New treatment options in status epilepticus: a critical review on intravenous levetiracetam

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Abstract: The effectiveness of levetiracetam (LEV) in the treatment of focal and generalised epilepsies is well established. LEV has a wide spectrum of action, good tolerability and a favourable pharmacokinetic profile. An injectable formulation has been released as an intravenous (IV) infusion in 2006 for patients with epilepsy when oral administration is temporarily not feasible. Bioequivalence to the oral preparation has been demonstrated with good tolerability and safety enabling a smooth transition from oral to parenteral formulation and *vice versa*. Although IV LEV is not licensed for treatment of status epilepticus (SE), open-label experience in retrospective case series is accumulating. Until now (August 2008) 156 patients who were treated with IV LEV for various forms of SE have been reported with an overall success rate of 65.4%. The most often used initial dose was 2000–3000 mg over 15 minutes. Adverse events were reported in 7.1%, and were mild and transient. Although IV LEV is an interesting alternative for the treatment of SE due to the lack of centrally depressive effects and low potential of drug interactions, one has to be aware of the nonrandomised retrospective study design, the heterogenous patient population and treatment protocols, and the publication bias inherent in these type of studies. Only a large randomised controlled trial with an adequate comparator will reveal the efficacy and effectiveness of this promising new IV formulation.

Keywords: Intravenous levetiracetam, status epilepticus, treatment algorithm

Introduction

Levetiracetam (LEV) is a new antiepileptic drug (AED), which is effective in focal and generalised epilepsies. In 1999, LEV received FDA approval as adjunctive therapy for partial onset seizures in adults with epilepsy, in 2003, an oral solution was released. LEV is now licensed as monotherapy for the treatment of partial onset seizures with and without secondary generalization and as add-on therapy for myoclonic and primary generalised tonic clonic seizures. In 2006, an intravenous (IV) formulation of LEV has been approved for the treatment of patients with epileptic seizures who are temporary unable to swallow. Moreover it allows the clinician a rapid titration in seizure emergency situations, like seizure clusters or status epilepticus (SE). IV LEV is not licensed for treatment of SE, but the results from recent retrospective uncontrolled studies suggest that IV LEV may be a useful alternative treatment option in patients with various forms of SE. SE is refractory to current first-line (benzodiazepines) treatment and second-line anticonvulsants (phenytoin, phenobarbital or valproic acid) in 30–40%. Therefore, additional treatment options yielding a higher success rate and a better tolerability are desirable. In a recent consensus document of the ILAE Task Force on Status Epilepticus summarising the results of a workshop held at the First London Colloquium on Status Epilepticus, IV LEV is listed as a 'treatment option for the stage of established SE' [Shorvon *et al*. 2008a]. Although there are no randomised controlled studies available, clinicians used this drug as soon as it was available on the market on an off-label basis [Trinka, 2007b; Shorvon *et al*. 2007b]. In the absence of class I or II evidence there is a need to inform the community adequately about the pharmacologic and experimental basis of the use in SE, the accumulated open-label experiences with their inherent bias, and the possible risks associated with this new

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treatment option. The purpose of this review is to critically review the currently available evidence of IV LEV in SE and its pharmacologic basis.

Identification of studies and search strategy

To identify completely published studies an electronic search of PubMed (01/2005–08/2008) and hand search of congress proceedings was performed. All studies published as full paper or abstract were eligible, if they investigated the efficacy of IV LEV in the treatment of SE. They were also included in this review, if they investigated the efficacy in a mixed population of patients with SE and other acute seizures or seizure clusters. Abstracts of single case reports, series less than three patients or series with insufficient description of diagnosis, type of status, type of intervention or outcome were not included. If an abstract was followed by a full paper, only the full paper was acknowledged. If an abstract was followed by another abstract of the same group of authors, the report with the higher patient number was included in this survey. If the patient numbers were identical, the first report of the group was included.

Pharmacokinetics of intravenous levetiracetam

LEV is characterised by a linear and time-invariant pharmacokinetic profile with low protein binding (less than 10% bound), lack of hepatic metabolism and minimal risk of systemic side-effects and drug interactions. Plasma half-life of LEV differs between 6 and 8 hours across studies. Sixty-six per cent of the dose is excreted unchanged by the kidneys. The major metabolic pathway of LEV (24% of dose) is an enzymatic hydrolysis of the acetamide group. The metabolites have no known pharmacological activity and are renally excreted. Overall the pharmacokinetic profile is favourable and of potential advantage in the treatment of status epilepticus (it has been reviewed extensively [Patsalos *et al.* 2006; Patsalos, 2004, 2003, 2000]).

