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Subclinical impairment of distal renal acidification induced by low-dose cyclosporin A therapy

C. Quereda, C. Soria, N. Gallego, J. Sabater, M. Bermejo, J. Pascual, and J. Ortuño

Nephrology Department, Hospital Ramon y Cajal, Madrid, Spain

Abstract. Twenty-nine psoriasis patients on 5 mg/kg cyclosporin A (CyA) therapy were studied for 3 months using the furosemide test. Five of them (17%) showed an abnormal renal acidification capacity after furosemide administration: The urinary pH did not sink under 5.3 after furosemide, while the ammonium and titrable acid levels were significantly low. There were no significant differences from controls regarding the serum potassium or fractional potassium excretion. Nevertheless, the transtubular potassium gradient was lower in patients with an abnormal furosemide test result. We conclude that some patients treated with a low dose CyA therapy developed an abnormality in the distal tubular acidification.

Key words: Immunosuppression – Cyclosporine A – Toxicity

Cyclosporine A (CyA) nephrotoxicity remains the greatest concern in the long-term use of the drug. Several toxic CyA-related effects in tubular function have been described in laboratory animals and in humans, including an impairment of the distal acidification capacity [1, 7, 9, 11]. Nevertheless, most of the clinical studies have been performed in patients with disorders which potentially may alter renal function, making the interpretation of results difficult. In this sense, psoriasis (Ps) patients treated with CyA constitute an excellent model for studying CyA nephrotoxicity [4, 5]. The aim of this work was to investigate the response of the renal tubular mechanisms of acidification to furosemide administration in a group of Ps patients treated with a low CyA dose by analysing its relationship with other renal function parameters.

Offprint requests to: Dr. C. Quereda, Servicio de Nefrologia, Hospital Ramon y Cajal, Cta de Colmenar Viejo, Km 9.2, E-28034 Madrid, Spain

Material and methods

After informed consent, 29 patients (18 males, 11 females) aged 19–59 years (mean 39.5) with severe Ps and normal basal renal function were treated with CyA. The initial dose was 5 mg/kg per day, which was continued for 3 months unless significant clinical side-effects appeared. Then, the drug was slowly tapered off over the next 3 months or stopped in the case of inefficacy. The renal function and electrolyte changes were evaluated monthly by the measurement of creatinine clearance and levels of serum and urine creatinine (Cr), urea, uric acid, sodium, potassium, chloride, total CO_2, magnesium, calcium and phosphate. The fractional excretion (FE) of Na, K and the transtubular K gradient (TTKG) were calculated. The blood CyA level was determined in each analytical control. The renal response to a furosemide test (FT) was performed at the end of the 3 treatment months. The results were compared with those obtained in 13 Ps patients who had not yet been treated with CyA and also with those of 19 Ps patients studied 1 month after stopping CyA treatment. The FT was performed in the morning, more than 12 h after the intake of the last CyA dose. Furosemide 80 mg was administered by the oral route, and new urine samples were then obtained hourly (1, 2, 3, and 4 h after administration) to determine the pH, acidification parameters, and electrolyte levels. The urinary pH was measured after voiding using a pHmeter. Titratable acid (TA) was determined by titration to pH 7.4a and ammonium (NH_4) using the Berthelo's reaction. Hydrogen excretion was calculated as: $[H+] = TA + NH_4$ and net acid excretion as (NAE) = $[H+]\text{-}CO_3H$. The analysis of variance for repeated measures and the paired-data Student's *t*-test were used in the statistical analysis. Data are presented as means and standard error of the mean (SEM); a P value of less than 0.05 was considered significant.

Results

Ps patients on CyA treatment had higher serum Cr (0.99 ± 0.03 vs 0.82 ± 0.12 mg/dl, $P < 0.01$), urea (35.9 ± 1.6 vs 29.8 ± 1.8 mg/dl; $P < 0.01$), and urate (5.73 ± 1.4 vs 4.59 mg/dl; $P < 0.05$) values than untreated Ps patients. Contrarily, serum magnesium (1.79 ± 0.03 vs 2.04 ± 0.04 mg/dl; $P < 0.01$) and total CO_2 (23.9 ± 0.37 vs 25.4 ± 0.59 mmol/l; $P < 0.05$) levels were lower. Patients studied after CyA withdrawal did not show any significant differences in any parameter as compared with the basal group. The FE Na, FE K and TTKG did not show any signficant differences among the 3 groups. Significant gly-

Table 1. Urinary response to furosemide in psoriasis patients

Group		Normal FT (n = 24)	Abnormal FT (n = 5)	Differences (P <)
U pH	b	5.59 ± 0.07	5.80 ± 0.21	n.s.
	p	4.64 ± 0.04	5.70 ± 0.26	0.01
U TA[a]	b	13.2 ± 0.84	8.83 ± 0.30	n.s.
	p	19.9 ± 1.01	13.50 ± 1.46	0.05
U NH_4[a]	b	23.9 ± 1.99	16.3 ± 2.00	n.s.
	p	38.9 ± 2.70	24.6 ± 4.03	0.05
U H^+[a]	b	37.1 ± 2.20	26.0 ± 1.7	n.s.
	p	54.5 ± 3.09	36.5 ± 3.2	0.01
U CO_3H^-[a]	b	3.01 ± 0.70	3.0 ± 1.7	n.s.
	p	46.70 ± 7.20	45.5 ± 6.8	n.s.
FE Na (%)	b	0.57 ± 0.08	1.07 ± 0.37	n.s.
	p	9.90 ± 2.29	8.3 ± 0.77	n.s.
EF K (%)	b	10.2 ± 1.0	11.1 ± 1.67	n.s.
	p	42.1 ± 5.8	37.3 ± 6.10	n.s.
TTKG	b	6.35 ± 0.42	4.07 ± 0.99	0.05
	p	7.94 ± 0.72	6.38 ± 1.52	n.s.

