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Brief communication

Management of restless legs syndrome by the partial D2-agonist terguride

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Abstract

Background: Terguride as a partial D2-receptors agonist seems suitable for treatment of restless legs syndrome (RLS).
Methods: Nine RLS patients without previous dopaminergic therapy received a daily dose of terguride (0.25 mg) 29.9 ± 16.9 (SD) days.
Results: Two patients enrolled in the study failed to turn up for a successive check up. The seven subjects who were re-examined complied with the therapy. Their RLS symptoms improved (as measured on the International RLS intensity scale), decreasing from 24.3 ± 5.3 to 14 ± 4.7 ($p = 0.014$). However, the terguride treatment did not significantly alter the daytime sleepiness or the subjective duration of nocturnal sleep. The daily dose was doubled in three patients who reported insufficient RLS improvement. One of the three patients later reported augmentation.

Keywords: Terguride; Partial D2-agonist; Restless legs syndrome; Augmentation

1. Introduction

Restless legs syndrome (RLS) is a chronic and relatively common disease adversely affecting the quality of life. At present, levodopa and dopamine agonists constitute the most often recommended medications for controlling idiopathic RLS [1] in the Czech Republic, even though no particular drug has ever been registered here for RLS treatment.

The objective of our investigation was to examine alternative avenues leading towards the management of RLS by using terguride (transdihydrolisuride), which as a partial agonist at the D2-receptors is better tolerated than full agonists. As an ergot derivative, terguride is known to inhibit the secretion of prolactin and/or increase secretion of the growth hormone from pituitary adenomas, but without the typical D2-agonist linked side effects such as nausea or emesis, even at high dosages. It has been assumed that its D2 partial agonistic properties are responsible for the absence of these adverse effects. Terguride, like other partial agonists, generates a smaller response than full agonists at identical receptor occupancy [2]. It has been successfully used in the treatment of pituitary adenomas to suppress the secretion of the growth hormone (1.5–4 mg/day) and prolactin (1–1.5 mg/day) [3,4]. Terguride has also proved efficacious in treating Parkinson's disease (2 mg/day) [5] as well as parkinsonism-like side effects of neuroleptic treatment (0.5–2 mg/day) [6]. Following oral administration, terguride will reach peak plasma concentration in 1 h. Its biological half-life is 4.3 h [4].

2. Materials and methods

Nine consecutively treated outpatients with no history of a dopaminergic therapy and with straightforward idiopathic RLS [7] and clinically significant symptomatology were treated with Mysalfon tablets (Léčiva, Czech Republic) each containing 0.5 mg of terguride hydrogen maleate. The patient group was composed of six men and three women whose mean age was 56 years (range 38–78), mean body mass index (BMI) 27.3 (±3.8 = SD) kg/m^2 and mean duration of RLS symptomatology was 13.7 (± 12.6) years. On clinical examination, but without performing a polysomnography, it appeared that none of these patients suffered from any other sleep disorder.

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Table 1
The terguride treatment effect on International RLS scale (I-RLS), subjective sleep duration and Epworth sleepiness scale in RLS patients

Patient			Pretreatment			Terguride 0.25 mg					Terguride 0.5 mg				
Number	Gender	Age (years)	I-RLS scale	Sleep duration (h)	ESS	Therapy duration (days)	I-RLS scale	Sleep duration (h)	ESS	Further recommendation	Therapy duration (days)	I-RLS scale	Sleep duration (days)	ESS	Further recommendation
1	F	46	35	4.5	13	22	10	7	8	Terguride 0.5 mg	26[a]				Pergolide
2	M	66	19	10	5	43	14	9	5	Terguride 0.25 mg					
3	M	45	25	6.5	8	34	21	6	8	Terguride 0.5 mg	26	15	6	8	Terguride 0.75 mg
4	F	78	26	9.0	4	14	11	9	4	Terguride 0.25 mg					
5	M	71	22	7	4	15	20	7	4	Terguride 0.5 mg	14	16	7	4	Terguride 0.25 mg
6	M	53	20	7	9	21[a]	12	7	8	Terguride 0.25 mg[b]					
7	F	48	23	7	15	60	10	7	9	Terguride 0.25 mg					
8	M	56	21	6.5	9										
9	M	37	30	4.5	7										
Average		55.6	24.6	6.9	8.2	29.9	14	7.4	6.6						
SD		13.2	5.2	1.9	3.8	16.9	4.7	1.1	2.1						

[a] The complaints worsened progressively after doubling the terguride dose and the patient herself discontinued the terguride treatment.
[b] This patient reported stomachache when taking terguride regularly and decided to take terguride only on days when RLS symptoms became too disagreeable. The same regimen was recommended within the last visit.

Seven of the group had never been treated for RLS before the commencement of the terguride therapy. The other two had previously received magnesium, carbamazepine and biperiden without substantial alleviation of their condition. One patient was treated with zolpidem 10 mg for more than 12 weeks prior to and during the application of terguride. All patients were advised to take 0.25 mg of terguride at the onset of their RLS symptoms or half an hour before going to bed. The daily dose was increased for those patients who were still dissatisfied with their condition at the time of their first check-up, recommended within 2–4 weeks. Those patients were asked to report for a second check up within the next 2–4 weeks.

At the beginning of the study and at each subsequent check-up the patients were asked to rate their condition on the International RLS scale (I-RLS scale) [8], to fill in the Epworth sleepiness scale (ESS) [9] and to establish subjectively the average duration of their nocturnal sleep within the previous 2 weeks period. Results were evaluated with *t*-test for paired values.

