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# Effect of Concurrent Lidocaine, Remifentanil and Methylprednisolone Use on the Clinical Effect of Sugammadex under General Anaesthesia in Rats

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## Abstract

**Objective:** In an *in vitro* study, lidocaine, remifentanil and methylprednisolone produced inclusion complexes with sugammadex, which lead to a decrease in free and active concentrations of sugammadex. When used concurrently with these drugs, it is likely that the time for sugammadex to reverse a neuromuscular blockade is going to be prolonged due to a synergistic pharmacokinetic or pharmacodynamic interaction. The aim of the present study was to investigate whether concurrent use of sugammadex with remifentanil, lidocaine and methylprednisolone led to a decrease in the neuromuscular blockade reversal effect of sugammadex produced with neuromuscular blockade agent (NMBA) rocuronium.

**Methods:** The present study included 42 male Wistar rats. They were randomised into 7 groups, with 6 rats per group. The first group was the control group, the second group received remifentanil and methylprednisolone, the third lidocaine and methylprednisolone, the fourth remifentanil, the fifth lidocaine, the sixth methylprednisolone and the seventh lidocaine and remifentanil. All groups were administered 3.2 mg $kg^{-1}$ rocuronium for neuromuscular blockade after the administration of study drugs. When the train of four (TOF) value was 0, all groups were administered 16 mg $kg^{-1}$ sugammadex for the reversal of neuromuscular blockade. With a TOF Watch SX device, the time to TOF ≥0.9 was recorded.

**Results:** When the control group was compared with Groups 3, 4, 5, 6 and 7, no statistically significant difference was found. However, in Group 2, time to TOF ≥0.9 was prolonged significantly when compared with the control group.

**Conclusion:** We suggest that remifentanil and methylprednisolone used concurrently with sugammadex lead to a decrease in sugammadex reversal effect by giving rise to decrease in its free and active concentrations probably via displacement in rats.

**Keywords:** Lidocaine, methylprednisolone, neuromuscular blockade, remifentanil, sugammadex

## Introduction

Sugammadex is a modified gamma cyclodextrin compound and a member of cyclodextrin molecule family, which reverses the neuromuscular blockade (NMB) by encapsulating steroid neuromuscular blocker agents and decreasing their free concentrations in the neuromuscular junction (1-3).

In addition, in an *in vitro* study carried out with sugammadex, an inclusion complex was formed with other compounds in addition to neuromuscular blockade agents (NMBAs) (4). Among these compounds, the formation of inclusion complexes with lidocaine, remifentanil and methylprednisolone, used commonly in anaesthesia practice, is quite important. Inclusion complexes formed with these drugs cause the free and active concentrations of sugammadex to decrease (4). However, this decrease did not cause any change in the clinical effect of sugammadex (4).

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In addition, these drugs are used commonly in combination in anaesthesia practice. When used concurrently, compared to being used on their own, a reversal time of neuromuscular blockade by sugammadex is likely to be prolonged due to pharmacokinetic or pharmacodynamic interaction. The aim of the present study was to investigate whether concurrent use of sugammadex with remifentanil, lidocaine and methylprednisolone led to a decrease in neuromuscular blockade reversal effect of sugammadex produced with NMBA rocuronium in rats.

## Methods

The present study was carried out in Gazi University Faculty of Medicine Animal experimental laboratory with the approval of Gazi University Faculty of Medicine, Animal Experiments Ethics Committee dated 07.10.2015-31725 and numbered 15.062. In the study, 42 male Wistar rats were included. Rats were supplied by the animal experiments laboratory of Gazi University and were followed throughout the study in laboratory *animal* breeding and *experimental* research center of Gazi University. The rats were kept at room temperature (21°C, humidity 30%) and 12-hour-night/12-hour-day cycle, and they were allowed to eat *ad libidum* 2 hours before anaesthesia administration.

