Topiramate use as treatment in restless legs syndrome

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Utilidad del topiramato en el tratamiento del síndrome de piernas inquietas

Summary

Introduction. *Restless legs syndrome is an underdiagnosed disorder of unknown etiology, that generates severe sleep and life quality disturbances. In its therapeutic approach, drugs with very different action mechanisms and variable results have been used.*

Methods. *Nineteen outpatients diagnosed of restless legs syndrome were studied observationally. A semistructured interview was carried out and physical variables (weight, arterial pressure and heart rate), sensitive and motor symptoms, effective dose of topiramate, side effects and fulfillment of the treatment at 30, 60 and 90 days were studied.*

Results. *The patients studied, with an average age of 62.052 ± 6.22 years, showed improvement in sensitive and motor symptoms, as well as non-significant reductions in cardiovascular parameters. The mean effective dose of topiramate was established at 42.1 ± 18.7 mg. A significant reduction in weight stands out among the side effects.*

Conclusions. *Topiramate is profiled as an effective treatment in restless legs syndrome, with good tolerability and minimal side effects.*

Key words: *Restless legs syndrome. Topiramate. Anticonvulsants.*

Resumen

Introducción. *El síndrome de piernas inquietas es un trastorno infradiagnosticado de etiología desconocida que genera severas alteraciones en el sueño y en la calidad de vida de los sujetos que lo padecen. En su abordaje terapéutico se han utilizado fármacos con mecanismos de acción muy dispares y resultados variables.*

Métodos. *Hemos estudiado de modo prospectivo y observacional 19 pacientes con este diagnóstico mediante entrevista clínica, control de variables físicas (talla, peso, tensión arterial, frecuencia cardíaca) y evaluación de sintomatología sensitiva y motora, dosis efectiva de topiramato, efectos adversos de la medicación y cumplimiento del tratamiento a los 30, 60 y 90 días.*

Resultados. *Los pacientes estudiados, con una edad media de 62,052 ± 6,22 años, mostraron una mejoría en la sintomatología sensitiva y motora, así como reducciones no significativas en los parámetros cardiovasculares, estableciéndose la dosis media efectiva de topiramato en 42,1 ± 18,7 mg. Entre los efectos secundarios destaca una reducción significativa en el peso.*

Conclusiones. *El topiramato se perfila como un tratamiento efectivo en el síndrome de piernas inquietas, con buena tolerancia y escasos efectos adversos.*

Palabras clave: *Síndrome de piernas inquietas. Topiramato. Antiepilépticos.*

INTRODUCTION

Restless legs syndrome (RLS) was first described in 1672 by Thomas Willis and received its name after the studies of Ekbom[1]. It is characterized by the appearance of paresthesias and dysesthesias in legs (it has also been described in the upper limbs[2]). It is typically nocturnal, exacerbates with rest and drives the individual to movement, that temporally relieves the symptoms. It is frequently underdiagnosed, is a disorder whose prevalence is found in 5% to 15% of the adult population and 10% to 35% of individuals over 65 years[3], thus being very frequent in the elderly.

RLS may present as a primary disorder that develops in young individuals and includes familial cases or may be secondary to physical disease. In the latter case, it is associated to iron deficit anemia[4], uremia and polyneuropathy. Many CNS drugs such as, for example, risperidone[5] or SSRI (sertraline, fluoxetine), may also cause or worsen it[6]. It is also known that the presence of musculoskeletal disease, heart disease, obstructive sleep apnea syndrome, cataplexy, carrying out of physical activities close to bedtime or the existence of an associated mental disorder increase its prevalence[7]. A very debatable association between RLS and Parkinson's disease has even been proposed[8].

Its etiology is unknown. In the genetic studies, it is observed that there seems to be a familial component in

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young patients, this being understood as either autosomal dominant inheritance[9] or involving the high activity allele of the MAO A gene as a factor in the severity of the syndrome in women[10].

