

Levetiracetam as second-line treatment of status epilepticus – which dose should be applied?*

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SUMMARY

Introduction. Since 2004 many treatment episodes in different stages of status epilepticus (SE) have been reported. Nowadays the use of levetiracetam (LEV) is recommended as a second-line treatment of SE, when the use of a benzodiazepine was not successful.

Aim. The evidence based on randomized controlled trials for the application of a particular weight-based dose of LEV as a second-line treatment in benzodiazepine refractory SE is investigated.

Methods. Pubmedsearches were undertaken using the terms “Levetiracetam-status-epilepticus-trials” and “Levetiracetam-status-randomized” on May 8th 2021. We identified 17 studies reporting treatment with LEV as second line treatment and reporting dosages in mg/kg body weight. We grouped the studies according to the reported dosages (i.e. 20–25 mg/kg; 30 mg/kg; 40 mg/kg, 60 mg/kg). For each group we calculated the mean efficacy rate and the standard deviation of the efficacy rate weighted for the number of cases in the different studies. Twelve studies compared LEV with 20 mg/kg phenytoin (PHT). In these studies, we analysed the relative efficacy rate in comparison to PHT with the same procedure.

Results. Seven studies used LEV 20–25 mg/kg, two studies 30 mg/kg, six studies 40 mg/kg and one study 60 mg/kg. Efficacy rate was highest in the group given 30 mg/kg (95% CI 87.5–90.1%). The relative efficacy rate with this weight-based dose was 1.12. This is just above the upper range of the 95% CI of the relative efficacy rate in studies using 40 mg/kg LEV (i.e. 1.11). The relative efficacy rates in the two other groups were considerably lower.

Conclusion. According to the randomized controlled trials published so far a weight-based dose of 30–40 mg/kg LEV may be appropriate for the treatment of benzodiazepine-refractory SE.

Key words: levetiracetam • weight-based dosage • second-line treatment • efficacy rate

INTRODUCTION

Since 2004 (Arrigo et al., 2004) many reports on the treatment of status epilepticus (SE) with levetiracetam (LEV) have been published. Based on a Pub-Med search on December 12th, 2011, 37 case series with 727 treatment episodes were analysed in 2013 (Rösche et al., 2013) and the efficacy rate of LEV in terminating SE was estimated to be in a range between 53.7 and 58.1%. Dosages ranged from 500 mg to 9000 mg/day and were

rarely reported in mg/kg. LEV had been used in all stages of SE. In an up-date in 2019 (Rösche et al., 2019) based on a new Pub-Med search on July 6th, 2018, additionally 13 case series or prospective studies with 412 treatment episodes were analysed and the efficacy rate of LEV was assessed as 55.0–59.4%. Eleven of the papers reported dosages in mg/kg and it was suspected that a loading dose of 30 mg/kg would be reasonable.

Nowadays the use of LEV is recommended as second-line treatment of SE, when the use of a benzodiazepine

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epine was not successful (Rosenow et al., 2020). Based on the interim analysis of the study by Chamberlain et al. (2020) presented by Kapur et al. (2019) a weight-based dose of 60 mg/kg was recommended.

AIM

The evidence based on randomized controlled trials for the application of a particular weight-based dose of LEV as a second-line treatment in benzodiazepine refractory SE is investigated.

METHOD

Pub-Med Searches with the terms “Levetiracetam-status-epilepticus-trials” and “Levetiracetam-status-randomized” on May 8th, 2021, revealed 137 plus 118 results. After excluding studies not reporting treatment with LEV as second line treatment and those not reporting dosages in mg/kg body weight, 17 studies remained. We grouped the studies according to the reported dosages (i.e. 20–25 mg/kg; 30 mg/kg; 40 mg/kg, 60 mg/kg). For each group we calculated the mean efficacy rate and the standard deviation of the efficacy rate weighted for the number of cases in the different studies. By this we calculated the 95% CI for the mean efficacy rates across the studies in each dosage group. Twelve studies compared LEV with 20 mg/kg phenytoin (PHT). In these studies, we analysed the relative efficacy rate in comparison to PHT. This was done by dividing the efficacy rate of LEV by the efficacy rate of PHT in each study. Then we calculated for each group the mean relative efficacy rate and the standard deviation of the relative efficacy rate weighted for the number of cases in the different studies. By this we calculated the 95% CI for the mean relative efficacy rates across the studies in each dosage group.

