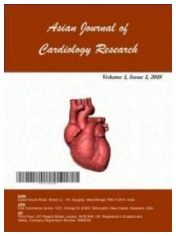

Asian Journal of Cardiology Research

2(1): 40-45, 2019; Article no.AJCR.49192

Hematological and Biochemical Changes Caused by Antidepressants Amitriptyline Induced Cardiac Toxicity in Male Rats

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Authors' contributions

This work was carried out in collaboration among all authors. Authors AEA and ET designed the study and wrote the protocol. Authors AG and SA performed the statistical analysis and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Sam Said, Department of Cardiology, Hospital Group Twente, Hengelo, The Netherlands.
Reviewers:
(1) Dr. John Ogedengbe, University of Abuja, Nigeria.
(2) Dr. Azab Elsayed Azab, Sabratha University, Libya.
Complete Peer review History: http://www.sdiarticle3.com/review-history/49192

Original Research Article

Received 09 March 2019
Accepted 18 May 2019
Published 23 May 2019

ABSTRACT

Objects: Amitriptyline is a widely used tricyclic antidepressant. Amitriptyline is well-known for its cardiovascular side effects and toxicity in psychiatric patients. However, the mechanisms underlying the cardiovascular side effects of amitriptyline remain largely undefined.
Aims: This study aims to show the hematological and biochemical changes in Amitriptyline induced cardiac toxicity in male rats.
Methodology: A total of 20 male albino rats were randomly and equally divided into 2 groups (10 rats each). G1: control group that included animals that did not receive any treatment during the experimental period. G2: Amitriptyline (Tryptizol; El Kahira Pharm And Chem Ind Co) group in which rats were injected intraperitoneally with Amitriptyline (70 mg/kg body weight/daily) for four weeks.
Results: Our results revealed that; a significant increase in sodium ions, alkaline phosphatase, AST, lipid profiles (cholesterol, triglycerides, LDL and HDL), and cardiac enzymes (CK-Mb, CPK, LDH and myoglobin) and insignificant decrease in platelets, white, and red blood cells, potassium ions, and total proteins in treated rats with amitriptyline as compared to control.

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Conclusion: Amitriptyline toxicity is life-threatening and can cause acute myocarditis in addition to the known cardiotoxic profile of tricyclic anti-depressant medications. Physicians should be aware of this rare entity as a differential diagnosis for myocarditis with an unknown etiology.

Keywords: Amitriptyline; antidepressant; cardiac enzymes; lipid profiles; electrolytes; rats.

1. INTRODUCTION

Cardiac dysfunction is the manifestation of multifactorial diseases, such as chronic heart failure, renal failure, metabolic disorders and cancer [1,2,3,4,5]. No other disease affecting humans is more severe and is associated with a greater mortality rate than psychiatric patients [6]. Many antidepressants have unwanted cardiovascular effects, so choosing between them may not be straightforward in patients with heart disease. Amitriptyline is one of the classical and typical tricyclic antidepressants which work on the central nervous system to increase the level of certain chemicals in brain [7]; Amitriptyline is also currently used for the treatment of patients with migraine [8].

Amitriptyline can cause dizziness and drowsiness during the first few hours after it is taken [9]. Amitriptyline acts as a serotonin-norepinephrine reuptake inhibitor, thereby increasing the concentration of these transmitters in the synapse [10]. Given the wide use of amitriptyline as antidepressant medication, it is important to discuss this case of its overdose presenting as myocarditis with pericardial involvement and provide a brief review of amitriptyline-induced cardio toxicity [11]. Therefore, the aim of this study is to show the changes in some hematological and biochemical parameters after the treatments of male rats with antidepressant amitriptyline.

2. MATERIALS AND METHODS

2.1 Experimental Animals

The experiment was performed on 20 male albino rats (*Rattus norvigicus*) weighing 150 g (±10) and of 9-10 weeks' age. They were obtained from the animal house of the National Research Center (Dokki, Giza, Egypt). The rats were housed in suitable plastic cages for one week before the experimental work for acclimation with anew room conditions and maintained on a standard rodent diet, with water available ad libitum. During the experiment, animals behavior were noticed and body weight at the beginning and the end of the experiment were measured. Animal maintenance and treatments were conducted in accordance with the Faculty of Science, Tanta University guide for the animal, as approved by the Institutional Animal Care and Use Committee (IACUC-SCI-TU-0050).

