NOVEL USES FOR CYCLOSPORINE A

Cyclosporine A (CSA) is an immunomodulating agent whose mechanism of action is related to its dampening effect on the function of helper T-lymphocytes. The drug has been found useful in clinical settings other than transplantation, such as certain hematologic, dermatologic, and connective tissue diseases. Because it has a high incidence of acute and chronic toxicity, CSA should be used only after more conventional measures have failed.

HEMATOLOGIC INDICATIONS

Although most beneficial in solid organ transplantation, CSA also has been successful in the prophylaxis of acute graft-versus-host disease (GVHD) in bone marrow transplantation. CSA combined with methylprednisolone or methotrexate is more effective than any single agent in the prevention of GVHD.

CSA in combination with antithymocyte globulin and methylprednisolone is beneficial in the treatment of aplastic anemia, according to the interim analysis of a German trial. Small trials have shown that CSA may benefit patients with pure red cell aplasia. Case reports indicate benefit in other hematologic diseases, including refractory idiopathic thrombocytopenic purpura, Hodgkin's disease (amelioration of the "B" symptoms), reduction of the titer of factor VIII inhibitors in the hemophilias, and autoimmune neutropenia of Felty's syndrome.

DERMATOLOGIC INDICATIONS

CSA was first reported as treatment for psoriasis in 1979. Subsequent publications confirmed its benefit in the treatment of severe psoriasis—namely plaque, erythrodermic, and pustular forms of the disease. Most investigators use a dosage of 5 mg/kg/day to 6 mg/kg/day to avoid acute toxicity. In one study, all 17 patients treated with 5 mg/kg/day improved, and 12 cleared completely within 3 months. The 41% relapse rate among these 12 patients 6 months after discontinuing CSA was no different than the rate expected with other antipsoriatic therapies.

Because CSA might favor the expansion of antigen-specific suppressor T-lymphocytes, it has been studied and found useful in recalcitrant atopic dermatitis, in which patients show a decreased number of suppressor cells. Case reports suggest that it may be useful in severe actinic dermatitis that has failed to respond to corticosteroids, PUVA, or azathioprine. Other potential uses include generalized cutaneous lichen planus, oral erosive lichen planus, alopecia areata, pemphigus vulgaris, and pyoderma gangrenosum.

TREATMENT OF CONNECTIVE TISSUE DISEASE

CSA has been studied in open, uncontrolled and blinded, controlled trials involving patients with rheumatoid arthritis (RA), Behcet's syndrome, juvenile dermatomyositis, systemic lupus erythematosus, Sjogren's syndrome, uveitis, primary biliary cirrhosis, and chronic active hepatitis.

CSA has been evaluated most extensively in RA, and at least three controlled trials demonstrate its efficacy. In all patients, CSA was used only after the failure of more conventional measures, including gold and d-penicillamine. All CSA-treated patients showed reduction in the number of swollen joints and improved global assessments. Although CSA has little effect on the erythrocyte sedimentation rate, C-reactive protein was significantly lowered in treated patients. Unfortunately, acute toxicity resulted in the discontinuation of CSA in up to 45% of treated patients within 6 months.

In trials of patients with Behcet's syndrome, control of uveitis was better with CSA, 10 mg/kg/day, than with colchicine or with prednisolone combined with chlorambucil. Fourteen chronically ill children with juvenile dermatomyositis who had failed combination therapy with corticosteroids and immunosuppressive agents responded to a maintenance dose of CSA ranging from 2.5 mg/kg/day to 7.5 mg/kg/day. The addition of CSA also allowed the reduction of maintenance prednisolone from a mean of 14 mg/day to 3 mg/day.

ADVERSE EFFECTS

Hypertension and renal dysfunction are the greatest cause for concern in CSA-treated patients. Nearly every rheumatoid arthritis patient treated with CSA has some rise in serum creatinine, and hypertension often accompanies renal impairment. The mechanisms of renal damage include primary vascular effects with resulting decreased renal blood flow, direct renal tubular injury, stimulation of interstitial cell proliferation which leads to fibrosis, and inhibited production of protective renal prostaglandins. These renal effects appear to be dose-related and may be less troublesome if a dosage of 3 mg/kg/day to 5 mg/kg/day is used to maintain a trough level below 200 ng/ml. Drugs that can produce synergistic toxicity, such as nonsteroidal anti-inflammatory

agents and aminoglycoside antibiotics,. should not be given simultaneously with CSA.

