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repolarization has been largely emphasized through regulatory recommendations since several non-cardiac drugs have been withdrawn because of an effect on QT interval prolongation inducing fatal ventricular tachyarrhythmias such as “torsades de pointes”.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.

RESULTS

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

Sotalol-induced increase in QTc is similar in both conditions. QT and QTc determination led to similar results.

Sotalol-induced increase in QT is markedly reduced by propranolol pretreatment. Pretreatment with Propranolol completely blunts sotalol-induced bradycardia.

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 H1 receptor antagonist) and Cisapride (a serotonin 5-HT3 receptor agonist), three compounds known to delay ventricular repolarization in humans.

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.

REFERENCES


