Seizure (2005) 14, 164—169

ELSEVIER

SEIZURE

www.elsevier.com/locate/yseiz

Intravenous valproate as an innovative therapy in seizure emergency situations including status epilepticus—experience in 102 adult patients

Christian N.A. Peters [a,*], Bernd Pohlmann-Eden [a,b]

[a] *Department of Neurology, Klinikum Mannheim, University of Heidelberg, Mannheim, Germany*
[b] *Epilepsy Research Foundation, Bethel Epilepsy Center, Bielefeld, Germany*

KEYWORDS
Status epilepticus;
Valproate;
Emergency treatment;
Antiepileptic therapy

Summary

Purpose: The emergency treatment of seizures is an important practical issue, in particular the therapy of status epilepticus. Antiepileptic drugs for this condition should be easy to use, show rapid action, have a long-lasting antiepileptic effect, and have minimal cardiopulmonary and other side-effects. Unfortunately, none of the presently available medications such as phenytoin and barbiturates seems to have all of these four properties. Intravenous valproate became available some years ago and first experiences show promising safety data and efficacy results.
Methods: We report a series of 102 adult patients who received standardized high dosage intravenous valproate in various emergency situations, including status epilepticus. The therapeutic goal was persistent seizure control, defined as successful interruption of clinical seizure activity within less than 15 min, followed by seizure freedom during intravenous therapy for at least 12 h. All side effects were documented.
Results: In 83/97 patients (85.6%) the therapeutic goal was achieved. Serious side effects were not documented in any patient. In particular there was no evidence of sedation, cardiorespiratory disturbances and hypotension as often seen in barbiturates and phenytoin. Mild side effects occurred in seven cases (6.9%).
Conclusions: The intravenous application of VPA seems to be an easy-to-use, safe and efficient formulation as an alternative to phenytoin in all seizure emergency situations including status epilepticus. Further controlled comparison studies have to be performed in the future.

Introduction

Valproate (VPA) is a well established first-line antiepileptic drug (AED) effective in a wide range of focal and generalized seizures.[1] There are several conditions under which a parenteral preparation of

* Corresponding author. Present address: Neurologische Universitätsklinik Mannheim, 68135 Mannheim, Germany. Tel.: +49 621 383 3205; fax: + 49 621 383 2158.
E-mail address: peters@neuro.ma.uni-heidelberg.de (Christian N.A. Peters).

1059-1311/$ — see front matter
doi:10.1016/j.seizure.2005.01.002

an AED is necessary, either because the patient is unable to take oral medication or because a rapid loading is required, e.g. in status epilepticus (SE). Beside short-acting benzodiazepines, only phenytoin and phenobarbital are in wide use as an intravenous preparation. Unfortunately, these have a narrow therapeutic window and a range of complicating side effects significantly limiting their practical administration. Phenobarbital may lead to major sedation and respiratory problems including apnoea and is reported to increase the risk of infections. Phenytoin can cause cardiac arrhythmias, requires an extra intravenous-line, has to be given very slowly and may induce severe problems at the injection site including the ''purple glove syndrome''.

Since the autumn of 1996, intravenous VPA is available in Germany. The reported experiences demonstrate a broad spectrum of indications ranging from a rapid switch of oral to parenteral application (e.g. children with severe gastroenteritis), to series of seizures and life-threatening grand-mal SE with promising safety data and efficacy results.[1–6] Experimental data supported this clinical observations revealing both a fast and long-lasting antiseizure effect for VPA.[7]

Therefore, the goals of this retro- and prospective study were to test, (1) if intravenous VPA is a safe and efficient treatment in heterogeneous conditions of seizure activity including SE, and (2) if these preliminary findings deliver promising results for further controlled clinical trials.

Methods

Patients

Data were available for 102 patients treated during a 4-year period between December 1996 and December 2000. Sixty-one patients (59.8%) were male, 41 female (40.2%). The mean age was 54.8 years, range 18–85 years. The data of all patients originated from a retrospective chart review. In 24 patients additional data from a prospective application survey was available, 21 patients were supervised during treatment by the authors with regard to this study.

Indication for rapid intravenous VPA treatment ranged from (1) urgent need for or switch to intravenous VPA ($n = 25$), (2) series of seizures, ($n = 34$), (3) status epilepticus in $n = 35$, to (4) others ($n = 8$) such as brainstem seizures ($n = 1$), posthypoxic myoclonia ($n = 2$), and probably non-epileptic seizure episodes ($n = 5$). These five patients were excluded from the efficacy analysis. SE was operationally defined according to the most recent classification as ongoing seizure activity for more than 10 min.[8] Series of seizures were defined as two or more distinct seizures within 24 h with interseizure intervals of regaining either consciousness or related functions. For an exact overview see Table 1.

