Reversible Brain Death*
A Manifestation of Amitriptyline Overdose

Karl L. Yang, M.D.;† and David R. Dantzker, M.D.‡

Tricyclic antidepressants are known to cause central nervous system depression. However, a generalized depression of brainstem functions is rarely reported. We report a patient in deep coma with complete absence of brain-stem reflexes after she had taken a large quantity of amitriptyline. With continuous supportive treatment, she eventually regained all neurologic function and made a full recovery.

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Tricyclic antidepressants (TCA) are among the most frequently prescribed medications in the United States. It is estimated that more than 20 million prescriptions are written each year in this country.1 Because of their wide availability and frequent usage, TCA overdose is the leading cause of drug-related hospital admissions.2 The toxic side effects of TCA are characterized by their anticholinergic activity as well as cardiac and cerebral toxicity. Reversible loss of selected brainstem functions in the setting of TCA overdose has occasionally been reported in the literature.3,4

The generalized absence of brainstem reflexes, however, is associated with deep coma and is considered to be a premonitory sign of a grave outcome. In fact, in many instances, a total absence of brainstem function has been used to define brain death.5 We report a patient with TCA overdose resulting in total absence of brainstem function who recovered without apparent neurologic sequela.

CASE REPORT

A previously healthy 46-year-old white woman was brought by the family to an emergency room with an amitriptyline overdose. It was estimated that she had taken approximately 9 g of amitriptyline about 1 h earlier. On arrival, the patient suffered a grand mal seizure, and 15 mg of diazepam (Valium) and 130 mg of phenobarbital were given to control the seizure and 2 mg of physostigmine was also administered in an attempt to reverse central nervous system toxicities. Blood pressure was 98/66 mm Hg, and pulse was 94 beats per minute. The patient was intubated and the initial arterial blood gas values showed a pH of 7.16, PaCO2 of 31 mm Hg, and PaO2 of 373 mm Hg on 100 percent oxygen. The ECG revealed a widened QRS complex (190 ms) and prolonged QT interval (866 ms). She had metabolic acidosis and anion gap of 24. Dopamine was started to maintain blood pressure. The patient remained severely hypotensive and epinephrine was added to the dopamine. Because of the continuing failure to respond to pressor therapy, she was transferred to our MICU for further treatment. On arrival, she had no spontaneous respiration. Neurologic examination revealed a comatose woman who did not respond to any painful stimulation. Both pupils were fixed and dilated. Corneal reflex and oculocephalic reflex were absent. All four extremities were flaccid and areflexic. Urine drug screen was positive for the presence of amitriptyline, benzoazepine, and phenobarbital. The serum amitriptyline level

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FIGURE 2. Chest roentgenogram following tetracycline pleurodesis from the hospital. A follow-up period of ten months disclosed no recurrence. Unfortunately, the patient died in February 1988 from extensive pneumonia.

DISCUSSION

Chemical pleurodesis has been used with good results in spontaneous pneumothorax in patients with diffuse parenchymal lung diseases such as cystic fibrosis,1 and several reports have indicated success in patients who are at high surgical risk, particularly the elderly.1 We had similar success in our patient with tetracycline pleurodesis. This patient did have a history of two spontaneous episodes of pneumothorax occurring prior to the diagnosis of acquired immunodeficiency syndrome; however, the three subsequent episodes occurred within a four-month period, indicating a more aggressive process of lung destruction typical of P carinii infection. He was then without further recurrence following tetracycline sclerosis for the ten months preceding his death.

One disadvantage often cited with tetracycline pleurodesis has been poor patient tolerance secondary to pain; however, adding lidocaine to the tetracycline has lessened this problem. Premedication with intravenous or intramuscular analgesics also has been helpful.

The success of this therapy should lead to consideration of this modality as an alternative to surgery in this high-risk group of patients with spontaneous pneumothorax.

