

Association of 5-HT₃B Receptor Gene Polymorphisms with the Efficacy of Ondansetron for Postoperative Nausea and Vomiting

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Purpose: Postoperative nausea and vomiting (PONV) is a common problem after general anesthesia. Although 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonists have significantly reduced PONV, over 35% of patients treated with ondansetron can experience PONV. In this study, we investigated whether the Y129S and -100_-102AAG deletion polymorphisms of the 5-HT₃B receptor gene affect the efficacy of ondansetron in preventing PONV.

Materials and Methods: Two hundred and forty-five adult patients who underwent laparoscopic cholecystectomy were enrolled. Ondansetron 0.1 mg/kg was intravenously administered 30 minutes before the end of surgery. Genomic DNA was prepared from blood samples using a nucleic acid isolation device. Both the Y129S variant and the -100_-102AAG deletion variant were screened for using a single base primer extension assay and a DNA direct sequencing method, respectively. The relationship between genetic polymorphisms and clinical outcomes of ondansetron treatment was investigated.

Results: Among the 5-HT₃B AAG deletion genotypes, the incidence of PONV was higher in patients with the homomutant than with other genotypes during the first 2 hours after surgery ($p=0.02$). There were no significant differences in the incidence of PONV among genotypes at 2–24 hours after surgery. In the Y129S variants of the 5-HT₃B receptor gene, there were no significant differences in the incidence of PONV among genotypes during the first 2 hours and at 2–24 hours after surgery.

Conclusion: The response to ondansetron for PONV was significantly influenced by the -100_-102AAG deletion polymorphisms of the 5-HT₃B gene. Thus, the -100_-102AAG deletion variants may be a pharmacogenetic predictor for responsiveness to ondansetron for PONV.

Key Words: Postoperative nausea and vomiting, 5-HT₃ receptor, ondansetron, genetic polymorphism

INTRODUCTION

Postoperative nausea and vomiting (PONV) is a common and unpleasant experience for surgical patients undergoing general

anesthesia.^{1,2} The incidence of PONV is approximately 20–30%, although it can be as high as 80% in patients with risk factors.¹ PONV may result in adverse events such as prolongation of the recovery period, delay of discharge, and postsurgical complications, and as such, it should be prevented by adequate management.^{3,4}

Selective 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonists have been widely researched and are currently used as the primary therapy for PONV prevention, as they have fewer side-effects such as sedation or extrapyramidal symptoms than other antiemetics.^{5–7} Although 5-HT₃ receptor antagonists have significantly reduced PONV, it is reported that over 35% of patients treated with ondansetron experience PONV.³ One reason for this unsatisfactory response may be individual differences in the biotransformation and disposition of 5-HT₃

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receptor antagonists due to gene polymorphisms related to pharmacokinetics.^{1,3} However, the variations in gene coding for the 5-HT3 receptor as a target structure of the drug may also affect the extent of PONV and the antiemetic effects of 5-HT3 receptor antagonists.⁸⁻¹¹

In previous pharmacogenomic studies, Y129S and -100_-102AAG deletion variants of the 5-HT3B receptor gene were found to be possibly associated with nausea induced by paroxetine and the clinical response of 5-HT3 receptor antagonists for chemotherapy-induced nausea and vomiting (CINV), respectively.^{9,10,12,13} We thus hypothesized that these polymorphisms might have a relationship with the therapeutic failure of 5-HT3 receptor antagonists for PONV treatment. In this study, we investigated whether the Y129S and -100_-102AAG deletion polymorphisms as variants of the 5-HT3B receptor gene affect the efficacy of ondansetron in preventing PONV in patients undergoing general anesthesia for laparoscopic surgery.

MATERIALS AND METHODS

After obtaining Institutional Review Board approval and written informed consent from all patients, 288 adult patients of the American Society of Anesthesiologists (ASA) physical status I or II and ages 18 to 65 years who were scheduled to undergo laparoscopic cholecystectomy were recruited in this study. Before the surgery, all patients were interviewed to determine their past medical history, including tobacco and alcohol use, the presence of previous postoperative nausea or vomiting, and motion sickness. Patients with a history of drug abuse, a known prolongation of the QTc interval on electrocardiography, morbid obesity (body mass index >31 kg/m²), antiemetics use within 24 hours before the study, and significant hepatic or renal disease were excluded from the study.