RLS has also been related with low levels or reduced response to dopamine, due to a decrease in the D2 receptor number or of its affinity[11] and it is known that its symptoms improve with dopaminergic therapy. Not only levodopa[12] but also agonists of the dopaminergic ergotaminic receptor such as pergolide as well as agonists of non-ergotaminc dopaminergic receptors such as pramipexole[13,14] and ropinirole[15] are beginning to be used in the treatment of RLS. In other patients (with a pain picture), good response to anti-epileptic drugs such as carbamazepine, clonazepam and gabapentin may be found[16-24]. Others drugs such as opiates[25] and hyposedative drugs that are useful in selected patients, but may have marked side effects in the elderly, or substances such as vitamin B12 and folic acid, have also been used. Correction of low iron levels if there is low ferritin, as well as changes in style of life, may also help to correct the symptoms[26,27].

On the neurophysiological level, abnormalities that are difficult to interpret based on present knowledge have been found. These are, for example, increase in cerebrospinal fluid of the hypocretin 1[28] levels, without alterations in the cortisol plasma rhythms, growth hormone and prolactin[29] and regions of the spinal cord and basal ganglia have been involved in its pathogenesis[30], which supports the dopaminergic hypothesis.

The diagnosis is based on the clinical symptoms of the patient with a normal neurological assessment, using polysomnographic registries and the Suggested Immobilization Test (SIT) as a complementary diagnostic methodology[31]. The differential diagnosis should be made with pictures such as paresthesias of the lower limbs, acathisia, etc.

The course is fluctuating at the onset and then becomes continuous and chronic. Among its complications, insomnia, deterioration in the quality of sleep and appearance of a depressive type affective order, stand out. The latter is confirmed when an EEG mapping pattern similar to that of depression is found[32].

Topiramate is a new anticonvulsant agent with a wide action mechanism, that acts, among other mechanisms, through the inhibition of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors that participate in opiate metabolism[33], through the blockade of calcium channels, potentiating the brain GABA concentrations, antagonizing the glutamatergic receptor and blocking the sodium channels[34]. Its indications include all types of epileptic seizures and its use in neuropathic pain, migraines, bipolar disorder, eating disorders and impulse control disorders is being studied. Sleepiness, ataxia, dysarthia, paresthesias, concentration difficulties, dizziness, vertigo, memory problems, anxiety, tremors, weight loss and psychomotor slow down are included among its adverse effects.

Antiepileptic drugs, as mentioned previously, have been traditionally used as treatment of RLS (carbamazepine, clonazepam, gabapetin), but evidence on the efficacy of new antiepileptics such as topiramate, tiagabine, vigabatrin or lamotrigine on the RLS symptoms is lacking. Our preliminary study aims to assess the safety and effectiveness of topiramate in the treatment of the sensitive and motor symptoms of patients with a diagnosis of restless legs syndrome as well as the changes produced on sleep itself and on the basic physiological parameters (weight, blood pressure, heart rate).

METHODOLOGY

An observational and prospective study was carried out on 19 patients with a diagnosis of Restless legs syndrome (American Classification of Sleep Disorders), referred to our service from area health care centers, with no previous treatment. Prior to their inclusion in the study all the patients underwent a basic physical examination, including neurological examination, basic laboratory and thyroid hormone analyses to identify possible etiological factors. All the patients gave their informed consent to participate in the study. The sample was made up of 15 men and 4 women, their mean age being 62 ± 6.2 years (range: 61-90 years).

A semistructured clinical interview was performed and physical parameters (systolic and diastolic BP, heart rate, height and weight) as well as medical disease backgrounds and concomitant drugs (given the importance of these factors in the etiology of restless legs syndromes) were assessed. Motor (involuntary movements, cramps and myoclonias) and sensitive (paresthesias, pain, pruritus, contractures, flaccidity) symptoms were also considered, scoring their seriousness between 1 and 5 (according to whether they were null, mild, moderate, serious or severe), their anatomic site (legs, arms, thighs, calves and feet) as well as their uni- or bilaterality, their course (stable, progressive or intermittently progressive), the possible improvement of the symptoms with temperature and/or alcohol and repercussion on the sleep disorder. The Epworth sleepiness scale was administered to evaluate daytime sleepiness (table 1).

In the case of the two patients who received treatment with psychodrugs (lormetazepam and citalopram), treatment was progressively withdrawn, the patients remaining psychodrug free for at least one week prior to the study onset.