Three studies evaluated efficacy, pharmacokinetics, tolerability and safety of IV LEV compared with oral administration, demonstrating bioequivalence [Baulac *et al.* 2007; Ramael *et al.* 2006a, 2006b]. Single-dose bioavailability of an IV formulation of LEV (15-minute infusion of 1500 mg) was equivalent compared to oral tablets in 18 healthy subjects [Ramael *et al.* 2006a]. In the same subjects multiple-dose tolerability and pharmacokinetics of 1500 mg IV LEV was compared with placebo in nine successive doses at 12-hour intervals. After multiple twice-daily infusions, steady state was reached within 48 hours. The most common treatment-related side-effects were somnolence and postural dizziness [Ramael *et al.* 2006b]. In another study, Ramael and Co-workers evaluated safety and tolerability of IV LEV at higher doses and faster infusion rates (2000 mg, 3000 mg and 4000 mg over 15 minutes and 1500 mg, 2000 mg and 2500 mg over 5 minutes) in 48 healthy subjects [Ramael *et al.* 2006a]. For the 15-minute infusion of the 2000-, 3000-, and 4000-mg doses, the mean C_{max} values were 55.6 μg/ml, 81.2 μg/ml and 145 μg/ml, which were achieved at (t_{max}) 0.5, 0.375, and 0.25 hours, respectively. For the 5-minute infusion of the 1500-, 2000-, and 2500-mg doses, the mean C_{max} values were 46.9 μg/ml, 60.6 μg/ml, and 94.3 μg/ml at 0.092, 0.125 and 0.083 hours respectively [Ramael *et al.* 2006a]. Usual plasma concentrations in chronic oral treatment ranges from 6 μg/ml to 17 μg/ml (trough) and 15.3 μg/ml to 42.5 μg/ml (peak) [Surges *et al.* 2008; Patsalos, 2000]. Adverse events like dizziness, somnolence, fatigue and headache after IV administration of LEV were comparable to the safety profile for the oral formulation and showed no clear relation to dose or infusion rate [Ramael *et al.* 2006a]. Baulac and Co-workers investigated the short-term tolerability of IV LEV (500–1500 mg/100 ml, 15 minutes, b.i.d.) as a substitute of the same oral dose in 25 adult patients with partial-onset seizures receiving adjunctive oral LEV. The tolerability profile was consistent with that of oral LEV with headache and fatigue (20%) as the most often reported adverse events [Baulac *et al.* 2007]. All events were judged as mild or moderate in severity, no discontinuations, and no serious adverse events or deaths were reported. No adverse event was related to seizure worsening during IV LEV treatment or brief follow-up [Baulac *et al.* 2007].

Mechanism of action of levetiracetam

The mechanism of action of LEV is poorly understood. In contrast to other AEDs it has no effect in two classic screening tests for AEDs in mice and rats, the maximal electroshock seizure (MES) and pentylenetetrazol (PTZ) models [Klitgaard *et al.* 1998; Loscher and Honack, 1993]. In other screening tests in rodents involving acute electrical or chemical stimulation it has

revealed a weak or modest effect [Loscher and Honack, 1993; Gower *et al*. 1992]. This is in striking contrast to the potent seizure suppression in genetic animal models and kindling models of chronic epilepsy [Loscher *et al*. 2000; Gower *et al*. 1995; Loscher and Honack, 1993]. Recently, the cellular mechanism of action in epilepsy has been comprehensively reviewed by Surges and Co-workers [2008]. In particular the specific binding of LEV to the vesicle protein SV2A [Kaminski *et al*. 2008; Lynch *et al*. 2004] is unique among the AEDs, which are currently in clinical use. However, the effect of chronically applied LEV seems to differ fundamentally from the acute effects of the drug and yet it is hard to conceive the relative contribution of the known mechanisms of LEV to its overall clinical efficacy in multiple seizure types [Surges *et al*. 2008].