REFERENCES

2 Eng RHK, Bishburg F, Smith SM. Evidence for destruction of lung tissues during Pneumocystis carinii infection. Arch Intern Med 1987; 147:746-49

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Failure of Long-term Digitalization to Prevent Rapid Ventricular Response in Patients with Paroxysmal Atrial Fibrillation*  

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Digitalis is frequently prescribed to patients with paroxysmal atrial fibrillation to reduce the ventricular rate during subsequent paroxysms. To verify the validity of this assumption, we determined the ventricular rate during

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Table 1—Drugs That Can Cause CNS Depression and Coma

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcotics:</td>
<td>Morphine, heroin, methadone, codeine, opiates</td>
</tr>
<tr>
<td>Sedatives/hypnotics:</td>
<td>Barbiturates, benzo diazepines, meperidate</td>
</tr>
<tr>
<td>Anticholinergic:</td>
<td>Atropine, tricyclic antidepressants, anti-histamine, phenothiazine</td>
</tr>
<tr>
<td>Cholinergic:</td>
<td>Organophosphate insecticides, neo stigmine, pyridostigmine</td>
</tr>
<tr>
<td>Others:</td>
<td>Salicylate, lithium, glutethimide, ethanol</td>
</tr>
</tbody>
</table>

was 2,350 ng/ml (therapeutic range 75 to 225 ng/ml) and phenobarbital level was 3 µg/mL (therapeutic range 15 to 35 µg/mL).

During the first 6 h in the MICU, her blood pressure remained low (75/50 mm Hg), despite an infusion of dopamine as high as 30 µg/min/kg. When norepinephrine was substituted for dopamine, her blood pressure rose to 130/70 mm Hg. Over the next 3 h, she was weaned from all pressor support. Twenty-four hours after the initial ingestion, spontaneous respiration was noted. Forty-eight hours later, both corneal and pupillary reflexes returned, and then oculocephalic reflex normalized 64 hours after the intoxication. Finally, after five days of hospitalization, the patient regained full consciousness. The neurologic examination at this time did not demonstrate any deficits.

**DISCUSSION**

Amitriptyline is an effective antidepressant. It is known that TCA potentiates the effects of amines on the CNS by blocking the re-uptake of norepinephrine at the nerve terminals.7 This action has also been used to explain the etiology of hypotension. After an initial hypertensive effect due to the blockage of norepinephrine uptake by the sympathetic nerve terminals, there is a gradual depletion of norepinephrine. Dopamine, which works partially through the release of endogenous norepinephrine, will be less effective in the setting of TCA overdose because of this, as seen in our patient.8

TCA overdose typically causes a brief period of excitement and restless ness, followed by grand mal seizures, dystonia, and coma. TCA have been reported to depress some brainstem reflexes and respiration.25 This is most commonly manifested as total ophthalmoplegia, opsonolusus, or bilateral internuclear ophthalmoplegia. However, to our knowledge, total absence of brainstem function, as in this case, has not been described. While phenobarbital can cause generalized brainstem depression,

* It has been suggested that various brainstem reflexes may differ in their sensitivity to TCA. Physostigmine, an acetylcholinesterase inhibitor, has been used to reverse the toxicity of TCA. In a single case report, it was noted that both corneal and pupillary reflexes returned to normal after physostigmine, but not oculocephalic reflexes. This suggests that oculocephalic reflex is more easily inhibited by TCA. This hierarchy of responsiveness is supported by our observation in the current case. As the amitriptyline levels fell, the patient regained her pupillary reflex first, then the corneal reflex. Finally, the oculocephalic reflex returned to normal 64 hours after the ingestion.

Generally, a patient with coma profound enough to eliminate brainstem function rarely recovers.11 However, patients with drug overdose may make a full recovery despite neurologic findings. Some of the commonly used medications that can cause coma are listed in Table 1. This case demonstrates the need for continuing active TCA management in any patient with an overdose of TCA despite their appearance on the initial assessment of having suffered an irreversible brain insult.

**REFERENCES**