Epilepsy & Behavior 27 (2013) 342–345

Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

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

Effects of antipsychotic drugs on the duration of interictal psychotic episodes in patients with epilepsy

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ARTICLE INFO

Article history:
Received 2 January 2013
Revised 19 February 2013
Accepted 24 February 2013
Available online 27 March 2013

Keywords:
Epilepsy
Interictal psychosis
Duration of psychotic episodes
Treatment
Antipsychotic drugs
First-generation antipsychotics
Second-generation antipsychotics

ABSTRACT

Treatment protocols for interictal psychosis (IIP) of patients with epilepsy have not yet been established. We aimed to clarify the effects of antipsychotic drugs (APDs) on duration of IIP episodes.

We studied 393 IIP episodes in 200 patients with epilepsy in accordance with our empirical treatment protocol. The duration of all the episodes and APD treatments were reviewed. Antipsychotic drugs were used in 338 episodes and not used in 55 episodes (non-APD group). The APDs used in the treatment of IIP episodes were divided into the following three groups: first-generation APDs (FAPD, n = 252), second-generation APDs (SAPD, n = 44), and the combination of first- and second-generation APDs (CAPD, n = 42). The non-APD group showed a significantly shorter episode duration than did the APD group ($F = 6.05$, $p = 0.014$). Among the 3 APD groups (FAPD, SAPD, and CAPD), there was a significant difference in duration of IIP episode ($F = 8.65$, $p = 0.000$). Whereas the duration of episodes was significantly longer in the CAPD group than in the other two groups, it was not significantly different between the FAPD and SAPD groups. Our findings further to clarify the nature of IIP and add further perspectives on treatment protocols for IIP.

1. Introduction

Every year, 0.3–0.4% of adults with epilepsy develop interictal psychosis (IIP) [1,2]. These psychotic episodes often have as much negative impact on their quality of life as their seizures. Despite the long history of clinical studies of IIP, treatment strategies for IIP have not been well established [3]. Although antipsychotic drugs (APDs) are indispensable for the treatment of IIP, there has been little evidence for their efficacies.

We previously reported that IIP episodes can last longer than one month in the vast majority of the cases (ranging from days to years), and their durations were often associated with individual vulnerabilities to psychosis [4]. In the current study, with a large number of IIP episodes (73 new episodes were added to the 320 episodes previously reported), we further analyzed whether the duration of IIP varied using different APDs.

2. Methods

2.1. Definition of IIP

Psychotic episodes were defined as the presence of hallucinations, delusions, or a limited number of severe behavioral abnormalities in accordance with the ICD-10 Classification of Mental and Behavioral Disorders [5]. Interictal psychosis is defined as (1) psychotic episode occurrence (2) under clear consciousness (3) without a decisive antecedent seizure or cluster of antecedent seizures and (4) with their first emerging psychosis after the development of epilepsy [6].

2.2. Subject selection

Since January 1980, 393 IIP episodes in 200 adults with epilepsy were consecutively registered onto our study database, which was established for multicenter studies involving epilepsy outpatient clinics of the National Centre Hospital for Mental, Nervous, and Muscular Disorders, Musashino Kokubunji Clinic, Adachi Mental Clinic, Jozen Clinic, Tenshi Hospital, and Asai Hospital. The majority (n = 320, 81.4%) of the IIP episodes were previously analyzed with reference to other clinical aspects [4]. Our patients with epilepsy and psychosis attended

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http://dx.doi.org/10.1016/j.yebeh.2013.02.025

their clinics every two to four weeks in accordance with the national health-care guidelines [4]. The patients' backgrounds [9] and the decision-making process for the treatment for IIP episodes [4,7,8] were described in detail in our previous articles. All IIP episodes were assessed and treated by consultant psychiatrists qualified in clinical psychiatry and epileptology. Prescribing APDs (timing, kinds, and dosages) was at the discretion of the treating consultant who made a decision based on clinical demands in accordance with the treatment strategy for IIP described above [7,8]. Butyrophenones, benzamides, and serotonin–dopamine antagonists were often used as first-line APDs. When psychomotor excitement, anxiety, or insomnia were conspicuous, APDs with sedative properties (e.g., phenothiazines) were also used. Other psychotropic non-APDs drugs, e.g., mood stabilizers, benzodiazepines, and antidepressants, were used. Patients with progressive brain diseases, dementing processes, or substance misuse were excluded. The study was approved by the relevant ethics committees of the participating institutions.

2.3. Duration of IIP episodes

Psychotic symptoms that lasted for 12 h or longer were assessed. Episodes lasting 12 to 36 h were counted as 1 day. Episodes lasting longer than a week were measured by weeks. Episodes of excitement, disinhibition, or negative symptoms without distinct psychotic symptoms were not included. In some cases where the termination of IIP episodes could not be confirmed, the period between the onset of IIP and the last assessment was operatively regarded as the duration of the episode.