The major inhibitory neurotransmitter in the central nervous system is gamma amino butyric acid (GABA). Drugs used as first-line agents in acute seizures and SE, like IV benzodiazepines or barbiturates exert their powerful antiseizure activity via the $GABA_A$ receptors. Contrastingly, there is no evidence for a direct effect of acutely applied LEV on the pre- or postsynaptic site of naïve GABAergic synapses [Margineanu *et al*. 2003, 1995], and $GABA_A$-receptor-mediated inhibitory currents of neuronal cell cultures and slice preparations [Poulain and Margineau, 2002; Rigo *et al*. 2002; Birnstiel *et al*. 1997]. However, two recent studies using hippocampal preparations and neuronal cultures of epileptic patients demonstrated that acutely applied LEV was able to reduce the zinc-induced allosteric inhibition of $GABA_A$ receptors [Rigo *et al*. 2002] and the rundown of repeatedly applied $GABA_A$ receptor currents [Palma *et al*. 2007]. Though, the stabilisation of the $GABA_A$ currents with reduced rundown after repeated stimulation appeared late (after 3 hours), it may still be relevant for the treatment of SE. Recent data also suggest that LEV also alters glutamatergic neurotransmission. *In vivo* experiments with iron-chloride ($FeCl_3$)-induced epileptic rats demonstrated suppression of glutamatergic excitation and enhancement of GABAergic inhibition in the epileptic and nonepileptic rats as a result of upregulation of glutamate and GABA transporters and downregulation of the glutamate transporter regulating protein GTRAP3-18 [Ueda *et al*. 2007]. *In vitro* experiments demonstrated a limited (<20%) reduction of evoked excitatory postsynaptic potentials in striatal slices [Costa *et al*. 2006] and a reversible reduction in AMPA-receptor currents in cortical neuron cultures of nonepileptic mice [Carunchio *et al*. 2007]. In another *in vitro* experiment, there was no effect of acute LEV application in evoked field potentials in hippocampal slice preparations of nonepileptic rats, whereas 3 hour preincubation with LEV led to a relative decrease in the amplitude of late field potentials which was use dependent [Yang *et al*. 2007].

Although the mechanism of action is far from clear, LEV seems to share some targets (with other antiepileptic drugs such as delayed rectifier channels and N- and P/Q-type calcium channels). In addition, LEV may exert some of its mechanisms of action via the unique binding to the vesicle protein SV2A. The mechanisms of action have recently been reviewed critically by Surges and Co-workers [2008].

Experimental basis for the use of levetiracetam in status epilepticus

In vivo studies showed that pretreatment with LEV protected against secondarily generalised activity from focal seizures induced by pilocarpine in mice (ED50 value = 7 mg/kg, i.p.), and pilocarpine and kainic acid in rats (minimum active dose = 17 and 54 mg/kg, respectively, i.p.) [Klitgaard *et al*. 1998]. Mazarati and Co-workers [2004] examined the effects of IV LEV in an experimental model of self-sustaining SE, induced in rats by perforant path simulation. Pre-treatment with IV LEV decreased (30 mg/kg) or prevented (50–1000 mg/kg) the development of self-sustaining seizures. During the maintenance phase of self-sustaining SE, IV LEV shortened (at 200 mg/kg) or aborted seizures (in doses of 500 or 1000 mg/kg). Thus, LEV was very effective when given before SE was established, was potent at high doses in established SE, but failed when given after very long stimulation [Mazarati *et al*. 2004]. Interestingly, coadministration of IV LEV significantly enhanced the anticonvulsant effects of diazepam, even with subtherapeutic levels of both drugs suggesting an (super-) additive effect.

Gibbs and Co-workers [2006] studied the effect of LEV on self-sustaining limbic SE in rats. Though LEV did not supress seizure activity at doses of 200 mg/kg or 1000 mg/kg given 15 minutes into SE, it exhibited significant improvement in behavioural seizure parameters. At doses of

1000 mg/kg it significantly improved several biochemical parameters, in many instances comparable to sham control levels suggesting neuroprotective properties in the self sustaining limbic SE model [Gibbs *et al.* 2006]. However, the same dose (1000 mg/kg) was not effective in preventing mitochondrial damage, when applied 5 hours after termination of SE [Gibbs and Cock, 2007]. Another study did not find any effect on epileptogenesis, neuronal damage, and behavioral alterations in rats treated with LEV after SE induced by electrical stimulation of the basal amygdala [Brandt *et al.* 2007]. Treiman and Co-workers [2007] found no efficacy of LEV in the cobalt-homocysteine model of experimental SE (in doses up to 1800 mg/kg). The authors suggested that a late entry to the brain was responsible for the lack of efficacy in this rat model.

Remarkably, LEV is highly effective in late-onset seizures of experimental models of SE but less effective if at all in the acute phase. In sum, our current knowledge is far from complete, but available data suggest that LEV is effective in experimental SE when applied early in the course, especially when coadministered with benzodiazepines. The antiseizure effect undergoes a time-dependent decrease, as seen with most other drugs clinically used in SE. LEV was neuroprotective in some models when applied early in the course, but not in others, therefore a definite conclusion on its neuroprotective properties in SE can not be drawn to date.

