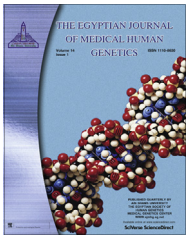
The Egyptian Journal of Medical Human Genetics (2013) **14**, 331–336

Ain Shams University

The Egyptian Journal of Medical Human Genetics

www.ejmhg.eg.net
www.sciencedirect.com



REVIEW

Resistance to ondansetron: Role of pharmacogenetics in post-operative nausea and vomiting

Kulsoom Farhat [a,*], Muhammad Ismail [b], Shabana Ali [a], Anwar Kamal Pasha [c]

[a] *Army Medical College (National University of Sciences & Technology), Pakistan*
[b] *Institute of Biomedical and Genetic Engineering, Pakistan*
[c] *Combined Military Hospital, Rawalpindi, Pakistan*

Received 28 January 2013; accepted 17 March 2013
Available online 4 May 2013

KEYWORDS

5-Hydroxytryptamine type 3 receptor antagonists;
Ondansetron;
Post-operative nausea and vomiting;
Polymorphism;
Pharmacogenetics

Abstract Post-operative nausea and vomiting is the most annoying and at the same time a dangerous side effect of general anaesthesia. Ondansetron is a routinely used anti emetic drug which is being administered by the trial and error principle. Though it did revolutionized the management of this condition but by and large failed to completely eliminate the problem. Recently an important factor possibly elucidating this failure is said to be the differing expression of genes controlling proteins that are involved in transport and receptors related to this drug. Quite surprisingly these transporter and receptor pathways have been found to be polymorphic and at the same time shown to be related to efficacy of the drug. The differentiation between those responding to treatment and those not responding may pave a way to individualize treatment for emesis to a greater extent. This review highlights the pharmacogenetics related to this commonly used anti-emetic drug in anaesthesia. It is visualized as a promising way to achieve the target of individualized therapy. It seems obvious that pharmacogenetics will become an important field of anaesthesia research in the future.

Contents

* Corresponding author. Tel./fax: +92 0512655589.
E-mail address: kulsoompasha@yahoo.com (K. Farhat), anwarkamalpasha@gmail.com (A.K. Pasha).
Peer review under responsibility of Ain Shams University.

Production and hosting by Elsevier

1110-8630 © 2013 Production and hosting by Elsevier B.V. on behalf of Ain Shams University.
http://dx.doi.org/10.1016/j.ejmhg.2013.03.003

1. Post-operative nausea and vomiting

A strong association of post-operative nausea and vomiting exists with general anaesthesia ever since the ether and chloroform times. Those were the times when the incidence of this was around 70–80%. With the current advances in anaesthesia practices, the average incidence has come down by 50% however in high risk groups it still remains up to 80% [1]. A survey was conducted by Macario et al. in 1999 where they found it to be the most common, objectionable and disturbing effect of general anaesthesia [2]. More recently several authors identified it as the "big little problem" [3,4] due to the undesirable outcomes posed by it. The researchers have designated the occurrence of post-operative nausea and vomiting to "early" when it is occurring within the first two hours after surgery, and when the similar complaints extend to the first post-operative day then they call it the "delayed" post-operative nausea and vomiting [5]. There are three stages of post-operative nausea and vomiting usually occurring within 24 h of surgery and these are nausea, retching and vomiting. Nausea is a subjective feeling in which there is an urge to vomit. Vomiting on the other hand is when the contents of stomach are forcefully thrown out of stomach through the mouth [6]. Retching precedes vomiting and is somewhat in between the two. It is the result of muscular movement of the abdomen that results in a non-productive outcome as it occurs when the stomach is empty [7]. Retching and vomiting can be quantified and are regarded to be objective as compared to nausea which is a subjective feeling.

