Cyclosporine nephrotoxicity

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■ Cyclosporine is a potent and useful immunosuppressive agent used primarily in conjunction with solid organ transplantation. The most serious adverse reaction that limits its use is nephrotoxicity due to effects on the renal vasculature, glomeruli, and tubular function. These effects result in a variety of clinical syndromes. This review outlines the clinical syndromes and discusses ways to minimize nephrotoxicity in patients receiving cyclosporine.
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CYCLOSPORINE NEPHROTOXICITY continues to be a significant clinical problem,[1,2] and its various manifestations must be fully understood to use cyclosporine effectively and safely. For this discussion, this multi-faceted problem is categorized into seven parts:

1. Hemodynamic effects on renal blood flow (RBF) and glomerular filtration rate (GFR),
2. Renal tubular effects,
3. Renal vascular effects,
4. Hypertension,
5. Synergy with other nephrotoxins or renal insults,
6. Long-term toxicity of interstitial fibrosis and tubular atrophy, and
7. Whether nephrotoxicity is dose-related.

HEMODYNAMIC EFFECTS ON RBF AND GFR

Several studies in rats[3–5] have confirmed that an infusion of cyclosporine has the immediate effect of decreasing RBF and GFR. Although this effect has not been confirmed in humans (studies are underway), a similar immediate reduction probably occurs. The mechanism for this reduction is unclear. In one study,[5] the immediate effects on GFR and RBF in the rat could be prevented with prior administration of an ACE inhibitor. Murray and Paller,[4] however, did not confirm this effect; they found that innervation of the kidney was necessary since a denervated kidney did not show these acute changes. Since the transplanted kidney is denervated (at least initially), this effect would not be present in a renal transplant recipient.

Apparently there is a similar reduction in GFR and RBF chronically.[6–9] In a study of humans, patients on cyclosporine after renal transplantation had a reduction in RBF (and to a lesser extent, GFR) that was reversed when the medication was discontinued.[10] Renal transplant recipients who were "converted" from cyclosporine to alternative immunosuppressive therapy have shown an improvement in renal function as assessed by a reduction in serum creatinine levels.[11–13] Studies of patients who have used cyclosporine for the treatment of autoimmune disease also have shown a reduction in GFR that was reversed after discontinuation of the medication.[14] This reversible effect on GFR was apparent after one year of therapy with cyclosporine.[14,15] The long-term effects on GFR and RBF are probably not me-

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diated through the renin-angiotensin system, since the renin levels tend to be low in both human [16,17] and animal models.[9,18,19] The mechanism may be due to direct effects of cyclosporine on the renal vasculature or mediated through the renal nerves. The decrease in GFR may be only partially due to the decrease in RBF.[20] A separate effect on the permeability of the glomerular capillary membrane (K_f) may account for some of the impairment of GFR.[20]

Renal prostaglandins may be the mediators for this effect on the GFR and RBF. Petric et al[21] and Smeesters et al[22] have shown that the reduction in GFR seen with the administration of cyclosporine in the rat model can be prevented in part by the administration of a thromboxane synthetase inhibitor. Elzinga et al[23] have also shown that the decrease in GFR and RBF seen in the rat model could be partly prevented by administering the cyclosporine in a fish-oil preparation high in eicosanoid precursors that change the distribution of prostaglandin production toward more vasodilating rather than vasoconstricting substances.[23] Makowka et al[24] have prevented cyclosporine-induced reduction in renal function and histologic injury by concomitant administration of prostaglandins. However, prostaglandins may reduce the immunosuppressive effects of cyclosporine.[25] These studies, if confirmed in humans, may have important clinical applications.

TUBULAR EFFECTS

A study of the use of cyclosporine in patients with uveitis has documented various abnormalities that probably are due to the tubular effects of the drug[26,27]:

1. There is a decrease in serum magnesium due to an increased fractional excretion of magnesium. This has caused clinical problems with transplant recipients.[28,29]
2. There is decreased secretion of potassium and a tendency toward hyperkalemia. This is often clinically insignificant unless associated with another condition that may predispose to hyperkalemia (e.g., renal failure, the use of ACE inhibitors, and/or potassium-sparing diuretics).
3. There is a decrease in hydrogen ion excretion, probably a Type IV renal tubular acidosis. This, when combined with the acidosis of renal insufficiency, may cause clinically significant acidosis.
4. There is a decrease in uric acid excretion with an increase in the uric acid level. This has been used as a possible marker for nephrotoxicity since there is a disproportionate rise in the uric acid compared to patients with similar degrees of renal insufficiency.

