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Efficacy of Zonisamide – Levetiracetam Comedication in Nine Adult Patients with Difficult to Treat Epilepsy and Intellectual Disability (A Case Series Report)

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Abstract

Aim: Few studies have concerned anticonvulsive combination therapies in epilepsies resistant to established antiepileptic drugs in monotherapy. We sought to delineate the effects of zonisamide – levetiracetam comedication (ZNS+LEV) in adults with intellectual disabilities (ID).

Material and Methods: Nine adult patients with drug resistant epilepsies and ID were treated in a routine outpatient setting with LEV or ZNS in combination with other anticonvulsants first and in a combination of both of them (ZNS+LEV) thereafter. Seizure frequency and behavioural effects were recorded in patients treated who approved to benefit from the combination of both substances but not when treated with only either of them.

Results: The longitudinal follow up of individual cases of patients with difficult to treat epilepsies and intellectual disabilitiy (ID) suggests that the combination of ZNS and LEV may be an effective and well tolerated option, even if LEV or ZNS alone or in either other combinations had failed to reduce seizure frequency.

Conclusions: These findings may not be generalized but request to perform further controlled studies on the efficacy and tolerability of the anticonvulsive therapy of ZNS in combination with LEV.

Introduction

Epileptic seizures and Epilepsy are common in persons with ID. Epidemiological studies suggest that up to 40% of people with ID (IQ < 70) have epilepsy [1]. The prevalence of seizures increases with increasing severity of ID. Thus the highest proportion of epilepsy (59%) among intellectually disabled children was found in the subgroup with profound ID [2]. Epilepsy in persons with ID is frequently characterized by multiple seizure types and a high rate of refractory seizures. The incidence of sudden unexpected death in epilepsy (SUDEP) was found to be more than three times higher in this group of patients compared with individuals with epilepsy but without ID [3, 4]. In their study with 214 intellectually disabled patients Kelly et al. found that antiepileptic drugs introduction and change resulted in seizure freedom for more than 40% of the subjects enclosed [3]. Of 240 seizure free patients with ID studied by Huber et al., 50.8% were on monotherapy, 38% were treated with two, and the rest received more than two anticonvulsants

Table 1: Characteristics of patients treated with LEV and ZNS in comedication.

Patient	Sex	Age (years)	Seizures Epilepsy(ICD)	Intellectual Disability	Other diagnoses / Etiology	Medication – other than AED (mg p.d.)
J.C.	f	31	GTCS, TS, ALS (G40.6)	severe	CP with mild bilateral spasticity, mainly of the legs	
G.A.	m	41	GTCS, TS, MS (right arm, bilateral) (G40.8)	moderate	hyperactive disorder	Olanzapin 5
K.M.	f	39	GTCS, SPS(focal motor right arm) (G40.6)	moderate - severe	Diabetes mellitus arterial hypertonia. Trisomy 21	Lansoprazol 15 Theophylline 150 Etilefrine 37.5 Insuline 12 (IE)
U.C.	m	26	GTCS, TS (G40.6)	severe	CP with bilateral spasticity mainly affecting the legs, and dystonia of the head and arms, impaired visual acuity, strabism, familial alpha-1, antitrypsin deficiency. Perinatal hypoxic-ischemic insult/intracerebral hemorrhage	
W.S.	f	29	GTCS, TS, CPS, ALS (G40.2)	severe	CP with bilateral spasticity accentuated on the left side; strabism; autoaggresive behavior	Venlafaxine 37.5
H.A.	m	23	GTCS, CPS (G40.2)	severe	Mild impairment of coordination; autoaggressive behavior. Interstitial deletion of the short arm of chromosome 3	Duloxetine 90 Trimipramin 10 Risperidone 1 Melatonin 4 Pantoprazol 20
W.B.	m	52	GTCS, ATS, CPS (G40.2)	severe (?)	Ataxia; autistic disorder; autogressive behavior. Postvaccination encephalopathy(?); on MRI: hippocampal sclerosis on the right side, reduced size of the fronal lobes, cerebellar atrophy	Melperon 125 Pantoprazol 20
K.K.	w	44	GTCS, SPS (focal motor seizures of the right Half of the body), ALS (40.6)	moderate	-	Ramipril 5
H.M.	m	42	GTCS, TS, MS (G40.8)	moderate	Behavior at times irritable and whiny	-

(for abbreviations of seisure types see Table 2)

[5]. Except from valproic acid (VPA) in combination with lamotrigine (LTG) there was no comedication with newer anticonvulsants in most of the cases in this study.

