adequacy, AED levels and side-effect profile. After their admission AED's were tapered gradually. The tapering of AEDs was done after admission in neurology wards prior to transfer to the EMU. A slow tapering protocol was done after reviewing the history and response to each AED- in situations where a definite history of response to a particular AED was seen, then that AED was not tapered. Those AEDs which were enzyme inducing and had produced no response were tapered first. In situations where it was not clear if there was any AED which has produced a response an enzyme inducing AED/those AEDs which were producing an adverse effect were tapered first. Dosage of tapering was only 25% of the dosage of AED per day. Phenobarbitone was reduced at a slower rate of 10% of the dosage. Benzodiazepines were not tapered so as to not provoke withdrawal seizures. After the patients underwent VEEG recording and an adequate number of seizures were recorded, the AED's were restarted. Modifications in the number and dosage of AEDs were done and the target was to keep the patient on a maximum of three AEDs. These would be the ones to which the patient had good response as per routinely maintained seizure charts and diaries and caregivers information. The choice of drugs was based on the treating epileptologists (MT) review, to be either that which was producing maximum side effects or was ineffective. Serum drug levels were done in all patients and drug dosage titration was done according to the drug levels. The primary outcome was the change in seizure frequency in the follow-up period of 6 months after reduction of the number of AEDs. Seizure frequency was determined from a seizure diary completed by the patient or caregiver, which was reviewed at routine monthly clinic visits. Secondary outcome measures were the AEP and the QOL. Adverse effects (AEs) were identified by the AEP questionnaire comprising of 21 questions. The AEP score has been widely used in epilepsy research [4–8]. The frequency of occurrence of each AE in the previous 4 weeks was rated on a 4-point digital scale (4 = frequent, 3 = sometimes, 2 = rarely and 1 = no occurrence). The total score, as a sum of the individual AED rating, indicates the total burden of AED's adverse effect. The patient AEP score was calculated at baseline and again after 6 months of the reduction of an AED.

We used Hindi translation of QOLIE-10, which is a self-administered questionnaire. It comprises of 10 questions about health and daily activities, one question about how much distress the person feels about problems and worries related to epilepsy and a review of what is most bothersome. The responses of the questionnaire were recorded. We also determined Cronbach's alpha, a marker of reliability to indicate how closely related a set of items are as a group. A relative coefficient of 0.7 or higher is considered acceptable in most situations. We found a reliability coefficient of 0.94. Further, all domains of QOL correlated well with each other indicating that these domains were interlinked. The follow-up assessment was done by a neurologist (VA) and pharmacologist (RJ) blinded to the patient treatment protocol. The seizure frequency and AEP score at 6-month follow up was compared to the baseline frequency.

3. Results

3.1. Subject characteristics

Of the 962 patients, 595 (61.8%) were males and 367 (39%) were females. The mean age at the time of presentation was 19.97 ± 11.37 years. Most of the patients (884, 93.84%) were under 40 years and 270 patients (28.66%) were under 10 years of age. The mean duration of epilepsy was 7.21 years (range: 1–28 years) and in most the duration of epilepsy was under 10 years (762 patients, 80.89%). The mean age of onset of epilepsy was 12.76 years with a range of 0.6–59 years. The etiology and seizure types are tabulated in Table 1.

3.2. Seizure frequency after reducing the number of AED

The mean number of AEDs received by each patient was 4.24 with a range of 3–6 AEDs. Most of the patients (58.38%) were receiving 4 AEDs while only 15 patients (1.59%) were on 6 AEDs. The average duration of stay of patients in the EMU was 5.4 ± 2.1 days. The total duration of stay of patients in hospital was 11.2 ± 3.2 days. After the tapering each patient received 2–3 AEDs with a mean of 2.65 AED per patient. The number of patients exposed to an individual AED has been depicted in Table 2.

Table 1
Etiology and seizure types.

Etiology	Number
Etiology of seizures	
Mesial temporal sclerosis	226 (24.0%)
Perinatal hypoxia	225 (23.9%)
Cortical dysplasia	198 (21.0%)
DNETs	56 (5.9%)
Gliosis secondary to infarction	45 (4.7%)
Post traumatic gliosis	43 (4.5%)
Gangliogliomas	41 (4.3%)
Post Infectious	32 (3.3%)
No substrate	96 (10.2%)
Types of seizures	
Focal dyscognitive seizures	607 (63.1%)
Focal motor seizures	34 (0.3%)
Focal sensory	6 (0.6%)
Focal progressing to bilateral convulsive-	28 (2.9%)
Drop attacks	192 (2.0%)
Myoclonus	23 (2.3%)
Multiple seizure types	31 (3.2%)
Reflex epilepsy (sound, touch, eating)	21 (2.1%)
Generalized tonic	16 (1.7%)
Clonic	1 (0.1%)
PNES plus focal seizures	3 (0.3%)