Dear Sir,

Cyclosporine A (CyA), widely used in organ transplantation as a potent immunosuppressive agent, is associated with some side effects such as nephrotoxicity [1,2] and hypertension [3]. The exact mechanism by which CyA causes an increase in blood pressure is not fully understood. It has been proposed that CyA-induced hypertension may be due to altered release and/or metabolism of eicosanoids [2], endothelin [4] and platelet-activating factor [2]. Serotonin (5-hydroxytryptamine) has been implicated in the regulation of blood pressure [5]. A fairly good correlation between blood pressure and whole-blood serotonin content in rats given CyA [6] as well as an increased level of whole-blood and plasma serotonin in kidney transplant recipients [7] prompted us to study a possible involvement of serotonin in CyA-induced hypertension in kidney transplant recipients.

The experiment was carried out on 12 patients after kidney transplantation, who maintained stable graft function with no evidence of rejection. The immunosuppressive regimen consisted of CyA (3.5 mg/kg), prednisone (2.5-5 mg/day) and azathioprine (100-150 mg/day). Blood was taken from the antecubital vein into 3.8% sodium citrate in a 9:1 volume ratio. The blood samples were divided into two: one for the measurement of CyA concentration and the second for serotonin level. The CyA level in the blood was assessed by the immunoassay using a monoclonal antibody. The whole-blood and platelet serotonin concentration was estimated using the spectrophotofluorimetric method as described by Drummond and Gordon [8].

A fairly good correlation between mean blood pressure and CyA trough levels (r = 0.62, p < 0.05, fig. 1; both systolic and dia-stolic blood pressures also correlated with CyA, F = 0.63, p < 0.01 and r = 0.45, p < 0.05, respectively) may be due to the low number of patients investigated. It is of interest that there was a relationship between whole-blood serotonin concentration and CyA level (r = 0.77, p < 0.01). In subjects with an increased concentration of serotonin in blood platelets, the level of CyA tended to be higher, giving a weak, but significant, correlation (r = 0.41, p < 0.05).
The pathogenesis of CyA-induced hypertension has been unknown. A role of renal and vascular mechanisms has been postulated. An enhanced sympathetic activity and increased production of thromboxane A2 on the one hand and a decrease in prostacyclin and endothelium-derived relaxing factor release from the endothelium on the other hand may also be involved in CyA-related hypertension. It has been indicated that CyA causes an elevation of plasma endothelin levels in renal transplant recipients, which in turn may contribute to the CyA-induced glomerular dysfunction [4]. However, in one study by Edwards et al. [9], there was no association between chronic CyA therapy in cardiac transplant patients (up to 2 years)

$$y = 0.22x + 86.41$$

$180$

$$r = 0.63$$

$p < 0.05$

Fig. 1. Correlation between mean blood pressure (MAP) and CyA trough levels in kidney transplant recipients.

and circulating plasma endothelin increases, nor was there any correlation established between circulating endothelin and posttransplantation hypertension and/or renal insufficiency. On the other hand, it has been reported that endothelin can stimulate the release of vasodilator prostanoids and endothelium-derived relaxing factor [10] from the endothelium, which may mediate the vasodilator, antiplatelet and anticoagulant actions of this peptide. Since in CyA-treated patients, nephrotoxicity is supposed to be associated with vascular damage, as reflected by a very high plasma level of von Willebrand factor antigen [11], increased levels of serotonin, particularly in plasma, together with endothelial damage or dysfunction, might provide conditions for exaggerated serotonergic amplification, influencing platelet aggregation and persistence of vasoconstriction [12]. Similar data were reported in essential hypertension [6]. Our findings of the correlations between the concentration of whole-blood and platelet serotonin and the CyA level in the blood do not preclude cause and effect but may suggest an involvement of serotonergic mechanisms in CyA-induced hypertension in renal allograft recipients.

References


CyA, Serotonin and Hypertension
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