CLINICAL PRACTICE

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Survival following repetitive ventricular fibrillation caused by monoamine oxidase inhibitor overdosing (MAOI).

Ilenuţa L. Danescu[3], Mihail S. Tudosie[2], Genica Caragea[1], Ruxandra Avram[1,3], Constantin Ştefani[2], Gabriela Cioca[4] , Radu A. Macovei[2,3]

Abstract: *One of the great dreams of humanity has been the improvement of its behavioural, affective and emotional status. Depression represents the suffering of beings over their existential course, as a point of passage between the human condition and its destiny. The attempts of psychiatry to introduce efficient and increasingly performing antidepressants represent one of medicine's great achievements. At the same time, antidepressant overdosing may lead to cardiotoxic manifestations presenting lethal risks as consequences [1]. We hereby present the case of a patient that was poisoned with tianeptine, ingested for suicidal purposes, who survived repetitive episodes of ventricular fibrillation, electrically converted to sinusal rhythm. The GC/MS analytical diagnosis played an essential part in detecting tianeptine in the biological samples. The rapid and very competent therapeutic intervention allowed for the patient's survival, despite further complications. A review of main tianeptine information is also presented, as this type of intoxication may have deadly consequences.*

Keywords: *tianeptine, ventricular fibrillation, acute intoxication*

INTRODUCTION

Tianeptine (fig. 1) was discovered and patented by the French Society for Medical Research in the 1960s. It is an atypical antidepressant, used mostly to treat major depressive disorder, but also to treat anxiety, asthma and irritable bowel syndrome. Regarding its chemical structure, tianeptine has the structure of a tricyclic antidepressant (TCA), but has a pharmacological profile that is very different from other TCAs and is grouped separately from those due to its unique mechanism of action [1]. As a modulator of the serotoninergic synapse, it has good efficiency in mild/moderate forms of depression associated or not with anxiety; it does not interfere with the metabolism of other drugs at the level of P45 cytochrome. Tianeptine does not have an affinity for muscarinic, alfa1-adrenergic or type 1 histaminergic receptors, which leads to less adverse events compared to TCAs.

Initial studies have shown that following acute and repeated administrations, the presence of tianeptine led to a decrease in extracellular levels of serotonin in rats' brains without a decrease in the release of serotonine, which is why it was called a "(selective) inhibitor of serotonine reuptake".

As opposed to TCAs and selective serotonine reuptake inhibitors (SSRI), tianeptine improves the synaptic uptake function of serotonine; despite all these, its efficiency against depressive episodes is comparable with that of TCAs and fluoxetine [2, 3]. Recently (2014), it has been demonstrated

[1] Military Medical Research Center, Bucharest, Romania

[2] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

[3] ICU II Toxicology, Clinical Emergency Hospital, Bucharest, Romania

[4] „Lucian Blaga" University of Sibiu, Romania

that tianeptine is an agonist of opioid receptors (MOR). Thus, as opposed to its therapeutic effects, MOR activation is probably the one responsible for tianeptine's toxicity in high doses, those that far surpass the normal therapeutic interval [1]. The therapeutic levels for tianeptine in whole blood, according to available data, are 0.3–0.7 mg/ml.

The absorption takes place almost entirely (99% bioavailability) at GI level, it is completely metabolized by the liver and it is not affected by the first pass effect [4]. Its distribution in the organism takes place quickly, 95% of it binds to plasma proteins (especially albumine) and the mean plasmatic half-life through distribution is approximately 0.7 hours.

Table 1. Adverse events for tianeptine – classified by frequency.

Type of adverse events	Adverse events
Common (frequency >1%)	Headaches (up to 18%) Dizziness (up to 10%) Insomnia/nightmares (up to 20%) Sleepiness (up to 10%) Dry mouth (up to 20%) Constipation (up to 15%) Nausea Abdominal pain Weight gain (~ 3%) Agitation Anxiety/irritability
Less frequent (frequency 0.1-1%)	Bitter taste Flatulence Epigastralgia Blurred vision Muscular pain Premature ventricular contractions Micturition disorders Palpitations Orthostatic hypotension Tremor
Rare (frequency <0.1%)	Hepatitis Euphoria ECG modifications Pruritus-like cutaneous reactions/alergy Muscular pain

Metabolizing in the liver takes place especially through beta-oxidation and, in a lower proportion, through N-demethylation, the main metabolites being propanoic acid (inactive metabolite) and pentanoic acid (active metabolite) [5]. Tianeptine is eliminated both renally and through extrarenal ways, mostly through urine (only 8 % is eliminated in unmetabolized form), fecces (15%), bile and has a half-life of 2-3 hours. [5].

