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Intravenous levetiracetam in clinical practice – Results from an independent registry

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ABSTRACT

Purpose: Most common clinical studies with antiepileptic drugs do not reflect medical everyday practice due to their strict in- and exclusion criteria and specifications of treatment regimens. Here we present a large non-interventional registry with the intention to evaluate the spectrum of applications in daily use and the efficacy and tolerability of intravenously given levetiracetam (LEV-iv).
Methods: In a prospective approach of 17 neurological and neuropediatric centres in Germany LEV-iv treated patients of all ages were included over a period of 10 months. The observational period was 10 days with daily documentation of LEV-iv administration, type and frequency of seizures, currently used drugs and doses, and adverse events (AEs). In addition, treatment efficacy and tolerability were assessed by patients and physicians at study end as well as practicability of LEV-iv using a five-step scale.
Results: In 95 patients LEV-iv was administered, 93 were included into the analysis. The median LEV-iv dose was 1500 mg (range 110–6000 mg) per day. Median age was 66 years (range 0.7–90.3 years). The majority of patients ($n = 70$, 75%) suffered from status epilepticus (SE, $n = 55$, 59%) and acute seizure clusters ($n = 15$, 16%). Of those with SE, 41 patients (75%) had SE for the first time. Acute seizure clusters and SE terminated in 83% after LEV-iv administration. A total of 29 adverse events were reported in 17 of the 95 patients from the safety set. Ten of these were at least possibly related to LEV-iv treatment. Slight decrease of blood pressure during the infusion (3 patients each) was captured most frequently. No serious side effect was observed. Physicians rated the efficacy and tolerability of LEV-iv treatment as good or very good in 78% and 82% of the cases, respectively.

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Conclusion: In this large observational study of everyday practise the use of LEV-iv exhibited a remarkable good response and tolerability in patients with acute onset seizures (mostly SE). Further randomized controlled studies, like the established status epilepticus trial (ESET) are needed to confirm these findings.

1. Introduction

In 2006, levetiracetam was approved as the first of the newer anticonvulsive drugs as an intravenous formulation (LEV-iv, Keppra iv®) for patients with epileptic seizures who are unable to take oral medications. Levetiracetam is most commonly approved as adjunctive treatment of partial onset seizures with or without secondary generalization, other approved indications include monotherapy treatment of partial onset seizures with or without secondary generalization, and adjunctive treatment of myoclonic seizures associated with juvenile myoclonic epilepsy and primary generalized tonic–clonic seizures associated with idiopathic generalized epilepsy.

Unlike other antiepileptic drugs (AEDs), the mechanism of action of levetiracetam appears to involve neuronal binding to synaptic vesicle protein 2A (SVA2) [1], inhibiting calcium release from intraneuronal stores, opposing the activity of negative modulators of GABA- and glycin-gated currents and inhibiting excessive synchronized activity between neurons [2]. LEV is characterized by a favourable pharmacokinetic profile with minimal plasma protein binding, negligible drug interactions and a lack of hepatic metabolism [3]. The approved LEV-iv administration appears to be well tolerated even at higher doses and faster infusion rates (1500–2500 mg administered over 5 min) [4].

With the introduction of the intravenous preparation of LEV there has been considerable interest in the use of LEV-iv for the treatment of status epilepticus (SE), although LEV is not approved for this indication. The favourable pharmacokinetic and safety profiles make LEV-iv a possible candidate for fast and effective treatment of SE, when first-line agents cannot be applied or do not work sufficiently [3]. First studies, reporting on small sample studies found LEV-iv to be efficacious in terminating SE in a high proportion of subjects [5–7]. A meta-analysis of published studies until 2013 calculated that the mean efficacy of LEV in convulsive benzodiazepine-resistant status SE was 69% [8].

The aim of the present study conducted as a prospective registry under normal clinical conditions was to evaluate the spectrum of application in daily use and the efficacy and tolerability of intravenously given Levetiracetam over an observation period of 10 days.

2. Methods

The study was approved by the institutional ethic committee and was carried out according to the Declaration of Helsinki and local health regulations. Written informed consent was obtained from patients before enrolment in the study. If patients were unable to give consent, consent was requested from their legal guardian or close relatives.

