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Letter to the Editor

Memantine Induces Reflex Syncope in Elderly Patients With Dementia: Results From the Syncope and Dementia Study (SYD-Study)

To the Editor:

Syncope has been diagnosed with increasing frequency in older patients with dementia.[1] Recently, SYncope and Dementia Study (SYD Study) demonstrated how the extensive use of hypotensive drugs is involved in the high prevalence of syncope due to orthostatic hypotension (≈50%).[2,3] However, very few data are available about the effect of psychotropic drugs used for the treatment of dementia and the development of syncope.

Thus, we analyzed the role of different psychotropic drugs used in the treatment of dementia on the incidence of different types of syncope in the population of the SYD Study. Briefly, the SYD Study is a prospective, observational, multicenter study involving 522 elderly subjects aged 65 years and older who had a diagnosis of dementia and transient loss of consciousness during the previous 3 months in patients enrolled in nursing home, acute care unit, syncope units, and units for Alzheimer diagnosis.[2] All participants were evaluated as the Syncope European Guidelines of Cardiology (ESC) guidelines recommend.[4] The psychotropic drugs considered are the following: Angiotensin-converting enzyme inhibitors (donepezil, rivastigmine, and galantamine), memantine, antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone), antidepressants (sertraline, fluoxetine, citalopram, escitalopram, paroxetine, fluvoxamine), anti-Parkinson drugs (levodopa, carbidopa, rasagiline, bromocriptine, amantadine), benzodiazepines, and antiepileptics (phenobarbital, carbamazepine, lamotrigine).

From 522 enrolled patients, a diagnosis of syncope was defined in 354. The mean age of the patients was 83.3 ± 6.4 years, with a female prevalence of about 60%. The mean Mini-Mental State Exam score at was 16.9 ± 5.4. The total number of drugs taken was 6.1 ± 2.7, with an average use of 1.22 ± 1.04 psychotropic drugs. Syncope due to orthostatic hypotension was the most frequent diagnosis (48.0%) followed by reflex syncope (26.8%) and cardiac syncope (12.7%), whereas syncope of unknown origin was only 10.5%. When all psychotropic drugs were analyzed for the type of syncope, only memantine administration was significantly associated with an increase of reflex syncope (45.0% vs 26.8%, $P < .001$) (Figure 1). When stratified for memantine administration, patients not taking memantine were younger and had higher Cumulative Illness Rating Scale scores than those taking memantine (1.3 ± 0.4 vs 1.6 ± 0.4, $P < .001$). In contrast, the Mini-Mental State Exam score was lower (14.8 ± 5.6 vs 17.2 ± 5.3; $P = .013$) and the number of psychotropic drugs taken was higher in patients in memantine therapy than in those not in therapy (2.4 ± 0.9 vs 1.0 ± 0.9, $P < .001$). As expected, Alzheimer disease was the type of dementia more prevalent in patients treated than in those not treated with memantine (52.5% vs 29.3%, $P = .003$). Among psychotropic drug combinations, only the association of memantine with antidepressant drugs was significantly associated with reflex syncope (10.8% vs 4.8%, $P = .036$). Univariate analysis shows a strong association between memantine and reflex syncope alone [relative risk (RR) = 2.24, 95% confidence interval (CI) 1.14-4.38] and in association with antidepressant drugs (RR = 2.41, 95% CI 1.03-5.67). Multivariate analysis adjusted for age and sex and number of psychotropic drugs confirmed the predictive role of memantine (RR = 2.11, 95% CI 1.06-4.15) and its association with antidepressant drugs (RR = 2.34, 95% CI 1.00-5.50) on reflex syncope.

Memantine represents, with acetylcholinesterase inhibitors, the only therapy approved for the treatment of moderate and severe Alzheimer disease stages. This drug acts as a noncompetitive antagonist of glutamate NMDA receptors counteracting glutamate "excitotoxicity" phenomena involved in the pathogenesis of this and other neurodegenerative pathologies, without interfering with the physiological neurotransmission.[5]

The results of our study show that memantine is significantly associated to reflex syncope with more than a doubled risk of reflex syncope at multivariate analysis. The mechanisms underlying this association between memantine and reflex syncope is unknown. There are several studies that have identified a lack of association between memantine and syncope—most notably a 2011 meta-analysis.[6] In a review of the French drug-vigilance registry, memantine showed only a few cases of cardiovascular adverse events, the most common being bradycardia.[7] Moreover, in association with donepezil, memantine was responsible for isolated cases of elongation of the PR interval.[8]

The mechanism by which memantine causes these effects are not recognized. It is known that the glutamate NMDA receptors are expressed outside the central nervous system also in the cardiovascular system, in particular on the endocardium and on myocardiocytes, where their stimulation has been correlated to the development of hypertension and a hyperadrenergic status.[9] A possible negative chronotropic effect or the sympatholytic actions of an NMDA antagonist such as memantine could partly explain the syncopal responses observed in our study.

In addition, the results of our study show that in patients treated with memantine, combinations with antidepressant drugs increase the risk of reflex syncope even more than memantine alone. An explanation of this synergistic effect is not known. It has long been known that the central serotonergic transmission plays a fundamental role in the genesis of reflex syncope.[10] Thus, blockage of the reuptake of serotonin in the synaptic space and,

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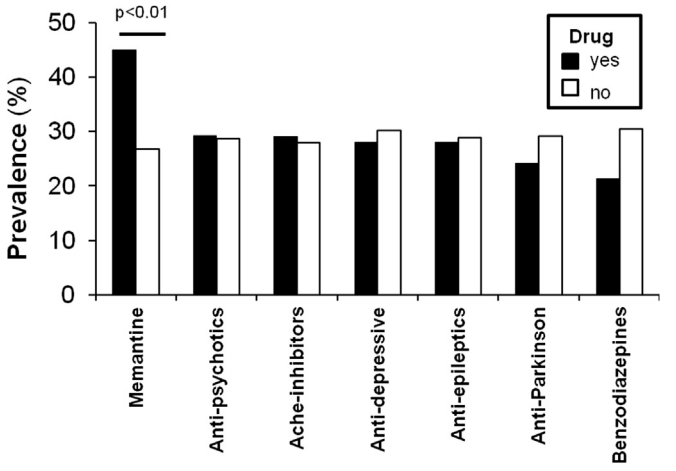

Fig. 1. Prevalence of reflex syncope in elderly patients with dementia stratified for the administration (yes/no) of psychotropic drugs.

therefore, an increase in the stimulation of serotonergic receptors in the regions of the central nervous system that control the peripheral resistance and heart rate may determine vasodilatation and bradycardia.[10]

Thus, in the SYD Study, reflex syncope was significantly associated with memantine, and combining memantine with antidepressant drugs synergistically increases the risk of reflex syncope. These data call for extreme caution in the selection of elderly dementia patients under treatment with memantine especially in combination with antidepressant drugs.

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