Case Report: Marked Effect of Cilostazol on Delirium in a Dementia Patient with Deep White Matter Lesions: Potential Etiology-Targeted Pharmacotherapy for Delirium

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Abstract: Antipsychotics have been mainly used as pharmacotherapy for delirium. Their use is, however, only considered a symptom-targeted, but not an etiology-targeted therapy. Moreover, antipsychotics may also have some adverse effects in elderly patients. We report a case of an elderly dementia patient with deep white matter lesions whose delirium was markedly resolved with a platelet aggregation inhibitor, cilostazol. No antipsychotic drugs were used. To our knowledge, there have been no reports regarding the effect of cilostazol on delirium, despite not a few studies on cognitive function of Alzheimer disease and cerebrovascular disease. This case suggests that cilostazol is a potentially effective agent as an etiology-targeted therapy for delirium due to its possible increased regional cerebral blood flow.

Keywords: Delirium, cilostazol, antipsychotics, etiology-targeted therapy.

INTRODUCTION

Antipsychotics have been the main pharmacotherapy for delirium. There is some, although still limited, evidence regarding the efficacy and safety of antipsychotics in the treatment of delirium [1]. Their use is, however, only considered a symptom-targeted, but not an etiology-targeted therapy. That is because, although it may well be multifactorial, the etiology of delirium is closely associated with the patient's physical or organic abnormalities, which take time to treat. Moreover, antipsychotics have often been clinically effective in sedating hyperactively delirious patients, but they may also have various kinds of adverse effects, which are sometimes severe, especially in elderly patients. Non-pharmacological approaches to the treatment of delirium in the elderly, rather than a symptom-targeted therapy, are currently being recommended [2, 3]. We report a case of an elderly dementia patient with deep white matter lesions whose delirium was markedly resolved with a platelet aggregation inhibitor, cilostazol. This case suggests that cilostazol could be a potentially effective, etiology-targeted pharmacotherapy agent for delirium.

CASE REPORT

An 84-year-old woman without personal or family history of psychiatric disease was treated for hypertension and diabetes with no history of cerebrovascular disease. She had been living alone, and then entered a nursing home. Her physical condition was well controlled with oral medication of antihypertensives (nifedipine 20mg/d, doxazosin 4mg/d and olmesartan medoxomil 10mg/d) and an antidiabetic (alogliptin 12.5mg/d). She did not take any sleep-aid medicine including hypnotics. Several month after entering the nursing home, although there were no particular incidents, she became agitated and disoriented every night, complaining with excitation that she would be killed or that she was imprisoned. Every following morning, she completely failed to remember the events.

A care provider in the nursing home urged her to visit a geriatric hospital, where an examination revealed moderate cognitive impairment (13 points by revised Hasegawa Dementia Scale). Brain CT showed moderate to severe periventricular lucency, several lacunar infarctions at the bilateral corona radiate, moderate enlargement of the lateral ventricle, and bilaterally mild atrophy of inferior angles of the lateral ventricle (Figure **1**). Cerebral blood flow could not be determined because that facility did not possess the equipment for single photon emission computed tomography (SPECT). Her blood pressure and blood-sugar level were normal, and no other physical findings could explain her impaired cognition. She was diagnosed with delirium based on vascular dementia characterized by deep white matter lesions. The cause of delirium was not clear, but she might have had mild dehydration or slightly lower blood pressure at night, which often induces delirium in patients with cerebrovascular impairment. Since it was very likely that antipsychotics would have her over-sedated or prone to falling, cilostazol at 100mg/day was prescribed, expecting its enhancement effect on regional cerebral blood flow.