The study was designed as a prospective non-interventional observational trial (according to §67.6 AMG [Medicinal Products Act]) in 17 neurological and neuropediatric centres in Germany from May 2008 to March 2009. Patients with any type of seizures or epilepsy syndrome were selected if previous treatment results were unsatisfactory and anticonvulsant therapy with LEV-iv was considered.

Baseline demographics and disease characteristics as well as previous and current AED use were recorded in the Case Report Form (CRF). Seizure frequency and seizure types were captured during a 4-week retrospective baseline period. Seizures were classified according to the International League against Epilepsy (ILAE) classification [9]. SE was defined as ongoing seizures or seizures without recovery of consciousness or clinical baseline conditions for at least 30 min.

Treatment, including diagnosis and control, did not follow any predefined study plan or interventions but only the medical practice. LEV-iv was administered according to the Summary of Product Characteristics over a 15 min period. Titration rate and final dose were determined based on the patient's response to therapy. The physician determined whether baseline AEDs were modified.

The observational period was 10 days with daily documentation of LEV-iv administration and type and frequency of the seizures, currently used drugs and doses, and adverse events (AEs). In addition, patients and physicians assessed treatment efficacy and tolerability at study end as well as handling of LEV-iv by physicians using a five-step scale. Without further operational definition patients and physicians were ask to rate efficacy and tolerability as 'very good', 'good', 'satisfactory', 'sufficient' or 'insufficient' and physicians were ask to rate handling of LEV-iv and the conversion to oral LEV treatment as 'very easy', 'easy', 'normal', 'difficult' or 'very difficult'.

Descriptive statistical methods like frequency counts and summary statistics with arithmetic mean, standard deviation (±SD) and median were used. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA, www.meddra.org). Missing values were not imputed.

3. Results

In 95 patients treatment with LEV-iv was started and their data was included in the safety set. Two patients were excluded from the efficacy analysis due to lack of sufficient seizure outcome data. The remaining 93 patients were included into the analysis. Median observation period was 10 days (range 1–376 days), median treatment duration was 2 days (range 1–13 days). 56% of patients had a LEV-iv treatment duration longer than 2 days.

Approximately half of patients were female, no woman was pregnant. Median age was 66 years (range 0.7–90.3 years), 15% of patients were children ≤16 years. In 59% of patients seizures were diagnosed within the last 24 h before study entry, in 25% 2–30 days before, 10% had a pre-existing epilepsy diagnosis longer than 30 days and only 6% for more than a year. Therefore, it can be concluded that at approximately 60% of patients or more did not have pre-existing epilepsy. Demographic data and baseline characteristics are summarized in Table 1.

58 (62%) patients were diagnosed with focal seizures, 23 (25%) patients had generalized seizures, and in 8 (9%) patients seizures were non-classifiable (4 patients data not available). Aetiology was most frequently cerebrovascular (41%), tumorous (10%) or infect-related (9%). 15 patients (16%) had acute seizure clusters and 55 patients (59%) had confirmed SE. Of those with SE, 41 patients (75%) had SE for the first time. Duration of SE before LEV-iv

Table 1
Patient characteristics.

Total	93 Patients
Female/male, *n* (%)	50/43 (54%/46%)
Mean age ± SE	55 ± 28 years
Median age (range)	66 (0.7–90) years
≤18 years	16 (17%)
19 to <50 years	14 (15%)
≥50 years	63 (68%)
Seizure type, *n* (%)	
Generalized	23 (25%)
Focal	58 (62%)
Not classifiable	8 (9%)
Data not available	4 (4%)
Aetiology, *n* (%)	
Cerebrovascular	38 (41%)
Dementia	5 (5%)
Infection	8 (9%)
Traumatic	7 (8%)
Residual situation	7 (8%)
Metabolic	3 (3%)
Genetic	4 (4%)
Tumour	9 (10%)
Toxic	5 (5%)
Malformation	3 (3%)
Others	23 (25%)
Status epilepticus, *n* (%)	55 (59%)
Seizure clusters, *n* (%)	15 (16%)
Duration of SE, *n* (%)	
<24 h	22 (40%)
24–72 h	13 (24%)
>72 h	15 (27%)
Not available	5 (9%)

administration was <24 h in 40% of SE patients, 24–72 h in 24% of SE patients and >72 h in 27% of SE patients.