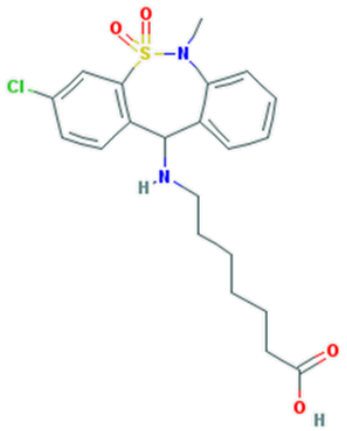
Compared to other TCAs, tianeptine can lead to significantly less cardiovascular, anticholinergic (such as constipation or dry mouth), sedative and appetite stimulating effects [6, 7]. Recent studies have shown that it is amongst the most hepatotoxic (hepatic lesions) antidepressants, although proof supporting this concern is limited [8]. Also, it has been shown that TCAs can lead to cardiac arrhythmia, even though the data for tianeptine is limited [9].

Based on adverse event frequency, they are classified according to table no. 1 [5, 6, 10].

The certitude diagnosis is established by identifying tianeptine in biological fluids.

Figure 1. Tianeptine 2D Structure form

https://pubchem.ncbi.nlm.nih.gov/compound/Tianeptine#section=Top



For this purpose, the GC/MS method (gas-chromatography coupled with mass spectrometry) is used. The GC/MS method, applied in the Analytical Toxicology Laboratory of the Military-Medicine Research Center, is performed by a GC/MS Varian SATURN 2000 computerized system: Varian gas-chromatograph STAR 3800 CX model and Varian mass spectrometer with an ion trap detector. The urine samples are analyzed using liquid-liquid extraction with organic solvents. For the extraction control, midazolam was used as an internal standard, which is

a benzodiazepine whose retention time is situated in a different range from that of tianeptine. Mass spectra libraries were used, namely Pfleger–Maurer–Weber, NIST 98 and Wiley 6.

Figure 2: Total ion chromatogram and the mass spectra obtrained for lidocaine (peak no. 1), for tianeptine (peak no. 2) and for midazolam (peak no. 3).