All patients were informed about the nature of the therapy and all consented to participate.

3. Results

The results of the medical re-examination performed after terguride 0.25 and 0.5 mg treatment are shown in Table 1. Two patients excused themselves for family reasons. The seven remaining respondents reported good compliance and tolerance of the drug. One patient, however, complained of a stomachache when taking the daily dose and decided to take terguride only on days when RLS symptoms became too disagreeable. All patients who completed a terguride therapy of at least 2 weeks reported an alleviation of RLS symptoms. I-RLS scale dropped in seven compliant RLS patients from the baseline 24.3 ($\pm$5.3) to the 14.0 ($\pm$4.7), $p = 0.014$. The ESS value and the subjective nocturnal sleep duration did not change significantly. One female patient (No. 1) reported symptoms of augmentation after dose doubling, even though the initial dose of 0.25 mg greatly relieved her pre-treatment RLS condition. No single patient reported any terguride-linked RLS rebound.

4. Discussion

The D2 partial agonist terguride proved efficacious in suppressing subjective symptoms of RLS without affecting subjective daytime sleepiness or individually established sleep duration. The apparent ineffectuality of terguride to alter the mean values of ESS and sleep duration may be due to the fact that neither of these variables was abnormal prior to treatment—except in patient No. 1, whose subjectively estimated nocturnal sleep of about 4.5 h increased to 7 h

after terguride treatment. Her high pre-treatment ESS score also improved after terguride intake.

Terguride may have influenced sleep indirectly by suppressing the abnormal motor activity at night, and also directly, by inducing drowsiness at night. Drowsiness has been described as the most common adverse effect during the treatment of hypophyseal adenoma [3]; not very surprising, since drowsiness has been reported as a side effect of some D2-agonists [10]. Daytime drowsiness, however, probably played only a minute role in our study because our patients received much smaller daily doses of terguride. Given the half-life of 4.3 h and the dose of 0.25 mg, the concentration of terguride in the plasma reached by midday ($<1/8$ of the initial value) is too low to induce any effects.

Terguride as a partial D2-agonist may actually display antidopaminergic properties in cases of dopamine hyperactivity or at high concentration [11,12], a phenomenon which could account for the single case of RLS augmentation observed after doubling the dose; at high concentrations terguride may begin to compete with the natural and more potent agonist dopamine for the D2-binding sites. The assumed terguride vs. dopamine competition may actually reduce D2-occupancy by the latter and manifest itself as an antidopaminergic effect. Hence, terguride can modulate the action of the endogenous agonist dopamine [13]. The augmentation effect was not observed at low doses because terguride at low concentrations in the brain may actually increase the total receptor occupancy by binding D2-receptors, which are still free. Possible augmentations of RLS caused by competition at D2-receptors are unrelated to the mechanism responsible for dose-dependent augmentation effects reported after carbidopa/levodopa intake [14] because high-dosed carbidopa/levodopa therapy may cause a depletion of dopamine at the presynaptic terminals. However, monitoring of long-term terguride efficacy, involving the collection of more data, would be helpful to evaluate whether the augmentation consistently occurs after a terguride intake.

In conclusion, terguride seems effective in controlling RLS in most of our patients in this small, open label study and the increase of the total occupancy of D2-receptors seems to us the most plausible explanation of its efficacy.

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References

[1] Comella CL. Restless legs syndrome. Treatment with dopaminergic agents. Neurology 2002;58(Suppl 1):S87–S92.
[2] Poch G, Zimmermann I. Simple pA2 estimate of partial agonists: Kaumann–Blinks method. J Pharmacol Methods 1999; 19:47–56.
[3] Marek J, Sramková J, Bauer J, et al. Terguride (9-10 transdihydrolisuride) in the treatment of hyperprolactinemia and acromegaly. In: MacLeod RM, Thorner MO, Scapagnini U, editors. Basic and clinical correlates. Padova: Livia Press; 1985. p. 779–86.
[4] Lapka R, Marek J, Rejholec V, et al. Pharmacokinetics of oral terguride in patients with a prolactinoma. Eur J Clin Pharmacol 1986; 30:363–5.
[5] Pacchetti C, Martignoni E, Bruggi P, et al. Terguride in fluctuating parkinsonian patients. A double blind study versus placebo. Mov Disord 1993;8:463–5.
[6] Filip V, Maršálek M, Hálková E, et al. Treatment of extrapyramidal side-effects with terguride. Psychiatry Res 1992;41:9–16.
[7] The International Restless Legs Syndrome Study Group, Walters AS. Toward a better definition of the restless legs syndrome. Mov Disord 1995;10:634–42.
[8] The International Restless Legs Syndrome Study Group, Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med 2003;4:121–32.
[9] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540–5.
[10] Frucht S, Rogers JD, Greene PE, et al. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 1999;52:1908–10.
[11] Brücke T. The partial dopamine receptor agonist terguride in the MPTP-induced hemiparkinsonian monkey model. Eur J Pharmacol 1988;148:445–8.
[12] Wachtel H, Dorow R. Dual action on central dopamine function of transdihydrolisuride, a 9,10-dihydrogenated analogue of the ergot dopamine agonist lisuride. Life Sci 1983;32:421–32.
[13] Clark WP, Bond RA. The elusive nature of intrinsic efficacy. Trends Pharmacol Sci 1998;19:681–8.
[14] Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. Sleep 1996;19:205–13.