

ANNOUNCEMENTS

NATIONAL KIDNEY FOUNDATION (NKF) ANNUAL SCIENTIFIC MEETING

The Annual Scientific Meeting of the National Kidney Foundation will be held November 1-3, 1996, at the Ernest N. Memorial Convention Center in New Orleans, LA. This meeting will offer participants a better understanding of the pathogenesis, diagnosis, cure, and prevention of kidney diseases. The presentations will provide the most current information to help participants formulate decisions in the direct care of their patients. Program highlights include *Are You Ready for Xenotransplantation?*; *Vexing Programs in Dialysis Patients*; *Glomerular Disease Progression? A Debate of the Issue*; *Dialysis Outcomes Quality Initiative (DOQI) Recommendations*. The meeting is a multidisciplinary program offering four separate tracks targeted toward nephrologists, renal dieticians, nephrology social workers, and nephrology nurses and technicians. The National Kidney Foundation, Inc. is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians, and designates this continuing medical education activity for 16.0 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association. For registration information, call 800-622-9010 or write to The National Kidney Foundation, 30 East 33rd Street, New York, NY 10016.

SIXTH ALEXIS CARREL CONFERENCE ON CHRONIC REJECTION AND GRAFT ATHEROSCLEROSIS

The Sixth Alexis Carrel Conference will be held in Banff, Canada on December 4-7, 1996. The meeting is aimed at transplant physicians, surgeons, pathologists, and immunologists, as well as health care professionals with an interest in transplantation. For information regarding registration and abstracts, please contact the conference organizer: Dr. Leendert C. Paul, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario M5B 1W8, Canada. Telephone: 416-867-3701; fax: 416-867-3709; e-mail: lpaul@utoronto.ca.

ADVANCED NEPHROLOGY: NEPHROLOGY FOR THE CONSULTANT

Advanced Nephrology: Nephrology for the Consultant, sponsored by the Division of Nephrology, Department of Medicine, University of California, San Diego, CA, will be held February 6-8, 1997, at The Hotel del Coronado, Coronado (San Diego), CA. The registration fee: is \$395 for physicians in practice, and \$175 for residents/fellows. This course is designated for 17 hours of AMA Category I Accreditation. For information, contact Shirley Kolkey, Course Coordinator, at 1660 Hotel Circle North, #220, San Diego, CA 92108. Telephone: 619-299-6673; fax: 619-299-6675.

JASN
The Journal of the American
Society of Nephrology

Frequency: One volume per year, beginning in January.

Correspondence concerning business matters should be addressed to: Customer Service, Subscriptions, Williams & Wilkins, 351 West Camden Street, Baltimore, MD 21201-2436. Telephone: (800) 638-6423 from anywhere in the United States and Canada. From other countries, call (410) 428-8555. Fax: (410) 528-8596.

For information on American Society of Nephrology membership, contact: Sherri Mara at (202) 857-1190. Annual dues include \$70.00 for journal subscription.

Correspondence regarding editorial matters should be addressed to: Jared J. Grantham, M.D., Editor, JASN, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160-7361.

Instructions to Authors appears in each issue.

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Volume index appears in the December issue. **Indexing/abstracting services:** The Journal is currently included by the following services in print and/or electronic format: Index Medicus, Current Contents (Clinical Medicine), and BIOSIS.

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NEORAL® Soft Gelatin Capsules (cyclosporine capsules for microemulsion)

NEORAL® Oral Solution (cyclosporine oral solution for microemulsion)

Caution: Federal law prohibits dispensing without prescription.

BRIEF SUMMARY: Please see package insert for full prescribing information.

WARNING: Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Neoral®. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Neoral® may be administered with other immunosuppressive agents. Increased susceptibility to infection and the possible development of lymphoma and other neoplasms may result from the degree of immunosuppression.