The tubular effects of cyclosporine seem to be distinctly different from aminoglycosides.[30] The typical increase in urinary enzyme excretion (e.g., lysozyme, N-acetyl-beta-glucosaminidose [NAG]) that is seen in aminoglycoside nephrotoxicity is absent.[31] Some tubular functions, such as urinary concentration, are well preserved. This argues against a structural effect on the tubular cells and probably indicates less toxic injury with cyclosporine than with aminoglycosides.

Specific pathologic changes in the tubular cells have been described after cyclosporine administration[32]: vacuolization, giant mitochondria, tubular atrophy, and interstitial fibrosis (specifically, a striped form). Some of these changes may be due to the vehicle in which the cyclosporine is administered. Animal studies suggest that the vacuolization of the tubular cell may be in part a nonspecific finding.[33] Isometric vacuolization (vacuoles of the same size) has been described as a specific effect of cyclosporine toxicity by Mihatsch et al.[32]

There may be other significant effects on cellular function. Studies of mitochondrial respiration have shown toxic effects due to cyclosporine.[34] Also, proliferation of tubular cells as assessed by incorporation of radiolabeled nucleic acids suggests a reparative response to some cellular injury.[31] This is an active area of investigation.

VASCULAR EFFECTS

Cyclosporine has distinct renal vascular effects. As mentioned previously, there are changes in RBF and GFR that are probably mediated through the renal prostaglandin system, and the renin-angiotensin system may play a role acutely within the first few hours of administration.

Studies have shown that an exudative and proliferative lesion of the vessel wall may develop during cyclosporine administration in spontaneously hypertensive rats.[35,36]

In a small percentage of patients, vascular changes have appeared to be similar to the hemolytic uremic syndrome, with the development of thromboses (consisting of red cells, platelets, and fibrin) in the microvasculature and glomeruli of the kidneys.[37,38] This may or may not be associated with thrombocytopenia. An obliterative vasculopathy with intimal thickening and deposits that may be associated with fibrin and platelet deposition has also been described and may lead to severe graft damage and loss.[39–41] This seems to be a very unusual form of nephrotoxicity in the nonrenal transplant patient. The interaction of this toxicity with vascular forms of renal transplant rejection is unclear, but may make the renal transplant patient more susceptible to these pathologic events.

One study has suggested an increased risk of thromboembolic problems in association with the use of cyclosporine after renal transplantation, possibly due to these vascular effects.[42] However, this was not confirmed by Gruber et al.[43]

The mechanism for these vascular effects may again be mediated through local prostaglandin synthesis. Increased thromboxane production or decreased prostacyclin induced by cyclosporine could be responsible for vascular deposits of platelets and fibrin and perhaps progressive thickening and deposits within the vascular wall. However, results of studies dealing with the effects of cyclosporine on the metabolism and production of the different types of prostaglandins have been inconsistent.[4,24,25,44–58] This is also an active area of investigation.

HYPERTENSION

Significant hypertension has been associated with the use of cyclosporine, both in transplant recipients[59–63] and in patients who have received the drug as treatment for autoimmune diseases.[15] The role of cyclosporine is hard to evaluate because of the multiple factors that may cause or aggravate hypertension in these patients. Adequacy of allograft function, the presence of diseased native kidneys, the possibility of renal artery stenosis, the effect of rejection, and the impact of corticosteroids all may play a role in the hypertension present after renal transplantation.[64,65] The incidence of hypertension, however, is higher in patients treated with cyclosporine, especially in high dosages, than with alternative immunosuppressive therapy.[63]

Myers et al[59] studied cardiac transplant recipients one and two years after transplantation and documented a significant increase in blood pressure in recipients receiving cyclosporine (mean blood pressure, 111 mmHg) compared to those receiving azathioprine (mean, 101 mmHg).

Renal transplant patients were studied before and after cyclosporine use and documented improvement in blood pressure associated with an improvement in RBF.[10] After cyclosporine use, the patients did not respond to ACE inhibition as treatment of their hypertension, suggesting that, in these long-term renal transplant patients, the renin-angiotensin system was not playing a role in the cyclosporine-induced elevation of blood pressure (Curtis JJ, personal communication). Supporting this are data from Bantle et al[16] that documented decreased renin activity in cyclosporine-treated transplant recipients.

