# EARLY, RAPID AND INEXPENSIVE IN VIVO EVALUATION OF POTENTIAL QTc PROLONGATION


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## INTRODUCTION

Evaluation of the potential of a new chemical entity (NCE) to delay ventricular repolarization has been largely emphasized through regulatory recommendations since several non-cardiac drugs have been withdrawn because of an effect on QT interval prolongation inducing fatal ventricular tachyarrhythmias such as "torsades de pointes".

Most of preclinical strategies for cardiovascular safety evaluation of an NCE include electrophysiological recordings in vitro on isolated cells and cardiac tissues as well as in vivo measurement of QT prolongation in various dog preparations.

For economical and ethical reasons, there is a need for an in vivo model allowing early and rapid assessment of cardiovascular safety of an NCE and predictive of a potential torsadogenicity through delayed ventricular repolarization.

We therefore aimed to set up a model of pentobarbital-anaesthetised guinea-pig, a species known to possess the specific ion channels similar to those in humans.

## MATERIALS AND METHODS

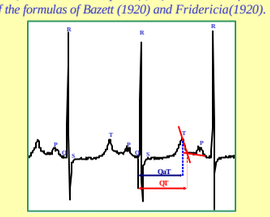
**Animals :** *Male Dunkin Hartley guinea-pigs / 250-400 kg (n = 6 in each group)*

*Standard housing conditions:*
- *Room Temperature : 18±2°C*
- *Hygrometry : 55±10%*
- *Light/dark cycle : 12h/12h*
- *Tap water and food (SAFE 106) : ad libitum*

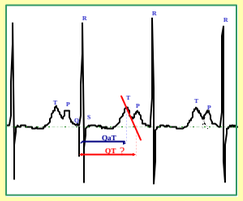
**Parameters measured:**
- *Heart rate (HR, bpm),*
- *ECG parameters (RR, PR, QRS, QT, QTcB, and QTcF intervals, ms),*
- *Systolic, diastolic and mean arterial pressures (mmHg),*
- *Left ventricular systolic pressure (LVSP, mmHg),*
- *dP/dt max (mmHg), dP/dt min (mmHg).*

**Surgical procedure:**
- *Anaesthesia with sodium pentobarbital (60 mg/kg, i.p.), body temperature : around 37° C,*
- *Artificial ventilation with $O_2$-enriched room air through tracheotomy (pH, $PO_2$ and $PCO_2$ within the physiological range).*
- *Catheters introduced into the jugular vein (for i.v. administrations) and carotid arteries (for the monitoring of arterial blood and left ventricular pressures and heart rate).*
- *Subcutaneous needle electrodes for ECG measurement, lead II.*

**Determination of QT and QaT intervals :** *ECG parameters manually measured (on six consecutive beats) from the print-out using a digitising table. QT interval measured from the beginning of the Q wave to both the peak (QaT) and the end of the T wave and corrected for changes in heart rate by use of the formulas of Bazett (1920) and Fridericia(1920).*




*Low Heart Rate*

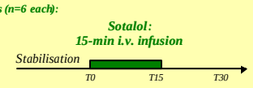


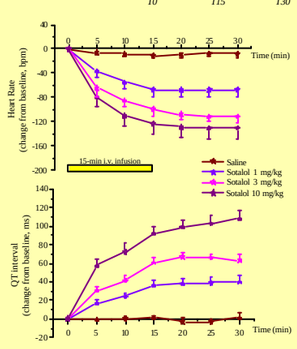

*T-P overlap at higher Heart Rate*

## RESULTS

**Kinetic of action of Sotalol on Heart Rate and QT in independent animals**

*Experimental groups (n=6 each):*
- *vehicle (saline)*
- *sotalol 1 mg/kg*
- *sotalol 3 mg/kg*
- *sotalol 10 mg/kg*

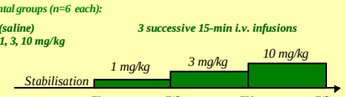


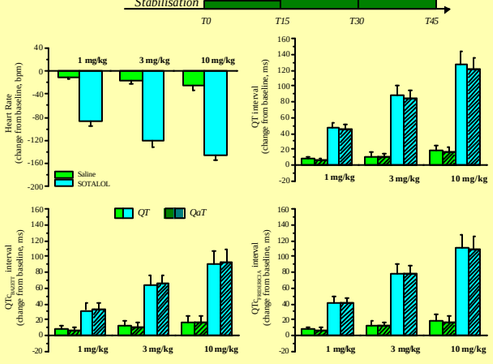




*Sotalol dose-dependently decreases Heart Rate and increases QT interval with maximal effects observed within 15 min following infusion.*

**Effects of increasing doses of Sotalol on Heart Rate, QT and QTc intervals Comparison between QT and QaT determination**

