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EFFECT OF AZITHROMYCIN IN QT INTERVALS ENLARGEMENT IN ICU PATIENTS

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Abstract

Azithromycin is a broad-spectrum macrolide antibiotic Indicated for the treatment of patients with mild to moderate infections. Moreover, Azithromycin Effects the normal electrophysiological function of heart and concurrent use can cause synergistic effect and leads to prolonged QT interval, Torsade's de points and even death. Several studies also reported the association between azithromycin QT prolongation. Patients with particular cardiovascular conditions such as low blood potassium, magnesium levels, Acute coronary syndrome etc…& and use of certain type of drugs can cause QT prolongation and Torsade's de points. This review tells regard the management of QT prolongation caused by Azithromycin and the alternative choice of drugs for azithromycin.

Keywords

QT interval Prolongation, Torsade's de points, ventricular arrhythmias, ventricular repolarisation, Azithromycin Syndrome.

INTRODUCTION

ELECTROCARDIOGRAM(ECG)

➢ The electrocardiogram (abbreviated as ECG or EKG) represents an electrical tracing of the heart and is recorded non-invasively from the surface of the body.[1] It was soon recognized as a robust screening and clinical diagnostic tool, and today it is used globally in almost every healthcare setting. [2].

➢ ECG is increasingly being used for monitoring patients on antiarrhythmics and other drugs, as an integral part of preoperative assessment of patients undergoing non-cardiac surgery, and for screening individuals in high-risk occupations and those participating in sports. [3]. It is an advanced computerized machine and used for diagnosing various cardiac diseases like [4] Tachycardia, murmur, shock, myocardial injury, ischemia, Cardiopulmonary resuscitation, Rheumatic heart disease [5] and Detecting pacemaker or defibrillator device malfunction, evaluating their programming and function. [6]

QT intervals

➢ Qt intervals represents the duration of ventricular electrical systole which includes ventricular activation and recovery. Measured from beginning of QRS complex to end of T wave. Excess of QT prolongation can show the myocardium Predisposition for the development of depolarisation which can trigger tachycardia such as TdP.

➢ Long QTc Interval was increased by conditions such as hypomagnesemia, hypokalaemia, hypocalcaemia and hypothermia. Drugs include azithromycin, clarithromycin, levofloxacin. Some cardiac drugs like class I and class III Anti arrhythmic drugs which shows rare side effects.

- TdP (Torsade's de points)-Very fast heart rhythm it starts in lower heart chamber (Ventricles). QT interval (QT_C) of >500ms[1] or an increase in the QT_C of >60ms[2] is generally considered to confer a high risk of TdP in an individual patient.
- Reversing of Torsade's de points by giving the drugs like IV magnesium sulphate, Chronotropic drugs like isoproterenol

The relationship between QT interval and the risk of TdP is not fully understood.

Table-1

QT_c values by Age and Sex

QT_c values by Age and Sex (ms) [9]			
	1-15 years (ms)	Adult males(ms)	Adult females(ms)
Normal	<440	<430	>450
Borderline	440-460	430-450	450-470
Prolonged (top 1%)	>460	>450	>470

QT prolongation

➢ QT prolongation is a measure of delayed ventricular repolarisation. It was primarily observed only in patients with a high baseline risk (e.g., preexisting cardiovascular conditions or concomitant use of other QT-prolonging drugs) [7]

➢ The QT interval of the electrocardiogram (ECG) varies from beat-to-beat, from day-to-day, and diurnally and is affected by numerous factors, including gender, age, autonomic tone, and heart rate. The QT interval is expressed as the QTc interval after adjusting for heart rate using any of several of correction formulas. QT prolongation itself does not adversely affect cardiac function but prolongation portends the possibility of more serious arrhythmias. [8]

