IJIRR

International Journal of Information Research and Review
Vol. 03, Issue, 09, pp. 2826-2829, September, 2016

Research Article

PRETREATMENT WITH ONDANSETRON BEFORE ANESTHESIA DOES NOT AFFECT THE ONSET OF ROCURONIUM-INDUCED NEUROMUSCULAR BLOCKADE

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ARTICLE INFO

Article History:

Received 25th June 2016
Received in revised form
17th July 2016
Accepted 26th August 2016
Published online 30th September 2016

Keywords:

Neuromuscular Blockade,
Ondansetron,
Serotonin Receptor Antagonist,
Rocuronium,
Train-of-four,
Acceleromyography,
Onset.

ABSTRACT

In animal studies, ondansetron, 5-hydroxytryptamine type-3 receptor antagonist, increases the effect of neuromuscular blockade of rocuronium, which associated with structural similarity of 5-hydroxytryptamine type-3 receptor to nicotinic acetylcholine receptor. We have examined whether ondansetron, which is often used to prevent nausea and vomiting after surgery, affects the onset time of neuromuscular blockade of rocuronium. A total of 52 adult patients were randomly allocated into either the saline group (N=27) or ondansetron group (N=25) for general anesthesia. The ondansetron group received 8 mg of ondansetron intravenously and the control group received 4 ml of normal saline intravenously 3 minutes before induction of anesthesia. Neuromuscular function was assessed by acceleromyography of the adductor pollicis with a train-of-four stimulation. The onset time was defined as the time in seconds from the start of injection of rocuronium until 0 of the train-of-four count. The onset time of rocuronium in the ondansetron group (145.4 ± 56.7, 95% CI: 122 to 169 sec) was not significantly different compared to that of the control group (133.0 ± 46.4, 95% CI: 115 to 151 sec) (P=0.394). Pretreatment of ondansetron before anesthesia induction did not affect the onset time of rocuronium induced neuromuscular blockade.

INTRODUCTION

In Korea, the perioperative administration of ondansetron (a serotonin type-3 receptor antagonist) is a popular method for preventing postoperative nausea and vomiting (PONV) (Jee *et al.*, 2010; McKenzie *et al.*, 1993). The 5-hydroxytryptamine type-3 receptor (5-HT3-R) is a member of the cys-loop ligand-gated ion channel (nicotinic acetylcholine receptor, GABA receptor A, glycine and excitatory amino acid receptor) superfamily; it has structural similarity to the nicotinic acetylcholine receptor (nAChR) (Karlin and Akabas, 1995). As such, an antagonist of 5-HT3-R may also affect nAChR (Vanner and Surprenant, 1990). In vitro experiments using *Xenopuslaevis* oocytes, or ex vivo studies using phrenic nerve-hemidiaphragm models, showed that a 5-HT_3-R antagonist enhanced the effects of the rocuronium-induced neuromuscular block (Ok *et al.*, 2003; Paul *et al.*, 2005). Ondansetron significantly reduced the half maximal effective concentration (EC_{50}) and the effective concentration for 90% (EC_{90}) of rocuronium and resulted in left-shifting of the concentration-response curve in the rat hemidiaphragm-phrenic nerve model (Ok *et al.*, 2003). Therefore, pretreatment with 5-HT_3-R antagonist (ondansetron) may quicken the onset time of rocuronium as it shows cross-reaction with rocuronium for nAChR under clinical conditions. This may enable administration of smaller doses of rocuronium for shorter procedures when pretreatment with 5-HT_3-R antagonist is performed. The aim of this study was to examine whether ondansetron clinically affected the onset time (seconds) of rocuronium (0.6 mg/kg)-induced neuromuscular blockade when ondansetron (8 mg / 4 ml) was given as a pretreatment.

MATERIALS AND METHODS

This study was a randomized, single-blinded, controlled clinical trial. The study was approved by Institutional Review Board, and written informed consent was obtained from each patient. Anesthesiologist who was evaluated and monitored the patient was blinded to the treatment administrated. We enrolled fifty-two healthy adult patients aged 20-60 years, classified as American Society of Anesthesiologists physical status I or II, and scheduled for simple abdominal surgery under general anesthesia. We excluded the patients in the study who were with a history of hypersensitivity to rocuronium

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and/or ondansetron, with a hepatic or renal disease, showed abnormal preoperative laboratory results in hepatic or renal test, a history of chronic medication which could interact with neuromuscular blocking drug, and partial or general paralysis. The patients were randomly allocated into either the control group (N = 27) or ondansetron group (N = 25) for general anesthesia by computer-generated random table. The ondansetron group received ondansetron (Zofran®, GSK, London, UK) 8 mg IV and the control group received normal saline 4ml IV 3 minutes before induction of anesthesia. Anesthesia was induced with fentanyl (Fentanyl Injection 2 ml, Han-lim Pharma., Korea) 2.0 μg/kg and propofol (Fresofol 1%, Fresenius Kabi, Austria) 2.5 mg/kg IV.