All the study patients received treatment with topiramate in single drug therapy, increasing the dose progressively from 25 mg to 100 mg, assessing the therapeutic response with the Clinical Global Impression scale (from seriousness to improvement) filled out by the physician and patient. All the drug adverse effects reported by the patients were controlled by the recording of side effects (UKU). Control of the evolution of the symptoms was performed at 15, 30 and 90 days.

The null hypothesis rejection level in the statistical analysis (performed with the SPSS statistical program) was located at $\alpha = 0.005$.

TABLE 1. Parameters studied

Baseline	*Baseline*	*15 days*	*30 days*	*90 days*	*Baseline*	*Baseline*	*15 days*	*30 days*	*90 days*
Demographic variable Age Gender Weight Height					Improvement with temperature Yes No				
Cardiovascular variables Systolic BP Diastolic BP HR					Improvement with alcohol Yes No				
Physical history					Family history Yes No				
Drugs consumption Yes No Specify					Patient CGI				
Toxic consumption Alcohol Others (specify)					Physician CGI				
Presentation form Idiopathic Symptomatic					Topiramate dose				
Sensorial symptoms Paresthesias Pain Pruritus Contracture Flaccidity					Sleep disorders Difficulty to initiate it Maintenance difficulty Early awakening Daytine fatigue Daytime sleepiness				
Motor symptoms Involuntary movements Cramps Myoclonias					Hours of sleep				
Symptom site Unilateral Bilateral Feet Calves Thighs Arms					Epworth scale				
Disease course Stable Remittent Intermittently Progressive					Family history of sleep disorders Definitive Possible Negative Unknown				
					Cumplimiance Yes No				
					Adverse efects None Sleepiness Ataxia Dysarthria Paresthesias Concentration difficulties Dizziness Vertigo Memory problems Anxiety Tremors Weight loss Psychomotor slow down				

RESULTS

Given the characteristics of the study (observational and non-randomized), our results are descriptive and are preliminary data of a study that aims to be larger from its onset.

Epidemiological data

Mean age of the patient sample of our study was 62.052 ± 6.22 years (range: 51-76 years), the majority being men (78.9 %) (n = 15). Mean weight of the subjects was 77.42 ± 9.06 (range: 62-92 kg) and we found that 19% of our patients presented obesity with the Quetelet index[35] (index > 30; mean value of our sample: 31.4). Two patients had a diagnosis of diabetes, and were treated with oral antidiabetics and insulin, respectively, maintaining stabilized and normalized fasting glucose values.

Cardiovascular parameters

A total of 36.8 % of the patients had baseline values coinciding with hypertension criteria, and two of

the patients received treatment with antihypertensive drugs.

RLS symptoms

The mean disease course time was 12.5 ± 2.34 years and the presentation was idiopathic in 63.6 % of the patients. A total of 84.2 % of the patients had a negative family history for RLS and the family background was unknown in the remaining subjects.

In 89.5 % of the patients, paresthesias appeared as the most frequent sensitive symptoms, involuntary movements (84.2%) and cramps (1 %) predominating among the motor symptoms. Only one patient had associated myoclonias. The symptoms were preferentially bilateral (89.5 %) and the most affected anatomic regions were feet (63.2 %) and calves (36.8 %). The disease course was continuous in 89.5 % of the patients and none of the patients experienced improvement with temperature changes. One of the subjects reported improvement with alcohol.

Mean sleep duration in baseline situation for these patients was 6 ± 1.154 hours (range: 3-8 hours) and 94.7 % of them presented alterations at onset of sleep, the maintenance of this being adequate.

Treatment with topiramate

Mean dose of topiramate administered was 42.1 ± 18.7 mg/day (range: 25-100 mg/day), with good tolerability to the drug and good treatment compliance, the adverse effects recorded being: sleepiness (15.8 %), paresthesias (5.3 %) and distal tremor (5.3 %). Another one of the side effects (assessed as positive by the patients) was weight decrease of 1.37 kg, that was the only parameter that reached significant variation ($p < 0.005$) in regards to the baseline visit (fig. 1).

Systolic and diastolic blood pressure baseline values decreased slowly and progressively during the study, but no statistically significant changes were observed in any of the parameters evaluated (heart rate and systolic and diastolic blood pressure) (fig. 1).

