Tricyclic Antidepressant Overdose

David A. Driggers, MD, Frederick Deiss, MD, Joseph F. Steiner, PharmD, and Daniel W. Hudgings, MD
Casper, Wyoming

DR. DAVID A. DRIGGERS (*Program Director*): Depression is one of the more common diagnoses made by the family physician[1] and often results in the prescription of tricyclic antidepressants. Unfortunately, this medication has become a far too commonly misused agent for self-destructive behavior and suicide attempts. Today's Grand Rounds will demonstrate the importance of the family physician's knowing not only how to prescribe antidepressants correctly but also how to manage an acute overdose.

CASE PRESENTATION

DR. FREDERICK DEISS (*Medical Director, Family Practice Center*): We are going to discuss today the case of Mr. R., a 38-year-old man well known to most of the family practice residents and faculty, the staff of the emergency room, and the psychiatrists in town. He has a long history of depression and has also been treated for peptic ulcer disease. He was found unresponsive at home at 7 AM by his sons, who also found a suicide note and empty pharmacy bottles for cimetidine, cyclobenzaprine, amitriptyline, alprazolam, and ibuprofen. These bottles bore the names of several physicians. The last prescription for amitriptyline was dated one month previously and was for 30 tablets of 150 mg each.

When examined in the emergency room, he had a temperature of 96.6 °F, pulse 109 beats per minute, blood pressure 130/80 mmHg. Pupils were 4 mm and equal. They reacted promptly, but minimally, to light. The pulse was regular, there were no murmurs, rubs, or gallops heard. No abnormalities were seen on a 12-lead electrocardiograph. Bowel sounds were present but distinctly hypoactive. Neurologically, he was unresponsive to pain and had no gag reflex. His deep tendon reflexes were normal. Chest x-ray examination showed a small middle lobe infiltrate on the right side. Arterial blood gas measurements were pH 7.40, carbon dioxide ($PaCO_2$) 4.79 kPa (36 mmHg), and oxygen (PaO_2) 9.86 kPa (74 mmHg) with bag-mask ventilation. The admitting assessment was polypharmacy overdose, of which the most potentially dangerous was amitriptyline.

DR. DANIEL HUDGINGS (*Family Practice Chief Resident*): The patient was transferred directly from the emergency room to the intensive care unit, where he was intubated and a large-bore Ewald tube was passed into his stomach. We were unable to recover anything suggestive of pills through the Ewald tube. He was given 50 g of activated charcoal through the tube, which was repeated every four hours. Sodium bicarbonate was given intravenously, bringing his urine pH to approximately 8 and his blood pH to 7.50. Over the next 24 hours, he improved neurologically, and his pulse rate decreased to the normal range. Urine output was 40 to 110 mL/h. He was extubated on the morning following admission. He developed a cough productive of yellow-colored sputum. Cultures were taken, and he was started empirically on cefoperazone pending results of sputum cultures.

His oxygen requirements continued to decrease and he was transferred to the intensive care step-down unit, where cardiac monitoring was continued for a full 24 hours after the overdose. Because sputum cultures subsequently grew Hemophilus influenzae and Branhamella catarrhalis, he was switched from cefoperazone to co-trimoxazole. He continued to receive charcoal intermittently, as the results of the qualitative tricyclic antidepressant screening test from the laboratory remained positive. (Our hospital is a small, remote, community hospital and cannot do quantitative measurements of serum tricyclic levels.) His urine toxicology screening test was negative.

The patient improved and was transferred on the third day to a psychiatric hospital, remaining adamant that, if discharged, he would attempt to do this again. He demanded a change of physicians. At the time of transfer to the psychiatric hospital, he was taking a double-strength dose of co-trimoxazole, one tablet twice daily to complete a ten-day course.

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From the University of Wyoming Family Practice Residency Program–Casper, Casper, Wyoming. Requests for reprints should be addressed to Dr. David A. Driggers, University of Wyoming Family Practice Residency Program–Casper, 1522 East A Street, Casper, WY 82601.

PHARMACOLOGY

JOSEPH STEINER, PHARM D (*Clinical Pharmacist*): This is a rather typical presentation of a tricyclic antidepressant overdose. Persons taking an overdose of tricyclic antidepressants will often concomitantly take other medications or alcohol. Usually, as in this case, the drug with the greatest toxicity is the tricyclic antidepressant. An overdose of tricyclic antidepressants causes a number of problems. The anticholinergic effects, especially on the gastrointestinal and urinary tracts, are prominent. The anticholinergic effect on the gastrointestinal tract may decrease gastric emptying, which may in turn slow absorption of the medication. As we will discuss, this delayed absorption is quite important in the management of the case. There are also central nervous system changes ranging from drowsiness to coma. Almost all of the tricyclic antidepressants and some of the other antidepressants, such as the tetracyclics, will decrease the seizure threshold, so that convulsions may develop. The cardiovascular toxicity is quite important. With an overdose there are unopposed norepinephrine effects on the heart. The tricyclic antidepressants will also produce a quinidine-like effect on the heart. Hypotension may occur, which, coupled with the quinidine effect and the unopposed norepinephrine effect, can produce serious cardiac arrhythmias.

