

## Treatment with lacosamide or levetiracetam in patients with renal replacement therapy. What is really known?

Maya Cuhls<sup>1</sup>, Julian Bösel<sup>1</sup>, Johannes Rösche<sup>1,2</sup>

<sup>1</sup> Klinik für Neurologie, Klinikum Kassel, Kassel, Germany

<sup>2</sup> Klinik und Poliklinik für Neurologie, Universitätsmedizin Rostock, Rostock, Germany

Received January 13, 2020

Accepted for publication on-line March 26, 2020

Published on-line April 4, 2020

### Correspondence

Johannes Rösche

Klinik für Neurologie, Klinikum Kassel

Mönchebergstraße 41-43, 34125 Kassel, Germany

Phone: 00 49 561 980 40 51

Fax 00 49 561 980 69 79

e-mail: johannes.roesche@med.uni-rostock.de.de

### SUMMARY

**Background.** Lacosamide and levetiracetam are commonly used in critically ill patients, who need an antiepileptic treatment in addition to several other medications. Since both drugs are eliminated via the kidneys, dosage has to be adapted to renal function especially in renal replacement therapy (RRT). In 2016 recommendations of dosage in this condition were based on three case reports only.

**Aim.** To elucidate the current data basis for recommendations on the dosage of Lacosamide and levetiracetam in patients on renal replacement therapy.

**Material and methods.** A search in MEDLINE and Web of Science with several core terms was performed. Papers reporting on doses and concentrations of lacosamide or levetiracetam in patients with renal replacement therapy were analysed.

**Results and discussion.** One phase-I study and three case reports concerning lacosamide and one case series with 22 patients and nine case reports concerning levetiracetam were identified. Whether 200 mg Lacosamide twice/day results in trough concentrations at least in the lower therapeutic range depends on the replacement rate used in continuous venovenous haemofiltration. Peritoneal dialysis seems to remove only a small portion of levetiracetam. Levetiracetam (1000 mg) every 12 hours may generate a trough concentration in the lower therapeutic range in continuous venovenous haemofiltration.

**Conclusion.** Due to the sparse and low quality data, current recommendations on dosing lacosamide or levetiracetam in patients undergoing renal replacement therapy have to be considered with caution and therapeutic drug monitoring may be useful in guiding patient management.

**Keywords:** peritoneal dialysis • intermittent haemodialysis • continuous venovenous haemofiltration

### BACKGROUND

Lacosamide (LCM) was approved in 2008 for the management of partial-onset seizures. Plasma protein binding for LCM is low (approximately <15%) in healthy subjects. Approximately 40% of the dose is eliminated in the urine as unchanged active drug. Overall, 94% of the dose is eliminated in the urine within 168 hours, mainly as inactive metabolites. It has demonstrated no clinically relevant pharmacokinetic drug-drug interactions (Cawello, 2015). Levetiracetam (LEV) obtained

initial approval from the FDA in 1999. It is not protein bound. 66% of the dose is eliminated unchanged and 27% is excreted in urine as an inactive metabolite within 48 hours. It shows very few drug–drug interactions as well (Patsalos, 2004). Therefore, both orally and intravenously applicable drugs are commonly used in those critically ill patients, who need antiepileptic drugs (AEDs) in addition to several other medications. A therapeutic range is recommended for LCM

of 5 mg/l–10 mg/l and for LEV of 12 mg/l–46 mg/l (Jacob and Nair, 2016). Since both drugs are eliminated via the kidneys, the dosage has to be adapted to renal function especially in renal replacement therapy (RRT). A comprehensive evaluation of literature concerning the effect of RRT on the pharmacokinetics of AEDs performed in May 25<sup>th</sup> 2016 (Smetana et al., 2016) identified just one paper on the use of LCM during intermittent haemodialysis (IHD) (Cawello et al., 2013) and two case reports on the use of LEV with continuous venovenous haemofiltration (CVVH) (Nei et al., 2015; New et al., 2016). Based on these data it was recommended to prescribe 200–600 mg/d LCM divided in 2 to 3 doses and LEV 1000 mg every 12 h respectively in patients with RRT.

### AIM

To investigate the current data that constitute the basis for recommendations on the dosage of LCM and LEV in patients undergoing RRT.