After treatment with topiramate, the sensitive symptoms disappeared in 57.9 % of the patients and the motor ones in 68.4 % (in these percentages, we only include those patients who reported total disappearance of the symptoms) (fig. 2).

After onset of treatment, a progressive, although not significant, increase was recorded in the sleep hours, the mean duration being 6.7 ± 0.80 hours at the end of the study.

At the onset of the study, the patient and physician coincided that the seriousness of the RLS was moderate while at the end of the study, 63.15 % of the patients manifested a degree of mild disease, coinciding with the medical criteria, in the Clinical Global Impression (fig. 3). A total of 89.48% of the patients were shown to have been very or quite improved, the percentage of patients who did not experience any improvement being 10.52 %.

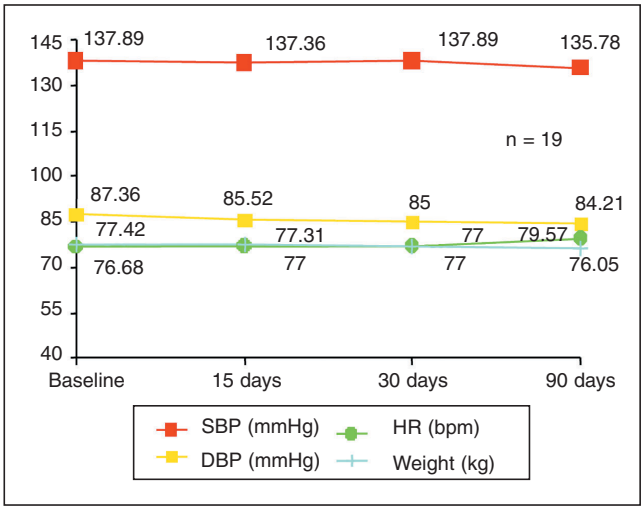

Figure 1. Variation in vital signs and weight. Change in blood pressure (systolic and diastolic), heart rate and weight during the follow-up time.

In regards to treatment compliance, 78.9 % of the patients fulfilled the treatment successfully, drop-outs being two due to sleepiness, one due to paresthesias and one absence of improvement, and all of the adverse reactions were mild.

DISCUSSION

The demographic data of our sample do not present important differences with those obtained in the different scientific literature: elderly ages predominate. Among them, compared to the young subjects who mainly have an idiopathic etiology, the presence of secondary etiological factors is very high.

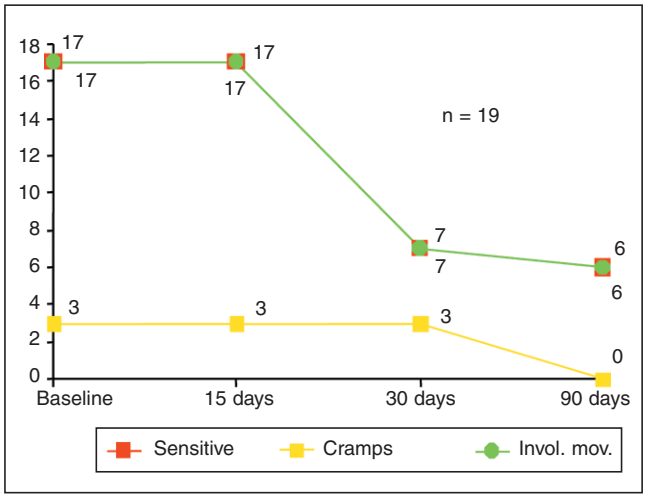

Figure 2. Variations in sensitive and motor symptoms. Change in total number of patients who report sensitive and/or motor alterations during all the study.