In general there are very few data to guide physicians on strategies for combining antiepileptic drugs, and this is especially true for the treatment of patients with ID. Yet this group does not only receive polytherapy to a substantial proportion, but is apparently more prone to the hazards of changing medication. Therefore it may be less risky to add a drug than to convert from one monotherapy to another in patients with ID or multiple handicaps. Among the newer anticonvulsants solely the VPA-LTG combination had been shown to be very effective not only in epileptic patients without ID but also in those with developmental disabilities [6].

In an outpatient service specialized in the comprehensive treatment of intellectually disabled persons with epilepsy, nine patients were identified who responded convincingly to a combination of ZNS and LEV (ZNS+LEV) but not to either of this anticonvulsants in other combinations. These cases will be described in detail.

Patients and Methods

Four female and five male patients between 23 and 52 years in age were treated as outpatients in a tertiary referral centre for the treatment of epilepsy. Eight out of nine patients were identified post hoc and independently as responders to the comedication of ZNS and LEV which was not recognized as a combination of peculiar effectiveness previously. In most of the cases

it was initially intended to substitute LEV for ZNS and vice versa. In one patient only (K.M.), who was previously treated first with LEV an then with ZNS unsuccessfully, ZNS+LEV was intended primarily.

All patients were intellectually disabled (severe ID in five, moderate ID in three and moderate to severe ID in one). Clinical characteristics of the patients are summarized in Table 1.

At the first visit all patients were under AED treatment; one was on monotherapy (H.A., LEV), five were on two anticonvulsants (G.A., U.C., W.S., W.B, K.K.), two on three substances (J.C., K.M.) and one received four different substances (H.M.). LEV was among the drugs given at visit 1 in four cases (together with topiramate (TPM) in one patient); none had ZNS in the anticonvulsant regimen at the first contact. The history revealed that one patient (K.M.) had previously been treated with LEV and had frequent seizures (no specification) and showed aggressive behaviour when treated with this substance; the same patient did not respond to ZNS either, when it was given prior to the first visit and independently from LEV. Another patient (H.M.) was previously treated with LEV, not combined with ZNS and had ongoing generalized tonic-clonic seizures (GTCS).

The dosages were ranging between 500 and 3500 mg/d for LEV and between 300 and 700 mg/d for ZNS, depending on the clinical symptomatology. The follow up under ZNS+LEV was 2 – 30 mo (mean: 14.8 mo).

Results

Only patients who turned out to be responders to LEV+ZNS were included in this report.

In one patient (J.C.) who did not respond to LEV alone but to LEV+ZNS, the dose reduction of LEV resulted in an increase of seizure frequency that could be reversed by raising LEV again. In two cases (U.C. and W.S.) a combination of LEV and TPM was changed to ZNS+LEV; one became seizure free (U.C.) and the other (W.S.) showed a substantial decline in seizure frequency thereafter. In another case (W.B.) it was tried to switch from VPA, LTG and LEV to VPA, LTG and ZNS; both combinations failed to improve seizure frequency but by adding LEV again to ZNS, LTG and VPA (the letter two anticonvulsants are now intended to be reduced) seizure freedom could be achieved. In this patient loss of appetite could be reversed by an additional medication with small doses of pregabalin (PGB). After withdrawing LEV from a combination of ZNS+LEV, LTG and VPA in another case (K.K.), this patient experienced a generalized tonic-clonic status epilepticus but became seizure free after adding LEV again (see Fig.1).

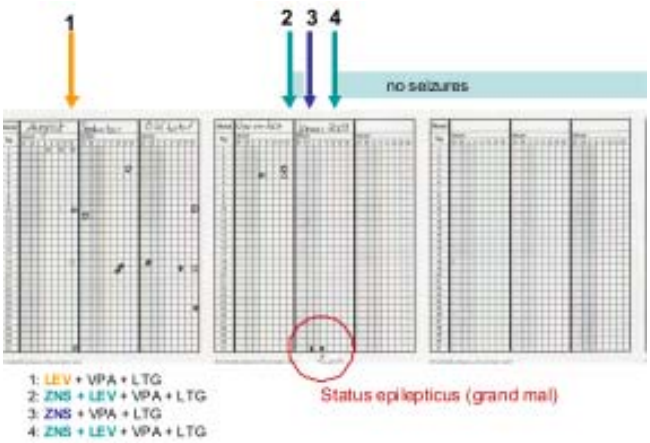

Figure 1: Patient K.K. - combination of ZNS and LEV.

