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SCIENTIFIC ARTICLE

Do metoclopramide and ondansetron alter mivacurium-induced neuromuscular blockade? – a randomised trial

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KEYWORDS

Mivacurium;
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Abstract

Background: We aimed to investigate the effects of metoclopramide and ondansetron on mivacurium neuromuscular blockade.

Methods: Seventy five, ASA I-II patients, aged 18-65 and scheduled for elective surgery requiring tracheal intubation were included in the study. The patients received metoclopramide 10 mg, ondansetron 4 mg or normal saline 5 mL; group M, group O, group NS (n = 25), respectively. Before anesthesia study drugs were administered in a volume of 5 mL. The level of plasma cholinesterase were obtained before and 5 minutes after the administration of study drugs and 5 minutes after the administration of mivacurium. Onset time, T25, T75, T25-75, T90 levels were compared with each other and differences between each patients were investigated. After recording T90, the study was terminated and surgery was started.

Results: Onset time was significantly shorter in group M, than the other two groups. Onset time in group O was significantly shorter than in group NS. In Group M T25, T75, T90 and recovery indices were significantly greater than in Group NS (p < 0.001). In Group O T25, T75 were greater than Group NS (p < 0.01 and p < 0.05, respectively). In Group M T75, T90 and emergence indices were significantly higher than Group O (p < 0.001, p < 0.01, p < 0.001, respectively). In Groups M and O, plasma cholinesterase levels decreased significantly (p < 0.001) after administration of study drugs and mivacurium. Plasma cholinesterase also was reduced in Group NS 5 minutes after the administration of mivacurium (p < 0.001).

Conclusion: Ondansetron is believed to be more reliable agent than metoclopramide when used with mivacurium.

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Introduction

Mivacurium chloride is a short acting non-depolarizing neuromuscular blocking agent rapidly hydrolysed by plasma cholinesterase (pCHE). Drugs which inhibit pCHE prolong mivacurium neuromuscular block.^{1,2} Delayed recovery from neuromuscular block may compromise respiratory effort and airway integrity during emergence from anesthesia. Metoclopramide, which hastens gastric emptying and decreases gastroesophageal reflux, is commonly used for prevention of nausea and vomiting in the early postoperative period.³⁻⁶ Metoclopramide inhibits pCHE,⁷ and giving it before mivacurium can prolong recovery time by 30%, probably via increased bioavailability caused by decreased plasma clearance of mivacurium.^{8,9} Ondansetron, a serotonin type-3 receptor antagonist, is also used to prevent nausea and vomiting.¹⁰ The serotonin type-3 receptor is found in both peripheral and central nervous systems. Ondansetron may also affect neuromuscular blockade by possible inhibiting of Ach releasing to neuromuscular junction.¹¹⁻¹⁴ In this placebo controlled, prospective, randomised and double blind study, we aimed to investigate the effects of metoclopramide and ondansetron on mivacurium neuromuscular blockade.

Materials and methods

After Hospital Ethics Committee approval and receipt of written informed consent, seventy five ASA I-II status patients, aged 18-65 and scheduled for elective surgery requiring tracheal intubation were included in the study. Patients with neuromuscular, liver and kidney diseases, or under medication known to affect neuromuscular transmission, with history of difficult intubation, malnutrition, alcohol abuse, fluid electrolyte disturbances, or BMI > 35 were rejected. The patients were randomly assigned according to computer-generated random number sequence into one of three groups to receive metoclopramide, ondansetron or normal saline; group M (n=25), group O (n=25) and group NS (n=25), respectively.

In the operating room monitoring of D_{II} derivated ECG, pulse oximetry and non-invasive arterial pressure was performed by Datex-Ohmeda CardiCap™/5 (GE, Finland). A peripheral intravenous line was inserted with 20 gauge catheter and 0.9 NaCl infusion was started.

Metoclopramide 10 mg, ondansetron 4 mg or normal saline were administered in a volume of 5 mL, 5 minutes before anesthesia induction. The study drugs were prepared by another physician so all drugs were administered blindly. Blood samples were obtained to measure the level of plasma cholinesterase activity, before and 5 minutes after the administration of study drugs and 5 minutes after the administration of mivacurium. During two hours, these samples were sent to be centrifuged in gel contained tubes at 5,000 rpm for five minutes. One ml of obtained serum were inserted to the eppendorf. Those samples were labeled as 1, 2, 3 in order. They were kept in -20°C in biochemistry laboratory. Plasma cholinesterase levels were measured colorimetrically with Vitros 250 Chemistry System (Ortho-Clinical Diagnostics, a Johnson Johnson Company).

Plasma cholinesterase reference level was considered as 4-12 U.mL⁻¹.

Anesthesia was induced with 2 $\mu\text{g.kg}^{-1}$ fentanyl and 2.5 mg.kg^{-1} propofol and patient was ventilated manually by mask with %100 oxygen until the intubation. During this time using TOF-Watch® SX (Organon, Ireland) and ulnar nerve of the non-cannulated arm was stimulated with supramaximal (50 mA) train of four stimulation to 1 Hz mode to obtain a %100 control level (EMAX).

