PEDIATRIC PHARMACOTHERAPY

A Monthly Review for Health Care Professionals of the Children's Medical Center

CYCLOSPORINE: TECHNIQUES FOR PATIENT MONITORING

Cyclosporin

Pharmacology Reviews

Immunosuppressive medications play a large part of the management of many pediatric illnesses. Cyclosporine is the primary tool used to prevent rejection following solid organ and bone marrow transplantation (1-3). It has been estimated that cyclosporine is given to more than 90% of children who have received a kidney transplant in the United States (3). In addition, the ability of cyclosporine to inhibit T-cell activation has been shown to have a role in the treatment of diseases such as nephrotic syndrome, refractory Crohn's disease and ulcerative colitis, biliary cirrhosis, aplastic anemia, rheumatoid arthritis, myasthenia gravis, and dermatomyositis (4-7)

As more children are placed on chronic immunosuppressive therapy, health care professionals in pediatrics need to be more aware of the issues related to long-term treatment with cyclosporine. This article will focus on strategies to monitor cyclosporine therapy. Readers who are interested in the pharmacology,

pharmacokinetics, and dosing of cyclosporine should refer to one of the recent extensive reviews of this therapy (6,7).

Evaluating Cyclosporine Concentrations

The clinical benefit of routine monitoring of cyclosporine serum concentrations remains controversial. The medical literature continues to feature articles debating the appropriate assay methodology, therapeutic ranges, and applications to dosing strategies (6,7) The ideal therapeutic range for most institutions has been determined from years of clinical experience rather than controlled drug investigations. As a result, there is considerable variation in the literature and among different practice groups.

At UVa, cyclosporine serum concentrations are analyzed with a RIA (TDX) assay using whole blood. Trough concentrations obtained immediately prior to a dose are recommended for routine monitoring. The target trough serum concentration range chosen for patients receiving solid organ transplants is 200-800 mg/ml at initial treatment, with a slightly lower range of 200-400 mg/ml for maintenance therapy. Higher serum concentrations are generally required for patients following bone marrow transplantation, while lower levels are often satisfactory in patients after renal transplantation.6 As with many routinely monitored therapies, a change in the trend of the values is of greater significance than an individual serum concentration.

Identifying Drug Interactions

The complex medication regimens required by most patients receiving cyclosporine make identifying potential drug interactions an important concern. Drugs known to cause immunosuppression should be used with caution in patients already receiving cyclosporine. Any beneficial additive suppression of immune function may be offset by an increased risk for infection. Adverse renal effects may be increased when patients receiving cyclosporine are given other nephrotoxic agents such as aminoglycosides, amphotericin, acyclovir, or nonsteroidal anti-inflammatory drugs (7).

Cyclosporine metabolism occurs via the hepatic cytochrome P450-A enzyme system with the production of at least 21 different metabolites. As a result, there are several significant interactions with drugs which also utilize this metabolic pathway. The following list includes drug interactions with cyclosporine (CSA) that have been reported in the medical literature.

Enzyme Inducing Agents (decrease CSA concentrations by increasing metabolism)

- carbamazepine
- phenobarbital
- phenytoin

- primidone
- rifampin
- valproic acid
- sulfamethoxazole-trimethoprim (mechanism is uncertain)

Enzyme Inhibiting Agents (increase CSA concentrations by decreasing metabolism)

- diltiazemb
- erythromycin
- fluconazole
- ketoconazoleb
- nicardipine
- verapamil
- nifedipinec
- imipenem-cilastatin (mechanism is uncertain)

Increased CSA Absorption (increase CSA concentrations)

- metoclopramide

Variable Effects:

- high-dose corticosteroids have variable effect on CSA concentrations; they may have potential neurotoxicity (possibly by interfering with metabolism)
- digoxin levels may increase during CSA administration (mechanism unknown)
- CSA may cause a reduction in the efficacy of oral contraceptives (mechanism unknown)
- CSA may cause prolonged paralysis by polarizing neuromuscular blocking agents (mechanism unknown)

Monitoring Adverse Effects

The adverse effects associated with cyclosporine can have a significant impact on the success of therapy. These can range from dose-limiting nephrotoxicity and CNS effects to cosmetic changes that may foster noncompliance. Nephrotoxicity is the greatest potential risk of long-term cyclosporine therapy. It has been estimated that some degree of renal dysfunction occurs in up to 40% of patients. The impairment is typically seen as a dose-dependent reduction in glomerular filtration rate, occurring within the first six months of treatment (4,6,7,10,11). The precise mechanism for this effect remains unknown, but appears to involve afferent arteriolar vasoconstriction. Alterations in prostaglandin/prostacyclin concentrations have been implicated, but many additional factors have also been proposed. On histologic examination, tubular atrophy and mesangial cell proliferation have been documented (11). Routine

monitoring of BUN and serum creatinine is recommended in patients receiving chronic therapy. When these values increase, most patients will respond to a reduction in cyclosporine dose without jeopardizing the efficacy of therapy. Concomitant administration of calcium channel blocking agents may have a cytoprotective effect and mitigate renal damage (6) Severe, irreversible damage caused by cyclosporine appears to be rare.

