Safety and efficacy of intravenous sodium valproate in the treatment of acute migraine

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Abstract

This multicenter study investigated the safety and efficacy of intravenous valproate in acute migraine attacks and the possible impact of prophylactic valproate pretreatment. Thirty-six patients established on migraine prophylaxis were administered 500 mg sodium valproate intravenously against acute migraine attacks. Pain development was assessed by visual analogue scale up to a 24 hours follow up interview to detect e.g. possible relapse symptoms. A subgroup analysis examined whether prophylactic treatment with valproate affected its acute anti-migraine efficacy. A meaningful headache reduction within two hours was achieved in all 12 patients with and in 20 out of 24 patients without valproate prophylaxis. Headache-associated signs and symptoms were substantially reduced. No serious side-effects were reported. The results confirm the therapeutic value of intravenous valproate in acute migraine attacks described in literature and show a beneficial effect on all investigated efficacy parameters with a trend to even better response in patients receiving valproate prophylaxis.

ORIGINAL ARTICLE

Introduction

In the prophylaxis of migraine, valproate (VPA) is a drug of first choice. Its clinical efficacy has been proven in many clinical trials: Hering and Kuritzky 1992 [1], Raskin 1993 [2], Jensen et al. 1994 [3], Mathew et al. 1995 [4], Rothrock 1997 [5], Kinze et al. 2001 [6]. For the treatment of acute migraine attacks with intravenously administered sodium valproate, almost only empirical reports and open studies are available (Mathew et al. 2000 [7], Norton 2000 [8], Edwards et al. 2001 [9], Krusz 2001 [10], Stillman et al. 2004 [11]) indicating that it alleviates headache quickly and reduces nausea/vomiting and photophobia which are often associated with migraine. At the same time it seems to enhance the activity of patients with as well as without aura: Mathew et al. 2000 [7]. Valproate can be administered even if ergotamine or triptans have been given immediately before.

The present study was set up not only to confirm the efficacy and tolerability of intravenously administered sodium valproate in the treatment of acute migraine attacks, but also to investigate whether

this therapeutic quality may in any way be affected by a pre-treatment with VPA in patients with established drug prophylaxis of migraine.

Patients and methods

Patients

In this prospective, open multicenter study patients with already established prophylactic migraine treatment who would – according to their physician's assessment – probably require acute migraine treatment within seven weeks after the baseline examination were included. Migraine without aura (1.1) and/or migraine with aura (1.2) according to the IHS – International Headache Society, Headache classification committee of the IHS, 1988 [12] must have adversely affected the patients' daily life so that they were in need of drug prophylaxis established for at least six weeks prior to inclusion into the study.

Methods

After informed written consent was obtained, the patients were checked for inclusion and exclusion criteria at baseline examination including the MIDAS questionnaire published by Stewart et al. 1999 [13] and their migraine was exactly diagnosed and classified according to IHS criteria, 1988 [12]. Then they were assigned to two parallel groups, depending on which kind of prophylactic medication was taken. In one group the patients' established migraine prophylaxis included a VPA preparation, in the other group it did not. At the baseline visit no study medication was given. Finally the patients were instructed to come to the outpatient clinic whenever they felt an acute migraine attack approaching. In principle, a maximum of seven weeks were allowed to pass between baseline examination and the occurrence of a migraine attack requiring acute treatment with intravenous valproate, but the start of the acute treatment immediately after the baseline investigation was also possible, provided the patient was well known to the (co-)investigator from the continuous prophylactic treatment.

On the day a patient came to the outpatient clinic for acute migraine treatment, first the actual attack was assessed in order to confirm the initial diagnosis. Then the medication taken during 24 hours prior to the attack was recorded. Thereafter the study medication was administered. The main parameters of the application, like the infusion flow rate and the dilution used, were recorded. It was also recorded whether the patients experienced any local or systemic side effects. The patients stayed at the outpatient clinic for not less than two hours and they were asked to describe the course of pain intensity by means of a VAS (visual analogue scale) and the associated symptoms at start of infusion, after 15, 30, 45, 60 and 120 minutes.

Twenty-four hours after the start of acute treatment the patients were interviewed once more, either personally or by phone, in order to describe the development of pain (according to the VAS used before), the associated symptoms, and the medication taken during the last 24 hours. Again, the patients were asked whether they had noticed any adverse effects. In order to obtain a measure of the patients' overall acceptance of the study treatment, their willingness to receive in future acute migraine attacks intravenous valproate again was explored.