The consequences of post-operative nausea and vomiting are far more than what one can appreciate, affecting patients in many ways. Usually it is said that among the various effects produced the prominent ones are physical, metabolic, psychological and economic. The complications related to the patient include the distress and the discomfort to the patient along with disruption of the wound with delayed healing and an overall bad surgical outcome. These all contribute to the post-operative morbidity creating an immense challenge to the surgical team as well as the operation theatre trained personnel. Moreover there is a significant burden on the economy of the country as the health care costs are increased extensively. The contributing factors to this remain the increased stay of the patients in the wards creating delay in discharge, postponement in resuming daily works and sometimes even readmissions become mandatory in the case of unpredictable complications.

Post-operative nausea and vomiting is believed to be a multifactorial problem. There is a long list of risk factors but only few appear to be clearly established. Among these are the female sex, any previous history of motion sickness or post-operative nausea and vomiting and the use of volatile anaesthetics, nitrous oxide and opioids in surgery. They all have proved from time to time to be the autonomous risk factors contributing to it in various settings. In spite of a large amount of research on the identification of risk factors and best possible treatments available, the data continue to reveal that in the post-operative rooms 20–30% of the patients experience post-operative nausea and vomiting [8]. The key cause of this treatment failure is attributed to the multifactorial genesis of post-operative nausea and vomiting [9]. Throughout the world a lot has been done till date to counter this annoying disturbance. Researchers have continued to focus on ways to prevent or treat it. Immense amount of resources, money and zealous efforts spent so far however failed to bring up a single simple solution [10].

Recently with new developments in science the pharmacogenetics is emerging as an interesting area of medical study. The genetic makeup is said to affect the response to different drugs. Thus the focus of researchers has now shifted to the genetic component likely to be playing an important role in post-operative nausea and vomiting. They assume that it may be responsible for treatment failure in some individuals leading to inter individual variations. The question still remains unanswered and demands further studies to establish a role of genetics in the management of post-operative nausea and vomiting. Kranke and colleagues (2009) strongly believed that post-operative nausea and vomiting should not be considered as the "big little problem", rather it should be viewed as a "big little opportunity" [8]. We are looking at this in the similar way hoping that any work in this regard will represent one of the many efforts towards a complete understanding of pharmacogenetics of post-operative nausea and vomiting.

2. Treatments options for post-operative nausea and vomiting

The treatment protocols for the control of post-operative nausea and vomiting can only be designed if there is complete know how of the risk factors accountable for post-operative nausea and vomiting. Up till now several pharmacological agents have come up for the management of this condition. These drugs are by and large grouped according to the type of receptor at which they act, usually as an antagonist. The receptors present in the vomiting centres include serotonin, dopamine, histamine and muscarinic receptors. The traditional antiemetic medications directed against these receptors are antihistamines, anticholinergics, and dopamine receptor antagonists. And the newer and recent introduction to this category is the 5-hydroxytryptamine-3 receptor antagonists (5-HT_3RAs) and the neurokinin receptor antagonists. However so far none of these drug classes are absolute in the suppression of post-operative nausea and vomiting and has just projected the image of an illusion as far as adequate control or elimination of PONV is concerned. In spite of all the strategies available, the problem of post-operative nausea and vomiting exists to the same extent [11].

3. 5-Hydroxytryptamine-3 receptor antagonists

5-HT_3RAs came into the markets for the treatment of chemotherapy induced nausea and vomiting in the early 1990s. Lately they are now also used for the prevention and treatment of post-operative nausea and vomiting [12] and they have made such a strong place in the patient's treatment plan alongside drugs for anaesthesia that they are regarded as the ''gold standard'' in this regard. The reason for this popularity lies in the fact that over the course of time they have proved to be far more effective and safer than the traditional antiemetic drugs. They are devoid of the side effects that the other commonly used anti emetics possess. They thus have transformed post-operative nausea and vomiting and chemotherapy induced nausea and vomiting treatment to some extent and have provided some relief to physicians, oncologists and anaesthesiologists.

