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The effect of perampanel on aggression and depression in patients with epilepsy: A short-term prospective study

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ABSTRACT

Purpose: Using specialized tools, we assessed patients receiving perampanel (PER) to investigate its effects on aggression and depression, as well as the impact of other concomitant antiepileptic drugs (AEDs) on those conditions.

Method: Seventy-seven patients with epilepsy were initially enrolled, then examined at entry and 12 weeks later (endpoint). At both examinations, assessments were performed with the Buss Perry Aggression Questionnaire (BAQ) and Neurological Disorders Depression Inventory for Epilepsy (NDDI-E). Ultimately, 59 patients completed the study.

Results: Total BAQ ($p = 0.013$) and NDDI-E ($p = 0.000$) scores at the endpoint were significantly increased in comparison with those at entry. Analysis with 4 subscales showed increases in both verbal and physical aggression, while multivariate analysis revealed that concomitant AED administration did not have a significant impact on the increase of BAQ or NDDI-E score. A dose-dependent effect of PER was confirmed in BAQ, but not NDDI-E results. PER was discontinued due to adverse psychiatric effects in 3.9% of the patients.

Conclusions: The present findings indicate that PER increases assessment scores indicative of aggression as well as depression. No additional aggression-augmenting effect was seen with concomitant AED administration.

1. Introduction

A variety of psychiatric symptoms are encountered in patients with epilepsy (PWE), which are now widely recognized to have effects more important than seizure frequency and may also be a more powerful determinant of quality of life in that population [1]. There is a large variety of factors associated with psychiatric symptoms in PWE. For effective treatment, it is important to first disentangle the amalgamated complex and focus attention on more potent determinants, while some antiepileptic drugs (AEDs) must be considered as causative factors.

Although perampanel (PER) has been shown to be a potent antiepileptic drug for generalized as well as focal to bilateral tonic clonic seizures, likely because of the unique properties of the anti-AMPA receptor [2], several studies have noted increased irritability associated with its administration, ultimately leading to serious aggressive behavior in some cases [3]. However, most previous reports are either retrospective in nature [4,5] or based on findings extracted from relevant spontaneous descriptions embedded in case notes using a computer-based random search method [6,7]. We performed the present prospective study using rating scales to confirm the aggression-augmenting effects of PER pointed out in previous investigations. Furthermore, we examined the impact of other concomitant AEDs on aggression augmentation and analyzed whether depression is likewise increased with PER administration.

2. Methods

2.1. Subjects

All PWE (age 18 years or older) who visited Aichi Medical University or Suzukake Clinic from July 2016 to August 2018 and given PER were asked to participate in this study. Those who could not answer the questions related to the rating scales because of profound or moderate intellectual disability (ID) or mental illness were excluded. Epilepsy and epileptic seizure classifications were determined based on definitions proposed by the International League Against Epilepsy [8]. Pharmacoresistent epilepsy was defined as seizures not controlled even when 2 or more AEDs were administered. Seizure frequency prior to initiation of PER was defined based on the number of focal seizures with impaired awareness (FSWIA), and focal to bilateral or generalized tonic clonic seizures (TCS) during the 12 weeks preceding the entry point.

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Table 1
Characteristics of eligible patients (n = 59).

Characteristics	Mean ± SD (range) or number (%)
Gender, male	26(44.1)
Age, years	35.3 ± 13.3(18-70)
Age at onset, years	16.4 ± 9.2(0-37)
Duration of illness, years	18.8 ± 14.2(0-58)
No. of concomitant AEDs	2.4 ± 1.2(0-6)
Psychiatric illness prior to entry	9(15.2)
Mild intellectual disability	8(13.6)
Post-therapeutic seizure freedom[a]	11(18.6)
Epilepsy classification	
Focal	51(86.4)
Generalized	5(8.5)
Others	3(5.1)
Seizure frequency[b] (0–3/4 or more)	38(64.4)/21(35.6)
AEDs with negative psychotropic trend (LEV,ZNS,TPM)	37(62.7)

[a] Four-week seizure freedom preceding study endpoint.
[b] Total number of seizures within 12 weeks preceding study entry.

