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Abnormal Electrocardiographic Effects of Tricyclic Antidepressants

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Abstract

The paper aims to review ECG and effects of Tricyclic Antidepressants (TCA) on ECG. ECG is the recording of the electrical conductivity of heart made by placing electrodes on the body. Antidepressants have lethal neurological and cardiovascular effects in depressive persons. TCA can cause abnormalities in the ECG pattern. It affects the conduction rate and slows the heart beat by blocking sodium channels that cause the elongation of QST complex which leads to abnormalities. QT is prolonged if > 440ms in men and > 460ms in women. Due to TCA, QT > 500ms that causes abnormalities. Brugada syndrome is also obtained by exposure to TCA. Doxepin slows down the conduction rate in patients with major depressive disorders. TCA causes symptomatic A-V blockage in patients with preexisting cardiovascular diseases. Desipramine and Immipramine cause sudden death in 6-9 years old children due to an overdose of these drugs. Antidepressants such as Agomelatine, Paroxetine, Serotonin Reuptake Inhibitors cause cardiac deformities in patients as well as pregnant women. Abnormality in ECG tells us about problems in the rhythmicity of heart. ECG can be used for the assessment of drugs that have electrophysiological effects.

Keywords: antidepressants, ECG, QST elongation, TCA

1. Introduction

1.1. Electrocardiogram (ECG)

The written record of a heart beat is known as electrocardiogram and electrocardiograph is the tool used to record it [1]. Electrocardiography (ECG or EKG) is the method of recording the electrical deed of the heart over a period of time by means of electrodes positioned on the skin. During each heartbeat, minute fluctuation in the electrophysiological pattern of depolarizing and repolarizing that ascend from the heart muscles are detected by these electrodes [2]. Figure 1 represents the waves of ECG.

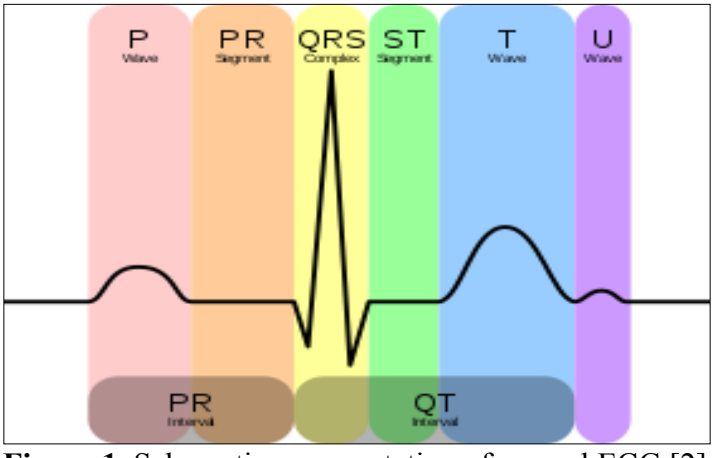

Figure 1. Schematic representation of normal ECG [2]

1.2. Etymology

It originates from the Greek word *Das Elektrokardiogramm*. The abbreviation is EKG or ECG [1].

2. History

- The concept of ECG was presented by an Italian Galvani in 1791.
- Two Germans, Kolliker and Muller, rhythmically created an electric current by nerve muscle preparation.
- Cardiogram, the first ECG for human beings, was produced by an Englishman Waller in 1887.
- Einthoven in 1901 invented his own device using a string galvanometer [1].

3. Antidepressants

Antidepressants are medications used for the cure of the main depressive syndrome and additional conditions such as dysthymia, nervousness disorders, fanatical–neurotic disorder, ingestion disorders, lingering agony, neuropathic discomfort and in various other conditions including dysmenorrhoea, snuffling, migraine and nap maladies. They may be given unaccompanied or in grouping with other prescriptions [3].

3.1. Tricyclic Antidepressants

TCAs are a group of prescriptions that are used chiefly as antidepressants. TCAs were discovered in the early 1950s. Due to 3 rings of atoms in their chemical configuration, they are named TCAs [4]. Figure 2 represents the chemical structure of TCA.

