Review

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Tricyclic Antidepressant Drug in Toxication

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Abstract

Tricyclic antidepressant (TCA) poisoning is one of the conditions that can lead to serious clinical consequences and require urgent medical attention. The clinical presentation of TCA toxicity can range from severe cardiotoxicity to mild antimuscarinic symptoms and signs. The most severe toxicity is to the cardiovascular, central nervous and peripheral nervous system. Sodium bicarbonate therapy is highly effective in treating arrhythmias and improving metabolic acidosis, although there is no known antidote for treatment. This review aims to present current information about the pathophysiology, clinical findings, diagnostic and therapeutic methods and prognosis of TCA poisoning.

Introduction

Tricyclic antidepressants are a class of drugs named after their structure with three benzene rings and are widely used in the treatment of various psychiatric conditions such as depression and anxiety disorders. Despite the many new drugs used in the treatment of depression, they are still the most commonly used group of antidepressant drugs after serotonin reuptake inhibitors (SSRIs)[1].

TCA's exert their antidepressant effects by inhibiting serotonin and noradrenaline reuptake. However, due to the narrow therapeutic index of these drugs, they carry a risk of serious toxicity at overdose of only a few times the therapeutic dose[2]. Therefore, TCA's are the main cause of morbidity and mortality in antidepressant-related poisonings.

Epidemiology

TCA poisonings are frequently encountered due to suicide attempts and accidental overdoses. In various studies, it has been reported that TCA poisoning is more common especially in young adults and middle age group. In addition, women have a higher risk of suicide attempt compared to men[3].

Pathogenesis

TCA's have a chemical structure consisting of a 7-membered central ring, 2 benzene rings on the outside and 3 aromatic rings including an aminopropyl region chain attached to the central ring4. TCA's may lead to serious complications due to their toxic effects on the central nervous and cardiac system. These drugs may cause cardiotoxicity by blocking Na+ channels, anticholinergic effects by inhibiting muscarinic receptors and seizures by antagonizing GABA-A receptors5. In addition, the effects of TCAs on K+ channels also play a role in the formation of cardiac arrhythmias. When TCA's are given at therapeutic doses, they are absorbed from the gastrointestinal system and reach their highest concentrations in plasma within 2-8 hours. In high

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dose intakes, decreased gastrointestinal motility due to their anticholinergic effects and ionization in acidic gastric fluids change their absorption kinetics and lead to delayed absorption. The oral bioavailability of TCA's is low and variable due to first pass elimination in the liver. This group of drugs is lipophilic. They are highly bound to tissues and plasma proteins, their virtual volume of distribution is large (15-40 L/kg) and their half-life varies between 7-58 hours depending on the drug[6,7]. Seventy percent of the total dose is excreted through the kidneys as inactive metabolites and the rest through bile[8].

Clinical Features

TCA's competitively suppress the action of acetylcholine at central and peripheral muscarinic receptors. This effect can be termed as anticholinergic effect. The main toxic effects of TCA's are on the central nervous system (CNS) and cardiovascular system. Cardiotoxic effects include hypertension and tachycardia, hypotension, cardiac conduction disorders and myocardial depression with membrane stabilizing effect9. With central antimuscarinic effect, they cause speech disorder, amnesia, ataxia, delusions, convulsion, delirium, agitation, confusion, sedation and coma, while with peripheral antimuscarinic effect, they cause fever, tachycardia, hypertension, dilated pupils, visual disturbance, urinary retention, dry skin, decreased oral and bronchial secretions, ileus, increased muscle tone and tremor [4,9].

Cardiovascular toxic effects are important for mortality in TCA poisoning. The cardiac effects of TCAs are caused by voltage-dependent Na+ and K+ channel blockade and postsynaptic inhibition of central and peripheral α-adrenergic receptors. Voltage-dependent Na+ channel blockade is the cause of arrhythmias, hypotension and conduction block caused by TCAs. Inhibition of fast Na+ channels in His-purkinje cells causes conduction abnormality[10]. Na+ channel blockade also results in hyponatremia, tachycardia, hypotension and acidosis. This effect is manifested on electrocardiography (ECG) as prolongation of PR and QRS and right axis deviation (RAD).

Severe sodium channel blockade causes hypotension, various heart blocks, RAD, QRS widening and ectopic heart beats as a result of negative inotropic effect. As a result of voltage-dependent K+ channel blockade, bradycardia and prolongation of QTc on ECG are observed[4]. QRS and QT prolongation seen on ECG is accepted as clinical evidence of cardiovascular toxicity[9,12]. Sinus tachycardia is a sensitive indicator of TCA intake, but it is not an indicator of whether a serious intoxication will develop[13].