Clinical studies in status epilepticus

Oral levetiracetam

The first case reports of LEV in SE used the oral formulation, most often applied via a nasogastric tube in critically ill patients with SE [Bhatia *et al.* 2008; Trabacca *et al.* 2007; Feleppa *et al.* 2006; Saguer *et al.* 2006; Veldkamp and Swart, 2006; Mehta and Wu, 2005; Pastor-Milan *et al.* 2005; Zaatreh, 2005]. These studies included 15 patients with varied types of SE (nonconvulsive = 11, convulsive = 2, myoclonic with coma = 1, not otherwise specified = 1) and suggested a good clinical efficacy with suppression of seizures in almost all cases and good tolerability of acutely administered and rapidly loaded oral LEV. Of practical relevance are two single case reports on patients with SE associated with acute intermittent porphyria, who were successfully treated with rapid loading of oral LEV, suggesting that LEV may safely be used in porphyria [Bhatia *et al.* 2008; Zaatreh, 2005].

Rosetti and Bromfield reported 13 episodes of SE (simple partial = 1, complex partial = 8, generalised convulsive = 4) in 12 patients treated with oral add on LEV [Rossetti and Bromfield, 2005]. The doses ranged between 1000 and 6000 mg/day. Three patients (23%) were 'probable responders', one responded to the treatment but subsequently died and five (38%) had an undetermined response [Rossetti and Brom field, 2005]. In a later study by the same authors the treatment responses of 23 patients, who received a mean daily dose of 2000 mg LEV (range 750–9000 mg) were retrospectively analysed [Rossetti and Bromfield, 2006]. Ten patients (43%) responded; all had received LEV within 4 days after the beginning of SE, which was significantly earlier than in nonresponders. None of the responders received LEV doses above 3000 mg/day. Other clinical or demographic factors were not predictive of good response. The authors suggested, that oral LEV should be instituted early in the course of status and doses beyond 3000 mg/day are unlikely to yield additional benefit [Rossetti and Bromfield, 2006]. Falip and Co-workers reported retrospectively on six patients with acute symptomatic focal SE who were treated with oral LEV. Doses were rapidly titrated with 1000–2000 mg/day starting dose and 2000–3000 mg/day maintenance dose. Four of six patients responded to the treatment; two reported somnolence and one responder died due to the underlying disease [Falip *et al.* 2006]. Another retrospective study reported six patients with refractory focal SE who responded to oral levetiracetam (500–3000 mg/day) within 12–96 hours. Four patients had acute symptomatic SE, two had a previous epilepsy diagnosis [Patel *et al.* 2006]. Rupprecht and Co-workers retrospectively analysed eight patients with nonconvulsive SE (NCSE), who received rapidly titrated oral LEV and compared the results with 11 patients with NCSE treated with conventional IV AEDs [Rupprecht *et al.* 2007]. The etiology of SE was vascular in four, viral encephalitis in one, and meningeoma in two patients. Four patients did not receive previous AED, two had carbamazepine, one phenytoin and one topiramate. Four patients had a previous history of focal onset seizures. The starting dose of LEV ranged between 500 and 1000 mg/day and was increased up to 2000 mg/day. All seizure activity stopped within

1–3 days after onset of oral LEV. The results did not differ from the 11 patients with conventional treatment, which consisted of IV benzodiazepines, valproate and phenytoin regarding efficacy, but patients in the LEV group had significantly fewer adverse events. One of eight had dizziness in the LEV group compared to toxic hepatitis after valproate (1/11), VPA induced hyperammonemic encephalopathy (3/11) and phenytoin intoxication (1/11) [Rupprecht *et al.* 2007].

Thus, there were in sum 58 patients with various forms of SE treated with oral LEV (500–9000 mg/day) reported in 13 case reports or case series with responder rates of 69% (43–100%) within 12 hours to 4 days after onset (onset of response was not always reported). The most often used effective dose was 2000–3000 mg/day. Adverse events were only reported in three patients (somnolence, dizziness) and were judged as mild. Almost all authors encouraged the early use of LEV as adjunctive therapy in SE.