Neoral® Soft Gelatin Capsules (cyclosporine capsules for microemulsion) and Neoral® Oral Solution (cyclosporine oral solution for microemulsion) have increased bioavailability in comparison to Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP) and Sandimmune® Oral Solution (cyclosporine oral solution, USP). Neoral® and Sandimmune® are not bioequivalent and cannot be used interchangeably without physician supervision. It is recommended that cyclosporine blood concentrations be monitored in patients taking Neoral® and that dose adjustments be made in order to avoid toxicity due to high concentrations and possible organ rejection due to low concentrations. For a given trough concentration, cyclosporine exposure will be greater with Neoral® than with Sandimmune®. If a patient who is receiving exceptionally high doses of Sandimmune® is converted to Neoral®, particular caution should be exercised. Comparison of blood concentrations in the published literature with blood concentrations obtained using current assays must be done with detailed knowledge of the assay methods employed.

INDICATIONS AND USAGE: Neoral® is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. Neoral® has been used in combination with azathioprine and corticosteroids.

CONTRAINDICATIONS: Neoral® is contraindicated in patients with a hypersensitivity to cyclosporine or to any of the ingredients of the formulation.

WARNINGS: (See boxed WARNINGS)

Cyclosporine, the active ingredient of Neoral®, can cause nephrotoxicity and hepatotoxicity when used in high doses.

It is not unusual for serum creatinine and BUN levels to be elevated during cyclosporine therapy. These elevations in renal transplant patients do not necessarily indicate rejection, and each patient must be fully evaluated before dosage adjustment is initiated.

Based on the historical Sandimmune® experience with oral solution, nephrotoxicity associated with cyclosporine had been noted in 25% of cases of renal transplantation, 38% of cases of cardiac transplantation, and 37% of cases of liver transplantation. Mild nephrotoxicity was generally noted 2-3 months after renal transplant and consisted of an arrest in the fall of the pre-operative elevations of BUN and creatinine at a range of 35-45 mg/dl and 2.0-2.5 mg/dl respectively. These elevations were often responsive to cyclosporine dosage reduction.

More overt nephrotoxicity was seen early after transplantation and was characterized by a rapidly rising BUN and creatinine. Since these events are similar to renal rejection episodes, care must be taken to differentiate between them. This form of nephrotoxicity is usually responsive to cyclosporine dosage reduction.

Although specific diagnostic criteria which reliably differentiate renal graft rejection from drug toxicity have not been found, a number of parameters have been significantly associated with one or the other. It should be noted however, that up to 20% of patients may have simultaneous nephrotoxicity and rejection.

A form of a cyclosporine-associated nephropathy is characterized by serial deterioration in renal function and morphologic changes in the kidneys. From 5% to 15% of transplant recipients who have received cyclosporine will fail to show a reduction in rising serum creatinine despite a decrease or discontinuation of cyclosporine therapy. Renal biopsies from these patients will demonstrate one or several of the following alterations: tubular vacuolization, tubular microcalcifications, peritubular capillary congestion, arteriopathy, and a striped form of interstitial fibrosis with tubular atrophy. Though none of these morphologic changes is entirely specific, a diagnosis of cyclosporine-associated structural nephrotoxicity requires evidence of these findings.

When considering the development of cyclosporine-associated nephropathy, it is noteworthy that several authors have reported an association between the appearance of interstitial fibrosis and higher cumulative doses or persistently high circulating trough levels of cyclosporine. This is particularly true during the first 6 posttransplant months when the dosage tends to be highest and when, in kidney recipients, the organ appears to be most vulnerable to the toxic effects of cyclosporine. Among other contributing factors to the development of interstitial fibrosis in these patients are prolonged perfusion time, warm ischemia time, as well as episodes of acute toxicity, and acute and chronic rejection. The reversibility of interstitial fibrosis and its correlation to renal function have not yet been determined. Reversibility of arteriopathy has been reported after stopping cyclosporine or lowering the dosage.

Impaired renal function at any time requires close monitoring, and frequent dosage adjustment may be indicated.

In the event of severe and unremitting rejection, when rescue therapy with pulse steroids and monoclonal antibodies fail to reverse the rejection episode, it may be preferable to switch to alternative immunosuppressive therapy rather than increase the Neoral® dose to excessive levels.

Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic anemia which may result in graft failure. The vasculopathy can occur in the absence of rejection and is accompanied by avid platelet consumption within the graft as demonstrated by Indium 111 labeled platelet studies. Neither the pathogenesis nor the management of this syndrome is clear. Though resolution has occurred after reduction or discontinuation of cyclosporine and 1) administration of streptokinase and heparin or 2) plasmapheresis, this appears to depend upon early detection with Indium 111 labeled platelet scans. (See ADVERSE REACTIONS)

Significant hyperkalemia (sometimes associated with hyperchloremic metabolic acidosis) and hyperuricemia have been seen occasionally in individual patients.

Hepatotoxicity associated with cyclosporine use had been noted in 4% of cases of renal transplantation, 7% of cases of cardiac transplantation, and 4% of cases of liver transplantation. This was usually noted during the first month of therapy when high doses of cyclosporine were used and consisted of elevations of hepatic enzymes and bilirubin. The chemistry elevations usually decreased with a reduction in dosage.

As in patients receiving other immunosuppressants, those patients receiving cyclosporine are at increased risk for development of lymphomas and other malignancies, particularly those of the skin. The increased risk appears related to the intensity and duration of immunosuppression rather than to the use of specific agents. Because of the danger of oversuppression of the immune system resulting in increased risk of infection or malignancy, a treatment regimen containing multiple immunosuppressants should be used with caution.

There have been reports of convulsions in adult and pediatric patients receiving cyclosporine, particularly in combination with high dose methylprednisolone.

Care should be taken in using cyclosporine with nephrotoxic drugs. (See PRECAUTIONS)

Because Neoral® is not bioequivalent to Sandimmune®, conversion from Neoral® to Sandimmune® using a 1:1 ratio (mg/kg/day) may result in lower cyclosporine blood concentrations. Conversion from Neoral® to Sandimmune® should be made with increased monitoring to avoid the potential of underdosing.

PRECAUTIONS: General: Cyclosporine is the active ingredient of Neoral®. Hypertension is a common side effect of cyclosporine therapy. (See ADVERSE REACTIONS) Mild or moderate hypertension is encountered more frequently than severe hypertension and the incidence decreases over time. Anti-hypertensive therapy may be required. Control of blood pressure can be accomplished with any of the common antihypertensive agents. However, since cyclosporine may cause hyperkalemia, potassium-sparing diuretics should not be used. Calcium antagonists can be effective agents in treating cyclosporine-associated hypertension. However, care should be taken since interference with cyclosporine metabolism may require a dosage adjustment. (See Drug Interactions)

During treatment with cyclosporine, vaccination may be less effective; and the use of live attenuated vaccines should be avoided.

Information for Patients: Patients should be advised that any change of cyclosporine formulation should be made cautiously and only under physician supervision because it may result in the need for a change in dosage.

Patients should be informed of the necessity of repeated laboratory tests while they are receiving the drug. Patients should be advised of the potential risks during pregnancy and informed of the increased risk of neoplasia.

Patients should be given careful dosage instructions. Neoral® Oral Solution (cyclosporine oral solution for microemulsion) should be diluted, preferably with orange or apple juice that is at room temperature. Grapefruit and grapefruit affect metabolism of cyclosporine and should be avoided. The combination of Neoral® Oral Solution (cyclosporine oral solution for microemulsion) with milk can be unpalatable.

Patients should be advised to take Neoral® on a consistent schedule with regard to time of day and relation to meals.

Laboratory Tests: Renal and liver functions should be assessed repeatedly by measurement of BUN, serum creatinine, serum bilirubin, and liver enzymes.

Drug Interactions: All of the individual drugs cited below are well substantiated to interact with cyclosporine.

Drugs That May Potentiate Renal Dysfunction

Antifungals gentamicin tobramycin vancomycin trimethoprim with sulfamethoxazole	Antifungals amphotericin B ketocanazole	Gastrointestinal Agents cimetidine ranitidine
Antineoplastics melphalan	Anti-inflammatory Drugs azapropazon diclofenac	Immunosuppressives tacrolimus

Careful monitoring of renal function should be practiced when Neoral® is used with nephrotoxic drugs.

