Cyclosporine-Associated Neurotoxicity

The Need for a Better Guide for Immunosuppressive Therapy

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Introduction

Heart transplantation has become the most effective treatment of end-stage heart failure in selected patients. More than 30,000 heart transplantations have been performed worldwide since its introduction in 1967, with a current 1-year survival rate of 85% and 5-year survival rate of 70%.

Besides the enormous survival advantage associated with heart transplantation compared with all other therapies, it also usually is associated with the restoration of a nearly normal age-predicted functional capacity.

In this issue of Circulation, Grimm and colleagues document with the use of P300-evoked potentials that patients with end-stage heart failure awaiting transplantations also have impaired cortical function, a finding that reaffirms that of previous reports using psychometric tests. These abnormalities also were totally normalized within 4 months of transplantation, which is consistent with the hypothesis of decreased cerebral perfusion as the cause of the impairment. These patients underwent repeated testing 12 months after transplantation. The results showed that the mean evoked potentials had declined to levels similar to those before transplantation, although none of the patients were thought to have any clinically detectable neurological symptoms. This suggests that evoked potentials are more sensitive than more traditional psychometric tests, which also were abnormal before transplantation, improved 4 months after transplantation, but did not change 12 months after transplantation. Using multiple regression analysis, Grimm et al found that the cumulative dose of cyclosporine was the only significant variable associated with the changes in cortical function.

Cyclosporine has been used as the primary immunosuppressive agent in heart transplantation for 15 years. Its introduction was associated with a significant improvement in survival, which led to a significant increase in the number of patients undergoing heart transplantation. Its use also has been associated with a decrease in the incidence and severity of rejection. However, the dosage of cyclosporine has decreased by nearly two thirds from the original recommendations of 15 to 20 mg·kg⁻¹·d⁻¹, largely because of the unacceptable renal toxicity and hypertension reported with higher doses.

Neurotoxicity is another recognized complication of cyclosporine use, having been reported in patients receiving liver, heart, kidney, and bone marrow transplantsations; nontransplant patients receiving the drug; and animal models. Several patients who developed neurotoxicity while on cyclosporine also reported that the symptoms or clinical findings were totally resolved when the drug was discontinued,
only to recur when the drug was reintroduced. The incidence of cyclosporine-associated neurotoxicity (CAN) ranges from 10% to 25%, with a peak in the early postoperative period with initial exposure to the drug and a gradual increase in the incidence over time with cumulative exposure. The clinical presentation may include tremors, restlessness, dysaesthesias of the palms and soles, seizures, and altered mental status with confusion and visual or auditory hallucinations; cortical blindness, encephalopathy, and coma are less common. These symptoms may occur alone or in combination and usually resolve in the reverse order of appearance. Risk factors include previous seizures or a cerebral vascular accident, hypertension, cholesterol <100 mg/dL, concomitant use of intravenous methylprednisolone, hypertension, hypomagnesemia, and high cyclosporine levels.

The diagnosis of CAN is often one of exclusion because of concomitant use of other neurotoxic agents such as methylprednisolone or the common presence of other factors such as hyponatremia, hypomagnesemia, or hyperglycemia that can mimic many of the neurological symptoms of CAN. The clinical symptoms are common but not always associated with elevated cyclosporine blood levels. Neurological symptoms in a transplant patient often prompt diagnostic scans that may demonstrate symmetrical, nonenhancing, low-density areas on CT scan and high-resolution T2 images on MRI scans; both are consistent with brain edema, which may be due to an inflammatory response to accumulation of cyclosporine in the brain. There is no clear predilection for specific areas of involvement of the brain, although the posterior regions may be involved more than anterior regions and white matter may be affected more often than gray matter.

Several mechanisms have been suggested to explain the neurotoxicity of cyclosporine, including hypocholesterolemia. Cyclosporine is a very lipophilic drug that exists largely in a bound state in the plasma, with 35% to 40% bound to erythrocytes, 55% to 60% bound to lipoprotein fractions, and <10% unbound or free. Low levels of cholesterol, which are common in patients with end-stage liver or cardiac failure, may increase the percentage of unbound drug, predisposing those patients to increased diffusion of cyclosporine across the blood-brain barrier or increased binding to other lipoproteins, resulting in increased uptake in the brain. Hypercholesterolemia may also result in upregulation of LDL receptors, which may increase intracellular transport of cyclosporine. There are significant numbers of LDL receptors in the white matter of the brain, which may lead to cyclosporine accumulation and the common scan abnormalities in this area. Patients with CAN have been reported to have fewer symptoms with similar blood levels of cyclosporine when serum cholesterol increased.

