Treatment of Restless Legs Syndrome With Tramadol: An Open Study

Hannu Lauerma, M.Sc.D., and Juha Markkula, M.D.

Background: Tramadol is a central analgesic that seems to have fewer side effects and a lower abuse potential than classical opioids. Since the treatment of restless legs syndrome (RLS) with levodopa or classical opioids is problematic, new treatment possibilities would be valuable.

Method: We treated 12 patients who fulfilled at least the minimal diagnostic criteria proposed by the International Restless Legs Syndrome Study Group as well as the criteria proposed by Gibb and Lees, some of them treatment resistant or prone to side effects of previous medications, with 50 to 150 mg of tramadol per day in an open study. The follow-up lasted from 15 to 24 months.

Results: Ten patients reported clear amelioration and 1 reported slight amelioration of their symptoms, while 1 reported no effect. Tramadol was described to be the most effective treatment and free of side effects when compared with several other treatments. No major tolerance against treatment effect emerged among those who needed only a single evening dose.

Conclusion: Compared with other treatments for RLS, tramadol seems to be superior in some cases, possibly because of its unique pharmacodynamic profile. Controlled studies are needed. Meanwhile, we believe that tramadol should be considered before other opioids are prescribed. We recommend intermittent treatment and careful monitoring.

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Received Nov. 14, 1996; accepted April 14, 1998. From the Department of Psychiatry, University Central Hospital of Turku, Finland (Dr. Lauerma), and the Department of Psychiatry, University of Turku, Finland (Dr. Markkula).

Reprint requests to: Hannu Lauerma, M.Sc.D., Medical Director, Mental Hospital for Prisoners, P.O. Box 49, SF-20251, Turku, Finland (e-mail: hanlau@utu.fi).

Idiopathic restless legs syndrome (RLS) is characterized by an unusual, almost indescribable unpleasant sensation in the lower extremities that results in an urge to move the legs. The symptoms occur at rest, and they are relieved by movement. Periodic sleep-related movements of the lower limbs usually occur in association with sleep arousal phenomena. This arousal is often reflected psychologically in anxiety and insomnia, and sometimes there are depressive manifestations. Anxiety, while modifying the subjective experience of the dysphoric sensation of restless legs, is not a causative factor. According to our clinical experience as well as the reports of the Restless Legs Syndrome Foundation,[1] clinicians seem to often misdiagnose or dismiss this treatable and sometimes serious disorder. Occasionally, it has even been considered a symptom of somatization or histrionic behavior, which is most unfortunate.

RLS may be caused by, for example, anemia or uremia, but the most common form is idiopathic and familial. The pathophysiology of idiopathic RLS is unknown, although a subcortical or spinal origin has been suggested.[2] Subjective symptoms of RLS are experienced by approximately 15% of the adult population,[3] whereas the prevalence of the idiopathic form of the syndrome has been estimated at 1% to 5% in the general adult population. The prevalence increases with age. Levodopa, the most effective treatment thus far, is effective in about 70% of the cases, but because of rebound restlessness[4] and other side effects, only approximately half of the patients reach remission during long-term treatment. Also, other dopaminergic agents are used. Opioids are effective in many cases, but side effects and the possibility of addiction limit their use to the most severe cases. Clonidine may alleviate RLS in some patients, but only 4 of 10 patients chose to continue the treatment in a controlled study.[5] Benzodiazepines are widely used, but, at least in severe cases, they are often ineffective and bear the risk of dependency. Short-acting potent benzodiazepines may cause amnestic wanderings, because in severe RLS the urge to walk is strong.[6]

Tramadol is an opioid analgesic that acts through the monoaminergic mechanisms as well as the μ receptor. After a single oral dose, the role of the μ receptor agonist component of the antinociceptive effect of tramadol appears to be minor; most of the analgesic effect is attributable to non-opioid properties.[7,8] Tramadol has been in clinical use since 1977 in Germany and recently gained marketing approval in the United States. Usual doses of peroral tramadol for a variety of pain conditions are from 50 to 100 mg up to 400 mg per day. According to clinical experience and research findings, it has a low abuse potential[9,10] and minor cardiovascular and respiratory side effects. Therefore, it seems to be an interesting candidate to

be used also in RLS. In a family study[11] where we described a patient with idiopathic familial RLS and a genetic predisposition to psychosis, we noted excellent short-term effect of tramadol on RLS in a single patient. A MEDLINE computer search up to January 1998 generated no report concerning tramadol and RLS. We now report on the long-term use of tramadol in 12 patients with idiopathic RLS.