2.2 Experimental Groups

The rats were randomly and equally divided into 2 groups (10 rats each). G1: A control group that included animals that did not receive any treatment during the experimental period. G2: Amitriptyline (Tryptizol; El Kahira Pharm And Chem Ind Co) group in which rats were injected intraperitoneally with Amitriptyline (70 mg/kg body weight/daily) for four weeks [12].

2.3 Blood and Serum Samples

Heparinized blood was collected from the inferior vena cava for complete blood picture (CBC) according to Basuony [13]. Serum was collected from the inferior vena cava and separated by centrifugation at 3000 rpm for 15 minutes. The collected serum was stored at -18°C until analysis for estimation of some blood parameters (CK-MB, CPK, LDH, Myoglobin, Cholesterol, LDL, HDL, Tg, total protein, Na and K). In keeping with the approach proposed by Whitaker [14], kits from Vitro Scient (Cairo, Egypt) were used to undertake the kinetic technique for measurement of the activity of serum lactate dehydrogenase (LDH). Meanwhile, the approach recommended by Zilva and Pannall [15] was adopted to perform an akinetic technique with kits from the same company (Vitro Scient) to measure serum levels of creatine kinase (CK). The approach suggested by Bishop et al. [16] was applied with the assay kit provided by Bioassay Systems (Hayward, CA, USA) to measure the serum levels of creatine-myoglobin (CK-MB). Last but not least, the approach proposed by Cummins et al. [17] was used with the assay kit provided by ReactivosSpinreact (Girona, Spain) to measure the serum levels of myoglobin.

The activities of serum AST were assayed by the colorimetric method according to Reitman and Frankel [18]. Serum ALP activity was measured according to Belfield and Goldberg [19] by using

a commercial kit. Serum levels of total protein were determined by using a commercial kit according to Bowers and Wong [20]. Serum potassium, and sodium ions levels were determined by using commercial kits (Sensa core electrolyte, India) according to Abd Eldaim et al. [21]. The concentration of cholesterol, triglyceride, high-density lipoprotein-cholesterol (HDL-C) and low density lipoprotein-cholesterol (LDL-C) were determined with Kits from ELLTECH according to Aldubayan et al. [22] and Salama et al. [23].

2.4 Statistical Analysis

Data were expressed as mean values ± SE and statistical analysis was performed using an unpaired t-test to assess significant differences among treatment groups. The criterion for statistical significance was set at $p<0.05$ for the biochemical data. All statistical analyses were performed using SPSS statistical version 21 software package (SPSS® Inc., USA).

3. RESULTS

3.1 Toxicity

Many of side effects appeared on rats after Amitriptyline administration such as weakness, loss of activity, increased perspiration, and increased or decreased appetite.

3.2 Biochemical Investigations

Table 1 revealed that; CK-MB, CPK, LDH, and myoglobin levels in serum increased ($P<0.05$) in the amitriptyline group compared with the control group. As well, serum AST and ALP levels were significantly increased ($P<0.05$) in the amitriptyline group compared with the control group (Table 1). Also, groups intoxicated by amitriptyline showed a significant increase in levels of serum cholesterol at ($p<0.0001$), serum LDL at ($P<0.0001$), serum HDL at ($p<0.0001$), and serum triglycerides at ($p<0.0001$) compared with the control group (Table 2). At the same time, serum total protein levels decreased ($P<0.05$) in the amitriptyline group compared with the control group (Table 3). Table 3 showed that; R.B.C.s, W.R.Cs, and platelets (PLT) indices levels in Amitriptyline group were poorly affected and showed low significant decrease when compared with the control group.

4. DISCUSSION

Amitriptyline overdose may cause a significant central nervous system effects, the presumed mechanism of action in overdose deaths is cardiac in nature, involving tachycardia, widening of the QRS complex, and various arrhythmias [24]. Consequently, care must be taken when interpreting postmortem amitriptyline levels. Deaths related to the toxic effects of amitriptyline are typically suicidal in nature [25].

