ELECTROCARDIGRAPHIC EVALUATION OF QT PROLONGATION IN ANAESTHETIZED GUINEA-PIG: AN EXPERIMENTAL METHOD TO PREDICT THE TORSADOGENIC POTENTIALITY OF DRUGS

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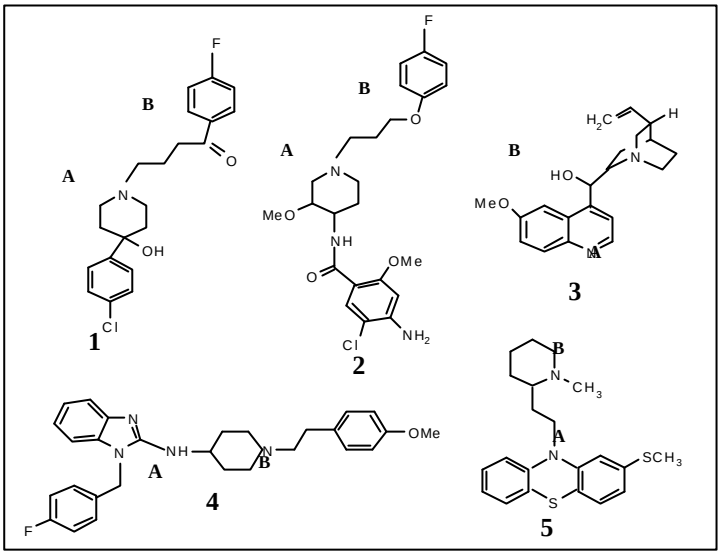
An uncommon cardiac disease is the long QT syndrome (LQT), characterized by a prolongation of the QT interval on the electrocardiogram (ECG). It is occasionally fatal, because it can produce a polymorphic ventricular tachycardia (torsade de pointes, TdP), which may cause ventricular fibrillation and then sudden death. The LQT syndrome is a disorder of cardiac repolarization caused by alterations in transmembrane ionic currents and can be congenital or acquired.
The congenital form is caused by mutations of genes encoding for the transmembrane ion-channel proteins. Actually, seven forms of LQT congenital syndrome are known (LQT_{1-7}); in particulary the LQT_1, LQT_2, LQT_5 and LQT_6 forms are associated with mutations in the genes encoding for the K^+ channels, the LQT_3 form is provoked by mutations in the gene that codes for Na^+ channel, while the aetiology of LQT_4 and LQT_7 forms is still unknown.
The acquired form can be also caused by several cardiovascular and non-cardiovascular drugs; such as antiarrhythmics, antipsicotics, antimicrobics, antimycotics, antihistaminic agents, cisapride and others. These compunds have different chemical structures and different therapeutic uses, but they have in common the ability to block the HERG K^+ channels, responsible for rapid voltage-gated K^+ current (I_{Kr}), which play an important role in the cardiac repolarization process; therefore these drugs prolong the action potential duration [1].
In fact, the cardiac action potential is controlled by a delicate equilibrium of inward and outward ionic flows and usually it is divided into five periods, depending on the prevalent type of ionic current. The entry of Na^+ and Ca^{++} into the cytosol is responsible of depolarizing currents (I_{Na}, I_{Ca}); whereas the exit of K^+ from the myocardiocytes causes repolarizing currents (I_{to}, I_{Kr}, I_{Ks}, and I_{KI}), leading the membranal potential to resting values.
The whole of all these microcurrents makes up the cardiac action potential, and the ECG reflects the sum of action potentials of all cardiomyocytes.
On the ECG, the first deflection (P wave) reflects the atrial depolarization, instead the QRS complex (composed by a small negative Q wave, a large positive R wave and a small negative S wave) represents the ventricular repolarization. Subsequently, a broad positive deflection (T wave) reflects the ventricular repolarization.
Usually, the QT interval is measured to determine the ventricular repolarization duration. Since the heart rate greatly influences this parameter, the QT interval is correlated with the heart rate (QTc). Several formulae are used, but the most popular is the Bazzet's formula (QTcB), where QT interval is divided by square root of RR interval (i.e. the inverse of the cardiac frequency).
Although in past time studies on drug-induced QT prolongation have been executed by elaborate but also expensive techniques (as expression systems of HERG channel), recently the possibility to use simpler and economical methods has called attention of researchers.
Therefore, the first aim of this doctorate work is: 1) to set-up a method to detect QT interval on experimental animals, 2) to analize the torsadogenic potentiality of drugs, and 3) to compare the chemical characteristics, to identify a possible structure-activity correlation.
To set-up the method, drugs, belongig to different therapeutic classes and already known in literature as torsadogenic, were used; they were: cisapride, astemizole, haloperidol, thioridazine and quinidine (Fig.1). They have provoked events of QT prolongation, TdP and several lethal events in humans; hence some of these are withdrawed from commerce [2].
The drugs have been tested on male guinea-pigs (380-430 g) anaesthetized by pentobarbital (60 mg/Kg i.p.) and were administered cumulatively by intravenous injections (i.v.). The ECG was recorded, by electrodes inserted in subcutaneous layer of guinea-pig limbs, at interval of 5,10, 20, 30 minutes after each administration. The QT interval was read in Lead II or Lead III.
All drugs produced a prolongation of QT interval and a reduction of cardiac frequency (increase of RR interval), also the QTcB value was increased.
The maximal increase (in ms) of QTcB value at the dose of 10 mg/Kg i.v. permitted to estabilish an efficacy scale: haloperidol> astemizole > cisapride> thioridazine> quinidine (Tab. 1).

As potency index, to compare drugs, the dose producing an increase of 50 ms of QTcB value has been considered. This evaluation permitted to estabilish a potency scale for drugs tested: cisapride> haloperidol> thioridazine> astemizole> quinidine (Tab. 1), that reflects indexes of potency measured on cloned HERG channels (cisapride> haloperidol> astemizole> thioridazine> quinidine) by several laboratories (Database: http://www.fenichel.net/QT%20stuff/pic50rat.htm).
In conclusion, the measurement of QT interval on ECG, in this experimental conditions, can be considered a valid method to analize the torsadogenic potentiality of drugs.
Finally, although these drugs belong to different therapeutic classes and present affinity for different pharmacological targets, they have in common a chemical characteristic, consisting of an aliphatic spacer chain with 3 or 4 C atoms, between a hindered basic nitrogen atom (A) and an aminic, hydroxyl or carbonyl group (B). This structural requisite could probably account for the interaction with the cardiac HERG K^+ channels.

Fig.1



1.haloperidol; 2. cisapride; 3. quinidine; 4. astemizole; 5. thioridazine.

Tab.1

Drugs	**Efficacy index** (ms)	**Potency index** (mg/Kg i.v.)
astemizole	128.1	1.1
cisapride	92.3	0.27
haloperidol	133.8	0.37
quinidine	79.3	1.8
thioridazine	84.6	0.61

References

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