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Treatment with brivaracetam in children – The experience of a pediatric epilepsy center

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ABSTRACT

Introduction: The new anticonvulsant brivaracetam is a levetiracetam analog which binds to the synaptic vesicle protein 2A, and inhibits excitatory neurotransmitters' release. Brivaracetam was Food and Drug Administration (FDA) and European Medicine Agency (EMA) approved in 2016 as adjunctive treatment for focal onset seizures in patients over 16 years of age, and in 2018 for children over four years of age. Our aim was to describe effectiveness and tolerability in real-life pediatric epilepsy clinic.
Methods: Cross-sectional retrospective chart review of patients under 20 years of age, treated with brivaracetam. Positive response to treatment was considered when 50% decrease in seizure frequency was noted. In responders to levetiracetam, positive effect was regarded if switching to brivaracetam maintained at least the same seizure control.
Results: Thirty-one patients (67.7% males), aged 13.8 ± 4.07 (6.9–20 years), were treated with brivaracetam 3.8 mg/kg ± 1.8. Age of onset of epilepsy was 5.7 ± 3.7 years; 20 patients had focal epilepsies; and 11 had epileptic syndromes (5 – Lennox–Gastaut, 3 – myoclonic absence, 3 – myoclonic–atonic). Responder rate was 45.2%, with no statistical difference under and over 16 years of age (40% vs. 54.5%, Fisher's exact test). Eight patients had better response to seizures compared to levetiracetam. Gender, duration of epilepsy, and dosage did not affect epilepsy control. Six patients had seizure aggravation. Adverse effects were rare: mild somnolence (6.4%), psychosis (3.2%), and nausea (3.2%).
Conclusion: Brivaracetam is an effective add-on treatment in focal, as well as generalized seizures in children, with negligible side effects, including children who failed previously on levetiracetam. Seizure exacerbation may occur, but it's reason is unclear.

1. Introduction

Calcium-dependent exocytosis of excitatory neurotransmitters from the synaptic vesicle protein 2A (SV2A) is involved in epileptogenesis in animal models [1], hence it is a target for antiepileptic drugs [2]. Levetiracetam was the first SV2A ligand to be marketed as an effective antiseizure drug in adults as well as children [2,3]. Brivaracetam, a n-propyl analog of levetiracetam, binds to SV2A with a 10–30-fold higher affinity, considered a more potent anticonvulsant [4,5]. Following several successful phase III trials [6–10], brivaracetam was approved in 2016 by the FDA and EMA as adjunctive treatment for focal onset seizures in patients over 16 years of age.

In May 2018, brivaracetam was licensed as an adjunctive therapy of focal seizures with or without generalization for children of 4 years and older. Data on safety and efficacy of brivaracetam in pediatric patients, especially in postmarketing studies are scarce. A recent large-scale postmarketing study by Villanueva et al. included only patients older than 16 years of age [11], while several smaller scale studies in adults included also a few younger patients [12–14]. A recent multicenter study by Schubert-Bast et al., in 34 children with focal epilepsy, revealed that brivaracetam had a similar efficacy and safety profile as in adults [15].

The aim of this study was to describe the experience of our pediatric epilepsy clinic in treatment of children with brivaracetam for focal as well as other types of epilepsy.

2. Material and methods

This research is a cross-sectional chart review study, conducted at the Pediatric Neurology Unit, Safra Children Hospital, Sheba Medical Center, Israel. This is a tertiary referral center for refractory epilepsy, treating over 1000 patients/year, ranging from neonates to 20 years of age. Between 2017 and 2019, 42 patients were prescribed brivaracetam. In patients over 16 years of age, the drug was prescribed as 4th line

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antiepileptic drug for patients with focal epilepsy, in line with the International and National Ministry of Health regulations. In patients under 16 years of age, brivaracetam is not yet approved by the local regulator, hence the drug was prescribed according to a named patient basis approval.

Patients treated with the drug at least two weeks were included in the study, and their charts were reviewed. Demographic parameters and data regarding epilepsy phenotype, seizure control, dosage regimen, and side effects were extrapolated from the charts. Percent of change in seizure frequency from baseline was recorded. Positive response to treatment (i.e., responder) was considered a 50% or more decrease in seizure frequency after three months of treatment. In patients considered responders to levetiracetam switched to brivaracetam, positive effect was considered if at least the same seizure control was maintained after the conversion.

The research was approved by the Institutional Ethical Committee: IRB#5843-19-SMC. The study was exempted from signing a patient informed consent form, since the data were retrospective and anonymized.