### MATERIAL AND METHODS

On September 15<sup>th</sup>, 2019 we searched in MEDLINE and Web of Science with the following core terms: (Lacosamide OR Levetiracetam) AND (Dialysis OR Hemodialysis\* OR Haemodialysis\* OR Renal Replacement). No date restriction was imposed on the search strategy. All papers reporting on dosages and plasma concentrations of these two AEDs undergoing RRT were included in the analysis. The reporting of the papers was grouped according to their reference to peritoneal dialysis (PD), IHD and CVVH.

### RESULTS AND DISCUSSION

#### Lacosamide

No reports were found about the influence of PD on the pharmacokinetics of LCM. Two papers on the use of LCM in patients undergoing IHD were identified. In a phase 1 study (Cawello et al., 2013), eight patients with end-stage renal disease, receiving haemodialysis were administered 100 mg of LCM. They received 100 mg of LCM 2.5 hours before a 4-hour session. It was observed that haemodialysis removed  $50.9 \pm 6.3$  g LCM which represented more than 50% of circulating LCM reaching a mean concentration of 0.89 mg/l compared with 2.19 mg/l when haemodialysis free. An anuric patient with acute kidney injury received a daily dose of 100 mg of LCM and an additional dose of 150 mg

post-haemodialysis. The concentration values were between 8.6 mg/l and 8.8 mg/l on dialysis days and also on non-dialysis days alike (Nei et al., 2019).

Two patients receiving LCM while undergoing CVVH have been published. One patient received 200 mg LCM twice/day intravenously (Franquiz et al., 2018) resulting in a peak concentration at steady state of 7.7 mg/l and a trough concentration of 5.9 mg/l. With the same dose of LCM in another patient a peak concentration of 7.4 mg/l and a trough concentration of 3.7 mg/l (Wieruszewski et al., 2018b) were measured. The lower trough concentration in the second case may be due to the higher replacement rate of 30 ml/kg/hr (Wieruszewski et al., 2018b) in contrast to 20 ml/kg/hr (Franquiz et al., 2018).

#### Levetiracetam

Two papers have reported on the effect of PD on LEV pharmacokinetics. In one patient 1000 mg LEV daily and 10-hour PD peak concentrations ranged from 42 mg/l to 56 mg/l and trough concentrations from 27 mg/l to 49 mg/l (Ratté et al., 2018). There was only a small amount of LEV removal by PD. This observation is supported by the case of a 73-year-old man (160 cm, 93 kg), who had been undergoing PD for two years. Eight weeks after being put on LEV 500 mg twice/day he presented to an emergency department with a Glasgow Coma Scale of 10. Unfortunately, no LEV concentrations were measured at this point. But even 24 hours after discontinuation of LEV, a concentration of 29.8 mg/l was recorded (Bathe et al., 2014).

We found two case reports on LEV treatment and IHD. A 43-year-old lean woman (158 cm, 48.1 kg) (Wieruszewski et al., 2018a) received a loading dose of 2000 mg, continuing with 500 mg of LEV daily and a supplemental dose of 750 mg post-dialysis. On off-dialysis days a peak concentration at steady state of 20.2 mg/l and a trough concentration of 12.2 mg/l were documented. About 85% of LEV was cleared within a 3-hour-dialysis session. A peak concentration of 31.2 mg/l and a trough concentration of just 4.47 mg/l were measured. A second 25-year-old lean woman (40 kg) developed seizures during IHD when given 500 mg LEV daily and a 250 mg supplementary dose after HD (Company-Albir et al., 2017) were given. After increasing the supplementary dose to 500 mg, peak concentrations ranging from 20 mg/l to 35 mg/l and trough concentrations ranging from 3.7 mg/l to 9.4 mg/l were measured. To achieve seizure freedom valproate was added.

**Table 1.** Summary of recommendations data on lacosamide and levetiracetam use in renal replacement therapy

Renal replacement therapy	Lacosamide	Levetiracetam
Peritoneal dialysis	No data	With a dose of 1000 mg daily, a trough concentration at least at the upper limit of the therapeutic range may result
Intermittent haemodialysis	100 mg daily with a supplementary dose of 150 mg post-haemodialysis may result in concentrations in the therapeutic range	500 mg daily with a supplementary dose of 750 mg post-haemodialysis may result in subtherapeutic trough levels. A dose of 1000 mg twice/day may be more sufficient.
Continuous venovenous haemofiltration	Whether 200 mg twice/day results in trough concentrations, at least in the lower therapeutic range, depends on the replacement rate used	1000 mg every 12 hours may generate a trough concentration in the lower therapeutic range.