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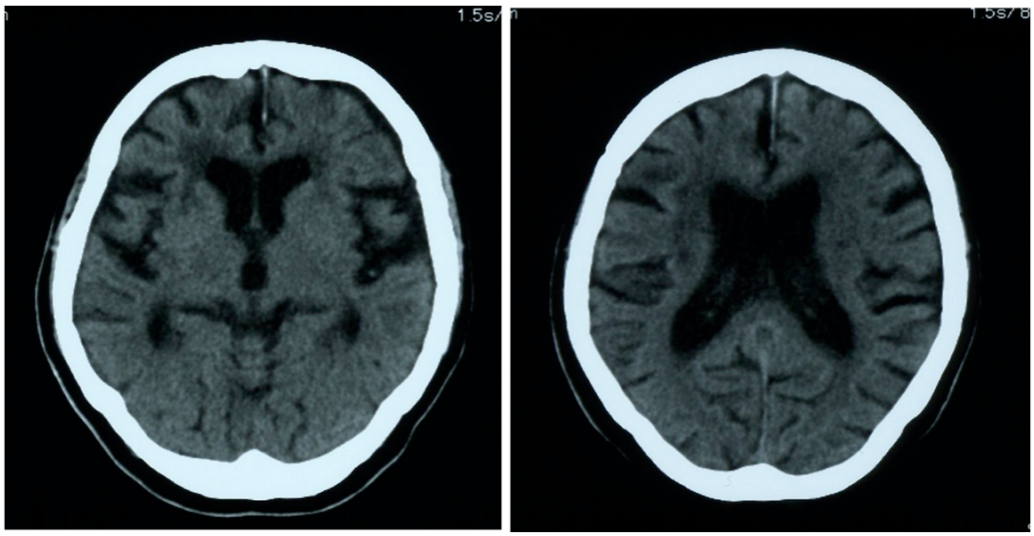

Figure 1: brain CT of this case.

Two days after beginning this medication, her nightly agitation, disorientation and delusion disappeared. A month later, tachycardia occurred as a side-effect, and cilostazol was tapered to 50mg/day. Delirium did not recur.

DISCUSSION

In the present case, cilostazol markedly improved delirium with agitation and delusion in a dementia patient with deep white matter lesions. The patient's periventricular white matter change was moderate to severe, and could not be explained at all by normal aging. For such hyperactive delirium as observed in this case, antipsychotics have usually been used to sedate these symptoms, but they were not needed in the treatment of this case. Adverse effects such as over-sedation and parkinsonism, which antipsychotics prescribed as symptom-targeted therapy could often induce in elderly patients, were not seen.

According to the drug information provided by the pharmaceutical company, cilostazol has two therapeutic actions, platelet aggregation inhibition and vasodilatation, for the main indications of cerebral infarction or arteriosclerosis obliterans. In the present case, these actions might have increased cerebral circulation and thereby improve cognitive function in a delirious patient with cerebrovascular lesions, although any improvement in cerebral brood flow could not be confirmed by SPECT. Tachycardia and bleeding tendency are known as more frequent adverse effects of cilostazol, and tachycardia did occur tractably.

Cilostazol has also been known as a phosphodiesterase inhibitor (PDE-I). PDE-I reduces the degradation of cyclic nucleotides, whose signaling is essential in cellular functions including neuroplasticity and neuroprotection. Increasing attention has recently been paid to PDE-I as an agent that could possibly treat age-related cognitive decline and Alzheimer disease (AD), although the effect of cilostazol on cognition in AD is also being tested [4]. Some studies have suggested that cilostazol may reduce cerebral ischemia and accumulation of amyloid β (Aβ), major potential risk factors for developing dementia [5]. Moreover, cilostazol may have anti-depressant effects on post-stroke depression through inhibition of neurodegeneration and promotion of neurogenesis, based on an animal model study [6]. Most of these findings concerning cilostazol are associated with enhanced cognitive function, although they do not refer to delirium. To our knowledge, there have been no reports regarding the effect of cilostazol on delirium.

In the treatment of delirium, while antipsychotics suppress agitation or psychosis to sedate delirium, cilostazol may improve regional cerebral blood flow and cure delirium. Its use is more inherent in the sense that the therapy targets the causes of, not symptoms of, delirium. The therapeutic actions of cilostazol may have a certain effect on delirium associated with cerebrovascular disease, as long as careful attention is paid to possible tachycardia and bleeding tendency. This application for delirium may well be called an etiology-targeted therapy.

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