Tricyclic Antidepressant Overdose

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Overdose from tricyclic antidepressants (TCAs) is increasing. TCAs are well absorbed orally, highly protein bound, and highly lipid soluble. Clinical features of poisoning with TCAs occur within 12 hours of ingestion, usually after a dose of 20 mg/kg or more. Clinical symptomatology involves various anticholinergic, central nervous system, and cardiovascular effects. Cardiovascular toxicity accounts for the majority of the fatalities and may include a hyperdynamic response, various arrhythmias and heart blocks, or severe hypotension. Prolongation of the QRS interval of 10 msec or more implies severe toxicity. Many factors limit the usefulness of drug levels in the overdosed patient. Treatment revolves around good supportive care and general poisoning management. The physician should no longer use physostigmine precipitously. Sodium bicarbonate is effective in treating many of the cardiovascular complications. Other cardiac drugs are used but with varying efficacy. Patients with significant signs or symptoms of toxicity require monitored hospitalization until clinically free of manifestations for 24 to 48 hours.

Overdosage with tricyclic antidepressant drugs has been reported as early as 1959, one year after their introduction to psychiatry. Because of the complex central and peripheral toxic effects of these drugs, the physician who treats the overdosed patient may find himself managing hypotension, coma with respiratory arrest, convulsions, complex arrhythmias, and myocardial depression. The purpose of this paper is to review the current body of knowledge on tricyclic antidepressants (TCAs) and their toxicity. Increased understanding of the mechanisms of toxicity, pharmacologic interactions, and clinical manifestations allows the outline of a rational mode of therapy for patients who present with TCA overdose.

The need for a safe, effective pharmacologic therapy for endogenous depression led to early acceptance of TCAs in the United States more than two decades ago. The subsequent reported incidence of profound toxic effects from overdose with these drugs has apparently not outweighed the benefits, as these drugs are prescribed more

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than 24 million times annually in the United States. The current indications for use of these drugs are endogenous depression and adjunctive therapy for enuresis in children.[1] The increasing incidence of overdose with these drugs correlates with prescribing practices, making them available to two high-risk populations: the accidental ingestion[2,3] in children less than five years of age, and the adolescent and adult suicidal ingestion groups.

Pharmacology

Tricyclic antidepressant drugs have a three-ring nucleus (hence the term *tricyclic*), consisting of a seven-membered central ring bounded by two benzene rings. Imipramine and amitriptyline each contain an aminopropyl side chain with three substitutions. These drugs are the parent tertiary amine compounds. Demethylation of these parent drugs produces the secondary amines, desipramine and nortriptyline, that are also pharmacologically active.[4] Doxepin (a tertiary amine) and protriptyline differ from the other TCAs in their central ring structure. These six drugs are the most commonly prescribed in the United States and are marketed under a variety of brand names. There has been recent approval of two other TCAs, trimipramine and amoxapine, and one tetracyclic antidepressant, maprotiline. Trimipramine is structurally and pharmacologically similar to imipramine, while amoxapine may possess a more rapid action but less potent activity compared with the other TCAs.[5] Maprotiline's antidepressant activity is similar to the older compounds,[6] but it may possess more adverse effects, particularly seizures.[7]

Actions

Four effects of therapeutic doses of tricyclics have been described: (1) sedation (phenothiazine-like effect), (2) central and peripheral anticholinergic effects, (3) blockade of the presynaptic uptake of amine neurotransmitters, the perceived etiology of the antidepressant action,[4] and (4) the antiarrhythmic, "quinidine-like" effect.[8,9] In toxic ingestions, the list is expanded to include myocardial and central nervous system depression.

Effects at Therapeutic Doses

Sedation

Tricyclics resemble phenothiazines chemically in this effect. The tertiary amines (imipramine, amitriptyline, and doxepin) are more sedative than are the secondary amines.[4] These sedative effects may result from their potent antihistaminic properties.[10]

Anticholinergic Effects

Both central and peripheral manifestations are seen. Tricyclics are competitive antagonists of acetylcholine at the neuroreceptor site. Anticholinergic manifestations are common at therapeutic doses and include dry mouth, constipation, urinary retention, and mydriasis.

