Successful treatment of epilepsia partialis continua due to Rassmussen encephalitis with perampanel

Katja Göde[1,2], Annette Grossmann[3], Johannes Rösche[4]

[1] Universitätsmedizin Rostock, Klinik und Poliklinik für Neurologie, Rostock, Germany

[2] Universitätsmedizin Rostock, Klinik für Psychiatrie und Psychotherapie, Rostock, Germany

[3] Universitätsmedizin Rostock, Institut für Diagnostische und Interventionelle Radiologie, Rostock

[4] Klinik Lengg, Zürich, Switzerland

Received December 14, 2015
Accepted for publication on-line March 18, 2016
Published on-line March 31, 2016

Correspondence
Johannes Rösche
Universitätsmedizin Rostock
Klinik und Poliklinik für Neurologie
Gehlsheimerstr. 20, 18147 Rostock, Germany
Phone: (49) 38 14 94 47 69
Fax: (49) 49 44 794
E-mail: roeschej@t-online.de

SUMMARY

Background. Epilepsia partialis continua (EPC) is a difficult to treat condition, which tends to be refractory to antiepileptic drugs (AEDs). We previously published two other treatment episodes of EPC due to stroke and vascular dementia with a possible effect of perampanel (PER).

Aim. With the publication of a third treatment episode of EPC terminated by the administration of PER we would like to suggest that PER may be an effective treatment option in this condition.

Material and Methods. We present a case where PER was the last AED introduced in the treatment of a patient with EPC and individual seizures due to Rasmussen encephalitis before his seizure frequency could be reduced significantly.

Results. A 44 years old male patient, who had been on a combination therapy of at least 4 AEDs since the age of 24, was admitted to our hospital presenting with an EPC. After the introduction of PER in the therapy EPC stopped and he remained seizure free for more than a year. Two of his other AEDs could be tapered of.

Conclusion. PER might be especially effective in EPC.

Key words: perampanel • Epilepsia Partialis Continua • Rasmussen encephalitis

BACKGROUND

Epilepsia partialis continua (EPC) is a difficult to treat condition, which tends to be refractory to antiepileptic drugs (AEDs) (Mameniskiene et al., 2011). Therefore common recommendations state that any drug effective in chronic epilepsy may be tried in this condition (Shorvon et al., 2008). Clinically and pathophysiologicaly a clear distinction may be made between three courses of non-Rasmussen EPC and EPC due to Rasmussen encephalitis (Mameniskiene et al., 2011). Inflammation and seizures in Rasmussen encephalitis may be caused by antibodies activating glutamate receptors especially GluR3. But it has to be admitted that in many patients with Rasmussen encephalitis none of the known antibodies against glutamate receptors were found (Varadkar et al., 2014) and especially antibodies to GluR3 were only infrequently found in a group of

30 patients with Rasmussen encephalitis (Watson et al., 2004). Unfortunately until now there is no commonly accepted definition of EPS. Mameniskiene et al. (2011) defined EPC as a condition of continuously repeated fragments of epileptic seizures (motor or sensory), with preserved consciousness, lasting around 1 h, and representing locally restricted epileptic activity. There is no commonly used upper limit for the time interval between two seizure fragments. Recently the Task Force of the International League against Epilepsy (ILAE) on Classification of Status Epilepticus (SE) proposed a new classification system of SE (Trinka et al., 2015a). On Axis 1 EPC is classified as SE with prominent motor symptoms (i.e. A.3.b.). On axis 2 Rasmussens encephalitis is listed among the autoimmune disorders causing SE (i.e. 12i) (Trinka et al., 2015a).

Perampanel (PER) is a selective noncompetitive Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionacid (AMPA)-receptor antagonist as adjunctive treatment of partial-onset seizures with and without secondary generalization in patients with epilepsy. After oral administration peak plasma concentrations of PER have been observed within 15 min to 2 hours after application (Steinhoff, 2012). PER distributes into the body tissue and the remaining plasma fraction has a terminal half-life of about 105 hours. Peak plasma concentrations as well as trough plasma levels increase for about 14 days if the initial daily dose is maintained.