2.1. Statistical analysis

Parameter frequencies, means, and medians were tabulated using descriptive statistics. Means between numerical parameters were compared using unpaired *t*-test, while nominal parameters were compared using chi-square or Student's exact test. All tests were two-tailed, and a p value of 5% or less was considered statistically significant. Statistical analysis was done using the IBM™SPSS™ Version 21 software, New York, USA.

3. Results

Thirty-one patients, 21 (67.7%) males, were enrolled in this study. Mean age was 13.8 ± 4.07 years; the youngest patient was 6 years of age, while the upper age limit was 20 years. Twenty patients (64.5%) were younger than 16 years of age. Age of onset of epilepsy was 5.7 ± 3.7 years (range: 1 month–13 years), and the lag time between onset of epilepsy and treatment with brivaracetam was 7.8 ± 4.4 years (0.9–15.9 years). Seizures were drug-resistant, after 3–16 antiepileptic drugs (mean: 9.1 ± 4.5). Twelve patients failed on additional treatments: ketogenic diet (9 patients), vagal nerve stimulation (10 patients), epileptic surgery (5 patients), steroids (2 patients), and cannabidiol (13 patients).

Twenty patients (64.5%) had focal onset epilepsies, and 11 (35.5%) had epileptic syndromes: 5 with Lennox–Gastaut syndrome, 3 with absence with eyelid myoclonus (Jeavons syndrome), and 3 with myoclonic–atonic epilepsy. Main seizure type was focal onset with impaired awareness in 17 patients (54.8%), followed by drop attacks in 7 patients (22.6%), absence in 3 (9.7%), focal to bilateral clonic in 2 (6.5%), and focal with preserved awareness in 2 (6.5%). Abnormal magnetic resonance imaging (MRI) findings were present in 12 patients, 5 of them with focal dysplasia, three with tumors, and three with destructive lesions (bleeding, porencephaly, and hypoxic–ischemic damage). Psychiatric comorbidity was found in 19 patients (61%): autistic spectrum disorder (6 patients), intellectual disability (5 patients), behavior disorder (2 patients), while anxiety, depression, psychosis, and obsessive–compulsive disorder were present in one patient each.

The indication for treatment with brivaracetam was seizure control in 19 patients (61.3%), side effects of levetiracetam in 4 (12.9%), and both in 8 (25.8%). Twenty-nine patients (93.5%) were previously exposed to levetiracetam. In 15 patients (48.3%), brivaracetam was started as a direct conversion from levetiracetam; in 5 of them, the conversion was abrupt (overnight switch) while in the remaining 10, the transition was gradual over two weeks. The mean dose of brivaracetam was 3.8 ± 1.8, ranging from 1.8 to 10 mg/kg (100–300 mg, 181.4 ± 54.7). For patients switched from levetiracetam, the ratio of dosing was 10:1 (from 5:1 to 15:1). Duration of treatment with brivaracetam ranged from 2 weeks to 24 months (6.7 ± 7.3 months). Brivaracetam was started as add-on therapy to a mean of 2.1 ± 1.25 antiseizure drugs (range: 1–7).

The mean reduction in seizure frequency was 59% ± 19.1%. Responder rate was 45.2%, with no statistical difference in patients below or above 16 years of age (40% vs. 54.5%, Fisher's exact test).

Gender, age, duration of epilepsy, dosage, and previous antiseizure drugs did not affect seizure control (Table 1). For patient with normal brain imaging, responder rate was 42% (8/19), while in patients with abnormal MRI findings, 50% (6/12) were responders (not significant). Likewise, type of epilepsy or main type of seizure did not influence response rate (Table 1). Treatment was effective not only in focal onset seizures, but also in drop attacks for patients with myoclonic–atonic epilepsy or Lennox–Gastaut syndrome (Table 1). Notably, two patients (out of three) with absence with eyelid myoclonus (Jeavons syndrome) had over 90% reduction in seizures and were switched to monotherapy. While brivaracetam was effective in patients with focal onset seizures with impaired awareness, none of the patients with other focal seizures (focal to bilateral tonic–clonic and focal with preserved awareness) responded to therapy (Table 1).

Interestingly, 13/29 (44.82%) of patients previously exposed to levetiracetam had a positive effect on seizure control with brivaracetam. Five patients which were already responders to levetiracetam, maintained the same level of seizure control after switching to brivaracetam. In addition, 8 patients had better seizure control on brivaracetam than levetiracetam (Table 2). Two patients who already had a 50% seizure reduction to levetiracetam, presented an added value of brivaracetam, with a 75% and 90% decrease in convulsions (Table 2). Six patients who previously failed on levetiracetam had a 64.17 ± 12.4% seizure reduction on brivaracetam (Table 2).

