Tricyclic Antidepressant Intoxication; Several Complications after an Acute Poisoning by Amitriptyline and Clomipramine

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Abstract
Tricyclic antidepressant (TCA) toxicity is common among children and adults due to widespread use. Tricyclic antidepressant drugs are widely used in suicide attempts and present a variety of deleterious effects. In this case report we present a patient with severe poisoning by ingestion of amitriptyline and clomipramine in which many complications were observed.

Keywords: Poisoning; Tricyclic antidepressant drugs; Amitriptyline; Clomipramine

Introduction
Medications most commonly used in pain management include anticonvulsants, tricyclic antidepressants. Treatment choices should take into account coexisting conditions, such as insomnia, depression, and anxiety [1]. Tricyclic antidepressants have been approved by the Food and Drug Administration (FDA) specifically to treat depression, with their generic or chemical names [2]. Tricyclic antidepressants are among the most commonly used drugs in suicide attempts, along with benzodiazepines, alcohol and acetaminophen, surpassed only by analgesics [3]. Although the risk of suicide is the same between tricyclic drugs and other antidepressants [3], tricyclic and depressant overdose is an important cause of mortality [4]. The death rates are higher when tricyclic drugs are used: 97% of all deaths due to antidepressant poisoning are caused by them [3]. Amitriptyline is a very frequently prescribed antidepressant agent and is very often involved in attempted suicides [5]. Clomipramine is dibenzazepine tricyclic antidepressants widely used in the treatment of depression [6].

Case Presentation
A 20-year-old woman, with no history of depression, was admitted to the emergency service because of an acute poisoning with a suicidal attempt. It seems that she had problems with her family, the family declared that she ingested the treatment of her mother, according to her family she ingested 43 capsules of Elavil (25 mg amitriptyline chloride per capsule) and 79 tablets of Anafranil (10 mg clomipramine per tablet). Totally she ingested 1075 mg of amitriptyline and 790 mg of clomipramine. She stayed in the intensive care unit for eleven days, and then she was transferred to the internal medicine department (Figure 1).

Clinical exams
When she was admitted to the emergency service clinical examination shows: 1. A score of Glasgow 5/15, a stunning arterial tension, 2. Pupils in reflective mydriasis with transitional passage in mydriasis Normal cardiopulmonary auscultation with flexible and movable abdomen, 3. She presented two generalized convulsive tonicclonic crises with biting tongue. Gynecological exam was without anomalies. Gastric lavage brought a yellowish liquid (Figure 2).

The Figure 2 showed an ECG with a narrow QRS with some ventricular extra systoles.

Toxicology Analysis
Toxicology screening of gastric lavage was positive with FOREST reagent and shows the presence of anti-tricyclic depressant.

The protocol: After alkaline extraction, we resumed residues with 1 ml of distillated water. We added 3 ml of FOREST reagent in our case the reaction has given a blue coloration that confirms the presence of anti-tricyclic depressant.
Figure 1: ECG1 was done in the emergency department at 09:19 min. The Figure 1 showed an ECG with wide QRS and under shift of the ST segment in anterior.

Figure 2: ECG2 was done in the emergency department at 09:36 min.
We advanced in toxicology screening to search the presence of Amitriptyline and the reaction was also positive. The table below show how we determined the presence of Amitriptyline in the gastric lavage; the control and the sample should be extracting in the same conditions (Table 1).

| Control                          | Sample                      |
|---------------------------------|-----------------------------|
| 5 ml of amitriptyline solution  | 5 ml of patient gastric lavage|
| we added 2 drops of NaOH 20%    |                             |
| We added 5 ml of ether          |                             |
| We shook, recovered ether and evaporated to dry in a tube with 2 a 3 glass marbles | |
| We added 2 drops of H$_2$SO$_4$ concentrate | |
| Positive reaction: Red coloration | Positive reaction: Red coloration |

Table 1: Protocols and results of amitriptyline Toxicology screening in Gastric lavage.