Table 1 Indications for intravenous valproate in 102 treatment episodes.

Treatment indication	Patients
Status epilepticus	35
Simple-partial	12
Complex-partial	14
Generalized tonic–clonic	6
Absence	3
Series of seizures (two or more seizures within 24 h)	34
Simple-partial	4
Complex-partial	2
Generalized tonic–clonic	27
Atonic seizures	1
Switch to intravenous therapy	25
Others	8
Total	102

Procedures

All patients were either admitted as emergency cases or were already hospitalized. Intravenous VPA therapy was always applied under supervision of an experienced epileptologist (BP or CP). Routine clinical laboratory tests including electrolytes, blood cell count, coagulation parameters, liver enzymes and kidney function were conducted in all patients, AED levels were measured in 97 of 102 patients. EEG (21-channel surface, Nihon Kohden Co.) was performed in all 35 SE patients and in 85 patients out of all 102 patients.

The patients received commercially available intravenous VPA (Orfiril® Injektionslösung, Desitin, Germany). The initial bolus application varied between 4 and 16 mg/kg BW (body weight) dependent on the severity of the clinical condition with the majority (74%) of patients receiving 15 and 16 mg/kg BW, given within 5–10 min, followed by a continuous infusion (flow control pump) of 0.5–4 mg/kg BW/h maintenance dosage within 2 h to 10 days.

Precise data of individual dosage is given for all 35 patients being diagnosed with SE (Table 2). Twenty-nine patients with SE or series of seizures had been pretreated without success by standard initial dosages for SE[8] of benzodiazepines (11

Table 2 Clinical data, dosage management and duration of intravenous valproate in 35 patients treated for status epilepticus.

Case	Age	Sex	Diagnosis	Seizure type	Bolus (mg)	Infusion rate (mg/h)	Duration
1	66	f	Subdural haematoma	SPS	500	—	—
2	67	m	Brain abscess	SPS	—	50	24 h
3	67	m	Brain abscess	SPS	—	120	4 h
						240	4 h
						120	8 h
4	23	m	Arteriitis nodosa	GTCS	900	187.5	4 d
5	75	m	Theophyllin—intoxication	GTCS	900	62.5	2 d
					600		
6	58	m	Cerebral venous thrombosis	CPS	900	125	12 h
7	60	f	Intracranial haemorrhage	GTCS	900	50	24 h
8	18	m	Epilepsy	Absence	900	—	—
9	62	f	Epilepsy	CPS	900	150	8 h
					300		
10	60	m	Wernicke's encephalopathy	SPS	900	125	24 h
11	66	f	Astrozytoma °III	SPS	600	37.5	2 d
12	68	f	Epilepsy	CPS	600	—	—
13	68	f	Epilepsy	CPS	600	100	12 h
14	68	f	Epilepsy	CPS	—	50	24 h
15	61	m	Alcoholism, SVE	CPS	—	50	24 h
16	75	f	Alzheimer's disease	CPS	900	125	12 h
17	39	m	Brain injury	GTCS	900	75	3 d
18	47	m	Familial microangiopathy	CPS	900	125	12 h
19	80	f	Stroke	GTCS	900	100	12 h
20	75	f	Glioblastoma	SPS	900	—	—
					900		
21	75	f	Glioblastoma	SPS	900	—	—
22	37	m	Epilepsy	Absence	900	83.3	24 h
23	46	f	Multiple sclerosis	CPS	900	125	12 h
24	54	m	Epilepsy	CPS	—	125	12 h
25	74	m	Cerebral metastasis	SPS	600	62.5	24 h
26	63	m	Intracranial haemorrhage	SPS/GTCS	900	125	2 d
27	85	f	Meningioma	CPS	600	125	3 d
28	83	f	Stroke	GTCS/SPS	900	200	12 h
					900 (90 min)		
29	49	m	Down-syndrome	CPS	—	62.5	24 h
30	83	f	Stroke	CPS	900	62.5	2 d
31	63	m	Encephalopathy	CPS	600	75	6 d
					600 (1 h)		
32	55	m	Epilepsy	GTCS	900	75	3 d
33	54	m	Epilepsy	Absence	—	125	21 h
34	66	f	Astrozytoma °III	SPS	—	150	12 h
35	77	f	Subcort. vasc. enceph.	SPS	600	87.5	3 d

Second bolus directly after the first bolus, except where mentioned. SPS: simple partial seizure; CPS: complex partial seizure; GTCS: generalized tonic—clonic seizure.

patients clonazepam, 6 patients diazepam, 4 patients clonazepam and diazepam and 3 patients midazolam), phenytoin (4 patients) or clonazepam and phenytoin (1 patient), before receiving the VPA infusion. Sixty-seven patients had a known history of seizures and were already treated with other oral AED than VPA such as carbamazepine and lamotrigine.

