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Non-Cardiac Medications Induced QT Prolongation in Cardiac patients: A Retrospective Analysis

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Cardiac patients are generally treated with cardiac medications but, when they develop other common conditions, they may have to be given the necessary non-cardiac medications. There are few such medications which, when given to the cardiac patients produces a potentially lethal drug interaction. The main aim of the study was to evaluate the prescription of non-cardiac medications that could cause QT interval prolongation among cardiac patients. Materials and methods: The medical records of 100 cardiac patients were collected from both the outpatients and inpatients of cardiology department. The list of medications prescribed to each subject was recorded and classified as cardiac and non-cardiac medications. The ECG changes reported in the literature for both cardiac & non-cardiac medications were collected. Frequency analysis of these medications having effect on QT interval was analyzed. Among the 100 cardiac patients, there were 70 males and 30 females. 86 of them were inpatients and 14 were outpatients. Majority of the patients (63%) were in the age group between 51-70 years. Aspirin (80%) and paracetamol (20%) were found to be the most commonly prescribed cardiac and non-cardiac medications respectively. Many cardiac patients received non-cardiac medications which are known to cause changes in ECG. Hence, wherever possible these medications should be replaced by an appropriate alternative drug which does not cause ECG changes. In situations where prescription of these medications becomes unavoidable, they should be used with caution in recommended doses and for the optimal period to prevent adverse cardiac effects.

Keywords: Cardiac Medications; Cardiac Patients; Drug Interaction; ECG; Non-cardiac medications; QT interval.

Cardiac patients are usually treated with medications such as ACE inhibitors, beta blockers, calcium channel blockers, diuretics, nitrates, cardiac glycosides, antiarrhythmic drugs and other groups of drugs. These patients may develop other common conditions such as respiratory infections, gastrointestinal problems or genitourinary disorders and they may have to be given the necessary non-cardiac medications. There are few non-cardiac medications which, when given to the cardiac patients could affect the cardiac function, and thereby produces additive drug interactions between non-cardiac and cardiac medications which can be potentially

fatal.[1,2] Around 40-50% of all the deaths due to cardiovascular causes are because of sudden cardiac deaths (SCDs)[3-5] and about 80-85% of these deaths are caused by ventricular arrhythmias.[6-8] Prolongation of ventricular repolarization is considered to be an important etiological factor responsible for causing ventricular arrhythmia[9,10] which may provoke a condition called as torsades de pointes (TdP), a specific type of abnormal heart rhythm that can lead to SCDs.[11-13]

One of the important risk factor thought to be responsible for TdP is the use of QT prolonging drugs.[14] QT prolongation can either be congenital or acquired.[15] While congenital QT prolongation is an inherited condition[16], acquired QT prolongation is most often drug-related.[17] There are certain factors that predispose the patients to QT prolongation/TdP and that include: age more than 65 years, female gender, bradycardia, diseases like hypertension, heart failure, myocardial ischemia, diabetes mellitus, hyperthyroidism, electrolyte abnormalities such as hypokalemia, hypocalcemia and hypomagnesaemia and use of certain cardiac and non-cardiac medications.[18-24]

QT prolongation is a well known side effect of the cardiac medications, mainly anti-arrhythmic medications,[25] but it can also occur with many non-cardiac medications.[26-30] The list of medications that are associated with QT prolongation/TdP are given below in table 1.

In the recent years, several non-cardiac medications have been withdrawn or restricted from its use in the market because of its potential to cause QT prolongation/TdP and sudden cardiac death. [10, 11, 31-33]

When these non-cardiac medications are given to cardiac patients, it becomes evident that the pro-arrhythmogenic potential of those medications can pose a significant public health problem[34] and there is a possibility for lethal drug-drug interactions.[35-39] So such medications need to be identified and a suitable alternative should be prescribed.

Hence, this retrospective study has been planned to evaluate the prescription of non-cardiac medications that could cause QT interval prolongation among cardiac patients.