Prior to the study 39 (42%) patients were treated with multiple AEDs and 27 patients (29%) with psycholeptics. Table 2 shows all drugs patients received at inclusion to the study. Of all patients with status epilepticus 47% had received other pharmacological treatment before LEV-iv was applied (41% benzodiazepines, 26% other iv-antiepileptics and 2% anaesthetics). Of all 95 patients 21 were pretreated with oral levetiracetam and 3 patients had already been treated with LEV-iv previously, thus 71 were naive to LEV. Overall, 80 (86%) patients had at least one concomitant disease, most frequently nervous system disorders ($n = 44$, 47%), vascular disorders ($n = 31$, 33%) and/or metabolic disorders ($n = 23$, 25%).

The main reasons for the introduction of LEV-iv (multiple answers possible) were in 29 (31%) patients a non-convulsive SE and in 18 (19%) patients convulsive SE. 18 (19%) patients had acute seizures or seizure series, respectively. In 17 (18%) patients, coma was documented as the main reason and in 21 patients other reasons were predominant, such as anticonvulsive prophylaxis, gastrointestinal reasons, planned surgery, or invasive examination. In 78 patients the acute reason for seizures was known, most frequently it was fever (11 patients), followed by encephalitis (4 patients) and dehydration (2 patients).

Table 2
Concomitant drugs patients received at inclusion to the study (total $n = 93$).

	n (%)
Patients receiving at least 1 drug	80 (86%)
Antiepileptics	39 (42%)
Psycholeptics	27 (29%)
Diuretics	20 (22%)
Analgesics	19 (20%)
Renin–angiotensin inhibitors	18 (19%)
Antibacterial drugs for systemic use	17 (18%)
Antacids	17 (18%)
Ophthalmics	17 (18%)
Beta blocking agents	16 (17%)
Antithrombotics	13 (14%)
Corticosteroids for systemic use	10 (11%)
Psychoanaleptics	10 (11%)

Table 3
LEV-iv doses ($n = 93$).

Dose per day (mg)	
Mean ± SE	1632 ± 863
Median (range)	1500 (110–6000)
Duration of LEV-iv, *n* (%)	
1 day	30 (32%)
2 days	19 (20%)
3–5 days	25 (27%)
>5 days	18 (19%)
Median (range) days	2 (1–13)

In 92 patients (99%) LEV was diluted in normal saline (in one patient in Ringer-lactate solution) and administered through a peripheral line. In 9 patients concomitant medication (analgetics, antiepileptics or antipsychotics) was administered with the infusion. The median dose of LEV-iv was 1500 mg (range 110–6000 mg) per day. Median number of infusions was 4 per patient (range 1–20) and median duration of treatment was 2 days (range 1–13 days) (Table 3). Mean daily dose was increased in 21 patients (23%) and reduced in 18 patients (19%).

Cardiovascular parameters (systolic and diastolic blood pressured, and pulse frequency) were documented in 81 patients (85%) prior, in 63 patients during and in 67 patients after LEV-iv infusion. Mean absolute values for systolic and diastolic blood pressure were 127/71 prior LEV-iv, 119/66 during LEV-iv and 123/69 after LEV-iv (in mmHg). Mean absolute values for pulse frequency were 90 prior LEV-iv, 89 during LEV-iv and 88 after LEV-iv (in bpm). Mean relative changes after LEV-iv compared to prior were −2% (SD 14%) for systolic and +1% (SD 20%) for diastolic blood pressure, and +1% (14%) for pulse frequency. Cardiovascular parameters were rated abnormal in 2 patients prior LEV-iv, in 3 patients during LEV-iv, and in one patient after LEV-iv.

Electrocardiograms were recorded in 62 prior LEV-iv, in 52 during, and in 49 after LEV-iv infusion. Prior to the LEV-iv infusion 5 patients showed abnormalities in ECG, but during and after infusion no abnormality was found.

SE or seizure clusters could be terminated in 58 of 70 patients (83%) in temporal relationship with LEV-iv administration. Overall efficacy of LEV-iv was rated by the physicians as 'very good' in 38 patients (41%), 'good' in 34 patients (37%), 'satisfactory' in 5 patients (5%), 'sufficient' in 7 patients (8%) and "insufficient" in 8 patients (9%, data of 1 patient not available). Patients self-assessed efficacy as 'very good' in 17 cases (39%), 'good' in 43 cases (19%), 'satisfactory' in 2 cases (1%), 'sufficient' in 2 cases (5%) and "insufficient" in 5 cases (11%, data of 49 patients not available).