Patients did not receive premedication. Upon arrival in the operating room, all patients were monitored with electrocardiography, noninvasive blood pressure, and pulse oximetry. Anesthesia was induced with thiopental 4-5 mg/kg, remifentanyl 1.0 µg/kg, and rocuronium 0.6 mg/kg. After induction of anesthesia, the patients' lungs were ventilated with 50% oxygen. Anesthesia was maintained with sevoflurane 1.5-2.0% and remifentanyl 0.1-0.2 µg/kg/min. Patients were kept warm using a forced-air warming system (Bair-Hugger®, Augustine-Medical, Eden Prairie, MN, USA) to maintain a body temperature of 36.0-37.0°C. Bispectral index (BIS) was measured continuously on a monitor (A-2000 BIS monitor, Aspect Medical Systems, Norwood, MA, USA) to maintain appropriate anesthetic depth throughout the operation. Thirty minutes before the end of surgery, ondansetron 0.1 mg/kg was administered intravenously, and ketorolac 60 mg was given for postoperative pain management. When the patients were able to obey commands, they were extubated. The total dose of remifentanyl during anesthesia, and the pain score (0=no pain, 10=most extensive pain) upon

arrival in the post anesthesia care unit were assessed.

The intensity of PONV was assessed during the first 2 hours after surgery and at 2-24 hours after surgery using a 10-cm visual analogue scale (0=no nausea, 10=most extensive nausea). At the same time, patients were monitored to determine whether an episode of vomiting occurred and whether antiemetics were administered. Episodes of retching were considered to be vomiting. During each time period, the maximal degree of PONV experienced by the patient was recorded, and any episodes of nausea, retching or vomiting were defined as the presence of PONV. If a patient experienced no episodes of nausea or vomiting after the administration of ondansetron, he or she was allocated to the no-PONV group. When the patient vomited or requested a rescue antiemetic, metoclopramide 10 mg was administered intravenously. Patients who reported a pain score >4 or requested rescue analgesics were treated with intramuscular injection of tramadol 50 mg. The primary endpoint of this study was the proportion of patients who did not experience any episodes of PONV after the administration of ondansetron for the prevention of PONV for each genotype group.

Genomic DNA was prepared from blood samples using a nucleic acid isolation device, QuickGene-mini80 (FUJIFILM, Tokyo, Japan). Genotyping for Y129S variants of the 5-HT3B receptor gene was screened through a single base primer extension assay using the ABI PRISM SNaPshot Multiplex kit (Applied Biosystem, Foster City, CA, USA) according to the manufacturer's recommendations. Analysis was performed using GeneMapper software (version 3.0; Applied Biosystems). Genotyping of the -100_-102AAG deletion variants of the 5-HT3B receptor gene was carried out using a DNA direct sequencing method. PCR was used to amplify one 5-HT3B fragment using UCSC In-Silico PCR. The PCR products were purified using a Multi-Screen384-PCR Filter Plate (Millipore, Billerica, MA, USA). The purified products were then sequenced using a BigDye Terminator Cycle Sequencing Kit and an ABI 3730xl automated sequencer (Applied Biosystems). Mutation analyses were performed using the Phred, Phrap, Consed, and Polyphred 5.04 software packages (University of Washington, Seattle, WA, USA).

Considering that the expected frequency of the AAG deletion allele was 16.5% based on a previous study,¹⁴ we estimated that to achieve a power of 90% ($\alpha=0.05$, $\beta=0.1$) when assuming a difference of 20% in the failure rate for ondansetron treatment among the genotypes, 240 patients would be required. Therefore, we recruited 288 patients to compensate for excluded patients. The frequencies of the single nucleotide polymorphisms (SNPs) were assessed for deviation from Hardy-Weinberg equilibrium using Fisher's exact test. Frequency differences in genotype, demographic data, severity of PONV, and incidence of PONV were compared by the chi-square test, Fisher's exact test, the Kruskal-Wallis test, or an ANOVA with Bonferroni correction as appropriate. Data were analyzed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). A value of $p<0.05$ was considered significant.