After obtaining a neuromuscular block control level, 0.2 mg.kg^{-1} mivacurium was administered and the patient was intubated. Anesthesia was maintained by MAC 1 sevoflurane in an equal parts O₂/N₂O mixture during operation and patient was ventilated to maintain normocapnia. Forearm skin temperature was kept greater than 32 °C.

The time from mivacurium injection up to performing 100% neuromuscular blockade was recorded as onset time. For assessment of neuromuscular transmission, TOF impulse with 50 mA current was used at 5 minutes intervals in first 10 minutes and once every minute after 10 minutes. T₂₅, T₇₅, T₂₅₋₇₅, T₉₀ were recorded during the study. Onset time, T₂₅, T₇₅, T₂₅₋₇₅, T₉₀ levels were compared with each other and differences between each patients were investigated. After recording T₉₀, the study was terminated and surgery was started.

At 1st, 3rd, 5th, 10th, 20th and 30th minutes after intubation, mean arterial pressure (MAP), heart rate (HR), ET-CO₂, SPO₂ were recorded. 0.5 $\mu\text{g.kg}^{-1}$ IV fentanyl and 10 mg IV efedrin were planned to be administered at the time of 20% increase or decrease of MAP respectively.

The data were statistically analyzed using SPSS version 13.0 (SPSS Inc., Chicago, IL). The Kruskal-Wallis test was used to assess differences among the three groups with respect to non-parametric variables. If this revealed significant differences, the Mann-Whitney U test was used to analyze differences between the groups in pairs. Nominal non-parametric data were analyzed using the Chi-square test and Fisher's exact test. Data were presented as mean \pm SD, median (range), and number of patients (percentage) per category. P values < 0.05 were considered to indicate statistical significance.

Results

The three study groups did not differ significantly in gender, ASA, age, weight, height and BMI (p > 0.05) (Table 1).

There were no differences in hemodynamic parameters between groups. Onset time was significantly shorter in group M than the other two groups. Onset time in group O was significantly shorter than in group NS. There was no significant difference in EMAX values (p > 0.05) (Table 2).

In Group M T₂₅, T₇₅, T₉₀ and recovery indices were significantly greater than in Group NS (p < 0.001). In Group O T₂₅, T₇₅ were greater than Group NS (p < 0.01 and p < 0.05, respectively). In Group M T₇₅, T₉₀ and emergence indices were significantly higher than Group O (p < 0.001, p < 0.01, p < 0.001 respectively) (Table 3).

Although plasma cholinesterase levels were all in the normal range, there were significant differences in groups (Table 4). In Groups M and O, plasma cholinesterase

Table 1 Demographic data (number, mean \pm standard deviation or number).

	Group M n = 25	Group O n = 25	Group NS n = 25
Gender (M/F)	4/21	5/20	4/21
ASA (I/II)	18/7	20/5	22/3
Age (year)	44.24 \pm 10.38	33.52 \pm 10.57	41.32 \pm 12.24
Weight (kg)	66.16 \pm 9.46	68.08 \pm 9.61	65.48 \pm 8.52
Height (cm)	163.84 \pm 5.41	166.36 \pm 7.33	162.92 \pm 5.61
BMI	24.60 \pm 2.96	24.50 \pm 2.00	24.60 \pm 2.36

ASA, American Society of Anesthesiologists; BMI, Body mass index; F, female; M, male; M, metoclopramide; NS, normal saline; O, ondansetron.

Table 2 MAX and onset time (mean \pm standard deviation).

	EMAX	Onset time (sec)
Group M	99.6 \pm 0.48	138.8 \pm 5.82 ^a
Group O	99.4 \pm 0.50	162.0 \pm 9.89 ^b
Group SF	99.3 \pm 0.47	168.8 \pm 7.67

levels decreased significantly ($p < 0.001$) after administration of study drugs and mivacurium. In Group NS, plasma cholinesterase level was found to reduce 5 minutes after the administration of mivacurium ($p < 0.001$).

Discussion

Metoclopramide and ondansetron are commonly given to prevent nausea and vomiting but their possible interactions with mivacurium are not fully understood. Metoclopramide

prolongs the action of succinylcholine, suggesting possible depression of pCHE activity,^{15–17} and indeed, it has been shown to prolong the effect of mivacurium.⁸ The 5-HT₃ antagonist ondansetron may cause increased sensitivity to the competitive neuromuscular blockade induced by non-depolarising muscle relaxants by reducing the release of Ach.¹⁴

We found that metoclopramide reduced the onset time of mivacurium significantly compared to ondansetron and saline; ondansetron reduced onset time significantly but to a lesser extent. Metoclopramide also reduced neuromuscular transmission more than ondansetron, but there was no difference between the two drugs in their effects on pCHE after giving mivacurium.