Neuromuscular function on the adductor pollicis was assessed by acceleromyography (TOF-Watch SX® monitor, Organon, Oss, Netherlands). Monitoring was done on the opposite side of the intravenous line. Surface electrodes were placed on cleaned skin over the ulnar nerve on the volar side of the wrist. We secured the position of the transducer by placing the thumb in a hand adapter (Hand Adapter®; Organon, Oss, Netherlands). The arm was fixed with a board and kept in the same position during the whole study procedure. After induction of anesthesia and loss of consciousness, the acceleromyography was calibrated. A train-of-four (TOF) stimulation was used (supramaximal square wave impulse of 200 μs duration, four stimuli at 2 Hz, 10-seconds interval). After having obtained stable baseline measurements, a bolus dose of rocuronium bromide (Esmeron®, N.V. Organon, Oss, Netherlands) 0.6 mg/kg that was diluted by 2 mg/ml was administered intravenously over 3 seconds. Then, the onset time was measured as the time in seconds from the start of injection of rocuronium until 0 of the TOF count. Just after endotracheal intubation, we measured hemodynamic variables such as systolic, diastolic blood pressure and heart rate. Intubating condition was also measured using modified grading system from the works by Fuchs-Buder *et al.*(2007).

The primary end-point of this study is the changes of onset time of rocuronium-induced neuromuscular block in the ondansetron pretreatment group compared to the control (saline) group. Munoz *et al.*(1997) showed the effect of ephedrine on the onset time of rocuronium was 72 ± 19 sec in the ephedrine group versus 98 ± 31 sec in the placebo group and 26% difference ($P < 0.001$). Based on the study, we calculated the sample size of this study with a power of 0.9 and type I error of 0.05 for the two tailed t-test, and minimum sample size was estimated to be 22 per each group. G*Power (version 3.1. Universitat Kiel, Germany) was used for the sample size calculation (Faul *et al.*, 2009). To account for approximate drop-out rate of 10%, at least 25 patients per each group were needed to support the statistical hypothesis of the study. The results were expressed as mean ± standard deviation or number of patients. GraphPad Prism version 6.0 for Windows (GraphPad Software, La Jolla, California USA, www.graphpad.com) and R for windows version 3.0 (R Foundation for Statistical Computing, Vienna, Austria. www.R-project.org) were used for statistical analysis. The data in this study were approximately and normally distributed and thus did not violate the assumptions of the t-test. There fore, patients' characteristics (age, body weight), dose of anesthetics (fentanyl, propofol, rocuronium), onset time of neuromuscular block and hemodynamic variables (systolic, diastolic and heart rate) were compared among groups by unpaired t-test with Welch's correction. The intubation condition among groups was compared by Fisher's exact test. P value less than 0.05 was considered statistically significant.

RESULTS

A total of 52 patients were enrolled, and all completed the study. There were no demographic differences between the two groups, in respect to age, sex, weight, dose of fentanyl and propofol (Table 1). The onset time of rocuronium in the ondansetron group (145.4 ± 56.7, 95% CI: 122 to 169 sec) was not significantly different compared to that of the control group (133.0 ± 46.4, 95% CI: 115 to 151 sec) ($P = 0.394$). In the assessment of endotracheal intubation condition, one case in saline group and two cases in ondansetron group were 'good' state. However, the rest of both groups were 'excellent'state and did not show a significant statistical difference ($P = 0.945$). Hemodynamic variables such as systolic, diastolic blood pressures and heart rate just after endotracheal intubation did not show any significant differences between the two groups (Table 1).

DISCUSSION

In this study, we confirmed that the pretreatment with intravenous ondansetron (8 mg) prior to anesthesia did not affect the onset time of the rocuronium-induced neuromuscular block. The 8.5% difference in the onset time of the rocuronium-induced neuromuscular block failed to show statistical significance ($P = 0.394$) or clinical importance. The administration of ondansetron inhibits the serotonin (5-hydroxytryptamine) type 3 receptors of the vagal afferent nerves of the gastrointestinal tract, the chemoreceptor trigger zone of the brain stem, and the receptors of the nucleus tractus solitarius.