RESULTS

Of the 288 patients assessed to participate in this study, 43 were excluded from the study due to refusal to participate or sampling error. Ultimately, a total of 245 patients were enrolled. There were no significant differences in patient characteristics and clinical data among genotypes (Table 1 and 2).

The frequencies of all genotypes were in Hardy-Weinberg equilibrium ($p>0.05$). Frequencies of the 5-HT3B AAG deletion genotypes were as follows: 77.6% for wild type, 19.6% for heteromutant, and 2.8% for homomutant. Among the 5-HT3B AAG deletion genotypes, the incidence of PONV was higher in patients with a homomutant genotype than other genotypes during the first 2 hours after surgery (Codominant model, $p=0.02$) (Table 3). This difference was also statistically significant when analyzed between the patients with and without the Ins/ins (Dominant model, $p=0.04$) or the Del/del genotype (Recessive model, $p=0.02$), respectively. There were no significant differences in the incidence of PONV among genotypes at 2–24

hours after surgery. In the Y129S variants of the 5-HT3B receptor gene, there were no significant differences in the incidence of PONV among genotypes during the first 2 hours or at 2–24 hours after surgery (Table 4).

The severity of nausea was significantly higher in patients with a homomutant genotype than other genotypes during the first 2 hours after surgery in the 5-HT3B AAG deletion genotypes ($p=0.02$) (Table 5). There were no significant differences in the severity of nausea among genotypes in the Y129S variants of the 5-HT3B receptor gene (Table 6).

DISCUSSION

The present study revealed a significant association between the -100_-102AAG deletion polymorphism and the efficacy of ondansetron. The patients with a homomutant genotype of the -100_-102AAG deletion variant had a higher incidence of PONV than other genotypes during the first 2 hours after sur-

Table 1. Patients and Clinical Characteristics of the Patients According to 5-HT3B AAG Deletion Genotype

Variable	Genotype		
	Ins/ins	Ins/del	Del/del
Number of patients	190	48	7
Gender (M/F)	80/110	20/28	3/4
Age (yr)	46 (21–65)	46 (23–65)	51 (45–57)
Weight (kg)	64.4 (10.3)	64.7 (11.2)	60.7 (10.9)
History of smoking	22	7	2
History of PONV	3	1	0
History of motion sickness	28	8	1
Duration of surgery (min)	72 (30)	70 (26)	74 (20)
Remifentanyl doses in OR (μ g)	505 (210)	504 (222)	656 (328)
Pain score in PACU	5 (3–6)	4 (3–6)	4 (3–4)
Number of patients who required rescue analgesics	93	30	3

Ins, insertion; Del, deletion; PONV, postoperative nausea and vomiting; OR, operation room; PACU, post-anesthesia care unit. Values are presented as mean (range) for age, median (interquartile range) for pain score, mean (SD), or number of patients.

Table 2. Patients and Clinical Characteristics of the Patients According to Y129S Variants of the 5-HT3B Receptor Gene

Variable	Genotype		
	AA	AC	CC
Number of patients	146	83	16
Sex (M/F)	64/82	33/50	6/10
Age (yr)	47 (23–65)	45 (21–65)	48 (31–61)
Weight (kg)	64.5 (10.3)	64.7 (11.4)	62.6 (6.8)
History of smoking	18	12	1
History of PONV	4	0	0
History of motion sickness	27	9	1
Duration of surgery (min)	73 (31)	70 (26)	69 (22)
Remifentanyl doses in OR (μ g)	513 (231)	505 (189)	501 (229)
Pain score in PACU	5 (3–6)	4 (3–6)	5 (4–6)
Number of patients who required rescue analgesics	71	47	8

PONV, postoperative nausea and vomiting; OR, operation room; PACU, post anesthesia care unit. Values are presented as mean (range) for age, median (interquartile range) for pain score, mean (SD), or number of patients.

gery; however, the Y129S genotypes were not related to the clinical response to ondansetron.

