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Influence of cyclosporin A (CyA) on renal handling of urate

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Hyperuricaemia is a frequent side-effect of cyclosporin A (CyA) therapy in renal transplant patients [1, 5–7, 11], and gout arthritis is the cause of considerable morbidity among these patients [5, 7, 8, 10, 11]. However, neither the potential predisposing factors nor the mechanisms of hyperuricaemia have been clearly elucidated. It has been reported that hyperuricaemia in patients on CyA is associated with a lowered glomerular filtration rate, or with a reduced urate clearance [2, 5, 7, 8, 10], due to an increase in the net tubular urate reabsorption or to a decrease in secretion [2, 5]. These conclusions are mostly supported by measurements of the basal clearance rate and fractional excretion of urate, but more precise studies of renal handling of urate by the renal tubule have seldom been performed [2]. The purpose of our study was to investigate the prevalence of hyperuricaemia in our population of renal transplant patients, as well as the risk factors involved. Furthermore, we have evaluated the mechanism of hyperuricaemia by a combined pyrazinamide and probenecid test allowing a better evaluation of urate transport processes than pyrazinamide alone.

Key words: Renal transplantation – Urate excretion – Cyclosporin A

Patients and methods

For the hyperuricemia prevalence study, 169 renal transplant-patients were selected, all of whom had stable graft function and serum creatinine lower than 2 mg/dl. The group comprised 96 males and 73 females, with a mean age of 38 ± 12 years, 80 on azathioprine (Aza) and 89 on CyA. Patient records were reviewed and the following data collected at 12 months: serum and urine urea, creatinine and urate, serum potassium and total CO_2 and the drugs taken at this time. Hyperuricaemia was considered to be present when serum urate level was greater than 8 mg/dl in males and 6.5 mg/dl in females.

The renal handling of urate was studied by a combined pyrazinamide and probenecid test in 31 selected renal transplant patients. All had normal renal function, no clinical evidence of chronic rejection and no history of renal calculi, and none was receiving diuretics or other drugs that alter the synthesis or excretion of urate. The patients were divided into two groups: group 1 comprised ten hyperuricaemic patients on CyA, and group 2 (the control group) comprised 21 normouricaemic patients, (nine on CyA and 12 on Aza.

The combined pyrazinamide and probenecid test consisted of two parts. After two 30-min basal clearances, a single dose of probenecid (2 g) was given orally and four 30-min clearances performed. Pyrazinamide (3 g) was then administered orally, and four additional 30-min clearance studies were performed from 60 to 180 min after pyrazinamide. Maximal uricosuria in the 2 h after probenecid and minimal uricosuria in the 3 h after pyrazinamide were chosen to determine maximal probenecid-induced uricosuria and maximal pyrazinamide inhibition on probenecid-induced uricosuria, respectively. Venous blood samples were obtained at minutes 0, 90, 150, 270 and 330 of the test. Urate, creatinine, sodium and potassium were determined in all blood and urine samples. Adequate urine flow was ensured by the administration of 500 ml tap water 20 min before the test and additional amounts equal to the voided volume after every urine collection. Calculations were performed as previously described [3].

Results

The clinical features of the renal transplant patients at 1 year are shown in Table 1. Hyperuricaemia was more frequent in patients receiving CyA, as was the mean serum urate. Furthermore, there was some degree of graft dysfunction in patients on CyA; serum creatinine was slightly higher and the total CO_2 was lower than in patients on Aza. Ages, sex ratio and percentage of patients on diuretics were similar in both groups. In the hyperuricaemic patients there was no difference in the serum creatinine in relation to immunosuppressive treatment (1.4 ± 0.4 mg/dl) in both groups of patients. However, 16 out of 18 hyperuricaemic patients on Aza (88.9%), and only 31 out of 53 hyperuricaemic patients

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Table 1. Clinical features of renal transplant patients according to immunosuppressive treatment

	Aza ($n = 80$)	CyA ($n = 89$)	P value
Sex (m/f)	51/29	45/44	NS
Age (yr)	38 ± 10	38 ± 13	NS
Serum urate (mg/dl)	6.1 ± 1.9	7.9 ± 1.9	< 0.001
Serum creatinine (mg/dl)	1.2 ± 0.3	1.4 ± 0.4	< 0.001
Serum total CO_2 (mEq/l)	25.5 ± 2.9	23.7 ± 2.8	< 0.001
No. of patients on diuretic (%)	39 (49)	36 (40)	NS
No. of patients with hyperuricaemia (%)	18 (24)	59 (60)	< 0.001

