Effect of angiotensin II type 1-receptor blocker candesartan on hypertensive Parkinson's disease

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Received 24 September 2009; received in revised form 30 September 2009; accepted 1 October 2009

Abstract

Angiotensin II receptor blocker (ARB) therapy has been proven to be well tolerated and effective in the management of hypertension, chronic heart failure with left ventricular dysfunction, and the prevention and progression of diabetic renal disease. ARB also shows various effects other than a depression effect. We investigated the effect of candesartan cilexetil, one of a number of angiotensin II receptor blockers (ARB) on Parkinsonian symptoms as well as mental symptoms in patients with hypertensive PD. We assessed Parkinsonian symptoms as well as mental function by UPDRS, PDQ-39, SDS, HAD, and SUBI. HAD-anxiety scores, total scores of UPDRS (parts 1-4), and scores of PDQ-39 were significantly decreased 6M after the therapy ($p<0.05$). Although little is known about the effect of the ARB on dopaminergic neurons, there is also a possibility of a placebo effect that plays an important role in the development of Parkinsonism. Alternatively, candesartan may reduce mental disorders associated with hypertension. Further studies are required to investigate the effect of ARB on motor or mental symptoms of Parkinson's disease.

Key Words: Angiotensin II receptor blocker, ARB, UPDRS, PDQ-39, SDS, HAD, and SUBI

Introduction

Candesartan cilexetil is one of a number of drugs of the angiotensin II receptor blocker (ARB) class. Their principal mode of action involves competitive blockade of the angiotensin II type 1 receptor, thereby modulating the activity of the rennin-angiotensin-aldosterone system. Angiotensin II receptor blocker therapy has been proven to be well tolerated and effective in the management of hypertension, chronic heart failure with left ventricular dysfunction and the prevention and progression of diabetic renal disease. Candesartan is a highly potent, long-acting and selective angiotensin II type 1 receptor blocker [1]. Candesartan cilexetil is among the newest drugs in the class that includes losartan, irbesartan, and valsartan. Candesartan cilexetil has more than 1000 times more affinity for the angiotensin II, type AT1 receptor ARBs, and the binding affinity and competitive angiotensin II receptor antagonism is stronger than that of losartan. Candesartan cilexetil has demonstrated reductions in blood pressure comparable to those of enalapril, with the rate of adverse events greater in the enalapril group. Dosage adjustments are not necessary in elderly patients or in patients with mild hepatic or renal dysfunction. In diabetic patients, blood glucose, hemoglobinA1c, and serum lipids are

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not affected. Clinical studies have demonstrated that the adverse effect profile of candesartan cilexetil was similar to that of a placebo and there were no dose-dependent adverse effects.

Parkinson's disease (PD) is a neurodegenerative disorder in which motor symptoms are initially predominant; however, as the disease progresses, cognitive deterioration becomes more evident. In fact, depressive symptoms commonly occur in Parkinson's disease (PD), affecting approximately 40% of patients in cross-sectional studies [2-4]. Depressive symptoms have also been recognized to be a major determinant of health-related quality of life in PD, and can affect functional ability, cognitive function, and caregiver quality of life [2-7]. Psychotic symptoms in Parkinson's disease (PD) have consistently been shown to be associated with poor outcome. PD psychosis tends to emerge later in the disease course, and disease duration represents one risk factor for its development. The use of anti-PD medications (particularly dopamine receptor agonists) has been the most widely identified risk factor for PD psychosis. Other risk factors discussed in the literature include older age, disease severity, sleep disturbance, cognitive impairment, dementia and/or depression. Recent efforts have aimed to explore the complex pathophysiology of PD psychosis, which is now known to involve an interaction between extrinsic, drug-related and intrinsic, disease-related components. The most important extrinsic factor is use of dopaminergic medication, which plays a prominent role in PD psychosis. When reduction in anti-PD medications to the lowest tolerated dose does not improve psychosis, further intervention may be warranted. Several atypical antipsychotic agents (i.e. clozapine, olanzapine) have been shown to be efficacious in reducing psychotic symptoms in PD. In the present study, we investigated the effect of candesartan cilexetil on Parkinsonian symptoms as well as mental symptoms in patients with hypertensive PD.