Since cyclosporine is associated with renal vasoconstriction and decreased RBF, agents that decrease renovascular resistance are attractive for treating hypertension. Calcium channel blockers are effective antihypertensive agents for this patient population.[66] Other drugs, such as centrally acting sympathetic blockers, other vasodilators (such as hydralazine or alpha blockers), and low doses of diuretics may also be useful. Beta blockers, which may be associated with further reductions in RBF, are probably best used only in combination with other agents that decrease renal resistance in the patient with refractory hypertension.

Bantle et al[16] documented an increase in extracellular fluid (ECF) volume associated with decreased peripheral renin activity in hypertensive patients treated with cyclosporine. They suggest that ECF volume expansion may play a role in hypertension and in suppressing peripheral renin in a physiologic response. Diuretics to control ECF volume expansion may thus be useful for controlling hypertension. High doses of diuretics should be avoided, however, since volume depletion causes an exaggerated loss of GFR during cyclosporine therapy.[67]

The pathophysiology of hypertension associated with cyclosporine is not entirely clear, and in addition to ECF volume expansion, may relate to the impairment of the normal pressor-natriuresis response in the normal kidney. This may be related to the vascular effects caused by cyclosporine as mentioned in the preceding section. The characteristics of the hypertension (low renin, decreased RBF, increased ECF volume, impairment of the pressor-natriuresis response) are similar to those of primary hypertension (low renin), and this may be a drug-induced model for this genetic/environmental disease.

SYNERGISTIC TOXICITY WITH OTHER NEPHROTOXINS OR RENAL INSULTS

The most clinically significant additive or synergistic renal injury after renal transplant is ischemia. Most cadaver kidneys undergo some degree of ischemic damage at the time of harvesting and implantation. Early clinical trials documented a slow recovery from ischemic acute renal failure in patients treated with cyclosporine[68,69] and a significant increase in the number of patients who never recovered, compared to the outcome in patients treated conventionally, with azathioprine, prednisone, and anti-lymphocyte preparations.[70,71] One-year graft survival in large registry studies documented worse results in kidneys that had undergone 24 to 48 hours of cold ischemia.[72] Animal studies have further substantiated the synergistic toxicity of ischemia and cyclosporine.[73–75] The mechanism for this may relate to the effects of cyclosporine on RBF or to compensatory changes that occur in a solitary kidney.[73]

Several techniques have been employed clinically to avoid this problem. One is to delay the onset of cyclosporine therapy until the kidney has recovered from its ischemic injury. The patient is given an anti-lymphocyte preparation to prevent rejection during this time of recovery.[76] An alternative technique is to use low dosages of cyclosporine and gradually increase the dosage as the kidney recovers. If the kidney does not recover, renal biopsy is performed and decreasing or stopping the cyclosporine should be considered. A third approach is to try to minimize the ischemic injury by limiting the cold ischemia time to less than 24 hours and minimizing warm ischemia at the time of harvest and transplant. Newer preservation techniques, including a new preservation medium, may also help reduce the ischemic insult to the kidney.[77] By using such techniques, ischemic acute renal failure requiring dialysis may be kept to an incidence of near 10%, allowing full dosages of cyclosporine from the time of transplantation in almost all patients.

Other nephrotoxic agents may act in an additive or synergistic fashion to worsen nephrotoxicity associated with cyclosporine. Aminoglycosides and amphotericin B have been reported to have this effect both in animals and in humans.[78–80] A preliminary report suggesting that acyclovir might increase the risk of nephrotoxicity has not been confirmed in a more recent study.[81] Mannitol, which usually protects against acute renal injury, may also induce synergistic toxicity,[82] although this has not been reported in humans.