Table 2. Results of the combined pyrazinamide–probenecid test

	Group 1 ($n = 10$)	Group 2 ($n = 21$)	P value
Sex (m/f)	5/5	14/7	NS
Age (yr)	35 ± 15	42 ± 11	NS
Serum creatinine (mg/dl)	1.3 ± 0.3	1.2 ± 0.2	NS
Serum urate (mg/dl)	8 ± 1.5	5.5 ± 1.3	< 0.001
FE urate (%)[a]	30 ± 13	46 ± 13	< 0.01
Urate secretion (% fl)	21 ± 9.2	32 ± 11.6	< 0.01
Presecretory reabsorption	91 ± 4.7	89 ± 4.9	NS
Postsecretory reabsorption/secretion	113 ± 27	113 ± 19	NS

[a] During probenecid-induced uricosuria

on CyA (58.4%) were on diuretics ($P < 0.005$). When comparing the hyperuricaemic and normouricaemic patients on CyA, those with high serum urate had increased serum creatinine (1.4 ± 0.3 vs 1.2 ± 0.2 mg/dl, $P < 0.005$).

The pyrazinamide–probenecid test showed a lower fractional urate excretion (FE urate) during the maximal probenecid-induced uricosuria, and a lower urate secretion in hyperuricaemic patients (group 1). However, there were no differences in either the presecretory reabsorption or the postsecretory reabsorption, expressed as postsecretory reabsorption/secretion, between the two groups (Table 2). The lower FE urate in group 1 was associated with a lower urine volume (5.1 ± 2.8 vs 8.2 ± 3.6, $P < 0.05$), despite a similar water balance. Therefore, tubular urate secretion correlated with fractional sodium excretion ($r = 0.46$, $P < 0.05$).

Discussion

Our study confirms the high prevalence of hyperuricaemia among renal transplant patients on CyA, similar to that reported previously [1, 11]. Differences between our patient series and other series could be attributed to the selection of the patient population, to the definition of hyperuricaemia, or to the time when the study was carried out [6, 7]. We identified two risk factors associated with hyperuricaemia: renal dysfunction and treatment with diuretics. The higher serum creatinine and lower total serum CO_2 levels in patients on CyA would indicate that the existence of graft dysfunction could explain the higher prevalence of hyperuricaemia, as well as the differences in graft function, between normouricaemic and hyperuricaemic patients on CyA. However, a correlation between serum creatinine or creatinine clearance and serum urate levels has not always found, suggesting that renal failure is not the sole determinant of this rise in serum urate [1, 11]. Concerning the influence of diuretics on the development of hyperuricaemia, nearly 90% of patients on either Aza or CyA taking diuretics had high serum urate, but it should be noted that about 40% of hyperuricaemic patients on CyA were not receiving diuretics, and a direct effect of the CyA on urate metabolism could not be proved.

The mechanism causing hyperuricaemia remains uncertain. There is no increased endogenous production of urate [1, 5, 7], and most data support the notion that CyA decreases urate clearance by the kidney [2, 7, 8, 11]. Renal tubular handling of urate has four components: glomerular filtration, proximal tubular reabsorption, proximal tubular secretion and postsecretory reabsorption. CyA could induce hyperuricaemia by modifying several steps in urate excretion. The combined pyrazinamide–probenecid test shows that urate retention is mainly caused by a decrease in urate secretion in the renal tubule, as has been reported previously [2], and no abnormalities on reabsorption were detected. This finding could not be a consequence of renal insufficiency because both groups had the same degree of allograft function, but similar serum creatinine levels do not truly reflect similar renal function [9]. Furthermore, the decline in the glomerular filtration rate produces an adaptive decrease in urate presecretory and postsecretory reabsorption, and a later decrease in urate secretion [4]. The association of lower excretion of urate with a tendency to retain water and sodium by the kidney suggests that the impairment in urate secretion is linked to disorders in renal handling of water and sodium into the proximal tubule, probably mediated by haemodynamic changes induced by CyA.

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