5-HT_3RAs include ondansetron, tropisetron, granisetron and dolasetron. All these antagonists have similar chemical structures to serotonin. They share similar efficacy and fine acceptability at equipotent doses, however slight differences exists in the side effect profiles of these. Most of the times when one has to choose among them, the decision depends basically upon the cost concerns, the safety of the drug, the ease of dosing, and the specific needs of the patient population in which it is to be used.

4. Ondansetron

Among all the 5-HT_3RAs the ondansetron is the most widely used drug to prevent post operative nausea and vomiting or chemotherapy induced nausea and vomiting. It is a carbazalone derivative that is structurally related to serotonin and possesses specific 5-HT subtype 3 receptor antagonism. It is assumed that it has no activity at dopaminergic, histaminergic, adrenergic, and cholinergic receptors. Ondansetron possesses a favourable drug profile like all 5-HT_3RAs. This drug is recognized by the adenosine triphosphate-binding cassette subfamily B member 1(ABCB1) drug transporter in the blood brain barrier which in turn determines the concentration of drug in the central nervous system. The site of action of ondansetron is the 5-HT_3 receptors in the central nervous system, the highest concentration of which are found in the solitary tract nucleus and the chemoreceptor trigger zone. Ondansetron produces its antiemetic effects by acting at these sites. Normally during general anaesthesia serotonin is released from the enterochromaffin cells. This serotonin stimulates the serotonin receptor which in turn activates the vomiting centre and that is how emesis is generated [10]. Ondansetron being a serotonin receptor antagonist binds to these receptors and competitively blocks them, in this way signals of emesis are prevented from travelling to the vomiting centre. The binding affinity of ondansetron for 5-HT3 receptors has a pKi value of 8.07. The affinity of ondansetron to its receptor plays a vital role in determining the duration of action and there is as such a lesser role of its half-life [13]. It is preferably given through the intravenous route as this route ensures adequate absorption and rapid distribution within the body. The half-life approximately ranges between 3 and 5 h and has duration of action of 4–48 h. The metabolism of the drug is extensive; initially there is hydroxylation and then conjugation. There is a decrease in the clearance of the drug with advancing age which is very much consistent with the deterioration in hepatic and renal functions in the elderly [12]. Likewise the hepatic and renal diseases will decrease the clearance of ondansetron.

The dose of ondansetron is variable, largely depending upon the age of the patient as well as the medical condition that is being treated. At the same time the dose also depends upon the other medical conditions that the patient may have. The clinicians have up till now no choice but to use the trial and error method to measure the response to ondansetron and adjust its dose. There is no evidence to compliment the rational use of drugs in treating emesis.

5. Pharmacogenetic issues related to ondansetron

As described earlier there is no complete elimination of post-operative nausea and vomiting even with the newer drugs, so is the case with ondansetron. This resistance to ondansetron is emerging as one of the most serious problems in the treatment of post-operative nausea and vomiting that is likely to have a complex genetic and acquired basis. It has been of great concern that patients get the best possible anti emetics during surgery and yet around 26% still require additional treatment in the post-operative period and 40% of patients require additional treatment for post-operative nausea and vomiting even after discharge from the hospital. Among the patients who complain of repeated vomiting, the majority are those who do document a similar family history too. It is now realized that the genes may be playing a vital role in determining the individual's response. Genetic differences influencing response to the pharmacotherapy of post-operative nausea and vomiting are under investigation. Candidate genes such as target receptors, transporters and other molecules important for pharmacotherapy are under investigation. These genetic variations are represented as single nucleotide polymorphisms (SNPs) in the human genome and they vary across the world population and are present in millions of number. In order to understand this it is essential to have the basic molecular concepts.