In a recent narrative review on real world clinical data of PER response rates ranging from 9% to 89% in focal epilepsies were reported (Trinka et al., 2015b). We previously published two other treatment episodes of EPC due to stroke (Rösche et al., 2014) and vascular dementia (Redecker et al., 2015) with a possible effect of PER. Both treatment episodes were part of a case series of 10 treatment episodes of SE with PER (Redecker et al., 2015). The other treatment episodes in this case series concerned subgroups of nonconvulsive SE. PER was the last drug introduced into the antiepileptic therapy or increased in dose within 24 hours before termination of the SE and without changes in the co-medication in both treatment episodes of EPC. This criterion (e.g. the last drug introduced into the antiepileptic therapy or increased in dose within 24 hours before termination of the SE and without changes in the co-medication) was recently proposed to be used by authors of future studies on the treatment of SE as one of their outcome criteria (Rösche, Redecker, 2015).

AIM

Recently the Task Force of the International League against Epilepsy (ILAE) on Classification of Status Epilepticus (SE) proposed a new classification system of SE (Trinka et al., 2015a). Case reports and studies using the new classification system of SE (Trinka et al., 2015a) may contribute to the development of specific treatment strategies for different subgroups of SE. With the publication of a third treatment episode of EPC terminated by the administration of PER we would like to suggest that PER may be an effective treatment option in this condition.

MATERIAL AND METHODS

Here we present a case where PER was the last AED introduced in the treatment of a patient with EPC and individual seizures due to Rasmussen encephalitis before his seizure frequency could be reduced significantly.

RESULT

We report a 44 years old male patient, who experienced his first epileptic seizures at the age of three. In the following years, he had 5–6 myoclonic and tonic seizures daily. At first, they just appeared in the left side of face, later the left side of his body was affected. At the age of 5 there were also generalized status epilepticus recorded. Several antiepileptic drugs (AED) didn't influence the seizure pattern. At the age of 26 he had about 12 short tonic seizures a day, nearly every second day. Because of therapy resistance against all first- and second-line-drugs available at this time, a pre-surgical work up was performed at this time. Thirteen tonic seizures with an electroencephalographic seizure pattern starting in the right temporal leads were recorded. A MRI showed a right hemispheric atrophy pronounced in the frontal and temporal regions. Despite the assumption that the epileptogenic region might be more extensive a temporal lobe resection was performed. Based on the obtained brain tissue a hippocampus sclerosis and chronic leptomeningoencephalitis representing a Rasmussen encephalitis was diagnosed. Therefore the diagnosis of Rasmussen encephalitis is based on the histopathological findings in combination with the occurrence of EPC (Varadkar et al., 2014). Unfortunately, the patient suffered a perioperative intracerebral haemorrhage causing a leftward hemiparesis and dysarthria. Afterwards, the frequency of tonic seizures was reduces to a maximum of 10 per month, additionally two to

