Effect of Anesthetic on QT Interval Measurements in Guinea Pigs

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Anesthetized guinea pig is a widely used model for early screening of drug-candidate effects on cardiovascular function. This species is gaining traction for use in conscious screening telemetry studies. For unconscious work, the majority of published studies use sodium pentobarbital (NaP) as the anesthetic of choice. However, NaP is an antagonist of the inward rectifying cardiac potassium channel IKs. Since the IKs is a component of the guinea pig cardiac repolarization sequence, this species can be exquisitely sensitive to IKs blockade. In this study we investigated the baseline vulnerability of the anesthetized guinea pig for safety pharmacology screening of drugs with potential to prolong the QT interval. Male guinea pigs (400-550g) were anesthetized with ketamine/xylazine (87/5 mg/kg, KET) or NaP (15-30 mg/kg) and surgically instrumented with a Millar catheter to measure arterial pressure. Electrocardiograms were recorded and PR interval, QRS duration, QT/QTc interval and arrhythmogenesis were monitored. Monitored parameters were compared with measurements obtained previously in conscious guinea pigs (CON). NaP anesthetized guinea pigs exhibited baseline QTcB intervals (342±3 ms, p<0.05) that were significantly increased compared to CON cohort (256±6 ms). QTcB intervals in the KET group (307±7 ms, p<0.05) were also increased as compared to CON group, but the changes were significantly less robust. Lower HR was observed in the KET group (215±9 bpm, p<0.05) as compared to CON (258±13 bpm) and NaP (250±6 bpm) groups. QRS duration was increased in the KET (45±0.8 ms) and NaP (44±0.3 ms) groups as compared to CON guinea pigs (29±1.3 bpm, p<0.05). No change in mean arterial pressure was observed between the groups. In summary, the choice of anesthetic appears to influence the QT interval in anesthetized guinea pigs compared to conscious animals. It is possible that anesthetics with additional inherent IKs blockade may overly sensitize the animal to agents that prolong the electrocardiographic QT interval. Consideration should be taken when selecting anesthetics for this model.

Introduction

The anesthetized guinea pig is a widely used model for early screening of drug-candidate effects on cardiovascular function. In recent years, this species is gaining traction for use in conscious telemetry screening. However, the vast majority of cardiac safety studies are performed in anesthetized guinea pigs with sodium pentobarbital as the anesthetic of choice. Is it well documented that sodium pentobarbital is an antagonist of the inward rectifying cardiac potassium channel IKs. Since the IKs is a component of the guinea pig cardiac repolarization sequence, this species can be exquisitely sensitive to IKs blockade. In this study we investigated the baseline vulnerability of the guinea pig anesthetized with ketamine and Nembutal for safety pharmacology screening of drugs with potential to prolong the QT interval.

Objectives

Investigate the baseline vulnerability of the anesthetized guinea pig for safety pharmacology screening of drugs with potential to prolong the QT interval.

Methods

Surgical Preparation: Male Dunkin Hartley guinea pigs (400-550g) were anesthetized with ketamine/xylazine (87/5 mg/kg IP, maintenance dose 44 mg/kg IP) or Nembutal (60 mg/kg IP, maintenance dose continuous IV infusion 6mg/kg/h). Once consciousness was lost, a Millar pressure catheter was placed in the carotid artery to measure arterial pressure. A lead II electrocardiogram was monitored throughout the experiment via electrodes placed in the skin of the right arm, left leg and chest of the animal. Body temperature was also monitored throughout the experiment. The jugular vein was cannulated for test compound administration. Animals anesthetized with Nembutal were also instrumented with an endotracheal tube for mechanical ventilation (~60 breaths/min with a tidal volume of ~7-8 mL/kg).