Blockage of the Amine Pump

One popular hypothesis for endogenous depression is the norepinephrine depletion hypothesis. According to this hypothesis, symptoms of depression are correlated with the level of norepinephrine (and serotonin) in the brain. Tricyclics block the reuptake of norepinephrine at the synapse, allowing for a longer sojourn of this neurotransmitter. It is thought that this mechanism may be the means by which tricyclics influence depressive symptoms.[4] Recent work is emphasizing the changes in the pre- and postsynaptic receptor sensitivity as contributing to the antidepressant activity.[11]

Antiarrhythmic Effect

A quinidine-like antiarrhythmic effect of tricyclics has been documented. In one study, imipra-

mine was shown to reduce atrial and ventricular arrhythmias at therapeutic antidepressant levels.[9]

Pharmacokinetics

Tricyclic antidepressants are well absorbed orally from the gastrointestinal tract and are rapidly distributed into tissue compartments because of their high lipid solubility, reflected by their large volumes of distribution. The TCAs are highly plasma protein bound (76 percent to 98 percent), with an alpha, acid glycoprotein as the major protein. Once a steady-state plasma drug level has been established, there is a positive correlation between drug level and clinical antidepressant response. This varies between 50 and 170 ng/mL, depending on the tricyclic.[12]

Because of their high lipid solubility, tricyclics are reported to show tissue levels 10 times greater than plasma levels, and myocardial levels have been reported to be 40 to 200 times plasma levels. Children, with lower lipid stores, may have higher blood levels at similar milligram per kilogram doses, possibly enhancing toxic effects.[12]

The TCAs are metabolized by demethylation, oxidation and aromatic hydroxylation, and glucuronidization via the hepatic microsomal enzyme systems and are excreted in the urine. A small portion of the drug is excreted unchanged and is detectable in the urine. The demethylated forms of amitriptyline, imipramine, and doxepin result in pharmacologically active metabolites.

Enhancement of the hepatic microsomal enzymes will alter the rate of metabolism of TCAs. Substances that act in this way include barbiturates, alcohol, and cigarettes and will increase the rates of metabolism of TCAs.[4,12] Gastric secretion and enterohepatic recirculation of TCAs have been described. This may account for as much as 30 percent of the ingested dose in a 24-hour period.[13] Theoretically, repeated oral doses of activated charcoal may remove this recycled drug, but evidence is currently lacking. The high degree of protein binding and large volume of distribution weigh against significant removal of TCAs by either nasogastric suction or multiple doses of activated charcoal.

Toxicologic Properties

Acute tricyclic antidepressant ingestion in excess of 20 mg/kg has been associated with toxic manifestations of myocardial depression, serious arrhythmias, coma, and respiratory arrest. However, death has occurred in a child with a dose of 200 mg. The lowest known fatal dose in an adult is reported at 500 mg, although survival is also reported in an adult after an acute ingestion of 10 g.[14] Toxic sequelae are complex and relate in part to the high lipid solubility of the drug and distribution into all body tissues, including the central nervous system.

Early toxic effects on the heart are mediated through anticholinergic mechanisms and are seen as narrow complex tachyarrhythmias. These may be hemodynamically significant and require treatment. With larger doses direct myocardial depression with decreased contractility and resultant hypotension are noted. His-Purkinje conduction is prolonged, and wide complex arrhythmias and sinoatrial and atrioventricular blocks are seen. Ventricular ectopy and arrhythmias are common and often refractory to treatment.[15-20]

Toxic effects on the central nervous system can be mediated through anticholinergic mechanisms and possibly through blockade of amine neurotransmitter reuptake. Alteration in neurotransmitter ratio in the brain has been speculated as a possible mechanism for the seizures and choreoathetosis commonly seen in TCA overdoses. Increased toxicity results in profound central nervous system depression, although the mechanisms are speculative.[21-23]

