

THERAPEUTIC ASPECTS OF TORASADE DE POINTES

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Summary

Torasade de pointes (TDP) are the polymorphic form of ventricular tachycardia (VT) which resulting from the prolongation of the QT interval. Manily it occurs with the administration of the anti-arrythmic drug although the several categories of the drugs such as anti-muscarinic or antipsychotics drugs also may be a cause of the TDP along with the numerous factors such as the hypokalemia, hypocalcemia, and hypomagnesia. There are the several other factors such as sex, age, and disease condition also may cause the TDP. This review approaches that the drug such as lidocaine, amiodarone should be used to treat the cardiac arrhythmia because these drugs act by without affecting the QT interval.

Keywords; Torasade de pointes, QT time prolongation, Hypokalemia, Early after depolarization

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Introduction

Dessterne has introduced the term TDP in (1966) a life threatening polymorphic form of (VT) occurs due to prolongation of QT time interval (1). TDP either may be congenital or acquired. Mainly it occurs with the administration of anti-arrhythmic drugs. Class IA and III anti-arrhythmic agents delaying the repolarisation and prolongs the QT interval which is a major cause of acquired TDP (2). Anesthetics may also influences the duration of QT interval. Volatile anesthetics, sevoflurane and isoflurane prolong QT, whereas the influence of halothane is controversial (2). The other drugs like cisapride and grepafloxacin were also removed from the US market due to the risk for QT prolongation and fatal arrhythmias. The reason to remove these drugs from the market was not only related to the inherent properties of the drugs but also, to the demonstrated failure of government mandated black box warnings and "Dear Doctor" letters to minimize in appropriate prescribing by physicians (3). Isoproterenol is contraindicated in patients with elevated blood pressure or ischemic heart disease, whereas institution of cardiac pacing requires experienced personnel and fluoroscopy (4).

Factors responsible for torasade de pointes

1. Circadian variation Due to the sympathetic and parasympathetic effect the QT time will increase about 20 ms at the night time as compare to the day time. The risk of prolongation of QT time in night may increase with cardiac disease (5).

2. Sex At the time of birth the men and women infants have the same QT time interval. But at the time of puberty the men QT time shortened about 20 ms due to the effect of androgen (especially testosterone) rather than estrogen (6). Although, women have the risk of disease 45% due to cardiovascular disease, but totally the women have the risk 70%.

3. Cardiovascular disease and Age The elderly groups of men and women was founds to be an increase the QT time as compare to the non elderly groups. The QT time also increase with cardiovascular disease subject as compare to the normal subject with same age group. (VT) prevalence rates increase in the middle decades of life, subsequently with the occurrence of structural heart disease (7).

4. Electrolytes Decrease in concentration of electrolytes such as hypokalemia, hypocalcaemia, also may prolong the QT time interval. Hypokalemia(Decrease the intracellular K^+ concentration) prolongs cardiac action potential, resulting in early after depolarization which ultimately prolongs the QT interval (8).

5. Long QT syndrome by birth TDP is may be congenital. The mutation of gene which are involves in the encoding of cardiac ion channel may be responsible for the long QT syndrome. Therefore the clinician should have the knowledge about family history of patient before prescribing the drugs that may have the risk of prolongation of QT time (9).

Drugs induced TDP The various drugs such as ciprofloxacin, anesthetics, antimuscarinic drugs, antiarrhythmic drugs which may induce TDP. There are several agents, such as anti-histaminic agents (e.g. terfenadine, which is a potent blocker of ionic potassium receptor), causes TDP but do not prolong action potentials. But the interaction of terfenadine with the inhibitors of CYP-450, a study has been proved that erythromycin alter the metabolism of terfenadine. Which leads to the accumulation of terfenadine and consequently it may alter the cardiac repolarisation (9). Thus, the ability to predict the cause of malignant arrhythmias, by any drug in any single patient or population is imprecise at best. Several mechanisms can

causes arrhythmias such as TDP, including rhythm transmission block, early after depolarization or prolongation of action potentials. Interestingly, drugs such as terfenadine only prolong the Q-T interval by 6 ms except in the case of heart failure when the Q-T prolongation is longer (10). Food and drug administration ordered to the manufacturer to send a 'Dear Doctor' letter to all physicians about the adverse effect of terfenadine in august 1990. And these reports then termed as Black Box warning followed in U.S. countries in 1992 (11). This pharmacologic agent is a strong IKr inhibitor, it is metabolized pre systemically by the cytochrome P450 system (Mainly by CYP3A4) (12). Example of the various drug induced TDP are given in the table 1.