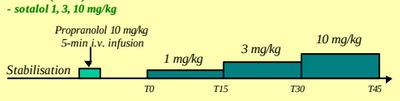
*Experimental groups (n=6 each):*
- *vehicle (saline)*
- *sotalol 1, 3, 10 mg/kg*



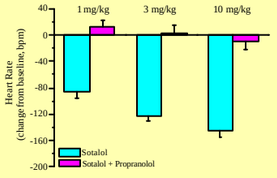




*Successive infusions of increasing doses of Sotalol dose-dependently decreases Heart Rate and increases QT and QTc intervals. QT and QaT determination led to similar results.*

*Experimental groups (n=6 each):*
- *vehicle (saline)*
- *sotalol 1, 3, 10 mg/kg*

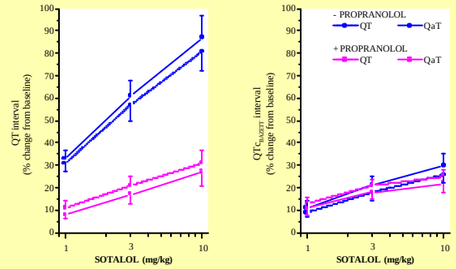



**Effects of Propranolol on Sotalol-induced bradycardia**




*Pretreatment with Propranolol completely blunts sotalol-induced bradycardia.*

**Effects of Propranolol on Sotalol-induced increase in QT and QTc intervals Comparison between QT and QaT determination**




*Sotalol-induced increase in QT is markedly reduced by propranolol pretreatment.*
*Sotalol-induced increase in QTc is similar in both conditions.*
*After propranolol pretreatment, QT and QTc intervals are almost similarly increased.*
*QT and QaT determination led to similar results.*

**Effects of Propranolol on Heart Rate, QT and QTc intervals**

| (n=12) | Propranolol (10 mg/kg) Before | After | |
|---|---|---|---|
| Heart Rate (bpm) | 287±27 | 195±30 | *** |
| QT interval (ms) | 151±11 | 178±17 | ** |
| $QTc_B$ | 329±12 | 319±24 | |
| $QTc_F$ | 254±12 | 262±20 | |

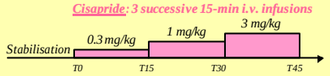
*Propranolol by itself decreases Heart Rate and increased QT interval but has no effect on QTc interval*

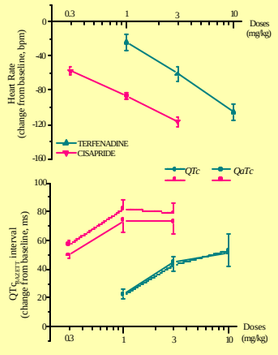
**Effects of Cisapride and Terfenadine on Heart Rate, QT and QTc intervals Comparison between QT and QaT determination**

*Experimental groups (n=6 each):*
- *vehicle (NaCl/DMSO/HCl)*
- *terfenadine 1, 3, 10 mg/kg*
- *cisapride 0.3, 1, 3 mg/kg*

*Terfenadine: 3 successive 15-min i.v. infusions*


*Cisapride: 3 successive 15-min i.v. infusions*




*Injection of increasing doses of Cisapride and Terfenadine dose-dependently decreases Heart Rate and increases QTc intervals. QT and QaT determination led to similar results*

## CONCLUSION

The present study shows that the pentobarbital-anaesthetised guinea-pig model is able to detect an increase in QTc induced by Sotalol (a β-adrenoceptor antagonist), Terfenadine (an histamine $H_1$ receptor antagonist) and Cisapride (a serotonin 5-$HT_4$ receptor agonist), three compounds known to delay ventricular repolarization in human.

Thus, this model represents a useful test to assess the potential for QTc prolongation of new chemical entities. When combined with measurement of other cardiovascular parameters and drug plasma levels, it can be a rapid and low-cost screening procedure to evaluate routinely the cardiac safety profile of drug candidates.

Whether this test should be limited to early discovery or included in the core battery remains to be discussed.

## REFERENCES


[1] DE CLERCK F. et al. (2002). In vivo measurement of QT prolongation, dispersion and arrhythmogenesis : application to the preclinical cardiovascular safety pharmacology of a new chemical entity. Fund. Clin. Pharmacol., **16**, 125-140.

[2] HAUSER D.S. et al. (2005). Cardiovascular parameters in anaesthetized guinea pigs: a safety pharmacology screening model. J. Pharmacol. Toxicol. Methods, **52**, 106-114.

[3] HAYES E. et al. (1994). Relationship between QaT and RR intervals in rats, guinea pigs, rabbits, and primates. J. Pharmacol. Toxicol. Methods, **32**, 201-207.

[4] TESTAI L. et al. (2004). QT prolongation in anaesthetized guinea-pigs: an experimental approach for preliminary screening of torsadogenicity of drugs and drug candidates. J. Appl. Toxicol., **24**, 217-222.