DNA (deoxyribonucleic acid) encodes the molecular structure of each protein present in the cell nucleus of humans. Basically DNA is comprised of a chain which has four types of nucleotide subunits. Each subunit has a sugar, a phosphate group, and one of the four bases which are adenine, cytosine, guanine, and thymine. It exists in the form of a double helix, in which two individual DNA strands twist around each other. In this structure guanine pairs with cytosine and adenine pairs with thymine in accordance with the base pairing rules. Any variation occurring within the sequence of the base pairs forms the genetic code. The entire complement of genes in an organism or cell is called its genome, which may be stored in one or more chromosomes. Humans have 23 pairs of chromosomes. A gene is a hereditary coding unit of a living organism composed of a specific DNA sequence occupying a specific position within a chromosome. All genes have a common structure that includes a 5′ untranslated region, exons, introns, and a 3′ untranslated region. An allele is any of two or more alternative forms of a gene occupying the same chromosomal locus. The most common type of human genetic or allelic variation is the SNP. Up till now, more than 13 million SNPs have been recognized. Other types of mutations like insertion, deletion,

translocation or inversion may also produce allelic variation. These allelic variations can change the phenotype of an organism quite appreciably [14]. In recent years, it has been recognized that genetic polymorphisms contribute to immense alteration in terms of drug responsiveness. The genetic polymorphisms form the basis of pharmacogenetics and one of the primary steps in this regard is to spot polymorphisms in the candidate genes. The differences in the genetic makeup at several steps can significantly alter the response of a person to the drug. The several steps in pharmacokinetics and dynamics like absorption, distribution, metabolism, elimination and concentration of drug at target sites can be altered under their influence. A budding list of polymorphisms exists in different classes of genes encoding these transporters, receptors and targets, and this has been associated to the effects of drug in human beings, playing an important role in therapeutic outcome. The well known variations in drug transporters and drug target genotype in different geographic regions of the world are enough to prompt the investigators to determine the frequency of its genotypes in local population.

6. Variation in genes encoding drug transporters

Drug transporters play a key role in the passage of drugs across the blood brain barrier thus determining the disposition of drugs. Similarly the transporter ABCB1 has a role in the pharmacokinetics of ondansetron which is a substrate for P-glycoprotein (P-gp) [15]. It is a protein traversing the membrane that plays the role of an efflux pump [16]. This function of ABCB1 apparently is very important as it seems to be protecting the central nervous system from toxic compounds. On the other hand, certain drugs are prevented from entering the central nervous system. Over 50 SNPs in ABCB1 have been documented, which are said to affect the expression and function of P-gp [17] which is a member of ABCB1 family [18]. The two SNPs are of particular significance. One is the mutation at position 3435 in exon 26 (3435C > T) and the second is a mutation in exon 21 at position 2677 (2677G > T/A). Due to the presence of association with differences in expression or function of P-gp, 3435C > T has been extensively studied. Among various populations, a synonymous SNP, 3435C > T (amino acid position 1145) and a non-synonymous SNP, 2677G > T/A (amino acid position 893) are the most common polymorphisms and reported to be in linkage disequilibrium [19–21]. In addition, these polymorphisms have shown a high inter-ethnic variability [22–25]. Siddiqui et al. in 2003 demonstrated that the epileptic patients with the TT genotype at ABCB1 3435 exhibited a better drug response [26]. Two years later a study conducted in Turkey concluded that the 3435C > T SNP of ABCB1 was associated with the efficacy of 5-HT_3RAs for CINV [27]. Recently Chio et al. in 2010 demonstrated a significant association between the ABCB1 gene polymorphism and the response to ondansetron in post-operative nausea and vomiting patients. The incidence of post-operative nausea and vomiting was lower in patients with 2677TT and 3435TT genotypes than other genotypes during the first 2 h after surgery. It is likely that there was a higher concentration of ondansetron in the central nervous system in patients with 2677TT and or 3435TT genotype and thus responded better to ondansetron [28]. Therefore, it is sensible to hypothesize that the availability of ondansetron across the blood brain barrier could be influenced by the genetic variance of this transporter. This in turn affects the antiemetic efficacy of ondansetron [11].

This large number of SNPs in ABCB1 have been identified and reported in populations such as African Americans, Europeans and Asians like the Japanese. However a lot more needs to be done. It may be possible to target treatment appropriately, if it becomes possible to predict the responsiveness of post-operative nausea and vomiting to ondansetron. Therefore, it would be of great interest to determine the SNPs in ABCB1gene in different populations and to establish the importance (if any) of the identified SNPs as potential determinant of altered drug response.