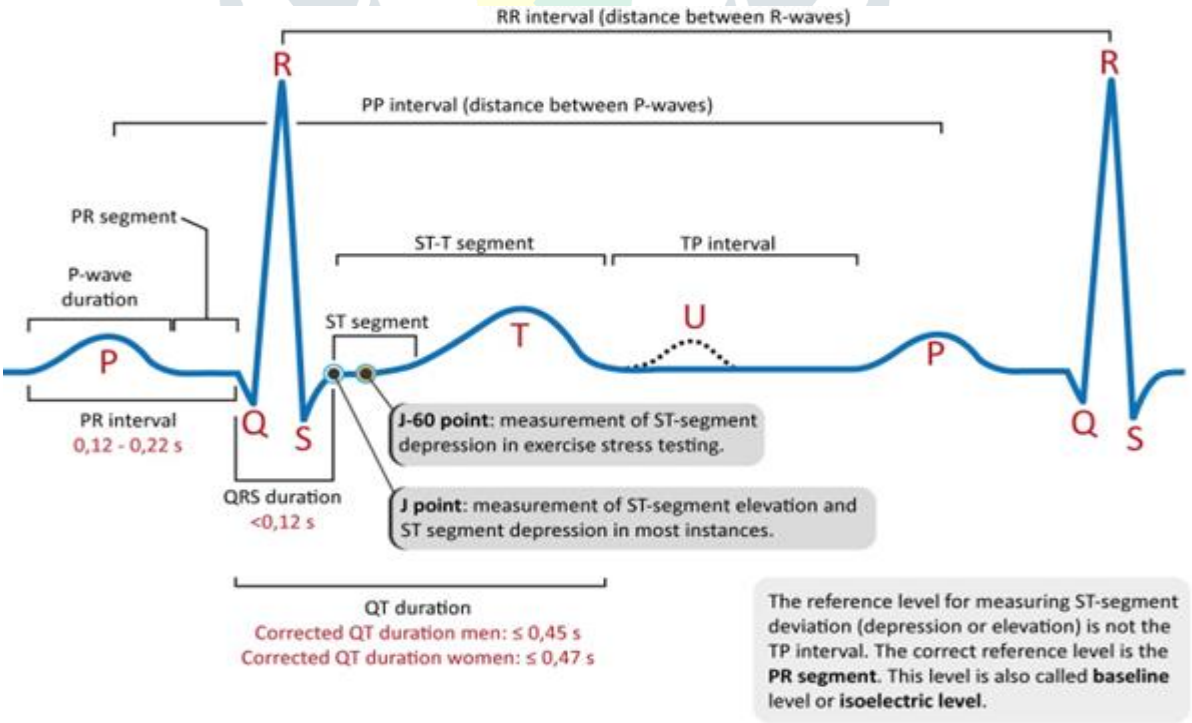

fig-1-a typical ECG

Mechanism of drug induced QT prolongation and Torsade's de points

- At cellular level the repolarisation phase of myocytes is taken by outward moment of potassium ions.
- There are different potassium channels subtypes present in heart.
- Two important potassium currents which are participating in ventricular repolarisation are the subtypes of delayed current.
  - I rapid
  - I slow
- I rapid is the most susceptible to proarrhythmic effect.
- Blockade of these two currents shows the prolongation of action potential and prolongation of QT Interval At the surface of ECG.
- The prolongation of repolarisation results in subsequent inward of depolarisation current known as early after depolarisation. This shows the increased dispersion of repolarisation TdP is provoked, which shows further re-entry of wave activity.
- Such phenomena are more readily induced in the His-Purkinje network and also from a subset of myocardial cells from the mid ventricular myocardium, known as M cells.
- Compared to subendocardial or subepicardial cells, M cells show much more pronounced action potential prolongation in response to I blockade.
- Resulting in a pronounced dispersion of repolarisation (that is, heterogeneous recovery of excitability), creating a zone of functional refractoriness in the mid myocardial layer, which is probably the basis of the re-entry that is sustaining the TdP.

