Original Article

Excellent uricosuric efficacy of benzbromarone in cyclosporin-A-treated renal transplant patients: a prospective study

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Abstract. Patients on cyclosporin A (CsA) often develop hyperuricaemia and gout. In transplant patients the use of uricosuric drugs for treating hyperuricaemia may be preferable to allopurinol because of the known interaction of the latter with azathioprine. We therefore prospectively studied the uricosuric efficacy of 100 mg benzbromarone (Bbr;Desuric®) daily in 25 CsA-treated renal transplant patients with stable graft function and hyperuricaemia (>359 μmol/l for females, >491 μmol/l for males).

Benzbromarone decreased plasma uric acid from 579 ± 18 μmol/l to 313 ± 24 μmol/l (mean $\pm$ SEM; $P < 0.001$) and thereby normalized plasma uric acid in 21 of 25 patients. The remaining four patients had creatinine clearances between 21 and 25 ml/min, the lowest of the entire study group. Mean fractional clearance of uric acid increased from $5.4 \pm 0.4\%$ to $17.2 \pm 1.0\%$ ($P < 0.001$). The relative decrease of plasma uric acid closely correlated with baseline creatinine clearance ($r = 0.67$; $P < 0.001$). CsA trough values were not influenced. None of the patients experienced any significant side-effects. As an unexpected find-ing, urinary uric acid excretion increased from 2082 ± 175 μmol/24 h to 3233 ± 232 μmol/24 h after 4 weeks' treatment with benzbromarone.

In conclusion, benzbromarone normalized plasma uric acid in all CsA-treated renal transplant recipients with a creatinine clearance >25 ml/min. Due to its excellent efficacy and lack of significant side-effects, benzbromarone appears to be preferable to allopurinol in CsA-treated renal transplant recipients with a creatinine clearance over 25 ml/min.

Key words: cyclosporin A; kidney transplant; hyperuricaemia; uric acid excretion; benzbromarone; uricosuric efficacy

Introduction

Transplant patients on cyclosporin A (CsA) have a greater prevalence of hyperuricaemia than patients on

conventional immunosuppression [1]. Asymptomatic hyperuricaemia occurs in up to 80% of patients, gout in 5–24% of patients [2,3]. A substantial number of patients therefore need treatment for hyperuricaemia. Since hyperuricaemia in these patients is mainly due to reduced renal uric acid clearance and not to increased uric acid production [3], increasing uric acid elimination via the kidney is a sensible approach. Moreover the interaction of allopurinol with azathioprine, which can lead to life-threatening leukopenia, militates against the use of allopurinol in patients on combined immunosuppression with CsA and azathioprine. Since the efficacy of uricosuric drugs has never been formally evaluated in CsA-treated renal transplant patients, we undertook a prospective study to answer the following questions: does the uricosuric drug benzbromarone effectively lower plasma uric acid in CsA-treated renal transplant patients? Is there a lower limit of graft function for the uricosuric effect? Does benzbromarone cause any significant drug interaction or side-effects in these patients?

Subjects and methods

Twenty-five consecutive CsA-treated renal transplant patients (10 females, 15 males) with stable graft function and hyperuricaemia were studied prospectively after giving written informed consent. Inclusion criteria were: (1) CsA therapy with ($n = 14$) or without ($n = 11$) azathioprine and/or prednisone, (2) hyperuricaemia (>359 μmol/l for females, >491 μmol/l for males), (3) stable graft function. Exclusion criteria were: (1) current treatment with any uricosuric drug or allopurinol, (2) unstable graft function, (3) known poor compliance. Two patients in the study group had a history of gout. After baseline measurements, the patients received 100 mg of benzbromarone daily for 4 weeks in addition to their established medication. No specific prescriptions regarding minimal fluid intake or urine alkalinization were given. Patients were asked for side-effects at 1 and 4 weeks of treatment. The following laboratory tests were performed at the beginning and at the end of the study: whole blood chemistry profile; platelet, red and white blood cell count; CsA blood trough levels; 24-h urine excretion of creatinine, urea, uric acid, protein, and calcium; microscopic examination of urine sediment. In addition the same examinations

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except 24-h urine analysis were performed after 1 week of treatment to detect early signs of toxicity or drug interaction.

Laboratory methods

Uric acid concentrations in plasma and urine were measured using a uricase method (Hitachi 737, Boehringer Mannheim), plasma and urine creatinine concentrations by a creatininase assay (Wako Chemicals GmbH, Neuss; Hitachi 737, Boehringer Mannheim). CsA whole blood 12 h trough values were measured with a TDx-FPIA-method (Abbott TDx cyclosporin monoclonal).

Statistical analysis

Statistical evaluation was performed using Student's paired t test. Correlations were evaluated using linear least squares regression; $P < 0.05$ was considered significant and two-sided tests were used throughout. Data are given as mean $\pm$ SEM.

