

Galantamine-induced pisa syndrome: Memantine as an alternative

Dear Editor

Pisa syndrome, or pleurothotonus, which was first described by Ekblom *et al.* (1972), is a condition characterized by sustained flexion of the body with the head to one side. It has been observed in patients with prolonged exposure to antipsychotics and also to be triggered in at least 14 reported cases by cholinesterase inhibitors (ChEIs) (Kwak *et al.*, 2000; Miyaoka *et al.*, 2001; Villarejo *et al.*, 2003; Cossu *et al.*, 2004; Vanacore *et al.*, 2005; Huvent-Grelle *et al.*, 2007). These case reports proposed that ChEIs-induced Pisa syndrome may resolve after the medication being discontinued or switched to another ChEIs, while others may be improved by locally injected botulinum toxin. However, the long-term management of these patients was not fully described or suggested. We report a case of galantamine-induced Pisa syndrome whose dystonia remitted after the discontinuation of galantamine and successfully switching to memantine.

A 65-year-old woman with 4-year history of moderate Alzheimer's disease (AD) was admitted to our geriatric psychiatric acute ward for amnesia, depressed mood, irritability, and disturbing behavior. At admission, she took galantamine 16 mg/day, sertraline 50 mg/day, and valproic acid 500 mg/day, in divided doses. Her mood and behavior symptoms were then partially stabilized. The regimen remained unchanged thereafter. After 6-months therapy, she gradually developed right laterocollis with slight-right axial deviation. On examination, magnetic resonance imaging of the brain showed no focal lesions other than cortical atrophy. Pisa syndrome was diagnosed by a neurologist. Galantamine was then discontinued with sertraline and valproic acid being maintained. Four weeks later, a trial to titrate memantine to 20 mg/day was initiated. Two weeks after switching

to memantine, the dystonia resolved without other adverse effects. After nine months of memantine treatment, the patient's cognitive function and psychiatric conditions were stable with no signs of Pisa syndrome.

In addition to donepezil and rivastigmine, there were three known case reports of Pisa syndrome induced by the newer ChEI agent galantamine (Cossu *et al.*, 2004; Huvent-Grelle *et al.*, 2007). Although the underlying pathology of drug-induced Pisa syndrome is still questionable, the most acceptable hypothesis for this syndrome is implicated to be a disturbance of cholinergic-dopaminergic balance (Villarejo *et al.*, 2003). Cholinergic excess can develop with the exposure to ChEIs in AD patients and result in Pisa syndrome. General management such as reducing the dosage of suspected medication or concomitant treatment with anticholinergic agents may exacerbate the cognitive impairment in AD patients. The switching among currently marketed ChEIs or re-challenging with previously used ChEIs may exert Pisa syndrome again or even be associated with mortality (Kwak *et al.*, 2000; Vanacore *et al.*, 2005; Huvent-Grelle *et al.*, 2007). Local botulinum toxin injection, as proposed by Cossu *et al.* (2004), may cause falling and require very large dose and repetition. With a simple and direct concept of bypassing the dopaminergic-cholinergic system, memantine, which acts by noncompetitively binding to glutamatergic N-methyl-D-aspartate (NMDA) receptors to prevent overstimulation by glutamate, can be an effective alternative. Previous case reports usually focused on the onset and resolution of ChEIs-induced Pisa syndrome in AD patients. However, the treatment to these patients should not be taken only as short-term management, and antidementia agents should be indispensable. The successful alternative with memantine in the current case suggests

an optimal long-term strategy for such patients, though more case studies are necessary.

Related issues such as the direct efficacy of memantine in treating ChEIs-induced Pisa syndrome remain unclear. Whether memantine will be an effective alternative for ChEIs other than galantamine also needs further studying. Moreover, the best timing, procedures, and dosages for switching need investigating. For example, the antidementia agent-free period in the current case might exert risk of ChEIs discontinuation syndrome and cognitive exacerbation. Some studies suggested that the combination of memantine and ChEIs had more cognitive benefits than monotherapy (Grossberg *et al.*, 2006). So theoretically, a treatment with the combination of memantine and reduced dosage of ChEIs could be tried and studied.

Our case highlighted the concept of sustained treatment for AD patients with ChEIs-induced Pisa syndrome and demonstrated an effective and safe alternative. For such circumstances or populations, the accurate diagnosis should be made, and a long-term alternative treatment, such as memantine, can be administered. Concomitant and regular monitoring of cognitive function and adverse effects is also necessary.

CONFLICT OF INTEREST

None known.

REFERENCES

- Cossu G, Melis M, Melis G, *et al.* 2004. Reversible Pisa syndrome (pleurothotonus) due to the cholinesterase inhibitor galantamine: case report. *Mov Disord* **19**: 1243–1244.
- Ekbom K, Lindholm H, Ljungberg L. 1972. New dystonic syndrome associated with butyrophenone therapy. *Z. Neurol* **202**: 94–103.
- Grossberg GT, Edwards KR, Zhao Q. 2006. Rationale for combination therapy with galantamine and memantine in Alzheimer's disease. *J. Clin Pharmacol* **46** (7 Suppl 1): 17S–26S.
- Huvent-Grelle D, Roche J, Camus FE, *et al.* 2007. Relationship between cholinesterase inhibitors and Pisa syndrome in a cohort of five French patients with Alzheimer's disease. *J. Am Geriatr Soc.* **55**: 1472–1475.
- Kwak YT, Han IIW, Baik J, *et al.* 2000. Relation between cholinesterase inhibitor and Pisa syndrome. *Lancet* **355**: 2222.
- Miyaoka T, Seno H, Yamamori C, *et al.* 2001. Pisa syndrome due to a cholinesterase inhibitor (donepezil): a case report. *J. Clin Psychiatry* **62**: 573–574.
- Vanacore N, Suzzareddu G, Maggini M, *et al.* 2005. Pisa syndrome in a cohort of Alzheimer's disease patients (Case report). *Acta Neurol Scand* **111**: 199–201.
- Villarejo A, Camacho A, Garcia-Ramos R, *et al.* 2003. Case report: Cholinergic-dopaminergic imbalance in Pisa syndrome. *Clin Neuropharmacol* **26**: 119–121.

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