Risk factors for Qt prolongation and Torsade's de points

There are two types of risk factors Modifiable and Non-Modifiable

Modifiable

1. Electrolyte disturbances

a. Hypocalcaemia (calcium < 4.65 mg/dL)
b. Hypokalaemia (potassium < 3.4 mmol/L)
c. Hypomagnesemia (magnesium < 1.7 mg/dL)

2. QT-prolonging medication polypharmacy

a) Concurrent use of ≥ 1 QT-prolonging medication

Non-Modifiable

1. Common diagnoses

a. Acute coronary syndrome
b. Anorexia nervosa or starvation
c. Bradyarrhythmia's < 45 bpm
d. Cardiac heart failure (ejection fraction < 40%; uncompensated)
e. Congenital long QT syndrome or other genetic susceptibility
f. Chronic renal failure requiring dialysis
g. Diabetes mellitus (type 1 and 2)
h. Hypertrophic cardiomyopathy
i. Hypoglycaemia

2. Pheochromocytoma
3. Status post cardiac arrest (within 24 hours)
4. Status post syncope or seizure (within 24 hours)
5. Stroke, subarachnoid hemorrhage, or other head trauma (within 7 days)
6. Personal or family history of QT interval prolongation or sudden unexplained death in the absence of a clinical or genetic diagnosis.
7. Elderly (> 65 years of age) [10]

ONE OF THE DRUGS WHICH CAUSING QT PROLONGATION

- March 2013 warning by US FDA That azithromycin may increase the risk of Sudden cardiac death it doesn't mean we must stop using it. We should however try to determine if our patients have cardiovascular risk factors and take appropriate Precautions. [10]
- Azithromycin triggered torsade's de pointes in 2001 a growing body of evidence Derived from post marketing surveillance Had linked Azithromycin Leads to cardiac arrhythmias such as QT interval prolongation which can progress to life threatening ventricular fibrillation. [11]
- Further in the 8 years period from 2004-2011 the US FDA Received a total 203 Reports of Azithromycin Associated QT prolongation, torsade's de pointes and ventricular arrhythmias.
- In total 203 Cases 65 cases show sudden cardiac deaths.
- In observational, non-randomised people Enrolled in the Tennessiee, Denmark they found over
- Over 5 days of therapy people who are taking azithromycin had a rate of cardio vascular death 2.88 times higher than in the people taking no antibiotic and 2.49 times higher than in the people taking amoxicillin. The increase in deaths did not persist after 5 days of therapy. This is time limited pattern which is directly correlated with expected peak azithromycin plasma levels during a standard of 5 days course.

Table-2-Risk of cardiovascular death in Tennessee Medicaid patients, Denmark and young to middle-aged Danish adults taking a 5-day course of azithromycin

Risk of cardiovascular death in Tennessee Medicaid patients, Denmark and young to middle-aged Danish adults taking a 5-day course of azithromycin					
Population	Azithromycin vs no antibiotic use		Azithromycin vs beta-lactam use		Overall cardiovascular mortality rate (per 1 million azithromycin
	Risk ratio	95% CI	Risk ratio	95% CI	
Tennessee	2.88	1.25-2.75	2.49	1.38-4.50	85.2
Denmark	2.85	1.13-7.24	0.93	0.56-1.55	15.4

THE FDA REVISES AZITHROMYCIN'S WARNINGS AND PRECAUTIONS

The FDA revises the warning and precautions of azithromycin drug label to include a warning about the potential risk of arrhythmias specifically QT interval prolongation and Torsade's de points march 2013 safety Announcement is given to healthcare professionals to use caution when prescribing azithromycin to patients known to have a high risk factors for drug related arrhythmias, including QT interval prolongation, Hypokalaemia, Hyper magnesia, bradycardia and Concurrent use of medication Which prolong QT interval.