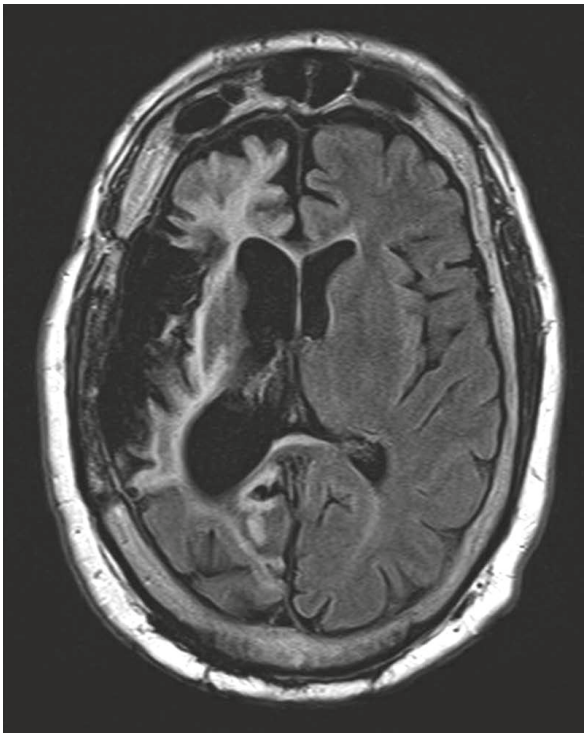

Figure 1. MRI Siemens Avanto, 1.5 T, tra Flair, 5 mm SD at presentation in our department showing the lesion after temporal lobe resection together with an hyperintense signal in subcortical and periventricular regions and typical ipsilateral atrophy of the head of caudate nucleus.

four seizures with myoclonic jerks in the face occurred each month. No immune therapy was established. After a series of seizures at the age of 43 the patient was referred from another neurological hospital to our unit. An MRI revealed the typical lesions related to Rasmussen encephalitis beside the lesion due to temporal resection but showed no signs of acute inflammation. MRI showed the lesion after temporal lobe resection (Figure 1) and in T1, with contrast agent, showing no pathological intracerebral enhancement but a slight dural enhancement after surgery.

No antibodies against glutamate receptors were found in the serum. At this time the patient was treated with a combination therapy of lamotrigine (LTG) 100 mg/day, levetiracetam (LEV) 3000 mg/day, clonazepam (CLN) 3 mg/day, phenytoin (PHT) 100 mg/day, valproate (VPA) 2400 mg/day and pregabalin (PGB) 300 mg/day. AEDs the patient received before were clobazam, gabapentin and methsuximide. Since he was 24, combination therapies of at least 4 AEDs had been performed. An initial routine-EEG in our department showed 12 focal seizure patterns with duration of about 20 seconds per episode associated with myoclonic jerks in the left side of the face in 20 minutes. Clinically the myoclonic jerks were seen with approximately the same frequency during the whole day. We decided to introduce PER with a starting dose of 6 mg/day, which we had used with some success in several cases of nonconvulsive SE before (Redecker et al., 2015). With this dose there should be a timeframe of at least a few hours in which the plasma concentration is on a therapeutic level even after the first administration. Three days later the EEG was free of seizure patterns and in the course of hospitalization no further focal seizures were recognized. During his hospital stay we tapered PHT off. Consequently, the blood level of LTG and VPA increased. The serum level of PER at the end of his first hospitalization in our department was 425 μg/ml. In three months later we reduced the dose of CLN to 2 mg/day. The blood level of PER had risen to 1570 μg/ml. His daytime sleepiness had increased. Therefore we also reduced the dose to 4 mg/day resulting in a blood level of 740 μg/ml. During a following hospitalization after a year we had to reduce the dose of VPA because of high free VPA serum level (28.97 mg/l). Because of thrombocytopenia, as a possible side effect of combination therapy of VPA, LTG and CLN, we reduced the dose of LTG to 50 mg/day. Furthermore the therapy with CLN was terminated. In the meantime no further seizures were recognized since treatment with PER. The patient was discharged with a combination therapy of VPA 1800 mg/day, LTG 50 mg/day, PGB 300 mg/day, LEV 3000 mg/day and PER 4 mg/day.

DISCUSSION

Treatment of EPC is still a problem because of its pharmacoresistance. In our patient, Rasmussen encephalitis was associated with early occurring severe seizures. After temporal lobe resection he still had focal motor seizures, sometime in series over hours resembling EPC. PER was the last AED introduced to therapy. Despite of reducing the doses of some other AEDs no further seizures were recognized. PER had a substantial effect on pharmacoresistant focal motor seizures and EPC due to Rasmussen encephalitis in our patient. This is of importance because in Rasmussen encephalitis AEDs often show no significant benefit. The effect of PER may be related to the possible pathophysiological role of the glutamatergic system in this condition. Studies in animals suggest that Alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionacid (AMPA) receptor-mediated

glutamatergic transmission is strengthened during an established status epilepticus (Rajasekaran et al., 2013). This may be another reason for the efficacy of PER in EPC apart from the role of the glutamatergic system in Rasmussen encephalitis. It has to be admitted that in a series of patients with mainly nonconvulsive status epilepticus PER showed only a limited effect in 17% of the treatment episodes (Rohracher et al., 2015).

