“Complete” loss of brain stem reflexes - not always brain death! Beware of amitriptyline overdose

Amit Kansal, Faheem Ahmed Khan, Muhammad Habibullah Rana

Abstract
We present a case of “complete” loss of brain stem reflexes following amitriptyline overdose, which mimicked brain death. This case highlights the complexities associated with clinical brain death determination and calls for close attention to details.

Based on previously published case reports, we analyse the relationship with the amitriptyline dose, blood level and timing of neurological recovery. Ours is the fourth case report in literature demonstrating “complete” loss of brain stem reflexes following amitriptyline overdose. The amount of amitriptyline ingested in these cases (including our case report) ranged from 500 mg to 9 g; the blood concentrations ranged from 1.35 microgram/ml to 3.43 microgram/ml. The neurological recovery seems to start by day two to four with complete neurological recovery by day five to seven.

Key words: Amitriptyline toxicity, brain stem reflexes, brain death.

Introduction
We report a case of “complete” loss of brain stem reflexes following amitriptyline overdose, which mimicked brain death.

Incorrect diagnosis of brain death has grave implications with regards to public as well as health care professionals’ trust regarding organ donation proceedings. Therefore it is paramount that clinicians involved are aware of confounders that can mimic brain death including amitriptyline overdose.

Based on previously published case reports, we also discuss the range of amitriptyline dose ingested, blood level and timing of neurological recovery. Once again, the clinicians & toxicologists need to be aware of likely trajectory of clinical recovery and not to jump to a conclusion of brain death too soon without attention to details.

Case report
A 52-year-old male with past medical history of benzodiazepine dependence and depression, sustained out-of-hospital cardiac arrest following ingestion of 20 tablets of amitriptyline (approximately 500 mg in total ~8 mg/kg) with suicidal intention. It was a witnessed collapse, but no bystander cardiopulmonary resuscitation (CPR) was performed. CPR was started after 18 minutes of collapse on arrival of paramedics; initial rhythm revealed pulseless ventricular tachycardia. Return of spontaneous circulation was achieved within six minutes after two shocks. Subsequently, patient was transferred to ED with bag mask ventilation. On arrival at ED, Glasgow coma score (GCS) was 3 (E1V1M1); pupils were dilated and fixed and there was no spontaneous respiration. Patient’s trachea was intubated without any need of induction agents.

He was hypotensive with blood pressure of 79/52 mmHg with tachycardia of 95 to 100 beats/min. 12-lead ECG showed changes typical of tricyclic antidepressants overdose (wide QRS complexes with slurred S wave, long QT, absent P and prominent R wave in the lead aVR). Amitriptyline overdose was managed with activated charcoal (administered through nasogastric route to decrease gut absorption) and intravenous sodium bicarbonate (with consequent improvement in long QTc).

CT brain was normal on day of admission. Decision was made to initiate therapeutic hypothermia.
Khan) did independent literature search to identify two reviewers (Amit Kansal and Faheem Ahmed Khan) did independent literature search to identify the commonest causes of drug poisoning. Overdose of tricyclic antidepressants is among one of the commonest causes of drug poisoning. (1) Ours is the fourth case in literature demonstrating "complete" loss of brain stem reflexes following amitriptyline overdose. Clinical presentation in our case raised a suspicion of brain death secondary to likelihood of HIE; which fortunately was not the case, very clearly. Patient had good neurological recovery subsequently.

