Donepezil in the Treatment of Narcolepsy

Helmut Niederhofer, M.D., Ph.D.

Department of Pediatrics, Regional Hospital of Bolzano, Bolzano, Italy

Abstract: Chronic excessive sleepiness impairs the daily life of patients suffering from narcolepsy. Antidepressants that enhance synaptic levels of noradrenaline and serotonin have been reported as having some therapeutic efficacy. For that reason, acetylcholinesterase inhibitors, which elevate acetylcholine levels, may have a protective function with respect to narcolepsy and cataplexy. The patient reported in this article received donepezil, 10 mg, for 3 consecutive months and showed an improvement of the Epworth Sleepiness Scale score from 20 up to 14.

Keywords: Narcolepsy, donepezil, acetylcholinesterase inhibitors


Narcolepsy is characterized by chronic excessive sleepiness that significantly impairs daily life. Narcoleptic symptoms interfere with participation in interpersonal and social activities. It is probably caused by the absence of hypothalamic hypocretin-containing neurons. Recent findings have revealed that a mutation of type 1 and 2 hypocretin receptors may also play a role in the etiology of narcolepsy. Up to now, amphetamines and antidepressants have been used for this condition. Amphetamines improve alertness regardless of the cause, which means that dopamine can decrease sleepiness. Antidepressants that enhance synaptic levels of noradrenaline and serotonin have been reported as having some therapeutic efficacy, suggesting the existence of additional mechanisms underlying narcolepsy. Hypocretin increases levels of acetylcholine and dopamine in the cerebrospinal fluid. Studies of animal models have demonstrated that acetylcholine levels are higher in narcoleptic canines with artificially induced cataplexy. For that reason, I hypothesized that those acetylcholinesterase inhibitors that elevate acetylcholine levels may have a protective function with respect to narcolepsy and cataplexy.

Report of Case

I describe a 34-year-old woman 6 months after the onset of narcolepsy. Disease onset occurred with excessive sleepiness and irresistible naps during the day. Six months previously, she was perfectly awake under the same conditions. I could not identify triggering factors or accompanying symptoms. The patient fell asleep regularly at work and was found napping at home. Clear-cut cataplexy with bilateral muscle weakness in the lower limbs and face muscles subsequently appeared, occurring daily and lasting a few seconds, together with 2 to 3 injurious falls per day, triggered by laughter.

This history was considered typical of classic narcolepsy with cataplexy, in the absence of sleep paralysis or hallucinations. Neurologic and psychiatric examinations, including polysomnography showed normal results (see Figure 1). For that reason, I decided not to add a Multiple Sleep Latency Test, since the clinical diagnosis was quite clear. Further trials with donepezil should of course include MSLT to verify a clinical diagnosis.

Family history was negative with regard to sleep or neurologic disorders. The initial Epworth Sleepiness Scale score was 20 (possible range 0-24, with higher numbers indicating greater sleepiness). Standard brain magnetic resonance imaging did not reveal any lesions. Before initiating donepezil, the patient did not receive amphetamine-like psychostimulants, such as methylphenidate, because these substances are not legally available in Italy. She refused to take non-amphetamine-like psychostimulants, such as modafinil. For that reason, I looked for alternatives. After obtaining informed consent, I initiated therapy with donepezil, 10 mg, (with the intention of increasing the acetylcholine level in the cerebrospinal fluid) for 3 consecutive months. One week after the start of treatment, improvement of both sleepiness and cataplexy were noticed. Afterward, only 2 attacks of cataplexy or irresistible nap were reported. The patient reported an improvement of her sleepiness, indicated by an improvement in the Epworth Sleepiness Scale score to 14. At the time of the last interview (the patient had been on donepezil for 3 months), the patient reported no reappearance of catalectic attacks leading to falls.

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Address correspondence to: Helmut Niederhofer, M.D., Ph.D., Regional Hospital of Bolzano, Department of Pediatrics, I-39100 Bolzano, Italy; E-mail: helmutniederhofer@yahoo.de

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DISCUSSION

This is the first report illustrating the clinical efficacy of donepezil, a highly selective acetylcholinesterase inhibitor, after the onset of narcolepsy symptoms. This finding suggests that, apart from the absence of hypocretin-containing neurons, which has been discussed as a possible cause of narcolepsy, other neurotransmitter systems may also be involved in the pathophysiology of narcolepsy. My observations suggest that narcolepsy is associated with diminished acetylcholine levels, but the absence of hypocretin-containing neurons is still the main reason for this disorder. If confirmed in controlled trials and with objective measures of sleepiness, this finding suggests that donepezil may be efficacious for the treatment of narcolepsy.

REFERENCES