LONG-TERM NEPHROTOXICITY OF CYCLOSPORINE

Initial studies by Myers et al[59] of heart transplant recipients showed a significant reduction in GFR of about 50% at one year after cardiac transplantation. These patients showed a small but significant worsening of renal function from years 1 to 2, but no significant reduction in GFR from years 2 to 3.[83] These patients were often treated with higher doses of cyclosporine in the early post-cardiac-transplant course than are currently employed, and levels were not monitored as closely as is now the case in most centers. It is possible that these patients, treated early in the experience with cyclosporine, exhibited more nephrotoxicity than current recipients of either cardiac or renal allografts. In several of these heart transplant recipients at Stanford and other centers, biopsy specimens showed evidence of chronic irreversible changes (tubular atrophy, fibrosis, and glomerulosclerosis).[59,84] Long-term animal studies have also suggested irreversible injury with interstitial fibrosis.[85]

At several centers, renal transplant patients have been maintained on cyclosporine for more than five years.[86] Long-term follow-up studies of these recipients have suggested that renal function tends to remain stable. However, patients who remain on cyclosporine may be a select group; the drug may have been discontinued in patients who had nephrotoxicity problems, in whom chronic progressive disease might develop. These patients may have been removed from long-term analysis. It may be that the risk of long-term nephrotoxicity and progressive chronic renal failure due to fibrosis and glomerulosclerosis is outweighed by the benefit of reducing the incidence of chronic rejection (the most frequent cause of chronic progressive loss of renal function in the renal transplant recipient).

Some centers have tried to eliminate the problem of long-term nephrotoxicity by converting patients from cyclosporine to therapy using prednisone and azathioprine.[12,87,88] Three studies of patients after such a conversion have documented a significant incidence of rejection episodes.[87,89,90] The rejection episodes usually respond to adjustment of the immunosuppressive therapy. Lorber et al[91] have suggested, however, that patients who undergo conventional therapy with azathioprine and prednisone after being given cyclosporine have a poor long-term graft survival due to late rejection. An alternative approach is to use "triple" therapy with low dosages of cyclosporine combined with prednisone and azathioprine.[92–94] Lower dosages of each individual agent may reduce drug toxicity and still maintain adequate immunosuppression.

More studies with larger numbers of patients followed for longer periods will be necessary to help determine the risk of chronic renal failure with cyclosporine and the benefits and risks of various conversion protocols.

IS NEPHROTOXICITY DOSE-RELATED?

The value of drug monitoring cyclosporine levels after transplantation remains controversial.[95,96] Several studies have documented a statistical correlation between low cyclosporine levels[97] and the risk of rejection and high cyclosporine levels and the risk of toxicity.[98] However, the overlap is significant and there is no cutoff that will allow the clinician to differentiate with certainty when trying to reach a clinical diagnosis. Nephrotoxicity can be seen with low levels of cyclosporine and rejection can be seen with therapeutic or even high levels. Some of the reasons for the difficulty in correlating levels with clinical effect are:

1. Pharmacokinetic profiles, peak levels, and rates of elimination may be more important than the standard trough cyclosporine level in determining risk of rejection or toxicity.[99,100]

2. How the drug is distributed within the body in the lymphoid tissues and other organs may be more important than the blood levels in determining clinical and toxic effects.[101]

3. Cyclosporine toxicity and rejection may occur simultaneously in many patients.

4. Metabolites of cyclosporine may or may not be measured, depending upon the technique, and may be important in determining either immunosuppressive effect or toxicity.

5. There may be significant individual variation in the therapeutic response to cyclosporine and individual susceptibility to the nephrotoxic effects of the drug.

In any case, cyclosporine monitoring helps to avoid extremely high or low levels that might be associated with noncompliance, unusual absorption or metabolism, and interaction with other drugs. Quantification of the interaction that may occur with drugs that affect the activity level of the P450 enzyme system in the liver may be one of the most important uses of cyclosporine monitoring. Several drugs have been shown to increase the activity of the P450 enzyme system,[102,103] increase the metabolic rate of cyclosporine, decrease the trough cyclosporine levels, decrease the risk of cyclosporine nephrotoxicity,[104] and increase the risk of rejection. These drugs include phenytoin sodium, phenobarbital, and rifampin. Drugs that decrease the activity of the P450 enzyme activity will decrease the rate of cyclosporine metabolism,[102,103] increase cyclosporine trough levels, increase the risk of cyclosporine nephrotoxicity, and increase the immunosuppressive effect of the drug. Erythromycin,[105] ketoconazole,[106–108] diltiazem,[109] and verapamil[110] have been shown to have this effect. Monitoring trough cyclosporine levels helps determine the appropriate cyclosporine dosage adjustment.

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