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Abstracts

Cyclosporin Nephrotoxicity in Experimental Animals and Humans.

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The introduction of cyclosporine (CsA) into clinical practice had a major impact on organ transplantation. However, with increasing use has come increased recognition that CsA has severe deleterious effects on renal structure and function. In recent years many studies have been devoted to understanding the cellular mechanisms of CsA-induced renal insufficiency. It is now recognized that CsA renal toxicity mainly manifests under three different syndromes: 1) acute reversible decrease in glomerular filtration rate (GFR) and renal plasma flow (RPF), 2) acute microvascular disease with the pattern of thrombotic microangiopathy, and 3) chronic irreversible renal damage. Evidence are available that all these clinical syndromes of CsA nephrotoxicity are related to changes induced by the drug on renal vessels. Experimental studies have failed to document that the activation of renin-angiotensin axis or sympathetic nervous system plays a relevant role in the development of CsA-associated renal vasoconstriction, which is the main causal factor of acute reversible decrease in GFR, whereas it is possible that changes in arachidonic acid metabolites with vasoactive properties contribute to this CsA-induced phenomenon. In this context, findings of increased urinary TxB₂ and protective effect of TxA₂ receptor blocking are of particular interest. More recently a role for endothelin, a potent vasoconstrictor protein product of the endothelial cell, has been suggested on the basis that in rats an anti-endothelin antibody or an endothelin receptor antagonist almost completely prevented the decline of GFR and RPF induced by CsA. Moreover, an increased urinary excretion of endothelin has been reported in renal transplant recipients after daily dosing with CsA associated with a parallel fall in GFR and RPF. Since the introduction of CsA in clinical practice, a syndrome of thrombotic microangiopathy resembling hemolytic uremic syndrome/thrombotic thrombocytopenic purpura has been recognized in humans and reproduced in experimental animals. This is a rare form of vascular toxicity attributed to CsA which may have a poor prognosis and possibly results from a direct toxic effect of CsA on vascular endothelium. The syndrome of chronic progressive deterioration of renal function associated with CsA was first recognized in humans. Until recently the possibility of reproducing this syndrome in animals in order to better understand its nature was addressed. As in humans, when animals were given CsA for more than 2 months they develop chronic renal insufficiency with tubular arteriopathy and interstitial fibrosis. A peculiar form of tubulointerstitial damage has been recognized in association with CsA, and called striped interstitial fibrosis, that is probably due to tubular collapse induced by afferent vasoconstriction. Recently studies suggested that CsA chronic nephrotoxicity may have a progressive course, with a pattern of pathological changes which include arteriopathy, tubular atrophy, and interstitial fibrosis. Signs of chronic damage to the kidney have been detected in cardiac transplant patients given CsA for >12 months. Despite stable GFR, some glomeruli were sclerotic, probably as a result of ischemia, and the remaining were larger than normal. In conclusion, the administration of CsA is associated with a renal damage probably caused by a peculiar vascular toxicity.

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