Other potential toxic effects include abdominal pain, nausea, paresthesias, tremors, gingival hyperplasia, hypertrichosis, liver dysfunction, and hyperuricemia. Non-Hodgkin's lymphoma and Kaposi's sarcoma have been seen in a small percentage of transplant patients.

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BIBLIOGRAPHY

Kahan BD. Cyclosporine. N Engl J Med 1989; **321**:1725–1738.

Gupta AK, Brown MD, Ellis CN, et al. Cyclosporine in dermatology. J Am Acad Dermatol 1989; **21**:1245–1256.

Bos JD. The pathomechanisms of psoriasis: the skin immune system and cyclosporin. Br J Dermatol 1988; **118**:141–155.

Yocum DE, Klippel JH, Wilder RL, et al. Cyclosporin A in severe, treatment-refractory rheumatoid arthritis. Ann Intern Med 1988; **109**:863–869.

KEYS TO EFFECTIVE MANAGEMENT OF CHRONIC CANCER PAIN

The biggest problem in the management of cancer pain is undermedication. Yet, most patients who have chronic cancer pain can be treated effectively in the primary care setting with oral morphine, the opiate of choice because of the huge body of data regarding its use.

The key to success is frequent, around-the-clock (every 4 hours) dosing, titrated to the patient's estimate of pain control. Individual pharmacokinetics and responses vary considerably, and "standard" opiate dosage recommendations are unlikely to be effective.

"Rescue dosing" should be a part of the regimen. This allows the patient to take an extra dose or another medication if pain intervenes before the next scheduled around-the-clock opiate dose. Rescue dosing not only gives the patient more control over the pain, which reduces anxiety, but also is a way to monitor the efficacy of the around-the-clock dosage. Frequent rescue dosing may indicate that the patient is undermedicated, that he should be taking a different medication, or that intervening pain may be due to some new problem.

INDIVIDUAL PHARMACOKINETICS

Addiction is rarely a problem in this population, and the patient should be reassured of this. The concept of "saving up" medication until it is "really needed" is a myth that has been perpetrated among the health care professions as well as the general public. Safe, effective pain management consists of frequent small doses at regular intervals. Oral morphine, in dosages ranging from 2.5 mg to 180 mg every 4 hours, is reliable in 85% to 90% of patients with chronic cancer pain, but individual pharmacokinetics must be considered.

New, sustained-release morphine tablets are convenient, though expensive. It is important that the tablet be swallowed intact; otherwise, the timed-release action may be altered and result in respiratory depression. The slow-release tablet should be started after the patient has established good pain control with liquid morphine every 4 hours. To determine the twice-daily (every 12 hours) sustained-release dose, the total 24-hour liquid morphine dosage is divided by two. If necessary, morphine also can be given rectally, intramuscularly, intravenously, sublingually, or subcutaneously.

OTHER CAUSES OF PAIN

Not all cancer pain is opiate-responsive. The patient may also require other drugs for pain not responsive to opiates. Nonsteroidal anti-inflammatory drugs are used for bone pain. Corticosteroids may be needed for pain from nerve compression or extensive soft tissue infiltration. Phenothiazines are antiemetic but also sedate and are co-analgesic. Antidepressants are often useful.

It is important to detect other causes of pain, ifor example, osteoporosis or duodenal ulcer. Pain also can be a consequence of chemotherapy, radiation, or surgery. Proper pain management should help the patient tolerate these treatments. New or increasing back pain should be treated as an emergency to rule out spinal cord compression. If there are neurologic deficits, magnetic resonance imaging is best for confirming the diagnosis.

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BIBLIOGRAPHY

Walsh TD, Cheater FM. Use of morphine for cancer pain. Pharm J 1983; **231**:525–527.

Kaiko RK, Stanley L, Wallenstein MS, et al. Analgesic and mood effects of heroin and morphine in cancer patients with postoperative pain. N Engl J Med 1981; **25**:1501–1507.