Study Medication

The ampoules for intravenous injection (CONVULEX® 100 mg/ml Solution for Injection, manufactured by GEROT Pharmazeutika, Vienna) contained 500 mg sodium valproate/5 ml solution each. In the treatment of an acute migraine attack they could be administered undiluted as a slow intravenous bolus injection (1 ml per minute, maximum of 5 ml), or diluted as an infusion. For infusion, the content of one ampoule was diluted in 50 ml or 100 ml of isotonic sodium chloride solution.

The minimum dose to be administered for the acute therapy was 300 mg, the maximum dose 500 mg of sodium valproate (one ampoule).

Statistics

Descriptive statistics, as appropriate, were used to describe the outcome. For sub-group analysis the null hypothesis of inferiority, $\pi 2 - \pi 1 \geq \delta 0$ was tested against the one-sided alternative hypothesis of non-inferiority, $\pi 2 - \pi 1 < \delta 0$ at the 2.5% significance level (with $\pi 1$ and $\pi 2$ as the event rates of test and control prophylaxis and $\delta 0$ as the non-inferiority margin set to 0.20).

As all patients treated with study medication finished the study in accordance with study protocol, only one single study population – the per protocol study population – was used for efficacy as well as safety evaluation. In view of the pilot character of this study no hypotheses about efficacy were proposed and the evaluation was explorative.

Results

The per protocol study population comprised 36 female patients aged from 23.3 to 60.4 years. ANOVA (between centres) and independent sample t-tests (between

Figure 1. Study flow chart

prophylaxis subgroups) could not detect significant differences in the demographics parameters between the prophylaxis subgroups. Thirty-four patients suffered from migraine without aura, one from migraine with aura and one from both. The patients had a mean migraine history duration of 25 years and a mean duration of migraine drug therapy of nine years. In the total study population as well as in both subgroups approx. three quarters of patients reported severe disability caused by migraine headache (MIDAS >21).

Twelve ($^1/_3$) of the patients received a migraine prophylaxis with oral VPA, whether alone or with comedication, established for at least two months (and thus formed the subgroup of patients with established VPA prophylaxis). Other prophylactic medications were based on different antiepileptics (gabapentin, topiramate, clonazepam) or calcium-antagonists (cinnarizine, diltiazem) or the tricyclic antidepressant amitriptyline. Patients with established VPA prophylactic therapy predominantly took 500 mg (nine cases) or 300 mg (two cases) as an evening dose, one patient took 1000 mg split into a morning and an evening dose. At the time of baseline examination, 13 patients had no prescription for a rescue medication to manage acute attacks. The other 23 patients used predominantly triptans and further analgesics or ergotamines. As required by study protocol there were no changes in the migraine prophylaxis during at least six weeks before the baseline visit or during the time between the baseline visit and the acute treatment.

The study centres reported quite different times between the onset of the acute attack and the start of infusion. Two groups of patients could be identified: patients with less than four hours and patients with more than four hours between the onset of an attack and the infusion of the study drug. Eight patients had already taken an acute treatment before receiving intravenous valproate.

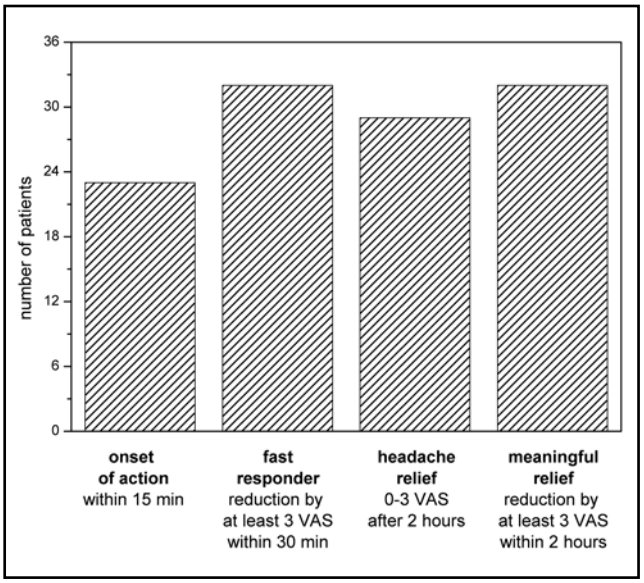

Figure 2. Proportion of responders to intravenous valproate.