It shows efficient antiemetic effects with lower incidences of side effects including sedation, hypotension or extrapyramidal symptoms, compared to other antiemetics such as droperidol or metoclopramide. Therefore, ondansetron is currently a popular drug for the prevention and treatment of perioperative nausea and vomiting. Additionally, 5-HT_3-R is classified as part of the ligand-gated ion channel superfamily, which also includes nicotinic acetylcholine receptors (Karlin and Akabas, 1995). As 5-HT_3-R and nAChR are similar in structure and function, cross-reactivity is possible between the drugs that act at each receptor (Cross *et al.*, 1995). In addition to the possibility of cross-reactivity due to the structural similarity of the two receptors, non-selectivity could also cause specific changes in the process of neurotransmitter release. Serotonin has been found to facilitate nicotinic transmission within the autonomic ganglia (Taylor, 1985). The administration of ondansetron would also interact with putative receptors at the neuromuscular junction or ganglia to inhibit acetylcholine release. This would diminish the neuromuscular response to stimulation and sensitize the patients to competitive neuromuscular blockade with non-depolarizing muscle relaxants. Several experimental studies have reported these observations. Paul *et al.* (2005) showed that dolasetron, ondansetron, and granisetron reversibly inhibited 5-HT_3A-R function at nanomolar concentrations; the 50% inhibitory concentrations (IC_{50}) were reported as 11.8, 6.4, and 0.2 nM

Table 1. Characteristics of each group

		Ondansetron group (N = 25)	Saline group (N = 27)	P value
Age (year)		38 ± 10	37 ± 8	0.764
Sex (male / female)		9 / 13	12 / 10	
Body weight (kg)		61.2 ± 9.2	63.0 ± 12.2	0.554
Fentanyl dose (μg/kg)		2.0 ± 0.0	2.0 ± 0.1	0.348
Propofol dose (mg/kg)		2.5 ± 0.1	2.4 ± 0.2	0.090
Rocuronium dose (mg/kg)		0.6 ± 0.0	0.6 ± 0.1	0.391
Intubation condition	Excellent	23 (46.9%)	26 (53.1%)	0.945
	Good	2 (66.7%)	1 (33.3%)	
Systolic BP (mmHg)		102.3 ± 8.9	106.8 ± 12.5	0.144
Diastolic BP (mmHg)		62.6 ± 8.1	58.0 ± 4.7	0.016
Heart rate (rate/min)		62.8 ± 12.4	66.9 ± 9.9	0.196
Onset time (sec)		145.4 ± 56.7	133.0 ± 46.4	0.390

Values are presented mean ± SD or number of patients. BP; blood pressure

for dolasetron, ondansetron and granisetron, respectively. Therefore, drugs that target specific ligand-gated ion channels may additionally affect other ion channel types. Ok *et al.* (2003) demonstrated, in an exvivo experiment with a rat phrenic nerve-hemidiaphragm preparation, that ondansetron depressed the twitch force in a dose-dependent manner, thus showing less potency than non-depolarizing neuromuscular blocking agents. Pretreated ondansetron (1 μg/ml) significantly reduced the EC_{50} and EC_{90}, respectively, of vecuronium (65% and 59%), rocuronium (53% and 56%) and atracurium (43% and 30%) compared to untreated groups. Additionally, Baek *et al.*(2006) conducted an exvivo experiment using rat phrenic nerve-hemidiaphragm preparations; ondansetron and rocuronium were injected simultaneously. In this study, 1 μg/ml and 10 μg/ml of ondansetron showed no effect on the rocuronium-induced neuromuscular blockade. However, an increased dose of 100 μg/ml of ondansetron potentiated the block effect of rocuronium.

In this study, pretreatment with intravenous ondansetron (8 mg) prior to anesthesia did not affect the onset time of the rocuronium-induced neuromuscular block. For the prevention of postoperative nausea and vomiting, injection of ondansetron at a clinical dose resulted in a maximal plasma concentration of approximately 100 ng/ml. This was much lower than the concentration reported by Baek *et al.* (2006). Despite the significant differences in drug potency between humans and rats, these differences were negligible; significant effects occurred at higher concentrations of up to 1,000 times in magnitude. Lien *et al.* (1993) reported similar results to our study; the treatment of ondansetron had no effect on the atracurium-induced neuromuscular block. They determined the log dose-response curves for the study groups (saline vs. ondansetron at 8 or 16 mg) and compared the curves using ANOVA. The maintenance infusion rate or the duration of the clinical recovery showed no significant differences between the groups. Additionally, dose-related changes were not reported for the 95% effective dose (ED_{95}). Therefore, they concluded that ondansetron (8 or 16 mg) could be used during the perioperative period without concerns regarding the potentiation of the non-depolarizing neuromuscular blockade.