### Radiologic Exam

**Cerebral CT in axial sections without the injection of iodinated contrast showed:** Lack of spontaneous brain parenchymal density anomaly, Lack of axial extra bleeding. Structures in place, ventricles not open and Free base tanks (Figure 3).

![Figure 3: Normal Cerebral Ct.](image)

### Biological Exams

Biological analysis performed in the emergency department indicated the presence of respiratory alkalosis; pH: 7.49, pCO$_2$: 214 mm/hg, pO$_2$: 27.2 mm/hg. The other biological parameters are normal (Table 2).

| Glycaemia | 7.56 mmol/l (3.89-5.50) | WC | 9.5 10$^7$/mm |
|-----------|------------------------|----|---------------|
| Urea      | 4.7 mmol/l (2.5-9.2)   | RC | 4.6 10$^3$/mm |
| CK        | 120 UI/l (<170 )       | HB | 12 g/dl       |
| LDH       | 317 UI/l (125-243)     | PLT| 438 10$^3$/mm |
| ASAT      | 27 UI/l (5-34)         | QT | 77%           |

Table 2: Biological exams.

She was admitted to the intensive care unit, she was intubated, ventilated and sedated. The patient was put under Adrenaline 3 µg/h, Gardinal to shoot electric syringe after she received 2 doses of valium and 1 bulb of rivotril without success.

**On the next day, clinic exams show:** Epileptic status rebel to the anti-convulsant treatment. Pupils initially intermediate and reactive Conduction disorder. QT elongation and intraventricular block. Arterial tension is 11/6 and pulse is 119 bpm.
After four days clinical exams showed: Spontaneous eye opening, Persistence of mydriasis, Improvement of hemodynamic terms. Later evolution was marked by the cessation of convulsive crises, improvement of hemodynamic state.

Biological Exams Evolution

Evolution of biological parameters showed that creatinine kinases increased since the third day of the intoxication, to reach values of 2130 UI/L, than it decreased from the fifth day to reach values of 650 UI/L in the sixth day.

Therapeutic management

In the table 3 we described treatment and doses during the admission in the intensive care unit. Noting that our patient was extubated at 11 h in the seventh day but the result was negative; at 14 h she was reintubated. In the same day and at 19 h the patient was extubated with success.

| Biological Exams | Day 1  | Day 2  | Day 3  | Day 4  | Day 5  | Day 6  |
|------------------|--------|--------|--------|--------|--------|--------|
| Glycaemia (3.89-5.50 mmol/l) | 7.56   | -      | -      | -      | 5.89   | -      |
| Urea (2.5-9.2 mmol/l) | 4.7    | 3.2    | -      | -      | 3.9    | 2.2    |
| Creatinine (50.40-110.50 μmol/l) | -      | 84     | -      | -      | 65     | -      |
| CK (<170 UI/L) | 120    | 526    | 2130   | -      | 1160   | 650    |
| LDH (125-243 UI/L) | 317    | 184    | 264    | -      | 230    | 175    |
| ASAT (5-34 UI/L) | 27     | -      | 41     | -      | 32     | -      |
| ALAT (0-55UI/L) | 13     | -      | 22     | -      | -      | -      |
| NA (136-146mmol/l) | 142    | -      | -      | -      | 137.3  | -      |
| K (3.6-4.6 mmol/l) | 4.6    | -      | -      | -      | 2.9    | -      |
| CRP (<6mg/l) | 5      | -      | -      | -      | 7.42   | 7.44   |
| PH (7.37-7.43) | 7.49   | -      | -      | -      | -      | -      |
| PCO₂ (37-43 mm Hg) | 214    | -      | -      | -      | 176    | 61     |
| PO₂ (75-100 mm Hg) | 27.2   | -      | -      | -      | 34.2   | 31.7   |
| HCO₃⁻ (22 a 26 mmol/l) | 20.2   | -      | -      | -      | 21.6   | 22.4   |

Discussion

One of the most common drugs overdosed, whether accidentally or intentionally, is tricyclic antidepressants [7]. The toxic effects of tricylic's are caused by four main pharmacological properties: Inhibition of norepinephine reuptake at nerve terminals, Direct a adrenergic block. A membrane stabilizing or quinidine-like effect on the myocardium and anticholinergic action (Table 4) [3-8].

