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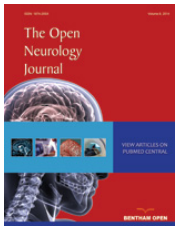

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LETTER

Tiapride for the Treatment of REM Sleep Behaviour Disorder in Dementia with Lewy Bodies: A Case Series

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Abstract:

Objective:

REM sleep Behaviour Disorder (RBD) in Dementia with Lewy bodies (DLB) may be attributed to a decrease in dopaminergic neurotransmission. Thus, we studied the therapeutic efficacy of the pre and postsynaptic D_2 and D_3 receptor antagonist tiapride, which at a low dosage preferentially blocks presynaptic dopamine receptors and consequently leads to feedback activation of dopamine synthesis and to increased extracellular levels of dopamine.

Methods:

Six consecutive patients presenting at our memory clinic with RBD in DLB, in whom melatonin had been ineffective and clonazepam was found inappropriate for clinical reasons, were treated with triapride at dosages between 50 and 150 mg for twelve weeks.

Results:

Tiapride was well tolerated by all patients. Five of the six patients, reported was a decrease of the self-perceived frequency of bad dreams and the intensity and severity of motor and vocal enactments during sleep. In four of these six patients, this was also the case in the view of the patients' bed partners.

Conclusion:

Tiapride may by an effective and well-tolerated treatment for RBD in patients with DLB.

Keywords: Tiapride, Treatment, REM sleep behaviour disorder, Dementia with Lewy bodies, Neurodegenerative, Inhibitors.

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1. INTRODUCTION

REM sleep Behaviour Disorder (RBD), a parasomnia with repeated episodes of dream-enactment behaviour [1], is frequent in neurodegenerative diseases [2], particularly in Dementia with Lewy Bodies (DLB) [3]. Consequently, it has been given increased diagnostic weight as a core clinical feature in the revised criteria for the clinical diagnosis of probable and possible DLB [4].

The two best established drugs for the treatment of RBD are melatonin and clonazepam [5]. Both have been found to be modestly effective. Melatonin may be advantageous because of its higher effectiveness for injury prevention and fewer side effects [6] compared to clonazepam [7, 8]. Second and third line alternatives for RBD treatment include acetylcholinesterase inhibitors, zopiclone, and Yi-Gan San [5].

A decreased dopaminergic neurotransmission could be the reason for the development of RBD. In DLB, there is a loss of dopaminergic midbrain neurons [9] and a decrease of dopaminergic neurotransmission [10, 11]. On this background, therapy trials with the D_2 and D_3 dopamine receptor agonist pramipexol have been conducted. The majority of the authors found modest improvements in RBD symptom severity and frequency [12 - 14], while others did not [15].

The benzamide derivate tiapride is a moderate, selective antagonist for both pre and postsynaptic D_2 and D_3 receptors [16, 17]. Tiapride is used to treat various neurological and psychiatric disorders, particularly dyskinesia, alcohol withdrawal syndrome, negative symptoms of psychosis, agitation and aggression in the elderly [18]. Presynaptic dopamine receptors are

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generally blocked by lower antagonist concentrations than postsynaptic receptors [19]. The blockade of the presynaptic dopamine receptors by low dose tiapride leads to feedback activation of dopamine synthesis and to increased extracellular levels of dopamine [18]. Thus, the dopaminergic effect through the preferentially presynaptic blockade of dopamine receptors by low dosages of tiapride may warrant a trial for the treatment of RBD in DLB. Compared to pramipexole, which also has a dopaminergic effect, tiapride has a more favourable side effect profile.

2. METHODS

The trial was performed in six consecutive patients with probable mild to moderate DLB [4] and RBD, in whom treatment with clonazepam was considered inappropriate because of the risk of falls, cognitive impairment, or sleep apnea and treatment with melatonin at dosages between 2 and 8 mg had had little or no effect. Patients had to have a bed partner, who could serve as an external information source.

RBD was ascertained by patient and bed partner history as well as polysomnography (PSG). All patients had a history of at least weekly violent dream enactment behavior. PSG showed tonic and phasic EMG activity during REM sleep in all patients and complex behavioral activity during REM sleep in four of six patients.

The patients were asked to score the frequency of unpleasant dreams according to Item 5 (h) of the Pittsburgh Sleep Quality Index (PSQI) [20] as either "0" (not during the past month), "1" (less than once a week), "2" (once or twice a week), or "3" (three or more times a week) before and twelve weeks after the initiation of tiapride treatment. After twelve weeks of tiapride, the patients and their bed partners were also asked whether frequency or severity of the motor and vocal behaviors during sleep improved, remained unchanged, or worsened. Due to cognitive problems, the self-assessments of the patients should be interpreted with due caution. They and the caregivers were encouraged to make notes on a preceding night immediately after waking up. Mild psychotic symptoms were present in some of the patients, as scenic visual hallucinations or as passing delusional misinterpretations of visual and auditory perceptions. As the applied dosages of tiapride were to low to expect an antipsychotic effect, we did not ask for psychotic symptoms in a standardized manner and did not observe an obvious effect of tiapride on psychotic symptoms. Tiapride has been found to cause increased prolactin levels in plasma, which can cause decreased libido, infertility and increased risk of breast cancer [21]. A side effect rarely reported to the FDA is rhabdomyolysis. Cardiac abnormalities such as prolongation of the QT interval and torsades de point also have been observed. Dosages above approximately 300 mg/day may induce tardive dyskinesia [22].