CLINICAL APPROACH

DR. HUDGINGS: The pharmacology to some extent dictates the clinical approach to such patients. It is important to know not only how long it has been since ingesting the substances, but also what and how much was taken. There are case reports of incomplete absorption as late as 24 hours after ingestion because of the delay in absorption caused by the anticholinergic effects. One needs to know whether multiple agents were taken, such as phenobarbital or some other toxic material that could be comparably dangerous. In the case of Mr. R., we simply did not know. He had apparently seen several physicians locally and had accumulated a supply of a variety of medications over the course of the months.

DR. DEISS: Family physicians must be aware of patients "doctor shopping," and possibly obtaining a supply of medications for whatever reason. In our experience, patients who have chronic pain, who exhibit addictive behavior, or who are depressed should be included in this worrisome category.

DR. HUDGINGS: One also needs to know of any concurrent illnesses. The examination, if the patient is comatose, must begin with securing an airway, making sure the patient is breathing, and that circulation is adequate. After that, a complete physical examination should be accomplished, with particular attention given to the presence or absence of gag reflex. As with Mr. R., a major problem with such patients is that they frequently develop aspiration pneumonia.

DR. DEISS: Mr. R. presented with hypothermia; however, a patient with a tricyclic antidepressant overdose may just as likely present with hyperthermia, as temperature regulation is upset by the central anticholinergic effects. The dilation of his pupils is also due to peripheral anticholinergic effects, as are his tachycardia and decreased bowel tone.

DR. HUDGINGS: Laboratory studies should include serum electrolytes and glucose. A significant anion gap raises the possibility of aspirin or other ingestions. A complete blood count may give some insight as to the presence or absence of a concurrent infection. A serum tricyclic antidepressant screening test (in a small hospital such as this one, this is by necessity a nonquantitative photometric test) and a urine toxicologic screening test should be done, looking for other intoxicating agents as well. Blood gas determinations are useful, both for assessing the clinical status and for estimating how much bicarbonate can be given.

The importance of an electrocardiogram and continuous cardiac monitoring must be emphasized. Boehnert and Lovejoy[2] note that the QRS duration is more predictive of seizures and arrhythmias than is the actual serum tricyclic antidepressant level. A chest roentgenogram can reveal aspiration pneumonia. Diagnosis is not usually a problem with these patients, but it is necessary to make certain that other intoxicating agents have not been missed. The differential diagnosis includes status epilepticus, myocarditis, and encephalitis.

DR. DEISS: A major problem with tricyclic antidepressant overdose patients is that they often appear stable and the case seems uncomplicated. You put them on the ward and order frequent routine checks, which sometimes are overlooked because the patient's condition looks good. Unfortunately, up to 24 hours later you may have a sudden arrhythmia and the patient is dead. Consequently, your orders should be specific. The patient should be observed, preferably in the intensive care unit, or at least monitored. Some authorities favor cardiac monitoring for as long as five days after ingestion. Do not get lax just because the patient looks good. Write orders for hourly monitoring or, if necessary, half-hourly monitoring with the results charted. I know of a recent case of a patient who died suddenly in an emergency room while no one was observing him.

These patients can be comatose, they can be agitated, they can be hypertensive, they can be hypotensive. The presentations are variable, and you have to watch for all the variations. The intensive care unit is the place to do

your watching. Although the normal fatal dose is greater than 2 g, deaths have been recorded in adults with as little as 0.50 g of tricyclic antidepressant and in children with as little as 0.33 g. Never forget that the amount of the dose may not have a great deal to do with the outcome.[3]

INITIAL MANAGEMENT

Management of tricyclic antidepressant overdose follows rather directly from the drug's pharmacology. The initial step is to get rid of the antidepressant materials in the stomach. Delayed gastric emptying makes this effort effective as late as 12 to 24 hours after ingestion. If the gag reflex and mental status are intact, one may certainly consider using ipecac. It must be recognized, however, that the use of ipecac does delay the administration of charcoal.[4] In Mr. R.'s case, we used a large-bore Ewald tube to assess the presence or absence of material in his stomach. It also permitted easy administration of the charcoal.