7. Variation in genes encoding drug receptors

The 5-HT_3 receptor is an ion channel that is ligand-operated [29]. It is found on parasympathetic terminals in the gastrointestinal tract, the nucleus tractus solitarius and area postrema of the central nervous system [30]. There are five different receptor subunits of the 5-HT_3 receptors recognized in humans up till now: 5-HT_3A, B, C, D, and E. A variety of effects are produced as a result of activation of theses 5-HT_3 receptors such as emesis and behavioural effects including anxiety, depression and cognitive disorders [31]. 5-HT_3RAs specifically bind to the 5-HT_3A, 5-HT_3B receptor complex and so does the ondansetron and produce its effects. The 5-HT_3B subunit has shown to be the most important for its functionality.

As with the transporters there is also an emerging list of polymorphisms found in the gene encoding the target site of ondansetron. The genetic variation in 5HT_3B receptor has markedly affected the individual responsiveness to the drug. Several studies in Caucasians have shown an association between polymorphisms in the gene encoding the 5-HT_3B receptor and antiemetic response to 5-HT_3RAs. A pharmacogenetic study in German Caucasian patients was performed by Tremblay et al., who were receiving chemotherapy drug regimens. Patients were given tropisetron or ondansetron prophylactically for chemotherapy induced nausea and vomiting. It was observed that the patients had the maximum intensity of nausea and vomiting after chemotherapy if they were homozygous for the 100–102AGG deletion variant of the 5-HT_3B receptor gene, whereas the patients had less of these complaints who were having the wild type. This study included 242 patients only and thus the data were required to be confirmed with much larger sample sizes [32]. Yet, another study by Shinn et al. in 2011 [33] explored possible associations between genetic polymorphisms in nine exons of gene encoding the 5-HTR_3B receptor in relation to the occurrence of post-operative nausea and vomiting. They failed to find the similar association as was earlier seen by Tremblay et al. However they found that 201–202 del of CA influenced the post-operative nausea and vomiting incidence [32]. Thus so far only two studies have been conducted in Caucasians one revealing an association between AAG deletion variant of 5HT_3B receptor gene and antiemetic response to 5-HT_3RAs [34] and the other one not going in favour of it [35]. Among the very few studies from Asia, one is conducted in Japanese and one on Indonesians [34,35]. Tanaka et al. were able to show that deletion AAG at position 100–102 of the 5-HT_3B receptor was significantly associated with the failure of response to 5-HT3B receptor antagonists in CINV

[34]. In Indonesia the frequency and haplotype of deletion AAG was studied. This effect of deletion AAG or its haplotypes needs to be explored in different populations in relation to unresponsiveness to $5HT_3$RAs. Pharmacogenetic findings cannot always be simply translated among ethnicities due to differences in allele frequencies, haplotypes and gene functionality. So far to best of our knowledge this area of research has remained unfocused in our part of the world. This area of the world has yet not given any reports in this regard.

There is limited information available so far providing data regarding ABCB1 and 5-HT_3B gene frequency status and allele frequency from different regions of the world. Studies have been carried out in some populations which have shown racial differences in these allelic frequencies. Therefore, it would be of great interest to determine the clinically significant SNPs in ABCB1 and 5-HT_3B genes in our population too and to establish any importance of these as potential determinant of altered drug responses. There is a possibility that the population in different geographic regions of the world may have widely varying genetic allele frequencies for clinically relevant SNPs. By identifying the allelic frequency of common alleles in different ethnic populations, a comprehensive dosing model that is applicable regardless of ethnicity can be developed. Confirmation of a predictive role of these SNPs could contribute to future individualized treatment for post-operative nausea and vomiting patients and thereby a better treatment outcome and long term economic benefit. This will help in drafting clinical guidelines for $5HT_3$RAs prescription leading to enhanced efficacy and safety of $5HT_3$RAs.