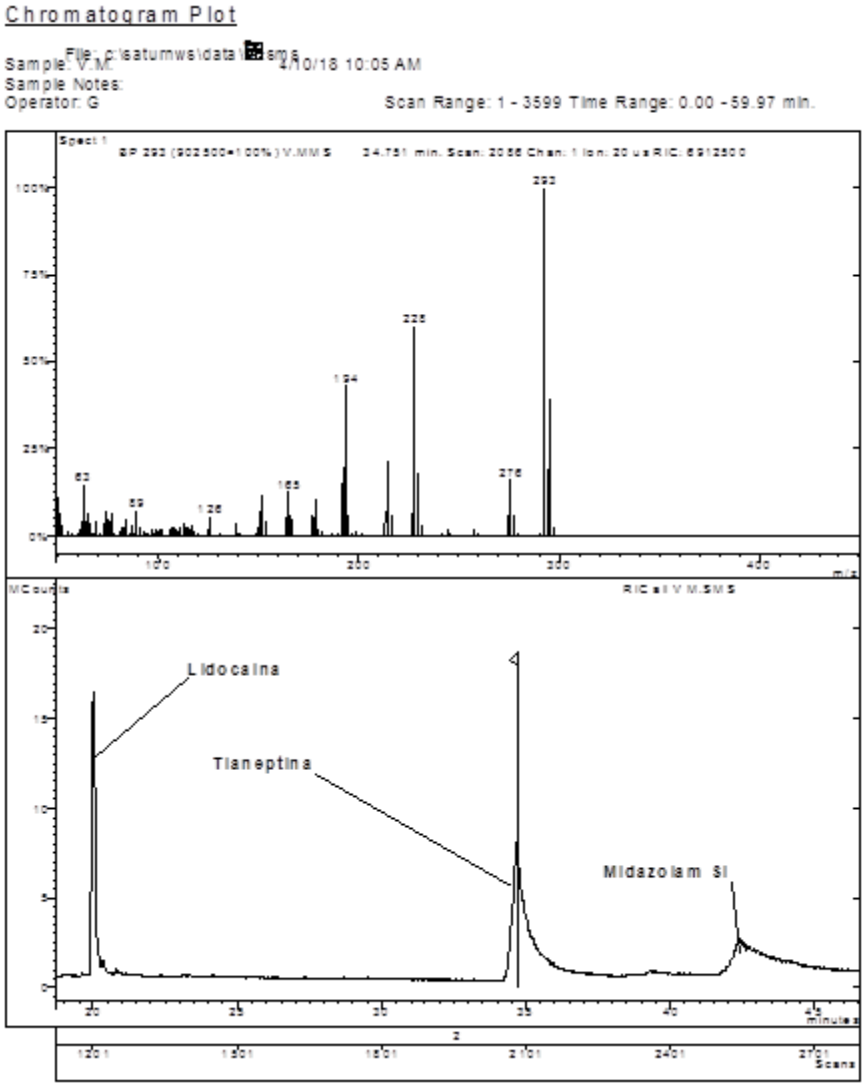


Table 2. The type of compound that was identified, its chemical formula and characteristic spectral lines

Identified compound	Chemical formula	Molecular mass	Spectral lines (m/z)
Lidocaine	$C_{14}H_{22}N_2O$	234	86, 234
Tianeptine	$C_{21}H_{25}ClN_2O_4S$	437	194, 214, 228, 276, 293
Midazolam (SI)	$C_{18}H_{13}ClFN_3$	327	310, 327

Following the analysis of the urine extract through the GC/MS method, the separation and identification of the following compounds were achieved: Lidocaine, Tianeptine and Midazolam (internal standard), presented in figure 2 and table 2.

CASE REPORT

Patient, aged 56 years old, with no pathologic history was brough by the medical ambulance to the Bagdasar hospital after being found at home following drug intake for suicidal purposes (declarated Nobixal –

Tianeptine) with agonistic respiration.

At home, the patient suffered two episodes of ventricular fibrillation, remitted after external electrical shocks (EES) applied by the ambulance medical staff. In the emergency care unit, the patient suffered another episode of ventricular fibrillation which responded to EES, with hemodynamic instability still persisting. Due to acute respiratory insufficiency, orotracheal intubation was necessarily performed.

Cardiological evaluation: arterial pressure 90/60 mmHg, AV 100 bpm, no murmurs, no rales, no edemas; ECG: regular sinusal rhythm, Q wave in DII, DIII, aVF.

The ECG shows a moderate/severe dystolic dysfunction of the left ventricle, most probably in the context of intoxication, followed by an EES, applied for rhythm disorders. The patient is sent to Emergency Clinical Hospital Bucharest, Intensive Care Unit II Toxicology.

Upon admission into Toxicology, the patient is in a serious condition sedated, orotracheal intubation with spontaneus respiration, presence of bilateral pulmonary vesicular murmur, hemodynamic instability on vasopressor support, arterial pressure = 100/58 mmHg, AV = 96/bpm, regular rhythm, normal abdominal movement, normal diuresis.

Biological parameters upon admission: increased values of glycemia, creatinine, liver enzymes (ALT and AST), LDH but also leukocytosis; coagulation tests being in normal ranges.

Table 3. Biological parameters

Sample	Result	
	Measured values	Normal values
Glycemia (*mg/dl*)	138	75-110
Urea (*mg/dl*)	25	19-43
Creatinine (*mg/dl*)	1.46	0.7-1.4
AST (*U/l*)	81	21-72
ALT (*U/l*)	107	14-50
LDH (*U/l*)	481	150-450
Sodium (*mmoles/l*)	144	137-145
Potassium (*mmoles/l*)	4.51	3.50-5.00
Leucocytes (*x 10^3/mm^3*)	16,8	4-9
Hemoglobine (*g/dl*)	13.10	12.6-17.2
Trombocytes (*x 10^3/mm^3*)	228	150-350
APTT (*sec*)	25.30	24-36.5
PT (*sec*)	13.1	11-14.5
INR	1.08	0.81-1.16

The toxicological urine analysis through the GC/MS method shows the presence of Tianeptine and Lidocaine.