Remarkably, 19.3% of the patients (6 patients) had seizure aggravation (Table 3). First four patients with exacerbation of seizures were switched overnight from levetiracetam (patients 1–4, Table 3); subsequently, we started a more gradual exchange, without encountering this phenomenon in patients swapped from levetiracetam. However, two additional patients, started directly on brivaracetam, had worsening of epilepsy control (patients 5,6 – Table 3). It should be noted that the dose used in those with worsening of convulsions was relatively low, albeit not statistically significant (3.1 ± 1.2 mg/kg vs. 4.02 ± 1.9 in those without seizure aggravation). Interestingly, three patients in this group had a certain type of epilepsy resembling benign epilepsy of childhood with centrotemporal spikes (patients 1.3,4 – Table 3). These three patients had drug-resistant seizures, originating from

Table 1
Characteristics of responder vs. nonresponder patients.

	Responders n = 14	Nonresponders n = 17
Males (%)	52.4	47.6
Age (years) (mean ± SD)	14.3 ± 3.5	13.4 ± 4.5
Age of onset of seizures (years) (mean ± SD)	5.4 ± 4.6	6.0 ± 2.9
Lag period to treatment (years) (mean ± SD)	8.8 ± 4.6	6.8 ± 4.1
Dose (mg/kg) (mean ± SD)	3.6 ± 1.6	4.0 ± 2.0
Duration of treatment (months) (mean ± SD)	10.5 ± 8.4	2.8 ± 2.9**
Number of previous antiepileptic drugs (mean ± SD)	8.5 ± 4.7	9.5 ± 4.4
Type of epilepsy (%)		
Focal onset epilepsy	40	60
Lennox–Gastaut syndrome	40	60
Absence with eyelid myoclonus (Jeavons syndrome)	66.7	33.3
Myoclonic–atonic epilepsy	66.7	33.3
Main seizure type (%)		
Focal onset with impaired awareness	47.1	52.9
Drop attacks	57.1	42.9
Myoclonic absence	66.7	33.3
Focal to bilateral tonic–clonic	0	100
Focal with preserved awareness	0	100

** $p < 0.01$.

Table 2
Patients with improved seizure control under brivaracetam vs. levetiracetam.

Patient number	LEV previously improved seizures	BRV switched from LEV	Dose of BRV (mg/kg)	LEV: BRV ratio	Seizure reduction (%)
1	Yes	Yes	1.8	8:1	75
2	Yes	Yes	5	10:1	90
3	No	No	5	–	75
4	No	No	3.3	–	75
5	No	No	2.5	–	60
6	No	No	6.4	–	50
7	No	No	2.5	–	50
8	No	No	2.8	–	75

BRV – brivaracetam, LEV – levetiracetam.

independent bilateral rolandic area and normal MRI findings; one had diurnal perioral twitching and two had secondarily generalized nocturnal seizures. All three of them were changed overnight from levetiracetam.

Only three patients (9.6%) reported side effects. One patient developed psychosis which recovered after discontinuing treatment; this patient had depression comorbidity and had developed previously the same side effect on levetiracetam. One patient reported mild somnolence, while another presented with somnolence and nausea.

4. Discussion

Brivaracetam is a new antiseizure drug, only recently approved by the FDA and EMA for treatment of focal seizures in children over 4 years of age, therefore postmarketing studies reporting efficacy and safety concentrate mainly on adults [11,12,14,16]. In this study, we described our experience with 31 young people exposed to brivaracetam in a real-life pediatric epilepsy clinic setup. Twenty patients younger than 16 years of age were treated according to named patient basis authorization since the drug was not approved by the regulatory authorities at the time. To the best of our knowledge, this is the second study reporting results on a pediatric group of brivaracetam-treated patients beside the study by Schubert-Bast et al. [15].

In our study, we found a high responder rate to brivaracetam treatment (45%), in all patients, regardless of age. This high responder rate is in line with results from postmarketing studies in adults [11,12,14], as well as children [15]. Interestingly, our patients were highly resistant to drug therapy (after a mean of 9.1 antiepileptic drugs), as opposed to children in the study by Schubert-Bast (mean: 1.7 antiepileptic drugs) [15], but efficacy was similar (45% vs. 47% responder rate). Likewise, high efficacy (39.7% responder rate) was achieved also in the study by Villanueva et al. [11] in which patients were previously treated by 7.9 antiseizure drugs.