AZITHROMYCIN

Azithromycin is a broad-spectrum macrolide antibiotic and it is available in a brand name of ***Azasite, Zithromax, Zmax*** *and it is available in the doses of* 500 mg/vial. [12] Tablet-250mg and 500mg.Azithromycin is indicated for the treatment of patients with mild to moderate infections caused by microorganisms. [13] Its absorption takes place in intestine by P glycoprotein. [14] Widely distributed in tissues with a steady state volume of 31.1 lit/kg. [12] Metabolism of Azithromycin is not been performed; however, this drug is eliminated by liver through bile. [15)] It is eliminated as an unchanged drug approximately 6% it is found in urine. The **half-life** of a drug is 68 hrs and clearance of drug 630 ml/minute when it is given in Iv dose. The mechanism of Azithromycin is binds to 23s portion of 50s bacterial ribosomal sub unit It shows the inhibition of bacterial proteins synthesis by preventing the transit of amino acyl tRNA [16]. The reduction in protein Synthesis depends upon macrolide concentration [17]. Azithromycin rapidly moves from Blood stream into the tissues and cross's the cellular membranes [16]. Like other macrolides acts as Bacteriostatic agent, it shows the inhibition of bacterial growth rather than directly killing the microorganisms [18]. Side effects is Arrhythmias, Vertigo, Pancreatitis, watery diarrhoea [19].Nausea and vomiting [20], QT interval Enlargement, Low blood pressure (21) Adverse effects like QTc interval Prolongation [22)], Life threatening

hypersensitive reactions to and Azithromycin such as anaphylaxis stevens Johnson syndrome. [23] Azithromycin contraindicated in patients who are using antidepressant drug Pimozide, Which Causes severe arrhythmia. [19].

CASE STUDY [24]

- A 37-year-old woman having a history of previous syncopal attacks in 2013,2014 and 2016 she was diagnosed with sinus tachycardia with no other abnormalities in ECG.she was offered beta blockers for symptomatic relief. She was admitted in emergency block with the complaints of sore throat, nausea and vomiting, cough she was diagnosed with viral pharyngitis. The patient did not feel well so azithromycin is prescribed she received 2 capsules of 250 mg azithromycin for 1 day on the same day she became unresponsive and had a cardiac arrest. PR was done for 26 min.ECG shows Ventricular fibrillation during CPR cycles she received two shocks and was started IV Amiodarone and her vitals were stable and next day she again developed Ventricular fibrillation when she was given azithromycin in ICU and results in three to four episodes of ventricular tachycardia and it was managed with electrical shocks.
- The ECG shows dilated left ventricle with severe LV dysfunction with ejection faction (EF)-20%. Severe mitral regurgitation, and moderate tricuspid regurgitation. She had another unstable ventricular tachycardia and underwent cardiac catheterization, which showed no significant coronary artery disease, and intra-aortic balloon pump was inserted. After a few minutes, she had cardiac arrest and required 4 shocks and was electively intubated.
- She was transferred to our tertiary care hospital for further management and possible left ventricular assist device (LVAD) insertion or heart transplantation. During transfer, she again had repeated episodes of ventricular fibrillation and torsade's de pointes (TdP). She was shocked in the ambulance and reverted back to sinus rhythm. Her initial echocardiogram upon presentation showed reduced left ventricular systolic function with ejection fraction around 10%, so the decision was to insert ECMO as a bridge to recovery. A veno-arterial ECMO was inserted in the Cardiac Surgery Intensive Care Unit (CS-ICU) at bedside.
- During her stay in the CS-ICU, she required several antihypertensive medications and vasodilators to control blood pressure. Her medications are illustrated. She was gradually improving, until extubating on the third day of admission to the CS-ICU. Later, after 12 days on ECMO, the left ventricular systolic function significantly improved, with EF of 50% to 55%. As a result, she was weaned off ECMO. After removal of ECMO, she recovered very well and was transferred to the general patient floor, where she was maintained on captopril 25 mg orally 3 times daily, metoprolol tartrate 50 mg orally twice daily, and amiodarone 200 mg orally daily. On day 17, she underwent subcutaneous implantable cardioverter defibrillator (ICD) insertion (model name: EMBLEM MRI S-ICD).
- She was discharged on day 18 on the following medications: captopril 25 mg orally 3 times daily, metoprolol tartrate 50 mg orally twice daily, and amiodarone 200 mg orally daily.

