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Effect of cyclosporin A on glomerular filtration rate in children with minimal change nephrotic syndrome

Sally-Anne Hulton*, Lyda Jadresic, Vanita Shah, Richard S. Trompeter, Michael J. Dillon, and T. Martin Barratt

Department of Paediatric Nephrology, The Hospital for Sick Children, Great Ormond Street and Medical Unit, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK

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Abstract. Cyclosporin A (CyA) is now commonly used in the management of children with steroid-dependent nephrotic syndrome. In order to assess nephrotoxicity related to CyA therapy, we measured glomerular filtration rate (GFR) on 123 occasions in 24 children with minimal change nephrotic syndrome receiving CyA. GFR was estimated from the plasma clearance of ^{51}chromium-EDTA every 3 months during CyA therapy of up to 27 months duration. There was a significant reduction in GFR after 3 months of CyA therapy [118 ± 33 (SD) to 93 ± 24 ml/min per 1.73 m^2] but no further fall thereafter, although the reduction in GFR was sustained for the duration of CyA therapy. This reduction in GFR appeared to be reversible upon cessation of CyA, but careful monitoring of renal function is necessary in such patients to prevent the development of longer term nephrotoxic sequelae.

Key words: Cyclosporin A – Glomerular filtration rate – Nephrotic syndrome – Nephrotoxicity

Introduction

Cyclosporin A (CyA) is now a well-recognised treatment for steroid-dependent minimal change nephrotic syndrome (MCNS) in childhood [1–3]. However, there is naturally concern about the potential for nephrotoxicity in the treatment of an essentially benign condition. Renal dysfunction as a result of CyA therapy is related to vasoconstriction resulting in a reduction of both renal blood flow and glomerular filtration [4]. Acute renal toxicity, assessed by plasma creatinine measurement, appears to be dose dependent and relatively mild. The pathogenesis of chronic nephrotoxicity induced by CyA has not been completely elucidated, although haemodynamic as well as toxic effects are probably implicated [5, 6].

The acute reduction in glomerular filtration rate (GFR) induced by CyA is due to a direct reversible impairment of renal haemodynamics [7]. In adults with normal renal function receiving CyA to treat psoriasis, renal plasma flow and GFR were significantly and persistently reduced while on low-dose therapy [8]. Two months after withdrawal of CyA, tubular function had returned to normal but the GFR remained significantly less than basal values.

In order to document the effect of CyA on renal function in children with MCNS, we monitored regularly GFR and plasma creatinine concentration. The efficacy of long-term CyA therapy in the maintenance of remission in children with MCNS is detailed in a separate report [9].

Patients and methods

Twenty-four children (aged 5–17 years) with steroid-responsive nephrotic syndrome were treated with CyA. A renal biopsy was performed in all patients during the 3 months before starting CyA, and confirmed minimal change histology. Patients with focal global or segmental glomerulosclerosis were not included in the study. Steroid therapy was withdrawn within 8 weeks of commencement of CyA. All but 7 of the children were still receiving CyA at the time the data were reviewed.

The initial treatment strategy was to treat patients with CyA for 12 months and thereafter to withdraw therapy, but in some patients it was continued for a longer period. If a deterioration in the renal function was noted whilst the patients received CyA, the therapy was discontinued until the function had returned to normal. A deterioration in renal function was defined as a reduction in the GFR by more than 20% below the baseline value with a concomitant rise in plasma creatinine concentration of at least 10%. An initial CyA dose of 5 mg/kg per day was given in two divided doses and thereafter the CyA dosage was adjusted every 2 weeks according to blood levels. The mean CyA dose used was 5.4 mg/kg per day (range 3.0–7.0 mg/kg per day) in order to maintain patients in remission and with whole blood trough levels between 50 and 100 ng/ml as measured by high-performance liquid chromatography (HPLC) [10].