They were randomised into 7 groups with 6 rats per group. The first group was the control group, the second received remifentanil and methylprednisolone, the third lidocaine and methylprednisolone, the fourth remifentanil, the fifth group lidocaine, the sixth group methylprednisolone and the seventh lidocaine and remifentanil. All rats were administered ketamine intraperitoneally (90 mg $kg^{-1}$) as an anaesthetic agent. An adequate anaesthesia depth was ensured by controlling the response of rats to painful stimuli (pinprick test). When there was no response to painful stimuli, an intravenous catheter was placed via the tail vein with a 24 G (gauge) intravenous catheter. In all the rats, standard-length proximal and distal needle electrodes (rhythm link subdermal needle 13 mm) were placed subcutaneously in the right femoral region, parallel to the femoral nerve trace. The transducer was fixed to the skin by ventromedial approach at the proximal end of the thigh, next to the tibial tuberosity (insertion point of the patellar ligament). After determining the supramaximal stimulation current, the femoral nerve was continuously stimulated at 1 Hz until the twitch height reached a stable plateau and calibrated the TOF-Watch S monitor (Calibration Mode 1). To control the respiration system, the neck region was opened with an incision at the midline. The trachea was freed with dissection, and tracheotomy was opened, whereas the intermittent positive pressure ventilation was administered at the respiration rate of 60-70 $min^{-1}$ and a tidal volume of 5-7 mL $kg^{-1}$ with a mechanical ventilator (Harvard apparatus, Inspira ASV). All rats were ventilated with 50% oxygen and 50% dry-air mixture. Subsequently, as study drugs, 1.5 mg $kg^{-1}$ lidocaine and 1 µg $kg^{-1}$ remifentanil was administered to the first group, serum physiologic solution to the second group, 1.5 mg $kg^{-1}$ lidocaine and 1 mg $kg^{-1}$ methyl prednisolone to the third group, 1 µg $kg^{-1}$ remifentanil to the fourth group, 1.5 mg $kg^{-1}$ lidocaine to the fifth group, 1 mg $kg^{-1}$ methylprednisolone to the sixth group and 1 mg $kg^{-1}$ methylprednisolone and 1 µgr $kg^{-1}$ remifentanil to the seventh group. In all groups, following the administration of study drugs, 3.2 mg $kg^{-1}$ rocuronium (N.V. Organon, Oss, Holland) was administered for neuromuscular blockade. The time of rocuronium administration was recorded. With TOF-Watch, series of impulses were repeated at intervals not shorter than 10 seconds at the 2 Hz speed, lasting for 2 ms and at the 4 supramaximal amplitude (1-5 mA). Then, the TOF stimulus impulse given to rats was recorded when the response to 4, 3, 2 and 1 stimuli decreased, and no response was obtained to TOF, namely when TOF was 0. When the TOF value was 0, all groups were administered 16 mg $kg^{-1}$ sugammadex for the reversal of neuromuscular blockade (N.V. Organon, Oss, Holland). With a TOF Watch SX device, the time to TOF ≥0.9 (time to recovery) was recorded. All rats were sacrificed at the end of the study.

### Statistical analysis

Data are expressed as the median (range). Normality tests using the Kolmogorov-Smirnov test were performed. The weight, body temperature and TOF were analysed using the Kruskal-Wallis test. In case of significance, the difference was confirmed using the Mann-Whitney U test, followed by a Bonferroni post hoc test. A p-value <0.05 was considered statistically significant. In two-by-two comparisons, according to the Bonferroni correction, a p-value of 0.008 was considered significant (each group was compared with the control group). Data were analysed using the IBM Statistical Package for the Social Sciences Statistics for Windows, Version 20.0 (IBM Corp., Released 2011, Armonk, NY, USA).

## Results

There was no statistically significant difference between the weight of rats divided into 7 groups, each including an equal number of rats (n=6; p=0.451). In addition, there was no significant difference between the groups with respect to the body temperature of rats, which was measured with an oesophageal probe (p=0.555).

In the first group, the time to the TOF value 0 was found to be median 44 (40-80) seconds, in the second 58.5 (52-80) seconds, in the third 41 (36-75) seconds, in the fourth 41 (35-70) seconds, the fifth 51.5 (35-62) seconds, the sixth 45 (35-58) seconds and the seventh 38 (28-56) seconds. No sta-

**Table 1. Weight (median), body temperature (median), time (median) to TOF 0 and TOF ≥90% in different groups and the comparison of groups with the control group in terms of the TOF ≥90% period**

| | Weight (gr) | Body temperature (°C) | Time to TOF 0 (sec) | Time to TOF ≥90% (sec) | p (Time to TOF ≥90% comparison with the control group) |
|---|---|---|---|---|---|
| Group 1: control | 252 (242-280) | 36.3 (36-36.9) | 44 (40-80) | 35 (24-60) | - |
| Group 2: remifentanil-methylprednisolone | 250.5 (245-285) | 36.3 (36-37) | 58.5 (52-80) | 102 (93-118) | 0.004¥ |
| Group 3: methylprednisolone-lidocaine | 276 (240-315) | 36.5 (36.3-36.8) | 41 (36-75) | 46 (42-68) | 0.037 |
| Group 4: remifentanil | 280 (242-290) | 36.4 (36-36.7) | 41 (35-70) | 54 (29-82) | 0.132 |
| Group 5: lidocaine | 274 (250-280) | 36.4 (36.2-36.6) | 51.5 (35-62) | 52 (35-62) | 0.065 |
| Group 6: methylprednisolone | 257.5 (240-263) | 36.4 (36-37.3) | 45(35-58) | 59 (40-68) | 0.024 |
| Group 7: remifentanil-lidocaine | 249.5 (245-300) | 36.5 (36.4-36.7) | 38 (28-56) | 59 (36-72) | 0.030 |
| p | 0.451 | 0.555 | 0.077 | 0.002* | |

*p<0.05, ¥Bonferroni correction p-value of =0.05/6=0.008. TOF: train of four

tistically significant difference was found between the groups (p=0.077) (Table 1).