Results

Plasma creatinine of the study patients ranged between 82 μmol/l and 276 μmol/l, creatinine clearance between 21 and 78 ml/min. Graft function remained stable throughout the study period (Table 1).

Benzbromarone significantly decreased mean plasma uric acid from 579 ± 18 μmol/l to 313 ± 24 μmol/l ($P < 0.001$; Table 1). Fall of plasma uric acid was rapid and sustained in all but two patients (Figure 1), and there was no significant change beyond the first week for the group as a whole. For 21 of 25 patients this decrease meant normalization of plasma uric acid. Fractional uric acid clearance increased from $5.4 \pm 0.4\%$ to $17.2 \pm 1.0\%$ ($P < 0.001$; Table 1). There was a good correlation between the percent decrease of plasma uric acid and both plasma creatinine ($r = -0.68$; $P < 0.001$; Figure 2) and creatinine clearance ($r = 0.67$; $P < 0.001$; Figure 3). Similarly, the increase of fractional uric acid clearance correlated well with creatinine ($r = -0.54$; $P < 0.005$) and creatinine clearance ($r = 0.58$; $P < 0.005$). The four patients in whom normalization of plasma uric acid was not achieved had creatinine clearances between 21 and 25 ml/min, the lowest of the whole study group.

While 24-h urinary creatinine excretion remained unchanged (9885 ± 2540 μmol/24 h versus 9971 ± 2377

Table 1. Results

	Before Bbr	1 week Bbr	4 weeks Bbr
CCR (ml/min)	49±4		47±4
P-UA (μmol/l)	579±18	281±20***	313±24***
fCUA (%)	5.4±0.4		17.2±1.0***
UVUA (μmol/24 h)	2082±175		3233±232**
UVCreat (μmol/24 h)	9885±2541		9971±2377
CsA trough level (μg/l)	162±80		162±72

Data are given as mean±SEM; **$P < 0.01$; ***$P < 0.001$.
Creatinine clearance (CCR), plasma uric acid (P-UA), fractional clearance of uric acid (fCUA), urinary excretion of uric acid (UVUA), urinary excretion of creatinine (UVCreat).
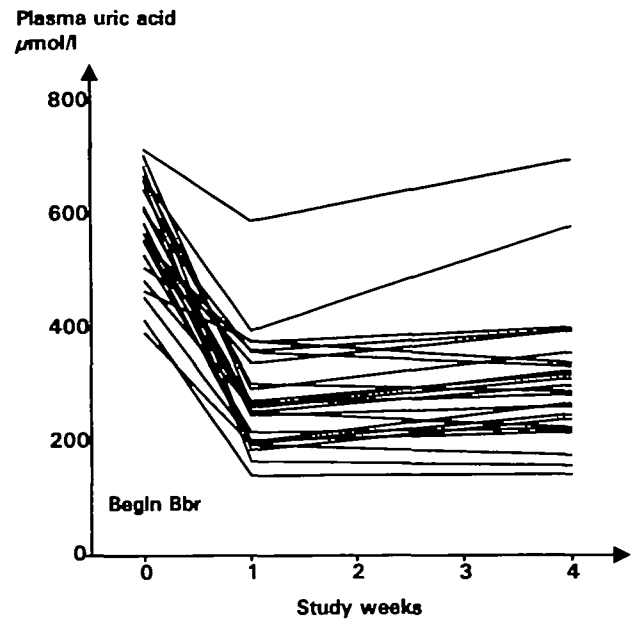

Fig. 1. Plasma uric (μmol/l) acid before, during, and at the end of benzbromarone (Bbr) treatment.
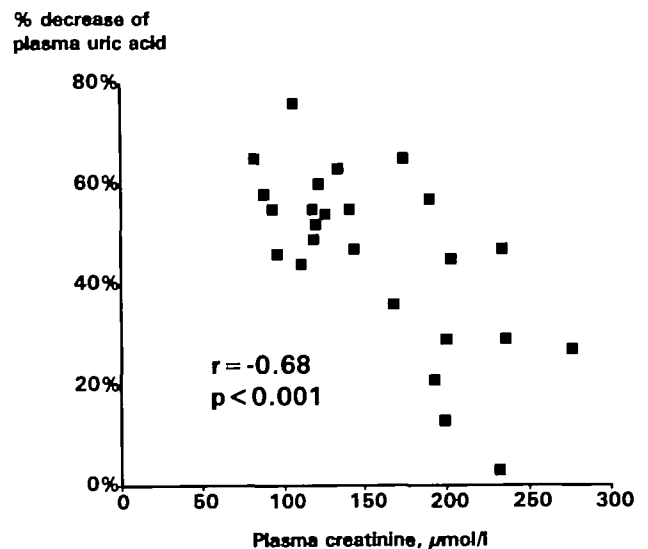
Fig. 2. Relative decrease (in percent of initial values) of plasma uric acid in function of plasma creatinine.

