Review Article:

Ventricular Arrhythmias; Iatrogenic Causes Recognition, Prevention and Management

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It is well known that drugs used for the management of cardiovascular diseases i.e. cardiac arrhythmia, cardiac failure, circulatory failure and conduction abnormalities can be harmful and produce life threatening arrhythmias and sudden death especially antiarrhythmic drugs belonging to Vaughn Williams classification 1A, 1C, 3 and 4 (Table 1).

Table 1.

Class	Action	Drugs
1A	Fast Na^+ channel blockers and prolongs repolarization	Procainamide
		Disopyramide
		Moricizine
1B	Shortens replorazation	Lignocaine
		Mexlitine
		Tocainide
		Phenytoin sodium
1C	Minimal effect on repolarization	Encainide
		Flecainide
		Propafenone
2	Beta blockers	Inderal
		Atenolol
		Metoprolol
3.	Action potential prolongation	Amiodarone
		Sotalol
		Bretylium
4.	Calcium channel blokders	Verapamil
		Diltazem
		Lidoflazine
		Bepradil
		Prenylamine

These drugs are reported to cause clinically important proarrhythmias in 3 to 12%[1,2] of cases and up to 16% of cases when assessed by electrophysiological studies[3]. It is not necessary that these agents should have toxic levels to produce harmful effects[4]. Class 4 drugs especially bepridil[5], lidoflazine[6], and Prenylamine[7] are used as coronary vasodilators outside USA. These have class I like properties, prolong QT interval and produce proarrhythmias. Other cardiac drugs especially inotropic agents (Digoxin, Dopamine, Dobutamine[8], Milrinone, Amrinone[9] and Flosequinone[10], Vasopressin[11] Atropine[12] and Thrombolytic therapy[13] are worth mentioning, as these can also produce life threatening arrhythmias.

Non cardiac drugs used for other ailments are equally important as these are commonly prescribed in clinical practice. These include Antidepressants, Neuroleptic agents, Antimalarials, Antibiotics, Antifungals, Antihistamines, Antiemetics, Bronchodilators, drugs used for urinary incontinence, cholesterol lowering, antiparkinsonism and chemotherapeutic agents.

The most dangerous and life threatening side effects are ventricular tachycardia, fibrillation and sudden death, and other relatively less serious effects like hypotension, negative inotropic effect, sinus brady or tachycardia. These drugs produce repolarization abnormalities in the conduction system of heart[14] producing prolongation of QT interval. Most characteristic of drug-induced proarrhythmia is polymorphous ventricular tachycardia called torsade de pointes in which the QRS axis progresses from positive to negative and back in sinusoidal pattern.

Some authors require QT interval prolongation as a part of the definition of torsade de pointes provoked by the same group of drugs[15, 16]. Torsade de pointes is characteristically initiated by a long -short cycle. A premature beat is followed by a compensatory pause, a supraventricular complex with abnormal QT prolongation and a further ventricular premature beat synchronous with T wave (R on T phenomenon) which precipitates polymorphic ventricular tachycardia. Torsade de pointes is usually self limiting and is associated with recurrent dizziness or syncope. However it may degenerate into ventricular fibrillation and sudden death.

What is QT and QTc Interval?

The QT interval is measured from the start of the QRS complex to end of T wave on the ECG, thus it includes complete depolarization and repolarization of ventricles. The QT interval is related with heart rate. The normal QT interval at heart rates of 60-100 beats per minute is 300-400ms. In females it is 10% greater than males[17]. When QT interval is corrected for the heart rate it is designated as QTc. To calculate QTc Bazett's formula is used, (QTc=QT/ RR). Whenever the QTc interval is greater than 450ms, it is abnormally prolonged. The best leads to check QT interval on ECG is lead II, V2, or V3 or the lead, which shows maximum QT prolongation[18]. QTc has its own limitation as the risk of arrhythmia is more during slow heart rates and QTc is shorter than QT at heart rate

<60/min[19]. The formula to calculate QTc interval has recently been revised[20]. Several studies have demonstrated the frequency of malignant ventricular arrhythmias and sudden death with the length of the QT interval on the ECG in different patient populations[21,22,23,24,25,26]. Many drugs causing repolarization abnormalities may have their greatest effect during slow heart rates because of reverse use dependence in K^+ channel antagonist effect. Another mechanism is that of producing an increase in serum cateholamines levels causing myocardial excitability and arrhythmias especially when used in patients with underlying heart disease and in large doses.