GFR was estimated from the plasma clearance of ^{51}chromium(CR)-EDTA using two blood samples and a single compartmental analysis [11] and was measured in all patients in the week before

* Present address: Department of Nephrology, Children's Hospital, Ladywood Middleway, Birmingham B16 8ET, UK

Correspondence to: S. Hulton

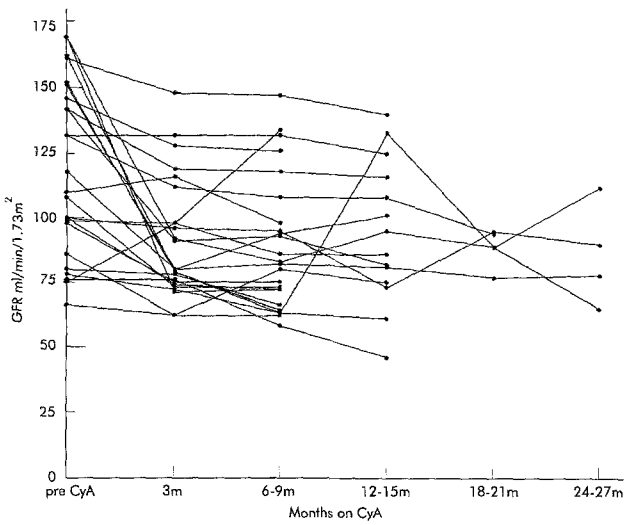

Fig. 1. Glomerular filtration rate (*GFR*) in individual patients before and during cyclosporin A (*CyA*) therapy

starting CyA (referred to as "pre-GFR") and thereafter three monthly for the duration of CyA treatment. The GFR was measured when the patients were not oedematous and the plasma albumin was ≥25 g/l. The majority of patients were in full clinical remission [i. e. qualitative testing (Albustix) of urine for 3 consecutive days indicating no proteinuria, in addition to lack of oedema and plasma albumin ≥25 g/l]. However, 5 patients had significant proteinuria at the time of the pre-GFR evaluation but the subsequent results in these patients did not differ significantly from the rest of the group (details of these patients are given in the results section).

Urinary albumin to urinary creatinine ratio (UA/UC, normal <0.1 mg/mg), plasma albumin and plasma creatinine concentration were analysed on the day of GFR estimation in all cases. Where possible an early morning urine sample was used to measure UA/UC. The plasma creatinine concentration was analysed using a modified kinetic Jaffé method with a coefficient of variation of 2.0%.

Results

Table 1 shows the values of GFR, plasma creatinine and plasma albumin concentrations and UA/UC in the patients receiving CyA therapy. Figure 1 shows the GFR in individual patients before CyA therapy and whilst on treatment. There was a significant reduction in GFR after 3 months of CyA therapy from 118±33 (SD) to 93±24 ml/min per 1.73 m² ($P = 0.001$ paired t-test), but thereafter no further reduction in GFR was observed. The mean GFR at 27 months was 86 ml/min per 1.73 m², still significantly lower than before CyA therapy. Eleven patients showed a reduction of 20% or more in GFR, but an elevated plasma creatinine was noted in only 4 of them.

The relationship between change in GFR and CyA dosage as well as level was analysed in the 12 patients who received CyA for more than 1 year, using simple regression analysis. No correlation was observed between the change in GFR and the mean dose or level of CyA during this period. When the analysis was confined to the first 3 months of treatment, during which period there was a significant fall in GFR in the group as a whole, there was still no correlation with CyA level or dose. The whole blood trough levels (mean ± SD) at 3 and 6 months were 57±21 ng/ml and 50±17 ng/ml, respectively.

The data on the 5 patients who had significant proteinuria at the time of the pre-GFR are given below. The pre-CyA findings in these selected patients were (mean ± SD): albumin 26±1 g/l, UA/UC 2.67±0.67 mg/mg and GFR 119±31 ml/min per 1.73 m². The GFR measurements after 3 months of CyA therapy in these patients also fell (87±16 ml/min per 1.73 m²), but were not significantly different from the other patients.

In 4 patients CyA was discontinued because of a deterioration in renal function as defined above. CyA was restarted within 1 month in 3 patients when the GFR had returned to at least 80 ml/min per 1.73 m². The fourth patient had a GFR persistently less than 80 ml/min per 1.73 m² 5 months after cessation of CyA, which therefore was not recommenced. However, in all 13 patients in whom CyA was eventually discontinued, the GFR measured 6 months after cessation of CyA therapy had returned to baseline (102±24 ml/min per 1.73 m²) and was not significantly different from the pre-CyA value.