Plasma Drug Levels

Plasma drug levels reflect only a small portion of the total body drug burden. Interpretation of plasma drug levels must take into consideration parent compound and active metabolites in both the protein-bound and free forms. The free (unbound) drug is the pharmacologically active portion and accounts for only 7 percent of the total plasma level. Early investigators found that increasing the pH of plasma resulted in a decrease in free drug, but other investigators have not agreed

with this mechanism.[24] The amount of pH change needed to show significantly increased protein binding was in excess of physiologic range. Other drugs also bound to the same plasma proteins could conceivably displace the tricyclic antidepressant and therefore increase free TCA levels and contribute to increased toxicity.[12,13]

Correlation of serial blood levels with clinical status shows that an acute total TCA level in excess of 1,000 ng/mL is strongly correlated with the development of serious arrhythmias (50 percent), coma (20 to 40 percent), and electrocardiogram findings of QRS prolongation in excess of 10 msec (100 percent).[25-28] These levels were obtained on patients presenting with an acute overdose in the first several hours after ingestion. Drug levels obtained more than 24 hours after ingestion do not correlate well with clinical findings. It is also difficult to interpret drug levels in the overdose patient who had been taking a TCA. Clinical symptoms may appear at lower plasma drug levels in these patients. These numerous factors limit the usefulness of drug levels in the overdosed patient.

Clinical Presentation

Clinical features of tricyclic antidepressant poisoning occur in the first 12 hours after ingestion. These are typically most dangerous in the 12-to-24-hour period, but large ingestions may present an immediate threat to life. Three systems are principally involved: the anticholinergic, the cardiovascular, and the central nervous systems.

Anticholinergic symptomatology appears initially and is present in most TCA overdoses. These effects include flushing, dry skin and mouth, hyperpyrexia, dilated pupils, cycloplegia, decreased gastric motility, constipation, and urinary retention.

The central nervous system manifestations are due to the anticholinergic and antihistaminic properties of the drugs. These effects vary from mild agitation or drowsiness to severe delirium, deep coma, or seizures. Initially there is a brief period of excitement followed by confusion, dysarthria, and visual and auditory hallucinations. Severe delirium may continue, or the patient may lapse into coma. Coma usually develops within six hours of the ingestion and seldom lasts more than 24 hours.[29] If coma persists for more than 48 hours, the physician should suspect a mixed ingestion, particularly with sedative-hypnotic compounds. The coma may simulate brain death with complete loss of brainstem and cerebral function. Continued resuscitative and supportive care is mandatory to ensure survival. Involuntary twitching, ataxia, myoclonus, or choreoathetosis, frequently seen with basal ganglion pathology, occurs commonly and is also a result of the anticholinergic properties of TCAs.[23] Generalized seizures occur in 10 percent to 20 percent of the patients.[20,28,30] Central nervous system depression may cause ventilatory failure and contribute to aspiration pneumonia. Seizures, agitation, and marked muscle activity can lead to rhabdomyolysis and acute renal failure.

Cardiovascular toxic reactions account for the majority of the fatalities and are the most difficult to treat. In the event of a mild overdose, a hyperdynamic circulation predominates, with tachycardia and a slightly elevated blood pressure. Marked myocardial depression characterizes the severe poisoning with life-threatening hypotension.

Electrocardiographic (ECG) manifestations are varied in TCA poisoning. Mild poisonings present as a sinus tachycardia or supraventricular tachyarrhythmias, the result of the anticholinergic effect of the drug. Severe poisoning is characterized by life-threatening conduction delays. This frequently occurs with doses of more than 20 mg/kg[20] and usually develops within one to two hours after ingestion.