Intravenous levetiracetam

Currently, there are seven published papers available, including three retrospective case series [Goraya *et al.* 2008; Ruegg *et al.* 2008; Knake *et al.* 2007] and four case reports [Abend *et al.* 2008; Altenmuller *et al.* 2008; Farooq *et al.* 2007; Schulze-Bonhage *et al.* 2007] on IV LEV. The overall success rate in these studies was 81.6%. All published full reports on IV LEV in SE are nonrandomised, uncontrolled retrospective case series (Table 1).

Retrospective case series

Knake and co-workers reported their experience with IV LEV for the treatment of 16 patients with 18 episodes of focal SE (complex partial SE with motor symptoms = 12, complex partial seizures without motor symptoms = 2; secondary generalised SE = 2) refractory to benzodiazepines [Knake *et al.* 2007]. The etiology was acute symptomatic in ten patients, cryptogenic in four, and remote symptomatic in four. Seven patients had a previous history of seizures. All patients but two received lorazepam as first stage treatment; the remainder had diazepam. Five patients received IV valproate before IV LEV; one received IV valproate and phenytoin before IV LEV was chosen. The clinical decision to apply IV LEV after failure of benzodiazepines was drawn in patients with elevated liver enzymes, cardiac arrhythmia or multiple comedication. SE was controlled in all patients, by the given combination of drugs. The loading dose of IV LEV varied between 250 mg and 1500 mg and was given within 30 minutes. The maintenance dose was 1000–7000 mg over the next 24 hours. There were no systemic or local adverse events except mild somnolence after termination of SE in two patients. Three patients received LEV prior to the SE and all but one (not assessed) received oral LEV after termination of SE (range 1500–3250 mg/day)

Another retrospective study reported on 50 critically ill patients treated with IV LEV for with various indications [Ruegg *et al.* 2008]. Twenty-four of them had SE, including three with post-anoxic myoclonus. Patients received 20 mg/kg over 15 minutes, followed 6 hours later by administration of 15 mg/kg IV LEV twice daily. SE ceased in 16/24 (67%) including four patients, who received LEV as first stage treatment for simple partial or NCSE because of severe obstructive pulmonary disease whereas the other patients received midazolam, valproate or phenytoin as comedication. Two patients died during the observation period due to their underlying disease (herpes simplex encephalitis, hypoxic encephalopathy after cardiopulmonary resuscitation). There were no serious adverse events reported; two patients in the whole series ($n = 50$) developed transient thrombocytopenia (55.000 and 82.000 µl) [Ruegg *et al.* 2008].

Goraya and Co-workers reported their experiences of IV LEV in a mixed population of children, adolescents and young adults, ranging from 3 weeks to 19 years [Goraya *et al.* 2008]. Patients received a mean dose of 50 mg/kg/day for a mean duration of 4.5 days. Two patients had status epilepticus refractory to phenytoin and phenobarbital due to cortical dysplasia (age 3 weeks) or nonaccidental head trauma (age 4 months); two other had acute repetitive seizures unresponsive to phenytoin and with multiple allergic drug reactions to AEDs. SE was aborted in one and improved in the other patient; acute repetitive seizures were fully controlled in both instances. Patients initially received 20–40 mg/kg in 15 minutes every 8 hours in infants and every 12 hours in older patients. The maximum daily dose was 115 mg/kg and 88 mg/kg in patients with status epilepticus, 48 mg/kg and 29 mg/kg in those with acute repetitive seizures. The authors reported that 'no adverse events were noted . . . and in no patients was intravenous

Table 1. Clinical characteristics and outcomes of patients with status epilepticus treated with intravenous levetiracetam, published as full papers.

Study	Patients	Age yrs (range)	Indication for IV LEV	Aetiology	Treatment	Outcome	Adverse events
Abend *et al.* 2008	1	23	1 = refractory complex partial SE	Symptomatic (stroke)	30 mg/kg (1840 mg) (rate not given)	100% (control of SE within 40 min)	None
Altenmüller *et al.* 2008	1	37	1 = absence SE	Idiopathic epilepsy, habitual absence SE	500 mg/5 min followed by 500 mg/15 min	100% (observation period 6 h)	None
Farooq *et al.* 2007	2	82–83	2 = complex partial SE	Remote symptomatic (stroke)	1000 mg/15 min	100% (control of SE within 20–25 min	None
Goraya *et al.* 2008	4	3 weeks to 16 years	2 = SE nos 2 = acute repetitive seizures	Symptomatic	20–40 mg/kg/15 min. max daily dose 115 mg/kg/day	50% 1 with marked seizure reduction 1 complete control of SE	None
Knake *et al.* 2008	16 with 18 episodes	35–90	12 = complex partial SE with motor symptoms 2 = complex partial SE without motor symptoms 4 = secondary generalised SE	Acute and remote symptomatic	250–1500 mg/30 min loading 1000–7000 mg/day maintenance	18/18 (100%) (in two episodes other AEDs were apllied after LEV)	2 = sedation
Ruegg *et al.* 2008	24/50 with SE	Adults	6 = simple partial SE 15 = complex partial SE 1 = generalised tonic–clonic SE 3 = (postanoxic) myoclonic SE*	Acute and remote symptomatic	20 mg/kg/15 min loading 15 mg/kg/12 h maintenance	16/24 (67%)	2 = thrombo-cytopenia
Schulze-Bonhage *et al.* 2007	1	29	1 = refractory complex partial SE	Cryptogenic epilepsy, AED withdrawal	1000 mg/15 min	100% control within 35 min	None

