Effects of the 5-HT$_{2A}$ Receptor Antagonist Sarpogrelate in Diabetic Patients with Complications
A Pilot Study

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Abstract

Objective: To investigate whether the newly developed selective serotonin (5-hydroxytryptamine$_{2A}$; 5-HT$_{2A}$) receptor antagonist sarpogrelate is effective in patients with diabetes mellitus in whom lower limb circulatory disorders were suspected.

Design and Setting: Open-label prospective study conducted in 23 hospitals in the central area of Honshu, Japan.

Patients: One hundred and nine patients with diabetes mellitus in whom lower limb circulatory disorders were suspected.

Interventions: Sarpogrelate, a selective 5-HT$_{2A}$ receptor antagonist, was administered at a dosage of 100mg three times daily for 3 months.

Main Outcome Measures: Ankle pressure index (API), vibratory sensation threshold determined using a C64 quantitative tuning fork, motor nerve conduction velocity, subjective symptoms (coldness, numbness, spontaneous pain, etc.), and blood serotonin levels.

Results: Ninety-nine patients were available for efficacy evaluations. The vibratory sensation threshold showed a positive correlation with API ($r = 0.358$, $p = 0.0015$) and motor nerve conduction velocity ($r = 0.507$, $p = 0.0002$) in patients with suspected blood flow deficiency and API $\leq 0.9$, indicating that it is useful as a clinical marker. The test drug significantly increased API ($p < 0.05$) and improved coldness, numbness and spontaneous pain. The vibratory sensation threshold, a marker for neurological disorders, increased significantly ($p = 0.004$). Lower limb peroneal motor nerve conduction velocity increased significantly in patients in whom it was $\leq 40$ m/sec before treatment ($p < 0.05$). Blood serotonin levels increased significantly after treatment ($p < 0.01$), suggesting that the test drug inhibits the release of serotonin from platelets. Adverse events (allergic symptoms, anaemia, headache, anorexia and nausea) occurred in eight of 109 patients (7.3%). All adverse events disappeared during treatment or after its discontinuation, and none was serious.
Conclusions: Sarpogrelate is well tolerated and the present results suggest that it is useful for both lower limb circulatory disorders and neuropathy associated with diabetes mellitus.

The prevalence of diabetes mellitus is expected to increase in most parts of the world,[1] and is rapidly increasing in Japan because of changing demography, aging of the population, and environmental changes such as a higher standard of living. According to a report released by the Ministry of Health and Welfare, Japan, in March 1998, the number of patients diagnosed with diabetes is estimated to exceed 6 million, while that of borderline patients at high risk of becoming diabetic is believed to be nearly 7 million.

Management and treatment of complications in diabetic patients in addition to the treatment of diabetes are important.[1] In particular, diabetic macroangiopathy is a determinant of the long-term prognosis of diabetic patients. Cerebrovascular disorders and peripheral arterial occlusion seriously affect patients’ quality of life. Recently, there has been progress in research in the field of diabetes. Our knowledge of its aetiology and pathology has increased over the past decade, leading to the development of a number of new, more effective drugs. However, few effective therapies for diabetic macroangiopathy have been made clinically available because many environmental, genetic and other factors are involved in this disorder.

A number of studies in recent years have shown that serotonin (5-hydroxytryptamine; 5-HT), a physiological amine that has been known for many years, is closely related to the regulation of blood flow in impaired blood vessels.[2-5] Serotonin has more receptor types than amines such as noradrenaline, and plays various roles in the body.[4] Recent studies have shown that it plays a major role in the development and progression of the vascular complications of diabetes.[6,7] However, only a few clinical studies have evaluated the effects of 5-HT₂A receptor antagonists on the clinical symptoms and objective markers of lower limb circulatory disorders and neuropathy associated with diabetes.[8] Therefore in the present study we evaluated the clinical efficacy of sarpogrelate, a selective 5-HT₂A receptor antagonist,[9] in treating vascular and neurological complications of diabetes.

Patients and Methods

Patients

Patients with diabetes mellitus in whom lower limb circulatory disorders were suspected were enrolled after obtaining written informed consent. Ethical approval for this study was obtained from the local research ethics committee.

At the time this study was conducted, the diagnostic criterion for diabetes in Japan was a fasting plasma glucose level of 140 mg/dl or higher or a 75g oral glucose tolerance test 2-hour value of 200 mg/dl or higher. A specialist at each participating institution made a diagnosis of diabetes based on these criteria. Patients enrolled in the study were undergoing alimentary therapy, taking oral hypoglycaemic drugs, or receiving treatment with insulin. Patients with both type 1 and type 2 diabetes were included. The ankle pressure index (API) is generally measured to diagnose vascular complications, but in Japan a partial modification of Fontaine’s severity classification is used for clinical diagnosis (grade I, coldness, numbness; grade II, intermittent claudication; grade III, resting pain; grade IV, ulcer, necrosis). In this study, patients with one or more of the above symptoms (coldness, numbness, intermittent claudication, pain and ulcer/necrosis) were investigated to explore the effectiveness of sarpogrelate against vascular complications of diabetes.

Protocol

In the open-label prospective study conducted in 23 hospitals in central Honshu, Japan, sarpogrelate 100mg three times daily (Mitsubishi Chem-