CONCLUSIONS

According to our case reports (this paper, Rösche et al., 2014; Redecker et al., 2015) PER may be an effective treatment option in EPC. This finding should be confirmed by further studies. The efficacy of PER in other types of status epilepticus has to be established.

CONFLICTS OF INTEREST

Dr. Rösche received speaker's honoraria from Eisai and UCB, served as medical advisor for Eisai, received a travel grant from Eisai and UCB and received financial support for an investigator-initiated trial from Pfizer. The other authors declare that they have nothing to disclose.

REFERENCES

Mameniskiene R., Bast T., Bentes C., Canevini M.P., Dimova P., Granata T. et al.: *Clinical course and variability of non-Rasmussen, nonstroke motor and sensory epilepsia partialis continua: A European survey and analysis of 65 cases*. Epilepsia, 2011, 52: 1168–1176.

Rajasekaran K., Joshi S., Kozhemyakin M., Todorovic M.S., Kowalsky S., Balint C., Kapur J.: *Receptor trafficking hypothesis revisited: Plasticity of AMPA receptors during established status epilepticus*. Epilepsia, 2013, 54 (Suppl. 6): 14–16.

Redecker J., Wittstock M., Benecke R., Rösche J.: *Efficacy of perampanel in refractory nonconvulsive status epilepticus and simple partial status epilepticus*. Epilepsy and Behavior, 2015, 45: 176–179.

Rohracher A., Höfler J., Kalss G., Leitinger M., Kuchukhidze G., Deak I. et al.: *Perampanel in patients with refractory and super-refractory status epilepticus in a neurological intensive care unit*. Epilepsy and Behavior, 2015, 49: 354–358.

Rösche J., Kampf C., Benecke R.: *Possible effect of perampanel on focal status epilepticus after generalized tonic-clonic status epilepticus*. Acta Neurologica Belgica, 2014, 114: 243–244.

Rösche J., Redecker J.: *Treatment of status epilepticus – A narrative review on the evidence so far and a proposal for the design of retrospective studies*. Eur. Med. Journ. Neurol., 2015, 3: 91–95.

Shorvon S., Baulac M., Cross H., Trinka E., Walker M.: *The drug treatment of status epilepticus in Europe: Consensus document from a workshop at the first London Colloquium on Status Epilepticus*. Epilepsia, 2008, 49: 1277–1284.

Steinhoff B.J.: *Das neue Antiepileptikum Perampanel*. Psychopharmakotherapie, 2012, 19: 202–208.

Trinka E., Hesdorfer D., Rossetti A.O., Scheffer I.E., Shinnar S. et al.: *A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus*. Epilepsia, 2015a, 56: 1515–1523.

Trinka E., Steinhoff B.J., Nikanorova M, Brodie M.J.: *Perampanel for focal epilepsy: insights from early clinical experience*. Acta Neurol. Scand., 2015b, DOI:10.1111/ane.12529

Varadkar S., Bien C.G., Kruse C.A., Jensen F.E., Bauer J., Pardo C.A. et al.: *Rasmussen's encephalitis: clinical features, pathobiology, and treatment advances*. Lancet Neurology, 2014, 13: 195–205.

Watson R., Jiang Y., Bermudez I., Houlihan L., Clover L., McKnight K. et al.: *Absence of antibodies to glutamate receptor type 3 (GluR3) in Rasmussen encephalitis*. Neurology, 2004, 63: 43–50.