Abbreviations: AED, antiepileptic drug; IV, intravenous; LEV, levetiracetam; nos, not otherwise specified; SE, status epilepticus; yrs, years.

levetiracetam discontinued because of side effects'. [Goraya *et al.* 2008].

Case reports

Schulze-Bonhage and Co-workers were the first to report the successful treatment of refractory complex partial SE with IV LEV [Schulze-Bonhage *et al.* 2007]. The 29-year-old female patient has been suffering from cryptogenic focal epilepsy since the age of 11 years and was evaluated for epilepsy surgery. Her medication, consisting of pregabalin and oxcarbazepine, was tapered down for prolonged video-EEG monitoring and ictal SPECT recording. She developed uncontrolled generalised tonic clonic seizures, which were treated with oral lorazepam (3 mg) followed by IV loading of phenytoin (250 mg at 50 mg/minute followed by 3 hour infusion of 750 mg) resulting in a plasma level of 17.1 mg/l). The patient remained disoriented with cycling alterations of consciousness, which could be clearly diagnosed as complex partial SE during video-EEG monitoring. Consecutively, 1000 mg IV LEV was applied over 15 minutes, which terminated SE within 35 minutes. Owing to ongoing isolated complex partial seizures over the next 8 hours, a further 1000 mg IV LEV was administered, which led to sufficient seizure control. No adverse events were reported. The same group published a well-documented case of a 37-year-old patient with prolonged absence SE during video EEG monitoring [Altenmuller *et al.* 2008]. The patient received 500 mg IV LEV over 5 minutes with further application of 500 mg in 15 minutes because of insufficient response. Repeated neuropsychological examinations after 500 and 1000 mg IV LEV revealed a dose dependent improvement of function, reaching normal levels after 1000 mg of LEV. There was no relapse during a follow up of 6 hours. Abend and Co-workers reported a 23-year-old patient with *de novo* focal status epilepticus refractory to initial treatment with 0.12 mg/kg lorazepam, followed by 20 mg/kg phenytoin [Abend *et al.* 2008]. After 3 hours without effect, he received 1840 mg (30 mg/kg) IV LEV resulting in a serum level of 35 μg/ml. SE ceased within 40 minutes. Two further cases with NCSE (83 and 82 years) were reported by Farooq and Co-workers [2007]. In one patient an accidental drop of LEV levels due to missed dose led to prolonged NCSE, lasting more than 12 hours. The patient received IV LEV (1000 mg over 15 minutes), which successfully terminated NCSE including all ictal EEG activity after 25 minutes. The other patient had a prolonged NCSE (>14 hours) which was treated with IV LEV as first-stage treatment. He received 1000 mg over 15 minutes which stopped seizure activity within 20 minutes [Farooq *et al.* 2007].

The clinical and outcome data of eight retrospective case series [Moddel *et al.* 2008; Broessner *et al.* 2007; Eue *et al.* 2007; Khongkhatithum *et al.* 2007; Morton *et al.* 2007; Nersesyan *et al.* 2007; Reinshagen *et al.* 2007; Seminario *et al.* 2007] and one prospective uncontrolled (ongoing) study [Van Huizen *et al.* 2008] including 107 patients, published as abstracts only are detailed in Table 2.