DR. STEINER: Indeed, it is important if you are doing gastric lavage to be sure that the tube is large enough. Tablets may be sizable, and if you can't bring them back out, you are not doing much good. Often in such cases where the patient takes a number of tablets, they tend to form concretions in the stomach.

DR. DEISS: A large orogastric tube, a 34 French or larger with the cuff inflated, is indicated. Small nasogastric tubes, such as Levin tubes, should not be used.

DR. HUDGINGS: The definitive treatment is the use of activated charcoal slurry. We used repeated large doses, 30 to 50 g every 4 to 12 hours. Volunteer studies using therapeutic doses of nortriptyline have demonstrated peak absorption at 4 to 6 hours.[5] Charcoal administered 30 minutes after ingestion decreased the peak serum levels in these studies. The probable mechanism is binding of the nonabsorbed tricyclic antidepressants. The actual clearance of serum amitriptyline is also increased with charcoal administration.[6] This result may be due to enterohepatic recirculation or actual tricyclic antidepressant secretion through the gut wall. Although charcoal absorbs imipramine from within the gastrointestinal tract, the clearance of serum imipramine is not affected by the oral administration of charcoal.[7] Thus, charcoal is helpful for nortriptyline, imipramine, and amitriptyline intoxications, although the mechanisms may not be identical. Charcoal is a benign therapy. One may give magnesium citrate to increase the transit of the charcoal through the gut. Some charcoal preparations contain sorbitol for this purpose.

DR. STEINER: Some recommend using charcoal with castor oil to stimulate the ileus, thus overcoming the anticholinergic effects and producing peristalsis. This treatment may be more effective than osmotic agents.

There are a number of controversies about treatment of tricyclic antidepressant overdoses, particularly concerning the use of physostigmine.[8] Physostigmine is a centrally acting anticholinesterase agent, so it will increase acetylcholine in the central nervous system. It is effective in only one third to one half of the patients with seizures, while it can, in itself, cause seizures in perhaps 10 to 20 percent of patients with tricyclic antidepressant overdose when so treated.

DR. DEISS: Clinically, there is no consensus as to when, if ever, physostigmine should be used. Nonetheless, most authors would say that physostigmine should be used in comas or complications of comas when nothing else works. Various manifestations of a tricyclic antidepressant overdose, such as delirium, hallucinations, coma, myoclonic and choreiform movements, and cardiac arrhythmias, often respond to physostigmine. It may be useful in situations such as tricyclic antidepressant coma complicated by pneumonia and, if the patient responds, for ruling out suspected brain death.

DR. STEINER: Physostigmine will produce excessive cholinergic activity with effects such as hypersalivation, bradycardia, hypotension, and convulsions. It is contraindicated in bradycardic patients or those with atrioventricular block because it may cause complete heart block or asystole. That the medication is short acting may necessitate frequent administrations or a continuous infusion. If severe hypersalivation or bradycardia occurs, atropine must be used immediately. One could quickly get into a vicious cycle by using physostigmine.

One other controversy in the treatment of tricyclic antidepressant overdoses is the use of toxicologic analysis. Early studies showed little relationship between clinical features and drug plasma concentration.[8] There was enough interindividual variation that tricyclic antidepressant metabolism and concentrations could produce high therapeutic levels in some patients and low toxic levels in others. In these studies, the active metabolites were not measured. However, a positive relationship between serum concentration of the tricyclic antidepressant and its active metabolites and clinical features of a large overdose have now been determined. When levels of greater than 1,000 ng/mL of drug and metabolites are detected, there is a higher incidence of coma, seizures, cardiac arrhythmias, and the need for artificial ventilation. Symptoms of mild poisoning still do not correlate well with serum concentrations, and as Dr. Hudgings mentioned, a QRS duration of greater than 0.1 sec is a more reliable and more easily obtainable predictor of central nervous system and cardiac toxicity.[2]

Thermoregulation is often affected. It may be necessary to use ice packs or a warming blanket.

COMPLICATIONS

DR. HUDGINGS: Seizures often occur with tricyclic overdoses. Although they are commonly treated with phenytoin, one could consider diazepam, which is more prompt in its action than phenytoin. There is some evidence that the use of diazepam does decrease amitriptyline clearance,[6] so this has to be weighed against its quicker onset. Airway protection is obviously necessary in these cases.

DR. STEINER: Diazepam has become the drug of choice for the treatment of tricyclic antidepressant seizures, although phenytoin has the additional antiarrhythmic effect, which may be beneficial in some patients. When phenytoin is used, an intravenous loading dose is required. Barbiturates should never be used for tricyclic antidepressant seizures because they may cause further respiratory depression.

