Clinical Effect of Dipyridamole in Patients with IgA Nephropathy

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Clinical effects of dipyridamole and carbazochrome sodium sulfonate in patients with IgA nephropathy are described. Oral administration of 300mg of dipyridamole and 180mg of carbazochrome sodium sulfonate per day was employed in the present study. Urinalysis and renal function tests, i.e. serum creatinine (s-Cr), blood urea nitrogen (BUN), glomerular filtration rate (GFR) and phenolsulfonphthalein (PSP) tests, were performed before and after the administration of dipyridamole. It was demonstrated that the administration of dipyridamole was effective in reducing the level of proteinuria in the patients. The administration of carbazochrome sodium sulfonate was not effective in reducing the proteinuria level. It was concluded that the administration of dipyridamole may be useful for treatment of patients with IgA nephropathy.

(Key Words: dipyridamole, carbazochrome sodium sulfonate, proteinuria, IgA nephropathy)

INTRODUCTION

IgA nephropathy is characterized by mesangial deposition of IgA with lower intensities of IgG, IgM and/or C3 in immunofluorescence (1, 2, 5). Generally, IgA nephropathy is considered to be an immune-complex-mediated glomerulonephritis (7). However, there is no specific treatment for patients with IgA nephropathy. Previous approaches have included tonsillectomy, immunosuppressive drugs, phenytoin and plasma exchanges (2). In Japan, antiplatelet drugs such as dipyridamole and non-steroidal anti-inflammatory drugs such as ibuprofen or aspirin have generally been used for patients with chronic glomerulonephritis including IgA nephropathy (3, 4). Carbazochrome sodium sulfonate which is effective in preserving the permeability of capillary walls is also used for hematuria in patients with IgA nephropathy.

The purpose of the present study was to determine if dipyridamole and carbazochrome sodium sulfonate improves the clinical findings such as proteinuria and/or hematuria in patients with IgA nephropathy.

MATERIALS AND METHODS

Patients: Thirty three patients with IgA nephropathy, 11 patients with chronic mesangial proliferative glomerulonephritis (PGN) (non-IgA nephropathy) and four patients with membranoproliferative glomerulonephritis (MPGN) were examined. Patients with IgA nephropathy whose biopsy specimens were stained predominantly for IgA in glomerular mesangial areas were included in this study after exclusion of patients with systemic lupus erythematosus, Henoch-Schoenlein purpura, liver cirrhosis or other systemic diseases. The histopathological changes of IgA nephropathy were classified in our studies as described previously (7). In brief, the minimal change (Grade I) is characterized by minimal thickening of mesangial areas. The slight stage (Grade II) showed mild thickening of mesangial areas with mild mesangial cell proliferation. The moderate stage (Grade III) was characterized by diffuse mesangial thickening, mesangial cell proliferation and segmental thickening of glomerular capillary walls. In addition to the changes observed in the moderate stage, an ad-
advanced stage (Grade IV) showed marked capsular adhesion, fibrocellular crescents, glomerular hyalinosis and/or sclerosis. All of these patients showed moderate or advanced stage of IgA nephropathy. The patients were all outpatients in the Nephrology Clinic of Tokai University Hospital.

**Drug administration procedures:** Carbazochrome sodium sulfonate (Adonae®, Tanabe Pharmaceutical Co. Ltd., Tokyo, Japan) was administered to all 33 patients at doses of 180 mg per day t.i.d. Among these patients, dipyridamole (Persantin®, Nippon Boehringer Ingelheim, Tokyo, Japan) was administered to 22 patients in the dipyridamole group at doses of 300 mg per day t.i.d. for 1–6 months (mean: 3.4 months). These dosages of carbazochrome sodium sulfonate or dipyridamole are used in many hospitals in Japan. The structural formulas of these drugs are shown in Fig. 1.

