Therapeutic Effect of Sarpogrelate, a New 5-Hydroxytryptamine Receptor 2A Antagonist, on Diabetic Nephropathy and Neuropathy

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Dear Sir,

Serotonin (5-hydroxytryptamine), which abounds in the dense granules of platelets, is released from platelets in case of injury and induces aggregation of platelets and contraction of vascular smooth muscle cells; however, under pathologic conditions such as atherosclerosis and ischemia of peripheral tissues, it contributes to the aggravation of atherosclerotic lesions and peripheral ischemia [1]. These actions of serotonin are exerted via 5-hydroxytryptamine receptors 2A (5-HT_{2A}) [1]. Sarpogrelate, a new 5-HT_{2A} receptor antagonist, inhibits serotonin-induced vasoconstriction and platelet aggregation [2] and has clinically been used to treat arteriosclerosis obliterans since 1993 in Japan. 5-Hydroxytryptamine receptors, recently identified as 5-HT_{2A}, have also been demonstrated in glomerular mesangial cells [3-5], which play a key role in glomerular sclerosis through proliferation and matrix synthesis in response to various stimuli [6]. Disturbance of microvascular circulation is one of the mechanisms in the pathogenesis of diabetic neuropathy [7, 8]. Thus, sarpogrelate could serve as a therapeutic agent for diabetic nephropathy and neuropathy. Accordingly, we performed a clinical evaluation of the usefulness of sarpogrelate in diabetic nephropathy and neuropathy.

Eight type II diabetes mellitus (DM) patients who gave their informed consent were enrolled (table 1). All the patients regularly visited the Outpatient Clinic of our Hospital every 2 weeks. They presented peripheral numbness, dysesthesia and decreased deep tendon reflex, while 2 of them also had neuropalgia (patients No. 4 and 8). A history of exposure to heavy metals or organic solvents was denied in all patients. Twenty-four-hour urinary albumin and transferrin excretions were 6.6-172 and 0.4-23.3 mg/day, respectively, indicating that all patients had mild diabetic nephropathy. None had overt proteinuria or elevated levels of serum creatinine (serum creatinine of all patients was less than 1.0 mg/dl). They were started on sarpogrelate at a dose of 300 mg/day (100 mg t.i.d., orally), and the changes in neurological signs and symptoms were checked at

regular visits of every 2 weeks. Both the 24-hour urinary albumin and transferrin excretions were measured at 1 and 3 months after sarpogrelate administration. Three months after the start of sarpogrelate administration, there were 3 patients in whom neurological symptoms, such as numbness and dysesthesia, had remarkably improved (patients No. 2, 3 and 8). In 1 patient (patient No. 8), painful neuropathy subsided in 3 months and analgesics (loxoprofen) could be discontinued. Both the 24-hour urinary albumin and transferrin excretions decreased in all the 3 patients who showed improvement of neuropathy, while they increased in all the remaining 5 patients. Since the 24-hour urinary albumin and transferrin excretions differed considerably among the 8 patients, the ratio of urinary albumin and transferrin excretions at 1 and 3 months to those at the start of sarpogrelate administration was calculated (fig. 1). At 1 month after the start of sarpogrelate administration, the ratio of urinary albumin excretion in the 3 neurologically improved patients was 0.548 ± 0.234 (mean $\pm$ SD) and that in the remaining 5 patients 1.986 ± 0.914 ($p < 0.05$, Student t test); at 3 months, the ratio in the 3 patients was 0.773 ± 0.345 and that in the 5 patients 1.973 ± 0.532 ($p < 0.02$). At 1 month after the start of sarpogrelate, the ratio of urinary transferrin excretion in the 3 patients was 0.495 ± 0.200 and that in the 5 patients 2.022 ± 0.837 ($p < 0.03$); at 3 months, the ratio in the 3 patients was 0.559 ± 0.164 and that in the 5 patients 2.640 ± 1.578 ($p = 0.063$). Between the 3 neurologically improved patients and the remaining 5 patients, there were no statistical differences in age, sex, body mass index, fasting plasma glucose, glycohemoglobin A1c, urinary albumin excretion and urinary transferrin excretion before the administration of sarpogrelate. Throughout the study period, no significant changes in blood glucose control were seen (fasting plasma glucose and hemoglobin A1c was 203 ± 75 mg/dl and $8.2 \pm 2.4\%$ at the start, and 178 ± 60 mg/dl and $7.8 \pm 2.2\%$ at the end, respectively), and the changes were not statistically different between the 3 and the 5 patients. Medication remained unchanged throughout the 3-month period. These findings demonstrated, for the first time, that sarpogrelate is a potential therapeutic agent for diabetic nephropathy and neuropathy in some patients with type II DM. Furthermore, all the 3 patients who showed neurological improvement also showed a decrease in both urinary albumin and transferrin excretion, the latter of which

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Months after sarpogrelate administration

Fig. 1. Changes in the ratio of urinary albumin (a) and transferrin (b) excretions at 1 and 3 months after sarpogrelate administration compared to those at the start. O = Changes in 3 patients whose neuropathy was improved after sarpogrelate administration; • = those in the remaining 5 patients.

Ratio

Ratio

Table 1. Patients' list, clinical characteristics before sarpogrelate administration and neurological symptoms 3 months after sarpogrelate administration

has recently been demonstrated to be a useful marker for the evaluation of the early stage of diabetic nephropathy [9]. These results suggest that pharmacological effects of sarpogrelate on the peripheral nervous system, such as an effect on improvement of microvascular circulation [2], also work similarly in the kidney, leading to both improving neurological symptoms and reducing urinary proteins. As for the relationship between serotonin and diabetic complications, elevated plasma levels of serotonin have been reported in DM patients, suggestively contributing to diabetic complications [10, 11]. In addition, Malyszko et al. [11] further reported that the response of platelets to serotonin is enhanced in patients with type II DM, compared to healthy controls, suggesting that serotonin contributes to the worsening of diabetic complications. Taken together, the present clinical trial indicates that sarpogrelate, a new 5-HT_{2a} antagonist, is a potential new agent for the treatment of diabetic nephropathy and neuropathy in some patients, in whom microvascular circulation disturbances caused by elevated plasma serotonin and enhanced serotonin responsiveness may be related to their patho-genesis, even though large clinical trials employing placebo controls are certainly needed to confirm it.

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