Additionally, a case series of 14 patients receiving doses ranging from 250 mg to 1000 mg LEV twice/day and 8 patients receiving 500 mg to 1500 mg daily with a supplementary dose after haemodialysis was published (Shive et al., 2017). LEV twice/day resulted in higher peak and trough concentrations than LEV daily. Since patients with LEV twice/day received a mean daily dose of 1367 mg and patients with LEV daily 1219 mg on days with dialysis and 812.5 mg on dialysis-off days, this difference may be explained by the differences in dosage. No recommendation for a specific LEV dose can be derived from this study.

Five case reports on patients receiving LEV while on CCVH have been published. In one 51-year-old woman who was administered a dose of 1000 mg LEV intravenously every 12 hours, trough concentrations of 19 mg/l were obtained (Louie et al., 2015). In a strongly built (175 cm, 116.9 kg) 67-year old man after a loading dose of 2000 mg LEV and maintenance doses of 1000 mg LEV every 12 hours were administered (Nei et al., 2015). Peak concentrations ranged from 26.5 mg/l after the loading dose to 39.8 mg/l at steady state. Trough concentrations ranged from 13.9 mg/l to 18.2 mg/l at steady state. In a 59-year-old tall man (187 cm, 83.4 kg) administered 1000 mg LEV every 12 hours, a peak concentration of 32.2 mg/l and a trough concentration of 16.1 mg/l (New et al., 2016) were measured. In a 78-year-old (93.2 kg) man treated with the same LEV dosage, a peak concentration of 30.7 mg/l and a trough concentration of 16.1 mg/l (Van Matre et al., 2017) were measured. In a 79-year-old man (175 cm, 90 kg) treated with a dose of LEV 1000 mg twice/day, a median concentration of 12.4 mg/l was measured (le Noble et al., 2017).

Unfortunately, the authors do not state the levels of peak concentrations and trough concentrations separately. But to avoid the large differences between peak

concentrations and trough concentrations they recommended continuous LEV infusion of 2000 mg/24 h.

## CONCLUSION

Due to the sparse and low quality data, current recommendations on dosing lacosamide or levetiracetam in patients undergoing renal replacement therapy have to be considered with caution and therapeutic drug monitoring may be useful in guiding patient management (table 1).

## CONFLICT OF INTEREST

J. Rösche reports speaker honoraria from Eisai unrelated to this work. J. Bösel reports speaker honoraria and travel support from Bard, Zoll, and Boehringer Ingelheim unrelated to this work. M. Cuhls has nothing to declare.

## REFERENCES

- Bathe S.K., Hiss M., Lichtinghagen R., Kielstein J.T.: *A missed opportunity – consequences of unknown levetiracetam pharmacokinetics in a peritoneal dialysis patient.* BMC Nephrology, 2014, 15: 49. [www.biomedcentral.com/1471-2369/15/49](http://www.biomedcentral.com/1471-2369/15/49).
- Cawello W.: *Clinical Pharmacokinetic and Pharmacodynamic Profile of Lacosamide.* Clin. Pharmacokinet., 2015, 54: 901–914. doi: 10.1007/s40262-015-0276-0.
- Cawello W., Fuhr U., Hering U., Maatouk H., Halabi A.: *Impact of Impaired Renal Function on the Pharmacokinetics of the Antiepileptic Drug Lacosamide.* Clin. Pharmacokinet., 2013, 52: 897–906. doi: 10.1007/s40262-013-0080-7.
- Company-Albir M.J., Ruiz-Ramos J., Solana Altabella A., Marqués-Minana M.R., Vicent C., Poveda J.L.: *Haemodialysis significantly reduces serum levetiracetam levels inducing epileptic seizures: Case report.* J. Clin. Pharm. Ther., 2017, 42: 774–775. doi: 10.1111/jcpt.12568.
- Franquiz M.J., Kalaria S.N., Armahizer M.J., Gopalakrishnan