In a further case (H.M.) previous LEV medication was not able to GTCS, and the combination of ZNS, LTG and VPA and that of felbamate (FBM), ZNS, LTG and VPA were likewise ineffective, but by changing to ZNS+LEV, LTG and VPA and then to ZNS+LEV and VPA a substantial reduction in seizure frequency was rendered. Anticonvulsive therapy was intended to be changed from LEV to ZNS in another patient (H.A.) who was, however, left on LEV+ZNS after marked seizure reduction had been achieved, and in one case (G.A.) the switch from oxcarbacepine (OXC) and LEV to ZNS+LEV led also to an obvious decrease in the frequency of GTCS. A last patient (K.M.) had been treated prior to visit 1 with LEV under which she experienced frequent seizures and developed aggressive behaviour; previous medication with ZNS could not influence seizure frequency either. Under a combination of FBM, LTG and VPA she still had up to 4 generalized tonic seizures per month, but LEV+ZNS reduced grand-mal frequency to 1 per two months. The courses of treatment in all patients are presented in Table 2.

Under ZNS+LEV only minor adverse effects were witnessed, with mild hyperactivity, slightly enhanced self-aggressive behaviour and irritability as well as slightly reduced lack of appetite being reported by the caregivers. Only anorexia was marked in one patient but could be treated by adding small doses of PGB. One patient (K.M.) had previously been shown serious aggressive

Table 2: Course of epilepsy in nine patients before and after combination therapy with zonisamide and levetiracetam.

Patient	Previous LEV or ZNS / date	Visit 1/ date	Medication (mg p.d.)	Seizures	Visit 2/ date	Medication (mg p.d.)	Seizures	Visit 3 / date	Medication (mg p.d.)	Seizures	Visit 4/ date	Medication (mg p.d.)	Seizures	Visit 5 / date	Medication (mg p.d.)
J.C.	-	11/06	VPA 2700 LTG 150 CLB 30	1-8 TS / mo	01/07	**LEV 3000** LTG 150 CLB 30	16 TS / 3 mo	10/07	**ZNS 300** **LEV 3000** LTG 150 CLB 5	3 GTCS / 7 mo	06/08	LEV ? 2100 **ZNS 400** LTG 150	**3 GTCS / 3 mo** **4 ALS / mo**	07/09	**LEV ?** **ZNS** LTG
G.A.	-	10/06	OXC 1800 **LEV 3500**	**11 GTCA / 8 mo** **frequent MS**	11/07	**ZNS 500** **LEV 3000**	4 GTCS/ 7 mo 2 MS / mo	04/09	**ZNS 600** **LEV 3000**	**2 GTCS / 9 mo** **? MS / mo**	-	-	-	-	-
K.M.	**LEV 2006 – frequent seizures, aggressive behavior ZNS 2007 frequent seizures**	11/08	LTG 175 VPA 750 **ZNS 600**	1-7 GTCS / mo	07/09	FBM 2160 LTG 200 VPA 600	**2-4 GTCS / mo**	09/09	**LEV 1500** **ZNS 400** VPA 450	**1 GTCS(?) / 2 mo**	-	-	-	-	-
U.C.	-	06/06	TPM 50 **LEV 3000**	1 GTCS / 2mo 1 TS / 2 mo	09/07	TPM 75 **LEV 3000**	**30 TS / mo**	06/09	**ZNS 400** **LEV 3000** TPM 75	**No seizures** **since 9/07**	-	-	-	-	-
W.S.	-	02/08	TPM 100 **LEV 3500**	3 GTCS / 5mo 41 TS / 5mo 3 ALS / 5mo	12/08	TPM 100 **LEV 3500**	**7 TS / mo** **1 GTCS/ mo**	09/09	ZNS 350 LEV 3000	**3 TS / 3 mo**	-	-	-	-	-
H.A.	-	01/08	**LEV 3500**	**1-4 GTCS / mo** **CPS several/ d**	10/08	**LEV 3000** **ZNS 400**	1 GTCS/ 3mo	07/09	LEV 3000 ZNS 400	**1 GTCS / 8mo**	-	-	-	-	-
W.B.	-	04/07	VPA 1500 LTG 125	1-2 GTCS / mo ATS frequently / d	07/07	**LEV 2000** VPA 1500 LTG 125	**4 GTCS / mo** **ATS frquently / d**	09/07	**ZNS 400** VPA 1500 LTG 125	**1 GTCS/ mo** **ATS frequently / d**	09/09	**LEV 500** **ZNS 400** VPA 1500 PGB 150 (to increase appetite)	**1 – 9 /2009 no seizures**	-	-
K.K.	-	10/07	LTG 200 VPA 1000	5-7 GTCS / mo	11/08	**LEV 2500** LTG 200 VPA 1250	**5 GTCS / mo**	12/08	LEV 2500 ZNS 400 LTG 200 VPA 1250	**no seizures for 4 weeks**	01/09	ZNS 400 LTG 200 VPA 1250	**GTCS –status (Jan 31th 09)**	08/09	**LEV 2000** **ZNS 400** LTG 200 VPA 1500
H.M.	**LEV 2007 continuous GTKA**	06/08	LTG 400 VPA 2000 PBM 250 CLB 20	8 GTCS / mo	08/08	**ZNS 500** VPA 1750 LTG 200 CLB 5	**1 GTCS / 2mo**	01/09	**ZNS 900** VPA 1250 LTG 125	**2 GTCS / mo** **MS several / d**	02/09	FBM 1500 **ZNS 700** VPA 750 LTG 100	**2 GTCS / mo** **severe**	09/ 09	LEV 3000 ZNS 400 VPA 1500