Though our cohort is small, it should be noted that brivaracetam lead to seizure control in patients with abnormal MRI findings, as well as those with normal imaging (50% vs. 42% responders). High efficacy in lesional epilepsy due to stroke was previously reported in adults by Villanueva et al. [11]. The high efficacy in patients failing more than 4 antiepileptic drugs, as well as in patients with lesional epilepsy, might be an important advantage for brivaracetam compared to other drugs.

As opposed to the paper by Schubert-Bast, in which only children with focal onset seizures were treated [15], in our study, we included also patients with other types of seizures. Having data on various types of seizures is an advantage, but the large number of small subgroups represents also a shortcoming, since no statistical significance can be reached. While caution is warranted in interpreting the results, brivaracetam seemed effective in focal seizures with impaired awareness, as well as atonic seizures (in myoclonic astatic epilepsy and Lennox–Gastaut syndrome) and myoclonic absences. Improvement of generalized seizure burden in epileptic encephalopathies like Lennox–Gastaut syndrome was found also by Willems et al. [13]. Generalized tonic–clonic seizures in idiopathic generalized epilepsies were also responsive to brivaracetam in the studies by Steinig et al. [12] and Strzelczyk et al. [14]. Effect of brivaracetam in absence seizures is controversial [12,14,17], while the drug was ineffective in myoclonic seizures [12] and absence epilepsy with eyelid myoclonus (Jeavons syndrome) [14]. In contrast, our two patients with Jeavons syndrome had a 90% reduction in seizures on monotherapy.

The mean dose used in this study was 3.9 mg/kg as suggested by extrapolation from adult dosage [18]. Nonetheless, the range of the dosage was wide, and the conversion ratio from levetiracetam was not consistent, since each investigator used his/her clinical judgment rather than a uniform regimen. We started the drug always as add-on treatment, but in two patients with Jeavons syndrome, we reached monotherapy. Data on monotherapy with brivaracetam are scarce, but a recent phase III trial in adults showed that conversion to low dose monotherapy was safe, but failed to show efficacy [6].

Most of our patients had been previously treated with levetiracetam, but still brivaracetam had a positive effect in 44.82% of patients. Notably, 6 patients who failed previously on levetiracetam achieved seizure control, while two patients had improved control of seizures compared to levetiracetam (Table 2). Therefore, previous lack of response to levetiracetam should not preclude treatment with brivaracetam.

In our study, we encountered seizure exacerbation in 19.3% of patients (6 patients). We initially attributed this phenomenon to the swift substitution of levetiracetam with brivaracetam, although this approach was safely used in a previous phase IIIb trial [19], as well as several postmarketing studies [12,15]. Nevertheless, after analyzing the final data (Table 3), we realized that our primary impression is not necessary true. Other parameters, as under dosing of brivaracetam or certain type of rolandic seizures, might have predisposed to seizure aggravation.

5. Conclusion

Brivaracetam is an effective treatment in focal, as well as generalized seizures in children. Efficacy in highly drug-resistant seizures as well as in lesional epilepsies, along with negligible side effects, might confer an advantage for brivaracetam treatment. Treatment should be attempted also in children who failed previously on levetiracetam. One should be aware the possibility of seizure exacerbation, but the causes for aggravation are unclear.

Table 3
Characteristics of patients with seizure exacerbation.

Patient number	Age (years)	Gender	Type of epilepsy	Type of seizure	Switch from LEV	Dose of BRV (mg/kg)	Ratio LEV:BRV
1	6.9	Male	Focal "rolandic" epilepsy	Focal preserved awareness	Overnight	5	12:1
2	19	Female	Lennox–Gastaut	Drop attacks	Overnight	3	12.5:1
3	12.4	Male	Focal "rolandic" epilepsy	Focal to bilateral tonic–clonic	Overnight	2.5	10:1
4	8.5	Male	Focal "rolandic" epilepsy	Focal to bilateral tonic–clonic	Overnight	2.3	10:1
5	12	Female	Lennox–Gastaut	Focal impaired awareness	No switch	4.4	–
6	14.5	Male	Focal onset epilepsy	Focal impaired awareness	No switch	1.8	–

BRV – brivaracetam, LEV – levetiracetam.

Declaration of competing interest

Andreea Nissenkorn: None.
Michal Tzadok: None.
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