Special edition

NEURONEWS
The Neurology Portal

VOL 7 – October 2008 ISSN 1864-6085

# Therapeutic monitoring in patients with epilepsy

## – Principles and case report about the control of seizure activity by intravenous valproate *(Orfiril® injection solution)*

Author:

**Prof. Dr. H. Stefan**
Epilepsy Center Erlangen (ZEE), Erlangen, Germany

MEDIZIN MEDIENVERLAG
CORPORATE PUBLISHING | eMARKETING

# Therapeutic monitoring in patients with epilepsy

**H. Stefan**

## Principles of epilepsy treatment

The aim of treatment for epilepsies is to control seizures without causing adverse effects by reaching the best possible quality of life. A satisfactory suppression of seizures is possible in 60 – 70% of patients. In patients with incomplete seizure control it is of importance to achieve seizure reduction and to diminish severity of seizures. The choice of the optimal drug is not only determined by seizure control but also by potential adverse effects. A disposition and accompanying diseases are varying individually. The choice of the optimised drug, titration rate and dosage needs to be individualised to achieve optimal effectiveness. The number of time-adjusted daily application and an optimised combination of antiepileptic drugs is important too. The combination of antiepileptic drugs bears a higher risk of side effects which might be influenced in part on the pharmacokinetic or pharmacodynamic properties of the drug.

Regarding today's numerous range of different antiepileptic drugs, the following indicators are of high significance:

- an optimal efficacy in the individual epileptic syndrome
- tolerability
- interactions
- dosage.

Since 30 – 40% of the patients suffering from epilepsy do not respond satisfactorily to a first anticonvulsant treatment, the question of further diagnostic possibilities with respect to a successful therapy arises.

## Differential diagnosis and classification of seizures and epilepsies

As seizures in general occur within a short period consequently a systematic observation is lacking and because of the patient's clouding of consciousness one is dependent on the reports of an observing person. Thus, considerable problems arise by incorrect and false descriptions *(Mannan and Wieshmann, 2003)*. In 20 – 25% of the patients non-epileptic seizures are classified as epilepsy and vice versa. They are mostly confounded with syncopies, psychogenic seizures, parasomnia, migraine or transitory ischemic attacks. Those 15 – 50% of patients are falsely treated with antiepileptic drugs. In a prospective controlled trial at our center in which clearly documented seizures by means of video-EEG have been compared with the information obtained from the patients immediately after seizure occurrence and some time later, showed that in 138 seizures only 49,3% could clearly be reported by the patients, 44% remained completely unnoticed.

The routine way to the diagnosis of an epileptic disease should be gone step by step. After identification whether epileptic or non-epileptic seizures are evident then a first step is the coordination according to the international classification of seizures and epileptic syndromes. Different phases of the epileptic seizure as well as postictal deficits can be recorded using the nucleus-shell-model *(Stefan et al. 2003)*. Considering etiology, age related circumstances and the course of epilepsy more complex entities can be determined susceptible to prognostic hints. Therefore we have to distinguish between the classification of epileptic seizures and the classification of epileptic syndromes. The knowledge about the epileptic syndrome is of high importance for a prognostic opinion and the choice of a medical or surgical treatment *(Stefan, 1999)*.

As example for such a proceeding the examination regarding efficacy and time related start of the effect of valproic acid (*e.g. Orfiril® injection solution*) in difficult to treat focal epilepsies is described.

Regardless efficacy and tolerability of new antiepileptic drugs the effect of drug withdrawal can be recorded with the TISA method in an objective way. Here, carbamazepine and lamotrigine strongly *tend more* to the occurrence of secondary generalized tonic clonic seizures compared to valproate *(Wang-Tilz et al. 2005)*.

