The Differential Effect of Nembutal and Ketamine/Xyloidone Anesthetic on Dofetilide-Induced QT Interval Prolongation

Liomar A. Neves, Hongjian Wang, Olga Tinakova, Jinbao Huang, Peter B. Senese, Michael R. Gralinski

CorDynamics, Inc., Chicago, IL - www.cordynamics.com

Abstract #902

Introduction

The anesthetized guinea pig is a widely used model for early screening of drug-candidate effects on cardiovascular function. They are excellent for predicting the potential of a test article to delay ventricular repolarization in humans as they have similar cardiac action potential and ECG characteristics. Many anesthetics have been studied in this model but sodium pentobarbital is the most widely used. Studies have documented that sodium pentobarbital is an antagonist of the inward rectifying cardiac potassium channel (IKr). Since the IKr is a component of the guinea pig cardiac repolarization sequence, this species can be exquisitely sensitive to IKr blockade. Because anesthetics can alter the sensitivity of a preparation to test articles it is necessary to assess its vulnerability in the guinea pig QT model. In this study we assessed the hemodynamic effects of increasing doses of dofetilide in the Nembutal and ketamine/xylazine anesthetized guinea pig model. Dofetilide is a Class III antiarrhythmic drug that increases refractoriness by antagonizing IKr. It has been associated with QTc prolongation and TdP arrhythmias in humans.

Objectives

Assess vulnerability of the Nembutal and ketamine/xylazine anesthetized guinea pig for safety pharmacology screening of drugs with potential to prolong the QT interval.

Methods

Surgical Preparation: Male Dunkin Hartley guinea pigs (400-44 mg/kg) were anesthetized with ketamine/xylazine (5.7/3 mg/kg IP, maintenance dose 44 mg/kg IP), or Nembutal (60 mg/kg IP, maintenance dose 50 mg/kg IP). Male guinea pigs were administered vehicle (10% hydroxypropyl beta cyclodextrin in saline) or dofetilide (0.25, 0.5, 1, 2, and 4 mg/kg) in 0.5 mL/kg of 10% hydroxypropyl beta cyclodextrin in saline (subject to doxylide: 0.0025, 0.005, 0.01, 0.02, 0.04, and 0.08 mg/kg, 0.5 mL/kg) and animals anesthetized with ketamine/xylazine received vehicle (10% hydroxypropyl beta cyclodextrin in saline) as a control. Hemodynamic and electrocardiographic measurements were determined for all groups. Administration of doxylide to either Nembutal or ketamine/xylazine anesthetized guinea pigs increases refractoriness by antagonizing IKr. It has been associated with QTc prolongation and TdP arrhythmias in humans. Anesthesia - Nembutal

Conclusion

In summary, the choice of anesthetic appears to influence the maximum QTc increases in anesthetized guinea pigs. Sodium pentobarbital anesthetized guinea pigs are more sensitive to QTc interval prolongation; and this should be the anesthetic of choice when screening agents for the potential to prolong QTc interval.