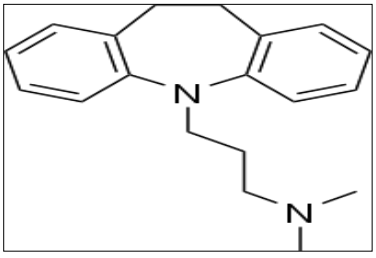

Figure 2. Chemical structure of TCA [4]

3.2. Mechanism of Action of TCAs

TCAs are collection of medicines used to cure sentimental or mood syndromes. Although an essential group of drugs, they are not supreme due to some side effects. Side effects of TCAs include

- histamine h1 receptor blockade which causes sedation
- α adenoreceptor blockade which causes postural hypotension
- Muscarinic acetylcholine receptor blockade which causes blurry visualization, dehydration and constipation [5]. Figure 3 represents the mechanism of action of TCA.

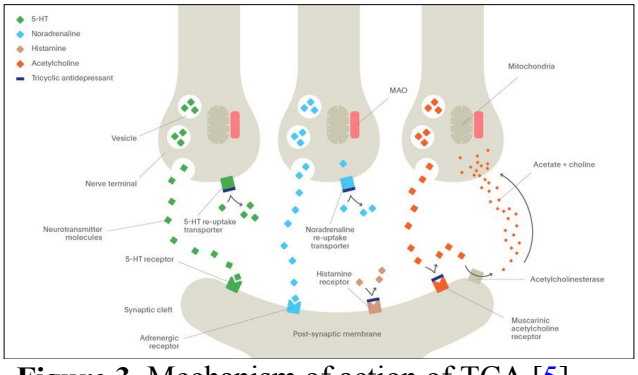

Figure 3. Mechanism of action of TCA [5]

4. ECG Abnormalities Due to Ingestion of TCA

TCA mediators are recognized for their possibly fatal cardiac and neurological effects in festering patients. For the estimation of TCAs' toxicity, the vitally admired apparatus known as 12-lead ECG is used. Due to ingesting TCAs, changes take place in the regularity of the heart beat and QT interval is extended. This shows that they are blocking sodium channels. QRC complex is greater than 0.10 sec. QT is extended if > 440ms in men or > 460ms in women. QT > 500 is connected with a greater danger of *torsades de pointes*. QT is unusually small if < 350ms. A helpful rule of thumb is that a typical QT is less than half the previous RR interval [6].

5. Brugada Electrocardiograph Pattern Due to Overdose of TCAs

The Brugada syndrome is an arrhythmogenic condition with aspect coved ST-segment rise of 2 mm or more in the right precordial leads (type 1 Brugada electrocardiogram pattern or "Brugada sign") and is likely to be accountable for at least 20% of unpredicted demises in patients with physically normal hearts. The Brugada sign has been designated in asymptomatic patients after interaction with a diversity of medications. 134 patients were admitted in ICU and separated into 3 groups including patients without abnormal ECG, patients with ECG anomalies but devoid of Brugada pattern, and patients with Brugada patterns. All patients were admitted from 1/1/2000 to 1/11/2004 to the ICU, later an action of deliberate self-poisoning was involved. Their ECGs were examined by a cardiologist. Out of 134 patients, 34% were without abnormalities, 37% were with extended QST complex (>100ms) and 17% were with extended ST interval (Brugada pattern). So, by taking an overdose of TCA, this syndrome takes place and eventually causes persistence in ST segment in ECG [7]. Figure 4 represents the Brugada pattern due to an overdose of TCA.

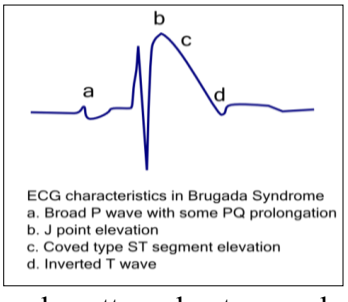

Figure 4. Brugada pattern due to overdose of TCA [7]

6. Abnormal ECG Patterns Due to Fluoxetine and Doxepin in Patients With Main Depressive Disorders

Forty patients with main depressive maladies were registered in a 6 week study and treated with fluoxetine (n=20) and doxepin (n=20). After every 2, 4 and 6 weeks, QST interval was observed. Patients taking doxepin (mean daily dosage at 6 weeks 169 +/-42 mg) were akin to those taking fluoxetine (37 +/- 18 mg) in their demographic variables and progress in sadness scores but offered further side effects including desiccated mouth ($p < 0.001$) and wooziness/faintness ($p = 0.005$). After 6 weeks, doxepin started escalating the heart rate, however, no such effect was caused by fluoxetine. So, it was concluded that doxepin caused persistence in QST complex after few weeks and slowed down the conduction rate [8].

