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Gabapentin for the Symptomatic Treatment of Chronic Neuropathic Pain in Patients with Late-Stage Lyme Borreliosis: A Pilot Study

S. Weissenbacher J. Ring H. Hofmann

Department of Dermatology and Allergy Biederstein, Technical University of Munich, Munich, Germany

Key Words
Lyme borreliosis · Gabapentin · Neuropathic pain

Abstract
Background: Chronic neuropathic pain occurs in 10–15% of patients with neuroborreliosis and is difficult to treat. ***Objective:*** We evaluated the effect of gabapentin monotherapy on residual pain in patients with neuroborreliosis after intravenous ceftriaxone treatment. ***Methods:*** Ten patients with neuroborreliosis and a long-lasting history of neurologic symptoms were treated with gabapentin, starting with 300 mg/day. Doses were raised over a period of 4–12 weeks to the individually effective and tolerated maximum dose (500–1,200 mg). Treatment was maintained until pain disappeared and then gradually reduced in dose over weeks. If symptoms recurred, the doses were raised again. Therapy was maintained over an average of 1–2 years. ***Results:*** Pain quality and pain quantity were evaluated using the McGill pain questionnaire and a visual analogue scale. There was an improvement of 'crawling' and 'burning' pain sensations, neck and radiating lumbar pain in 9/10 (90%) patients as well as a positive effect on mood, general feeling of health and quality of sleep in 5/10 (50%) patients. The average dose leading to a clear-cut pain reduction was 700 mg. ***Conclusions:*** In an open pilot study (10 patients), gabapentin monotherapy which has to our knowledge not been published as treatment of chronic neuropathic pain in patients with late Lyme borreliosis is efficacious in treating pain associated with neuroborreliosis and can thus improve quality of life in these patients.

Introduction

Lyme borreliosis is a tick-borne, stage-related disease caused by *Borrelia burgdorferi* sensu lato with *B. burgdorferi* sensu stricto, *B. garinii* and *B. afzelii* as the most frequent genospecies in Europe. It is primarily transmitted in Europe by the tick *Ixodes ricinus* [1]. Depending on the stage, the clinical manifestations of the disease are variable. Early Lyme disease can be localized (erythema migrans) or disseminated (multiple erythemata migrantia) with cranial nerve palsies and meningitis occurring often in the disseminated stage [2, 3]. Late Lyme borreliosis with neuroborreliosis being the most common manifestation in Europe occurs weeks to years after infection. Patients typically complain of myalgia, arthralgia, dysaesthesia or paraesthesia, 'crawling' and 'burning' pain sensations, neck and radiating lumbar pain, fatigue as well as mood and memory disturbances [4]. Alteration of primary afferent function like deafferentation or hyperexcitability or direct injury to central neurons for example due to *Borrelia* infection can contribute to persistent peripheral or central neuropathic pain and abnormal sensation [5]. First-line therapy is parenteral ceftriaxone. Persisting

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Prof. Dr. H. Hofmann
Department of Dermatology and Allergy Biederstein
Biedersteinerstrasse 29
DE–80802 München (Germany)
Tel. +49 89 4140 3181, Fax +49 89 4140 3581, E-Mail H.Hofmann@lrz.tum.de

symptoms usually do not respond to additional courses of antibiotics but may improve with symptomatic therapy [1]. Persistent neuropathic pain occurs in 10–15% after antibiotic treatment of neuroborreliosis and is difficult to treat. Currently, the standard treatment for neuropathic pain consists in the application of various tricyclic antidepressants (amitriptyline, desipramine, clomipramine) either as monotherapy or in combination, e.g. with carbamazepine or opioids. However, pain is sometimes incompletely relieved even by opioids [6]. Unfortunately, only about 50% of patients treated in clinical trials experience pain relief in the absence of intolerable adverse effects [7]. We evaluated the effect of gabapentin monotherapy on residual pain in patients with neuroborreliosis after ceftriaxone treatment.

Methods

Ten patients – 8 female and 2 male – with a mean age of 61.5 years (range from 45 to 80 years) were investigated in a single-centre pilot study. Patients were selected with proven neuroborreliosis and persistent neuropathic pain in spite of sufficient (at least 14 days with 2 g/day) antibiotic treatment with intravenous ceftriaxone therapy. Neurologic symptoms had been present from 5 months to 10 years. The main complaints were paraesthesia, crawling and burning pain in the lower extremities, neck and radiating lumbar pain with deterioration usually at night. Oral treatment with gabapentin, a 1-aminomethylcyclohexane acetic acid (Neurontin®, Parke-Davis/Pfizer, Division of Warner-Lambert Co., Morris Plains, N.J., USA) was started with 300 mg/day. Doses were raised slowly (by 100–300 mg/day) over a period of 4–12 weeks to the maximum individually tolerated and effective dosage. The maximum doses given were between 500 and 1,200 mg. Treatment was then maintained until pain disappeared followed by slow reduction of doses over weeks. If symptoms recurred, doses were raised again. Therapy was continued for an average of 1–2 years. No other analgesics were taken during the study.