Drugs That Alter Cyclosporine Levels: Cyclosporine is extensively metabolized. Cyclosporine concentrations may be influenced by drugs that affect microsomal enzymes, particularly cytochrome P-450 III-A. Substances that are inducers of cytochrome P-450 could decrease metabolism and increase cyclosporine concentrations. Substances that are inhibitors of cytochrome P-450 could increase metabolism and decrease cyclosporine concentrations. Monitoring of circulating cyclosporine concentrations and appropriate Neoral® dosage adjustment are essential when these drugs are used concomitantly.

Drugs That Increase Cyclosporine Concentrations

Calcium Channel Blockers diltiazem nicardipine verapamil	Antifungals fluconazole itraconazole ketoconazole	Antibiotics clarithromycin erythromycin	Glucocorticoids methylprednisolone	Other Drugs allopurinol broncospirine danazol metoclopramide
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Drugs That Decrease Cyclosporine Concentrations

Antibiotics nafcillin rifampin	Anticonvulsants carbamazepine phenobarbital phenytoin	Other Drugs octreotide ticlopidine
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Rifabutin is known to increase the metabolism of other drugs metabolized by the cytochrome P-450 system. The interaction between rifabutin and cyclosporine has not been studied. Care should be exercised when these two drugs are administered concomitantly.

Other Drug Interactions: Reduced clearance of prednisolone, digoxin, and lovastatin has been observed when these drugs are administered with cyclosporine. In addition, a decrease in the apparent volume of distribution of digoxin has been reported after cyclosporine administration. Severe digitalis toxicity has been seen within days of starting cyclosporine in several patients taking digoxin. Cyclosporine should not be used with potassium-sparing diuretics because hyperkalemia can occur. During treatment with cyclosporine, vaccination may be less effective. The use of live vaccines should be avoided. Myositis has occurred with concomitant lovastatin, frequent gingival hyperplasia with nifedipine, and convulsions with high dose methylprednisolone. Further information on drugs that have been reported to interact with cyclosporine is available from Sandoz Pharmaceuticals Corporation.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Cyclosporine gave no evidence of mutagenic or teratogenic effects in appropriate test systems. Only at dose levels toxic to dams, were adverse effects seen in reproduction studies in rats. (See Pregnancy)

Carcinogenicity studies were carried out in male and female rats and mice. In the 78-week mouse study, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In the 24-month rat study, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. Doses used in the mouse and rat studies were 0.01 to 0.16 times the clinical maintenance dose. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related.

No impairment in fertility was demonstrated in studies in male and female rats.

Cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A recent study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes *in vitro* gave indication of a positive effect (i.e., induction of SCE), at high concentrations in this system.

An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. The most common forms of neoplasms are non-Hodgkin's lymphoma and carcinomas of the skin. The risk of malignancies in cyclosporine recipients is higher than in the normal, healthy population but similar to that in patients receiving other immunosuppressive therapies. Reduction or discontinuance of immunosuppression may cause the lesions to regress.

Pregnancy: Pregnancy Category C. Cyclosporine has been shown to be embryo- and fetotoxic in rats and rabbits following oral administration at maternally toxic doses. Fetal toxicity was noted in rats at 0.8 and rabbits at 5.4 times the human maintenance dose of 6.0 mg/kg, where dose corrections are based on body surface area. Cyclosporine was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations.

There are no adequate and well-controlled studies in pregnant women. Neoral® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The following data represent the reported outcomes of 116 pregnancies in women receiving cyclosporine during pregnancy, 90% of whom were transplant patients, and most of whom received cyclosporine throughout the entire gestational period. The only consistent patterns of abnormality were premature birth (gestational period of 28 to 36 weeks) and low birth weight for gestational age. Sixteen fetal losses occurred. Most of the pregnancies (85 of 100) were complicated by disorders, including pre-eclampsia, eclampsia, premature labor, abruptio placentae, oligohydramnios, Rh incompatibility and fetopelvic dysfunction. Preterm delivery occurred in 47%. Seven malformations were reported in 5 viable infants and in 2 cases of fetal loss. Twenty-eight percent of the infants were small for gestational age. Neonatal complications occurred in 27%. Therefore, the risks and benefits of using Neoral® during pregnancy should be carefully weighed.

Nursing Mothers: Since cyclosporine is excreted in human milk, nursing should be avoided.

Pediatric Use: Although no adequate and well controlled studies have been completed in children, patients as young as one year of age have received Neoral® with no unusual adverse effects.