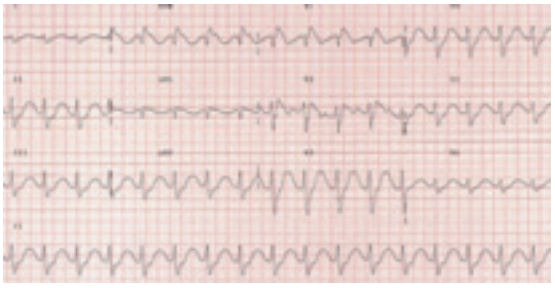

Figure 1: Cause of intoxication in the studied patients. MDT= Multiple Drug Toxicity.

Laboratory

Laboratory tests may reveal leukocytosis, hypopotassemia, hypocalcemia, hyperglycemia, and elevated liver function tests (aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, lactate dehydrogenase, prothrombin time)[8]. Hypopotassemia may be observed at the time of initial presentation and may be secondary to sodium bicarbonate (NaHCO3) treatment.

If rhabdomyolysis develops due to recurrent seizures, elevated myoglobin, creatine kinase and potassium values may be found. Mixed type acidosis is most commonly seen in blood gas[14]. This is mostly due to elevated lactate levels as a result of respiratory depression and the hypotension that develops as a result of myocardial suppression causing tissue perfusion disorder[15].

Diagnosis

TCA intoxication should be considered in patients with QRS widening and QT prolongation accompanying findings such as lethargy, coma and seizure. Routine biochemical tests, ECG, blood gas measurement and chest radiography in patients with pulmonary edema are helpful in the diagnosis. The diagnosis of TCA intoxication is usually based on clinical findings. Electrocardiography (ECG) is one of the most important diagnostic tools; widened QRS complex and QT prolongation are typical. Sinus tachycardia is a sensitive indicator of TCA ingestion but is not an indicator of whether severe intoxication will develop4. Serum TCA levels can be measured but are not usually necessary for emergency treatment decisions.

Treatment

The aim of the initial evaluation is to identify life-threatening problems and initiate supportive treatment. Patients should first be evaluated for confusion, hemodynamic instability and respiratory failure. Then, intravenous access should be established, hydration should be started, cardiac monitoring and ECGs should be provided. A foley catheter should be inserted to prevent urinary retention and a nasogastric tube should be inserted if bowel sounds are absent. Patients who are initially asymptomatic may deteriorate rapidly in follow-up. Therefore, these patients should be followed very closely for the first few hours.

Activated charcoal treatment for gastrointestinal decontamination should be performed if the airway is protected and the patient is stable. Activated charcoal decontamination may be effective up to 2 hours after drug intake16. Since acidosis may increase cardiotoxicity and neurotoxicity, acidosis should be prevented. Seizures may occur after intoxication. Benzodiazepines can be used in the treatment of seizures, but anticonvulsants such as phenobarbital or propofol should be considered in resistant seizure cases. Sodium bicarbonate treatment should be given to hemodynamically unstable patients with seizures and patients with QRS prolongation[16]. Sodium bicarbonate treatment is given as 1 meq/kg intravenous bolus to narrow the QRS and maintain serum pH between 7.5-7.55, and then infusion treatment is started.

Intravenous fluid therapy should be started in hypotensive patients. Sodium bicarbonate treatment should be added to fluid treatment. However, if fluid and sodium bicarbonate treatment does not respond to hypotension, alpha-adrenergic agents should be started. If bradycardia does not respond to sodium bicarbonate, temporary pacemakers should be used. Antiarrhythmic drugs should be considered in acute TCA poisoning in cases not responding to sodium bicarbonate treatment. Class Ia (procainamide, quinidine, disopyramide) and class Ic (flecainide) are well-known sodium channel blockers and should not be used in acute TCA poisoning[13]. Intralipid emulsion treatment should be considered in hemodynamically unstable patients who receive an overdose of lipophilic TCAs. Dialysis and hemoperfusion are not effective in the treatment of TCA intoxication. Because TCAs are highly protein-bound and have a large volume of distribution and do not respond to dialysis[8].

Conclusion

Tricyclic antidepressant toxicity is an emergency situation with high mortality and morbidity. It should be managed and managed by a team consisting of an emergency physician, nurse, poison control specialist, cardiologist and neurologist. As in all poisoning cases, airway and respiratory stabilization should be provided first and circulation should be managed appropriately. Patients who are having seizures, hemodynamically unstable, and have QRS prolongation should be given sodium bicarbonate treatment. Temporary pacemaker treatment should be considered for patients with bradycardia. After interventions in the emergency department, hydration and close follow-up in the intensive care unit are recommended. The prognosis is generally good for patients treated in a timely manner. If a suicide attempt is suspected at the patient's discharge, a psychiatric consultation should be planned for the patient. Parents should be encouraged to keep all medications in a locked cabinet out of reach of children[17,18].

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