Before prescribing a QT prolonging medicine [25]

- Screen for other risk factors for QT prolongation, including possible medicine interactions and electrolyte abnormalities. Correct any modifiable risk factors.
- Baseline ECGs should be performed in high-risk patients, or in patients receiving more than one QT prolonging medicine. A non-QT prolonging medicine should be considered in these patients if possible.
- Do not prescribe a QT prolonging medicine to patients already receiving a Class I or Class III anti-arrhythmic medicine.
- Patients should be advised to avoid consuming grapefruit juice, liquorice or any complementary medicines in addition to a QT prolonging medicine.

Monitoring [26]

- All patients should be advised to report symptoms of arrhythmia or any conditions that could lead to hypokalaemia or renal dysfunction.9,10
- ECGs should be performed in all patients with symptoms of arrhythmia and periodically in patients at high risk of QT prolongation/TdP.
- If there are risk factors for electrolyte disturbance, electrolytes should be measured periodically. Hypokalaemia or hypomagnesaemia should be corrected.

After occurrence of TDP [27]

- Sustained episodes or unstable patients require DC cardioversion.
- Intravenous magnesium sulphate should be given immediately.

- The suspect medicine should be withdrawn and any electrolyte abnormalities corrected.
- Cardiac pacing or isoprenaline infusion should be considered for refractory cases.

TREATMENT [28]

- Treatment for long QT syndrome may include lifestyle changes, medications, and surgery.
- Treatment varies but may include magnesium or other fluids given by IV to correct electrolyte imbalances.
- Medications won't cure long QT syndrome, but they can help protect against possible life-threatening heart rhythm changes.

Medications used to treat long QT syndrome may include

1. Beta blockers. These heart drugs are standard therapy for most patients with long QT syndrome. They slow the heart rate and make long QT episodes less likely. Beta blockers used to treat long QT syndrome include nadolol (Corgard) and propranolol (Inderal LA, InnoPran XL).
2. Mexiletine. Taking this heart rhythm drug with a beta blocker might help shorten the QT interval and reduce the risk of fainting, seizure or sudden death.

Some people with long QT syndrome need surgery to control the heartbeat. Surgery or other procedures used to treat LQTS

- Left cardiac sympathetic denervation (LCSD) surgery. LCSD surgery is usually only recommended for people with long QT syndrome and persistent heart rhythm problems who can't take or tolerate beta blockers. It doesn't cure long QT syndrome, but it does help reduce the risk of sudden death. In this procedure, surgeons remove specific nerves along the left side of the spine in the chest. These nerves are part of the body's sympathetic nervous system, which helps control the heart rhythm.
- Implantable cardioverter-defibrillator (ICD). An ICD is a battery-powered unit that's implanted under the skin near the collarbone — similar to a pacemaker. The ICD continuously monitors the heart rhythm. If the device detects an irregular heartbeat, it sends out shocks to reset the heart's rhythm. It can stop a potentially life-threatening arrhythmia.

3. **Pacemaker** - This device help people who have an abnormally slow heart rate.

4. Stellectomy

- Left cervicothoracic stellectomy is another antiadrenergic therapeutic measure used in high-risk patients with long QT syndrome (LQTS), especially in those with recurrent cardiac events despite beta-blocker therapy.
- Stellectomy decreases the risk of cardiac events in high-risk patients with LQTS, although it is more effective in patients. Although this technique decreases the risk of cardiac events, it does not eliminate the risk. (28)

5. Gene-specific therapy is an area under investigation in the treatment of long QT syndrome (LQTS). For example, because LQT3 is associated with gain-of-function mutations in sodium channels, antiarrhythmic agents with sodium channel blocking properties have been suggested as gene-specific therapy for patients with LQTS. Nevertheless, this area is complex and requires further investigations and studies.