All patients received 500 mg of sodium valproate, the maximum dose determined by study protocol, 34 of them as an infusion after dilution in 50 ml or 100 ml 0.9% sodium chloride solution and two as an undiluted bolus injection. The duration of the infusions ranged from 15 to 45 minutes, the bolus injections were accomplished in five minutes. The mean interval from infusion onset to discharge was 2.5 hours, mainly due to the observation period of two hours required by study protocol. However, in most patients substantial pain relief was obtained considerably earlier and from the clinical point of view they could have been discharged earlier.

Collective efficacy

The onset of action (defined as VAS-pain scale reduction by at least one point) was observed in 23, i.e. approx. $^2/_3$ of the patients already after 15 minutes. Eleven additional patients experienced an onset of action between 15 and 30 minutes after the start of the infusion. Hence, 34 (more than $^9/_{10}$) of the patients reported an onset of action within the first half an hour. Thirty-two patients fulfilled the criteria of the primary efficacy parameter *Meaningful Relief* (defined as improvement of at least three VAS points within two hours). The number of patients considered *Fast Responders* (showing a decrease in VAS of more than three points within 30 minutes) was 32 as well. *Headache Relief*, a clinically relevant pain reduction (VAS score of three or less after two hours) was achieved in 29 equal to approx. $^8/_{10}$ of the patients.

In all but one patient the associated symptoms (nausea, vertigo, vomiting, bed rest necessary, photo- and phonophobia) decreased during or after the intravenous administration of valproate. Thirty-five patients became free of symptoms by the end of the observation period of two hours, only one patient (who became free of symptoms within the first 30 minutes) experienced a recurrence of symptoms between 60 and 120 minutes after the injection of a short valproate bolus. The other 26 patients ($^7/_{10}$) became symptom-free within one hour. Similar to the reduction of pain measured by the VAS, the most substantial decrease in associated symptoms was obtained during the first 60 minutes of the therapy (Table 1).

Table 1. Number of patients becoming free of associated symptoms

Symptom-free after	Frequency	Cumulative frequency	Cumulative percent
0–15 minutes	6	6	17%
15–30 minutes	6	12	33%
30–45 minutes	11	23	64%
45–60 minutes	3	26	72%
60–120 minutes	9	35	97%
post 120 minutes	1	36	100%

All patients completed the 24-hour interview, 11 appearing in person and 25 interviewed via telephone. Twenty-nine ($^{8}/_{10}$) of the patients remained pain-free within the first 24 hours after finishing parenteral valproate treatment, only seven reported a recurrence of headache (relapse). However, all seven patients had initially experienced a significant pain reduction by more than three VAS-scale points due to the intravenous valproate treatment. All these patients except one used a rescue medication to treat the relapse headache which showed a pain intensity and associated symptoms similar to those preceding study treatment. Twenty-nine patients (more than $^{8}/_{10}$) declared they would again prefer an administration of intravenous valproate in their next acute migraine attack, only seven patients were not willing to receive this treatment in future.

In order to provide a global impression of overall efficacy, the composite parameter *Maximum Therapeutic Result* was defined. It integrates the following efficacy parameters and comprises all their requirements: **1)** *Meaningful Relief* (improvement of at least three VAS points within two hours), **2)** *Headache Relief* (VAS score of three or less after two hours), **3)** *Symptom-free After Two Hours* (no associated symptoms after two hours), **4)** *Sustained Pain-Free* (no relapse = recurrence of headaches within 24 hours) and **5)** *Positive Patient's Preference* (willingness to receive intravenous valproate again). The *Maximum Therapeutic Result* according to the above described definition was achieved in 23 (approx. $^{2}/_{3}$) of the patients.

Subgroup analysis

Patients with an established VPA prophylaxis showed in all efficacy parameters a better outcome than patients with a non-VPA prophylaxis (all differences of proportions less than 0), but superiority could not be proven. However, several parameters (*Fast Responders, Meaningful Relief, Headache Relief, Patients' Preference, Maximum Therapy Result*) gave significant non-inferiority p-value at the 2.5% level (2.5%, since the non-inferiority test is a one-sided test) applying a non-inferiority margin of 20%. Detailed figures are compiled in Table 2.

The benefit was most apparent in the *Maximum Therapeutic Result* which was achieved in the subgroup with established VPA prophylaxis in 10 out of 12 patients (event rate 0.83), but only in 13 out of 24 patients (event rate 0.54) in the subgroup with prophylactic medication without VPA. The relative benefit increase (RBI) of the *Maximum Therapeutic Result* reached 53.8%.