World over genetic variations are under investigation. It is the utmost obligation on our part to consider and explore the genetic variations in our area too. The information gained through such studies will help in drafting guidelines for newer researchers in the field of pharmacogenetics. We will add not only to the knowledge of aetiology of post-operative nausea and vomiting which is considered to be multifactorial, but we may be able to explore the genetic basis for the inter individual variations to the study drug. This recognition of the relation between genotype and drug response is highly expected to affect the medical practice.

References

[1] Apfel CC, Laara E, Koivuranta M. A simplified risk score for predicting postoperative nausea and vomiting. Anesthesiology 1999;91:693–700.

[2] Macario A, Weinger M, Carney S. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. Anesth Analg 1999;89:652–8.

[3] Nelson T. Postoperative nausea and vomiting: understanding the enigma. J Perianesth Nurs 2002;17(3):178–89.

[4] Lichtor J, Glass P. We are tired of waiting. Anesth Analg 2008;107(3):353–5.

[5] Apfel C, Roewer N, Korttila K. How to study postoperative nausea and vomiting. Acta Anaesthesiol Scand 2002;44:470–4.

[6] Watcha MF, White PF. Postoperative nausea and vomiting, its etiology, treatment and prevention. Anesthesiology 1992;77:162–84.

[7] Habib AS, Chen YT, Taguchi A, Hu XH, Gan TJ. Postoperative nausea and vomiting following inpatient surgeries in a teaching hospital: a retrospective database analysis. Curr Med Res Opin 2006;22(6):1093–9.

[8] Kranke P, Roewer N, Smith A, Piper S, Wallenborn J, Eberhart L. Postoperative nausea and vomiting: what are we waiting for? Anesth Analg 2009;108(3):706–12.

[9] White P, O'Hara J, Roberson C, Wender R, Candiotti K. The impact of current anti-emetic practices on patient outcomes: a prospective study on high-risk patients. Anesth Analg 2008;107(2):452–8.

[10] Gan T. Mechanisms underlying postoperative nausea and vomiting and neurotransmitter receptor antagonist based pharmacology. CNS Drugs 2007;21(10):813–33.

[11] Ho K, Gan T. Pharmacology, pharmacogenetics, and clinical efficacy of 5HT3 receptor antagonists for postoperative nausea and vomiting. Curr Opin Anaesthesiol 2006;19:606–11.

[12] Gan TJ. Selective serotonin 5-HT3 receptor antagonists for postoperative nausea and vomiting. CNS Drugs 2005;19:225–38.

[13] Aapro M. Granisetron: an update on its clinical use in the management of nausea and vomiting. Oncologist 2004;9:673–86.

[14] Palmer SN, Giesecke NM, Body SC, Shernan SK, Fox AA, Collard CD. Pharmacogenetics of anesthetic and analgesic agents. Anesthesiology 2005;102:663–71.

[15] Yamamoto C, Murakami H, Koyabu N. Contribution of P-glycoprotein to efflux of ramosetron, a 5-HT3 receptor antagonist, across the blood–brain barrier. J Pharm Pharmacol 2002;54:1055–63.

[16] Marzolini C, Paus E, Buclin T, Kim RB. Polymorphisms in human MDR1 (P-glycoprotein): recent advances and clinical relevance. Clin Pharmacol Ther 2004;75:13–33.

[17] Jeong H, Herskowitz I, Kroetz DL, Rine J. Function-altering SNPs in the human multidrug transporter gene ABCB1 identified using a saccharomyces-based assay. PLoS Genet 2007;3(3):e39.

[18] Hoffmann U, Kroemer HK. The ABC transporters MDR1 and MRP2: multiple functions in disposition of xenobiotics and drug resistance. Drug Metab Rev 2004;36:669–701.

[19] Kim RB, Leake BF, Choo EF, Dresser GK, Kubba SV, Schwarz UI, et al. Identification of functionally variant MDR1 alleles among European Americans and African Americans. Clin Pharmacol Ther 2001;70:189–99.