Hypertension is also a relatively common adverse effect, occurring in 13-30% of patients. Most patients will respond to therapy with antihypertensives without requiring discontinuation of cyclosporine therapy. Many institutions use calcium channel blocking agents to take advantage of their multiple beneficial effects (7).

Nearly 1/4 of patients will experience adverse CNS effects. These effects typically consist of headache, depression, confusion, tremor, paresthesia, or blurred vision and typically resolve with dose reduction. Seizures may result when serum cyclosporine concentrations are greatly elevated. Adverse CNS effects are more likely to occur in patients with concomitant hypomagnesemia, hypertension, hypocholesterolemia, or high serum concentrations of aluminum. Other patients at higher risk for CNS toxicity include those who are also receiving large doses of corticosteroids and patients who accumulate high concentrations of the M17 metabolite of cyclosporine (6).

Hypertrichosis, acne, and gingival hyperplasia are also fairly common, occurring in approximately 20-50% of patients. These effects frequently respond to dose reduction and rarely require discontinuation of therapy (4,7). The significance of these reactions, however, should not be underestimated in the adolescent and young adult population where their occurrence may lead to noncompliance.

Nausea, vomiting, and diarrhea are reported to occur in 3-4% of patients, primarily affecting those receiving the oral solution. Hyperlipemia (increased cholesterol, LDL, and triglyceride levels) has been linked to cyclosporine use, but appears to be reversible when therapy is discontinued (1). This area remains controversial, with some research showing little long term effect from these changes (12). Alterations in serum electrolytes such as hyperkalemia and hypomagnesemia may also occur, worsening hypertension and CNS effects (7). Occasionally, male patients will exhibit gynecomastia as a result of a cyclosporine-induced increase in prolactin and reduction in testosterone (7).

Allergic reactions are rare, occurring in approximately 1 in every 1,000 patients treated. It is believed to be a reaction to the IV cyclosporine vehicle (polyoxyethylated castor oil) rather than the drug itself. Patients experiencing anaphylactic reactions to the IV product have been given oral products without incident. Other rare adverse effects include hepatotoxicity and thrombocytopenia. Serum bilirubin, liver function tests, and platelet counts should be monitored periodically in children receiving cyclosporine. The development of lymphomas, especially non-Hodgkin's lymphoma, has been reported in patients receiving cyclosporine, although causality has not been clearly established (7,13).

Enhancing Patient Compliance

Noncompliance remains a significant problem with cyclosporine administration. It has been estimated that as many as 50% of pediatric transplant recipients fail to follow their prescribed medication regimens (14). In severe cases, noncompliance has been suggested as a factor in graft failure. The true impact of this problem is difficult to assess, since the few available studies vary widely in methodology (14,15). The best approach for avoiding noncompliance may be improving patient education. A thorough understanding of the importance of immunosuppressive therapy is necessary for the patient and family. Discussions about medications should be included not only at the initiation of therapy, but also during follow-up to reinforce the need for compliance and address any patient concerns.

One of the greatest problems in maintaining patient compliance with cyclosporine regimens is the difficulty in drug administration. Oral cyclosporine is available in both a capsule dosage form and as a liquid. Children who are receiving doses less than 25 mg or are unable to ingest capsules must be given the oral solution. This preparation is formulated in a modified olive oil vehicle and has a concentration of 100 mg/ml.7 The major disadvantages associated with the liquid dosage form are its poor taste and the difficulty in obtaining precise dosage measurements. If the oral solution must be used, it should be diluted with regular or chocolate milk, cranberry juice, or orange juice (personal communication, Mark D. Grebenau, MD, PhD, Sandoz Pharmaceuticals). This will help to mask the taste of the cyclosporine and provide a more soluble vehicle. Periodic changes in the diluent may help to make the liquid more tolerable. The oral solution should be stored at room temperature and should be mixed with diluents already at room temperature. Glass cups, bottles, and utensils are preferable, since cyclosporine binds to plastics. If plastic must be used for young children, it should have a smooth hard surface.