| S.NO. | Category | Example of drugs | Mechanism of action | Toxic effects |
|-------|-----------------------|---|---|--|
| 1 | Antipsychotics | | | |
| | | Chlorpromazine Haloperidol Trifluoperazine Thioridazine Fluphenazine Risperidone | D2 receptor blocking action Thioridazine (a low potency phenothiazine) have marked central anticholinergic action | Chlorpromazine produce QT prolongation by directly depressing the heart Thioridazine and resperidone produce the TDP. |
| 2 | Antiarrhythmics | | | |
| | class1A Class3 | Quinidine Procainamide Disopyramide | Na ⁺ channel blocking property , prolong the action potential duration Increase the effective refractory period and prolong the QT interval | On rapid i.v. injection produces TDP. |
| | | Dofetilide Bretylium Ibutilide | These drugs act by blocking the rectifier K ⁺ channel ,and ultimately prolongs the APD and QT interval also | Produces the TDP. |

| | | | | |
|---|---|--|---|---|
| 3 | Antimicrobial Antimalarial Antifungal | | | |
| | | Quinine Chloroquine Mefloquine Sparfloxacin Ketoconazole | Antimalarial drugs act by accumulate into the infected RBCs. | Quinine& mefloquine produce the TDP by QT prolongation. Sparfloxacin prolongs the QT interval and produce the TDP. |
| 4 | Miscellaneous | | | |
| | | Cisapride Vasopressin | Cisapride act by (a) D2 antaonism (b)5-HT ₄ agonism (c)5-HT ₃ antagonism At the higher concentration cisapride blocks delayed rectifying K ⁺ Channel in heart –prolongs the QT interval | Ultimately produces torasade de pointes. |

Drugs induced TDP (9)

Pathogenesis of TDP

Various mechanisms for TDP have been suggested. The mechanism however, that causes TDP might differ from that which maintains it. It has been appears possible that TDP has multiple causes resulting as a final common pathway for the electrocardiography, pattern viewed as characteristic for TDP.

1. Early after depolarization's and triggered automaticity

In some pathophysiological cases a normal cardiac action potential may be followed by an abnormal depolarization and when this depolarization reaches to threshold it may resulting in secondary upstrokes, which then propagate and intitiate the abnormal rhythm. These depolarizations may give rise to premature action potentials or even trains of potentials that have been known to as triggered activity (13). There are two form of triggered rhythm are

known; 1. Generally result from Ca^{2+} overload (Digitalis intoxication, ischaemia-reperfusion). 2. Repolarization during phase 3 is fluctuating and membrane potential oscillates. If the amplitude of oscillation is large, it will activate the neighboring tissue and then a series of impulse are propagated, this results from depression of delayed rectifier K^+ current (14).

Reentry based on dispersion of repolarization

Non uniform prolongation of action potentials is a factor for reentry and has been proposed as the probable mechanism of TDP (dispersion hypothesis). Two or more re-entry when interact within two ventricular area, they may induce different waves of excitation which contend with each other and obtained the characteristic electro physiologic pattern. Thus the impulsive termination TDP can be explained by block of conduction in the pathway of re-entry (15).

Treatment of TDP

Treatment is directed at withdrawal of the offending agent, infusion of magnisium sulphate, anti-arrythmics, and electrical therapy as needed. Because of the polymorphic nature of TDP, synchronized cardio version may not be possible, and the patient may require an unsynchronized shock or (defibrilation).

Isoprenaline This is an example of beta adrenergic agonist. They generally are used to stimulate the force and rate of contraction. There chronotropic activity is effective in the emergency treatment of TDP, bradycardia or heart block (16).

Lidocaine Class IB antidysrhythmics stabilize cell membranes, and blunts phase 0 of the action potential, resulting in shortens repolarization. Lidocaine is used by intravenous infusion to treat the ventricular tachycardia resulting in prevent the ventricular fibrillation after the myocardial infraction (17). The net effect of lidocaine is to decrease firing of ectopic foci to achieve a normal rhythm to ressert itself. But amiodarone is the preferable drug than the lidocaine.

Magnesium sulphate Drug of choice for TDP, it also may be useful to treat prolongation of QT interval, especially where hypomagnesaemia is present. Magnesium act as a cerebral vasodilator and also blocks the voltage dependent Ca^{+2} channel. On the other hand it antagonize the action of NMDA receptors in the brain and also attenuates glutamate stimulation which decreases calcium influx during ischemic injury (18). When treating with magnesium sulfate, the regular monitoring for hypomagnesaemia is require because an overdose can cause cardio respiratory collapse and paralysis.

Sodium bi carbonates it is used when the patient It is used when the patient is suffering from bicarbonate responsive acidosis having the pH ≤ 7.0 mainly resulting from tricyclic antidepressent overdose or from hyperkalemia. But regular use is not requires (19).

Amiodarone Amiodarone is highly lypophilic,iodine containing drug. Newest of the antidysrhythmics used to treat (VT), generally it is considered a class III antidysrhythmic, although it has pharmacologic characteristics of all 4 classes. Drug of choice used in the treatment of refractory hemodynamically unstable VT. Prehospital studies suggest that the amiodarone is safe for use prehospital setting. Amiodarone inhibits the abnormal automaticity in most tissue it prolongs the action potential duration.

Conclusion

TDP is a ventricular tachycardia which resulting from prolongation of the QT time interval. There are various risk factors responsible for the prolongation of the QT interval such as sex, menstrual cycle, cardiovascular disease, and deficiency of electrolytes such as hypokalemia, hypomagnesemia may also results the torasade de points. Treatment strategies involve the use of antidysrhythmic drugs like amiodarone, lidocaine which blunts the phase 0 of the action potential which results in the repolarization shortening. And net effect is to attain a normal rhythm and restart itself.

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