Mean ± standard error of the mean
[a] µmol/min · 100 ml FG
b, basal, prefurosemide; p, peak value postfurosemide; FT, furosemide test; U, urinary; FE, fractional excretion; TTKG, transtubular potassium gradient; TA, titratable acid

cosuria was absent in all cases. The mean lowest level of the postfurosemide urinary pH was higher in CyA-treated than in untreated patients (4.87 ± 0.09 vs 4.59 ± 0.03, $P < 0.05$). The peak postfurosemide urinary TA and NH_4 excretion were lower, although not significantly so. In 5 patients from the CyA-treated group (17%), the lowest postfurosemide urinary pH was always above 5.3, while in all untreated patients, pH values sank below 5.3. These 5 patients with an abnormal FT result did not show any significant differences when compared with those with a normal one as regards the CO_3H^- excretion. Nevertheless, the peak urinary NH_4, TA and NAE were significantly lower (Table 1). Total CO_2 concentration was also lower in patients with an abnormal FT results (22.1 ± 0.7 vs 24.6 ± 1.7 mmol/l, $P < 0.01$), while serum CR (1.2 ± 0.18 vs 0.95 ± 1.2 mg/dl, $P < 0.01$) and urea (47.2 ± 3.6 vs 35.7 ± 8 mg/dl, $P < 0.05$) levels were higher. Serum Na, K and urate levels were not significantly different. Basal or postfurosemide excretion of Na or K and the FE Na and FE K values were also similar. Nevertheless, the basal TTKG was lower in the group with an abnormal FT result (4.07 ± 0.99 vs 6.35 ± 0.42, $P < 0.05$). The blood CyA levels were similar in patients with a normal or abnormal FT result. Three of the patients with an abnormal FT result while on CyA therapy had normal PF test results 1 month after CyA withdrawal, but in 2 patients the abnormality continued, persisting in 1 of them for 3 months after stopping CyA treatment.

Discussion

Little is known about the potential renal damage induced by the prolonged use of low CyA doses or whether there is a threshold level of CyA dosage free of renal toxicity [2, 10]. We have studied the renal response to the FT in Ps patients treated with low CyA doses. This diuretic enhances Na^+ reabsortion in excess of Cl^- in the cortical collecting tubule, thus creating a favourable lumen-negative electric gradient that facilitates the exit of K^+ and H^+ ions. The FT gives similar information to that provided by the infusion of sodium sulphate, but it is easier to perform and free of relevant secondary effects [8].

Five of our patients (17%) had an abnormal FT result. In these patients the postfurosemide urinary pH did not sink below 5.3 and a lower increase of NH_4, TA and NAE was seen than in patients with normal tests, but a similar CO_3H^- level, suggesting impairment of the distal mechanisms of acidification. The renal function was more extensively affected in these patients as shown by higher serum urea and Cr and lower total CO_2 values. Similar results have been found by Heering and Grabensee [7] in renal allograft patients treated with CyA: 23% of them showed an incomplete form of distal tubular acidosis with an inability of the sodium sulphate infusion to lower the urinary pH. Although the effects of CyA on the renin-angiotensin system are conflicting, hypoaldosteronism has been described as a cause of hyperkaliemic metabolic acidosis in transplant patients [1, 7, 9]. Nevertheless, this mechanism is unlikely in our patients: the impairment of renal function was minimal, significant hyperkaliemia was absent, and the basal and postfurosemide FE K values were normal. In addition, contrary to our cases, patients with hypoaldosteronism were able to lower their urinary pH by the stimulus of systemic acidosis or postfurosemide. In acute experiments in rats, Batlle et al. [4] observed a tubular impairment of acidification not mediated by renin-aldosterone abnormalities. In this model of CyA nephrotoxicity, diminished H^+ secretion was associated with impaired distal K^+ secretion when the treatment was prolonged for more than 8 days, suggesting a voltage-dependent type of distal renal tubular acidosis. However, on day 3 of therapy, the impairment of H^+ secretion but not the abnormalities of K^+ secretion could be demonstrated. The feature that is critical in the distinction of the two most common types of distal renal tubular acidosis (voltage-dependent or secretory) is the ability to secrete potassium. Our patients did not develop significant hyperkaliemia after CyA treatment, a finding also described by other authors using a similar dose schedule to ours [2, 3, 10]. The basal and postfurosemide urinary K excretion were also similar to those before CyA treatment and also similar in patients with a normal or abnormal FT result, suggesting that CyA induces an alteration in the H^+-ATPase pump even using low doses for short periods of time.

Nevertheless, we cannot exclude a voltage-dependent mechanism to explain the impairment of acidification found in our study. Our patients with an abnormal FT result presented with a low basal TTKG, and the possibility exists that potassium alterations become more evident with time or when using other, more aggressive methods. Bantle et al. [3] were able to demonstrate a defect of potassium secretion of CyA-treated renal transplant recipients only after the administration of exogenous potassium chloride. Finally, it is possible that the FE K values in our patients with an abnormal FT result, although within

the normal range, were inappropriately low in the presence of renal impairment.

We conclude that the FT discloses subtle alterations in distal acidification in low dose CyA-treated non-renal patients. Although these alterations are subclinical and seem to be reversible after drug withdrawal, we do not know whether they reflect structural anomalies which could become permanent and progressive with long-term treatment. The utility of the test in the early diagnosis of nephrotoxocity should be studied further.

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