Renal biopsies were performed in 5 patients, 4 of whom had been on CyA for 24 months. In the other patient, the biopsy was performed after 6 months of CyA therapy, when the GFR failed to return to its baseline level. In these biopsies only minor histological features of small areas of tubular atrophy with associated mild interstitial fibrosis and chronic inflammatory cell infiltration were noted. The blood vessels were normal. There was no evidence of glomerulosclerosis or arteriolopathy as associated with CyA toxicity. Immunochemical staining revealed no significant deposition of immunoreactants.

Table 1. Glomerular filtration rate (GFR) plasma creatinine, plasma albumin concentration and urinary albumin to urinary creatinine ratio (UA/UC) in patients on cyclosporin A (CyA) therapy (mean ± SD)

Months of CyA	No. of patients	GFR (ml/min per 1.73 m²)	Creatinine (μmol/l)	UA/UC (mg/mg)	Albumin (g/l)
pre	24	118±33	56±11	0.69±1.10	31±5
3	24	93±24	64±14	0.02±0.17	36±3
6	24	87±31	63±13	0.41±1.70	37±3
9	19	87±24	62±12	0.02±0.03	37±3
12	12	105±23	61±10	0.43±1.06	35±3
15	7	86±18	58±11	0.51±0.81	32±7
18	5	89± 2	61±10	1.85±1.70	30±3
21	4	89±16	61± 6	0.67±0.46	31±4
24–27	4	86±20	65± 9	1.05±1.13	31±6

Discussion

Our study has demonstrated that CyA therapy in MCNS results in a significant fall in GFR, estimated from the plasma clearance of ^{51}Cr-EDTA, during the first 3 months of treatment. Thereafter no further significant fall in GFR was noted, although the reduction in GFR was sustained for the duration of CyA therapy. There are three possible explanations for these findings. Firstly, glomerular hyperfiltration associated with the nephrotic syndrome could account for the higher pre-treatment GFR values [12], and with sustained remission, a lower GFR after 3 months of therapy would be expected. Secondly, steroid withdrawal may be implicated in the reduction in GFR seen at 3 months, as steroid therapy was withdrawn within 8 weeks of starting CyA. Thirdly, the reduction in GFR may be directly related to CyA therapy and its effect on renal haemodynamics. We were unable to show a relationship between the change in GFR and either CyA level or CyA dosage used in our patients. The cardiac transplant recipients in the original report associating CyA therapy and nephropathy received higher doses of CyA than those used in our patients (300–350 ng/ml trough levels measured by radioimmunoassay in the transplant group compared with 50–100 ng/ml trough level measured by HPLC in our patients) [13]. This may account for the lesser degree of nephrotoxicity seen in our group.

We cannot satisfactorily explain the sudden peak in the 12-month GFR seen in 1 patient (Fig. 1). This patient had experienced a relapse during the 10th month of CyA therapy for which she received prednisolone treatment tapered over a 6-week period. At the time of the 12-month GFR estimate, the patient was in remission (plasma albumin 38 g/l, UA/UC 0.03 mg/mg).

Inulin clearance was used to assess GFR in the cardiac transplant recipients treated for 12 months with CyA, and showed a significant fall in GFR when compared with patients treated with azathioprine [13]. There are few published studies measuring GFR by slope clearance method in patients with MCNS on CyA. Most studies have used creatinine clearance to estimate GFR. Studies of renal impairment in cardiac transplant recipients receiving CyA have reported nephrotoxicity, as assessed by serum creatinine and clearances, to be as high as 87% at 1 year and 96% at 2 years on treatment [14]. The slope clearance of inulin or ^{51}Cr-EDTA is superior to creatinine clearance as an estimate of the GFR [11, 15]. Adult patients with MCNS treated with CyA for a short period (12 weeks) showed no deterioration in GFR as assessed by a constant infusion technique using ^{125}iodine-iodothalamate [16]; prolonged use appears to be associated with a sustained reduction in GFR and increase in plasma creatinine that is dose related [17, 18]. Children with MCNS receiving CyA therapy for 9 months showed a reduction in creatinine clearance that improved on tapering of CyA [19]. One of a group of eight children on long-term CyA showed a reduced GFR (measured by clearance of ^{51}Cr-EDTA), although all had an initial increase in serum creatinine of 5%–10% at the start of therapy [20]. In most reports the reduction in GFR appears to be dose related and, fortunately, this form of nephrotoxicity appears to be reversible upon cessation of the medication; however, attention should be paid to any deterioration in renal function in patients receiving CyA to avoid long-term nephrotoxic sequelae.