A total of 29 treatment emergent adverse events (TEAEs) were reported in 17 of the 95 patients from the safety set (72%) during the observational period. Ten of these in 6 patients were at least possibly related to LEV-iv treatment as judged by the physician (Table 4). Slight decrease of blood pressure during the infusion was captured most frequently ($n = 3$). In these patients the adverse event was resolved by reducing the speed of infusion. All other side effects (restlessness, fatigue, loss of appetite, cough, increased upper airway secretion, infusion-related reaction, insufficient efficacy) occurred only in one patient each. All side effects are in line with the Summary of Product Characteristics of Keppra®.

Thirteen serious TEAEs (sTEAEs) occurred in 8 patients (8%). Three patients (3%) died due to their basic diseases and two patients had an aggravation of seizures. All other sTEAEs occurred

Table 4
TEAEs related to LEV-iv ($n = 10$ in 6 patients).

	N
Decrease of blood pressure	3
Restlessness	1
Fatigue	1
Loss of appetite	1
Cough	1
Increased upper airway secretion	1
Infusion-related reaction,	1
Insufficient efficacy	1

only in one patient each. None of the reported sTEAEs had a causal relationship to LEV-iv, as rated by the treating physicians.

Overall tolerability of LEV-iv was rated by the physicians as 'very good' in 46 patients (50%), 'good' in 42 patients (46%), 'satisfactory' in 2 patients (2%), 'sufficient' in 1 patient (1%) and 'insufficient' in 1 patient (1%, data of 1 patient not available). Patients self-assessed tolerability as 'very good' in 15 cases (34%), 'good' in 23 patients (52%), 'satisfactory' in none, 'sufficient' in 3 patients (7%) and "insufficient" in 3 patients (7%, data of 49 patients not available).

Physicians rated overall handling of LEV-iv in 58 cases (67%) as 'very easy', in 25 cases (25%) as 'easy' and in 4 cases (5%) as 'normal'. No one judged the handling as 'difficult' or 'very difficult' (data of 6 patients not available). After the LEV-iv period, 74 patients (80%) continued on oral levetiracetam. Of 71 (75%) patients, that had been naïve to LEV before the study, 47 (66%) continued on oral levetiracetam. The adjustment from intravenous to oral administration was rated as 'very easy' in 49 cases (63%), 'easy' in 25 cases (32%) and 'normal' in the remaining 4 patients (5%, data of 15 patients not available).

In 14 patients (31%) treatment was discontinued during the observational period. One patient discontinued due to an adverse event (increased upper airway secretion). In three patients, anticonvulsant response was considered insufficient and LEV-iv was discontinued. Two patients discontinued on their own request, another patient was lost to follow up. The remaining 6 patients discontinued due to adverse events related to their basic disease.

4. Discussion

This prospective non-interventional observational trial presents 95 patients in whom LEV-iv was administered. Most of them were patients with acute status epilepticus at the time of presentation. In 83% of patients, status epilepticus or seizure clusters terminated after LEV-iv administration. Only mild, transient side effects were observed.

It has been suggested that LEV-iv may be a safe and effective therapy in the management of SE, although data to support this are limited. In animal models, LEV-iv has been reported to abort SE, as well as enhance the effect of diazepam, even when both were given at subtherapeutic doses [10]. Evidence to support the use of LEV-iv for SE in humans was initially limited to retrospective chart reviews and case reports.

One of the first reports of LEV as treatment in SE documented termination of refractory SE in 3 of 12 patients (26%) under treatment with oral LEV as add-on therapy [11]. Another report by Rosetti and colleagues described the outcome of 23 patients who received nasogastric LEV within 4 days of SE onset [12]. Ten of these patients (43%) responded to a median dose of 2000 mg/day. It was concluded that escalating the dosage beyond 3000 mg/day is unlikely to provide an additional effect, and that early treatment with LEV-iv leads to increased efficacy compared to later introduction of treatment.