Patients and Methods

Clinical assessment

The subjects of this study include three groups; Group 1, hypertension with PD (n=16), Group 2, hypertension without PD (n=9), and Group 3 (n=10), normal controls. All were selected from Japanese patients who had been treated at Tokushima University Hospital or Tokushima National Hospital from April 2006 to January 2008 and who had agreed to participate in the study. The diagnosis of hypertension was based on old World Health Organization criteria and new World Health Organization/International Society of Hypertension criteria. The PD patients fulfilled the following criteria by Calne at al. [8] and they all responded to at least some anti-Parkinson drugs. All hypertensive patients received oral administrations of candesartan cilexetil (8 mg/day). Other therapies, including anti-Parkinson drugs, remained unchanged during the study. The patients were evaluated two, four and six months after treatment by a measurement of blood pressure while in a sitting position, the Hospital Anxiety and Depression Scale (HADS), the Parkinson's Disease Questionnaire (PDQ)-39, the Self-rating Depression scale (SDS) [9], the Unified Parkinson's Disease Rating Scale (UPDRS) [10], and the WHO Subjective Well-being Inventory (SUBI). The HAD is a self-screening questionnaire for depression and anxiety. It consists of 14 questions - seven for anxiety and seven for depression [11,12]. The PDQ-39, the most widely used Parkinson's Disease specific measure of health status, contains thirty-nine questions, covering eight aspects of quality of life [13]. We classified the SUBI scales as the mental health degree (positive feelings) and the fatigue (negative feelings) of the heart, and called these positive SUBI and negative SUBI, respectively.

Statistical analysis

We used StatView for Windows (version 5.0) for statistical analysis. Non-paired data and paired data were analyzed by the non-parametric Mann-Whitney U test and Wilcoxon's signed rank test, respectively.

Results

In this study, data from patients with PD and hypertension (Group 1) were compared with those from age-matched controls; Group 2, hypertension without PD (n=9), and Group 3 (n=10), normal controls. The mean (± SE) age was Group 1, 68.7±2.5 y; Group 2, 63±2.5 y; Group 3, 66.1±4.4 y. Oral administrations of candesartan cilexetil (8 mg/day) rapidly reduced blood pressure, which was normalized in both Group 1 and Group 2 from two months after the start of this drug (data not shown). We assessed Parkinsonian symptoms as well as mental function using the UPDRS, PDQ-39, SDS,

HAD, and SUBI.
Figure 1 shows the profiles of depression scale. Scores of the SDS (Figure 1A), HAD-depression (Figure 1B) and HAD-anxiety (Figure 1C) were significantly increased in patients with PD compared with those in controls ($p<0.05$). In Group 1, HAD-anxiety scores were significantly decreased six months after the therapy ($p<0.05$); however, SDS and HAD-depression scores