The selection of anticonvulsants for different focal or generalized epilepsies is shown in the latest report of licensing status of approval *(Fig. 1).*

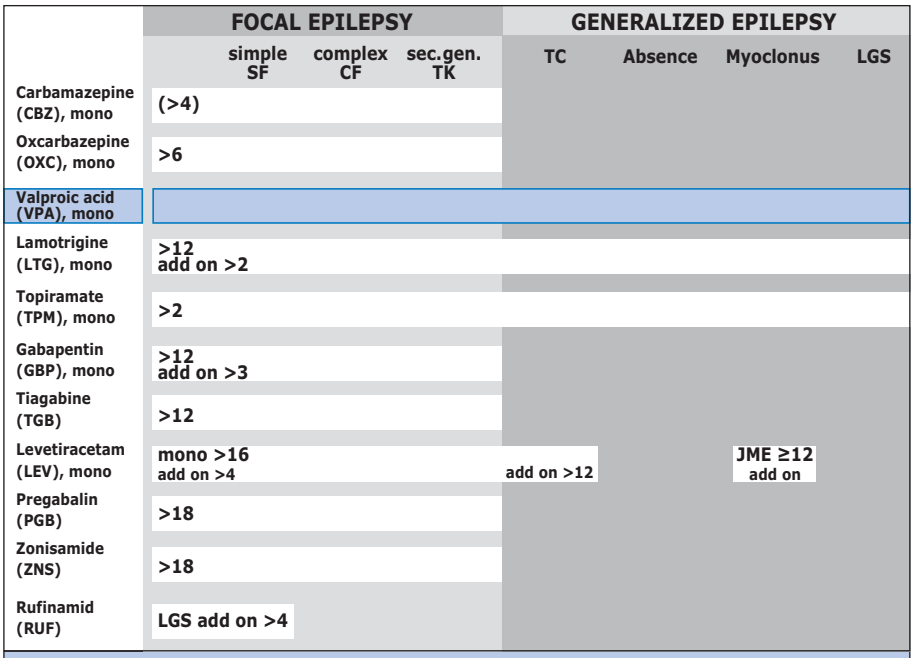


**Fig. 1:** The selection of anticonvulsants for different focal or generalized epilepsies is shown in the latest report of licensing status of approval.

## Examination methods for diagnostics and therapy

As an additional most often used examination tool in routine diagnostics besides the wake-/sleep-EEG is the MRI. For an intensive monitoring with long-term recordings the mobile long-term-EEG recording (MLE) and the simultaneous video EEG recording (SDA) can be employed including serum concentration measurements of the taken medication *(Tab. 1).*

An assessment of the gain of information regarding the different examination methods such as routine EEG, ictal routine EEG, long-term video EEG for therapeutic monitoring in patients with epilepsies is shown in Table 2. In this table it is demonstrated that in difficult to treat epilepsies the supervision of the diagnosis by means of video EEG monitoring and an improved classification may lead to better treatment results *(Tab. 2).*

The reasons for this are

1. an objective documentation of seizure events
2. their coordination in epileptic and non-epileptic seizures
3. as well as their classification and also frequency of occurrence.

As 40 – 50% of patients are unaware of their seizures while sleeping therefore long-term recordings for 24 hours or for several days may be helpful. As to our experiences one can gain with a continuous 72 hours long-term video EEG monitoring 60 – 79% new pioneering results with respect to an optimizing treatment.

**Table 2:** It is demonstrated that in difficult to treat epilepsies the supervision of the diagnosis by means of video EEG monitoring and an improved classification may lead to better treatment results.

| Routine-EEG / intensive-(video-EEG)-monitoring | Detection of epileptiformal EEG activity | Knowledge gain |
|---|---|---|
| Routine-EEG | + | 40% |
| Routine-EEG ictal | + | 2,5 – 7% |
| Long-term(video/ EEG) ictal | + | 50 – 70% |
| New classification | | 48 – 84% |
| Seizure reduction | | 60 – 70% |
| Clinical signs | | 67 – 72% |

**Table 1: Main Indications for EEG measurement**

| | |
|---|---|
| 1. | Identification of epileptic activity (focal, generalized; markeness) |
| 2. | Initial data for control of therapy (ground activity, unspecific source localization and epileptiformactivity, the latter especially in generalized regular bilateral-synchronous spike-wave activity) |
| 3. | Psychic symptome (intoxication, psychosis, other psychic changes) |
| 4. | Difficult to control epilepsy, changes in results and symptomes, seizure frequency, pharmacoresistance |
| 5. | Reduction of medication |

## Testing of antiepileptic drugs

A new sensitive and objective examination method is the so called "therapeutic intensive seizure analysis" *(TISA, Stefan et al., 2004)*. These analysis helps to quantify objective data, e.g. seizure frequency and seizure severity. This can lead to significant results even with a minor

number of patients. The study design allows the comparison of a substance with placebo or with different dosages of a drug. This objective documentation of seizures can proof the superiority of a substance compared to another or the stronger effectivity of one dosage.
In addition to an objective measurement of effectivity by quantifying seizure activity with respect to frequency, duration and severity neuropsychological testing can repeatedly be carried out during monitoring and being correlated with the serum concentration of the applied substance.
Other investigations showed in comparison of 100 mg to 200 mg topiramate a significantly better efficacy of 200 mg. The parenteral application of the MHD of oxcarbazepine also showed a significant effect.