The 5-HT3 receptor antagonists have been used effectively in order to prevent PONV.^{5,7} Unfortunately, all patients do not show a favorable outcome when the drug is administered.³ This therapeutic failure may be partially explained by other complex mechanisms of PONV, such as the effects of histamine, dopamine, and opioids other than 5-HT3.^{1,15} Considering the increased occurrence of PONV in several generations of the same family, considerable concordance of PONV in twins, and the established high risk of PONV in children with a family history of PONV, the individual variability of drug responses can also

be associated with inherited differences in genes modifying the drug's actions.¹⁰ This variability in drug action may be pharmacokinetic or pharmacodynamic.⁸ Genetic variations affecting the efficacy of 5-HT3 receptor antagonists have also been studied from a pharmacokinetic and pharmacodynamic perspective.^{10,13,16}

The primary target in pharmacokinetic investigations includes the CYP450 2D6 isoform (CYP2D6) associated with metabolic pathways of 5-HT3 receptor antagonists. Polymorphic variations of the CYP2D6 system may induce ultra-rapid metabolism and subsequent therapeutic failure of 5-HT3 receptor antagonists.¹⁰

Table 3. Effects of 5-HT3B AAG Deletion Genotype on the Efficacy of Ondansetron for Postoperative Nausea and Vomiting

Genotypes	First 2 hrs		2–24 hrs	
	No PONV	PONV	No PONV	PONV
Ins/ins	119 (62.6)	71 (37.4)	167 (87.9)	23 (12.1)
Ins/del	25 (52.1)	23 (47.9)	44 (91.7)	4 (8.3)
Del/del	1 (14.3)	6 (85.7)	7 (100.0)	0 (0.0)
<i>p</i> values				
Overall	0.02		0.49	
Ins/ins vs. Non-Ins/ins	0.04		0.31	
Non-Del/del vs. Del/del	0.02		1.00	

Ins, insertion; Del, deletion; PONV, postoperative nausea and vomiting. Values are number of patients (%).

Table 4. Effects of Y129S Variants of the 5-HT3B Receptor Gene on the Efficacy of Ondansetron for Postoperative Nausea and Vomiting

Genotypes	First 2 hrs		2–24 hrs	
	No PONV	PONV	No PONV	PONV
AA	89 (61.0)	57 (39.0)	131 (89.7)	15 (10.3)
AC	48 (57.8)	35 (42.2)	73 (88.0)	10 (12.0)
CC	8 (50.0)	8 (50.0)	14 (87.5)	2 (12.5)
<i>p</i> values				
Overall	0.67		0.90	
AA vs. AC+CC	0.49		0.65	
AA+AC vs. CC	0.44		0.69	

PONV, postoperative nausea and vomiting. Values are number of patients (%).

Table 5. Effects of 5-HT3B AAG Deletion Genotype on the Efficacy of Ondansetron for Nausea Severity

Genotypes	First 2 hrs	2–24 hrs
Ins/ins	0 (0–3)	0 (0–0)
Ins/del	0 (0–4)	0 (0–0)
Del/del	4 (2–5)	0 (0–0)
<i>p</i> values		
Overall	0.03	0.43
Non-Del/del vs. Del/del	0.02	0.33
Ins/ins vs. Non-Ins/ins	0.05	0.26

Ins, insertion; Del, deletion. Values are median (interquartile range).

Table 6. Effects of Y129S Variants of the 5-HT3B Receptor Gene on the Efficacy of Ondansetron for Nausea Severity

Genotypes	First 2 hrs	2–24 hrs
AA	0 (0–4)	0 (0–0)
AC	0 (0–3)	0 (0–0)
CC	0 (0–4)	0 (0–0)
<i>p</i> values		
Overall	0.67	0.53
AA+AC vs. CC	0.37	0.35
AA vs. AC+CC	0.81	0.36

Values are median (interquartile range).