2.2. Study design

This was a 12-week short-term observational study that investigated changes in aggression and depression following PER administration in epilepsy patients who newly received PER. The study protocol and that used for seeking informed consent were approved by the ethics committee of Aichi Medical University. Patients provided written informed consent in that regard, then were examined at the entry and again 12 weeks later (endpoint). At both examinations, each patient was given the Buss Perry Aggression Questionnaire (BAQ) and Neurological Disorders Depression Inventory for Epilepsy (NDDI-E).

Clinically relevant variables, including gender, age at study entry, age at epilepsy onset, duration of epilepsy, prehistory of psychiatric illness, presence of ID, number of concomitant AEDs (1 vs. 2 or more), seizure freedom after initiation of PER, epilepsy type (focal, generalized, others), seizure frequency at entry (0–3 vs. 4 or more during 12-week study period regardless of seizure type), concomitant AEDs reported to have negative psychotropic effects (LEV, ZNS, TPM), and PER daily dose (2 and 4 mg vs. 6 and 8 mg) were investigated. Details regarding the clinical variables examined are listed in Tables 1 and 2. PER was given daily to pharmacoresistent patients, and titrated steadily by 2 mg every 4 weeks until they became seizure free or complained about side-effects, which led to a slowing of the speed of titration. Seizure freedom after initiation of PER was defined as no recurrence of FSWIA or TCS at the endpoint or 4 consecutive weeks prior to the endpoint.

For analysis, we examined whether total BAQ and NDDI-E scores before and 12 weeks after beginning PER administration were significantly different. Additionally, we investigated clinical variables showing effects on differences for each score between the baseline and endpoint.

Table 2
Concomitant AEDs.

Name	Number of patients	Daily dose (mg) Mean ± SD(range)
Levetiracetam	34	1926.5 ± 760.0(1000-3000)
Carbamazepine	29	591.4 ± 163.7(200-900)
Valproate	17	670.6 ± 439.8(100-1400)
Lamotrigine	15	268.3 ± 121.2(100-450)
Topiramate	14	153.6 ± 63.4(50-300)
Lacosamide	8	362.5 ± 74.4(200-400)
Phenobarbital	8	78.8 ± 32.8(15-120)
Clobazam	7	6.8 ± 4.3(3-15)
Phenytoin	6	353.2 ± 103.3(244-538)
Zonisamide	2	350.0 ± 212.1(200-500)
Clonazepam	1	1.0 ± 0
Diazepam	1	1.0 ± 0

2.3. Questionnaires

The BAQ is a self-rating scale composed of 24 items presented in a Likert format and has quickly become the standard for measurement of aggression [9]. Factor analysis of the items has yielded 4 subscales; physical aggression, verbal aggression, anger, and hostility. Ando et al. investigated the validity and reliability of the Japanese version of the BAQ [10], and Nakano confirmed the applicability of the original 4-factor model in Japanese subjects [11]. Among the 4 subscales covered by the BAQ, verbal aggression and physical aggression represent the instrumental or motor component of behavior for the purpose of hurting or harming others. On the other hand, anger, which involves physiological arousal and preparation for aggression, represents the emotional or affective component of aggressive behavior, as well as hostility, which consists of feelings of malevolence and injustice, and represents the cognitive component of behavior. The NDDI-E is a self-administered 6-item screening instrument developed for rapid identification of major depressive episodes in PWE [12] and widely used throughout the world. Tadokoro et al. confirmed the validity and reliability of the Japanese version [13].

2.4. Statistical analysis

A paired *t*-test was employed to compare total BAQ and NDDI-E scores, used as indexes of aggression and depression, respectively, obtained at both the study entry and endpoint. As a subsidiary analysis, BAQ subscales were also compared. Additionally, multivariate regression analysis was performed to examine the impact of basic clinical variables and AED use on the differences between the baseline and endpoint for the total BAQ and NDDI-E scores. All variables that showed a p-value less than 0.05 were examined as independent variables potentially relevant to the dependent variables. The statistical software package SSPS, ver. 22, was used, with a p-value less than 0.05 considered to indicate statistical significance.

