

History/ Background

Celexa (citalopram) is a selective serotonin reuptake inhibitor (SSRI) that was FDA-approved in 1998 for the treatment of depression. The chemical structure of citalopram is unrelated to that of other SSRIs or of tricyclic, tetracyclic or other available antidepressant drugs. It has been reported to be the most serotonin selective of the SSRIs.

Mechanism of Action

The mechanism of action of citalopram as an antidepressant is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from its inhibition of CNS neuronal reuptake of serotonin. Animal studies suggest that citalopram has minimal effects on norepinephrine and dopamine neuronal reuptake.

Kinetics, Metabolism

Citalopram is rapidly absorbed from the GI tract and has peak concentrations within 2 to 4 hours. Food does not seem to affect its absorption. The volume of distribution of citalopram is about 12 L/kg and it is approximately 80% protein bound. Citalopram is metabolized mainly through the liver, with a mean terminal half-life of about 35 hours.

Clinical Symptoms

Citalopram has been reported to cause cardiac conduction delays. Animal studies suggested that death is likely due to QTc prolongation with subsequent fatal arrhythmias. The culprit - a cardiotoxic metabolite called didemethyl-citalopram (DDCT). Although some authors believe citalopram to be as safe as other SSRIs in overdose, others believe it to be much more toxic. There have been multiple case reports and case series describing ECG changes after citalopram overdose. These changes include widening of the QRS, nonspecific ST-T changes, bundle branch blocks, ventricular fibrillation, and severe sinus bradycardia. These are especially prominent when the ingestion is greater than 600 mg. Other toxicity noted after overdose include seizures, hypotension, metabolic acidosis, hypokalemia, and syncope. Typically, when the ingestion is less than 600 mg mild symptoms such as nausea, dizziness, diaphoresis, tachycardia, and drowsiness are reported. Recently reported in the literature was a case of a young (21yo) healthy female who developed QTc interval prolongation after ingestion of only 400mg of citalopram. The ECG effects did not occur in this patient until 13 hours post ingestion. The late cardiac effects may be due to the toxic metabolite DDCT which reaches peak concentrations between 6-7 hours and may even be delayed even further in overdose. Further animal literature indicates that citalopram inhibits cardiac Na⁺ and Ca²⁺ channels, has class I and IV anti-arrhythmic effects, and may be pro-arrhythmic secondary to intraventricular conduction delays and shortening of repolarization.

Citalopram is also known to bind to histamine receptors with the same affinity as clomipramine, an older tricyclic antidepressant (TCA).

Given its effect on serotonin levels, it is possible that citalopram may cause or contribute to serotonin syndrome. Symptoms of serotonin syndrome can be divided into three groups: mental status changes (agitation, lethargy, hallucinations, seizures, coma, etc), neuromuscular (clonus, muscle rigidity, ataxia, nystagmus, opisthotonos, trismus, etc), and autonomic instability (diaphoresis, tachycardia, hypertension or hypotension, flushing, diaphoresis, salivation, etc).

Differential Diagnosis/ Triage

Given all this information, it appears citalopram may not be quite as simple and benign of an overdose as may have been first believed. To put this all into perspective, the normal daily dose of citalopram is 20-40mg a day. Therefore life-threatening toxicity may result with ingestion of only 10 tablets of the 40mg tablets or 20 tablets of the 20mg tablets. Toxicity in overdose is similar to that of a TCA overdose – QRS/QT prolongation, ventricular arrhythmias, Na⁺ channel blockade, hypotension, metabolic acidosis, seizures. However, two very important differences do exist between the two. First, TCAs tend to produce tachycardia in overdose whereas citalopram may produce tachycardia or severe bradycardia. Secondly, tricyclic antidepressant toxicity usually occurs very rapidly within 6 hours, and if no symptoms are noted within 6 hours the patient can be discharged. Citalopram overdoses however may not produce ECG

changes and seizures until 13 hours later. Therefore these patients should be admitted to a medical intensive care unit for cardiac monitoring and seizure precautions for at least up to 13 hours post ingestion. It is also important to rule out other medical causes.

Decontamination and Treatment

Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric lavage and use of activated charcoal should be considered if ingestion occurred within the past one to two hours. Although there is currently no data on whether or not activated charcoal administered after an hour would be of any benefit in decreasing metabolite concentrations, one may wish to consider its use given its pharmacology, the significant toxicity associated with citalopram, and the fairly benign side effect profile of activated charcoal. Both gastric lavage and activated charcoal administration should be performed only if they can be done with minimal risk to the patient. Due to the large volume of distribution of citalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be beneficial.

Monitoring and Labs

Obtain a baseline 12-lead ECG and obtain serial EKG's. The patient should have continuous cardiac monitoring. Monitor VS closely. Citalopram level is not clinically useful and therefore not recommended. Following a significant overdose, monitor CBC, UA, liver and kidney functions, electrolytes, fluid status

and creatine kinase (CK) enzymes since rhabdomyolysis has developed. EEG may be indicated in patients who develop seizure activity or altered mental status.

Management

There are no specific antidotes for Celexa™. Provide good symptomatic and supportive care. Treat seizures with benzodiazepines, such as lorazepam or midazolam. Based on the proposed mechanism of cardiovascular toxicity, sodium channel blockade, sodium bicarbonate may actually be of benefit if cardiovascular abnormalities do occur. A potential indication for NaHCO₃ in the setting of citalopram overdose includes widening of the QRS duration greater than 100 milliseconds (0.1 seconds). Serotonin syndrome typically resolves with good supportive care after the offending drugs are stopped. Sever cases of serotonin syndrome may respond to treatment with cyproheptadine, a non-specific serotonin blocking agent.

References :

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