7. Abnormal ECG Patterns Due to Antidepressants in Patients With Cardiovascular Disease

Depressed persons with cardiovascular malady, chiefly bundle branch block, when cured with TCAs were at an elevated level of increasing indicative A-V block causing abnormalities in QST curve, than patients without cardiovascular disease. The persons without former cardiac illness indicate benign effects of ECG on treatment with drug [9].

8. Effect of TCAs, that is, Desipramine and Immipramine in Children

In the first issue of "The Medical Letter on Drugs and Therapeutics" (1990), it was reported that throughout regular dealing with **Desipramine**, unexpected deaths occurred in 8-9 years old children. The first case of death of an 8 year old child was caused due to unacquainted prescriptions of medicine for 2 years for Attention Deficit Hyperactivity Disorder (ADHD). In another incident, an 8 year old boy was also treated for 6 years with this drug for the same disorder. The third case was of a 9 year old boy who was treated with this drug for an indefinite time. A 6 year old girl for school obsession was cured with **Immipramine** (15mg/kg/d), without ECG monitoring. Death was due to the overdose of the drug and improper monitoring of ECG, as the prescribed drug dose for children is 5mm/kg/d. All of these cases exhibit asymptomatic, generally minute, but statistically noteworthy elevations in diastolic blood pressure, heart rate, and ECG proof of continuation of cardiac conduction parameters [10].

9. Relationship Between Antidepressants And Cardiovascular Pathology

Depression and cardiovascular disease are closely related clinical units. Depression seems equally to ground and exacerbate cardiovascular illness. Cardiovascular syndrome is in turn linked with a high incident of depression. Depression is linked with an increased transience in cardiovascular disease and later on Myocardial Infarction (MI) and stroke. Numerous antidepressants have cardiotoxic characteristics. Tricyclic medications are extremely cardiotoxic in overdose and can tempt cardiovascular infection and aggravate consequences in established cardiovascular infection. Reboxetine, duloxetine and venlafaxine have been identified to increase blood pressure. Most antidepressants have an unbiased or supportive effects in numerous cardiovascular maladies [11].

10. Heart Rate Variability in Major Depressive Disorder and after Antidepressant Treatment with Agomelatine and Paroxetine

Earlier studies recommend that Heart Rate Variability (HRV) is decreasing in Major Depressive Disorder (MDD). Though, whether this lessening is attributable to the disorder per se or to prescription, as antidepressants could also disturb HRV, is still being argued. There is an absence of evidence regarding the effects of agomelatine, a new antidepressant, on HRV. We examined whether HRV is abridged in MDD and equates the effects of agomelatine and paroxetine on HRV. For this purpose, we conscripted 618 substantially fit and unmedicated patients with MDD and 506 strongly agreed who were aged between 20–65 years. Frequency-domain dealings of resting HRV were acquired at the time of enrollment for all members. For patients with MDD, these trials were set again after 6 weeks of either agomelatine or paroxetine monotherapy. Compared with fit subjects, unmedicated patients with MDD revealed considerably lesser alteration (total HRV), low frequency (LF), and high frequency (HF) HRV, and also a higher LF/HF ratio. The severity of depression freely contributed to reduced HRV and vagal tone. Fifty-six patients finished the open-label experiment ($n = 29$ for agomelatine, $n = 27$ for paroxetine). Between-group studies exposed an important group-by-time collaboration for LF-HRV and HF-HRV, compelled by escalations in LF-HRV and HF-HRV merely after agomelatine usage. Within the paroxetine-treated group, there were no substantial variations in mean R-R intervals or any HRV indices. We then resolved that MDD is linked with abridged HRV, which is inversely correlated to depression rigorousness. Compared with paroxetine, agomelatine has an extra vagotonic effect, signifying better cardiovascular care. Clinicians should study HRV effects while choosing antidepressants particularly for depressed patients who previously have reduced cardiac vagal tone [12].