Prolongation of the QRS 10 msec or more implies severe toxicity and usually correlates with a plasma level of 1,000 ng/mL or more,[28] but there are exceptions.[31] The ECG will show a progression from prolonged PR and QRS intervals to various AV blocks, followed terminally with severe bradycardia and an idioventricular rhythm and cardiac arrest. Various re-entry arrhythmias may occur and include premature ventricular contractions, ventricular tachycardia, bigeminy, and fibrillation. The prolongation of the QT interval predisposes the TCA-overdosed patient to torsades de pointes.[32] The recent mortality from significant poisoning is approximately 3 percent.[20,30] There are several reports of delayed complications, including relapsing coma, recurring arrhythmias, and death.[33-36]

Treatment

The most important aspects of treating tricyclic antidepressant poisoning are good supportive care and general poisoning management. A majority of patients respond to these alone.[33,37] The physician should first maintain a good airway and assure proper ventilation of the patient, which may include suctioning or positioning of the head and neck in the noncomatose patient or intubation in the comatose patient.

Preventing the absorption of the drug is most important. The anticholinergic effects of TCA may delay absorption for many hours, and the initiation of basic poisoning management is mandatory up to 18 hours after the ingestion.[38] If the mental status is adequate, the physician should use syrup of ipecac to empty the stomach contents. The comatose patient or a patient without an adequate gag reflex needs intubation with a cuffed endotracheal tube and gastric lavage with a large-bore orogastric tube. The physician should lavage the stomach with the patient in the left lateral, head-down position. Continual nasogastric suction removes little more and may cause severe metabolic derangements.[3]

Activated charcoal is effective in preventing absorption of TCA. The physician should use dosages 10 times the amount of the ingested drug or 50 to 100 g if unknown. Repeated doses are probably unnecessary, and a recent study casts doubt on the quantitative aspects of the enterohepatic circulation process.[39]

Cathartics such as sodium or magnesium sulfate should follow activated charcoal. Dialysis and forced diuresis are not helpful because of the large volume of distribution and the high protein binding of the drugs.[38,40,41]

Central Nervous System Complications

It is best to manage uncomplicated coma by supportive care alone. The physician should no longer use physostigmine as a diagnostic modality in the comatose patient, nor should he or she try it precipitously as an antidote for TCA overdose. It is not specific for anticholinergic drugs,[42,43] and it has many side effects. Physostigmine, a cholinergic drug, hydrolyzes the enzyme choline esterase, which is responsible for the metabolism of acetylcholine. It is the only choline esterase inhibitor that enters the central nervous system. The side effects include excessive salivation leading to respiratory insufficiency, generalized convulsions if given too rapidly, spontaneous emesis, urination, defecation,[44] and, most important, bradycardia, hypotension, and asystole.[45]

Physostigmine is an effective antidote for TCA-induced seizures, but many favor the use of diazepam[29,38] or phenytoin as the first-line drug. It is wisest to avoid physostigmine if the patient has bradycardia, conduction delays, or hypotension, although some seizure patients will respond to no other drug.[38] The dose is 2 mg intravenously over 2 to 5 minutes, repeated in 10 to 15 minutes if there is no effect. The pediatric dose is 0.5 mg,[44] repeated every 10 minutes to a maximum dose of 2 mg. The physician may repeat the dose every 20 to 30 minutes if there is an effective response. The antidote for physostigmine is atropine sulfate in one half the original physostigmine dose. The disadvantages of diazepam are that it increases the central nervous system depression and has a short duration of action. Phenytoin should be used cautiously, as it may cause hypotension, bradycardia, and conduction delays similar to TCA.[45-47]

The physician may use physostigmine for uncontrolled delirium or myoclonus. Diazepam is an alternative if bradycardia, hypotension, or severe conduction delays exist. Antipsychotic drugs such as haloperidol and chlorpromazine have anticholinergic properties similar to TCA and can potentiate the overdose.

