

Comparison of effects of sugammadex and neostigmine on QT_c prolongation in rabbits under general anesthesia¹

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ABSTRACT

PURPOSE: To compare the effects of sugammadex and neostigmine, used to antagonize the effects of rocuronium, on the QT_c interval.

METHODS: This study used 10 adult New Zealand white rabbits of 2.5-3.5 kg randomly divided into two groups: sugammadex group (Group S, n:5) and neostigmine group (Group N, n:5). For general anesthesia administering 2 mg/kg iv propofol and 1 mcg/kg iv fentanyl, 0.6 mg/kg iv rocuronium was given. Later to provide reliable airway for all experimental animals V-Gel Rabbit was inserted. The rabbits were manually ventilated by the same anesthetist. After the V-Gel Rabbit was inserted at 2, 5, 10, 20, 25, 27, 30 and 40 minutes measurements were repeated and recorded. At 25 minutes after induction Group N rabbits were given 0.05 mg/kg iv neostigmine + 0.01 mg/kg iv atropine. Group S were administered 2 mg/kg iv sugammadex.

RESULTS: Comparing the QT_c interval in the rabbits in Group S and Group N, in the 25th, 27th and 30th minute after muscle relaxant antagonist was administered the QT_c interval in the neostigmine group rabbits was significantly increased (p<0.05).

CONCLUSION: While sugammadex, administered to antagonize the effect of rocuronium, did not significantly affect the QT_c interval, neostigmine+atropine prolonged the QT_c interval.

Key words: Sugammadex. Electrocardiography. Neostigmine. Rabbits.

Introduction

QT interval refers to the period between ventricular depolarization and repolarization observed on electrocardiogram. It includes the period from the onset of the QRS complex to when the T wave returns to the isoelectric line. QT interval changes with heart rate (HR) and QT corrected for heart rate is named QTc. It is known that many anesthetic agents, such as sevoflurane and opioids, prolong the QT interval on ECG. Prolongation of QT interval linked to medication may speed up life-threatening arrhythmias like torsades de point and cause a variety of cardiovascular complications¹⁻³.

Muscle relaxants are routinely used as an important component of general anesthesia. Neostigmine is the agent most frequently used to remove non-depolarizing block during general anesthesia⁴⁻⁵. However used alone neostigmine may cause a variety of side effects such as nausea, vomiting, prolonged QT interval and bronchoconstriction. The use of atropine aims to antagonize these effects⁶. Studies have proposed sugammadex, a cyclodextrine analogue, as a fast and reliable agent to remove non-depolarizing block⁷. In addition use of sugammadex has been determined to cause hypotension, cough and nausea. However studies are available showing that sugammadex has minimal effect on QT interval.

The hypothesis of our study is that sugammadex will have less effect on the QT_c interval on ECG compared to the combination of atropine+neostigmine. In this study we created a general anesthesia model using rabbits to evaluate only the effects of general anesthesia without surgical stimulus. We aimed to compare the effects of sugammadex and neostigmine on the QT_c interval when used to antagonize the effects of rocuronium.

Methods

This study used 10 adult white New Zealand rabbits weighing 2.5-3.5 kg. Necessary permissions for the experiment were obtained from Canakkale 18 Mart University Animal Experiment Ethics Committee and the study took place in the experimental research center in Canakkale 18 Mart University. Experiments were performed in accordance with the "Animal Welfare Act and the Guide for the Care and Use of Laboratory animals prepared by the Canakkale 18 Mart University, Animal Ethical Committee".

Before the study began the rabbits were clinically evaluated for behavior, respiratory and cardiovascular system problems and no negative result was found for animals included in the study. All experiments took place between 09.00 and 16.00. During the experiments the animals were fed with standard rabbit food and were given continuous access to water. The temperature of the shelter was kept at 21±2°C. The animals were randomly divided into two groups: the sugammadex group (Group S, n:5) and neostigmine group (Group N, n:5). Rabbits included in the study were fasted for eight hours prior to the anesthesia induction. Before general anesthesia, all rabbits were administered 10 mg/kg ketamine for premedication. After waiting 20 minutes, the animals were monitored with ECG. Then a vein was opened in the ear using a 26 G cannula and fluid resuscitation was begun. O₂ of 4 L/min was administered through a mask. During anesthesia mean arterial pressure was monitored in the rabbits through arterial cannulization of the opposite ear. For general anesthesia after administering 2 mg/kg iv propofol and 1 mcg/kg iv fentanyl, 0.6 mg/kg iv rocuronium was given. Later to provide reliable airway for all animals V-Gel Rabbit (V-gel rabbit R-3 Docsinnovent® Ltd. London, UK) was inserted, the animals were linked to an anesthetic device (Anesthesia Machine w/O₂ Flush Model M3000PK Parkland Scientific Lab And Research Equipment. Florida, USA) and were manually ventilated. To maintain anesthesia 50% oxygen, 50% air mix was used with 1 MAC isoflurane. The rabbits were manually ventilated by the same anesthetist to a respiration count of about 40/minute and pressure of 15 cmH₂O (about 10ml/kg) appropriate for rabbit physiology. Before induction basal heart rate and mean arterial pressure values were recorded. After the V-Gel Rabbit was inserted at 2, 5, 10, 20, 25, 27, 30 and 40 minutes measurements were repeated and recorded. To evaluate oxygenation of the rabbits, before induction and at 10 and 40 minutes after induction blood gases were taken and recorded (Blood Gas Analyzer – Gastat 600 Series, Techno Medica Co. Ltd. Yokohama, JAPAN). At 25 minutes after induction Group N rabbits were given 0.05 mg/kg iv neostigmine + 0.01 mg/kg iv atropine. Group S were administered 2 mg/kg iv sugammadex. When the rabbits' spontaneous respiration was observed at sufficient levels, the V-Gel Rabbit was removed and animals were taken to recovery.