[20] Ozawa S, Soyama A, Saeki M, Fukushima-Uesaka H, Itoda M, Koyano S. Ethnic differences in genetic polymorphisms of CYP2D6, CYP2C19, CYP3As and MDR1/ABCB1. Drug Metab Pharmacokinet 2004;19:83–95.

[21] Kimchi-Sarfaty C, Oh JM, Kim IW, Sauna ZE, Calcagno AM, Ambudkar SV, et al. A "silent" polymorphism in the MDR1 gene changes substrate specificity. Science 2007;315:525–8.

[22] Hoffmeyer S, Burk O, Von Richter O, Arnold HP, Brockmoller J, Johne A, et al. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. Proc Natl Acad Sci USA 2000;97:3473–8.

[23] Ameyaw MM, Regateiro F, Li T. MDR1 pharmacogenetics: frequency of the C3435T mutation in exon 26 is significantly influenced by ethnicity. Pharmacogenetics 2001;11(3):21721.

[24] Cascorbi I, Gerloff T, Johne A, Meisel C, Hoffmeyer S, Schwab M, et al. Frequency of single nucleotide polymorphisms in the P-glycoprotein drug transporter MDR1 gene in white subjects. Clin Pharmacol Ther 2001;69:169–74.

[25] Schaeffeler E, Eichelbaum M, Brinkmann U, Penger A, Asante-Poku S, Zanger UM, et al. Frequency of C3435T polymorphism of MDR1 gene in African people. Lancet 2001;358:383–4.

[26] Siddiqui A, Kerb R, Weale ME. Association of multidrug resistance in epilepsy with a polymorphism in the drug-transporter gene ABCB1. N Engl J Med 2003;348:1442–8.

[27] Babaoglu MO, Bayar B, Aynacioglu AS, Kerb R, Abali H, Celik I. Association of the ABCB1 3435C > T polymorphism with antiemetic efficacy of 5-hydroxytryptamine type 3 antagonists. Clin Pharmacol Ther 2005;78:619–26.

[28] Choi EM, Lee MG, Lee SH, Choi KW, Choi SH. Association of ABCB1 polymorphisms with the efficacy of ondansetron for postoperative nausea and vomiting. Anaesthesia 2010;65:996–1000.
[29] Walstab J, Hammer C, Bonisch H, Rappold G, Niesler B. Naturally occurring variants in the HTR3B gene significantly alter properties of human heteromeric 5-hydroxytryptamine-3A/B receptors. Pharmacogenet Genomics 2008;18:793–802.
[30] Hardman J, Limbird L, Gilman A. Goodman & Gilman's The Pharmacological Basis of Therapeutics. New York: McGraw-Hill Medical Publishing Division; 2010.
[31] Niesler B, Kapeller J, Hammer C, Rappold G. Serotonin type 3 receptor genes: (HTR3A, B, C, D, E. Pharmacogenomics 2008;9:501–4.
[32] Tremblay PB, Kaiser R, Sezer O. Variations in the 5-hydroxytryptamine type 3B receptor gene as predictors of the efficacy of antiemetic treatment in cancer patients. J Clin Oncol 2003;21:2147–55.
[33] Shinn HK, Jang EH, Park CS, Lee HS, Kang JH. Genetic polymorphisms in the serotonin receptor type 3B gene (HTR3B) and the clinical response to ondansetron in Koreans. Mol Cell Toxicol 2011;21:148–56.
[34] Tanaka M, Kobayashi D, Murakami Y. Genetic polymorphisms in the 5-hydroxytryptamine type 3B receptor gene and paroxetine-induced nausea. Int J Neuropsychopharmacol 2008;11:261–7.
[35] Perwitasari DA, Straaten VD, Wessels J, Gelderblom AJ, Guchelaar HJ. Differences in 5 hydroxytryptamine 3B haplotypes frequencies between Asians and Caucasians. Int J Bio Marker 2012;27(1):34–8.