Table 1. Changes in serum cardiac enzymes [CK-MB, CPK, LDH, Myoglobin, Aspartate transaminase (AST), and alkaline phosphatase (ALP)] levels in experimental groups

Particulars	Control group	Amitriptyline group
CK-MB(ng/ml)	0.1382±0.001****	0.2958±0.004
CPK(U/l)	3517±75.08****	5174±186.7
LDH10-5(U/l)	172.8 ± 13.75****	565.8 ± 24.87
Myoglobin (ng/ml)	13.88 ± 0.259****	17.78 ± 0.128
AST (U/L)	154.6 ± 4.366****	281.4 ± 5.105

** The significant difference was analyzed by T-test unpaired. Values are expressed as mean± SEM. T-test was significant at p<0.05. T-test unpaired was significant from corresponding amitriptyline at NSP=0.1234; *P=0.0332; **P=0.0021; ***P=0.0002; ****P<0.0001.G1, control group; G2, Amitriptyline group*

Table 2. Changes in serum lipid profiles (cholesterol, Tg, HDL, LDL and VLDL) levels in experimental groups

Particulars	Control group	Amitriptyline group
Cholesterol (mg/dl)	93.2±1.772****	178±5.376
Tg (mg/dl)	110.4 ± 1.631****	191.2 ± 4.913
HDL (mg/dl)	14.2 ± 0.3742****	19.6 ± 0.6
LDL (mg/dl)	54.92 ± 1.883****	127 ± 4.122
VLDL (mg/dl)	22.08 ± 0.3262****	38.24 ± 0.9826

** The significant difference was analyzed by T-test unpaired. Values are expressed as mean± SEM. T-test was significant at p<0.05. T-test unpaired was significant from corresponding amitriptyline at NSP=0.1234; *P=0.0332; **P=0.0021; ***P=0.0002; ****P<0.0001. G1, control group; G2, Amitriptyline group*

Table 3. Changes in serum total protein, sodium ions (Na+), potassium ions (K+), RBCs, WBCs and PLTs levels in experimental groups

Particulars	Control group	Amitriptyline group
Total protein(g/dl)	7.01 ± 0.074****	5.326 ± 0.058
Na (mEq/l)	136 ± 0.257****	152.3 ± 2.29
K (mEq/l)	5.054 ± 0.0206****	4.132 ± 0.0356
R.B.Cs (mill./cmm)	7.14 ± 0.27*	6.09 ± 0.31
W.B.Cs (103Ul)	6.35 ± 0.50*	3.68 ± 0.36

** The significant difference was analyzed by T-test unpaired. Values are expressed as mean± SEM. T-test was significant at p<0.05. T-test unpaired was significant from corresponding amitriptyline at NSP=0.1234; *P=0.0332; **P=0.0021; ***P=0.0002; ****P<0.0001. G1, control group; G2, Amitriptyline group*

In this study, these results were in accordance with Boles et al. [26] who showed that the amitriptyline doses have different effects on enzymatic levels. The higher dose (25 mg/kg) increased the creatine phosphokinase, creatine kinase-MB, total protein, lactate dehydrogenase, and myoglobin levels. Experimentally, Acosta and Ramos [27] have shown that amitriptyline induced severe abnormalities of the sarcolemma integrity using LDH release of cultured myocardial cells as a criterion for cell damage. Also, in the current study, there was significantly increase in cholesterol, triglycerides, and LDL and an increase in HDL levels in the amitriptyline group (G2).

Gurer et al. [28], who explained that amitriptyline, affect the heart muscle due to changes in the level of cholesterol and triglycerides. Also, Kaur et al. [29] showed that amitriptyline may be responsible for cardiac dysfunction. Concentrations of cholesterol and triglycerides in the serum they were significantly elevated in rabbits managed antidepressants involved. This study shows that enzymes AST and ALP were significantly elevated by amitriptyline intoxication in the amitriptyline group (G2). Findings of this study showed a significant elevation in serum alkaline phosphatase in rat groups intoxicated by the amitriptyline (G2).

In this study showed the elevation levels of serum aspartate aminotransferase (AST) under the effect of amitriptyline as marker of cytotoxicity in groups under study which supported by the result estimated by Afify et al. [30]. The results of this study showed the effect of amitriptyline poisoning on the blood, different parameters of blood parameters. Red blood cell indices showed a significant reduction in the amitriptyline group (G2). In addition, the results showed that amitriptyline could cause thrombocytopenia and a decrease in white blood cell count in the amitriptyline group (G2), unlike the control group (G1). The results were consistent with Tousson et al. [31]. The higher dose of amitriptyline increased concentrations of Na, k levels in serum this is consistent with previous studies Thorstrand et al. [32].

5. CONCLUSION

Amitriptyline toxicity is life-threatening and can cause acute myocarditis in addition to the known cardiotoxic profile of tricyclic anti-depressant medications. Physicians should be aware of this rare entity as a differential diagnosis for myocarditis with an unknown etiology.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle3.com/review-history/49192