In sum, 156 patients with various forms of SE were treated with IV LEV with an overall success rate of 65.4% (102/156). The reported adverse event rate was low (7.1%, 11/156). Most commonly reported adverse events were mild sedation, dizziness, headache, nausea, and transient thrombocytopenia. However, none of the published studies (apart from the interim report of a nonrandomised open trial [Van Huizen *et al.* 2008]) had a prospective design and all studies were uncontrolled. The definition of SE was not always given in detail, especially in paediatric studies and studies from refractory cases in intensive care units. In addition, most studies included rather heterogenous patient groups. The treatment protocols varied significantly and plasma levels were rarely reported. Furthermore one has to be aware of the inherent publication bias. Nevertheless, the treatment results obtained with IV LEV are promising and support the well-known broad spectrum efficacy and good tolerability of this drug.

Is there a place for intravenous levetiracetam in the treatment algorithm of status epilepticus?

The medical treatment of SE, with its most severe form generalised tonic clonic SE, still relies on potentially neurotoxic and sedative substances, like benzodiazepines, phenytoin, or phenobarbital, as a first-line agent [Shorvon *et al.* 2008a; Meierkord *et al.* 2006; Minicucci *et al.* 2006; van Rijckevorsel *et al.* 2006, 2005; Holtkamp *et al.* 2003]. The current situation is characterised by the lack of randomised controlled studies (class I or II) in this field and it is not realistic that this will be changed in the

Table 2. Clinical characteristics and outcomes of patients with status epilepticus treated with intravenous levetiracetam, published as abstracts only.

Study	Patients	Indication for IV LEV	Aetiology	Treatment	Outcome	Adverse events	Study design
Broessner *et al.* 2007	13	6 = seizure clustering during video-EEG monitoring 4 = refractory nonconvulsive SE 3 = following successful treatment of nonconvulsive SE	Not available	Bolus dose: 11/13 1000 mg 2/13 500 mg	3/4 (75%) responder	None	Retrospective case study
Eue *et al.* 2007	22	Refractory SE after BZD: 7 = complex partial 5 = generalised tonic-clonic 3 = simple partial 3 = nonconvulsive 2 = myoclonic 2 = subtle	19 = symptomatic 3 = cryptogenic	Bolus dose of 1000 mg: 12/22 15-min infusion 10/22 2 injections of 500 mg	10/22 (46%) responder: 2/2 myoclonic 2/3 simple partial 4/7 complex partial 1/3 nonconvulsive 1/2 subtle 0/5 generalised tonic-clonic 12/22 (54%) nonresponder	No serious adverse events; prolonged somnolence reported in elderly patients, but difficult to distinguish between this and post-seizure twilight state	Retrospective case study
Khongkhatithum and Goyal, 2007	34 (children)	15 = unability to swallow 15 = seizures 3 = partial SE 1 = seizure prophylaxis	14 = symptomatic 20 = cryptogenic	15–30 mg/kg bolus dose, then 15–50 mg/kg/day	28/34 (82%) responder: 6/34 (18%) nonresponder 0/3 (0%) responder with SE	None	Retrospective case study
Moddel *et al.* 2008	48	36 = SE after failing at least 1 other AED 8 = fast loading 4 = replacement for oral therapy		30/48 500–2000 mg, then 3000 mg/d (median; range 1000–9000) 18/48 not available	'Favourable' outcome (ambulatory patients) in 48% responders versus 0% nonresponders 'adverse' outcome (death or continuing coma/stupor) in 24% responders versus 100% nonresponders Letality in 4% responders versus 45% nonresponders SE: 25/36 (69%) responders	2/48 nausea and vomiting leading to aspiration pneumonia in 1	Retrospective case study

Morton *et al.* 2007	3	3 = refractory SE	2 = remote symptomatic 1 = acute symptomatic	Bolus dose: 1/3 18.4 mg/kg 1/3 18.5 mg/kg 1/3 20 mg/kg	2/3 (67%) responder	None	Retrospective case study
Nersesyan *et al.* 2007	6	6 = nonconvulsive SE	2 = idiopathic 4 = not available	6/6 1000 mg bolus dose	6/6 (100%) responder 1 responder died on day 4 due to acute respiratory failure	3/6 transient somnolence 1/6 headache	Retrospective case study
Reinshagen *et al.* 2007	6	Refractory SE: 2 = myoclonic SE 1 = complex-focal nonconvulsive SE 1 = subtle SE 1 = generalised SE 1 = burst-suppression EEG pattern	3 = acute symptomatic 1 = remote symptomatic 2 = not available	1/6 6000 mg 5/6 not available	5/6 (83%) responder 1/6 (17%) nonresponder 1 patient died	1/6 optical hallucinations after long-lasting coma under high-dose of LEV	Retrospective case study
Seminario *et al.* 2007	3	SE: 1 = epilepsia partialis continua 1 = nonconvulsive 1 = status myoclonus	1 = acute symptomatic 1 = remote symptomatic 1 = idiopathic	Bolus dose: 2/3 1000 mg 1/3 3000 mg	1/3 (33%) responder (status myoclonus) 2/3 (67%) nonresponder	No statement	Retrospective case study
Van Huizen *et al.* 2008	11	Add-on treatment to standard IV regimen in SE: 5 = generalised-convulsive 5 = partial 1 = nonconvulsive	Not available	Bolus dose: 2500 mg (added to standard IV regimen)	7/11 (64%) responder 4/11 needed ICU treatment 1/11 died on day 9 due to multi-organ failure (nonconvulsive SE)	1/11 desaturation (Sat 75% O_2) during and shortly after administration	Prospective, non randomised