Additional case series followed and included patients with repetitive seizures of different seizure types. Patel et al. described six patients with complete cessation of SE 12–96 h after initiation of oral LEV [13]. Knake et al. reported 18 episodes of SE in 16 adults, which subsided after the addition of LEV-iv to the drug regimens [14]. Berning et al. described termination of SE in 25 of 32 elderly and multimorbid patients (78%) after administration of LEV-iv plus benzodiazepines [15]. Similar responder rates after treatment with LEV-iv were found by Gamez-Leyva et al. and Möddel et al. reporting termination of SE in 71% of 43 patients, respective 69% of 36 patients [5,16]. As second-line treatment after unsuccessful use of benzodiazepines LEV-iv had a success rate of 38/78 patients without significant adverse events [17]. LEV-iv was especially effective in elderly patients with vascular SE, while cryptogenic SE, primarily generalized SE and SE due to brain anoxia were associated with poor response [16]. LEV-iv seems to be reasonably tolerable even in multimorbid and critically ill patients, and even when high dosages were applied within short time [15]. Another study compared eight patients with non-convulsive SE in whom SE was terminated by LEV-iv within 3 days in 11 patients treated with conventional intravenous AED. The efficacy was similar, but the side-effects were much more severe with conventional AEDs [18]. Larger cohorts in adult patients basically confirmed an useful risk-benefit ratio of LEV-iv [6,7,19]. Data to support LEV-iv use in children with acute seizures or refractory SE are even more limited, but in case reports and in observational studies LEV-iv has also been reported to be an effective and safe adjuvant therapy in children with refractory SE [20,21]. The established status epilepticus trial (ESET) [22] was designed to compare the use of fos-phenytoin, valproate and levetiracetam regarding their efficacy in treating SE among patients older than 2 years after the use of benzodiazepines, and will possibly add further information to this important topic.

Consistently with other studies, there were few side effects reported, and none of them were considered as serious. There were 3 deaths within the observation time, representing 3% of study population. However, all of these deaths could be attributed to the underlying disease and were not related to the use of LEV-iv. This suggests that LEV-iv has no significant side effects and is well tolerated in patient population of different ages, including children and elderly. Also, it has no common cardiovascular side effects.

This prospective, observational study is limited by multiple factors including its uncontrolled naturalistic design with an inconsistent population, aetiology and semiology of seizures. Also, there is missing or incomplete data for some of the patients. However, it adds valuable information about the treatment of patients with SE and difficult to treat seizures or epilepsies in daily practice. Efficacy, tolerability and handling under routine practice were rated in most patients as good or very good.

5. Conclusions

The present study demonstrates that LEV-iv shows favourable qualities regarding efficacy tolerability and handling for the use in patients of different ages. Our study included a large number of patients with SE. In these patients, similar results to retrospective chart reviews were achieved supporting the use of LEV-iv as alternative treatment option in SE. Large, prospective, randomized, controlled studies are warranted to investigate the efficacy and safety of LEV-iv for the treatment of SE.

Conflict of interest statement

Dr. Lang received a research grant from UCB, travel grants from UCB and Eisai, speakers honoraria from UCB, Eisai, Desitin, Janssen-Cilag and Medtronic and has served as a paid consultant for UCB

and Eisai. Dr. Stephani received speakers honoraria from UCB, Eisai, Viropharm, Desitin and has served as a paid consultant for UCB and Eisai. Dr. Burghaus received speakers honoraria from UCB, Eisai, and Desitin. Dr. Evers received honoraria and research grants within the past five years by AGA Medical (now St Jude), Allergan, Almirall, AstraZeneca, BerlinChemie, CoLucid, Desitin, Eisai, GlaxoSmithKline, Ipsen Pharma, Menarini, MSD, Novartis, Pfizer, Reckitt-Benckiser, UCB. Dr. Kellinghaus received speakers honoraria from UCB, Eisai, Desitin and has served as paid consultant for UCB and Eisai. Dr. Seitz received consultant honoraria from UCB, Desitin, and Eisai. Dr. Happe has received speakers honoraria, travel grants and payment for advisory boards from UCB Pharma and mundipharma as well as travel grants from Abbott during the last three years. Dr. Bast received honoraria from Desitin, Esai, UCB and Viropharma as speaker and/or consultant. Dr. Hoffmann received research grants, speakers honoraria or payments for advisory boards from Allergan, Bayer, Biogen,Boehringer Ingelheim, CSL Behring, Diamed, Genzyme, Grifols, Ipsen, Merck-Serono, Merz, Novartis, Octapharm, Pfizer, Teva, Talecris, UCB. All other authors reported no conflicts of interest.

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