Hypomagnesemia is another potential mechanism that is commonly associated with seizures in patients receiving cyclosporine, especially in pediatric and adolescent patients and those with previous eleptogenic focus. Cyclosporine causes dysfunction of the proximal tubule of the kidney, resulting in impaired magnesium absorption and increased magnesium clearance. Both cyclosporine and magnesium depletion may lower the seizure threshold, and treatment with magnesium may improve symptoms or prevent recurrence of seizures without the use of antiepileptic drugs, which may interfere with cyclosporine metabolism (eg, diphenylhydantoin). Cyclosporine also causes the release of the potent vasoconstrictor endothelin from endothelial cells, which may cause microvascular damage and/or changes in permeability of the blood-brain barrier. Finally, cyclosporine may cause direct toxic effects on neuronal cells or may be associated with neural demyelination.

The treatment of CAN is to reduce the dose or discontinue the drug entirely, depending on the severity of symptoms. This approach has been associated with a significant improvement of symptoms in more than two thirds of patients by 48 hours and nearly all patients have total recovery if the drug is discontinued for a period of time. Several patients have been switched to tacrolimus without the return of neurological symptoms, although neurotoxicity is more common with tacrolimus than cyclosporine.

The observation of almost total reversibility of neurotoxicity with a reduction in the dose of cyclosporine is encouraging but indirectly focuses on the most difficult problems in the management of immunosuppressive drugs: How much can cyclosporine (or other immunosuppressive drugs) be safely reduced, and what is the ideal dose for the individual patient to prevent such toxicity? The usual approach in immunosuppressive therapy is to maximize immunosuppressive efficacy, ie, prevent rejection, which is now possible in >50% of heart transplant patients, and to minimize toxicity. Cyclosporine dosing is usually guided by target blood levels, but there are no uniformly accepted guidelines for these target levels. Recently, cyclosporine levels that were maintained >400 ng/mL for the first 6 months after transplantation were associated with significantly less rejection and no increased nephrotoxicity in a series of 200 patients. However, the pharmacodynamic effects of cyclosporine are highly variable. Many patients who have developed side effects such as nephrotoxicity have remained free of rejection when the drug levels were maintained between 100 and 200 ng/mL over several years. Specific alloreactivity is determined by many factors, including human lymphocyte antigen matching, and the target levels that may be ideal for some or even most patients may constitute overimmunosuppression in others, as evidenced by the high percentage of patients who have been successfully weaned off steroids without recurrent rejection. It is the cumulative amount of immunosuppression, ie, of all drugs used, that determines the risk of serious complications such as malignancy or cumulative effects such as neurotoxicity.

Several new approaches, including measurement of the intracellular enzyme calcineurin, are being investigated in an attempt to monitor the immune system and to provide more of a bioassay of immunosuppression. Both tacrolimus and cyclosporine work by binding to a specific binding protein (cyclophilin) in the cytoplasm, and the formed complex then inhibits calcineurin. This results in inhibition of the calcium-dependent signaling pathway involved in the activation of nuclear activating factors necessary for transcription of genes responsible for production of cytokines such as interleukin-2 that are necessary for clonal expansion of the effector cells of rejection. Measuring calcineurin may describe better the intracellular effect of a given blood level of cyclosporine or tacrolimus and help minimize the significant pharmacodynamic variability and toxicity by adjusting the dose based on a biological effect. Another approach that is somewhat more difficult to quantify is the use of the mixed lymphocyte reaction between the recipient and stored donor cells. Hyporeactivity to these donor specific cells helps to describe the level of “effective” immunosuppression.

The goal of immunosuppressive therapy is to use the smallest effective amount. Better methods of assessing this therapy will help minimize the side effects of drugs that have helped make transplantation such a life-saving treatment for many patients with end-organ disease.
The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

**Footnotes**


