

Cyproheptadine

Serotonin syndrome is a potentially fatal adverse drug reaction resulting from excessive central or peripheral serotonergic activity. Drug interaction between multiple serotonergic drugs at therapeutic doses, and less frequently, overdoses of single serotonergic agents cause this syndrome. The syndrome encompasses a wide range of clinical findings, which usually occur within six hours of the ingestion of multiple proserotonergic drugs. Clinical features of serotonin syndrome include a triad of altered mental status, autonomic dysfunction, and neuromuscular changes. Symptoms may range from agitation, diarrhea, tachycardia, diaphoresis, mydriasis, tremor, myoclonus, and hyperreflexia in mild to moderate cases to delirium, coma, hyperthermia, muscle rigidity, hypertonicity and in severe cases.

Mechanism/Indications: Cyproheptadine is a histamine-1 receptor antagonist with nonspecific 5-hydroxytryptamine (5-HT)-1A and 5-HT_{2A} antagonistic properties. It is the recommended antidote for the treatment of serotonin syndrome in the setting of incomplete response to supportive therapy including aggressive cooling and benzodiazepines. While it exerts weak anticholinergic actions, cyproheptadine's antidotal properties are attributed to the blockade and competition at 5-HT (serotonin) receptors. A dose of 12–32 mg will bind 85%–95% of serotonin receptors.

Dosing: The adult dose is 12 mg orally initially, then 2 mg given every 2 hours if patient remains symptomatic. The adult maximum dose is 32 mg in 24 hours. Children should receive 0.25 mg/kg/day divided every 6 hours with a maximum of 12 mg/day. It is available as a 2 mg/5 oral syrup and a 4 mg tablet, which may be crushed and administered via a nasogastric tube. Cyproheptadine is not available for IV use. For both children and adults, the dose should be titrated up until the maximum recommended daily dosage is achieved or the patient becomes asymptomatic.

Adverse Effects/Contraindications: Cyproheptadine may lead to sedation, but this side effect is consistent with the goals of management and should not deter clinicians from its use. It may also produce transient hypotension due to the reversal of serotonin-mediated increases in vascular tone. Common side effects of cyproheptadine may include nausea, vomiting, diarrhea, abdominal discomfort and anticholinergic effects such as dry mouth.

Cyproheptadine should be avoided in patients with hypersensitivity to cyproheptadine. Cyproheptadine has anticholinergic properties and, therefore, relative contraindications to its use include asthma, narrow angle glaucoma, urinary tract obstruction and GI obstruction. Information regarding safety is lacking in children under 2 years of age.

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For more on cyproheptadine:

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- Kapur S, Zipursky RB, Jones C, Wilson AA, DaSilva JD, Houle S. Cyproheptadine: a potent in vivo serotonin antagonist. *Am J Psychiatry* 1997;154(6):884.
- Manini AF. Monoamine Oxidase Inhibitors. In: Hoffman RS, Howland MA, Lewin NA Nelson LS, Goldfrank LR, editors: *Goldfrank's Toxicologic Emergencies*. 10th ed. New York NY, 2015;993-1001.

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