Headache Relief was achieved faster in the subgroup of patients receiving VPA prophylaxis, though the difference was not statistically significant. "Mild to no pain" (VAS score below four) was reached (on the average) after 45 minutes in the subgroup of patients with VPA prophylaxis, but only after 60 minutes in the non-VPA group (Figure 3).

The intervals between the onset of the acute migraine attacks and the administration of intravenous valproate (= "untreated periods") were not equal. For evaluation, the patients' data were divided into two groups according to the untreated period (longer or shorter than four hours). Overall, the response was quite similar in size in both subgroups. However, the subgroup with untreated periods of less than 4 hours contained more responders (*Headache Relief*) but also more patients with a relapse. Furthermore, the intensity of headache (measured by means of the VAS) decreased somewhat faster in patients who received intravenous valproate sooner after the onset of the attack, compared to those with a prolonged untreated period (Figure 4).

Safety evaluation

According to study protocol the systemic tolerability and local tolerability at the injection site were assessed and recorded in the Case Report Form (CRF) both during the stay at the clinic and during the following 24 hours. Sodium valproate was very well tolerated, both as intravenous injection and infusion. No deaths or other serious adverse events occurred and none of the

Table 2. Subgroup analysis

	Events			Event rates (proportions)				Difference of proportions	Non-inferiority[2]	
	all	non VPA	VPA	all	non VPA	VPA	RBI[1]	VPA – non-VPA	p	Sig (2.5%)
Patients included	36	24	12	--	**π1**	**π2**				
Fast responders	20	12	8	0.56	0.50	0.67	33.3%	–0.17	0.017	yes
Meaningful relief	32	20	12	0.89	0.83	1.00	17.0%	–0.17	0.006	yes
Headache relief	29	18	11	0.81	0.75	0.92	22.2%	–0.17	0.010	yes
Symptom-free in 60 min	26	17	9	0.72	0.71	0.75	5.9%	–0.04	0.073	
Sustained pain-free	29	19	10	0.81	0.79	0.83	5.3%	–0.04	0.061	
Patients' preference	29	18	11	0.81	0.75	0.92	22.2%	–0.17	0.010	yes
Maximum therapy result	23	13	10	0.64	0.54	0.83	53.8%	–0.29	0.002	yes

[1]RBI (Relative Benefit Increase) expresses of the amount of increase in the rates of positive events: (π2 – π1)/ π1
[2]Non-inferiority: Difference of proportions is less than 20% (δ0)

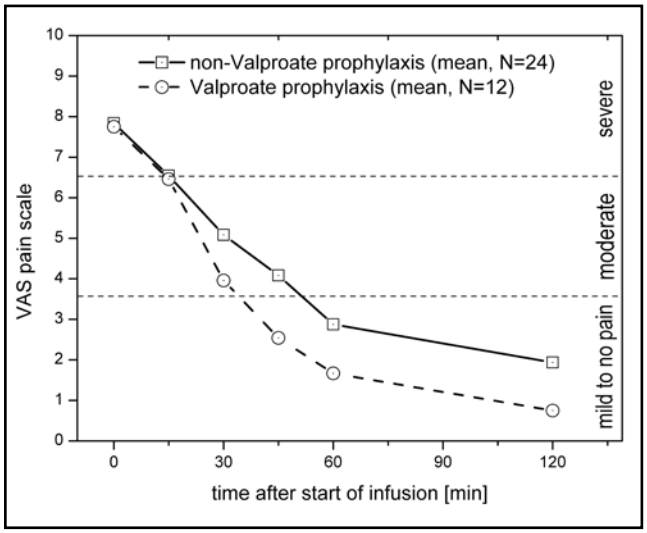

Figure 3. Comparison of VAS pain scores – non-VPA vs. VPA prophylaxis.

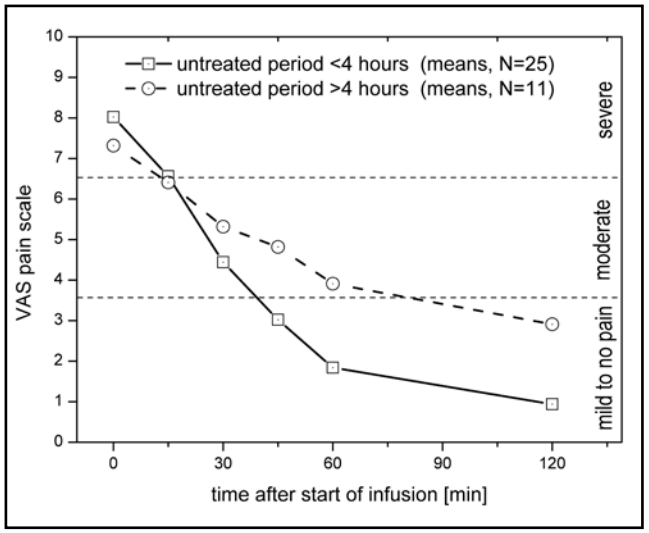

Figure 4. Course of the VAS pain score.

