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FEATURE ARTICLE

PEER REVIEWED

Recognizing Dangerous Poisonings in Primary Care: Part 1, Antidepressants

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The 5 most common causes of poisoning-related fatalities in the United States are antidepressants, antihistamines, cardiovascular drugs, opioids, and pesticides.[1] Drug poisonings, particularly mild cases, are often exceptionally difficult to recognize. Slightly dilated pupils, mild tachycardia and hypertension, slight fever, and tachypnea are all constitutional symptoms that fit myriad working diagnoses, but autonomic instability is a hallmark of drug poisonings. Motor stiffness and hyperreflexia are frequently seen with a number of drug poisoning syndromes, although not with pesticide poisoning.[2,3]

This 6-part review article series helps sort out some of the more common symptoms, interactions, and therapeutic considerations in the clinical approach to a patient whom you suspect may be experiencing the effects of the most common types of poisoning.

This article, the first in the series, covers antidepressant poisonings. Other articles in the series cover antihistamines, cardiovascular drugs, opioids, and pesticides, and one article specifically covers serotonin syndrome.

Background

Antidepressant is a general term encompassing a wide array of commonly prescribed medications, including tricyclic antidepressants (TCAs), selective serotonin-reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs). While they have long been prescribed for the management of psychiatric disorders, antidepressants also have been effective in the treatment of chronic pain, smoking cessation, anorexia, and other neuropsychiatric disorders.

In the 2011 annual report of the American Association of Poison Control Centers' National Poison Data System,[1] antidepressants were the 6th most common drug category involved in toxic human exposures, with 107,528 contacts. In patients older than 20 years, they were the third leading cause of toxic exposures and accounted for the fourth highest number of fatalities, at 8.1%. Toxic antidepressant exposures also had the 10th greatest rate of increase among the other 25 categories evaluated; because of their increasing use, the associated rate of poisonings also is projected to increase.

TCA Poisoning

Widely prescribed from the late 1950s through the 1980s, TCAs were one of the first antidepressant classes available for general use. They have since been largely replaced by SSRIs.[4] In addition to treating depression, TCAs also have been used in the management of chronic pain, insomnia, migraines, anxiety, obsessive-compulsive disorder, and eating disorders. Their therapeutic effects are primarily mediated by blockade of norepinephrine, dopamine, and serotonin reuptake by presynaptic nerves. TCAs also exhibit central and peripheral anticholinergic, antihistaminic, anti-α_1 adrenergic, and anti $GABA_A$ properties.[4] They

are rapidly absorbed by the gastrointestinal (GI) tract and, due to their lipophilic properties, have a large volume of distribution.

The most frequent cause of TCA poisoning is supratherapeutic oral ingestion, which can occur with other synergistic coingestants such as MAOIs (fever, seizures), epinephrine and clonidine (malignant hypertension), and cimetidine (magnification of adverse effects due to increased blood levels).

Symptoms of pure TCA poisoning include altered mental status, delirium, headache, myoclonus, dizziness, weakness, GI tract symptoms, and anticholinergic effects.[5] Life-threatening manifestations include cardiac arrhythmias (particularly ventricular tachycardia and ventricular fibrillation) and cardiac conduction delays due to blockade of fast sodium channels within the myocardium and the His-Purkinje system, seizures, hypotension, and respiratory depression.[6,7] Relevant electrocardiographic (ECG) changes include QRS intervals greater than 100 milliseconds, an R wave of 3 mm or greater in the aVR lead, or a terminal QRS vector between 130° and 270°.[6,7] Persons with underlying ischemic cardiac disease may be especially sensitive to the cardiotoxic effects of TCAs.

Symptomatic patients who present in a primary care setting, those with suicidal intent, or victims of malicious administration should be immediately referred to an emergency department (ED). A focused history, ECG, and immediate monitoring of respiratory, cardiovascular, and neurologic status should be performed. Patients with a QRS duration greater than 100 milliseconds on ECG should be stabilized immediately, given sodium bicarbonate, and transported to the ED. While no formal toxic dose has been established, patients who have ingested more than 5 mg/kg (except in cases of desipramine, nortriptyline, trimipramine, and protriptyline ingestions) or an unknown amount also should also be promptly referred to the ED. GI tract decontamination with activated charcoal may be started in the outpatient setting; however, the use of ipecac syrup is not advised, and treatment should not delay medical transport. Benzodiazepines may be used in cases of TCA-induced convulsions, and intravenous fluids have been shown to be helpful in stabilizing cardiopulmonary status. Asymptomatic patients with an interval greater than 6 hours between ingestion and presentation are unlikely to develop symptoms and can be safely monitored in the outpatient setting.[8,9]

SSRI Poisoning

SSRIs are a newer class of antidepressants, introduced in the late 1980s, that have largely supplanted TCAs as agents in the first-line management of depression. Additional uses include treatment of generalized anxiety disorder, obsessive-compulsive disorder, and neuropathic pain.[10] In 2011, SSRIs accounted for 47,000 exposures reported to US poison centers but just 2 fatalities. However, as the prevalence of prescribed SSRIs increases, overdose fatalities are expected to rise.[1]

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The therapeutic effects of SSRIs are mediated by inhibition of serotonin reuptake within the central and peripheral nervous systems. Compared with TCAs, SSRIs have an increased safety profile and are less-effective at blocking norepinephrine reuptake, and they have less potential to antagonize muscarinic, histaminic, and adrenergic receptors. Symptoms of SSRI overdose are generally mild and include nausea, vomiting, and diarrhea. Insomnia, anxiety, and hypomania also can occur but mainly affect persons with long-term SSRI use.[11,12]