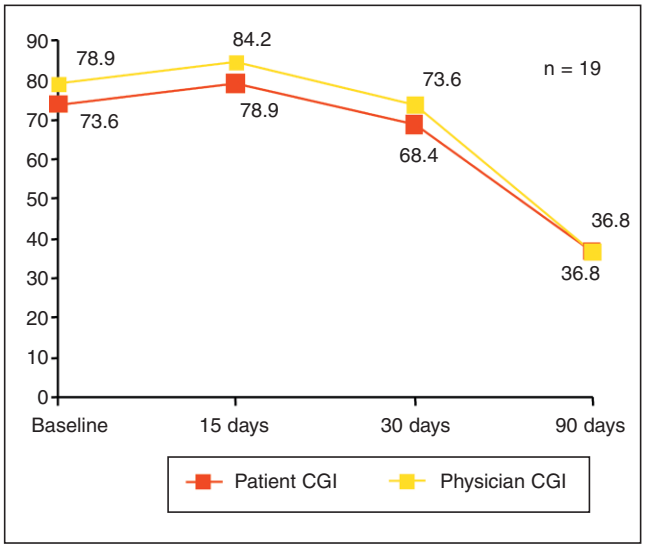

Figure 3. Variation (%) in CGI by patient and physician. Clinical global impression (in percentage) according to which the patient or physician finds the patient moderately/extremely ill.

Our patients do not present any family history of RLS (we remind you that Aldrich[1] had already said that the data published on 50 % of patients with a family background were not sufficiently tested). They are subjects having a long history of symptom evolution, since this is an underdiagnosed clinical entity (they are patients whose evolution may even be 20 years or more[1]) with difficulty in initiating sleep, but no problems in sleep maintenance seem to exist. The predominance of the symptoms is bilateral and in the lower limbs.

Classically, RLS has been treated with multiple drugs, among which antiepileptic drugs (carbamazepine, clonazepam, gabapentin) occupy an important place, above all in the initial moments, in those pictures that occur with pain. In the existing reviews of the literature, we have not found any RLS treatment studies with topiramate.

In our study, given the elevated age of our patients, we have used low doses of topiramate, that seem to be effective both in the improvement of the sensitive (even though one of the adverse effects of topiramate found in the medical literature are paresthesias) as well as motor symptoms (involuntary movements, cramps). We must point out that the seriousness of the symptoms (whether sensitive or motor) were originally scored from 1 to 5 according to whether the intensity of these were null, mild, moderate, serious or severe, but, given the limited reliability of the patient to classify improvement, we have only considered those patients who reported total disappearance of the symptoms when analyzing the results.

The side effects reported have been those characteristically described in different studies with topiramate and weight loss has been assessed as positive by the patients.

Although the reduction in symptoms and change in the parameters evaluated have not been statistically significant except for weight, the patients assess the result of the treatment (CGI) and the increase in the number of total hours of sleep as positive.

These results are encouraging for patients with a clinical picture that does not have clearly established treatment strategies, but the limitations of our study must be stressed. These are due to: *a*) the small number of patients we included (the difficulty to obtain subjects with this diagnosis must not be forgotten) that takes external predictive force away from the study. The studies found in the literature when the efficacy of the different antiepileptic drugs is evaluated are also characterized by a reduced number of subjects studied (8^{19}, 9^{17}, 16^{18} and 24^{16} patients in the case of studies with gabapentin, 6^{22}, 16^{20} and $20^{19,24}$ patients in treatment with clonazepam and 100^{23} patients treated with carbamazepine); *b*) the absence of homogeneity in the scales and questionnaires used to be able to test and compare studies (analogue questionnaires of pain, Pittsburgh sleep questionnaire, CGI, Epworth Scale or anxiety and depression scales, of improvement of the symptoms or recording of adverse effects); *c*) compared to the studies that include a polysomnographic study of the patients with RLS, we think that, given that the RLS is a clinical diagnosis (compared to the nocturnal myoclonias whose diagnosis is polysomnographic), its postponement does not affect the significance of our data, although it is one of the parameters that should be considered in the future to study sleep disorders in greater depth, and *d*) the evaluations of the therapeutic response have been performed by the therapists, which also involve a possible bias.

The results should be considered as a preliminary study, that makes it possible to glimpse at the therapeutic possibilities of topiramate in RLS, improving the sensitive and motor symptoms characteristic of this disorder and increasing sleep duration in these patients.

CONCLUSIONS

As has been mentioned in several studies published, the therapeutic resources used in the treatment of restless legs syndrome are many. Among them, drugs with diverse action mechanisms, such as levodopa, dopaminergic agonists, opiates or antiepileptics are found. Among the latter drugs, we must include topiramate, at low doses (50 mg/day) as a possible therapeutic alternative, with promising results in the control of the clinical symptoms and with scarce side effects.

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