ADVERSE REACTIONS: The principal adverse reactions of cyclosporine therapy are renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia. Hypertension, which is usually mild to moderate, may occur in approximately 50% of patients following renal transplantation and in most cardiac transplant patients.

Glomerular capillary thrombosis has been found in patients treated with cyclosporine and may progress to graft failure. The pathologic changes resemble those seen in the hemolytic-uremic syndrome and include thrombosis of the renal microvasculature, with platelet-fibrin thrombi occluding glomerular capillaries and afferent arterioles, microangiopathic hemolytic anemia, thrombocytopenia, and decreased renal function. Similar findings have been observed when other immunosuppressives have been employed posttransplantation. Hypomagnesemia has been reported in some, but not all, patients exhibiting convulsions while on cyclosporine therapy. Although magnesium-depletion studies in normal subjects suggest that hypomagnesemia is associated with neurologic disorders, multiple factors, including hypertension, high dose methylprednisolone, hypocholesterolemia, and nephrotoxicity associated with high plasma concentrations of cyclosporine appear to be related to the neurological manifestations of cyclosporine toxicity.

In controlled studies, the nature, severity and incidence of the adverse events that were observed in 493 transplanted patients treated with Neoral® were comparable with those observed in 208 transplanted patients who received Sandimmune® in these same studies when the dosage of the two drugs was adjusted to achieve the same cyclosporine blood trough concentrations.

The following reactions occurred in 2% or less of Sandimmune®-treated patients: allergic reactions, anemia, anorexia, confusion, conjunctivitis, edema, fever, brittle fingernails, gastritis, hearing loss, hiccups, hyperglycemia, muscle pain, peptic ulcer, thrombocytopenia, tinnitus. The following reactions occurred rarely: anxiety, chest pain, constipation, depression, hair breaking, hematoma, joint pain, lethargy, mouth sores, myocardial infarction, night sweats, pancreatitis, pruritus, swallowing difficulty, tingling, upper GI bleeding, visual disturbance, weakness, weight loss.

Increased susceptibility to infection and the possible development of lymphoma and other neoplasms may result from the degree of immunosuppression.

Sandoz Pharmaceuticals Corporation, East Hanover, New Jersey 07936 SEPTEMBER 1995 38371902

INNOVATION

Through Microemulsion

- Neoral® demonstrates intrasubject variability of drug exposure (%CV) [measured by the area under the concentration-vs.-time curve] in renal transplant recipients of 9% to 21% compared to 19% to 26% for Sandimmune® (cyclosporine)
- Neoral provides increased bioavailability¹ with adverse events* comparable to those of Sandimmune when the dosage of the two drugs is adjusted to achieve the same cyclosporine blood trough concentrations
- Routine monitoring is required and dosage adjustments may be necessary in both de novo patients and maintenance patients converted from Sandimmune to Neoral†
- Neoral and Sandimmune are not bioequivalent and cannot be used interchangeably without physician supervision
- Neoral offers an important option for the prevention of organ rejection in renal, liver, and heart allogeneic transplant recipients

NEORAL[®]
cyclosporine capsules and
oral solution for microemulsion



*The principal adverse reactions of cyclosporine therapy are renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia.

†For de novo patients, start with the same Neoral dosage you would use with Sandimmune. For maintenance patients, conversion to Neoral is generally safe and well tolerated: Start with a simple 1:1 dosage conversion to Neoral (see boxed warning). Adjust the Neoral dosage to attain preconversion blood trough concentrations. The daily dose of Neoral should always be given in two divided doses (b.i.d.).

Please see brief summary of prescribing information and boxed warning for Neoral on the adjacent page.

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Reference

1. Mueller EA, Kovarik JM, van Bree JB, et al. Pharmacokinetics and tolerability of a microemulsion formulation of cyclosporine in renal allograft recipients—a concentration-controlled comparison with the commercial formulation. *Transplantation*. 1994;57:1178-1182.

 **SANDOZ**
SANDOZ PHARMACEUTICALS CORPORATION
EAST HANOVER, NEW JERSEY 07936

NEO-0895-01 Printed in U.S.A. 4/96