

Case Report

Cardiopulmonary Bypass Support for Tricyclic Poisoning: A Case Report

Carl Sheppard, BS, RRT, CCP

Providence Medical Center
Portland, Oregon

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ABSTRACT

Cardiopulmonary bypass as an adjunct to the treatment of acute tricyclic antidepressant poisoning has not been well documented in the literature. In December of 1993, Providence Medical Center used such an adjunct for cardiac support on a 17 year old male with acute tricyclic antidepressant poisoning. The patient had ingested 2500 to 3500 mg of imipramine. Lab tests confirmed imipramine ingestion and ruled out alcohol, acetaminophen or salicylate combinations. The patient arrived via ambulance to the emergency room with a coarse supraventricular rhythm with wide QRS complexes. Over the next 20 minutes the QRS complex became increasingly wider and the rhythm more bizarre until pulses were lost. Repeated attempts to correct the dysrhythmia were unsuccessful and cardiopulmonary resuscitation was eventually initiated. The patient was transported to the operating room and placed on cardiopulmonary bypass. After several hours of bypass and charcoal hemoperfusion, the patient's cardiac rhythm improved to a supraventricular rhythm. The patient was weaned from bypass and transferred to the cardiac care unit where hemodetoxification continued. Postoperatively the patient had a cardiac index of 2.4 L/min/m² and systemic vascular resistance of 942 dynes/sec/cm⁻⁵ on norepinephrine of 2 mcg/kg/min. Imipramine and desipramine levels were down to 250 ng/ml and 500 ng/ml respectively. Neurologic function, however, did not resume and life support was terminated on postoperative day three.

Address correspondence to: Carl Sheppard, Providence Medical Center, 4805 NE Glisan Street, Portland, OR 97230

INTRODUCTION

The introduction of the tricyclic antidepressant (TCA) imipramine came in the 1950s as a treatment of severe depressive disorders. Since then several new derivatives have entered the market and by the 1970s the estimated prescriptions for TCA exceeded 20 million annually (1). Furthermore, tricyclics were approved by the FDA as an adjunct treatment for nocturnal enuresis, thus increasing distribution into the homes of children, where accidental poisoning may occur. Over the last decade, tricyclic antidepressants have resulted in more fatal overdoses than any other class of drugs (2).

The treatment modalities for TCA poisoning are varied and controversial. Some cases merely require cardiac monitoring, while others must be treated for arrhythmias or given ventilatory support. The severe overdoses may require multiple therapies which may include the management of seizures and arrhythmias through diuresis, dialysis and hemoperfusion for detoxification, and cardiopulmonary bypass for cardiac support.

PHARMACOKINETICS

Tricyclics block the re-uptake of catecholamines from the synaptic clefts of central and peripheral neurons (3,4). This action causes a higher concentration of neurotransmitters (norepinephrine, serotonin and dopamine) that corrects the deficiency associated with depressive disorders. Tricyclics also have other significant effects including cholinergic and peripheral alpha adrenergic blocking activity.

Imipramine is rapidly and completely (>95%) absorbed in the alkaline environment of the small intestine. Peak plasma levels occur 2 to 8 hours after ingestion but vary considerably in patients given identical doses (5,6). Plasma levels greater than 100 ng/ml represent major toxification (7-10). Data from animal studies show that steady state tissue concentrations are greatest in the lungs, brain, adipose and plasma, respectively. The high degree of binding results in a volume of distribution (Vd) in the range of 10 to 20 L/kg for imipramine and 10 to 50 L/kg for desipramine (5). TCA is widely distributed to plasma proteins and various tissues. Plasma protein binding of imipramine and desipramine ranges from 60 to 96% and influences the distribution greatly (5). Plasma constituents such as alpha₂-acid glycoproteins, lipoproteins, complement C3 and albumin all bind with TCA. Their respective plasma levels can account for individual distribution variability by as much as fourfold. Less than 11% of imipramine exists in the plasma in "free" form and this correlates significantly with cerebrospinal fluid levels.