- For example, Ruan and colleagues found that mexiletine, a sodium channel blocker, can facilitate F1473 mutant protein trafficking, resulting in a net effect of a further increase in the sodium current and a worsening of QT prolongation in a subset of patients with LQTS who have this specific mutation.
- retrospective cohort study of 34 LQT3 patients, Mazzanti et al found evidence that mexiletine is an effective therapy. The median duration of oral mexiletine therapy was 36 months. Mexiletine significantly shortened QTc, reduced the percentage of patients with arrhythmic events, reduced the mean number of arrhythmic events per patient, and reduced the annual rate of arrhythmic events. [29]

Alternative therapy in ICU patients

Antibiotics therapy is given according to risk factors and type of microorganisms. Duration of treatment according to response and severity of disease and complications.

1. Patients with CAP in ICU-7 to 10 days
2. Patients with Pneumonia-14 days
3. For infective endocarditis- Minimum 2 weeks for uncomplicated cases and 4 to 6 weeks complicated cases.

4. Azithromycin and Levofloxacin is efficacious in treating but due to their adverse reactions US FDA given warnings regarding possible risk of QT prolongation by giving these drugs and severity of disease which may leads to death. So, these drugs will be stopped.

5. Combination therapy-

- Amoxicillin+ Clavulanic acid
- Ampicillin+ Sulbactam
- Pipercillin + Tazobactam

Drugs to be avoided [30]

1. Antihistamines-

- Terfenadine
- Astemizole
- Diphenhydramine (Benadryl): For allergies

2. Gastrointestinal medications

Cisapride (Propulsid), for oesophageal reflux and acid indigestion, should be avoided.

3. Antifungal drugs

Antifungal agents to be avoided include the following:

- Ketoconazole (Nizoral): For fungal infections
- Fluconazole (Diflucan): For fungal infections
- Itraconazole (Sporanox): For fungal infections

4. Psychotropic drugs

- Tricyclic antidepressants (Elavil, Norpramin, Vivactil): For depression
- Phenothiazine derivatives (Compazine, Stelazine, Thorazine, Mellaril, Trilafon): For mental disorders
- Butyrophenones (Haloperidol): For mental disorders
- Benz isoxazole (Risperdal): For mental disorders
- Diphenylbutylpiperidine (Orap): For mental disorders

5. Medications for potassium loss

- Indapamide (Lozol): For water loss, edema
- Other diuretics
- Medications for vomiting and diarrhoea

6. Antibiotics

- Erythromycin
- Trimethoprim and sulfamethoxazole
- Pentamidine

Lifestyle modifications [31]

1) Manage emotions. Being very excited, angry or surprised can trigger heartbeat changes in some people with long QT syndrome.

2) Check your medicines. Avoid drugs that could cause prolonged QT intervals.

3) Get regular health checkups. If you have changes in your symptoms or condition, your health care provider may update your treatment plan or suggest additional treatments.

4) Know which sports are safe.

5) Check for startling sounds. Turn down the volume on doorbells and other devices (such as telephones) that may startle you, especially during sleep.

Conclusion

Azithromycin Is a broad-spectrum macrolide antibiotic used for treating mild to moderate infections. Azithromycin effects the electrophysiology heart and shows QT interval prolongation, Torsade's de points and even death. US FDA Added warning to drug insert as QT prolongation Leads to life threatening condition Torsade's de points. As we observed from the above case by using azithromycin patient resulted in dilated left ventricle with severe left ventricle dysfunction with EF-20% and other conditions for developing Torsade's de points Are low blood potassium, magnesium Levels. As it is having a side effect that doesn't mean we must stop using it. We should however try to

determine if patients having any cardiovascular risk factors and late appropriate precautions alternative drug therapies amoxicillin+ Clavulanic acid, ampicillin+sulbactum piperacillin+tazobactum. Treatment for long QT Syndrome including lifestyle Changes and electrolyte balancing. Medications won't cure long QT syndrome but they can help to protect against life threatening heart rhythm changes.

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