## Computer supported seizure detection in emergency cases (status epilepticus)

In the field of intensive medicine the EEG can deliver essential additional information in the treatment course of a status epilepticus. In a first phase of the tonic clonic seizure there is a dominance of motoric manifestations which, however, can distinctly regress in its sequence so that in the end the status is only to be identified as non-convulsive "electrical" status. This requires continuous long-term EEG recordings. The recording of seizure frequency and duration of a non-convulsive status is only to objectify by carrying out long-term EEG monitoring. For a targeted conduction of therapy in the course of a status epilepticus the epileptic activity in long-term EEG can be an important indicator.

Various examinations point out, that persisting epileptic activity can be associated with an unfavourable treatment effect or elevated mortality rate *(de Lorenzo et al. 1998, Jaitly et al. 1997)*. An important task for the intensive EEG monitoring is to clarify which correlation exists between epileptic activity and prognosis regarding seizure control and functional recovery. Appropriate methods of the computer supported analysis can today be applied in quantifying seizure activity (frequency, severity, duration) in the long-term course *(Hopfengärtner et al. 2007)*. Of great importance is that these results are available for the physician within short *(Fig. 2)*.

## Neuropsychological examinations during therapeutic monitoring

Cognitive side effects of antiepileptic drugs today can be recorded with an easy to handle computer supported test system *(Pauli et al. 2007)*.

This computer supported cognitive emotional testing in epilepsy (CCTE) is mainly be employed in first anticonvulsant applications, change in medication and combination therapy as well as in epilepsy in the elderly in order to fix an individual and optimal well-tolerated dosage.