Two reviewers (Amit Kansal and Faheem Ahmed Khan) did independent literature search to identify case reports of complete loss of brainstem function following amitriptyline overdose. We identified only three other case reports. (2-4)

On the other hand, there are several case reports of "partial" loss of brainstem functions in the setting of TCA overdose. (5-7) It appears that the oculocerebral reflex is most easily inhibited, (5) and during recovery the patient regains pupillary reflex first, then the corneal reflex and finally the oculocerebral reflex. (2,5)

Amitriptyline is highly protein bound and has a large volume of distribution, resulting in long elimination half-life of 31 to 46 hours. (1) Coma and life threatening cardiovascular events usually manifest within a few hours of ingestion. (1)

The amount of amitriptyline ingested in cases with severe neurological toxicity with complete loss of brain stem reflexes (including our case report) ranged from 500 mg to 9 g; the blood concentrations ranged from 1.35 microgram/ml to 3.43 microgram/ml (Table 1). The neurological recovery seems to start by day two to four with complete neurological recovery by day five to seven. (2-4) Clinicians need to be careful of the possibility of CYP2D6 enzyme deficiency leading to sustained elevation of plasma concentration and prolonged coma. One case report has highlighted this abnormal metabolism due to deficiency in CYP2D6; the neurological recovery started by day six and complete neurological recovery occurred by day 12. (8) Initial plasma concentration in that study was similar to ones described in the above-mentioned case reports (1.57 microgram/ml). (8)

There have been no case reports of nitrazepam being the sole cause of loss of brain stem reflexes. In view of very toxic blood amitriptyline levels, nitrazepam is unlikely to be primary toxin responsible for all the neurological signs observed in our study. Nitrazepam could have conferred anti-epileptic effect though.

To summarize, this case report establishes that a significantly high dose of amitriptyline can lead to a complete loss of brain stem function and highlights the complexities associated with brain death determination.

Discussion

Overdose of tricyclic antidepressants is among one of the commonest causes of drug poisoning. (1) Ours is the fourth case in literature demonstrating "complete" loss of brain stem reflexes following amitriptyline overdose. Clinical presentation in our case raised a suspicion of brain death secondary to likelihood of HIE; which fortunately was not the case, very clearly. Patient had good neurological recovery subsequently.

Patient had complete neurological recovery by day 6. Later on he was transferred to psychiatric hospital for suicidal intention and violent behaviour. Written informed consent was taken from the next-of-kin for case report to a medical journal.

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Table 1

<table>
<thead>
<tr>
<th>Plasma Concentration (µg/ml)</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.35 - 3.43</td>
<td>Recovery</td>
</tr>
<tr>
<td>&lt; 1.35</td>
<td>No Recovery</td>
</tr>
</tbody>
</table>

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Table 1. Amitriptyline dose, blood level and timing of neurological recovery

<table>
<thead>
<tr>
<th>Drug (dose)</th>
<th>Onset of symptoms</th>
<th>Start of recovery</th>
<th>Complete recovery</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline (9 g) Serum amitriptyline level: 2.35 microgram/ml (2350 ng/ml)</td>
<td>~ 1 hour after ingestion</td>
<td>24 hours after ingestion</td>
<td>Day 5</td>
<td>(2)</td>
</tr>
<tr>
<td>Amitriptyline (unknown dose) Total serum amitriptyline level: 1.35 microgram/ml (1348 ng/ml)</td>
<td>On admission</td>
<td>Day 4 after ingestion</td>
<td>Day 5</td>
<td>(3)</td>
</tr>
<tr>
<td>Amitriptyline 1.5 g and two benzodiazepines (diazepam 150 mg and lorazepam 15 mg)</td>
<td>Found unresponsive at home after 38 hours of last seen well</td>
<td>Day 2 after ingestion</td>
<td>Day 7</td>
<td>(4)</td>
</tr>
<tr>
<td>Amitriptyline (500 mg) and nortriazepam (unknown quantity) Total serum amitriptyline level: 3.43 microgram/ml (amitriptyline 2.8 microgram/ml &amp; nortriptyline 0.63 microgram/ml)</td>
<td>On admission</td>
<td>Day 2 after ingestion</td>
<td>Complete neurological recovery by day 6</td>
<td>Our case</td>
</tr>
</tbody>
</table>

Legend: Therapeutic serum levels of amitriptyline: 0.075-0.225 microgram/ml.
References