RESULTS

Nine studies were conducted in paediatric patients only. The mean age of patients in these studies ranged from 2.5 years (Nalisetty et al., 2020) to 4.9 years (Nazir et al., 2020). Just eight studies included adults or elderly people. In two of them, the mean age of patients was between 61.5 and 68.5 years (Wongjirattikarn et al., 2019; Nene et al., 2019). In 5 other studies the mean age ranged from 34.8 years (Mundlamuri et al., 2015) to 39.2 years (Misra et al., 2012). In the study by Chamberlain et al. (2020) the mean age of children was 6.1 years of adults 42.6 years and of older adults 73.8 years. Kapur et al. (2019) reported an interim analysis of Cham-

berlain et al. (2020). Therefore, this study was excluded from the statistical analysis. Six studies reported the treatment of generalized convulsive SE exclusively. Only two studies (Dalziel et al., 2019, Chamberlain et al., 2020) were not in the 20–25 mg/group.

No study included patients with absence status epilepticus. Seven studies applied LEV 20–25 mg/kg (table 1), two studies 30 mg/kg (table 2), six studies 40 mg/kg (table 3) and one study 60 mg/kg (table 4). From the study of Misra et al. (2012) only the subgroup of patients, who were treated because of ongoing seizure activity 10 minutes after the administration of LZP, was included. As can be seen in figure 1 efficacy rate was highest in the group given 30 mg/kg (95% CI 87.5–90.1%). Only one study compared 22 patients given LEV 30 mg/kg with 30 patients given PHT 20 mg/kg. The relative efficacy rate was 1.12 (figure 2). This is just above the upper range of the 95% CI of the relative efficacy rate in the six studies comparing the use of 40 mg/kg LEV with 20 mg/kg PHT (i.e. 1.11). The relative efficacy rates in the two other groups were considerably lower.

DISCUSSION

Although it seems reasonable to compare efficacy rates of randomized controlled trials in a defined clinical setting, several limitations of our study must be highlighted.

First of all, the study populations are not comparable. Chamberlain et al. (2020) reported a higher efficacy rate in children than in adults and elderly people. All studies applying 40 mg/kg were performed in a paediatric setting. Therefore, the high efficacy rates in this group may lead to an overestimation of the efficacy rates in adults and elderly. However, the relative efficacy rate in the subgroup of children given 60 mg/kg was 1.06, this was still lower than the lower limit of the 95% CI in the 40 mg/kg group (i.e. 1.09). One reason for the higher efficacy rates in paediatric patients may be the inclusion of episodes with febrile SE. On the other hand, apart from the older adults in the study by Chamberlain et al. (2020) the eldest patients were in the 20–25 mg/kg group (Wongjirattikarn et al., 2019; Nene et al., 2019). But out of the three other studies of adult patients in this group (Misra et al., 2012; Mundlamuri et al., 2015; Chakravarthi et al., 2015) only Mundlamuri et al. (2015) reported a higher efficacy rate. Therefore the low efficacy rate in the 20–25 mg/kg group cannot be explained by the inclusion of elderly patients.

It has to be emphasised that the efficacy rates were

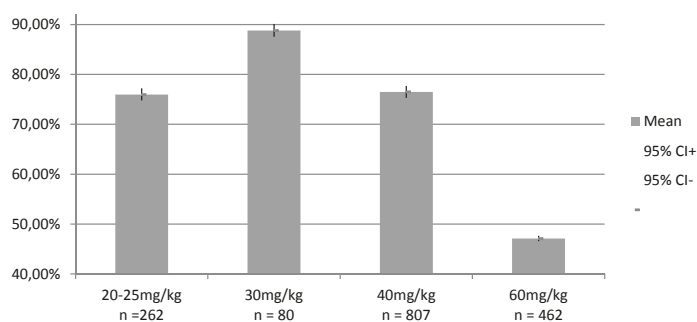


Figure 1. Efficacy rates of different Levetiracetam loading doses.