3. Results

Among 105 patients given PER, 28 were excluded from analysis because of age under 18 years (n = 7), moderate or severe ID (n = 20), or severe psychosis (n = 1). Ultimately, 77 patients agreed to participate in the study. Eleven patients dropped out of the study within 4 weeks after entry and another 7 at the endpoint. The reasons for dropping out were premature discontinuation of PER because the patient judged the effect to be insufficient (n = 5) and adverse effects (n = 9). Of those 9 who discontinued because of adverse effects, increased psychiatric symptoms was given as the reason by 3 (3.9% of total cases), while other adverse effects noted by those were somnolence (n = 2), gait disturbance (n = 1), bradycardia (n = 1), reduced understanding (n = 1), and physical weariness (n = 1). Furthermore, 4 patients withdrew consent to participate in the study, failed to complete the follow-up examinations, or changed the AED given concomitantly with PER. Ultimately, 59 patients completed the study. The enrolled patients included 33 females and 26 males. Average age at the time of entry was 35.3 years (SD = 13.3). Relevant clinical data are presented in Table 1. The average dose of PER at the study endpoint was 3.5 mg (SD = 1.3), at which time 20 patients were receiving a dose of 2 mg/day, 33 were receiving 4 mg/day, and 6 were receiving 6 mg/day.

The total BAQ score was significantly increased at the endpoint as compared to the entry point (p = 0.013) (Table 3). In subscale analysis, verbal aggression and physical aggression were shown to be significantly increased (p = 0.045, p = 0.040, respectively), while anger showed an increasing trend (p = 0.083). As for hostility, there was no significant difference or trend of difference between the entry and endpoint for any of the subscales.

Table 3
BAQ and the NDDI-E in eligible patients (n = 59).

	At the entry Mean ± SD(range)	At the 12 weeks Mean ± SD(range)	p-value
BAQ	64.8 ± 13.9 (40-103)	68.4 ± 14.9 (37-108)	0.013
Verbal aggression	14.3 ± 3.2 (8-24)	15.1 ± 3.5 (8-22)	0.045
Physical aggression	16.2 ± 5.4 (6-27)	17.6 ± 5.6 (7-34)	0.040
Anger	14.6 ± 5.0 (6-25)	15.6 ± 4.5 (8-25)	0.083
Hostility	19.7 ± 5.3 (10-33)	20.2 ± 5.2 (11-33)	0.274
NDDI-E	11.9 ± 4.0 (6-22)	13.7 ± 3.9 (6-23)	0.000

BAQ: Buss Perry Aggression Questionnaire. NDDI-E: Neurological Disorders Depression Inventory for Epilepsy.

NDDI-E score was significantly increased at the endpoint as compared to the entry point (p = 0.000) (Table 3). Based on the results, depression was noted in 7 (11.9%) of the 59 patients at the entry point and 14 (23.7%) at the endpoint.

Comparisons between increase in BAQ and clinical variables showed age at epilepsy onset (p = 0.033), total BAQ score at entry point (p = 0.021), and dose of PER at endpoint (p = 0.021) to be independent variables demonstrating a p value of less than 0.05. Multivariate analysis of these independent variables revealed that total BAQ score at entry (B = -0.309, p = 0.002) and dose of PER at the endpoint (B = 14.072, p = 0.002) each had a statistically significant impact on increased BAQ score (R^2 = 0.234). As for NDDI-E results, clinical variables that demonstrated a p-value less than 0.05 were age at study entry (p = 0.048), duration of epilepsy (p = 0.046), ID (p = 0.040), total BAQ score at entry (p = 0.041), and NDDI-E score at entry (p = 0.000). Multivariate analysis of these independent variables revealed that NDDI-E score at the entry point (B = -0.436, p = 0.000) had a statistically significant impact on increased NDDI-E score at the endpoint (R^2 = 0.228) (Tables 4 and 5).