DR. DEISS: As supportive treatment, external stimuli should be decreased to minimize the tendency to produce seizures.

DR. HUDGINGS: Cardiotoxicity is also of great concern. In addition to a supraventricular tachycardia, one almost always sees an increased QRS and PR interval in patients with cardiac problems from tricyclic antidepressant overdose. Cardiotoxicity without these electrocardiographic findings is uncommon.

DR. DEISS: Mr. R. did not have a prolonged QRS on admission, but absence of any cardiac abnormalities may produce a sense of false security, because the cardiac manifestations may present at any time during the first 24 hours after an overdose. For this reason, the patient's ECG should be continuously monitored for at least the first 24 hours. Deaths after 24 hours from tricyclic antidepressant overdoses are usually associated with noncardiac causes such as pulmonary or cerebral anoxia.

DR. STEINER: The ECG changes seen with tricyclic antidepressant overdose may resemble ventricular or supraventricular tachycardia or bundle branch block. Atrioventricular block or bradycardia are also seen in severe poisonings. These effects are probably due to a combination of the tricyclic antidepressant's quinidine-like effects and anticholinergic effects, which in turn permit an unopposed increase in norepinephrine effects.

DR. HUDGINGS: Vigorous treatment of the acidosis appears to reduce the cardiotoxic effects. The mechanism of the arrhythmias is certainly different from that of coronary artery disease. The prognostic significance of arrhythmias from tricyclic antidepressant overdose is unknown. There are reports in the literature of successful recovery without neurologic deficit following prolonged cardiac massage. Temporary pacemakers are also sometimes successful in overdosed patients who experience cardiac arrest. Shock is a common presentation, and it is thought to be due to reduced capillary permeability. One should certainly monitor for shock by placing a Foley catheter and looking at the urine output. A marked decrease in urine output is a warning that cannot be ignored. Vigorous resuscitation with fluid infusion and the vasopressor with which one is most familiar should be started. No single catecholamine has been shown to be superior to the others in this setting.

DR. STEINER: As a therapy for ventricular arrhythmias, sodium bicarbonate has become an important therapeutic measure, especially for any patient with a QRS interval of 100 ms or greater, a sign of severe cardiac toxicity. A blood pH of from 7.5 to 7.55 is the most desirable. A 0.5 to 2 mEq/kg intravenous bolus followed by an intravenous drip of two ampules of sodium bicarbonate in 1 L of 5 percent dextrose in water is the solution that should be started on all tricyclic antidepressant overdose patients. This solution yields 88 mEq of both sodium and bicarbonate. It is thought that the antiarrhythmic effect of sodium bicarbonate in tricyclic antidepressant overdose is due to not only the alkalinization but also to the increased extracellular sodium concentrations that diminish the arrhythmogenic actions of the tricyclic antidepressants.[9,10] Hyperventilation may produce a similar antiarrhythmic effect if the patient is mechanically ventilated.[11]

DR. DEISS: Ventricular arrhythmias that do not respond to sodium bicarbonate are treated with either phenytoin or physostigmine. Propranolol is indicated for life-threatening ventricular arrhythmias in children with tricyclic antidepressant overdose.

DR. STEINER: Because of the anticholinergic and quinidine-like effects, antiarrhythmics such as quinidine, procainamide, other class IA antiarrhythmics, and atropine are contraindicated. Magnesium, calcium, potassium, and possibly lidocaine are ineffective in the treatment of tricyclic antidepressant-induced arrhythmias.

DR. HUDGINGS: Hemodialysis and hemoperfusion have not been shown to be effective. Urine alkalinization to increase renal excretion may be helpful; but, in any case, bicarbonate therapy for cardiac arrhythmias is helpful and will accomplish the alkalinization of the urine.

DR. STEINER: The tricyclic antidepressants are highly protein-bound, which prevents their dialysis. Forced diuresis has also been found to eliminate very little medication and, in fact, may be dangerous if cardiac function is impaired.

DR. HUDGINGS: It is worth noting that fatal tricyclic antidepressant overdose does not preclude kidney or cornea donation.

CONCLUDING COMMENT

DR. HUDGINGS: This case illustrates the wisdom of prescribing tricyclic antidepressants in less than lethal quantities and of assessing carefully the risk of suicide. In

continued on page 236

continued from page 234

the absence of other treatment modalities, depressed patients at risk for suicide usually need medication, but this must be done with caution. Depending on the potential for suicide, prescriptions should not be refillable and the amounts should be limited to a total that is below the potentially lethal dose (15 to 20 mg/kg of amitriptyline).

Anticipatory guidance is important in the outpatient setting. Patients must understand the lethal nature of their medications and the need to keep them away from children.

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