MATERIALS AND METHODS

Before initiating the study, Institutional ethics committee clearance (IHEC/05/2013/Desp. No.265/Dt:27.11.2013) was obtained.

This is a type of observational study which was conducted retrospectively by collecting the data from the medical records of 100 cardiac patients who have attended the outpatient department of cardiology and also admitted in the cardiology ward as inpatients. The personal identity of the patients was not revealed in any part of the manuscript. All the data collected from the patients was analyzed for the lists of medications prescribed to them and were recorded. It was then classified into cardiac and non-cardiac medications. The influence of these cardiac and non-cardiac medications on ECG was gathered through literature search. The effect of non-cardiac medications on the ECG, particularly QT interval was recorded and evaluated.

Inclusion criteria

1. Medical records of patients who were taken the cardiac or non-cardiac medications that are known to cause QT prolongation were included in the study
2. Both sexes were included in the study and the upper age limit was set at 70 years

Exclusion criteria

1. Medical records of patients with other causes for QT prolongation such as heart failure, myocardial ischemia, hypertension, diabetes mellitus, hyperthyroidism, and electrolyte abnormalities such as hypokalemia, hypocalcemia and hypomagnesemia were excluded from the study

The data generated from this study was entered in Microsoft excel sheet. Descriptive analysis was done for all the categorical variables such as age, gender, category of medications and data were expressed as frequencies (percentages).

RESULTS AND DISCUSSION

The analysis of the medical records of 100 cardiac patients showed that 86 of them were inpatients and 14 were outpatients.

The frequency analysis of the different characteristics of the study participants such as

Table 1. Examples of medications that have association with QT prolongation/TdP

Cardiac medications	Non-cardiac medications
Antiarrhythmic drugs	Antipsychotic drugs
Quinidine	Haloperidol
Amiodarone	Thioridazine*
Procainamide	Chlorpromazine
Disopyramide	Queitapine
Dofetilide	Risperidone
Ibutilide	Ziprasidone
Sotalol	Clozapine
Cardiovascular drugs	Antidepressant drugs
Bepridil	Amitriptyline
Dopamine	Desipramine
Dobutamine	Citalopram
Adrenaline	Escitalopram
Indapamide	Doxepin
Isradipine	Fluoxetine
Nicardipine	Sertraline
Moexipril	Venlafaxine
	Antihistaminic drugs
	Terfenadine*
	Astemizole*
	Antimotility drugs
	Domperidone
	Cisapride*
	Antiemetic drugs
	Ondansetron
	Dolasetron
	Antimicrobial drugs
	Levofloxacin
	Moxifloxacin
	Grepafloxacin*
	Sparfloxacin*
	Erythromycin
	Azithromycin
	Metronidazole
	Antimalarial drugs
	Quinine
	Chloroquine
	Antifungal drugs
	Ketoconazole
	Fluconazole
	Antiprotozoal drugs
	Pentamidine
	Antiviral drugs
	Amantadine
	Anticancer drugs
	Tamoxifen
	Nilotinib
	Lapatinib

* Drugs withdrawn or restricted from its use in the market

age, sex and the category of medications is listed below in table 2.

The above frequency analysis table represents that among study participants, 70% were males 30% are females. Most of the participants (63%) were in the age group between 51-70 years. The analysis also showed that the study participants had higher incidence of taking non-cardiac medications (64%) than cardiac medications (36%).

Eroglu TE et al in their study observed that the users of non-cardiac QT prolonging medications have a higher risk of SCDs and death than users of cardiac QT prolonging medications. They also showed that women are more vulnerable to QT prolongation and confer a higher SCDs risk than men and that their risk was more elevated with non-cardiac QT prolonging medications.[8]

In a population-based study by Straus SM et al, even with more modest QT prolongation, nearly three-fold risk of SCDs were observed in approximately 8000 elderly men and women over the age of 55 years.[40]

Cardiac medications and QT interval

The cardiac medications which were given to the cardiac patients include aspirin, clopidogrel, enalapril, metoprolol, carvedilol, amlodipine, nitroglycerine and digoxin. Among these medications, aspirin (80%) was the most commonly prescribed cardiac medication in cardiac patients. The list of commonly prescribed non-cardiac medications to the cardiac patients is given below in figure 1.