Table 4
Variables associated with the difference of the total BAQ score or the NDDI-E score between the entry and the endpoint using univariate analyses.

Variable	*P* value (*r*)	
	Total BAQ score	NDDI-E score
Gender, male	0.398 (0.112)	0.895 (-0.018)
Age, years	0.518 (-0.086)	0.048 (0.258)
Age at onset, years	0.033 (-0.277)	0.822 (-0.030)
Duration of illness, years	0.458 (0.098)	0.046 (0.261)
No. of concomitant AEDs	0.456 (-0.099)	0.450 (-0.100)
Psychiatric illness prior to entry	0.531 (0.083)	0.410 (-0.109)
Mild intellectual disability	0.541 (0.081)	0.040 (0.268)
Post-therapeutic seizure freedom*	0.950 (-0.008)	0.447 (-0.101)
Epilepsy classification		
Focal	0.653 (0.060)	0.289 (0.140)
Generalized	0.926 (-0.012)	0.073 (-0.235)
Others	0.560 (-0.078)	0.549 (0.080)
Seizure frequency**	0.931 (0.011)	0.945 (0.009)
AEDs with negative psychotropic trend (LEV,ZNS,TPM)	0.695 (0.052)	0.414 (0.108)
The total BAQ score at the entry point	0.021 (-0.299)	0.041 (-0.267)
The total NDDI-E score at the entry point	0.405 (-0.112)	0.000 (-0.477)
Dose of PER at the end point	0.021 (0.300)	0.383 (0.116)

BAQ: Buss Perry Aggression Questionnaire. NDDI-E: Neurological Disorders Depression Inventory for Epilepsy, AEDs: antiepileptic drugs. LEV: levetiracetam, ZNS: zonisamide, TPM: topiramate, PER: perampanel.

* Four-week seizure freedom preceding study endpoin.

** Total number of seizures within 12 weeks preceding study entry.

Table 5
Variables associated with the difference of the total BAQ score or the NDDI-E score between the entry and the endpoint using multivariate analyses.

Variable	Standardized coefficients (β)	*P* value	Collinearity (VIF)	Adjusted R^2
Total BAQ score				
Constant		0.001		0.234
Total BAQ score at the entry	−0.309	0.002	1.058	
Dose of PER at the endpoint	14.072	0.002	1.058	
NDDI-E score				
Constant		< 0.001		0.228
NDDI-E score at the entry	−0.436	< 0.001	1.000	

BAQ: Buss Perry Aggression Questionnaire. NDDI-E: Neurological Disorders Depression Inventory for Epilepsy. PER: perampanel.

4. Discussion

The present report presents the first prospective results suggesting that PER administration increase scores of assessment tools indicative of aggression and depression, as well as the dose-dependent nature of its effect on aggression. It is important to note that because most of the enrolled patients were given less than 6 mg PER, these results superficially contradict previous reports that did not find negative psychotropic effects of PER at doses under 6 mg. Ettlinger found aggressive behavior in 2.8% of patients given 8 mg of PER and in 6.3% of those given 12 mg, in contrast to an increase in 0.7% of those given a placebo [6]. Chung et al. showed that the frequency of aggressive behavior was nearly doubled in patients who received PER at 6 mg as compared to those given 2 or 4 mg, or a placebo [7]. However, it should be noted that in the present study as well, only 3 (3.9%) of the entire cohort of 77 discontinued PER use because of adverse psychiatric effects. Likewise those authors also noted that only 0.9–2.6% of their patients discontinued PER because of aggression that emerged during treatment, which was confirmed by the present results. Furthermore, in another study that included naturalistic clinical settings, the rise of irritability or aggression was reported to be negated [14]. The findings of Liguori et al. agreed with those and emphasized that psychiatric issues are less conspicuous in patients receiving PER as compared to those given levetiracetam [4]. Therefore, it is important to note the disparity between total BAQ score and clinically noticeable aggressive behavior. PER is known for its potent efficacy as well as unique mechanism of action, and has been shown to be a first-in-class, non-competitive selective AMPA receptor antagonist [15]. The present findings suggest that a slight or moderate increase in aggressiveness or depressive mood change can be well tolerated in most cases in view of the potent antiepileptic efficacy of this compound.