36 patients reported any systemic or local adverse reactions at the injection site, both during the intravenous administration of 500 mg sodium valproate and within 24 hours after study drug application.

Discussion

Today the oral prophylactic treatment with VPA is a well accepted and documented first-line choice for the preventive therapy of migraine: Hering and Kuritzky, 1992 [1], Raskin, 1993 [2], Jensen et al., 1994 [3], Mathew et al., 1995 [4], Rothrock, 1997 [5], Kinze et al., 2001 [6]. Nevertheless, on the treatment of acute attacks of migraine with intravenous valproate almost only empirical reports and open studies are available at present. No scientific investigations exploring whether the efficacy of the acute treatment with intravenous valproate is in any way affected by an already established prophylactic treatment with oral VPA have been published until now.

In our study 36 patients with established migraine prophylaxis were prospectively treated on a non-randomized, open-label basis to investigate the safety and efficacy of intravenous valproate in acute therapy of moderate to severe migraine headaches. Furthermore, a subgroup analysis was performed to obtain information about a possible influence of migraine prophylaxis on the efficacy of acute treatment.

In the present study a large majority of patients experienced a fast and considerable pain reduction within two hours after injection of sodium valproate without any undesirable effects. These results confirm the data from literature about the safety and overall efficacy of intravenous valproate (especially regarding the parameter *Meaningful Relief* which was the primary parameter also in the present study). Mathew et al., 2000 [7] used a fixed and relatively low dosage of valproate and accomplished an efficacy rate of 56%, whereas Edwards et al., 2001 [9] had a higher fixed dosage of 500 mg (as in the present study), but also longer durations of headache before onset of the acute treatment. Stillman et al., 2004 [11] allowed intravenous valproate dosages up to 1 000 mg (patients taking oral valproate) and 1 200 mg (patients who were valproate-naïve) and reported an efficacy rate of 82%, close to the efficacy of the present study of 81%. All three authors report a fast relief of associated symptoms and minimal side-effects (Table 3).

The results obtained from the subgroup analysis revealed in patients already receiving VPA prophylaxis a beneficial effect on all efficacy parameters. The most apparent differences were observed in *Headache Relief* and in the *Maximum Therapeutic Result,* the latter showing a relative benefit increase of 53.8%. Though the differences did not reach statistical significan extent in any of the studied therapeutic parameters, the outcome of the study could have important implications for migraine therapy. Theoretically, patients in whom a prophylaxis with VPA was unable to prevent an acute migraine attack might have been considered predisposed not to respond to an acute therapy with the same active substance. However, our findings overcome such concerns about a possible unfavourable influence of VPA prophylaxis on its efficacy in the acute intravenous treatment. On the contrary, the efficacy of VPA in migraine therapy, both as a preventive and as an abortive drug, is not only confirmed, but it appears that prophylactic and acute treatment schemes do not interfere with, but probably even support each other.

In addition to the requirements of the protocol, it was evaluated whether the duration of the untreated period between the onset of an attack and the intravenous valproate administration had any effect on the outcome. The results indicate that the probability of a successful treatment is higher the sooner valproate is injected after onset of an acute attack.

Table 3. Comparison of the present study with published data.

Source	Numbers of attacks treated	VPA dosage	Duration of headache [hours]	Meaningful Relief within 2 hours
Mathew et al., 2000 [7]	66	300 mg	7	56%
Edwards et al., 2001 [9]	20	500 mg	46	60%
Stillman et al., 2004 [11][1]	130	300–1 200 mg	no data	82%
Present study (2006)	**36**	**500 mg**	**7**	**81%**
VPA prophylaxis	12		11.6	92%
non-VPA prophylaxis	24		12.8	72%

[1]not only migraine headache, recruited also patients with chronic daily headache and with unclassifiable chronic headache

Conclusion

Sodium valproate is a well tolerated substance with good efficacy and known advantages in the treatment of acute migraine attacks, e.g. it can be administered even immediately after ergotamine or triptans. In addition, there is now good evidence that an established prophylactic VPA therapy does not negatively influence, but probably enhances the beneficial effects of intravenously administered valproate in the treatment of acute attacks.

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