The rise in plasma creatinine concentration of at least 10% that was seen in those of our patients in whom the GFR fell significantly may be helpful in alerting the clinician to impaired renal function in this group of patients, thus obviating the need for regular GFR estimation. We do not suggest that GFR measurements be undertaken every 3 months, as in this study, but do recommend a GFR be documented prior to or soon after starting CyA therapy in order to establish a baseline value for each individual. Thereafter, the GFR should be measured when a significant elevation of the plasma creatinine is noted. If CyA dose reduction does not modify the renal function, then discontinuation of the drug should be considered.

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Ask the expert*

How can you differentiate neonatal Bartter's syndrome from hyperprostaglandin (-uria) E_2 syndrome?

Key words: Bartter's syndrome – Hyperprostaglandin E_2 syndrome – Pathophysiology

Most likely there is no difference between the two disorders which are described as neonatal Bartter's syndrome and hyperprostaglandin E_2 syndrome. However, I think there are good reasons not to extend the term "Bartter's syndrome" to a very complex neonatal disease. These reasons are: (1) from the term hyperprostaglandin E_2 syndrome one can deduce increased prostaglandin E_2 (PGE_2) activity which explains most of the renal and systemic symptoms of this disorder, e. g. polyuria, fever, diarrhoea, vomiting, osteopenia; (2) prostaglandin synthesis inhibitors, such as indomethacin, have proven to be the most effective therapeutic intervention, however in Bartter's last hypothesis on the pathogenesis of his syndrome the prostaglandins were thought to be of minor pathophysiological importance, with no good reason [1]; (3) the term "Bartter's syndrome" is used by internists and by Bartter himself as a mild disease in young adulthood which focuses almost exclusively on hypokalaemic alkalosis with normal blood pressure, despite increased renin-angiotensin-aldosterone activity; (4) in 1957 the two American paediatricians Rosenbaum and Hughes [2] described the first young patient who probably had a hyperprostaglandin E_2 syndrome, 5 years before Bartter described his new syndrome [3].

Based on my experience in internal medicine, including collaboration with Frederic C. Bartter and his colleagues at the National Institute of Health and my later specialisation in paediatrics, I would like to propose the following differentiation between hyperprostaglandin E_2 syndrome and Bartter's syndrome, as shown in Table 1.

In both disorders increased urinary excretion of PGE_2 is observed [4, 5]. In addition, the hyperprostaglandin E_2 syndrome is characterised by elevated urinary levels of PGE-M (the major urinary metabolite of the E prostaglandins), indicating an increased renal *and* systemic PGE_2 activity [4]. Classical Bartter's syndrome and Gitelman's syndrome have many features in common. Hypomagnesaemia as such is not a specific feature of Gitelman's syndrome [6], since renal wasting of magnesium is seen in most hypokalaemic tubulopathies.

H. W. Seyberth
Department of Paediatrics, Philipps University, Deutschhausstrasse 12, 35033 Marburg, Germany

Table 1. Differentiation of hyperprostaglandin E_2 syndrome and Bartter's syndrome

	Hyperprostaglandin E_2 syndrome	Bartter's syndrome including Gitelman's syndrome	References
Time of presentation	Prenatal onset with polyhydramnios and prematurity, postnatal life-threatening course	Diagnosis most frequently in early adulthood	[4, 5]
Symptoms and signs	Polyuria, polydipsia, unexplained fever, diarrhoea, vomiting, generalised convulsions, hypokalaemic alkalosis, osteopenia, nephrocalcinosis, failure to thrive	Isolated tubular disease with hypokalaemic alkalosis, tetanic episodes associated with hypomagnesaemia, short stature	[4–7]
Tubular function			
Max. concentration	<300 mosmol/kg	500–800 mosmol/kg	[4]
Chloride reabsorption	Normal	Decreased	[1, 4]
Calciuria	Increased	Decreased	[7, 8]
Tamm-Horsfall protein	Reduced synthesis	Normal	[9]
Renal morphology			
Ultrasound	Increased medullary intensity	Normal	[4, 10]
Histology	Marked hypertrophy of the juxta glomerular apparatus	Enlarged juxtaglomerular apparatus	[11]
	Focal tubular and interstitial calcification with interstitial fibrosis and tubular atrophy	Not present	[11]

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* The editors invite questions for this section