From the list of cardiac medications prescribed to the cardiac patients, it was found that none of the patients were found to be taking cardiac medications that have significant effect

Table 2. Frequency analysis of the different characteristics of the study participants

Age (in years) n=100	
30-50	37
51-70	63
Sex n=100	
Male	70
Female	30
Medications	
Cardiac	36%
Non-cardiac	64%

on QT interval in ECG. The most commonly prescribed cardiac medications in our study are aspirin, clopidogrel and metoprolol. However, there are no any reports or evidences to prove the fact that these cardiac medications have an effect on QT interval prolongation.

Non-cardiac medications and QT interval

The non-cardiac medications that were given to the cardiac patients include paracetamol, domperidone, azithromycin, ciprofloxacin, levofloxacin, cotrimoxazole, fluoxetine, amitriptyline fluconazole and ketoconazole. Among these medications, paracetamol (20%) was the most commonly prescribed non-cardiac medication in cardiac patients. The list of commonly prescribed non-cardiac medications to the cardiac patients is given below in figure 2.

From the list of non-cardiac medications prescribed to the cardiac patients, it was found through literature search that 60% of the non-

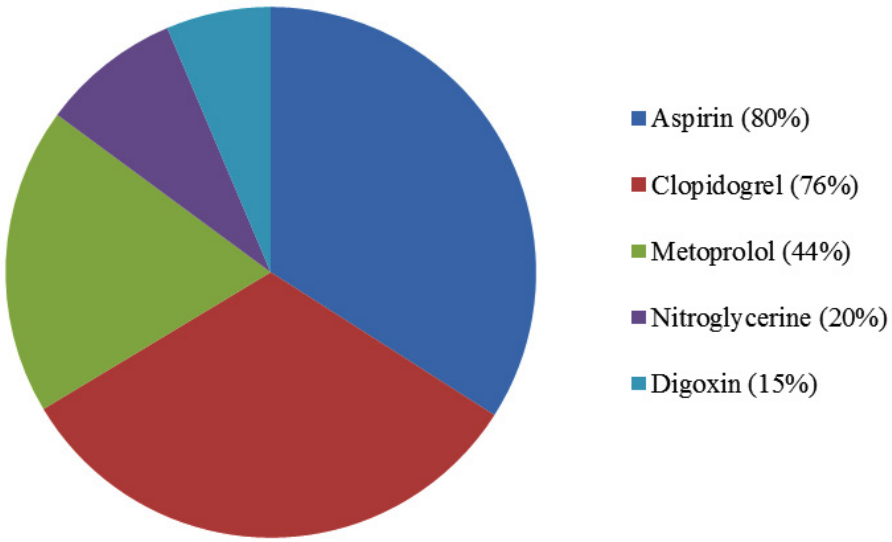

Fig. 1. List of Commonly prescribed cardiac medications

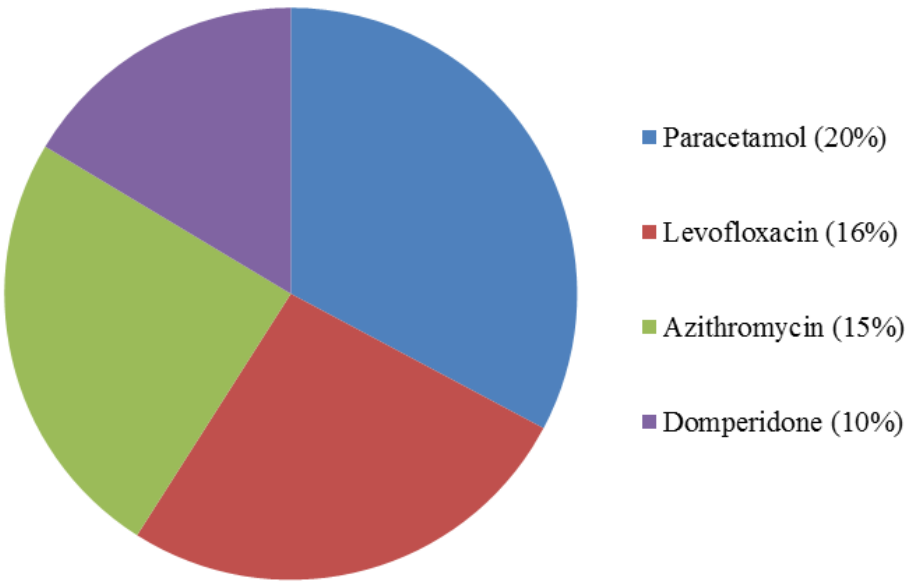

Fig. 2. List of commonly prescribed non-cardiac medications

cardiac medications have significant effect on QT interval in ECG. [26,28-31] Among the prescribed non-cardiac medications, the drugs that were found to significantly affect the QT interval in ECG include levofloxacin, azithromycin, domperidone, amitriptyline and fluconazole. There are many literature evidences available to prove the fact that these commonly prescribed non-cardiac medications have a significant effect on QT interval. However, there are no any reports of QT interval prolongation documented with the most commonly prescribed non-cardiac medication in our study, paracetamol.

An observational study conducted by Li K et al to determine the effect of intravenous ondansetron on QT interval showed that administration of 4 mg intravenous ondansetron showed a significant increase in QT interval (p-value < 0.05).[41]

In a study done by Field J et al, it was observed that domperidone at the conventionally used doses causes QT prolongation in 6% of patients.[27]