In the first group, the time to recovery (TOF value ≥90) was found to be 35 (24-60) seconds, in the second 102 (93-118) seconds, the third 54 (29-82) seconds, the fourth 46 (42-68) seconds, the fifth 52 (35-62) seconds, the sixth 59 (40-68) seconds and the seventh 59 (36-72) seconds. The difference between groups was statistically significant (p=0.002; Table 1).

In two-by-two comparisons, according to the Bonferroni correction, a p-value of =0.05/6=0.008 was considered significant (each group was compared with the control group). When the control group was compared with Groups 3, 4, 5, 6 and 7, there was no statistically significant difference found. However, when control groups were compared with Group 2, time was found to be significantly prolonged (p=0.004; Table 1).

## Discussion

Sugammadex is a water soluble modified gamma dextrin, which traps NMBA in its lipophilic cavity. This sugammadex/NMBA complex leads to a decrease in the concentration of free NMBA in the circulation, and hence it becomes possible for the receptor to be bound to acetyl choline (1, 5, 6). Sugammadex binds to rocuronium and vecuronium with an extremely high affinity. In the study by Zwiers et al. (4), sugammadex produced inclusion complexes with three hundred other complexes in addition to NMBAs (4), and it was determined that only four drugs (flucoxacillin, fucidic acid, hormonal contraceptives and toremifen) can delay the time of TOF to increase over 90% significantly, with a displacement reaction. In addition, it produced inclusion complexes with lidocaine, remifentanil and methylprednisolone, which are commonly used in anaesthesia practice. When sugammadex is used with any of these drugs, a displacement reaction with an NMBA brought about a decrease in free and active concentrations of sugammadex. Nevertheless, this decrease did not lead to a decrease in its clinical efficiency (4). In addition, in the study by Gulec et al. (7), dexamethasone administered in anaesthesia induction had no effect on time to 90% for TOF after sugammadex, and Ozbilgin et al. (8) determined that sugammadex could bind to digoxin and delay its cardiovascular toxicity. In addition, in the study by Ozer et al. (9), an earlier reversal of neuromuscular block by sugammadex was found in patients receiving steroids, particularly dexamethasone. In the same study, methylprednisolone, lidocaine and remifentanil were used concurrently with sugammadex, which is used as an NMBD, may lead to the inhibition of reversal effect by sugammadex of neuromuscular blockade produced by rocuronium. In the present study, similar to the study by Zwiers et al. (4), the TOF value of >90% was considered as recovery, because the recovery with a TOF value >70% is associated with residual NMB. When TOF values range between 0.7 and 0.9, adverse effects associated with inadequate airway protective reflexes and muscular weakness are observed. Therefore, the authors suggested that the TOF ratio is a better definition of recovery whether it is >90% or not (10, 11). In the present study, as in the study by Alex et al. (4), statistically significant difference was not found in time to TOF of 0 and the time to TOF >90% after the administration of sugammadex in the lidocaine group. In addition, with remifentanil and methylprednisolone, there was no significant prolongation in time to TOF >90%. Furthermore, in the remifentanil-lidocaine and methylprednisolone-lidocaine groups, there was no statistically significant prolongation in time to TOF >90%. However, in the remifentanil-methylprednisone group, statistically significant prolongation was

found in time to TOF >90%, likely to be prolonged due to the synergistic effect of remifentanil and methylprednisone. In the study by Zwiers et al. (4), when these two drugs were used by themselves, they led to a decrease in free and active concentration of sugammadex, but there were no alterations in its clinical efficacy. However, the effect of these two drugs when used in combination was not investigated in their study. In the present study, it was established that when these two drugs were used concurrently, there was a decrease in the reversal effect of sugammadex, that is the time to TOF >90% was significantly prolonged (p=0.004).

## Conclusion

We suggest that remifentanil and methylprednisolone used concurrently with sugammadex lead to a decrease in the reversal effect of sugammadex by reducing its free and active concentration probably via displacement in rats.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Gazi University School of Medicine (07.10.2015-31725 and numbered 15.062)

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**Author Contributions:** Concept - T.K.; Design - T.K., E.K.; Supervision - T.K., E.K.; Resources - T.K.; Materials - T.K.; Data Collection and/or Processing - T.K., E.K., T.A.; Analysis and/or Interpretation -T.K., E.K., T.A., S.M., G.O.T., S.E.; Literature Search - T.K., E.K.; Writing Manuscript - T.K.; Critical Review - T.K., E.K., T.A., S.M., G.O.T., S.E.; Other - T.K., E.K., T.A.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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