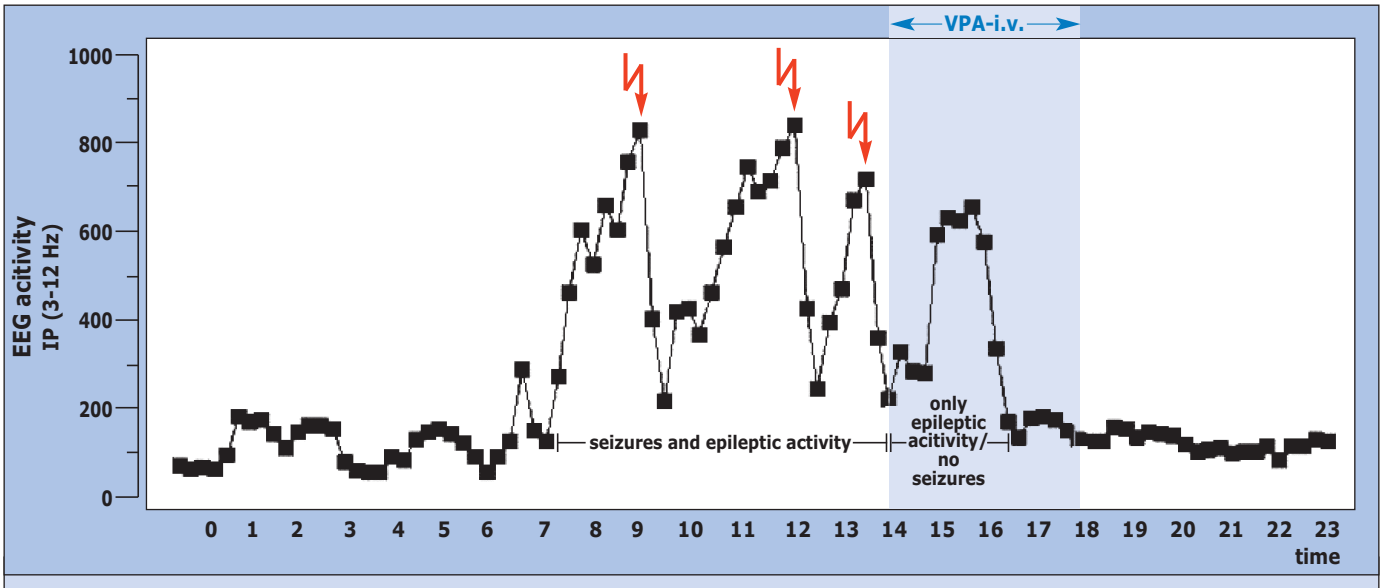


**Fig. 2: Long term EEG of a 30 year old female patient with idiopathic generalized epilepsy.** Three tonic clonic seizures, a none convulsive status, controlled by 900 mg intravenous valproate **(Orfiril® injection solution)** is demonstrated in the figure. The curve shows the course of the epileptic activity in long-term EEG. The quantification of long-term EEG activity *(by the method of Hopfengärtner et al. 2007)* was used to guide valproate treatment.

Tonic clonic seizure

## Conclusion

In summary, by aid of the TISA technique a better computer supported seizure detection *(see e.g. in figure 2: application of* ***Orfiril® injection solution*** *in a patient with repetitive seizures)* and cognitive emotional testing we have methods at our hands providing practical decision aids which we did not have formerly. In addition to seizure control cognitive changes can be perceived earlier and the individual dosage adjusted accordingly. This could be an important precondition for more easy to handle in- and outpatient treatment.

**Corresponding Author:**
Prof. Dr. H. Stefan
Epilepsy Center in Erlangen (ZEE)
Universitätsklinikum Erlangen
Schwabachanlage 6
D-91054 Erlangen

## References

De Lorenzo RJ, Waterhouse EJ, Towne AR. Presurgical nonconvulsive status epilepticus after control of convulsive status epilepticus. *Epilepsia 1998;38: 833-840.*

Hopfengärtner R, Kerling F, Bauer V, Stefan H. An efficient, robust and fast method for the offline detection of epileptic seizures in long-term scalp EEG recordings. *Clin Neurophysiol. 2007; 118:2332-2343.*

Jaitly R, Sgro JA, Towne AR, Ko D, de Lorenzo RJ. Prognostic value of EEG monitoring after status epilepticus: a prospective adult study. *J Clin Neurophysiol. 1997;14:326-334.*

Mannan JB, Wieshmann UC. How accurate are witness descriptions of epileptic seizures? *Seizure 2003;12:444-447.*

Pauli E, Kerling F, Stefan H. Meet the Professor, Erlangen, October 2007.

Stefan H. Epilepsien: Diagnose und Behandlung. Georg Thieme Verlag, 3. Auflage 1999.

Stefan H. Ictal signs – cerebral localizations and propagation. *Nervenarzt 2003; 74:527-536.*

Stefan H, Wang Y, Pauli E. Monitoring effects of the antiepileptic drugs by continuous video-EEG over several days: therapeutic intensive seizure analysis (TISA). *Epilepsy Research 2004;75:755-762.*

Wang-Tilz Y, Tilz C, Wang B, Pauli E, Koebnick C, Stefan H. Changes of seizures activity during rapid withdrawal of lamotrigine. *Eur J Neurol. 2005:12:280-288.*

## Imprint

**The Neurology-Portal NeuroNews**

Editorship for special publications:
Dr. med. Susanne Schweizer

Publication in the Internet available:
www.neuronews.de/media/doc/therapeutic_epilepsy_eng_Stefan_10-08.pdf

Managing director: Beate Döring

Publishing house:

MEDIZIN MEDIENVERLAG
CORPORATE PUBLISHING | eMARKETING

MedienCompany GmbH
Medizin-Medienverlag
Zeppelinstr. 71-73
D-81669 Munich/Germany
Phone: ++49 (0)89 – 45835-301
Fax: ++49 (0)89 – 45835-306
www.mediencompany.de
www.medizin-medienverlag.de
Email: info@mediencompany.de

ISSN 1864-6085 (Print)



Printed in Germany

NEURONEWS
The Neurology Portal

NeuroNews is an international freely accessible online platform for all doctors and pharmacists operated by the publishing house MedienCompany GmbH, Medizin-Medienverlag, Munich/Germany.