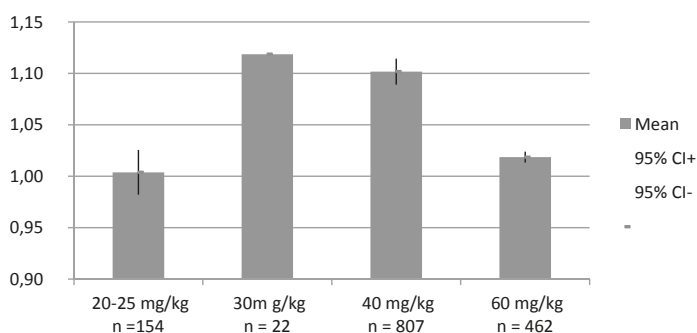


Figure 2. Relative efficacy rates in comparison to 20 mg/kg Phenytoin of different Levetiracetam loading doses.

lower in studies of treatment of generalized convulsive SE only. A subgroup analysis of the four studies of generalized SE only in the 20–25 mg/kg group (Mundlamuri et al., 2015; Chakravarthi et al., 2015; Nene et al., 2019; Nazir et al., 2020) reveals a mean efficacy rate of 74.43% (SD 5.99%). The only study focussing on generalized convulsive SE in the 40 mg/kg group (Dalziel et al., 2019) had an efficacy rate of 50%. This is not much above the efficacy rate in the group of children reported by Chamberlain et al. (2020). But it is questionable whether the difference in types of SE is crucial for the different results because in a retrospective study comparing four intravenously applied antiseizure medications (ASMs) according to four different efficacy criteria, no criterion revealed a significant difference of efficacy rate of a specific ASMs in different types of SE (Redecker et al., 2017). The low efficacy rate in the study by Dalziel et al. (2019) may be a result of the efficacy criterion as well (see below).

Another problem may be that the published doses were not applied to all patients because the weight-

based dosing was capped at a certain body weight. In the ESETT trial (Chamberlain et al., 2020) this was the case at a body weight of 75 kg. Since in this trial 48.2% of adults and 0.9% of children only had a higher body weight the really applied weight-based dose was obviously lower in adults than in children (Sathe et al., 2020). But at least in the adults the efficacy rate of LEV was not significantly lower in patients with a body weight higher than 75 kg than in the others. From this it may be suspected that lower weight-based doses than 60 mg/kg may be at least equally effective. Another problem may be consequent to the different outcome criteria. From preclinical data it is reasonable to assume that after intravenously application of LEV 1500 mg peak concentrations in the brain occur as late as after one hour (Nicolas et al., 2016). This may be an explanation for the results of Navarro et al. (2016), who found no superiority of 2500 mg LEV given immediately after 1 mg clonazepam over placebo when evaluated 9 minutes after the end of the infusion. As can be seen in table 3 one of the studies applying 40 mg/kg LEV evalu-

Table 1. Studies with administration of 20–25 mg/kg Levetiracetam

Reference	Criterion of efficacy	LEV group n =	Dosage	Efficacy rate	Efficacy rate of comparator
Misra et al., 2012	Not clearly defined for patients who received LEV after LZP	10	20 mg/kg	70%	LZP 1 mg/kg 88.9%
Mundlamuri et al., 2015	No recurrence of seizures after 30 minutes of infusion of study drugs	50	25 mg/kg	78%	PHT 20 mg/kg 68%, VPA 30 mg/kg 68%
Chakravarthi et al., 2015	Termination of seizure activity within 30 min after the beginning of the drug infusion	22	20 mg/kg	59.1%	PHT 20 mg/kg 68%
Wongjirattikarn et al., 2019	Seizure control within 24 hours after drug administration	20 brand LEV/20 generic LEV	20 mg/kg	75%/65%	n.a.
Nene et al., 2019	No recurrence of seizures after half an hour of infusion of study drugs	58	20–25mg/kg	74,1%	VPA 20–25 mg/kg 68,3%
Vignesh et al., 2020	Control of convulsive status epilepticus at the end of 15 minutes after completion of study drug infusion (20 minutes)	32	20 mg/kg	94%	PHT 20 mg/kg 89%, VPA 20 mg/kg 83%
Nazir et al., 2020	24 h.	50	25 mg/kg	78%	VPA 25 mg/kg 92%, PHT 20 mg/kg 88%

