Cyclosporine A

CAS: 59865-13-3
MF: $C_{62}H_{111}N_{11}O_{12}$
MW: 1203
Solubility: Slightly soluble in water and saturated hydrocarbons; very soluble in methanol, acetone, and diethyl ether [1].

Major use
Cyclosporine A is a hydrophobic cyclic undecapeptide produced by the fungus *Tolypocladium inflatum*. Used in organ transplantation. Immunosuppressant action directed mainly against T-lymphocytes resulting in inhibition of cell-mediated immunity and, to a lesser extent, antibody production [1].

Human toxicity
Headache, nausea, CNS depression, transient renal insufficiency, hypertension, dysesthesias, taste abnormalities, facial flushing, GI upset, tremor, fasciculation, peripheral edema and abdominal swelling, and hepatotoxicity have been reported following overdose [2].

Therapeutic doses: Initially, 15 mg/kg 4 to 12 hours prior to transplantation. This single daily dose is continued for one to two weeks postoperatively and then tapered each week to a maintenance dose of 5 to 10 mg/kg/day. For renal transplant patients doses of 10 to 14 mg/kg/day may be used; doses of 3 mg/kg/day have been used successfully in selected renal transplant patients [2].

Cyclosporine A does not appear to be highly toxic orally. Doses of 30 to 400 mg/kg produced only minor symptoms [2].

The therapeutic plasma concentrations are 0.05 to 0.3 mg/l. Nephrotoxicity has been associated with plasma levels greater than 0.25 mg/l, and hepatotoxicity with levels greater than 1 mg/l [2].

Kinetic data
Absorption: Variable and incomplete oral absorption (absolute bioavailability is about 30%).

Volume of distribution: the reported volume of distribution in renal failure patients following intravenous administration of cyclosporine A varies from 1.5 to 7.5 l/kg [2].

Distribution: cyclosporine A binds to cell membranes, including erythrocytes. 41% to 58% is contained within erythrocytes. Its levels in serum are approximately 33% to 47% of those measured in whole blood until saturation of erythrocytes occurs [2]. Cyclosporine A is distributed largely outside the blood volume; the distribution in blood is concentration dependent [2].

The plasma half-life: cyclosporine A appears to exhibit first-order kinetics even following large overdoses. In 3 reported overdose cases, the apparent half-lives were 7-70 hours [2].

Time to peak: peak blood levels occur around 3.5 hours after oral ingestion [2].

Protein binding: about 90%, mainly to lipoproteins [2].

Metabolism and excretion
Cyclosporine A is extensively metabolized by the cytochrome P-450 III-A enzyme system in the liver. There are at least 25 metabolites that have been identified; biological activity of the metabolites is considerably less than those of the parent compound [2].

Excretion: only 6% of a dose is excreted in the urine; 0.1% of the dose is excreted unchanged. The principal route of excretion is the bile [2].

Pharmacological mechanisms
The exact mechanism of action is unknown. Cyclosporine A alters primary immune responses by suppressing helper T-lymphocyte proliferation, activation, and release of lymphokines [2].

Toxicological mechanisms
In animal models, cyclosporine A produces evidence of structural renal damage within 4 days of receiving oral doses of more than 25 mg/kg/day. Structural damage is generally confined to the descending limb of the loop of Henle in the proximal tubule. Stimulation of the renin-angiotenson-aldosterone system may play a part. In animals receiving greater than 25 mg/kg/day hyperbilirubinemia, hypoalbuminemia, and altered serum liver enzymes have been noted. Changes are accompanied by centrilobular fatty changes, endoplasmic reticulum dilatation, and loss of ribosomes [2].

Target organs: kidney, liver.

References

1. HSDB, TOXNET (2005).
2. Poisindex, Thomson Micromedex (2006).

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