**Disease activity:** Urinalysis for proteinuria and hematuria was also performed before and after the study. Total amounts of proteinuria per day were quantitated repeatedly using Urimate®–P (Sumitomo Bakelite Co., Ltd. Tokyo, Japan). Since 1/50 of the urine output for 24 hr was accurately obtained by Urimate®–P, it was easy to quantitate the amounts of proteinuria per day in an outpatient clinic. Effects of dipyridamole or carbazochrome sodium sulfonate in improving proteinuria were divided into three grades as follows: improvement (more than 0.25 g/day), no change (0.00–0.24 g/day) and aggravation. An average of more than one red blood cell in a microscopic field under high-power magnification (×400) of urinary sediments was defined as microscopic hematuria. The following clinical examinations were performed before and after the study: levels of serum creatinine (s-Cr), blood urea nitrogen (BUN) and blood or urinary fibrinogen degradation products (FDP). Glomerular filtration rate (GFR) and the phenolsulfonphthalein (PSP) test were also examined before and after the study. Statistical significance was evaluated by Fisher's test and the Mann-Whitney U test.

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**Fig. 1** Structural formulas of dipyridamole (Fig. 1-1) and carbazochrome sodium sulfonate (Fig. 1-2)
RESULTS

The results of the present study are summarized in Tables 1, 2 and 3.

(a) Effects of proteinuria

Improvement in proteinuria after the administration of dipyridamole was observed in 11 out of 22 patients (50.0%) with IgA nephropathy treated with dipyridamole and carbazochrome sodium sulfonate. No change in proteinuria after such administration was seen in the remaining 11 patients (50.0%). Improvement in proteinuria was observed in three out of 11 patients (27.3%) treated with carbazochrome sodium sulfonate without dipyridamole. No change or aggravation after such administration was found in five and three out of 11 patients (45.5% or 27.3%), respectively, in the group treated with carbazochrome sodium sulfonate without dipyridamole. Improvement in proteinuria after administration of dipyridamole and carbazochrome sodium sulfonate (dipyridamole group) was significantly more frequent than that after administration of carbazochrome sodium sulfonate without dipyridamole (non-dipyridamole group) in patients with IgA nephropathy ($\chi^2 = 6.9241, P < 0.05$) (Table 1). There were significant differences in effects of dipyridamole on proteinuria among the patients with IgA nephropathy and those with other glomerular diseases ($\chi^2 = 6.1022, P < 0.05$) (Table 2).

(b) Effects on hematuria

Improvement in hematuria after the administration of dipyridamole was observed in two out of 22 patients (9.1%) in the dipyridamole group of IgA nephropathy cases. No change or aggravation was observed in 19 or one out of 22 patients (86.4% or 4.5%) in the dipyridamole group of IgA nephropathy cases, respectively. No improvement in hematuria after the administration of carbazochrome sodium sulfonate without dipyridamole was observed in any of the patients. No change or aggravation after such administration was observed in eight and three out of 11 patients (72.7% or 27.3%) in the non-dipyridamole group of IgA nephropathy cases, respectively.

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<tr>
<th>Table 1</th>
<th>Clinical effects of dipyridamole on proteinuria in patients with IgA nephropathy</th>
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<td></td>
<td>Improvement</td>
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<tr>
<td>Dipyridamole group</td>
<td>11</td>
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<td>Non-dipyridamole group</td>
<td>3</td>
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<td>$\chi^2 = 6.9241, P &lt; 0.05$</td>
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<th>Table 2</th>
<th>Clinical effects of dipyridamole on proteinuria in patients with IgA nephropathy and other glomerular diseases</th>
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<tr>
<td></td>
<td>Improvement</td>
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<td>IgA nephropathy</td>
<td>11</td>
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<td>Other glomerular diseases (n = 9)</td>
<td>2</td>
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<td>$\chi^2 = 6.1022, P &lt; 0.05$</td>
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<th>Table 3</th>
<th>Clinical effects of dipyridamole on hematuria in patients with IgA nephropathy</th>
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<td>Improvement</td>
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<td>Dipyridamole group</td>
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<td>Non-dipyridamole group</td>
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<td>$\chi^2 = 4.2916, P &gt; 0.1$</td>
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Hematuria after the administration of dipyridamole and carbazochrome sodium sulfonate (dipyridamole group) was not significantly improved compared with that after the administration of carbazochrome sodium sulfonate without dipyridamole (non-dipyridamole group) in patients with IgA nephropathy ($\chi^2=4.2916, P>0.1$) (Table 3). There were no significant differences in effects of dipyridamole on hematuria among patients with IgA nephropathy and those with other glomerular diseases ($\chi^2=1.3200, P>0.1$).