11. Antidepressants and Risk of Mortality in Heart Failure (HF) Patients

Depression is a menacing element causing death in patients with Heart Failure (HF), though, healing depression with antidepressant treatment does not appear to increase persistence. 121,252 HF patients ongoing first hospitalization were stratified based on antidepressant usage and an analysis of clinical depression. Overall, 15.6% (19,348) received antidepressants at starting position, of which 86.7% (16,780) had no finding of clinical depression. Female gender, older age, greater socio-economic rank, other comorbidities, bigger usage of statins,

spironolactone and aspirin, lesser usage of beta-blockers and ACE-inhibitors, larger HF rigorousness and an analysis of clinical depression were unconventionally linked with antidepressant usage. Patients using no antidepressants with clinical depression and patients using antidepressants with or without clinical depression faced a considerably greater danger for all-cause transience (HR, 1.25; 95% CI, 1.15–1.36; HR, 1.24; 95% CI, 1.22–1.27; HR, 1.21; 95% CI, 1.16–1.27, respectively) and CV-mortality (HR: 1.17; 95% CI, 1.14–1.20, P < .001; HR: 1.20; 95% CI, 1.08–1.34, P < .001; HR: 1.21; 95% CI, 1.12–1.29, P < .001, correspondingly) as compared to patients not consuming antidepressants and lacking depression in accustomed study [13].

12. Serotonin Reuptake Inhibitors (SSRIS) and Cardiovascular Function

One of the key prescription sets usually used to cure depression that affects cardiovascular function is Selective Serotonin Reuptake Inhibitors (SSRIs) which were principally presented in 1980 [14]. These medicines are normally recommended in diverse disease situations for the reason of their great ability, cost-benefit, ease of usage and preferred side effects, particularly on the cardiovascular system. Also, SSRI-related deadly happenings and life-threatening problems have been presented to be the lowest when compared to other sorts of antidepressants [15]. Cardiac demise connected to administrating SSRIs has infrequently been told. In this regard, the supremely common cardiovascular-related side effects of SSRIs comprise trivial bradycardia and hypotension, slight QRS elongation, and first-degree cardiac block. Infrequently, vasoconstriction succeeding the administration of high-dose SSRIs, may affect the patient by causing MI [16].

13. Refractory Arrhythmias due to Imipramine Poisoning in Young Patients

TCAs are used to cure a diversity of mental syndromes and are considered a usual reason of lethal drug poisoning. This study reports a young woman with no antiquity of cardiac infections who was taken to the emergency section with heart palpitation, feebleness, and weariness. Later, she turned out to be comatose and experienced hypotension and refractory arrhythmia. Lastly, she was being analyzed with imipramine poisoning [22].

14. Second Generation Antidepressants and Cardiovascular Events

Diverse indication recommend that second generation antidepressants may increase the threat of cardiovascular and cerebrovascular

happenings. Secondary studies of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) longitudinal cohort study were directed. The usage of selective Serotonin Reuptake Inhibitors, Serotonin and Norepinephrine Reuptake Inhibitors, bupropion, nefazodone, and trazodone was measured throughout the reference line (2003-2007) in-home visit. The consequences of CHD, stroke, CVD demise, and all-cause transience were evaluated every 6 months and judged by therapeutic record analysis. Among 29616 participants, 3458 (11.7%) used an antidepressant of concern. Transitional models modifying everything but bodily and intellectual fitness found an enlarged threat of severe CHD (hazard ratio [HR] = 1.21; 95% CI = 1.04-1.41), stroke (HR = 1.28; 95% CI = 1.02-1.60), CVD demise (HR = 1.29; 95% CI = 1.09-1.53), and all-cause transience (HR = 1.27; 95% CI = 1.15-1.41) for antidepressant consumers. In wholly accustomed models, antidepressant use was related with a minor upsurge in all-cause transience [17].

15. Antidepressants and Risk of Cardiovascular Outcomes

This study proposes to analytically examine studies measuring the relations between the use of antidepressants (ADs) and the threat of cardiovascular (CV) consequences. A complete set of 99,367 event cases of CV consequences who encountered annexation norms were recognized from 22 observational studies. Compared with non-consumers of ADs, the use of SSRIs was related with an enlarged threat of cerebrovascular infection (RRs, 1.24; 95% CI, 1.15 to 1.34), whereas the use of TCAs was connected with an enlarged threat of severe heart illness (RRs, 1.29; 95% CI, 1.09 to 1.54) [18].