Pain intensity (especially paraesthesia, crawling and burning pain) was measured by visual analogue scale (VAS pain), and pain quality and quantity were assessed by the McGill pain questionnaire [8]. VAS pain is a numerical scale ranging from 0 ('no pain') to 100 mm ('maximum pain'). Pain severity was measured before and after therapy. Pain quality/quantity was evaluated based on the McGill pain questionnaire validated for determination of the properties of pain experience. It consists primarily of three major classes – sensory, affective and evaluative qualities of pain called the pain rating index (PRI) and the present pain intensity (PPI). The sum of points given for each item (total McGill pain questionnaire score) ranging from no pain (score of 0) to worst pain (score of 4) were determined as well as the different items chosen. The McGill pain questionnaire was completed before and after therapy. Adverse events were recorded throughout the studied period. Two years after the end of the study, a telephone survey was performed to evaluate the occurrence of relapses.

Results

The dose of gabapentin showing a clear-cut effect on pain was individually variable and corresponded partially to the maximum dose. It ranged from 500 to 1,200 mg gabapentin with a mean effective dose of 700 mg. Gabapentin reduced pain intensity in 9/10 (90%) patients. According to the definition of analgesic efficacy [6], 4/10 (40%) patients experienced at least 50% pain relief, 5/10 patients (50%) had less than 50% decrease in pain and 1/10 (10%) patient had no response to gabapentin. In this patient, 600 mg/day could not be increased because of dizziness which always appeared when elevating the dose. Patients reported an improvement especially of crawling and burning pain and radiating lumbar pain. There was no improvement of numbness in 4/10 (40%) patients and no improvement of myalgias in 2/10 (20%) patients (table 1).

The VAS pain score before therapy from 50 to 100 mm VAS decreased to values from 10 to 60 mm after therapy. The comparison of the mean VAS pain score before and after therapy showed a reduction from 64 to 35 points. A VAS pain score of >50 mm was found in 6/10 (60%) patients before therapy and in 2/10 (20%) patients after gabapentin treatment (fig. 1a).

Evaluation of the quality/quantity of pain by the McGill pain questionnaire revealed generally similar findings to the VAS pain intensity data. The total pain rating index (PRI_T) which is the total score of the McGill pain questionnaire (points) ranged from 5 to 75 before and from 1 to 57 after therapy.

This corresponded to a reduction of the mean PRI_T from 38.8 to 25.3 comparing pain before and after gabapentin therapy. The PRI_T itself is subdivided into 4 different categories, the sensory (PRI_S), affective (PRI_A), evaluative (PRI_E) and miscellaneous (PRI_M) pain rating index, with each of them showing as well a reduction after treatment with gabapentin. The PRI_S decreased from 21.9 to 15.7, the PRI_A from 4.8 to 3.2, the PRI_E from 2.0 to 1.5. The reduction of the PRI_M from 9.8 to 4.8 was significant.

The PPI which is the total score of the present pain intensity decreased as well from an average value of 8.3 (range from 1 to 20) before treatment to an average value of 5.9 (range from 1 to 17) after therapy. A comparison of the scores of the PRI and the PPI before and after therapy is shown in figure 1b and c.

The most frequent items chosen in the McGill pain questionnaire describing the present pain were similar before and after therapy: 'radiating, tugging, tiring, ach-

Table 1. Data of 10 patients with late-stage Lyme borreliosis treated with gabapentin