Figure 4: Normal ECG was done at third day in intensive care unit.

Figure 5: Normal ECG was done at fourth day in intensive care unit.

After eleven days the patient was transferred to the internal medicine department. Her Glasgow score was 15/15. She was afebrile, with an arterial tension of 12/70, preserved Diuresis, a discrete laryngeal edema and a bilateral mydriasis discreetly reactive.
SO₂ (95-99 %) 99.8 - - - 99.6 90.1
GB 9.5 - - 12.3 8.16 -
GR 4.6 - - 4.3 3.8 -
HB 12 - - 12.2 10 -
PLT 438 - - - 279 -
QT 77% - - - - -

Table 3: Biological exams during the admission.

Day 1 Voluven (hydroxyethyl starch), Bicarbonate 250 cc, Glucose solution 1 bottle (500 ml) *4+1 bulb Kcl+1 bulb Mg, Hypnovel (midazolam) 20 cc, Fentanyl 20 cc, Gardinal (Phénobarbital) 600 mg, Noradrenaline, Adrenaline (at 21 h), Augmentin (Clavulanic acid+ Amoxicillin) 1g*3, Enoxa 0.6 (Enoxaparin), Mopral (Omépazole) 1 bulb.

Day 2 Voluven (hydroxyethyl starch), Bicarbonate 250 cc, Glucose solution 1 bottle(500 ml) *4+1 bulb Kcl+1 bulb Mg, Hypnovel (midazolam) 20 cc, Fentanyl 20 cc, Gardinal (Phénobarbital) 600 mg, Adrenaline, Augmentin (Clavulanic acid+Amoxicillin) 1g*3, Enoxa 0.6 (Enoxaparin), Mopral (Omépazole) 1 bulb, Ciprofloxacine 1bottle*2.

Day 3 Bicarbonate 250 cc, Glucose solution 1 bottle (500 ml)*4+1 bulb Kcl+1 bulb Mg,Gardinal (Phénobarbital) 600 mg, Augmentin(Clavulanic acid+ Amoxicillin)1g*3, Enoxa 0.6 (Enoxaparin), Mopral (Omépazole) 1 bulb, Ciprofloxacine 1bottle*2.

Day 4 Voluven (hydroxyethyl starch), Glucose solution 1 bottle (500 ml)*4+ 1 bulb Kd+2 bulb Nacl, Hypnovel (midazolam) 20 cc, Fentanyl 20 cc, Augmentin (Clavulanic acid+ Amoxicillin)1g*3, Enoxa 0.6 (Enoxaparin), Mopral (Omépazole) 1 bulb, Ciprofloxacine 1bottle*2.

Day 5 Voluven (hydroxyethyl starch), Glucose solution 1 bottle (500 ml)*4+1 bulb Kcl+2 bulb Nacl, Hypnovel (midazolam) 20 cc, Fentanyl 20 cc, Augmentin (Clavulanic acid+ Amoxicillin)1g*3, Enoxa 0.6 (Enoxaparin), Mopral (Omépazole) 1 bulb, Ciprofloxacine 1bottle*2.

Day 6 Fresubin 1 bottle, Glucose solution 1 bottle (500 ml) *2+1 bulb Kd+2 bulb Nacl, Augmentin (Clavulanic acid+ Amoxicillin) 1 g*3, Enoxa 0.6 (Enoxaparin), Mopral (Omépazole) 1 bulb, Ciprofloxacine 1bottle*2.

Day 7 Fresubin 1 bottle, Glucose solution 1bottle(500ml)*2+1 bulb Kcl+2 bulb Nacl, Augmentin (Clavulanic acid+ Amoxicillin) 1 g*3, Enoxa 0.6 (Enoxaparin), Mopral (Omépazole) 1 bulb, Ciprofloxacine 1bottle*2.