μmol/24 h), urinary uric acid excretion was significantly increased at the end of the 4 weeks treatment (2082 ± 175 μmol/24 h before Bbr, 3233 ± 232 μmol/24 h after 4 weeks of Bbr, $P < 0.001$). Only two patients' uric acid excretion, however, was in the hyperuricosuric (> 4800 μmol/24 h) range, namely 4862 μmol/24 h and 7105 μmol/24 h. Microscopic evaluation of urine sediment revealed no pathological microhaematuria nor crystalluria during treatment. There were no changes of CsA trough levels (162 ± 80 before versus 162 ± 72 μg/l after Bbr) and no signs of toxicity in the haematological or in the blood chemistry profile. Except for one patient with known irritable colon who reported increased diarrhoea, no side-effects
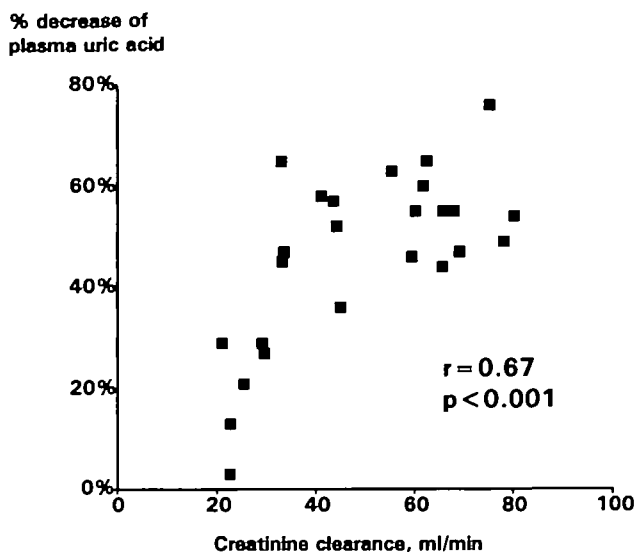
Fig. 3. Relative decrease (in percent of initial values) of plasma uric acid in function of creatinine clearance.

were noted. There were no episodes of gout or any evidence of urolithiasis.

Discussion

The efficacy of uricosuric drugs, well-documented in gouty, non-transplant patients [4], has not been formally evaluated in CsA-treated renal transplant patients so far. The use of uricosurics in these patients could be questioned because (a) reduced GFR [5,6] and (b) impaired tubular handling of uric acid due to CsA-induced proximal tubular dysfunction [7–11] could potentially impair their effect. The present data, however, demonstrate an excellent efficacy of benzbromarone in lowering plasma uric acid within 1 week in all patients with a creatinine clearance >25 ml/min. Even in the four patients with a creatinine clearance <25 ml/min there was still a moderate effect at 1 week (fall of plasma uric acid 17–41%). The fact that this effect was not sustained in two of these patients, may be due to non-compliance. Similar results have been reported in non-transplant patients with comparable renal function [6,12,13] as well as in a group of renal transplant patients on conventional immunosuppression [14]. There is therefore no evidence for impaired uricosuric efficacy of benzbromarone in CsA-treated renal transplant patients. That benzbromarone is less effective in patients with low creatinine clearances most probably reflects diminished postsecretory reabsorption in the renal tubule such as occurs with increasing renal failure [15,16]. Postsectretory reabsorption is the presumptive site of action of uricosuric drugs [17].

The 50% increase of urinary uric acid excretion (Table 1) after 4 weeks of benzbromarone represents an interesting, albeit unanticipated finding. Our expectation was that despite the increment in clearance, urinary excretion of uric acid would return to baseline

by reaching a new steady state after 4 weeks' treatment with benzbromarone. Two possible mechanisms may be considered: either steady state conditions were not yet achieved because some of the patients were still mobilizing uric acid from soft tissue microdeposits, or extrarenal (mainly intestinal) uric acid excretion might have decreased with decreasing plasma uric acid [18,19] and therefore a higher percentage of daily uric acid load was excreted via the kidney. Still, true hyperuricosuria (>4500 µmol/24 h for females, >4800 µmol/24 h for men) occurred in only two patients. Microscopic analysis of urine sediment never gave any evidence of increased crystalluria or haematuria. Since intratubular flow in the distal nephron of renal transplant patients (having only one functioning kidney) is greater than in normals, their risk of stone formation is probably lower at any degree of uric acid excretion. Of course, a larger and longer study would be required to ascertain that this risk is indeed not increased. In our personal experience, following 12 renal transplant patients for at least 1.5 years (median 4 years, range 1.5–6 years), we never observed any stone formation.

We conclude that benzbromarone is an efficacious and safe drug for treating hyperuricaemia in CsA-treated renal transplant patients with a creatinine clearance over 25 ml/min. In patients with creatinine clearances below 25 ml/min or plasma creatinine over approximately 250 µmol/l, allopurinol probably remains the preferred drug. Either treatment, however, should be given to symptomatic patients only.

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