



Do antipsychotic drugs increase seizure frequency in epilepsy patients?

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Abstract

To investigate whether addition of antipsychotic drugs (APD) would increase seizure frequency in epilepsy patients who were already treated with anti-epileptic drugs (AED), we compared a one-year seizure control outcome in 150 epilepsy patients with APD treatment for psychiatric conditions and 309 epilepsy patients without APD treatment matched for ages at epilepsy onset and the baseline evaluation and types of epilepsy. The seizure frequency was recorded at the baseline (immediately before the start of APD) and after the 1st, 3rd, 6th and 12th months. The seizure outcome at each of the four follow-up points was compared with the baseline. The seizure outcome was compared between the two groups as a whole and according to the types of epilepsy (idiopathic generalized and partial epilepsies). In the APD group, the seizure outcome was also analyzed according to the types of APD (first and second generation APD and combination of first and second generation APD) and the types of psychiatric conditions (psychosis and non-psychosis). The seizure outcome was significantly better in the APD group than control group at all the four follow-up points. According to the epilepsy types, the improvement in the seizure outcome was only observed in the patients with partial epilepsy. Of the APD group, there was no significant difference in the seizure outcome according to the types of APD or the psychiatric conditions. In epilepsy patients who are already treated with AED, APD treatment seems safe in seizure control outcome for treatment of psychiatric conditions.

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1. Introduction

Patients with epilepsy often exhibit psychosis, psychomotor excitements or related conditions. The prevalence of psychiatric disorders in epilepsy patients is significantly higher than in the general population (Gudmundsson, 1966). As in functional psychosis in patients without epilepsy, antipsychotic drugs (APD) are often used for the treatment of psychiatric conditions in those with epilepsy (Karouni et al., 2010; Kerr et al., 2011; Adachi et al., 2013). APD have long been considered as proconvulsants (Itil and Soldatos, 1980; Oliver et al., 1982; Haddad and Sharma, 2007; Kumlien and Lundberg, 2010). Possibilities of the increase in seizure frequency have sometimes prevented physicians treating epilepsy patients with APD although there is little evidence that patients who were taking therapeutic dosages of anti-epileptic drugs (AED) exhibit seizure aggravation with the treatments of APD (Ojemann et al., 1987; Alldredge, 1999; Gross et al., 2000). APD were found to lower seizure threshold in experimental conditions (Oliver et al., 1982; Melduram, 1988); de novo seizures after the administration of APD were mainly reported in patients in functional psychosis who were not treated with AED (Alper et al., 2007; Kumlien and Lundberg, 2010).

Patients with intractable epilepsy sometimes exhibit seizure aggravation during a course of the illness (Okazaki et al., 2011). Such aggravation may happen at the time of treatment with APD for their psychiatric and/or behavioral difficulties. Since the seizure aggravation is often caused by inter-related clinical factors (e.g., insomnia, fatigue, and non-compliance with AED) (Okazaki et al., 2011), it is sometimes difficult to attribute the aggravation of seizures into only the administration of APD. One way of examining the effects of the APD administration on seizure frequency is to compare patients with and without treatment of APD in a controlled manner, which has been scarce so far. In addition, our knowledge on the long-term seizure prognosis while treated with APD is limited and needs to improve because mental and behavioral problems in epilepsy patients often persist; thus long-term APD treatment is required in many cases (Adachi et al., 2013).

In this study with a large cohort of epilepsy patients who were already treated with AED, we compared seizure frequency for a one-year follow-up period between patients who recently started on APD and those without APD treatment in order to investigate effects of adding APD on seizure frequency.

2. Experimental procedures

2.1. Subjects

We reviewed consecutive records of 150 epilepsy patients who started taking APD (APD group) in the period between April 1, 1993 and December 31, 2011 at the National Center Hospital, Adachi Mental Clinic, Jozen Clinic, Tenshi Hospital, Asai Hospital, or Musashino Kokubunji Clinic. The interval of regular clinical reviews ranged from one week to three months in accordance with the national treatment guidelines; the frequency of contacts depended on the patients' conditions and needs. All the patients suffered from either partial epilepsy or idiopathic generalized epilepsy. All of them also had various psychiatric symptoms, including hallucinations,

delusions, psychomotor excitements, and/or challenging behavior, for which they were treated with APD. None had a progressive neurodegenerative disease, a developing brain mass lesion requiring surgical treatments, substance misuse nor a dementing process. Consultant neuropsychiatrists qualified in both epileptology and psychiatry treated these patients.

We also reviewed clinical records of 309 epilepsy patients who did not take APD during the follow-up period. These were extracted from our multi-institutional epilepsy database (Adachi et al., 2012; Hara et al., 2013), matched for ages at onset of epilepsy and at the time of the baseline evaluation, duration of epilepsy, and type of epilepsy by a study coordinator (NA) blind to the other clinical details, including seizure frequency and AED taken.

The treatment strategies for the use of AED and APD were determined by the patients' attending consultant neuropsychiatrists following our consensus guideline of psychiatric treatment for epilepsy patients with psychiatric symptoms (Onuma, 1987; Adachi, 2005). The regimen and dosage of APD were set in accordance with the psychotropic drug prescription standards for Japanese patients (Toru, 2001).

2.2. Study design

The design of this comparative study is similar to that in our previous study of effects of antidepressants on seizure frequency (Okazaki et al., 2011). We set five evaluation points during the one-year follow-up period: baseline, the end of the 1st, 3rd, 6th and 12th months. The baseline was immediately before the start of APD treatment in the APD group and at the matched time-point in the control group. The consultant neuropsychiatrists evaluated following items at the baseline and the four follow-up points in every patients. This study was approved by the Ethics Committees of the institutions participated.

2.3. Demographic and clinical items

At the baseline evaluation, the following demographic and clinical variables were noted for both the APD and control groups: 1) sex, 2) age at the evaluation (=age at the start of APD), 3) age at onset of epilepsy (time of their first afebrile seizure), 4) duration of epilepsy (the interval between ages at onset and at the evaluation, 5) type of epilepsy (idiopathic generalized epilepsy (IGE) or partial epilepsy (PE)) based on ictal semiologies, electroencephalograms and neuroimaging in accordance with the International Classification of Epilepsies (Commission on Classification and Terminology of the International League Against Epilepsy, 1989).

2.4. Frequency of seizures and epilepsy treatment

At the baseline and subsequent follow-up time-points, the following two items were recorded: 6) frequency of seizures, 7) the number and dosage of AED taken as an index of AED treatment.

The classification of seizure frequency is shown in more detail elsewhere (Adachi et al., 1998). In brief, it was classified into six categories at each evaluation time-point: no seizure for 3 years or longer, seizure every few years, yearly, monthly, weekly or daily. Seizure diaries recorded by the patients and/or carers were used where necessary. Seizure outcome was then calculated as a change at each evaluation point against the baseline and defined in three categories: increased, unchanged, or decreased.

2.5. APD treatment and psychiatric condition

For the APD group only, the additional two items were evaluated: 8) types and dosage of APD administered, 9) psychiatric diagnosis for the APD treatment in accordance with the ICD-10 Classification of Mental and Behavioural Disorders (World Health Organization, 1992)

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