Table 2: Drugs causing ventricular arrhythmias

Class	Drugs	
Antidepressants	Amitriptyline	(elavil)
	Doxepin	(sinequen)
	Impiramine	(tofranil)
	Trimipramine	(surmontil)
	Clomipramine	(anafranil)
	Despiramin	(nonpramin)
	Nortriptylin	(panelor)
	Protriptyline	(vivactil)
	Maprotiline	(ludiomil)
	Lithium	(eskalith)
Neuroleptics	Thioredazine	(milleril)
	Haloperidol	(haldol)
	Pimozide	(ofap)
	Trifluoperazine	(stelazine)
Antihistamines	Terfenadine	(seldane)
	Astemizol	(hismanol)
Antimicrobial	Erythromycin	
	Spiramycin	
	Trimethoprim-sulphamethoxazole	(septran)
	Pentamidine	
Antimalarials	Quinine	
	Chloroquine	(resochin)
	Halofantrine	(halfan)
	Hydroxychloroquine	
Antifungal	Amphoteracin	(conventional & liposomal)
	Ketoconazol	(nizarol)
Antiemetic	Chloropromazine	
Emetic	Ipecac	
Antiserotonin	Ketanserin	
Antiparkinsonism	Levodopa	
	Amantadine	(symeterel)
	Terodiline	
Bronchodilators	Salbutamol	(ventolin)
	Ephedrine	
	Adrenaline	
	Theophylline	
Hypnotics & Narcotics	Chloralhydrate	
	Cocaine	
	Heroin	
Antitachycardia	Adenosine	

Antidepressants:

Tricyclic antidepressants have potentially serious cardiovascular effects. These have class 1 like effect, thus reduce conduction velocity in purkinje fibers, APDs and the refractory periods and in ventricular tissues these are unaffected[27,28]. The most common ECG changes include ST-T wave changes, prolongation of QT, PR interval and QRS duration[2930,31]. The tricyclic have quinidine like effect and may exert both antiarrhythmic and proarrhythmig effect. The effectiveness of imipramine and nortriptyline as antiarrhythmic agents has been demonstrated in patients with and without depression[32,33]. There was several reports of ventricular arrhythmias when these drugs are used in patients with underlying heart disease especially conduction defects and depressed LV function[34] and when used in combination with phenothiazine like Thioredazine, Haloperidol[35,36]. Serious repolarization abnormalities, QT interval prolongation, Torsade-de-pointes have also been described with other antidepressant drugs like after maprotriline poisoning[37,38]. Serious arrhythmias have been published with lithium toxicity but are not associated with therapeutic level[40].

Neuroleptics:

The drugs in this particular group are commonly prescribed to psychiatric patients, often in high doses and in combination with other group of drugs. The cardiovascular mortality of patients with chronic psychosis exceeds that of the general population[41] .ECG abnormalities are common in patients taking phenothiazines, in 25% of patients[42]. In an other study 49% of patients have definite T wave abnormalities[43]. Numerous reports of ventricular arrhythmias with cardiac repolarization abnormalities including QT interval prolongation, abnormal T wave or large U wave in association with phenothiazines[44,45] often these occur in young adults and result in sudden death. About half the episodes occur within a month of initiating drug. Thioridazine when used in daily dose of >100mg cause QT, T &U wave abnormalities in 50% of treated causes[42,46,47] and maximum effect is produced within 4-5 days of starting therapy[47]. About half the pts with proarrthmia had recelived doses in excess of 800 mg /day. Occasionally doses <150mg/day have been involved[48] .The electrophysiology of Thioridazine is similar to quinidine and prolongs APDs in ventricular tissues[49,50] but not purkinje tissues[51,52] and produce its proatthythmic effect .VT and SCD has occurred in pts taking chlorpromazine is similar to quinidine and prolongs produce its proarrhythmic effect. VT and SCD have occurred in pts taking chlorpromazine but many of these patients were also taking Thioridazine. Trifluoperazine produce ECG changes[46] and reports of VT are rare. Torsade has also been reported with haloperidol especially

when used I.V[54]. Reports of unexplained sudden death associated with pimozide in dose excess of 20mg/day[55].

Antihistamines:

The newer non-sedating antihistamines especially astemizole and terfenadine have been used extensively for allergic problems in the recent year. Terfenadine is extensively studied regarding its cardiac toxicity. Ina study involving 27 patients[56,57]. Eleven were taking other drugs, 6 has cirrhosis or were alcoholic. At least 9 patients had one or more other factors that predisposed to Torsade-de pointes including pre-existing QT prolongation, heart disease or hypokalaemia. Terfenadine prolongs action potentials and refractory periods by blocking K+ channels. Terfenadine is converted in to active metabolites by the liver (Isoenzyme YP3A4).