Treatment with tiapride was initiated with a dosage of 50 mg before going to sleep. The patients were seen every four weeks. At weeks 4 and 8 after treatment initiation, the dosage of tiapride was adjusted. If there was no or little therapeutic effect, the dosage would be increased in 50-mg steps. If the respective reports of patient and caregiver were discordant, which may be the case because the patient's report refers to subjective experience, the caregiver's report to external observation, we aimed for a consensus integrating both views and suggested dose changes on this basis. In case of side effects, the dosage would be reduced by 50 mg or the treatment would be discontinued.

All procedures involving human subjects were done in accordance with the ethical standards of the Committee on Human Experimentation of Mannheim Medical Faculty and in accord with the Helsinki Declaration of 1975.

3. RESULTS

The patients were five men and one woman at ages between 63 and 78 years (mean: 71.8 years). Individual patient data are given in Table **1**.

Table 1. Individual patient data.

Age [Years], Sex	Age at DLB Onset [Years]	Medication for DLB [mg/day]	Age at RBD Onset [Years]	RBD Duration [Years]	PSQI 5(h)		Motor and Vocal Behavior after 12 Weeks of Tiapride		Final Tiaprid Dosage [mg]
					Before	After 12 Weeks	Patient	Bed Partner	
72, male	68	levodopa/carbidopa 200/50 rivastigmine patch 4.6	66	6	3	1	+	+	50*
73, male	70	levodopa/carbidopa 400/100 rivastigmine capsules 12 pramipexole 1,05	71	2	2	0	+	+	100
78, male	72	levodopa/carbidopa 600/150 rivastigmine patch 9.5 rotigotine patch 8	75	3	2	2	=	=	100
74, male	72	levodopa/carbidopa 400/100 rivastigmine patch 9.5	71	3	3	0	+	+	50
71, female	70	levodopa/carbidopa 300/75 donepezil 5	70	1	2	1	+	=	100
63, male	61	levodopa/carbidopa 300/75 donepezil 10	62	1	2	1	+	+	150

The individual patient data for DLB (dementia with Lewy bodies) and RBM (REM sleep behavior disorder) are given. Under "PSQI 5(h)" the patients' answers to item 5(h) of the Pittsburgh Sleep Quality Index are listed. The perception of the nighttime motor and vocal behavior of the patient by the patient himself and his bedpartner are coded as "+" (improved), "=" (unchanged), "-" (deteriorated).

*: This patient initially experienced a substantial improvement of sleep under a dosage of 50 mg tiaprid. Subsequent to increasing the dosage to 100 mg, sleep deteriorated. After having returned to the initial dosage of 50 mg, sleep improved again.

The age of onset of DLB was between 61 and 72 years (mean: 68.8. years). All patients were treated with levodopa and a cholinesterase inhibitor (rivastigmine in four patients, donepezil in two); two patients were additionally under treatment with a dopamine agonist (one with pramipexole, one with rotigotine). The age at onset of RBD was between 62 and 75 years (mean: 69.2 years); in two patients, the onset of RBD preceded the onset of DLB. The mean duration of RBD was between one and six years (mean: 2.7 years). The frequency of bad dreams as assessed by the PSQI was reported as "once or twice a week" by four patients, as "three or more times a week" by two patients.

Tiapride was well tolerated by all patients. Extrapyramidal side effects were not observed. The final dose was 50 mg in two patients, 100 mg in three, and 150 mg in one patient. One patient reported that under 50 mg tiapride, the frequency of bad dreams decreased from twice or three times a week down to less than once a week. When we further increased the dose to 100 mg, the bad dreams appeared more frequently and more vividly again. After subsequent reduction of the dosage to 50 mg, frequency and intensity of the bad dreams decreased again.

In five of the six patients, self-perceived frequency of bad dreams and intensity and severity of motor and vocal enactments during sleep decreased under tiapride treatment. In four of the six patients, this was also the case in the view of the patients' bed partners. At all assessments, the association between patient and caregiver reports was high. No effects were observed on motor or psychotic symptoms or on daytime behavior, particularly no sedation. However, fluctuations as a typical symptom of DLB may have impaired the assessment of such side effects.

4. DISCUSSION

Tiapride was found effective for the treatment of RBD in DLB in four to five out of six patients. The effective dose was between 50 and 150 mg. In one patient, we observed decreased efficacy at increasing dosage. Thus, tiapride may be considered as a treatment option in patients with RBD in DLB, in whom melatonin was found ineffective or little effective and clonazepam could not be used because of the increased risk for falls, cognitive impairment and worsening of sleep apnea.

At the comparatively small dosages applied, tiapride mainly blocks the presynaptic dopamine receptors and enhances dopaminergic neurotransmission [18]. Thus, improvement of RBD under a low-dose tiapride treatment supports the assumption of a role of the dopaminergic system in the generation of DLB [8, 11].

At the dosages we applied, tiapride has a very low risk for extrapyramidal side effects, such as akinesia or akathisia. Additionally, tiapride has a relatively high regional selectivity for limbic areas. One study found that, in contrast to haloperidol, tiapride shows over three times as much affinity for limbic than for striatal areas [18]. However, under long-term treatment, it may increase the prolactin level [21], which may in turn decrease libido and increase the risk of breast cancer and osteoporosis. Tiapride has only a small potential for pharmacokinetic interactions and its serum level is well controllable, because it has no relevant oxidative liver metabolism and is eliminated renally with a serum half-life of three to four hours [22].

Given the considerable impairment caused by RBD in patients with DLB and the limitations of alternative treatments, the further exploration of the therapeutic potential of tiapride may be warranted.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures involving human subjects were done in accordance with the ethical standards of the Committee on Human Experimentation of Mannheim Medical Faculty.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from all participants prior to publication.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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