Patient	Age/sex	Antibiotic therapy of Lyme borreliosis	Complaints after antibiotic therapy	Duration of complaints	VAS		PRI_T		PPI		Maximum dose mg	Duration of therapy months	Response to gabapentin
					before	after	before	after	before	after			
1	62/f	Cef 2 g/2 weeks	back pain, numbness, paraesthesia, crawling and burning pain, fatigue, myalgias, headache, dizziness	3 years	50	30	73	40	12	7	1,200	18	PR
2	62/f	Dox 200 mg/2 weeks Cef 2 g/3 weeks	back pain radiating to the legs, crawling and burning pain, feeling of restlessness, fatigue	9 months	60	60	14	25	7	7	600	8	NOR
3	80/m	Cef 2 g/3 weeks	back pain, numbness, dysaesthesia of the right side of the back, hypaesthesia between shoulders, burning pain in neck and arms	9 months	80	10	5	1	1	1	500	2	CR
4	56/f	Cef 2 g/3 weeks Cefu 500 mg/3 weeks	back pain radiating to the legs, numbness, paraesthesia, dysaesthesia, crawling and burning pain, fatigue, arthralgias, myalgias, tachycardia, nuchal pain, headache	4 years	50	20	20	10	4	2	500	8	CR
5	64/f	Cef 2 g/3 weeks Dox 200 mg/3 weeks	lumbar pain radiating to the legs, numbness of the legs, paraesthesia, dysaesthesia, crawling and burning pain, swelling of the joints	2 years	50	30	22	9	6	3	600	5	PR
6	47/m	Cef 4 g/3 weeks twice	numbness, dysaesthesia, crawling and burning pain, fatigue, arthralgias, myalgias, palpitations of the heart, nuchal pain, visual impairment	1 year	50	30	22	24	10	7	600	15	CR
7	45/f	Dox 200 mg/3 weeks Pen 10 MU/3 weeks	back pain radiating to the legs, numbness, paraesthesia, dysaesthesia, crawling, feeling of restlessness, fatigue, arthralgias, myalgias, tachycardia, nuchal pain, headache, visual and hearing impairment, dizziness	10 years	60	20	44	15	6	3	800	2	CR
8	67/f	Pen 10 MU/4 weeks	back pain radiating to the legs, numbness, crawling and burning pain, fatigue, arthralgias, myalgias, heart palpitations, hearing and visual impairment	4 years	80	60	75	57	9	7	1,200	2	PR
9	62/f	Dox 200 mg/3 weeks	nuchal pain, numbness, paraesthesia, crawling and burning pain, hearing impairment	10 years	60	40	57	41	20	17	600	4	PR
10	70/f	Dox 200 mg/3 weeks Cef 2 g/2 weeks	back pain radiating to the legs, crawling, fatigue, arthralgias, myalgias, nuchal pain, headache, visual impairment	5 months	100	50	56	31	8	5	600	1	PR

f = Female; m = male; Cef = ceftriaxone; Dox = doxycycline; Cefu = cefuroxime; Pen = penicillin; PR = partial remission; NOR = no remission; CR = complete remission.

ing'. In addition to the reduction of pain in the investigated group, gabapentin had a positive effect on mood, general health and sleep interference in 5/10 (50%) patients.

No severe adverse events were experienced. Gabapentin therapy was well tolerated. Minor adverse events were reported by 7/10 (70%) patients. One had slight headache, 2 reported moderate fatigue and 4 patients experienced initial dizziness disappearing with continuation of therapy except in 1 patient.

Two years after the end of the study, 8/10 (80%) patients were asked about the occurrence of relapses and the present pain medication. All 8 patients reported an overall improvement of frequency and intensity of pain and quality of life. Four out of 8 patients do not take any pain medication, 2/8 patients take low-dose Neurontin when needed (100–200 mg/day) and 2/8 patients take other pain medications (e.g. ibuprofen) when needed.

Discussion

In this pilot study, gabapentin, a 1-aminomethylcyclohexane acetic acid, a structural analogue of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), was found to be effective in the treatment of neuropathic pain of neuroborreliosis by reducing symptoms like crawling and burning pain, neck and radiating lumbar pain. The effective dose varied for each individual. There was no sufficient improvement in numbness and myalgias.

Gabapentin was initially introduced as an anti-epileptic drug for the treatment of partial seizures with or without secondary generalization [7, 9–12]. Besides epilepsy, it is used for the treatment of migraine, bipolar illness or movement disorders, namely restless legs syndrome, essential tremor or nystagmus [13, 14]. It is also described to relieve pain in patients with Guillain-Barré syndrome [15], postpoliomyelitis [16] or HIV neuropathy [17]. Moreover, it has a positive effect on mood and quality of