Analysis

We analyzed efficacy and side effects of intravenous VPA. Primary outcome was defined as successful interruption of clinical seizure activity within less than 15 min, followed by seizure freedom during intravenous therapy for at least 12 h in those patients with SE. In those patients with series of seizures or those undergoing medication changes, the goal was seizure freedom during intravenous therapy for at least 12 h. All patients were asked if they experienced or had experienced any problems, which they thought were attributable to their medication. All individual adverse events were documented and analyzed.

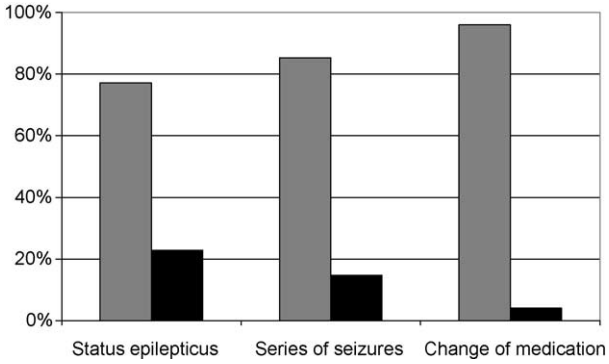

Figure 1 Efficacy of intravenous valproate in 35 patients with SE, in 34 patients with series of seizures, and in 25 patients who underwent switch from oral to intravenous treatment (grey bars: seizure control and black bars: treatment without success).

Results

Tolerability and safety

Serious side effects were not documented in any patient. In none of the 35 SE patients and in none of the 34 patients with series of seizures were significant cardiorespiratory side effects including hypotension observed.

Mild side effects, reported by individuals being conscious, occurred in 7 out of 102 applications (6.8%): Three patients complained of an unspecific feeling of warming with dizziness for some seconds during fast bolus injection. One patient had to be withdrawn because of a moderate generalized allergic skin reaction, which disappeared within a few hours after discontinuation of therapy. Another patient had nausea and vomiting for 3 h which stopped despite of continuation of the therapy and one patient had mild fatigue. In one patient we observed a transient tremor of both hands. There were no reactions at the injection site.

Efficacy

Ninety-seven of the 102 patients were eligible for efficacy analysis, as five patients had to be excluded retrospectively because of the non-epileptic nature of their seizures. In 83 of 97 patients (85.6%) the primary outcome criterion of seizure freedom as defined was achieved. Sub-group analysis showed efficacy of intravenous VPA in 27 out of 35 patients with SE (77.1%), in 29 out of 34 patients with series of seizures (85.3%), and in all but one out of 25 patients who were switched to intravenous treatment (96.0%), which is illustrated in Fig. 1. In the last group of patients, two were seizure free, the others had had seizures before the switch. Within the SE group, patients with complex-partial SE responded best (92.9% or 13/14 patients seizure free), compared to simple-partial SE (83.3% or 10/12 seizure free), generalized tonic–clonic (GTC) SE (66.7% or 4/6 patients) and atypical absence-status (0/3).

Looking at the 14 cases with primary treatment failure, the following three subgroups can be recognized:

1. *Late responders*: In five patients VPA was efficient, but only after a delay. In three out of those (two with a series of GTC, one with intravenous VPA substitution) a GTC seizure recurred within 15 min: increased dosage of VPA finally led to complete seizure freedom. In the remaining two a simple-partial SE required the administration of an additional bolus of 12 mg/kg BW VPA to achieve complete seizure control.
2. *Highly drug resistant SE*: Of these seven patients, five were absolutely refractory to any AED treatment: Two died still in SE due to their underlying illness, two had an absolutely pharmacoresistant SE (complex-partial and generalized tonic–clonic, respectively) to any drug treatment lasting for months and died later, one was discharged while still having an intermittent atypical absence-status and was lost to follow-up. Of the other two patients, one had a complex-partial SE due to a ganglioglioma and the other simple-partial SE due to a brain abscess. Both patients became seizure-free after surgical treatment.
3. *Responders to other AEDs than VPA*: Only two patients were in this group. One patient had an atypical absence-status, promptly reacting to benzodiazepines, the other one had several GTC seizures which got controlled by high dosage of VPA, however, ending into a complex-partial

SE, which could be easily interrupted by a standard dosis of intravenous phenytoin.