Experimental Plan: ECG and blood pressure were continuously monitored throughout the experiment with the NOTOCORD-Hem (Software 4.3 NOTOCORD Inc., Croissy sur Seine, France) data capture system. Individual animals were deemed acceptable for use in the study if they exhibited acceptable hemodynamic parameters during the approximate 15-30 minutes equilibration period. Baseline hemodynamic and electrocardiographic parameters were obtained for 15 minutes followed by escalating doses of dofetilide administered into a jugular vein. Guinea pigs anesthetized with ketamine received 0, 0.1 and 0.3 mg/kg dofetilide at 2 mL/kg over a period of 1 minute followed by 29 minute-recovery period. Animals anesthetized with Nembutal received 0, 0.0025, 0.005, 0.01, 0.02, 0.04, and 0.08 mg/kg dofetilide at 0.5 mL/kg over a period of 5 minutes followed by 10 minute-recovery period

Hemodynamic and Electrocardiographic Measurements: Average values taken from 20 second blocks of consecutive cardiac cycles uninterrupted by interference of ectopic beats were used for analysis. Measurements were taken at baseline, and every 1 minute during the monitoring period. The monitoring period began at the initiation of that test period's respective dose. Values from each individual animal were pooled to determine an average for each variable for each group. Monitored parameters were compared with measurements obtained previously in conscious telemeterized guinea pigs.

Effects of Anesthetic on Mean Arterial Pressure, Heart Rate, PR Interval and QRS Duration in the Guinea Pig

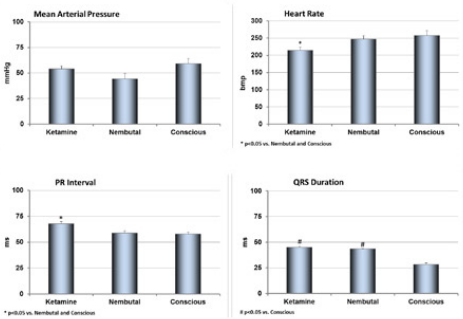
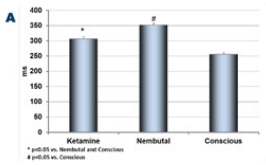


Figure 1. *Effects of ketamine and Nembutal on baseline mean arterial pressure, heart rate, PR interval and QRS duration in guinea pigs. Data obtained in anesthetized guinea pigs were compared with measurements obtained previously in conscious telemeterized guinea pigs. Values are expressed as mean±SEM, with n=4-8. Data were analyzed by using a one-way ANOVA followed by post hoc Newman-Keuls test.*

Effects of Anesthetic on QTcB Interval in the Guinea Pig



Effects of Anesthetic on Potency of Dofetilide to Increase QTcB Interval in the Guinea Pig

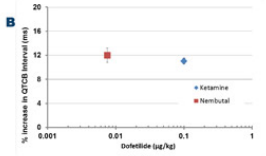


Figure 2. *A- Effects of ketamine and Nembutal on baseline QTcB duration in guinea pigs. Data obtained in anesthetized guinea pigs were compared with measurements obtained previously in conscious telemeterized guinea pigs. B- Maximal % of change in QTcB interval with 0.1mg/kg and 0.0075 mg/kg dofetilide in guinea pigs anesthetized with ketamine and Nembutal, respectively. Values are expressed as mean±SEM, with n=2-3. Data were analyzed by using a one-way ANOVA followed by post hoc Newman-Keuls test.*

Summary

- Nembutal anesthetized guinea pigs exhibited baseline QTcB intervals (352±7 ms, p<0.05) that were significantly increased compared to conscious cohort (256±6 ms).
- QTcB intervals in the ketamine group (307±7 ms, p<0.05) were also increased as compared to conscious group, but the changes were significantly less robust.
- The dose of dofetilide that produced approximately 10% maximal increase in QTcB was approximately 13 times higher in guinea pigs anesthetized with ketamine as compared to Nembutal. However complete dose response curves with dofetilide in ketamine anesthetized guinea pigs is warranted.
- Lower HR was observed in the ketamine anesthetized group (215±9 bpm, p<0.05) as compared to conscious (258±13 bpm) and Nembutal (247±10 bpm) groups.
- QRS duration was increased in the ketamine (45±0.8 ms) and Nembutal (44±0.2 ms) groups as compared to conscious guinea pigs (29±1.3 bpm, p<0.05).
- No change in mean arterial pressure was observed between the groups.

Conclusion

In summary, the choice of anesthetic appears to influence the QT interval in anesthetized guinea pigs compared to conscious animals. It is possible that anesthetics with additional inherent IKs blockade such as sodium pentobarbital may overly sensitize the animal to agents that prolong the electrocardiographic QT interval. Consideration should be taken when selecting anesthetics for this model.