Postoperative nausea and vomiting (PONV) is a frequent and distressing complication of anaesthesia and surgery with an average incidence ranging between 20% and 30%, but up to 80% in high-risk groups. PONV may result in further complications including dehydration, electrolyte imbalance, suture tension and dehiscence, venous hypertension, bleeding, and aspiration. In a preoperative survey, the most undesirable outcome from their most undesirable to their most desirable was nausea as the fourth most undesirable and pain ranked third in the survey.  

The aetiology of PONV is multifactorial involving patient, surgical, and anaesthesia-related factors. On the basis of two independent studies, Apfel and colleagues developed a simplified risk score for predicting PONV in adult patients undergoing anaesthesia and surgery. They found that female gender, non-smoking status, history of motion sickness, and postoperative use of opioids are the most important risk factors. The incidence of PONV in the presence of none, one, two, three, or four of these risk factors was 10%, 21%, 39%, 61%, and 79%, respectively. A number of other factors are thought to be associated with the risk of experiencing PONV, including age, duration of anaesthesia, the use

---

**Editorial II**

**Genetic polymorphisms in the cytochrome P450 system and efficacy of 5-hydroxytryptamine type 3 receptor antagonists for postoperative nausea and vomiting**

Postoperative nausea and vomiting (PONV) is a frequent and distressing complication of anaesthesia and surgery with an average incidence ranging between 20% and 30%, but up to 80% in high-risk groups. PONV may result in further complications including dehydration, electrolyte imbalance, suture tension and dehiscence, venous hypertension, bleeding, and aspiration. In a preoperative survey, the most undesirable outcome from their most undesirable to their most desirable was nausea as the fourth most undesirable and pain ranked third in the survey. The aetiology of PONV is multifactorial involving patient, surgical, and anaesthesia-related factors. On the basis of two independent studies, Apfel and colleagues developed a simplified risk score for predicting PONV in adult patients undergoing anaesthesia and surgery. They found that female gender, non-smoking status, history of motion sickness, and postoperative use of opioids are the most important risk factors. The incidence of PONV in the presence of none, one, two, three, or four of these risk factors was 10%, 21%, 39%, 61%, and 79%, respectively. A number of other factors are thought to be associated with the risk of experiencing PONV, including age, duration of anaesthesia, the use

---

16 Heidland UE, Strauer BE. Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption. *Circulation* 2001; 104: 1477–82

---

doi:10.1093/bja/aen246

---

441
of volatile anaesthetics, type of surgery, and type of anaesthesia (general anaesthesia vs regional anaesthesia).2

A central mechanism in PONV is the release of serotonin from the enterochromaffin cells in the gastrointestinal tract. Serotonin binds to visceral receptors of the 5-hydroxytryptamine type 3 (5-HT3) subtype, stimulating vagal afferents terminating in the nucleus tractus solitarius (NTS).4 At least six other neurotransmitters are thought to be involved in PONV, that is, dopamine, muscarine, acetylcholine, neurokinin-1, histamine, and opioids.2 There are a number of different antiemetics for the pharmacological treatment of PONV. Most act by selectively blocking receptors involved in the transmission of emetic stimuli to the NTS. Antiemetics with five different sites of action have been developed. These act by blocking receptors for dopamine (D2), histamine (H1), acetylcholine (muscarinic), neurokinin (NK1), or serotonin (5-HT3).4

In the early 1990s, 5-HT3 receptor antagonists became available for treatment of chemotherapy-induced nausea and vomiting. More recently, the use of 5-HT3 receptor antagonists has been extended to include prevention and treatment of PONV.5 Dolasetron, granisetron, ondansetron, and tropisetron are among the 5-HT3 receptor antagonists with documented effect in prevention and treatment of PONV.5 All act by competitively and selectively binding to the 5-HT3 receptor thereby blocking serotonin and preventing emetic inputs from reaching the NTS. The 5-HT3 receptor antagonists act both centrally (NTS in which 5-HT3 receptors are abundant) and peripherally (primarily in the vagal nerve terminals).5