Metabolism of imipramine and desipramine occurs almost exclusively in the liver with less than 5% excreted unchanged in the urine. The elimination of imipramine occurs by demethylation to the active metabolite desipramine and to a lesser degree by aromatic 2-hydroxylation to 2-hydroxyimipramine. Half-life varies with the dose ingested (volume of distribution) and generally runs in the area of 20 hours. The half-life of other TCA drugs may extend up to four times that long, especially in those patients

ingesting large amounts. Metabolism can be inhibited by drugs which interact with the cytochrome P450 system.

ADVERSE EFFECTS

Signs and symptoms of TCA poisoning include restlessness, agitation and visual and auditory hallucinations. Hyperreflexia, myoclonus and grand mal seizures are common. Other symptoms range from cardiac arrhythmias, hypotension, bundle branch block, abnormal deep tendon reflexes, unconsciousness, respiratory depression, to cardiac arrest and death. The cardiac effects are wide and varied, and represent the most life-threatening symptoms. Of particular interest is the widening of the QRS interval. Several studies have shown that all patients with significant overdoses (>1000 ng/ml) had a QRS duration greater than 100 msec (7,8,10,11). The negative inotropic effects of TCA are believed to be caused by inhibition of adenosine triphosphate phosphohydrolase, the enzyme which regulates sodium and potassium balance across the myocardial cell membrane.

CASE REPORT

A 17 year old male (height 173 cm, weight 77 kg) arrived via ambulance to the emergency room with an imipramine overdose. The family found the subject unconscious and having seizure activity. The emergency medical services were summoned immediately to the residence, where paramedics found the subject hypotensive and unresponsive. The time elapsed between the onset of symptoms and the discovery of the patient by the family was unknown. Past medical history was negative except for the patient's current treatment for depression. Intubation occurred enroute for markedly decreased respirations. Examination in the emergency room revealed the patient to have good color, femoral pulses and urine output. His electrocardiogram showed a supraventricular type rhythm with wide QRS complexes. Charcoal lavage was given along with other support drug therapy including dopamine, lidocaine, epinephrine, phenytoin, and multiple boluses of sodium bicarbonate for alkalization. Over the next 20 minutes the patient's QRS complex became increasingly wider, and his rhythm more bizarre until pulses were lost. At this point cardiopulmonary resuscitation (CPR) was initiated. The patient was bolused with more bicarbonate and epinephrine and countershocked several times, but never regained a pulse. Due to the patient's young age and otherwise healthy condition, a cardiac surgeon and nephrologist were consulted for possible cardiopulmonary bypass (CPB) with hemoperfusion.

The patient was transported to surgery, with CPR in progress, and placed on emergency cardiopulmonary bypass for cardiac support. A standard open heart bypass circuit with an arterial line filter was used. A sternotomy was quickly performed and cannulation was easily achieved via the aorta and right atrium while internal cardiac massage was continued. Heparinization was achieved with a loading dose of 30,000 units (mg/kg) and

10,000 units in the pump prime. Bypass was immediately initiated and the patient stabilized with an arterial pressure greater than 50 mmHg. On the advice of the Poison Control Center, the patient was intentionally maintained alkalotic (pH 7.47 to 7.58) and hypernatremic (>150 mEq/L) with multiple ampules of sodium bicarbonate and hyperventilation. Charcoal hemoperfusion was initiated with the aid of a dialysis unit using a charcoal cartridge^a. The dialysis unit withdrew volume from the sampling manifold of the bypass circuit and returned it to the cardiotomy. This method of connection is easy and fast, but may limit flow due to the small orifice of the sampling manifold. Our blood flow to the dialysis unit was 150 to 200 ml/min. Charcoal hemoperfusion was maintained throughout the cardiopulmonary bypass procedure in an attempt to lower the plasma levels of imipramine. Hemoconcentration and furosemide were used in conjunction with the charcoal hemoperfusion. Seventy-five grams of albumin were added to the extracorporeal circuit to aid in volume expansion and imipramine binding.