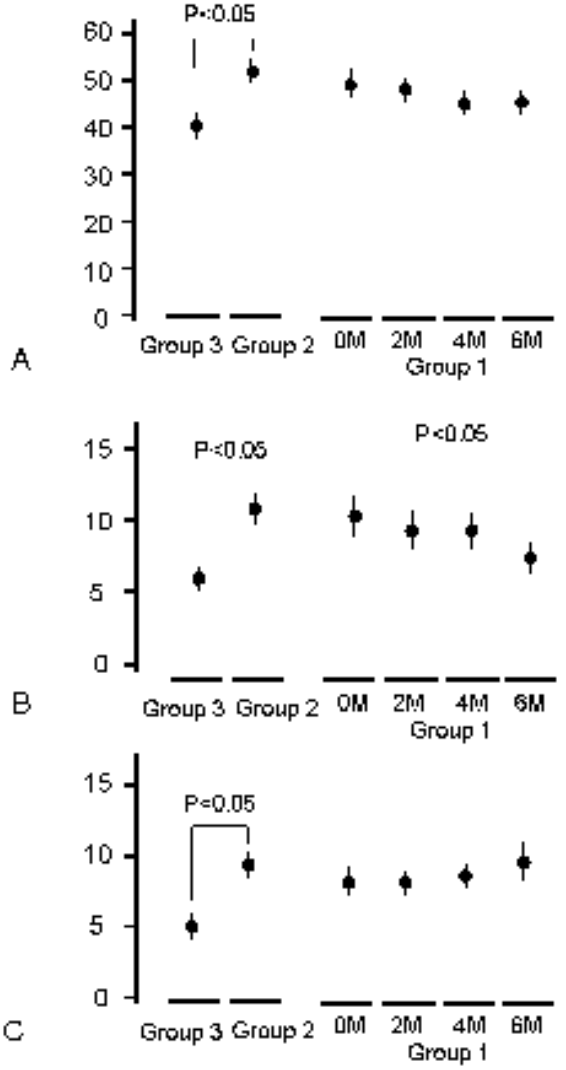

Figure 1. Scores of the SDS (A), HAD-depression (B) and HAD-anxiety (C) during candesartan therapy. Group 1, hypertension with PD (n=16), Group 2, hypertension without PD (n=9), and Group 3 (n=10), normal controls. Scores of SDS, HAD-depression and HAD-anxiety were significantly increased in patients with PD compared with those in controls ($p<0.05$). In Group 1, HAD-anxiety scores were significantly decreased six months after the therapy ($p<0.05$); however, SDS and HAD-depression scores were not significantly changed during the therapy

were not significantly changed during the therapy.

Figure 2 shows the effect of candesartan cilexetil on PD-related motor and/or mental symptoms. Total scores of the UPDRS (parts 1-4) were significantly decreased six months after the therapy, but scores of individual parts were not significantly changed. Scores of the PDQ-39 were significantly increased in patients with PD ($p<0.05$). In group 1, scores of the PDQ-39 were significantly decreased four months and six months after

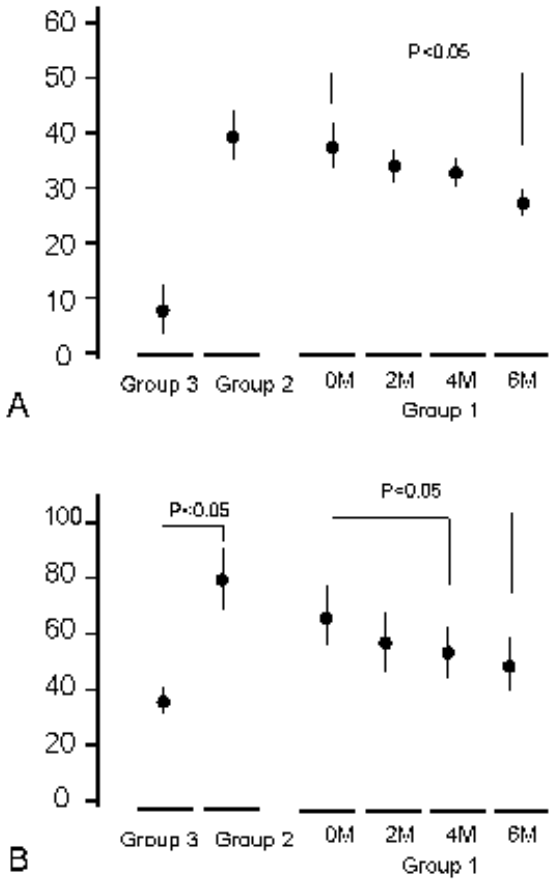

Figure 2. The effect of candesartan cilexetil on PD-related motor and/or mental symptoms. Group 1, hypertension with PD (n=16), Group 2, hypertension without PD (n=9), and Group 3 (n=10), normal controls. Total scores of the UPDRS (A) were significantly decreased six months after the therapy, but scores of individual part were not significantly changed. Scores of the PDQ-39 (B) were significantly increased in patients with PD ($p<0.05$). In group 1, scores of the PDQ-39 were significantly decreased four months and six months after candesartan therapy.

candesartan therapy.
We carried out further examination of mental status using the SUBI. Neither the scales of positive SUBI or negative SUBI were

significantly changed in patients with PD compared with those of controls. In addition, these scales were not significantly changed during candesartan therapy.