Variations in genes encoding the target molecule of a drug as pharmacodynamic factors are associated with an alteration of drug activity.⁸ As the primary target of 5-HT₃ receptor antagonists, the 5-HT₃ receptor is a ligand-operated ion channel that includes five different receptor subunits (5-HT_{3A}, B, C, D, and E) identified in humans.^{8,17} The 5-HT_{3A} subunits are capable of forming a functional homomeric complex of the 5-HT₃ receptor, whereas the 5-HT_{3B} subunit forms a heteromeric complex through an association with the 5-HT_{3A} subunit.^{8,16} The primary differences between the homomeric 5-HT_{3A} and heteromeric 5-HT_{3A}/3B complexes are biologic characteristics, conductance, and other slight differences in their pharmacological properties.^{8,17} The function and expression of the 5-HT₃ receptor can be affected through variation of the genes coding its subunits; in particular, polymorphisms of the 5-HT_{3B} subunit gene can modify the pharmacological and functional properties of the 5-HT₃ receptor.^{17,18} The Y129S and -100_-102AAG deletions investigated in this study are the typical genetic variations of the 5-HT_{3B} subunit.^{9,10,16} Y129S is a substitution of an amino-acid located in the coding region of the 5-HT_{3B} subunit gene. Sugai, et al.¹² demonstrated that the Y129S polymorphism significantly affected the incidence of nausea induced by paroxetine; however, in a previous study on the efficacy of 5-HT₃ receptor antagonists in CINV, the Y129S polymorphism did not change the incidence of CINV.¹³ In this study, the Y129S polymorphism also did not change the response to ondansetron for PONV. Although this inconsistency may be explained by differences in factors such as paroxetine use, emetogenic chemotherapy administration, and general anesthesia, the reason for the inconsistent results is not clear.¹² The -100_-102AAG deletion is a 3-base pair deletion within the 5' untranslated region of the 5-HT_{3B} subunit gene.¹⁰ Tremblay, et al.¹³ demonstrated that this deletion variant in the promoter region was significantly associated with a high incidence of CINV, whereas Rueffert, et al.⁹ did not confirm this specific result in patients with PONV. The present study showed that patients who were homomutant for the AAG deletion genotype had a higher incidence of PONV than other genotypes. The discrepancy between Rueffert's and our results may have been caused by differences in patient characteristics and study design.⁹

Despite our favorable result, the functional impact of the -100_-102AAG deletion on the 5-HT_{3B} receptor subunit is not yet obvious, and an *in vitro* study on the functional aspects of polymorphisms related to the 5-HT_{3B} receptor subunit is still lacking.¹³ Furthermore, various issues related to the interactions existing between the subunits that make up the 5-HT₃ receptor have not been fully explained, even though the 5-HT_{3B} receptor subunit is likely to play an important functional role, considering the current knowledge about the 5-HT₃ receptor.¹⁸ However, a previous study using secondary structure prediction showed that this polymorphism can cause a structural modification of mRNA when compared with the wild type.¹⁹ Meineke, et al.²⁰ demonstrated that the -100_-102AAG deletion increased

the promoter activity of the 5-HT_{3B} receptor gene *in vitro*. In addition, this variant is a deletion of three nucleotides. Therefore, it could have a much greater impact on the receptor function than other single nucleotide polymorphisms.¹³

We found that the response to ondansetron for PONV did not differ according to the 5-HT_{3B} -100_-102AAG deletion genotypes at 2–24 hours after surgery; however, in this study, 89% or more patients did not suffer from PONV between 2 and 24 hours, which may explain the lack of association observed during this time period.

There are a variety of risk factors that can affect the development of PONV. It is well-documented that female gender, a previous history of PONV or motion sickness, the use of intravenous opioids, and non-smoking status are the main predictors of PONV.^{15,21} In this study, we did not find any significant differences in these predictors based on genotype. In order to minimize the influence of anesthetic and surgical factors on our results, we enrolled patients who underwent an identical surgical procedure and performed general anesthesia using the same anesthetic agent while maintaining BIS values at a constant level. Furthermore, our study confirmed that genotype distribution of the Y129S SNP and -100_-102AAG deletion of the 5-HT_{3B} receptor gene was in accordance with Hardy-Weinberg equilibrium, suggesting that our finding involving this receptor gene is likely robust.

We concluded that the response to ondansetron for PONV was significantly influenced by the -100_-102AAG deletion polymorphisms of the 5-HT_{3B} gene. Taking these results into account, the -100_-102AAG deletion variants may be a pharmacogenetic predictor of responsiveness to ondansetron for PONV. Further research is needed to clarify the functional role of this polymorphism in the 5-HT_{3B} subunit and the interaction between the 5-HT₃ receptor subunits.

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