- M., McCarthy P.J., Badjatia N.: *Lacosamide Pharmacokinetics in a Critically Ill Patient Receiving Continuous Venovenous Hemofiltration*. *Pharmacother. J. Hum. Pharmacol. Drug Ther.*, 2018, 38: e17–e21. doi: 10.1002/phar.2063.
- Jacob S., Nair A.B.: *An Updated Overview on Therapeutic Drug Monitoring of Recent Antiepileptic Drugs*. *Drugs R. D.*, 2016, 16: 303–306. doi: 10.1007/s40268-016-0148-6.
- Le Noble J.L.M.L., Foudraine N.A., Kornhips F.H.M., van Dam D.G.H.A., Neef C., Janssen P.K.C.: *Extracorporeal Clearance of Levetiracetam During Continuous Venovenous Hemofiltration in a critically Ill Patient and New Dosing Recommendation*. *J. Clin. Pharmacol.*, 2017, 57: 536–537. doi: 10.1002/jcph.844.
- Louie J.M., Raphael K.L., Barker B.: *Levetiracetam Use with Continuous Renal Replacement Therapy*. *Ann. Pharmacother.*, 2015, 49:1079–1080. doi: 10.1177/1060028015591845.
- Nei S.D., Beam W.B., Kashani K.B., Wieruszewski P.M.: *Lacosamide Use with Intermittent Hemodialysis*. *Ann. Pharmacother.*, 2019, 53: 323–324. doi: 10.1177/1060028018808579.
- Nei S.D., Wittwer E.D., Kashani K.B., Frazee E.N.: *Levetiracetam Pharmacokinetics in a Patient Receiving Continuous Venovenous Hemofiltration and Venoarterial Extracorporeal Membrane Oxygenation*. *Pharmacotherapy*, 2015, 35: e127–e130. doi: 10.1002/phar.1615.
- New A.M., Nei S.D., Kashani K.B., Rabinstein A.A., Frazee E.N.: *Levetiracetam Pharmacokinetics During Continuous Venovenous Hemofiltration and Acute Liver Dysfunction*. *Neurocrit. Care*, 2016, 25: 141–144. doi: 10.1007/s12028-016-0242-1.
- Patsalos P.N.: *Clinical Pharmacokinetics of Levetiracetam*. *Clin. Pharmacokinet*, 2004, 43: 707–724. doi: 0312-5963/04/0011-0707/S31.00/0.
- Ratté M.T., Barker B.C., Middleton E., Johnson S.A.: *Levetiracetam Use in Peritoneal Dialysis*. *Ann. Pharmacother.*, 2018, 52: 942–943. doi: 10.1177/1060028018770164
- Shive H.J., Tylor M., Sands K.A.: *Comparison of Levetiracetam Dosing Regimens in End-Stage Renal Disease Patients Undergoing Intermittent Hemodialysis*. *Ann. Pharmacother.*, 2017, 51, 862–865. doi: 10.1177/1060028017713294.
- Smetana K.S., Cook A.M., Thompson Bastin M.L., Oyler D.R.: *Antiepileptic dosing for critically ill adult patients receiving renal replacement therapy*. *J. Crit. Care*, 2016, 36: 116–124. doi: 10.1016/j.jcrc.2016.06.023.
- Van Matre E.T., Mueller S.W., Fish D.N., MacLaren R., Cava L.F., Neumann R.T., Kiser T.H.: *Levetiracetam Pharmacokinetics in a Patient with Intracranial Hemorrhage Undergoing continuous Veno-Venous Hemofiltration*. *Am. J. Case Rep.*, 2017; 18: 458–462. doi: 10.12659/AJCR.902709.
- Wieruszewski P.M., Kashani K.B., Rabinstein A.A., Frazee E.: *Levetiracetam Pharmacokinetics in a Critically Ill Anephric Patient on Intermittent Hemodialysis*. *Neurocrit. Care*, 2018a, 28: 243–246. doi: 10.1007/s12028-017-0441-4.
- Wieruszewski P.M., Lopez-Ruiz A., Albright R.C., Fugate J.E., Barreto E.F.: *Lacosamide Pharmacokinetics in a Critically Ill Patient During Continuous Renal Replacement Therapy*. *J. Pharm. Pract.*, 2018b, (ahead of print) doi: 10.1177/0897190018803765.
-