Day 8 Glucose solution 1 bottle (500 ml) *2+1 bulb Kcl+2 bulb Nacl Augmentin (Clavulanic acid+ Amoxicillin) 1 g*3, Enoxa 0.6 (Enoxaparin), Mopral (Omépazole) 1 bulb, Ciprofloxacine 1bottle*2, Hydrosuccinate hydrocortisone 100 mg*4.

Day 9 Glucose solution 1 bottle(500ml) *2+1 bulb Kd+2 bulb Nacl, Augmentin (Clavulanic acid+ Amoxicillin) 1 g*3, Enoxa 0.6 (Enoxaparin), Mopral (Omépazole) 1 bulb, Ciprofloxacine 1bottle*2, Hydrosuccinate hydrocortisone 100mg*4.

Day 10 Glucose solution 1 bottle (500 ml) *2+1 bulb Kcl+2 bulb Nacl, Augmentin (Clavulanic acid+Amoxicillin)1 g*3, Enoxa 0.6 (Enoxaparin), Mopral (Omépazole) 1 bulb, Ciprofloxacine 1bottle*2, Hydrocortisone hydrocortisone 100 mg*4.

Day 11 Glucose solution 1 bottle (500 ml) *2+1 bulb Kcl+2 bulb Nacl, Augmentin (Clavulanic acid+ Amoxicillin)1 g*3, Enoxa 0.6 (Enoxaparin), Mopral (Omépazole) 1 bulb, Ciprofloxacine 1bottle*2, Hydrocortisone hydrocortisone 100 mg*4.

Table 4: Therapeutic management and doses state used in Intensive care unit.

In the table 5 we described the variation of many parameters; temperature, blood pressure and heart rate.

| Temperature (°c) | Blood pressure (SAP/DAP) | Heart rate |
|-----------------|--------------------------|------------|
| Day 1           | 37.5                     | 99/54      | 118        |
| Day 2           | 37.5                     | 123/71     | 112        |
| Day 3           | 38                       | 124/82     | 113        |
| Day 4           | 37.7                     | 116/79     | 94         |
| Day 5           | 37.3                     | 122/83     | 95         |
| Day 6           | 37.9                     | 131/84     | 110        |
An overdose of these substances can lead to neurological and cardiac complications, including conductive disorders, various arrhythmias (sinus tachycardia and different ventricular arrhythmias), and myocardial depression by blocking cardiac calcium and potassium channels [7].

According to the American Association of Poison Control Centers (AAPCC) report, rate of antidepressant poisonings was 8.2% [9]. Acute poisonings account for more than 1 million illnesses worldwide annually, 1 as a common medical emergency, acute poisoning may be due to accidental or deliberate ingestion, injection or inhalation of medicinal drugs or other chemicals [9]. There were 9809 admissions, of which 1583 (16.1%) patients, including 601 (38%) males were intoxicated with TCA. The mean age of the subjects was 26.5±10 years [9]. According to the study of Mandour RA, the incidence of cyclic antidepressant poisoning is higher in female than in male. Males to females' ratios are 1:1.19 [2]. Para suicides were most frequent in the young females' 67.37% before 30 years old and 60% for males over 30 years old [2]. Overall, 63% of Para suicides were committed by patients taking TCA, of which Amitriptyline and Dothiepin that are usually prescribed were responsible for the majority of cases [2].

Depression has been consistently reported in 40-60% of suicides [10]. Although intentional TCA overdose carries only a 3% mortality rate [4]. Although data concerning the minimum toxic dose are scarce, some studies have correlated moderate toxicity with doses of 600 mg to 750 mg of Clomipramine, while doses above 750 mg have been correlated with severe complications [10].

Like other tricyclic antidepressants, Clomipramine blocks the reuptake of the Catechol amines Norepinephrine and dopamine as well as serotonin by the presynaptic nerve terminal, thereby increasing the concentrations of the monoamines in the synaptic cleft. During chonic drug administration, clomipramine is metabolized to Norclomipramine, an active metabolite that accumulates in plasma. Over 90% of the drug is eliminated from the body within two weeks of administration, primarily in urine (60%) and faeces (30%) [11].