Following an initial presentation of sporadic cases [16], several reports showed ID to be a risk factor for precipitating aggressive behavior in PWE given PER [17–20]. Notably, those studies, which limited enrollment to patients with ID, strongly indicated that PER has effects to exacerbate aggressive behavior [18] or adverse psychiatric effects [19,20]. In contrast, Shanker et al. reported that PER was well tolerated by PWE with moderate to profound ID [21]. The present findings also failed to show a negative impact of ID on total BAQ score. Nevertheless, this issue requires careful reappraisal, because of exclusion of profound and moderate ID patients from the present cohort.

Another issue repeatedly noted in prior studies is the interrelationship of PER administration with that of other known AEDs that augment aggression. A recent study conducted by Chen et al. listed levetiracetam and zonisamide as AEDs with negative behavioral side-effects [22]. However, in contrast to a previous case series study of PWE with ID [18], post hoc analysis reported by Chung et al. revealed that concomitant administration of levetiracetam and topiramate did not

increase the number of aggressive incidents by PWE given PER [7]. In agreement with those findings, the present study results did not reveal any additional negative behavioral impact of these compounds on either total BAQ or NDDI-E score. According to Buss and Perry, among the 4 subscales of the BAQ, physical and verbal aggression correspond to predatory and instrumental aggression, while anger and hostility are associated with impulsive aggression, indicating an emotionally charged aggressive response [8]. Our findings showed that predatory and instrumental aggression, i.e., aggression that is easily noticeable, was augmented in patients given PER. In contrast, Kato et al. found impulsive aggression to be the main component ameliorated by lamotrigine administration in PWE [23]. There is no doubt that aggression is a composite of multiple heterogeneous components, and different antiepileptic drugs seem to exert either a negative or positive influence on the different components of aggression in a manner independent of each other.

In the present patients, NDDI-E scores were also increased. In agreement with previous studies, it is interesting to note that despite the small number of patients, multivariate analysis revealed a PER dose-dependent increase in BAQ, a trend not seen in the NDDI-E results. Together, the present findings suggest that depression and aggression in patients given PER are independent events that require separate analysis. Furthermore, they suggest that neither depression nor aggression at the point of entry predict greater susceptibility to psychiatric symptoms following initiation of PER. Villanueva et al. [17] presented the only known study that examined the predictive value of pre-treatment psychiatric symptoms. In addition to intellectual disability, they noted that aberrant personality trait is a risk factor for later development of aggression following administration of PER. Our results do not indicate the predictive value of pre-treatment aggressive or depressive states, because of a number of factors, such as short observation period, small sample size and the ceiling effect of the questionnaires, which limit the applicability of the present study. These are important issues that require further investigation.

The limitations of the present study are apparent. The observation period was short and changes in scores might have been less apparent with a longer observational period, as many patients with aggression or depression may have either dropped out or adapted over time. Indeed, our results could be biased as a result of withdrawals because of psychiatric side-effects, at least to some extent. However, the impact was minimal, because only 3 patients dropped out for that reason. It should also be noted that prior to beginning PER administration we informed the patients of possible appearance of irritability or aggressiveness after initiating treatment with the compound. Although this is an indispensable ethical procedure that must be included in any non-randomized prospective study, such notification may have influenced the answers to the questionnaires. Finally, while the BAQ is an effective tool for assessment of a slight or moderate increase in aggressive mood, it might fail to detect an extremely agitated aggressive situation owing to the growing insensitivity to one's own behavior in correspondence with the increasing aggression.

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