Twenty-nine patients had received benzodiazepines or intravenous phenytoin in standard adult dosages[8] without success before treatment with intravenous VPA. Five of these were refractory to benzodiazepines and intravenous phenytoin in a maximum dose and became seizure-free under intravenous VPA.

Discussion

The emergency treatment of seizures is an important practical issue. This is particularly true for SE, where the mortality rates may be still as high as 25%. Early aggressive treatment seems to be absolutely necessary in this life-threatening condition. The AED should ideally fulfill the following criteria: (1) be easy to use, (2) show rapid action, (3) have a long-lasting antiepileptic effect, (4) finally, have minimal cardiopulmonary and other side-effects. Unfortunately, none of the presently available medications such as phenytoin and barbiturates seems to have all of these four properties.[8]

In our opinion, intravenous VPA might be an interesting alternative in this context for several reasons. It is well known to have a variety of action sites in the experimental setting[10] explaining its excellent efficacy in most seizure types. In an electrically induced SE-model in animals, VPA suppressed seizure activity after 30 s,[7] being faster than diazepam and phenytoin, both of which showed more prominent sedation.

The history of intravenous application of VPA in patients is a fairly recent one. Since the first observations of its high efficacy combined with excellent safety data in a small study group of patients with SE by Price[3], a few uncontrolled open studies followed,[4,5,2,6] all of them confirming the therapeutic value of this new formulation.

Our own preliminary data have shown its good antiepileptic effects both in a series of seizures and in different kinds of SE including GTCS-SE, with a success rate of approximately 80%. Interestingly, intravenous VPA could terminate seizure activity in most of the cases where different established AEDs (benzodiazepines and intravenous phenytoin) had previously failed. Our efficacy rates of up to 80% and more correspond to other recent studies in adults[2–5] and children,[6] where most patients had also been pretreated unsuccessfully with standard benzodiazepines. Treatment failure in our study population mainly occurred in those individuals, who were either refractory with any AED, had an underlying life-threatening condition or revealed a highly epileptogenic lesion such as a brain abscess. Only two patients showed seizure control after a switch to an alternative medication.

In the two small adult case series[5,4] (n = 20 and 23, respectively), a treatment regimen with an initial bolus treatment of 15 mg/kg BW and a subsequent infusion with 1 mg/kg BW/h of either 5–6 h[5] or 24 h,[4] interrupted on-going SE in 80–85% of cases controlled by EEG-monitoring in one study.[4] Major systemic side effects were not observed in either study. Ueberall et al.[6] treated 41 children in SE, who had been refractory to benzodiazepines, phenytoin and barbiturates before, by means of intravenous VPA, using an initial bolus of 20–40 mg/kg BW, followed by an infusion with 5 mg/kg BW/h. SE could be successfully interrupted in 78% (32 out of 41) of the children, in the majority (n = 27) within 2–6 min. Seizure control was assessed by EEG-monitoring in all patients.

There were no major safety problems in our entire study group of 102 patients with a wide spectrum of therapeutic indications. This is in perfect agreement with all above mentioned efficacy studies, even in studies where very high dosages of up to 9.6 g/d were applied,[3] and with those studies, in which the safety aspect of intravenous VPA was particularly addressed.[9,10] Due to the mainly retrospective character of our study, we might have missed some minor side effects, which may not have been documented in the charts but there have clearly been no serious adverse events.

More recent experiences with high bolus application of intravenous VPA with up to 40 mg/kg BW and rapid loading with a rate of up to 6 mg/kg BW/min[11–14] demonstrate both excellent efficacy and safety. The two manufacturers in Germany now recommend an initial loading dose of 15 mg/kg BW over a time period of up to 30 min followed by an infusion at 1–2 mg/kg BW/h over 12–24 h, which is close to the regimen we used in our study. Meanwhile we have administered dosages of 4800 mg up to 9600 mg over 24 h in cases of SE that were difficult to treat, without any evidence of severe side effects.

