Zolpidem in Parkinson's disease

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Jankovic and Marsden[1] suggest that drugs that enhance neurotransmission of γ-aminobutyric acid (GABA) could be helpful in Parkinson's disease, but there is little evidence to support this claim. Zolpidem, an imidazopyridine short-acting hypnotic drug used to treat insomnia, shows high selectivity for the benzodiazepine subtype receptor BZ_1, which is part of the $GABA_A$-receptor complex. The highest density of zolpidem-binding sites is in the output structures of the basal ganglia: the ventral globus pallidus and the substantia nigra pars reticulata.[2] We observed a 61-year-old woman with a 25-year history of Parkinson's disease who received zolpidem for insomnia. After the first 10 mg dose, she showed no drowsiness, but a substantial improvement in akinesia and rigidity. Such antiparkinsonian effects were similar to those of levodopa. Other hypnotics (triazolam, zopiclone) were ineffective. This patient received zolpidem (10 mg four times daily) without dopaminergic drugs for 5 years, with relief from Parkinsonian symptoms and no side-effects. We therefore conducted a double-blind, placebo-controlled crossover study of zolpidem in ten patients with clinically diagnosed Parkinson's disease.[3]

The mean age of the patients was 69·9 years (SD 11·9), their mean disease duration was 9·2 years (6·9), and their mean Hoen and Yahr score in "off" conditions was 2·9 (1·2). Zolpidem was administered in one 10 mg oral dose. All antiparkinsonian medication was withheld 12 h before assessment. We used the motor examination part of Unified Parkinson's Disease Rating Scale to assess motor function before administration of drug (baseline) and 1 h after administration. A positive response was defined as a decrease of more than 20% in the baseline score.[4] Zolpidem produced significant motor improvement (table). Six patients (three of the four most severely affected and three of the six less severely affected) showed motor improvement of between 21% and 59%, mostly in facial expression, rigidity, akinesia, bradykinesia, posture, and gait. In zolpidem responders, clinical effects on Parkinsonian symptoms appeared about 45–60 min after administration of the drug and lasted for about 2–4 h. Thus, compared with the latency and duration of zolpidem's hypnotic effect, latency of antiparkinsonian effects was slightly longer, whereas their duration was shorter. Zolpidem did not induce dyskinesias, even in the three patients who had had levodopa-induced dyskinesias. The only adverse effect associated with zolpidem was drowsiness, which occurred in four patients (mild in one, moderate in another, and severe in two patients). No drowsiness was observed in three of the four most severely affected patients.

	All patients (n=10)	Responders (n=6)	Non-responders (n=4)
Scores on placebo			
Baseline	37·4 (22·3)	37·7 (23·6)	37·0 (23·6)
1 h after administration	37·0 (22·1)*	37·5 (25·3)	36·2 (20·0)
Mean improvement (%)	0·9	2·4	-1·1
Scores on zolpidem			
Baseline	39·9 (22·4)	40·2 (24·9)	39·5 (21·7)
1 h after administration	32·9 (19·4)†	28·7 (18·6)	39·2 (21·4)
Mean improvement (%)	18·4	30·2	0·6

*p=0·42 *vs* baseline; †p=0·0089 *vs* baseline (Wilcoxon signed-rank test).

Mean (SD) scores for motor examination part of Unified Parkinson's Disease Rating Scale of ten patients with Parkinson's disease on placebo or zolpidem

These preliminary findings suggest that zolpidem therapy could be helpful in a subpopulation of Parkinsonian patients, possibly with severe Parkinson's disease. There is increasing evidence that in Parkinson's disease, nigrostriatal dopamine deficiency leads to overactivity of inhibitory neurons in the internal globus pallidus, with subsequent overinhibition of the thalamus and the cerebral cortex.[5] Zolpidem might induce selective inhibition of GABAergic inhibitory neurons in the internal globus pallidus and the substantia nigra pars reticulata. This mechanism should activate both the thalamus, with the supplementary motor area, and the peduncolopontine nucleus, with the reticulospinal and vestibulospinal pathways. If so, zolpidem could provide a pharmacological equivalent of posteroventral pallidotomy.[5] Selective GABAergic agonists, such as zolpidem, that act within the basal ganglia may represent a new therapeutic approach in Parkinson's disease and could be beneficial in patients who have complications associated with long-term levodopa treatment.

1 Jankovic J, Marsden CD. Therapeutic strategies in Parkinson's disease. In: Jankovic J, Tolosa E, eds. Parkinson's disease and movement disorders. Baltimore and Munich: Urban and Schwarzenberg, 1988: 95–119.

2 Langer SZ, Arbilla S, Scatton B, Niddam R, Dubois A. Receptors involved in the mechanisms of action of zolpidem. In: Sauvanet JP, Langer SZ, Morselli PL, eds. Imidazopyridines in sleep disorders. New York: Raven Press, 1988: 55–70.

3 Gibb WRG, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1988; **51:** 745–52.

4 Schwarz J, Tatsch K, Arnold G, et al. 123I-iodobenzamide-SPECT in 83 patients with de novo parkinsonism. *Neurology* 1993; **43** (suppl 6): S17–S20.

5 Grafton ST, Waters C, Sutton J, Lew MF, Couldwell W. Pallidotomy increases activity of motor association cortex in Parkinson's disease: a positron emission tomographic study. *Ann Neurol* 1995; **37:** 776–83.

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