(c) Laboratory data of patients with IgA nephropathy

Although improvement in proteinuria was observed in some patients in the dipyridamole group as well as the non-dipyridamole group of IgA nephropathy cases, there were no significant differences in the levels of s-Cr, BUN, or blood or urinary FDP examined both before and after the administration of dipyridamole. There were no significant differences in the values of GFR or PSP tests both before and after the administration of dipyridamole. There were no side effects of dipyridamole and/or carbazochrome sodium sulfonate such as headache, nausea, hepatitis or fever in patients with IgA nephropathy and other glomerular diseases throughout the study.

DISCUSSION

The present study showed that dipyridamole was effective in reducing the amount of proteinuria in some patients with IgA nephropathy. In short-term administration, i.e. a mean of 3.4 months, 300 mg of dipyridamole was effective in improving proteinuria in patients with IgA nephropathy. However, none of the patients given dipyridamole administration showed disappearance of proteinuria during the study period. Improvement of proteinuria in patients in the dipyridamole group was significantly more frequent than that in patients in the non-dipyridamole group among patients with IgA nephropathy. No side effects were observed in any patient during administration of dipyridamole and/or carbazochrome sodium sulfonate.

IgA nephropathy is a well-recognized clinicopathologic entity that was first described by Berger 1969 (1). Although IgA nephropathy is generally considered to be an immune-complex-mediated glomerulonephritis, there is no specific treatment for this disease. It is considered that platelet aggregation is one of the exacerbating factors in glomerular injuries in patients with IgA nephropathy (6, 8, 9). In Japan, antiplatelet drugs such as dipyridamole, and non-steroidal anti-inflammatory drugs such as ibuprofen or aspirin are frequently used for patients with IgA nephropathy (3, 4). Dipyridamole has several pharmacological actions as follows: (a) inhibition of thromboxan A2 synthesis and cyclic-AMP-phosphodiesterase activity in platelets, (b) release of prostacycline from vascular walls and (c) increasing the anionic charged barrier on the glomerular basement membrane. On the other hand, the actions of carbazochrome sodium sulfonate are generally considered to be preservation of the permeability of capillary walls, and increases in the vascular resistance. Shigematsu et al. (6) reported that one third of IgA nephropathy patients had acute necrotizing capillary loop lesions where local activation of the coagulation process played an important role in injury of the glomerular capillary loops. It has been postulated that the addition of segmental lesions with active coagulation to slowly progressive sclerotic glomerular lesions may accelerate glomerular deterioration. Recently, Woo et al. (8) reported the elevation of beta-thromboglobulin (a platelet specific protein released during platelet aggregation) concentration in plasma from patients with various types of glomerulonephritis. Woo et al. (9) also reported that plasma antithrombin III (a naturally occurring coagulation inhibitor) may play a role in the disease activity in patients with IgA nephropathy. The present study showed that the administration of dipyridamole was effective in decreasing proteinuria in some patients in moderate or advanced stages of IgA nephropathy. Although rebiopsy of patients after treatment with dipyridamole was not performed for ethical reasons, it is assumed that the administration of dipyridamole might influence the clinical course of these histopathological changes in patients with IgA nephropathy. However, administration of dipyridamole was not effective in reducing the degree of hematuria in these patients. On the other hand, carbazochrome sodium sulfonate which affects the
stabilization of capillary walls was used for hematuria in patients with IgA nephropathy as well as other glomerular diseases. We have used this drug for patients in the minimal or slight stage of IgA nephropathy. In the present study, the administration of carbazochrome sodium sulfonate was not effective in reducing the degree of hematuria and/or proteinuria in patients in the moderate or advanced stage of IgA nephropathy.

It was concluded that the administration of dipyridamole may be useful for the improvement of proteinuria in patients with IgA nephropathy. Further clinical trials on dipyridamole in patients with other glomerular diseases are warranted.

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