Discussion

Extensive studies have been focused on the risk factors of Parkinson's disease [14,15]. The most frequently mentioned risk factors are: 1. Age: most people who suffer from it are over 60 years of age; 2. Sex: in most epidemiological studies there are no differences to be found in prevalence of PD according to sex; 3. Genetic: no gene has been identified as being responsible for idiopathic PD.; 4. Craneoencephalic trauma: this factor can have a systematic bias; 5. Neurotoxins: a great deal of research has been focused on the relation between PD and direct or indirect exposition to compounds such as MPTP; 6. Antioxidants: it is thought that if ingested in sufficiently high quantities, either as part of the diet or in the form of supplements, they might reduce the risk of PD; 7. Smoking: several studies have shown a negative relation [14]. There are several RF for PD, although no single decisive triggering factor has been found to date. Epidemiologic studies of vascular conditions as risk factors for PD have also been carried out. A decreased risk of PD has been associated with a history of diabetes, and this effect was stronger in men and particularly in male nonsmokers [16]. Results of this large prospective study suggest that Parkinson's disease risk is not significantly related to history of hypertension, hypercholesterolemia, or diabetes but may modestly decline with increasing blood cholesterol levels [15]. Therefore, hypertension may be accidentally complicated by Parkinson's disease in the patients of Group 1.

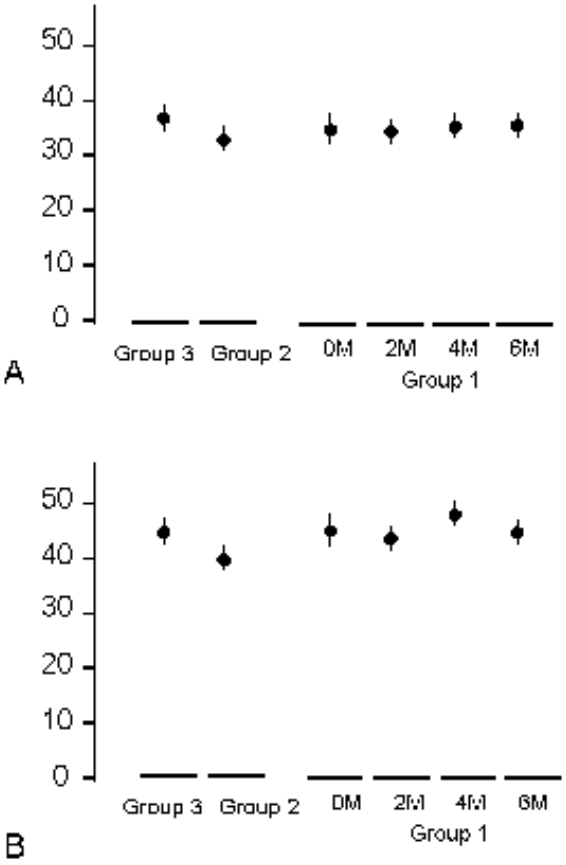

Figure 3. Scores of positive SUBI (A) and negative SUBI (B). Neither the scales of positive SUBI or negative SUBI were significantly changed in patients with PD compared with those of controls. In addition, these scales were not significantly changed during candesartan therapy.

ARB shows various effects other than a depression effect. Candesartan decreased blood glucose levels in patients with hypertension [17]. This agent provided effective migraine prophylaxis, with a tolerability profile comparable with that of placebo [18]. In the present study, we found beneficial effects of candesartan cilexetil on blood pressure levels as well as on Parkinsonian symptoms. We assessed Parkinsonian symptoms as well as mental function using the UPDRS, PDQ-39, SDS, HAD, and SUBI. The HAD-anxiety scores, total scores of the UPDRS (parts 1-4), and scores of the PDQ-39 were significantly decreased six months after the therapy. To our knowledge, this is the first report that has mentioned an anti-Parkinsonian effect of ARB. Although little is known about the effect of the ARB on dopaminergic neurons, there is also a possibility that placebo effect may play an important role in the development of Parkinsonism. Alternatively, candesartan may reduce mental disorders associated with hypertension. Further studies are required to investigate the effect of ARB on motor or mental symptoms of Parkinson's disease.

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