There were a few limitations. First, the sample size used in this study was small. On the basis of previous literature (H. R. Munoz *et al.*, 1997), we assumed that the pretreatment with ondansetron would have resulted in a 30% more rapid onset of action. However, we confirmed a difference of only 8.5%, which may be attributable to the small sample size. Second, we measured the onset time of the rocuronium-induced neuromuscular block as TOF = 0. There were negligible differences in the timing between the onset of twitch force depression (more than 95% of the maximal twitch force), and TOF = 0. If we were to measure the 95% reduction in the twitch force contraction as a parameter of the onset of action, different results may have been obtained. Lastly, we did not measure the recovery profile of the rocuronium-induced neuromuscular block; this would have provided additional, useful information regarding the effect of ondansetron. In conclusion, pretreatment with ondansetron (8 mg) prior to anesthesia had no significant clinical effect on the onset time of the rocuronium-induced neuromuscular block. It is recommended that a full intubating dose should be administered, even in addition to the pretreatment with ondansetron, for achieving the standard induction with rocuronium. Further studies are needed to investigate the effects of ondansetron pretreatment on the recovery profile of patients and its interaction with reversal agents.

Acknowledgement

This study supports by department funding only.

Declaration of C.O.I.

All of authors declare no competing interests.

REFERENCES

Baek, C.W., Kang, H., Jung, Y.H., Park, J.W., Jung, H.S., Lee, Y.K., Yang, H.S. 2006. Effects of Ondansetron and Granisetron on Rocuronium-induced Neuromuscular Blockade in a Rat Phrenic Nerve-hemidiaphragm Preparation. *Korean J. Anesthesiol.* 51, 94.

Cross, K.M.L., Foreman, R.C. and Chad, J.E. 1995. Enhancement by 5□hydroxytryptamine and analogues of desensitization of neuronal and muscle nicotinic receptors expressed in Xenopus oocytes. *Br. J. Pharmacol.* 114, 1636–1640.

Faul, F., Erdfelder, E., Buchner, A. and Lang, A.-G. 2009. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav. Res. Methods 41, 1149–60.

Fuchs-Buder, T., Claudius, C., Skovgaard, L.T., Eriksson, L.I., Mirakhur, R.K., Viby-Mogensen, J., Medicine, C., Institutet, K. and Ireland, N. 2007. Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. Acta Anaesthesiol. Scand. 51, 789–808.

Munoz, A. G. Gonzalez, J. A. Dagnino, J.A.G. and A.E.P., 1997. The effect of Ephedrine on The Onset Time of Rocuronium. *Anesth Analg* 85, 437–440.

Jee, H. R., Yoon, Y.S., Jang, H.J., C.H., 2010. Prophylactic antiemetic effects in gynecologic patients receiving fentanyl IV-patient controlled analgesia: comparison of combined treatment with ondansetron and dexamethasone with metoclopramide and dexamethasone. *Korean J. Anesthesiol.* 59, 335.

Karlin, A., Akabas, M.H., 1995. Toward a structural basis for the function of nicotinic acetylcholine receptors and their cousins. *Neuron* 15, 1231–1244.

Lien, C.A., Gadalla, F., Kudlak, T.T., Embree, P.B., Sharp, G.J., Savarese, J.J. 1993. The effect of ondansetron on atracurium-induced neuromuscular blockade. *J. Clin. Anesth*. 5, 399–403.

McKenzie, R., Kovac, A., O'Connor, T., Duncalf, D., Angel, J., Gratz, I., Tolpin, E., McLeskey, C., Joslyn, A. 1993. Comparison of ondansetron versus placebo to prevent postoperative nausea and vomiting in women undergoing ambulatory gynecologic surgery. Anesthesiology 78, 21–8.

Ok, S.Y., Kim, S.C., Kim, S.I., Lee, J.S., Jung, J.Y., Hwang, K.H., Kim, S.Y. 2003. Effects of Ondansetron on the Neuromuscular Block of Vecuronium, Rocuronium or Atracurium in a Rat Phrenic Nerve-Hemidiaphragm Preparation. *Korean J. Anesthesiol*. 45, 650–655.

Paul, M., Callahan, R., Au, J., Kindler, C.H. and Yost, C.S. 2005. Antiemetics of the 5-hydroxytryptamine 3A antagonist class inhibit muscle nicotinic acetylcholine receptors. Anesth. Analg. 101, 715–21, table of contents.

Taylor, P. 1985. Ganglionic stimulating and blocking agents, in: Gilman, A., Goodman, L., Rail, T., Murad, F. (Eds.), Goodman and Gilman's The Pharmacological Basis of Therapeutics. Macmillan, New York, p. 215.

Vanner, S. and Surprenant, A. 1990. Effects of 5-HT3 receptor antagonists on 5-HT and nicotinic depolarizations in guinea-pig submucosal neurones. *Br J Pharmacol* 99, 840–844.

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