Lab values were constantly monitored and included arterial and venous blood gases, electrolytes, glucose and lactic acid. Hypokalemia and hyperglycemia were a constant finding necessitating close monitoring. The potassium level at the initiation of bypass was 2.3 mEq/L and a total dose of 110 mEq of potassium chloride was required over the course of the pump run to maintain blood levels between 3.5 and 4.8 mEq/L. Blood glucose levels ranged from 206 to 271 units and were not corrected. Activated clotting times (ACT) were greater than 1000 seconds at all times during bypass with heparin concentrations ranging from 3.0 mg/kg down to 1.5 mg/kg at termination of bypass. Norepinephrine proved more effective than phenylephrine to control blood pressure, and was used during 70% of the bypass time.

After four hours of normothermic bypass and charcoal hemoperfusion, the patient's cardiac rhythm gradually improved. The patient was eventually weaned from bypass with the aid of lidocaine and norepinephrine drips. Postoperatively the patient had a cardiac output of 4.5 L/min, a cardiac index of 2.4 L/min/m², and a SVR of 942 dynes/sec/cm⁻⁵ on norepinephrine at about 2 mcg/kg/min. Imipramine and desipramine levels were still elevated at 250 ng/ml and 500 ng/ml, respectively. Charcoal hemoperfusion continued 17 hours postoperatively in the cardiac care unit along with continuous cardiac monitoring. After several days of neurological evaluations, the patient was diagnosed with no neurologic function and removed from all life support systems.

DISCUSSION

Tricyclic antidepressants are widely used for their treatment of endogenous depression and represent one of the most common classes of drugs involved in intentional overdoses (8-10,12).

Central nervous system effects are common following

TCA poisoning and may progress to seizures and coma. The cardiotoxic effects are a result of anticholinergic, sympathomimetic and electrophysiologic ("quinidine-like") properties with disturbances in both impulse formation and conduction. Widening of the QRS complex in excess of 100 msec is a sign of severe intoxication and a variety of arrhythmias may appear. Hypertension may be seen early in the clinical course but is usually transient and replaced by hypotension.

Treatment for TCA poisoning is largely supportive in nature. Syrup of ipecac increases the aspiration hazard in patients with decreased mental status or seizures and should be avoided. In addition, the prolonged emetic effect of ipecac may cause an unacceptable delay in charcoal instillation. Gastric lavage should be performed and both activated charcoal and a cathartic administered to help reduce absorption (12,13). The prolonged elevation of TCA plasma levels warrants close observation, especially cardiac monitoring, and should continue for 24 to 72 hours even if the patient is asymptomatic. Sustained drug levels may have played a part in the unexpected cardiac deaths in some patients three to six days post-overdose (9).

Seizures should be managed with diazepam and phenytoin (4,6,8,14). Diazepam should be considered the first line agent to halt seizure activity due to its availability, rapid onset of action, and reported success in treating TCA induced seizures. Diazepam's antiseizure effects diminish within 20 minutes and a longer acting anticonvulsant agent, such as phenytoin, should be administered after diazepam. Phenytoin has been recommended as the long acting anticonvulsant because of its coincident antiarrhythmic and anticonvulsant properties (4,6,8,15).

Arrhythmias and hypotension most often respond to alkalization using sodium bicarbonate to maintain a blood pH of 7.45 to 7.55. Sodium bicarbonate has been shown to restore contractile strength in ventricular muscle poisoned with imipramine (16), and has also been successful in the treatment of resistant cardiac tachy- and bradyarrhythmias. It is also believed that alkalization will increase the binding of TCA thereby reducing the fraction of free active drug in the circulation. Kingston has shown hyperventilation to be immediately effective, and suggests that the reversal of acidosis is probably more important than the alkali therapy of bicarbonate (17).

Hypotension often requires fluid volume expansion and albumin should be a first choice consideration. Albumin is a well known volume expander and readily binds with tricyclic antidepressants (5). Van Brunt reports hypoalbuminemia and acidemia increase free levels of tricyclic antidepressants (18). Vasopressors should be administered with caution since TCA poisoned patients may be predisposed to the dysrhythmogenic potential of such agents. Phenylephrine may be effective in controlling blood pressure, but norepinephrine is the drug of choice because of its more complete recruitment of alpha receptors.