Motamed et al.¹⁶ studied the effect of 10 and 20 mg metoclopramide on mivacurium-induced neuromuscular blockade. Ten or 20 mg metoclopramide before an intubating dose of mivacurium hastened the onset of maximum blockade by 30% and prolonged recovery by at least 50%. Time

Table 3 T₂₅, T₇₅, T₉₀ and recovery indices (minute) (mean \pm standard deviation).

	T ₂₅	T ₇₅	T ₉₀	Recovery index
Group M	20.92 \pm 1.70 ^a	27.92 \pm 1.75 ^{a,b}	33.40 \pm 1.77 ^{a,c}	7.00 \pm 0.70 ^{a,b}
Group O	19.80 \pm 2.12 ^d	25.04 \pm 2.38 ^e	30.44 \pm 2.88	5.48 \pm 0.87
Group NS	17.56 \pm 2.45	23.12 \pm 2.83	29.72 \pm 3.03	5.24 \pm 0.87

M, metoclopramide; NS, normal saline; O, ondansetron.

^a $p < 0.001$; comparing with Group NS.

^b $p < 0.001$; comparing with Group O.

^c $p < 0.01$; comparing with Group O.

^d $p < 0.01$; comparing with Group NS.

^e $p < 0.05$; comparing with Group NS.

Table 4 Plasma cholinesterase levels (med \pm standard deviation).

	PC1	PC2	PC3
Group M	6.502 \pm 0.922	5.674 \pm 0.817 ^a	5.033 \pm 0.790 ^a
Group O	6.124 \pm 1.418	5.634 \pm 1.387 ^a	4.884 \pm 1.203 ^a
Group NS	5.895 \pm 1.204	5.894 \pm 1.204	4.998 \pm 1.190 ^a

M, metoclopramide; NS, normal saline; O, ondansetron; PC1, plasma cholinesterase level in first blood sample; PC2, plasma cholinesterase level 5 min after administration of study drug; PC3, plasma cholinesterase level 5 min after administration of mivacurium.

^a $p < 0.001$ evaluation in group.

to 25% recovery was significantly greater in both metoclopramide groups compared to saline. A slight but significant reduction in cholinesterase activity was detected 2 minutes after the administration of 20 mg metoclopramide. In our study only 10 mg metoclopramide decreased pCHE activity significantly.

El Ayass and Hendrickx found a reduction of mivacurium infusion rate and a delay in neuromuscular recovery after metoclopramide 10 or 20 mg in their randomised double blind placebo-controlled study of 45 patients.¹⁸ There was no significant change in the onset time compared to saline, probably due to an inadequate number of patients. Plasma cholinesterase level decreased in both metoclopramide groups. The recovery indices were greater with metoclopramide compared to saline. While there were significant increases in the time to recovery at 25%, 50%, 75% and 90% with 20 mg, there was only 75% and 90% increase in the time of recovery with 10 mg, compared to saline. We had similar results with this study; 10 mg metoclopramide prolonged the recovery time and indices by 25%, 75% and 90% and decreased pCHE level significantly.

Skinner et al.⁸ investigated the influence of 15 mg.kg⁻¹ metoclopramide on pCHE and the duration of action of mivacurium in a randomised double-blind study of 30 patients. Onset time and recovery index were not affected, but there was a reduction of pCHE activity at the time of maximum blockade with both metoclopramide and saline. An increased time to recovery of T₁ to 25%, 75% and 90% was seen in the metoclopramide group.

Lien et al.¹⁴ found that 8 and 16 mg ondansetron did not affect the neuromuscular blockade induced by atracurium in their study of 30 patients; ondansetron may thus be preferable as an antiemetic agent when used with other muscle relaxant agents other than mivacurium. We found that 4 mg ondansetron did not affect mivacurium-induced neuromuscular blockade.

Mivacurium is hydrolyzed by pCHE, an enzyme whose activity is known to be affected by age, gender, ethnic groups and by some physiologic and pathologic situations. Lepage et al.¹⁹ studied factors affecting biological variations in total pCHE in 3,372 apparently healthy subjects more than four years old. They concluded that genetic factors, hormonal status, age and some medications and, especially in males, BMI, affected pCHE. In our study we excluded patients who were more than 65 years old and with BMI > 35. In our study it was important to show that pCHE activity was indeed in the normal range, because low pCHE activity causes prolongation of mivacurium induced neuromuscular blockade.^{20,21} After giving metoclopramide and ondansetron, enzyme levels decreased in different ratios. After mivacurium, enzyme levels decreased significantly in all groups but stayed within the normal range, with no significant difference between groups.

Considering that 10 mg metoclopramide prolonged mivacurium-induced neuromuscular block, we believe that neuromuscular function should be monitored during surgery in order to avoid the complications of excessive dosage. Because ondansetron did not prolong T₉₀ or recovery indices, and affected other parameters of neuromuscular blockade less than metoclopramide, we believe that it is a

more reliable agent than metoclopramide when used with mivacurium.

Conflicts of interest

The authors declare no conflicts of interest.

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