The inhibitors of this isoenzyme like Ketoconazole[58], Itroconazole[59] Erythromycin[60] Trolendomycin increase the serum level of Terfenadine and produce the serious ventricular arrhythmias. In normal individuals and in recommended doses it does not prolong the QT interval. Torsade has been reported in pts using over doses of astemizole[61,62] polymorphic ventricular tachycardia has also been reported after use of recomended doses, however in one case the plasma level of astemizole were elevated[63]. Serious Torsade has been reported in Pts with pre-existing QT interval prolongation[64].0

Antimicrobials:

Erythromycin has dose related quinidine like effects slowing phase O, prolonging APDs and producing EAD[65], by blocking IK delayed rectifier channel. Erythromycin may cause QT prolongation of QT interval when given in combination with other drugs like terfenadine. QT prolongation and VT when given I.V in high dose It also prolongs QT interval when given in combination with other drugs like terfanadine. QT prolongation and cardiac arrest has been reported after spiramycin administration in an infant[66]. Reports have been published regarding repolarization abnormalities and ventricular arrhythmia with co-trimexazole[67] and pentamidine[68] when given I.V.

Antimalarials:

Quinine prolongs QTc but one third of the potency of quinidine[69]. Torsade has been reported with quinine and chloroquine at toxic level[70]. Halofantrine used to treat multi drugs resistant falsiparm malaria, causes does related prolongation of Qt. Interval and has been associated with bradycardia, heart block, syncope and death .Pts with prior QT prolongation are at a very high risk of SCD[71,72,73]. QT interval prolongation is more marked in patients who have already used mefloquine (It does not prolong QT if used alone.

Antifungal:

Ventricular arrhythmias has been described with conventional and liposomal amphotericin when given I.V. in patients with hyperkalaemia and renal failure, but reports have also been published in patients with normal electrolytes and renal function[74,75,76]. QT interval prolongation and ventricular arrhythmias is described with ketoconazole when used with terfenadine[77,78] .It probably does not prolong QT interval when used alone.

Antiemetic:

Chlorpromazine can produce ventricular tachyacardia and sudden death.

Emetic:

The principal alkaloid of ipecac are emetine and caphaeline. Emetine can have serious cardiovascular effects[79,80]. This drug is usually used by the psychiatric Pts with eating disorders having self induced vomiting and laxative abuse, which in addition can cause severe electrolyte imbalance and serious atrial and ventricular arrhythmias may occur and death has been reported[81,82].

Antiserotonin:

Eight cases have been reported with this new serotonin antagonist, ketanerin, producing QT producing and proarrhythmia. Seven of these have pre-existing quinidine or diuretic therapy[83].

Antiparkinsonism:

Amantidine an antiviral and antiparkinsonism agent structurally related to tricyclic antidepressants may also produce torsade in toxic level[84] especially in Pts with liver and renal disease. Levodapa act on dopaminergic receptors and can produce atrial and ventricular arrhythymias especially in Pts with ischemic heart disease[85].

Anticholinergic:

Terodiline, an anticholinergic drug with Ca+ blocking properties is used in PTS with urinary incontinence can produce cardiac dysrhythmia including bradycardia, heart block, ventricular fibrillation and VT usually of Torsade-de pointes type[86,87]. These are more common in Pts with preexisting ischemic heart disease, old age, and with other cardioactive drugs. Terodiline prolongs QTc interval and QT dispersion in asymptomatic individuals[88,89].

Bronchodilators:

Drugs used in bronchial asthma are alpha and beta-adrenergic stimulant and potentially can cause serious ventricular arrhythmias especially in patients with heart disease particularly with adrenaline, ephedrine and Aminophylline.

Hypnotics and Narcotics:

Torsade-de-pointes has been described after

chloralhydrate poisoning[90,91,92]. The cardiovascular effects of cocaine are complex[93,94,95]. Its effect resembles with class 1antiatthythmic drugs producing depression of depolarization and slowing of conduction velocity. Refractoriness of depolarization and slowing of conduction velocity. Refractoriness of atrial and ventricular muscle is also prolonged. PR, QRS and QT interval may be prolonged. VT of torsade type and ventricular fibrillation has been reported with cocaine abuse[96]. Heroin produce various electrocardiographic abnormalities_including prolongation of QT interval ST and T wave changes and various arrhythmias particularly bradyarrhythmias Sudden cardiac death has also been reported with heroin abuse[97].