The above reported high efficacy rates of >80% including our own experience are very promising, but have to be interpreted with caution, as they are still results from open study designs, or retrospective small case series.[15] It is also difficult to compare them with other data, as most publications with regard to any antiepileptic treatment in SE are either anecdotal case reports or open studies with only a small number of patients. Systematic prospective comparisons of different AEDs, randomized and double-blind, are extremely rare: to our knowledge there are only three studies,[16–18] and only one with a larger population.[18]

In this prospective multi-centre, double-blinded comparison study, 570 patients randomly received different therapeutic regimens (phenytoin, diazepam + phenytoin, phenobarbital and finally lorazepam), but unfortunately VPA was not included. The reported low efficacy rate of only 55% in this study, independent of the chosen drug, is mainly due to the selection of patients in this study and the long duration of the SE before recruitment.[18]

Against this background it now seems necessary to perform a controlled randomized double-blind trial in SE to compare the efficacy and tolerability of intravenous VPA with phenytoin or fosphenytoin. Several open questions, such as loading and maintenance dosis, target groups and time point of application in a new decision algorithmus for SE have to be addressed in the future.

In conclusion, the intravenous application of VPA seems to be a highly efficient and safe treatment in many seizure emergency situations including SE. Our data strongly support that the profile of VPA includes a fast action beside the well known slow-acting mechanisms.[19] It can have an effect even in cases when other first-line AEDs have failed, but shows a significantly better tolerability, is easier to handle and can be switched directly to a long-term antiepileptic therapy of first choice. Further controlled comparison studies have to be performed in the future.

Acknowledgement

We are very grateful to Dr. Peter Carlen, Professor of Neurology, Toronto Western Hospital, University of Toronto, who carefully reviewed this manuscript and gave helpful suggestions.

References

1. Chadwick D. Standard approach to antiepileptic drug treatment in the United Kingdom. *Epilepsia* 1994;**35**(Suppl. 4): S3—10.
2. Rosenfeld WE, Leppik IE, Gates JR, Mireles RE. Valproic acid loading during intensive monitoring. *Arch Neurol* 1987; **44**:709—10.
3. Price DJ, Intravenous valproate. Experience in neurosurgery.Chadwick DW, editor. *Proceedings of the 4th International Symposium on Valproate and Epilepsy International Congress and Symposium Series*, Vol. 152. 1989;p. 197—203.
4. Giroud M, Gras D, Escousse A, Dumas R, Venaud G. Use of injectable valproic acid in status epilepticus: a pilot study. *Drug Invest* 1993;**5**:154—9.
5. Czapinski P. Intravenous valproate acid administration in status epilepticus. *Epilepsia* 1995;**36**(3):265.
6. Ueberall MA, Trollmann R, Wunsiedler U, Wenzel D. Intravenous valpraote in pediatric epilepsy patients with refractory status epilepticus. *Neurology* 2000;**54**:2188—9.
7. Hönack D, Löscher W. Intravenous valproate: onset and duration of anticonvulsant activity against a series of electroconvulsions in comparison with diazepam and phenytoin. *Epilepsy Res* 1992;**13**:215—21.
8. Lowenstein DH, Alldredge BK. Status epilepticus. *N Engl J Med* 1998;**33**:970—6.
9. Devinsky O, Leppik IE, Willmore LJ, et al. Safety of intravenous valproate. *Ann Neurol* 1995;**38**:670—4.
10. Ramsay RE, Uthman BM, Leppik IE, et al. The tolerability and safety of valproate sodium injection given as an intravenous infusion. *J Epilepsy* 1997;**10**:187—93.
11. Naritoku DK, Mueed S. Intravenous loading of valproate for epilepsy. *Clin Neuropharmacol* 1999;**22**:102—6.
12. Venkataraman V, Wheless JW. Safety of rapid intravenous infusion of valproat loading doses in epilepsy patients. *Epilepsy Res* 1999;**35**:147—53.
13. Wheless JW, Venkataraman V. Safety of high i.v. loading doses of valproate. *Epilepsia* 1998;**39**(Suppl. 6):50.
14. Limdi NA, Faught E. The safety of rapid valproic acid infusion. *Epilepsia* 2000;**41**:1342—5.
15. Pohlmann-Eden B, Peters CNA. Use of Intravenous valproate in status epilepticus. *Akt Neurologie* 2001;**28**:480—6.
16. Leppik IE, Derivan AT, Homan RW, Walker J, Ramsay RE, Patrick B. Double-blind study of lorazepam in status epilepticus. *J Am Med Assoc* 1983;**249**:1452—4.
17. Shaner DM, McCurdy SA, Herring MO. Treatment of status epilepticus: a prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin. *Neurology* 1988;**38**:202—7.
18. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. *N Engl J Med* 1998;**339**:792—8.
19. Loescher W. Valproate: a reappraisal of its pharmacodynamic properties and mechanisms of action. *Prog Neurobiol* 1999; **58**(1):31—59.