16. Risk of Cardiac Defects in Pregnancy Due to the Use of Antidepressants

Whether the consumption of selective SSRIs and other antidepressants during gestation is linked with an enlarged threat of inherited cardiac weaknesses is unclear. In brief, there are apprehensions about a probable link between paroxetine use and right ventricular outflow tract blockade and between sertraline consumption and ventricular septal faults. A total number of 64,389 women (6.8%) used antidepressants in the course of their first trimester. A total of 6403 newborns who were not exposed to antidepressants were born with a cardiac fault as compared with 580 newborns with contact. Links between antidepressant consumption and cardiac weaknesses were tempered with growing levels of adjustment for perplexing [19].

17. Use of Paroxetine During Pregnancy and Cardiovascular Deformities

Up to one ifth of women during the gestation phase experience temperate to severe depressing indications. Prenatal period may be a period of danger mutually for the novel inception and for the reoccurrence of depression, with the proportion of depression increasing from 7% to 20%. Depression during the period of gestation is linked with deprived motherly diet, insufficient weight increase, smoking, liquor and other ingredient consumption, as well as an enlarged threat of post partum depression. The number of antidepressant recommendations for the period of gestation enlarged four-fold between 1992 and 2006, with an aggregate of 4.8% of women getting a recommendation in the earlier months of gestation in the UK. Occurrence rates were assessed to be 4.5% (2009) in Canada and up to 13% (2007) in the US. The most often used cure for depression in gravid women is SSRIs, accounting for roughly 80% of recommended antidepressants for the period of gravidity. The extensive consumption of antidepressants during the period of gravidity makes it vital to recognize the protection and threat of opposing consequences in the fetus [20].

Until 2005, paroxetine was deliberated to be nontoxic for use during the period of gestation. However, succeeding consequences from a minor unpublished study directed by the constructer, there were ideas of an upsurge in the threat of cardiac deformities in newborns with *in utero* contact to paroxetine, as compared with those that were not exposed to paroxetine. This resulted in an amendment of the merchandise tag to embrace caution against the danger of cardiac deformities with prenatal contact/exposure to paroxetine [20].

18. Cardiovascular Adversative Effects of Psychotropic Drugs

The maximum number of patients who take psychotropic drugs are at a small peril for cardiovascular adversative effects from these medicines and need merely routine checking. However, patients with severe psychological complaints, persons with a private or personal antiquity of cardiovascular illness, or individuals getting high dosage or numerous medicines are considered at a great danger of illness and transience from cardiovascular opposing effects. Such patients may require extra cautious cardiovascular checking. Figure 5 shows common cardiovascular adverse effects due to several antidepressants [21].

19. QTC Prolongation due to Amitriptyline Intoxication

Amitriptyline, a normally used tricyclic antidepressant negotiator, has

Class/ Medication(s)	Common cardiovascular adverse effects
SSRIs	Minimal at therapeutic dosages
TCA: Amitriptyline	Abnormal heart rhythm, low BP, tachycardia, heart block
TCA: Imipramine	QTc prolongation

Figure 5. Common cardiovascular adverse effects due to numerous antidepressants [21]

influential cardiotoxic effects particularly in great quantities. The serum and urine levels of amitriptyline doses are not connected with the harshness of noxiousness; so, it increases the significance of ECG aberrations. The elongation of QTc can be a prognostic indicator of cardiotoxicity. An experiment was conducted on rats. They were divided into four sets. The first was the controller set, the second was the amitriptyline + saline group, the third was the amitriptyline + metoprolol group, and fourth was the amitriptyline + diltiazem group. ECG of rats was noted under anesthesia. In amitriptyline set, QTc period was extended compared with all other sets. The extension of QTc was smaller in amitriptyline + metoprolol set and amitriptyline + diltiazem set as compared to amitriptyline set [23].

20. Conclusion and Recommendations

TCA can cause abnormalities in the ECG pattern. It affects the conduction rate and slows the heartbeat by blocking the sodium channels. It causes the elongation of QST complex that leads to abnormalities. It also causes sudden death in children, young people and also pregnant women due to overdose. Since these drugs are important for curing some disorders but they also have some side effects if exposed to for a long term. So, long term exposure without proper prescription must be avoided. ECG can be used to check the rhythmicity of heart; if an abnormal pattern occurs that means something is wrong inside the heart. We can also use ECG for the assessment of drugs with subtle electrophysiological effects.

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