Hypotension

Circulatory management may be difficult. Hypotension is the result of the myocardial depressant and the peripheral vasodilatory effects of the drug as well as the conduction delay. A Swan-Ganz catheter is most helpful in guiding fluid management. Most recommend the use of crystalloids initially,[38,40] but the physician must avoid fluid overloading an already depressed myocardium. Military antishock trousers (MAST) provide a reversible fluid challenge and may be helpful in guiding the use of crystalloids in patients without a Swan-Ganz catheter. Sodium bicarbonate may be

helpful, as it reverses TCA-induced dysrhythmias and hypotension.[36,48-50] The dosage is 1 to 3 mEq/kg, titrated to a pH of 7.4 to 7.5.[40]

Fluids and sodium bicarbonate are effective in the majority of the patients. If these fail, the physician must use pressors. The selection of which pressor agent is controversial. All may cause arrhythmias, and they often fail to raise the blood pressure effectively. The use of levarterenol bitartrate or dopamine with both $beta_1$ and alpha properties is probably the best choice. It is wise to avoid digitalization, since most of these patients have underlying heart blocks and conduction disturbances.[15] Catheterization of the bladder will avoid urinary retention, a common problem in these patients.

Cardiac Complications

Supraventricular tachyarrhythmias occur commonly, and treatment is usually not necessary unless they are hemodynamically significant or they occur in patients with underlying heart disease. Sodium bicarbonate is effective and should be used initially.[36,48-50] Physostigmine and propranolol are the next choices, although verapamil may become a better alternative. Propranolol will worsen myocardial depression and should be used only for supraventricular tachyarrhythmias with a normal QRS complex. Some recommend practolol, a cardioselective beta-blocker with less myocardial depressant action.[51]

The treatment of ventricular arrhythmias is extremely troublesome. The physician should use sodium bicarbonate as the first-line drug.[36,48-50] Beta-blockers and physostigmine are controversial. There are reports of their efficacy in this setting,[49,51-54] but both can potentiate hypotension, bradycardia, and conduction delays. More traditional ventricular antiarrhythmic agents also have their drawbacks. The usefulness of lidocaine is questionable, but some use it as the second-line drug after sodium bicarbonate.[40,49] Bretylium may be an even better alternative to lidocaine, since it is effective against ventricular arrhythmias and has the added feature of not depressing the myocardium. TCAs block the amine uptake mechanism and may prevent bretylium from gaining access to the adrenergic nerves, but this does not appear crucial to bretylium's antiarrhythmic actions. Nothing is known about its use in the setting of TCA-induced ventricular arrhythmias.

Phenytoin may be useful for ventricular arrhythmias, but it is not an innocuous drug. There are several reports of fatal cardiac death with its use. Many of these deaths occur similarly to those from TCA with conduction delays, idioventricular rhythm, and asystole.[45-47] The physician should inject phenytoin at a rate of 50 mg/min or less, with cardiac monitoring and frequent blood pressure recordings.[46,55] Lower rates are necessary in the elderly or in patients with heart disease. The total dose is titrated to the control of the arrhythmia, but not exceeding 1 g (15 mg/kg) in the adult. It is important to avoid the use of type I antiarrhythmic drugs, quinidine, procainamide, and disopyramide, since they have actions similar to those of TCAs.

Conduction defects imply significant poisonings. Treatment is essential if accompanied by hypotension or severe arrhythmias. There are no reports of treating non-life-threatening conduction delays to prevent future catastrophes. Sodium bicarbonate is the first drug for life-threatening conduction delays. Recent reports would suggest phenytoin as the second-line drug after sodium bicarbonate.[45,55] There are individual reports of the efficacy of physostigmine, propranolol, and practolol, but previously mentioned drawbacks limit their usefulness. The physician may try emergency pacing as a final effort.

The physician should carefully monitor in an intensive care unit all patients with a QRS interval of 10 msec or more, cardiac arrhythmia, or central nervous system or peripheral manifestations. Most recommend further hospitalization for 24 to 48 hours after the patient is completely free of all signs and symptoms.[38,40] Appropriate psychiatric consultation is mandatory. Asymptomatic patients need basic poisoning management and psychiatric consultation. Observation for eight hours is essential before considering the patient safe for medical discharge.

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