2.4. Investigation items

The following patients' characteristics were evaluated: 1) age at onset of epilepsy; 2) years of follow-up (from the first visit to the institutes after the development of IIP until 31 December 2011); 3) type of epilepsy (based on ictal semiologies and clinical examinations in accordance with the International Classification of Epilepsies [10]); 4) lateralization of epileptiform discharges: left, right, and bilateral (including symmetrical bilateral discharges, independent discharges but equivalent frequency bilaterally, and no epileptiform discharges observed in GTCS on awaking) [11]; 5) the presence of mesial temporal sclerosis (MTS) in brain MRI with qualitative analysis [12]; 6) any psychotic disorders in their first degree relatives [13]; and 7) intellectual function (mental retardation [full scale IQ (FIQ) $\leq$ 70], borderline intellectual functioning [FIQ 71–84], and normal [FIQ $\geq$ 85] in accordance with the DSM 4 [14]).

The following episode-specific factors were recorded: 1) age at the episode; 2) frequency of habitual seizures over a 3-year period or longer immediately before the episode (classified into six categories: daily, weekly, monthly, yearly, less than yearly, and seizure-free for more than 3 years) [11]; 3) the number of antiepileptic drugs (AEDs) taken; 4) AED regimen (the number or dosage) within one month before the onset of the episode (categorized into increased, decreased, increased/decreased, or unchanged); 5) APD treatment (any APDs taken before or after the beginning of the episodes); and 6) APD time-lag (the duration between onset of the IIP episode and start of APD treatment).

Types of APD were classified as first generation (FAPD: butyrophenones, phenothiazines, benzamides, and others) and second generation (SAPD: serotonin–dopamine antagonists, dibenzothiazepines, multi-acting receptor-targeted antipsychotics, and dopamine system stabilizers). Dosage of APD was converted to chlorpromazine equivalent (CE) mg/day [15,16].

2.5. Analysis

Analysis of variance (ANOVA) was used to examine the differences in duration of the IIP episodes by each condition. Pearson's or Spearman's rank correlation coefficients were used to examine the relationship between duration of the IIP episode and linear/rank-ordered clinical factors. The significance level was set at <0.05. Bonferroni correction was used to avoid risk of multiple comparisons. SPSS 14.0 [SPSS Inc., Chicago] was used for all statistical analyses.

3. Results

3.1. Episodes and patient profiles

Three hundred ninety-three IIP episodes of the 200 patients with epilepsy (107 men and 93 women) were treated in our institutions. The total mean follow-up period of the 200 patients was 15.0 years (SD: 10.4, median: 13, range: 1–57). The patients had a mean of 2.0 IIP episodes (SD: 1.4, median: 2, range: 1–8); 96 patients had single IIP episodes, and 104 patients had multiple IIP episodes (12 patients developed IIP episodes 5 times or more).

The mean age at onset of the IIP episode was 31.0 years (SD: 10.4, median: 28, range: 14–66), and the mean interval between onset of epilepsy and that of the IIP episode was 18.9 years (SD: 9.3, median: 18, range: 0–55). Seizure frequencies at the onset of the IIP episode were as follows: no seizures in 80 patients, less than yearly in 29, yearly in 97, monthly in 89, weekly in 76, and daily in 22. The mean number of AEDs taken was 2.2 (SD: 1.3, median: 2, range: 0–7).

The clinical characteristics of the different treatment procedures are shown in Table 1. Of the 393 IIP episodes, 55 episodes were treated without any APDs throughout the episode (non-APD group), and the remaining 338 episodes were treated with APDs during the course of the episodes (APD group). There was no significant difference between the non-APD and APD groups except for the duration of

Table 1
Clinical characteristics between the non-APD and APD (FAPD, SAPD, and CAPD) groups.

	Non-APD (n = 55)	APD (n = 338)	FAPD (n = 252)	SAPD (n = 44)	CAPD (n = 42)
Age at the IIP episode (years)	31.7 (12.1)	30.9 (10.0)	31.4 (0.6)	29.8 (9.2)	28.9 (7.2)
Duration of epilepsy (years)	15.7 (10.5)[a]	19.5 (9.0)	19.0 (9.2)	21.0 (9.2)	20.4 (7.2)
Seizure frequency	6/3/11/16/16/3	74/26/86/73/60/19	55/21/64/51/47/14	7/3/14/12/6/2	12/2/8/10/7/3
Number of AEDs at the IIP episode	2.3 (1.2)	2.2 (1.3)	2.2 (1.4)	2.3 (0.9)	2.2 (1.3)
APD time-lag (weeks)	(–)	10.1 (29.1)	10.1 (26.7)	9.6 (25.0)	10.5 (48.3)
Number of APDs	(–)	1.5 (0.7)	1.4 (0.6)	1.1 (0.3)	2.4 (0.9)[b]
Max dosages of APD (CE mg/day)	(–)	470.7 (533.6)	408.1 (478.8)	395.5 (411.0)	925.4 (719.1)[b]

The figures above are the mean (SD) except for the seizure frequency.
Seizure frequency was categorized as the following 6 ranks: seizure-free for 3 years or more/less than yearly/yearly/monthly/weekly/daily.
Antipsychotic drug time-lag is the duration between onset of the IIP episode and start of APD treatment.
[a] The non-APD group had a significantly shorter duration of epilepsy than did the APD group ($F = 8.12$, $p = 0.005$).
[b] The CAPD group took a significantly larger number of APD ($F = 52.1$, $p = 0.000$) and higher dosages of APD ($F = 19.3$, $p = 0.000$) than did either the FAPD or the SAPD group.