Abbreviations: AED, antiepileptic drug; BZD, benzodiazepines; IV, intravenous; LEV, levetiracetam; SE, status epilepticus.

near future for several reasons, which are beyond the scope of this review, but have been addressed recently [Rosenow and Knake, 2008; Shorvon *et al*. 2008a, 2007a; Trinka, 2008]. A recent Cochrane review identified 11 studies of convulsive and nonconvulsive SE [Prasad *et al*. 2007]. It has been concluded that IV lorazepam was superior than diazepam in the early stage of SE (stage I). In addition, data from the VA trial on SE have shown that lorazepam is superior to IV phenytoin alone and as least as good as diazepam followed immediately by phenytoin or phenobarbital alone [Treiman *et al*. 1998]. Based on available class I evidence, lorazepam has been widely accepted as the treatment of choice in early SE. There are no randomised controlled trials in stage 2 (established SE) of status epilepticus and recommendations are purely based on open-label class IV studies and expert opinion [Rosenow and Knake, 2008; Trinka, 2007b; Meierkord *et al*. 2006; Kramer *et al*. 2005; Rosenow *et al*. 2002]. Current first- and second-stage treatment leaves approximately one-third of patients with SE uncontrolled, who eventually will require admission to intensive care with all the inherent risks of mechanical ventilation. Therefore, less toxic substances for the treatment of SE are needed. IV valproate is used as an alternative since the beginning of the 1990s; accumulated open-label experience has been published extensively and has been recently reviewed [Trinka, 2007b]. Although there are three randomised prospective studies from India with IV valproate available [Misra *et al*. 2006; Mehta *et al*. 2007; Agarwal *et al*. 2007], the lack of an adequate comparator, low statistical power and the unusual treatment algorithm used in these studies, make the results difficult to interpret. Levetiracetam has no significant interactions with other drugs, an almost ideal pharmacokinetic profile, a broad spectrum of efficacy, and allows a smooth transition to oral maintenance therapy. The IV solution was approved in 2006 based on bioequivalence studies and the first case reports followed within 1 year [Shorvon *et al*. 2007a]. The accumulated evidence from open-label studies suggest a high overall efficacy of around 65%, which is comparable with the effect of IV valproate or phenytoin in retrospective series [Trinka, 2007b], but suffers from several biases, concerning inclusion criteria, reporting of the results, and publication bias as the most important. Current published evidence suggests that IV LEV is remarkably well tolerated in patients with SE compared with existing treatment options. At this stage IV LEV can be regarded as a treatment option in stage 2 of generalised convulsive SE (established SE), when benzodiazepines have failed and contraindications against the use of phenytoin or valproate are present [Shorvon *et al*. 2008b; Trinka, 2007a]. Furthermore, IV LEV may be used a treatment option in stage 3 of SE (refractory SE) but its role in the treatment algorithm is unclear and has to be determined [Bleck, 2007]. In patients with absence SE, myoclonic SE, simple partial and complex partial SE, where irreversible brain damage is unlikely even after prolonged duration, IV LEV may be used earlier. As with generalised convulsive status, current strength of recommendation is low according to the available (retrospective) open-label uncontrolled (class IV) evidence. The quality of these type of studies have to be improved and peer reviewers as well as journal editors have to strengthen their criteria for acceptance.

The way out of the dilemma would clearly be a large, adequately powered, randomised, actively controlled trial [Rosenow and Knake, 2008; Shorvon *et al*. 2008a]. As long as this cannot be expected in the near future, we have to rely on open-label observational studies with a well-designed prospective design. Expert opinion and guidelines may strengthen the back of the treating physician, when drugs are used off label, but quite obviously this cannot replace randomised controlled studies.

Conflict of interest statement

None declared.

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