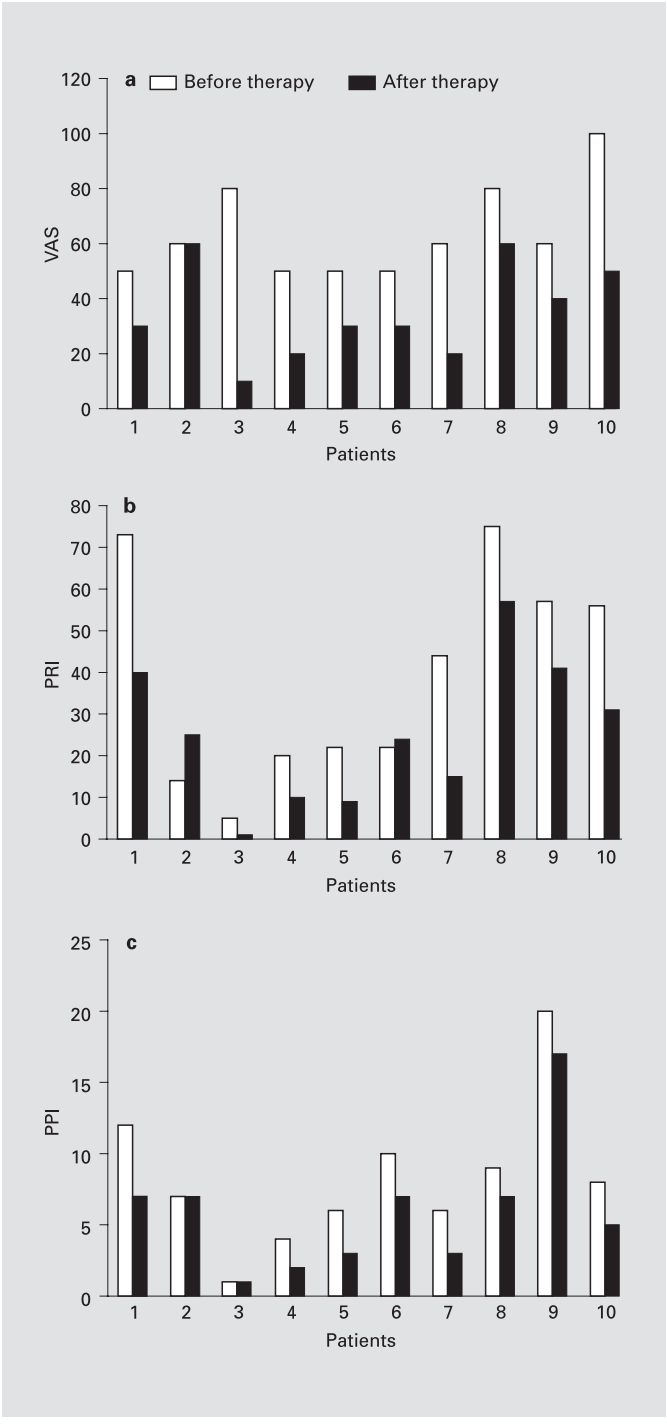

Fig. 1. a VAS pain score in 10 patients with late Lyme borreliosis before and after therapy with gabapentin. **b** PRI in 10 patients with late Lyme borreliosis before and after therapy with gabapentin. **c** PPI in 10 patients with late Lyme borreliosis before and after therapy with gabapentin.

life [7, 9, 18] which was also seen in our study with 5/10 (50%) patients recording this phenomenon. Recently gabapentin has been approved for the treatment of postherpetic pain [7, 13, 18–20] and diabetic neuropathy [9, 13, 20–22].

The exact mechanism of action of gabapentin is not completely understood. Gabapentin is lipophilic and penetrates the blood-brain barrier [7, 10, 23] which is necessary to act centrally on pain. It increases the concentration of GABA in the brain [23, 24]. However, it is neither a GABA agonist nor an inhibitor of GABA uptake or degradation and is not metabolically converted to GABA [9, 23, 24]. It increases the activity of partially purified glutamic acid decarboxylase, thus increasing the synthesis and concentration of GABA from glutamate in brain tissue. The elevation of GABA in turn is related to seizure control [10, 23, 24].

Pain including neuropathic pain is antagonized through a central mechanism via modulation of spinal cord neuronal calcium channels [25]. This inhibition of high-voltage-activated calcium conductance is caused by binding with high affinity on the $\alpha_2\delta$-subunit of the Ca^{2+} channel [10, 23, 24, 26–29]. It also activates Ca^{2+}-dependent K^+ channels. Some authors describe an inhibitory effect of gabapentin on voltage-activated sodium channels [10, 23, 24] whereas Stefani et al. [26] in their studies noticed no effect on the Na^+ current.

Moreover gabapentin reduces the release of several monoamino neurotransmitters, which are responsible for the anxiolytic effects and analgesia, increases serotonin concentrations leading to changes in sleep patterns and inhibits neuron death via glutamate synthesis by branched-chain amino acid amino transferase [10, 23, 24].

Compared to carbamazepine and opioids, gabapentin has only few side-effects with somnolence and dizziness being the most frequent ones [7, 9, 10, 13, 19, 20, 30]. This agrees with our study. Four out of 10 (40%) patients reported slight dizziness which disappeared during continuation of therapy. There are no significant drug interactions [10]. It should not be abruptly discontinued, because of the development of a withdrawal syndrome similar to that after alcohol or benzodiazepine with irritability, agitation, anxiety, tachycardia, diaphoresis or even confusion [30].

In this open uncontrolled study, gabapentin was efficacious as symptomatic therapy of pain in patients with neuroborreliosis when symptoms persist in spite of antibiotic treatment.

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