Recording ECG

Electrocardiogram records were made in accordance with the method reported by Uzun *et al.*⁸ The electrodes at the extremities were used to take measurements at basal (0 min.) and at 2nd, 5th, 10th, 20th, 25th, 27th, and 30th minutes after intubation. ECG data was converted to a digital environment (Poly-Spectrum 12 channel ECG-System, Poly-Spectrum-8, Neurosoft, 5, Voronin str., Ivanovo, Russia). ECG records were converted to 1 mV=20 mm, rate 50 mm/s and filter (35 Hz) and the I, II, III, aVR, aVL and aVF derivations were recorded. The QT interval was calculated as the period from the start of the Q wave to the end of the T wave. Corrected QT interval (QT_c) was calculated according to the formula reported by Bazett⁹.

Statistical analysis

All statistical analysis was performed using SPSS 15 (SPSS Inc., Chicago, IL, USA) statistical software for Windows. Normal distributed data were given as mean±SD, data with non-normal distributions were expressed as median and dichotomous data were given as percent. Significance level of the difference between two groups was analyzed using parametric t-test for normal distributing variables and with the non-parametric Mann-Whitney U test used for non-normally distributed variables. The Mann-Whitney U test was used to compare differences in QT_c between groups basal, post-entubation, 2th min. , 5th min. , 10th min. , 20th min. , 25th min. , 27th min. , 30th min. Values were considered to be significantly different when the p value was less than 0.05.

Results

The average weight of rabbits in the sugammadex group was 2.9±0.5 kg while the neostigmine group had an average weight of 3±0.4 kg, with no statistically significant difference. The study results from Group S and Group N showed no statistically significant difference in terms of blood gas parameters (Table 1).

TABLE 1 - Mean values of blood gases parameters before induction, at 15th and 40th minute in Groups N and S.

	Group N	Group S	p
pH	7.36	7.36	
PO ₂ (mmHg)	94.2± 2.4	96.1±2	> 0.05
PCO ₂ (mmHg)	38.2±1.3	37±1.4	
HCO ₃ (mmol/L)	23.5±1	23±1	

p: In both groups there was no significant statistical difference in mean values of blood gases parameters.

In addition the mean arterial pressure and heart rate values from both groups were similar during the experiment (Tables 2 and 3).

TABLE 2 - Mean values of arterial pressure in Groups N and S.

MAP(mmHg)	Group N	Group S	p
Basal	88±1	86±1	
post-entubation	83±2	82±1	
10 th min.	79±1	80±1	
20 th min.	78±1	77±2	> 0.05
25 th min.	76±1	78±1	
27 th min.	82±1	84±1	
30 th min.	89±1	87±1	

p: In both groups there was no significant statistical difference in mean values of arterial pressure.

TABLE 3 - Heart rate values in Groups N and S.

HR	Group N	Group S	p
Basal	207±2.5	210±1.5	
post-entubation	194±4.7	192±3.8	
10 th min.	192±2.1	191±3.3	
20 th min.	185±1.8	185±1.5	> 0.05
25 th min.	184±2.9	182±3.9	
27 th min.	184±1.5	183±1.9	
30 th min.	189±3.1	191±3.6	

p: In both groups there was no significant statistical difference in mean values of heart rate.

Comparing the QT_c interval in the rabbits in Group S and Group N, the measurements at 5th, 15th and 20th minutes were similar to basal readings. However at the 25th, 27th and 30th minutes after muscle relaxant antagonist was administered the QT_c interval in the neostigmine group rabbits was significantly prolonged (Figure 1).