METHOD

Patients with RLS, after they had given their informed consent, were recruited from the practices of the authors. All cases fulfilled at least the minimal diagnostic criteria proposed by the International Restless Legs Syndrome Study Group,[12] as well as the criteria proposed by Gibb and Lees.[13] Additionally, all patients reported distressing insomnia. Eight cases were identified as familial. The patients were prescribed tramadol for RLS, and the effect was closely monitored at the follow-up visits a minimum of 3 months apart. The patients also had the opportunity to contact the authors by phone between appointments. Clinically, RLS was considered to be severe if it caused severe insomnia and markedly affected the patient's capacity to function or to enjoy life during the daytime. The clinical treatment response was considered to be "satisfactory" if the patient reported a definite but not complete effect and to be "good" if the symptoms disappeared completely or almost completely.

Symptoms of RLS are often difficult to describe verbally, and the main complaint varies from patient to patient. Therefore, uniform numeric evaluation of severity is problematic. We chose to ask the patients how they estimated the overall severity (i.e., whatever symptoms they considered to disturb their lives the most) on a scale from 0 to 100, "0" meaning no symptoms at all and "100" the most severe intensity of symptoms one can imagine. Because the distribution of values was not normal, a nonparametric Wilcoxon-Pratt 1-sample rank sum test was used to compare the subjective distress before and after tramadol treatment. Since the patients were allowed to change to any other known treatment for RLS, and many of them had some experience on previous treatments, a patient's willingness to continue the treatment was chosen as one parameter to evaluate the clinical effectiveness of tramadol. The side effects were monitored by carefully asking the patients to report any unexplained sensations or possible side effects they had experienced during the treatment.

RESULTS

Eight female and 4 male patients entered the study. The mean age of the female patients was 57 years (range, 29–78 years) and 56 years (range, 43–69 years) for the male patients. Characteristics of the patients are described in Table 1. The follow-up time of those who continued the treatment was a mean of 22.8 months (median = 17; range, 15–26 months).

Ten of 12 patients considered tramadol more effective than drugs tried in the past, 1 felt some relief, and 1 felt no relief. Seven of the 12 patients reported total or almost total disappearance of RLS symptoms when using tramadol. One patient with no treatment effect and 1 patient, who on principle did not want to use any drug that was classified as an opiate, were the only ones who did not want to continue the medication. As compared with other treatments (presented in Table 1), tramadol was reported by patients to exert a clear effect within 1 hour of ingestion. Those patients who were familiar with feelings of anxiety and the effect of benzodiazepines reported that the effect of tramadol is subjectively different from that of benzodiazepines and that tramadol does not reduce anxiety but produces a tranquil, relieved feeling that is closely accompanied by disappearance of the restlessness or pain in the lower extremities.

In the numeric evaluation, 1 patient could verbalize the effect of tramadol only by saying that it was "of some help." In her case we used the "without drug" estimate to describe also the effect of tramadol in statistical analysis. These data could not be obtained from the 2 patients who discontinued the treatment. Therefore, these patients were not included in the analysis. Values before treatment ranged from 55 to 100 (median = 90) and after treatment, from 0 to 55 (median = 5). The "without drug–with drug" difference was a mean of 75.5 (median = 82.5). The difference was statistically significant ($p = .0039$, Mann-Whitney nonparametric test).

As a side effect, 1 patient reported severe abdominal pain with 100 mg but tolerated 50 mg, which seemed to be enough to alleviate the RLS. One patient reported slight and transient morning dizziness and 2 experienced transient feelings of tremor that had not been present in clinical examination. One patient reported experiencing a kind of mild itching sensation on the skin after taking tramadol. However, no urticaria or other signs of allergic reactions emerged, and he continued to use tramadol because he considered this itching to be harmless compared with RLS. In 1 case for 2 months of the study, the need to use tramadol 50 mg 3 times a day was associated with gradual reemergence of symptoms. By alternating treatment with levodopa, however, a satisfactory-to-good response has remained over 15 months.

DISCUSSION AND CONCLUSIONS

All of the restrictions of an open study and the relative small number of patients should be borne in mind when drawing conclusions based on our material. However, we consider (1) the quite striking effect described by the patients, (2) the unusually high proportion of patients willing to continue the treatment, and (3) the reduction of

Table 1. Characteristics and Treatment Responses of Patients Who Had Restless Legs Syndrome (RLS) and Were Treated With Tramadol