A microemulsion formulation of cyclosporine is under investigation.16 This product improves the bioavailability of cyclosporine two to four-fold and reduces fluctuations in absorption, allowing the use of oral doses similar to the current recommendations for intravenous administration. It is also more palatable and may help to improve compliance.

In summary, the use of cyclosporine remains essential in the management of children with transplanted organs or autoimmune diseases. Health care professionals should be aware of the many complexities of cyclosporine monitoring, including evaluating serum concentrations, identifying drug interactions, and assessing adverse reactions. In addition, attention to patient compliance is necessary to ensure opitmal benefit from chronic cyclosporine therapy.

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Pharmacology Literature Review

Ceftazidime Review

This is an extensive review of the clinical uses of ceftazidime. Studies demonstrating in vitro and in vivo antibacterial efficacy are reviewed, as well as pharmacokinetic properties and adverse effects. Both the pharmacokinetics and efficacy sections contain information related to the use of ceftazidime in patients with cystic fibrosis. In addition, the issue of bacterial resistance is addressed. Rains CP, Bryson HM, Peters DH. Ceftazidime: An update of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. Drugs 1995;49(4):577-617.

Compliance with Medications

The authors of this article present an interesting discussion of issues related to patient noncompliance with medication regimens. For example, reducing the number of doses a patient must take each day has not always been found to result in an improvement in patient compliance. The authors focus on the advantages and disadvantages of using serum concentration monitoring as a tool to identify noncompliant patients. Rudd P, Lenert L. Pharmacokinetics as an aid to optimising compliance with medications. Clin Pharmacokin 1995;28(1):1-6.

Digoxin Drug Interactions

There are many drugs that may interfere with digoxin, affecting both its efficacy and toxicity. This review contains a well organized table of these interactions, ranked according to clinical significance. This may be a valuable reference to those who prescribe antiarrhythmics or follow children receiving digoxin. Magnani B, Malini PL. Cardiac glycosides: Drug interactions of clinical significance. Drug Safety 1995;12(2):97-109.

Methotrexate Pharmacokinetics

Glomerular filtration rate and methotrexate elimination were evaluated in 18 children beginning treatment for leukemia. GFR values were highly variable among the patients studied, but on average were similar to those reported for healthy children. A significant correlation was found between methotrexate clearance and GFR. Interestingly, 6 of the children received amphotericin during the study period, resulting in a drop in GFR without a concurrent increase in serum creatinine. Murry DJ, Synold TW, Pui C et al. Renal function and methotrexate clearance in children with newly diagnosed leukemia. Pharmacotherapy 1995;15(2):144-9.

Placental Drug Transfer

This extensive review covers not only the mechanisms of placental drug transfer but also reviews the available data on many medications in current use. A large section is devoted to a review of antimicrobials. The authors cite nearly 300 studies and case reports in their paper. Pacifici GM, Nottoli R. Placental transfer of drugs administered to the mother. Clin Pharmacokin 1995;28(3):235-69.

Theophylline Dosing Equations

The accuracy, precision, and reliability of two previously published theophylline dosing equations were evaluated in 46 premature infants with apnea. Actual maintenance doses required to achieve therapeutic serum concentrations did not correlate with the doses determined from either of the equations (r= 0.296). The recommendations made from using the dosing equations were least accurate in infants < 30 weeks gestational age. This study confirms the high degree of variability in theophylline pharmacokinetics among premature infants. Bhatt-Mehta V, Johnson CE, Donn SM et al. Accuracy and reliability of dosing equations to individualize theophylline treatment of apnea of prematurity. Pharmacotherapy 1995;15(2):246-50.

Vitamin K Review

The pharmacologic properties of vitamin K are presented, as well as a summary of the various clinical uses of exogenous vitamin K. Discussions of the use of vitamin K prophylaxis in neonates and children with leukemia are included. The controversy surrounding the antenatal administration of vitamin K to prevent IVH in premature neonates is also addressed. Thorp JA et al. Current concepts and controversies in the use of vitamin K. Drugs 1995;49(3):376-87.

Formulary Update
The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 3/24/95:

1. Vinorelbine (Navelbine) was added to the formulary for the treatment of resistant breast cancer and small-cell lung cancer.
2. Lamotrigine (Lamictal) was approved for use. This anticonvulsant has been used successfully in the treatment of many seizure types, including Lennox-Gastaut syndrome.
3. Doxapram (Dopram) was added to the formulary for the treatment of apnea of prematurity in patients who do not respond to theophylline. This product has been used at UVA for many years, but this approval will allow the creation of specific ordering screens for MIS and maintenance of a stock supply.

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