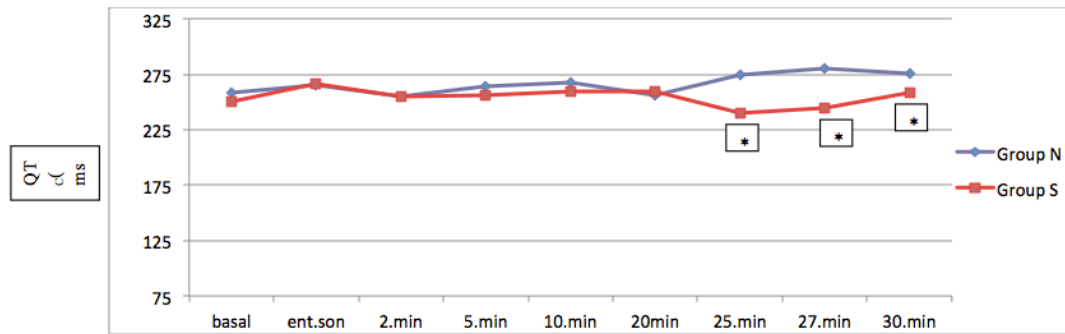


FIGURE 1 - Groups N and S the variation with time of the QT_c interval. 25th, 27th and 30th minutes after muscle relaxant antagonist was administered the QT_c interval in the neostigmine group rabbits was significantly prolonged.

Discussion

This study created a model to evaluate the effects of general anesthesia without surgical stress. We observed that the use of neostigmine+atropine significantly increased the QT_c interval on ECG compared to sugammadex.

The administration of anesthesia affects the QT interval at varying stages. Autonomic nerve system changes developing especially during general anesthesia cause changes in the QT interval¹⁰. Fear before surgery, agents used for anesthetic induction, laryngoscopy and endotracheal intubation procedures or developing hemodynamic and neuroendocrine responses have been researched to explain rhythm disorders observed on electrocardiography^{11,12}.

Muscle relaxants are widely used to make endotracheal intubation easier during anesthesia induction and to provide the muscle relaxation which is necessary for surgery. While the effect of muscle relaxants on the patient may have clinically ended, some of the nerve-muscle junction receptors may be blocked by muscle relaxant agents. This situation is known as postoperative residual curarization (PORC). PORC is an important factor increasing the morbidity and mortality in the period after surgery¹³.

Neostigmine, a cholinesterase inhibitor, is an agent frequently used to remove non-depolarizing block during general anesthesia¹⁴. Used alone neostigmine may bring out side effects such as bradycardia and increased salivation. As a result to antagonize the side effects of neostigmine during removal of non-depolarizing block it is necessary to use muscarinic antagonists such as atropine¹⁵. However as the use of atropine stimulates the anti-muscarinic receptors, cardiovascular, gastrointestinal and respiratory side effects may be observed. The muscarinic antagonist agents may cause side effects such as tachycardia, blurred vision and sedation^{16,17}. A case study in the literature reported a patient

operated under general anesthesia who developed heart block after neostigmine administration, followed by increased QT_c interval, who responded to two doses of atropine and returned to normal 4 hours after the operation¹⁸. Medications used for reverse should both quickly remove the muscle relaxant effect and cause minimum side effects.

Sugammadex is a modified cyclodextrine agent which selectively binds to steroid-based muscle relaxants. As sugammadex directly binds to steroid-based muscle relaxants in plasma, it has no effects on the neuromuscular junction. As a result its effects start quickly and it causes fewer side effects¹⁹. Comparing sugammadex to neostigmine it is known to more quickly reverse the neuromuscular block produced by rocuronium under general anesthesia²⁰. Cammu *et al.*²¹ in a study of healthy volunteers used sugammadex after a single dose of rocuronium and vecuronium and observed important changes in vital signs on ECG. In another study it was determined that sugammadex with a dose of 1-8 mg/kg minimally affected the QT_c interval³. However sugammadex is only effective when used with steroid-based muscle relaxants²².

There is no experimental or clinical study evaluating the effects of atropine neostigmine combination and sugammadex on QT_c interval in the literature. In our study we created a general anesthetic model in rabbits to evaluate the effects of sugammadex and neostigmine on QT_c interval without surgical stimulus. Compared with the atropine and neostigmine combination, we determined the QT_c interval in rabbits treated with sugammadex was significantly shorter.

In our study after the airway device was inserted the QT_c interval in both groups increased. During general anesthesia linked to medications used for both anesthetic induction and isoflurane used to maintain anesthesia, we observed an increase in QT_c interval compared to basal values, though not at significant levels. After reverse while there was no change in the

QT_c interval in the sugammadex group, the QT_c interval in the neostigmine+atropine group significantly increased. We believe the increase in the neostigmine group may be linked to the anti-muscarinic effects of atropine.

On the other hand we believe the lack of definite change in the sugammadex group may be related to sugammadex only binding with rocuronium in plasma and not affecting the nicotinic and muscarinic receptors.

Conclusion

While sugammadex administered to antagonize the effect of rocuronium did not significantly affect the QT_c interval, however, neostigmine+atropine prolonged the QT_c interval.

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