Patient	Sex	Age (y)	Type of Disorder	Other Diseases	Responses to Previous Treatments	Subjective Distress (scale: 0–100) Before/After Tramadol	Continued/ Discontinued Treatment	Dose of Tramadol	Effect	Follow-Up (mo)
1	M	69	Idiopathic, familial	No other diseases.	Benzodiazepines ineffective; levodopa efficacious for about a year.	Before: 95 After: 0	Continued	150 mg/d	Disappearance of symptoms for 4 mo, then gradual reemergence of symptoms during 2 mo. With alternating treatment with levodopa, satisfactory-to-good results remain.	15
2	F	63	Idiopathic, familial	Two cases of suicide and one case of psychotic illness in the family. Short-term efficacy of tramadol described in a family study.[11]	Benzodiazepines and carbamazepine ineffective; selegiline proved to be effective but caused an adverse reaction.	Before: 90 After: 15	Continued	50–100 mg/d	First disappearance of symptoms, then effect gradually diminished during 6 mo. After a short drug vacation, almost total disappearance of symptoms with 50 mg.	24
3	F	68	Idiopathic, familial	Arthrosis.	Sodium valproate and benzodiazepines ineffective; levodopa of some help but caused nausea and dizziness.	Before: 100 After: 0	Continued	50–100 mg/d	50 mg/d ameliorated and 100 mg/d eliminated symptoms. After 3 mo, some fading of response but still satisfactory effect remains.	23
4	M	56	Idiopathic, familial	No other diseases.	Physiotherapy and homeopathy ineffective.	Before: 100 After: 35	Continued	50 mg	50 mg effective in decreasing number of nightly walking periods by 50%. 100 mg caused dizziness. Uses 5–7 times/wk, no decrease in response.	22
5	F	54	Idiopathic, familial	Further complicated by low iron in serum. Anxiety independent from RLS.	Only partial response to iron substitution. Clonazepam 0.25–0.5 mg effective, but the patient was afraid of dependency. Previous psychotherapy for anxiety.	Before: 85 After: 5	Continued	50 mg	50 mg eliminated symptoms. Alternates using intermittently either clonazepam or tramadol to avoid the risk of dependency.	20
6	F	78	Idiopathic, familial	Coronary heart disease, arthrosis, essential hypertension.	Several antidepressants and benzodiazepines used without success. Levodopa ameliorated a little, adding buprenorphine helped some more.	Before: 55 After: could not verbalize.	Continued	50–100 mg/d	Tramadol substituted for buprenorphine resoriblets; effect approximately equal.	20
7	F	51	Idiopathic	Obesity, lumbar discus prolapse.	Diazepam ineffective; little help from clonazepam 1 mg. Initial excellent response to levodopa faded in about 6 mo.	Data could not be obtained.	Discontinued	50–100 mg/d	No treatment effect.	…
8	F	49	Idiopathic, familial	No other diseases.	No previous treatments.	Before: 90 After: 0	Continued	50–100 mg/d	50 mg ameliorated and 100 mg eliminated symptoms. In continuous treatment, some fading of response in a few weeks. If used intermittently, good response remains.	23
9	F	29	Idiopathic, familial	No other diseases.	No previous treatments.	Before: 80 After: 0	Continued	50 mg/d	50 mg nocte eliminates symptoms. Uses when needed (approximately once a month for a few days); good effect remains.	22
10	M	43	Idiopathic	Essential hypertension, hypercholesterolemia.	No previous treatments.	Before: 95 After: 10	Continued	50–100 mg/d	Keeps a few days drug-holiday every 2 wk; good effect remains.	23
11	F	64	Idiopathic	Also primary insomnia or slight benzodiazepine dependency because of prolonged use of temazepam?	Temazepam 40 mg, some effect.	Data could not be obtained.	Discontinued	50–100 mg/d	Patient was able to reduce the use of temazepam by half but discontinued tramadol after a few days because she did not want to use a drug that was classified as an opiate.	…
12	M	55	Idiopathic	Essential hypertension.	No previous treatments.	Before: 90 After: 5	Continued	50 mg/d	Uses occasionally when needed. 50 mg eliminates symptoms. When used every night for more than 2 wk, some fading of response.	18

symptoms over a prolonged period of time to point toward the beneficial effect of tramadol on RLS. In particular, we are impressed by the sustained effect in patients either who initially have been resistant to other medications or who, after good primary response, have suffered from complications when using levodopa, the most effective medication for RLS known so far.

As benzodiazepines, dopaminergic agents, and classical opioids for RLS are prone to cause side effects, we believe that tramadol should be considered at least before other opioids are prescribed because it seems to have fewer side effects and a lower abuse potential than classical opioids. None of our patients was depressive at the time tramadol was used, but there is a recent single case study suggesting a risk of tramadol-induced depression.[14] Although the risk of major side effects seems to be relatively low, careful monitoring and evaluation of treatment effect are crucial, because some patients may need a slight dose increase due to diminishing efficacy. We recommend intermittent use and minimizing the dose taken in the evening for idiopathic RLS. Controlled trials are required to confirm these initial findings and to clarify the role of tramadol as a treatment for RLS.

Drug names: buprenorphine (Buprenex), carbamazepine (Tegretol and others), clonazepam (Klonopin), clonidine (Catapres), diazepam (Valium and others), divalproex sodium (Depakote), levodopa (Larodopa), selegiline (Eldepryl), temazepam (Restoril and others), tramadol (Melanate).

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