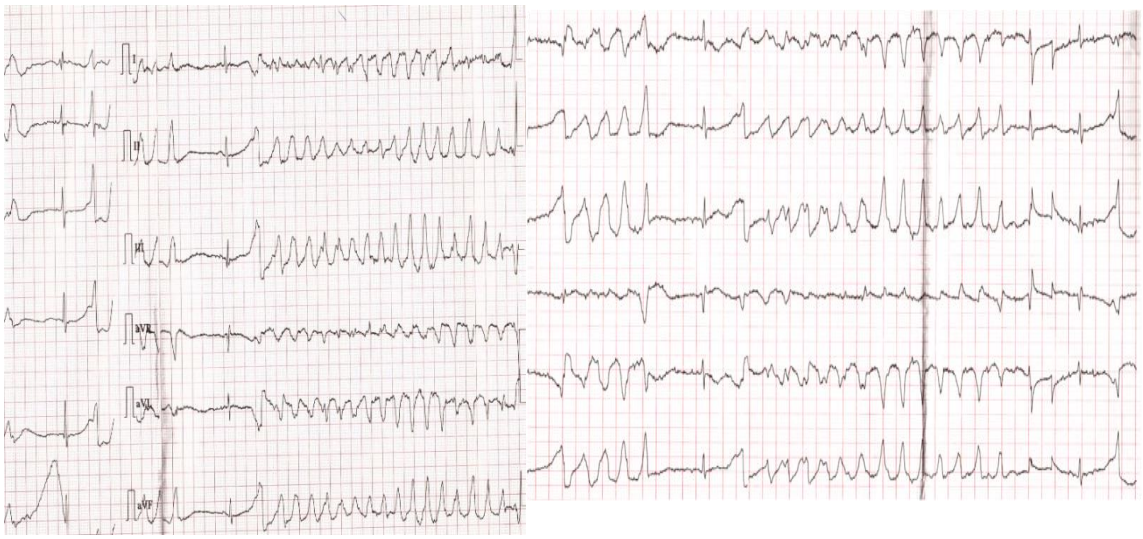
Gastric lavage was applied and activated charcoal was administered through the naso-gastric tube; it were applied volemic, electrolitical and acido-basic repletion and complex clinical – biological monitoring. After 24 hours from admission in ICU II Toxicology, the ECG monitoring registers a new ventriculary fibrillation episode, followed by cardiac arrest. The resuscitation protocol was applied, the maneuvers were efficient. Intensive care measures being were continued, ventilatory support, vasopressor support – with dopamine in the continuous infusion, antiarrhythmic drug – Amiodarone continuous infusion, Lidocaine 1% in infusion. After 96 hours from admission, the patient is hemodynamically stable and the vasopressor support is suppressed; also the patient is weaned from ventilator support. The therapy continued with hepatotrofic and neurotropic drugs, with gastric protectors and general nursing. The evolution was favorable.

Psychiatric evaluation reveals a persistent suicidal idea, depressive facies and a marked depressive disposition, the patient was reffered to a psychiatric unit.

At cardiological reevaluation, 9 days after admission: the patient is hemodinamically stable, arterial pressure 108/77 mmHg, cardiac frequency 77 bpm. Regular rhythm, no murmurs, presence of bilateral pulmonary vesicular murmur, no stasis rales; ECG: sinusal rhythm, cardiac frequency 70 bpm, no ST segment modifications. Cardiac echography: left ventricle not dilated, VSTD 48 mm, not hypertrophied, SIV=PP= 10 mm, no segment kinetics disorders, with conserved ejection fraction 55%, no valve disorders, no pulmonary hypertension; pericardial liquid of 3 mm in diastole, laterally from right ventricle, no hemodynamic impact; diastolic dysfunction – delayed relaxation type.

The patient leaves the hospital toxicologically healed, conscious, cooperative, hemodynamically and respiratoriy balanced; stable from a cardiological point of view under antiarrhytmic treatment with Amiodarone.

Figures 3, 4: Cardiac rhythm abnormalities (episodes of polymorph ventricular tachycardia in the context of long QT syndrome) in the absence of diselectrolithemia, acidosis or hypoxemia after tianeptine overdose.



CONCLUSIONS

Although compared to TCAs, which have been proven scientifically to cause cardiac arrhythmia, the data for tianeptine is limited, the above case reiterates the possibility, even low, but with a deadly risk associated, of malignant arrhythmias being caused by it.

Although proof supporting the hepatotoxic potential of MAOI is limited, overdosing on the aforementioned generated phenomena of hepatic cytolysis, which is indicated by increased enzyme levels.

A correct management of acute poisoning with unclear substances, whether accidentaly or voluntary, involves a precise assessment and promptly initiated therapy.

GC/MS analytical method is the confirmatory method for urinary toxicological screening for a diagnosis of certainty in the case of acute drugs poisoning and is important in order to establish an effective therapeutic course.

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