Serotonin syndrome is a rare but life-threatening complication that presents with the triad of altered mental status, autonomic instability, and neuromuscular dysfunction and is caused by excessive stimulation of the 5-HT_{1A} and 5-HT_{2A} receptors. Manifestations are varied and can include restlessness, confusion, myoclonus, and hyperreflexia.[13] The onset generally occurs within 6 hours of ingestion and is seen most commonly in individuals on multiple serotonergic agents or in those who are on long-term SSRI therapy. The most common drug combinations reported to cause serotonin syndrome are a MAOI plus an SSRI or a MAOI plus clomipramine. Serotonin syndrome is a clinical diagnosis; however, criteria such as the Hunter Serotonin Toxicity Criteria (84% sensitive, 97% specific) and the Sternbach criteria have been formulated to help expedite diagnosis.[10,11,13,14] Using the Hunter criteria, only a few variables are required to accurately predict serotonin toxicity: spontaneous clonus, inducible clonus, ocular clonus, agitation, diaphoresis, tremor, and hyperreflexia. The Sternbach toxicity prediction criteria are broader and include the use of a known serotonergic agent, lack of other possible causes, lack of use of a neuroleptic agent, and the presence of at least 3 of the following: altered mental status, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, discoordination, and fever.

In the primary care setting, all patients suspected of suicidal intent, those who have been the victim of malicious administration, or who have significant symptoms should be immediately referred to the ED regardless of the dose reported. Individuals who have ingested up to 5 times an adult therapeutic dose with mild symptoms and asymptomatic patients may be observed at home. In this group, no clinical benefit has been seen with administration of activation charcoal or induction of emesis.[11,15]

Individuals with suspected serotonin syndrome should be immediately stabilized according to Advanced Cardiac Life Support guidelines and transported to the ED. The mainstay of treatment includes discontinuation of any offending agents and supportive measures to stabilize vital signs. Benzodiazepines may be given for agitation and have been shown to improve mortality in animal models. An ECG should be performed to evaluate for QTc prolongation, particularly if the suspected agent is citalopram due to its documented cardiotoxicity.[16]

Patients with temperatures exceeding 41°C should be emergently sedated, intubated, and paralyzed to prevent development of severe complications such as metabolic acidosis,

disseminated intravascular coagulation, acute renal failure, and rhabdomyolysis. Serotonin antagonists such as cyproheptadine may be given if there is little improvement in mental status and vital signs with supportive care alone. All adjunctive therapy should be coordinated with emergency medical services and with the local poison control center.[11] Cyproheptadine is a serotonin receptor-blocking agent as well as a histamine H_1 blocker that also has been used as an antipruritic, an appetite stimulant, and for the treatment of postgastrectomy dumping syndrome. It also has mild anticholinergic properties.

MAOI Poisoning

MAOIs were discovered in 1952 and were one of the first medication classes used for the clinical treatment of depression. Due to their many drug interactions, their need for dietary restrictions, and their toxicity, they have gradually fallen out of favor as first-line medications, but they are still prescribed for the treatment of atypical depression.

Inhibition of monoamine oxidase causes an increased cytoplasmic concentration of biogenic neurotransmitters including epinephrine, norepinephrine, dopamine, and serotonin.[13] MAOIs also act as competitive inhibitors of amine transport out of the synapse and provoke the release of stored amines from presynaptic vesicles, resulting in a greater amine concentration and effect. The 2 MAO subtypes, MAO-A and MAO-B, differ in their anatomic distribution and their metabolic activity.[17]

Unique to MAOIs is the possibility of precipitating a hypertensive crisis when used concurrently with ingestion of food containing dietary amines, particularly tyramine. Tyramine is a monoamine commonly found in cheese, alcoholic beverages, processed meats, fruits, beans, and fish. Derived from the amino acid tyrosine, it functions as an indirect agonist by increasing synaptic concentrations of norepinephrine and dopamine. It is metabolized by gastrointestinal MAO-A. The use of MAOIs, particularly MAO-A subtype inhibitors, may precipitate a hypertensive crisis. Patients taking MAO-B subtype inhibitors, however, are much less vulnerable to drug reactions, which generally occur only at supratherapeutic doses when isoenzyme selectivity is substantially reduced.[13]

Symptoms of MAOI overdose can vary and include headache, altered mental status, agitation, hyperthermia, hyperreflexia, diaphoresis, and seizures. A prodrome of MAOI toxicity has been suggested by Linden and colleagues[18] consisting of 4 phases: asymptomatic; neuromuscular excitation and sympathetic hyperactivity; central nervous system depression and cardiovascular collapse; and secondary complications for survivors. Significant overlap exists in the clinical manifestations of MAOI toxicity and serotonin syndrome, making a firm diagnosis difficult in the absence of a detailed history. No physical examination findings or laboratory test results are pathognomonic for MAOI toxicity, but the presence of ocular clonus is suggestive.[13,18]

In the primary care setting, patients who are symptomatic, those with suspected suicidal intent, victims of malicious administration, or those who have ingested more than 2 mg/kg of an MAOI should immediately be referred to an ED. Treatment of MAOI poisoning is largely supportive and should be directed toward stabilization of vital signs with monitoring of cardiovascular, respiratory, and neurologic status. Sedation with benzodiazepines may be given to counteract muscular hyperactivity, hyperthermia, and agitation. Administration of a serotonin antagonist to diminish the effects of excessive serotonin has been suggested but has not been well studied.[13]

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