LEV = Levetiracetam, LZP = Lorazepam, PHT = Phenytoin, VPA = Valproate

Table 2. Studies with administration of 30 mg/kg Levetiracetam

Reference	Criterion of efficacy	LEV group n =	Efficacy rate	Efficacy rate of comparator
Gujjar et al., 2017	Control of seizures with no recurrence over next 24 h	22	82%	PHT 20 mg/kg 73,3%
Handral et al., 2020	Cessation of seizures within 10-20 min following the end of the infusion	58	91,4%	HT 30 mg/kg 93,1%

fPHT = Fosphenytoin, LEV = Levetiracetam, PHT = Phenytoin

ated the treatment effect five minutes after completion of the infusion (Dalziel et al., 2019) and had by far the lowest efficacy rate in this group (i.e. 50%). But even this was slightly higher than the efficacy rate in adults or elderly one hour after start of infusion of 60 mg/kg (Chamberlain et al., 2020). Therefore, the different outcome criteria may not explain the differences of efficacy rates between the groups of studies with different weight-based doses.

CONCLUSION

According to the randomized controlled trials published so far, a weight-based dose of 30–40 mg/kg LEV may be appropriate for the treatment of benzodiazepine-refractory SE. It may be more efficacious than

PHT in these doses. This is in line with a review published in 2014 (Yasiry and Shorvon, 2014).

CONFLICTS OF INTEREST

J. Rösche reports speaker honoraria from Eisai unrelated to this work. B. Schade reports speaker honoraria from Novartis unrelated to this work and support for consulting hours for patients with multiple sclerosis from Bayer and Novartis unrelated to this work.

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Table 3. Studies with administration of 40 mg/kg Levetiracetam

Reference	Criterion of efficacy	LEV group n =	Efficacy rate	Efficacy rate of comparator
Lyttle et al., 2019	Median time from randomization to seizure cessation 35 min.	152	70%	PHT 20 mg/kg 64%
Dalziel et al., 2019	Cessation of seizure activity 5 min after completion of infusion of the first trial drug.	119	50%	PHT 20 mg/kg 60%
Noureen et al., 2019	Cessation of a clinical seizure within 30 minutes after the end of drug administration	300	92,7%	PHT 20 mg/kg 83,3%
Wani et al., 2019	No clear time frame before additional "mini bolus"	52	71%*	PHT 20 mg/kg 46,1%
Nalisetty et al., 2020	Seizure termination within 20 minutes after infusion	32	93,75%	fPHT 20 mg/kg PHT equivalents 69%
Appleton et al., 2020	„median time to seizure cessation 35 min in the LEV group“	152	70%	PHT 20 mg/kg 64%

* After exclusion of patients, who received an additional „minibolus“. LEV = Levetiracetam, fPHT = Fosphenytoin, PHT = Phenytoin, VPA = Valproate

Table 4. Studies with administration of 60 mg/kg Levetiracetam

Reference	Criterion of efficacy	LEV group n =	Dosage	Efficacy rate	Efficacy rate of comparator
Chamberlain et al., 2020	Absence of clinically apparent seizures with improved consciousness and without additional ASM at 1 h from start of drug infusion.	C: 225 A: 186 E: 51	60 mg/kg	C: 52% A: 44% E: 37%	C: VPA 40 mg/kg 52%, fPHT 20 mg/kg PHT eq 49% A: VPA 46%, fPHT 46% E: VPA 47%, fPHT 35%

ASM = antiseizure medication, C = children, A = adults, E = elderly, fPHT = Fosphenytoin, LEV = Levetiracetam, PHT = Phenytoin, VPA = Valproate

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