Table 3: Other drugs

Clofibrate	Cholesterol lowering drug[97]
Amsacrine	Chemotherapeutic agent[101]
Taxine	(102)
Loratadine	Long acting antihistamine[103]
Succinylcholine	Drug used for myopathy[104]
Levomepromazine	Drug used as analgesic and sedative[105]

Table 4: Non pharmacological causes of Q.T. interval prolongation:

Cardiac
Ischemic heart disease
Myocarditis
Mitral valve prolapse
Rheumatic fever
Bradycardia
Bundle branch block.
Autonomatic imbalance:
Increased vagal tone.
Idiopathic QT prolongation.
Electrolyte imbalance:
hypokalaemia
Hypocalcemia.
Hypomagnesemia
Metabolic abnormalities:
Hypothyroidism
Alcoholism[106]
Hypothermia
Hypoparathyroidism
Low caloric diet
CNS causes:
Subarachnoid hemorrhage
Raised intracranial pressure
Head injuries.
Intracranial tumors

Antitachycardia:

Adenosine is a rapidly metabolized_endogenous purine nucleoside. It is a short acting useful drug in the treatment and diagnosis of cardiac arrhythmia .It is effective in terminating SVT involving atrioventricular node as a part of the circuit. Recently reports have been published regarding polymorphic VT induced with the administration adenosine especially in paients with preexisting organic heart disease[98,99]. Adenosine prolongs QTc interval in patients with positive stress test[100] QTc interval was analyzed in patients undergoing dypridamol or adenosine stress test to evaluate ischemia .It was found that QTc interval significantly prolonged in patients with positive stress test.

Many other drugs nor commonly used have the potential to produce repolarization abnormalities effecting QT interval and producing ventricular arrhythmias

It is very important for the clinician to know about the non-pharmacological causes, which can prolong the QT interval and may provide substrate for the life threatening arrhythmias when used with these drugs mentioned in Table 2&3.

Prevention:

As these drugs carry a clinically important risk of repolarization abnormalities, so a careful assessment of the risk-benefit ratio is important before prescribing these drugs. Following precautions should be taken.

1. These drugs should be avoided or extreme caution should be taken in Pts having pre-existing disease mentioned in Table -4.
2. A careful dose titration is important as most of these drugs produce their proarrhythmic effect in high or toxic doses.
3. One should be aware of interaction of these drugs, as some of these drugs produce there proarrhythmic effect when used with other potential drugs e.g. antihistamine when combined with antifungal and antibiotics and H2 receptors antagonist like cimetidine, ranatidine[107].
4. Sporadic ECG in psychiatric patients receiving antidepressant and other neuroleptic drugs is helpful. Majority of serious cardiac events occurs in the first six hours. Sinus tachycardia, QT, QRS prolongation and right axis deviation are important predictors of tricyclic toxicity[108,109].
5. These drugs should be avoided or very cautiously in low doses be given in patients with poor liver and renal function as majority of these drugs are metabolized in liver and excreted by the kidneys.

Management

Management is aimed at controlling arrhythmias until the drugs and its metabolites have been eliminated. For some agents it may take several days.

1. Any patient on these drugs presenting with palpitation, presyncope or syncope should

immediately have ECG, blood sample for electrolytes and drugs level be taken. Any change in QRS duration, QT interval, brady or tachycardia ST-T wave changes should be critically evaluated .It may also be appropriate to arrange ECG monitoring either in or out of hospital.

2. Immediately stop the offending drug.
3. Cardiovert the life threatening arrhythmia with D.C. shock. Do not use antiarrhythmic drugs as these may worsen the condition.
4. Correct electrolyte imbalance if present.
5. As these drugs produce their greatest proarrhythmic effect by prolonging QT interval during slow heart, so these arrhythmias are treated with atrial or ventricular pacing at rate of 90-100 /min. Isoprenaline infusion is an alternate if this facility is not available.
6. Magnesium infusion is effective in terminating Torsade-de-pointes even in normal serum Mg+ level[110,111,112].
7. Drug overdose especially tricyclic antidepressants may need gastric lavage and charcoal. Ipecac is not recommended for emesis. Gastric lavage is not recommended in comatose or sedated patients due to possibility of aspiration[113,114].

Abbrevations used:

VT -ventricular tachycardia. VF-ventricular fibrillation. APD -Action potential diastolic .SVT Supraventricular tachycardia .Pts -patients CNS- central nervous system

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