The toxicity usually occurs at doses exceeding 10 mg/kg. However, serious signs of toxicity can occur even in low doses. For this reason, estimated amount of drug taken based on anamnesis alone may be misleading [12].

For amitriptyline, serum levels of 50-200 ng/ml are considered to be therapeutic, but >1000 ng/ml is a toxic concentration [12]. Amitriptyline mainly acts by inhibiting the uptake of amines by nerve terminals, but also has antimuscarinic and antihistamine properties [13]. Neurological side-effects are common and amitriptyline over dosage causes initial excitement and delirium that may be followed by convulsions and coma like in our case [13].

Hypotension occurs as a result of myocardial depression owing to sodium channel blocking properties as well as α-receptor antagonism. Seizures occur as a result of sodium channel blockade and c-amino butyric acid antagonism [14], as was the situation in our case. An intraventricular conduction delay manifests because of sodium channel blockade and QT prolongation occurs as a result of potassium efflux blockade [14] Amitriptyline was rapidly distributed from plasma into tissues also in the present study; its plasma concentration declined by about 75% within 30 min [15]. In cases of high-dose ingestion, marked CNS depression, seizures, hypotension, and cardio toxicity predominate, whereas anticholinergic effects prevail in low-dose ingestion. Amitriptyline overdose can, therefore, cause serious disturbances in the cardiac conducting system, resulting in severe cardiac arrhythmia [14]. Amitriptyline is a tricyclic antidepressant; it has a high rate level of genotoxicity [16]. It was reported to have a damaging effect on both somatic and germ line cells [17,18]. Indeed amitriptyline induces a dose dependent effect. It causes structural and numerica chromosome abnormalities. It has a negative action on both mitotic index and meiotic activity. It increases significantly the malformations of sperm morphology and we thought that this drug might interfere with genetic, molecular process mainly in microtubules polymerization and some signaling cell paths like Desipramine [19] in addition to the inhibition of the DNA repairation program. However, these hypotheses should be studied experimentally and demonstrated by further molecular investigations.

Our patient ingested a higher dose of drugs (790 mg of Clomipramine and 1075 mg of Amitriptyline). She developed several complications following to this intoxication. It is important to highlight that rhabdomyolysis is a very rare complication of tricyclic antidepressive agents. And its physiopathology has not been clarified yet [4].

NaHCO₃ seems to improve hypotension and normalize QRS duration rapidly in most patients treated, and improve mental status changes in almost one half [20]. Sodium bicarbonate also narrows the QRS complex and decreases dysrhythmias. Previous reports have not provided a minimum or maximum dose for sodium bicarbonate therapy [21], our patient was treated with 250 mL of sodium bicarbonate per day for three days. Some author declared that they used Seventy-five 50-mL ampules of 7.5% sodium bicarbonate over a 10-hour period as boluses and part of a continuous infusion in a case of 53 year old woman with severe TCA toxicity [21].

Candice et al reported in their case of 19 year old woman that the use of intravenous sodium bicarbonate in a dose of 150 mL × 8.4% (150 mmol bicarbonate), causing rapid resolution of the electrocardiographic abnormalities [22].

Tricyclic drugs are widely used in suicide attempts with a substantial difference between different types of antidepressants and present

Table 5: Variation of Temperature, Blood pressure and Herat rate in Intensive care unit.

|   |   |   |
|---|---|---|
| Day 7 | 38 | 125/76 |
| Day 8 | 37.5 | 117/73 |
| Day 9 | 37.3 | 118/75 |
| Day 10 | 37.2 | 121/77 |
| Day 11 | 37.2 | 116/75 |
several toxic effects. Even though dysrhythmia is the most worrisome complication, rhabdomyolysis should be remembered and investigated in cases of clomipramine poisoning. Sodium bicarbonate is the first-line drug in the treatment of TCA intoxication [7].

Disclosure of Interest

The auditors declare that they have no conflicts of interest concerning this article.

Statement of Human Rights

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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