Sodium bicarbonate alkalization is the first and best treatment for ventricular arrhythmias associated with TCA poisoning (4,6-9,19). Lidocaine can be used for ventricular arrhythmias, however this drug is a negative inotrope and may

^a Gambro Dialysation GmbH & Co. KG, Germany

impair myocardial function. Phenytoin has been shown to be effective against refractory arrhythmias especially if associated with heart block and may be considered the drug of choice (8). Pacemaker insertion may be used for heart block or severe bradycardia unresponsive to drug therapy.

Since some of the toxic effects of tricyclic antidepressants are anticholinergic in nature, physostigmine salicylate has been used as an antidote in some cases with limited success. The value of physostigmine is controversial; it has been recommended by some authors (20-26) but not by others (6,11,27,28) who have cautioned against its routine use. Newton (27) showed that physostigmine reversed most of the effects of tricyclic drugs with maximum effect evident five minutes after injection, but the effects were short-lived and the patients soon returned to their previous condition. Physostigmine readily enters the central nervous system and blocks cholinesterase, thereby inhibiting degradation of acetylcholine at the receptor site. Since TCA induced cardiotoxicity is largely unrelated to the drug's anticholinergic effects, physostigmine probably should not be used routinely due to its side effects and short duration of action, but may be indicated in severe TCA poisoning refractory to other therapies. Atropine should always be available to reverse signs of untoward cholinergic action such as bradycardia.

TCA plasma levels, although useful in confirming ingestion, do not accurately reflect the true toxicity status and rarely correlate with the amount of drug ingested or cleared from the system. Some limited success has been noted in the literature for the use of charcoal hemoperfusion (29), but forced diuresis, dialysis and hemoperfusion are not generally considered effective measures in eliminating TCA because of its low plasma levels, high protein binding and excessive tissue distribution (5,30,31).

Full support using CPB already plays a crucial role in numerous cardiac support modalities such as accidental hypothermia, supported percutaneous coronary angioplasty, and cardiac arrest. As several authors advocate (32-34), it also makes sense to use CPB as a viable treatment for drug overdose. Several animal studies have shown the efficacy of using CPB as an adjunct therapy for lidocaine, desipramine and imipramine toxicities (22-35). Two case studies report successful resuscitation of bupivacaine-induced cardiac arrest and massive propranolol overdose utilizing CPB support (36,37).

Our aggressive attempt to revive and support the patient was based on patient age, good health and clinical appearance. Elapsed time from initiation of CPR to the initiation of CPB was 66 minutes. Neurologic assessment can be unreliable in the presence of drug overdose and should not be considered a primary indicator of terminating CPR efforts, especially in young subjects with TCA poisoning (38,39). Unfortunately, with this patient, there was no documentation of the elapsed time between the patient's initial unconsciousness and the call for medical assistance. The patient was placed on CPB on an emergency basis for cardiac arrest from TCA poisoning. CPB was uneventful and after four hours meaningful cardiac function was sufficiently

restored to maintain a mean arterial pressure above 60 mmHg. The patient was weaned off bypass with minor pharmacologic support and the remainder of the operation continued without incident. To our knowledge, this was the first attempt at cardiopulmonary bypass support for TCA poisoning in humans.

CONCLUSION

Alkalinization with sodium bicarbonate and hyperventilation are the treatments of choice for tricyclic poisoning. Gastric lavage with activated charcoal is indicated to reduce absorption. Most management for seizures and arrhythmias lean toward diazepam and phenytoin. Physostigmine may be warranted in severe poisoning refractory to other therapies. Forced diuresis, dialysis and hemoperfusion are considered ineffective therapies. CPR should be continued on young patients for extended periods of time. Previous case histories by Southall (38) and Orr (39) have reported successful recoveries after prolonged external cardiac compressions (150 min and 90 min, respectively) in young patients (ages 3 and 19 years) for imipramine overdose.

Cardiopulmonary bypass should be considered a life saving modality for cardiac dysrhythmia refractory to drug therapy, and should play an active role in resuscitation if indicated.

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