Catelya LG et al studied about the effect of levofloxacin on QT interval in 24 patients who received 500 mg of the drug once daily. Of all the patients who received levofloxacin, six patients (25%) had developed QT prolongation and two of them showed significant QT prolongation (p-value < 0.05).[42]

In a study done by Choi Y et al, to evaluate the risk of exposure of the antibiotic azithromycin on QT prolongation, it was showed that the risk of QT prolongation was increased in the elderly people aged between 65-79 years.[43]

In a retrospective, observational study conducted by Funai Y and colleagues on 87 patients receiving tricyclic antidepressants (TCAs) it was found that TCAs even at lower than normal doses significantly prolonged the QT interval (p value < 0.01).[44]

In one case study report by Tholakanahalli VN et al, a 68-year-old female patient was given oral fluconazole for her Candida infection with otherwise no any risk factors for TDP. The patient was normal for 7 days after starting fluconazole and on day 8, she suddenly developed TDP which gets resolved when fluconazole was discontinued.[45]

Assumptions and limitations

As the data this study was collected retrospectively from the case sheets of the cardiac patients, only limited information available in the case sheets could be considered. Inclusion of more number of subjects and prospective collection of data would have added more value to the present study.

Future extension of the work

The authors are planning to collect the same data prospectively in cardiac patients and to assess the ECG changes with various non-cardiac medications.

CONCLUSION

Cardiac patients frequently receive medications for other associated ailments. These non-cardiac medications may affect the cardiac functions and influence the effect of cardiac medications. From this study, it was found that many cardiac patients received non-cardiac medications that significantly affect the QT interval. Hence, wherever possible these medications should be replaced by any other suitable one that does not affect the heart. If it is not possible, these medications should be used with caution as per recommended dose for very short period to avoid any cardiac effects such as myocardial infarction, heart failure and life threatening ventricular arrhythmias including TdP. Since the development of TdP is rare and multifactorial, the knowledge on drug that causes QT prolongation/TdP is essential while treating patients.

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Conflict of Interest

There is no conflict of interest.

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