A, absence; ALS, absence like seizures; ATS, atonic seizure; CPS, complex partial seizures; GTCS, gereralized tonic clonic seizure; MS, myoclonic seizures; TS, tonic seizures; CLB, colbazam; FBM, felbamate; LEV, levetriacetam; LTG, lamotrigine; OXC, oxcarbazepine; PGB, pregabalin; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide.

behaviour when treated with LEV but she was reported as “little more ludicrous” only, when treated with ZNS+LEV. Favourable behavioural effects under ZNS+LEV were seen in four patients, who were described as “attentive”, “more balanced” and with “enhanced spontaneity”; loss of weight was a positive effect in one patient. Table 3 summarizes adverse and favourable effects of ZNS+LEV in all patients reported.

Table 3: Adverse events and favourable (besides anticonvulsive) effects under the comedication of ZNS with LEV.

Patient	Adverse events under ZNS +LEV	Positive (not anticonvulsive) effects of ZNS + LEV
J.C.	none	none
G.A.	mild hyperactivity	none
K.M.	little more ludicrous	none
U.C.	none	attentive, mood more balanced
W.S.	slightly reduced appetite	mood more balanced
H.A.	autoaggressive behavior mildly enhanced	none
W.B.	loss of appetite / weight	attentive, mood more balanced
K.K.	none	loss of weight
H.M.	slightly enhanced irritability	attentive, enhanced spontaneity

Discussion

Altough monotherapy is recognized to be the gold standard for drug treatment of epilepsy, duo- or polytherapy are unavoidable in most of the cases with difficult-to treat seizure disorders. This is frequently the case in individuals with more severe forms of ID or multiple handicaps. Very few publications refer to the efficacy and tolerability of antiepileptic treatment in defined combinations in this population. Controlled studies on patients with developmental disorders are extremely difficult to perform for various reasons, mainly due to the high heterogeneity of this population [7]. Thus clinicians treating patients with ID lack empirically based guidance in their therapeutic decisions. Single case descriptions and case series are not able to fully bear down this shortcoming but are able to create hypotheses for further studies and may be a valuable clue in daily clinical practice.

A rational polytherapy should fulfill different criteria, namely that two combined substances display different mechanisms of action (MOA) and do not develop unfavourable pharmacodynamic and pharmacokinetic interactions [8]. The MOA of LEV differs most likely fundamentally from that of ZNS and is believed to modulate neurotransmission via binding to the synaptic vesicle protein 2A and it may reduce neuronal excitability by inhibiting intracellular Ca^{2+}-release from intraneuronal storage. It does, however, not affect GABAergic neurotransmission and has no specific effect on neuronal low-voltage-gated T-type calcium channels [9-11]. ZNS has been shown to modulate the latter, to be a weak inhibitor of the carbonic anhydrase, and is likely to modulate neurotransmission (serotonin, dopamine and acetylcholine) [12]. Both substances display little pharmacokinetic interactions and both have been proven to be broad spectrum anticonvulsive drugs [9,12].

LEV has unfavourable psychotropic / behavioural effects, particularly by inducing depression and aggressive behaviour [13]. This was also true in a group of patients with ID which was comparable to the nine patients presented in this paper [14].

None of these patients, however, experienced serious mood or behavioural disturbances under ZNS+LEV. In three subjects caregivers had the impression that the patients‘ mood was more balanced and two of this three patients and another individual were perceived to be more attentive with ZNS+LEV.

Nevertheless four patients have been described as mildly worsened in their behaviour. One of the latter had been treated with LEV separately few years before, when she displayed serious aggressive behaviour that was not observed under ZNS+LEV. This may indicate that ZNS is able to lessen unfavourable psychotropic effects of LEV. Because serious behavioural problems had previously observed in epilepsy patients with ID who were successfully treated with LEV separately, it seems unlikely that a presumed positive psychotropic effect of ZNS+LEV is linked to seizure control [14].

To answer this question and to further prove favourable pharmacodynamic interactions of ZNS and LEV in patients with difficult-to-treat epilepsies, future comparative studies are desirable.

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