All of the 5-HT3 receptor antagonists are administered orally or i.v. Dolasetron is a produg that is rapidly converted to the active metabolite hydrodolasetron by the enzyme carbonyl reductase.5 Granisetron is highly selective for the 5-HT3 receptor with an affinity that is 4000–400 000 times greater than for other receptors.6 Ondansetron is less specific compared with other 5-HT3 receptor antagonists, because it binds to 5-HT1B, 5-HT1C, µ-opioid, and α1-adrenergic receptors also. The affinity for the 5-HT3 receptor, however, is 250–500 times greater than for other receptors.6 The 5-HT3 receptor antagonists are metabolized by cytochrome P450 (CYP) enzymes which constitute a family of more than 30 isoenzymes.7 They are abundant in human hepatocytes and are important in the metabolism of endogenous substances and xenobiotics. More than 90% of human Phase 1 metabolism of xenobiotics (e.g. 5-HT3 receptor antagonists) is associated with the isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.7 CYP2D6 is thought to be associated with metabolism of approximately 20% of all drugs used clinically.3 The 5-HT3 receptor antagonists are metabolized through different pathways. Hydrodolasetron and tropisetron are primarily degraded by CYP2D6, whereas granisetron and ondansetron are primarily degraded by CYP3A4. A significant proportion of ondansetron, however, is degraded through secondary pathways by CYP1A2, CYP2D6, and CYP2E1.6 Extensive inter-individual variation in human drug metabolism leads to a number of different outcomes in patients treated with the same drug. This is mainly due to genetic polymorphisms together with induction or inhibition of enzymes involved in drug metabolism leading to increased or decreased enzymatic activity.9 Increased metabolic activity leads to lower serum concentration of the drug, thus increasing the risk of undertreatment or therapeutic failure. Conversely, decreased metabolic activity leads to higher serum concentration, thus increasing the risk of adverse effects and toxicity.10 On the basis of their metabolic status, patients may be divided into the following phenotypes: normal enzymatic activity (extensive metabolizer, EM), poor enzymatic activity (poor metabolizer, PM), reduced enzymatic activity (intermediate metabolizer, IM), and increased enzymatic activity (ultrarapid metabolizer, UM).10

Traditionally, the metabolic status of CYP2D6 has been determined by the administration of a known CYP2D6-specific substrate (e.g. dextromethorphan or desbrisquine) and subsequent collection of urine samples at certain time points.11 The method is reliable, but it is time-consuming and shows significant intra-individual variability. A modern alternative to the traditional phenotyping is genotyping by simple PCR assays. The CYP2D6 gene copy number can be determined by using a gene-specific probe, whereas the CYP2D6 genotype can be determined by 5' nuclease assay specific for known alleles with decreased, normal, or increased enzymatic activity. These methods require only a small amount of blood from the patient and are easily carried out in most laboratories.11 Several human CYP isoenzymes are encoded by polymorphic genes resulting in marked inter-individual variation in the ability to metabolize various drugs, including CYP2D6 for which more than 60 allele variants, in addition to the wild type (CYP2D6*1A), and more than 30 subvariants have been described.12 These variants are the result of single nucleotide polymorphisms (SNPs), deletions, additions, gene rearrangements, or deletion or duplication of the entire gene, and result in decreased or increased enzymatic activity.13 So far three alleles resulting in increased enzymatic activity (*1XN, *2XN, and *35X2), five resulting in normal activity (*1B, *1C, *2A, *33, and *35), six resulting in decreased activity (*9, *10A, *10B, *10X2, *17, and *41), and 27 null alleles (*3A, *4A, *4B, *4C, *4D, *4K, *4X2, *5, *6A, *6B, *6C, *7, *8, *11, *12, *13, *14A, *15, *16, *18, *19, *20, *21A, *21B, *38, *42, and *44) have been described.12 As more CYP2D6 alleles are identified, genotyping could be used to predict the metabolic status on the basis of allele composition.

Duplication alleles only predict about 20% of all individuals with UM phenotype.8 Thus, other unidentified genetic or environmental factors produce UM phenotype in the remaining 80%. Certain SNPs, however, appear to be overrepresented in UM individuals. A study14 indicates that the 31G>A (Val111Met) polymorphism is significantly
more frequent in UM subjects than in EM subjects \((P=0.04)\). It may be possible to predict PM phenotypes in Caucasian individuals on the basis of their genotype because the variation in non-functional alleles among Caucasian subjects is relatively small (i.e. *3, *4, *5, *6, *7, and *8).\(^{15}\)

Three studies\(^ {16–18}\) have examined the relationship between genetic polymorphisms of CYP2D6 and clinical efficacy of antiemetic treatment with 5-HT\(_3\) receptor antagonists. Candiotti and colleagues\(^ {16}\) clearly demonstrated that patients with multiple copies (\(\geq3\)) of the CYP2D6 gene or a genotype associated with UM phenotype had an increased incidence of failure of ondansetron to prevent postoperative vomiting. They studied 250 female patients undergoing general anaesthesia with isoflurane who were given ondansetron, 4 mg, 30 min before extubation, and all subjects were genotyped and designated as either PM, IM, EM, or UM. The incidence of vomiting in UM subjects 45.5% (five of 11) was significantly increased compared with PM, IM, and EM subjects (8.3%, 16.7%, and 14.7%, respectively). The authors concluded that patients with three normally functioning CYP2D6 alleles might benefit from prevention and treatment with antiemetics that are not metabolized by CYP2D6.

A prospective, randomized study\(^ {7}\) suggested that prophylaxis with granisetron (metabolized independent of CYP2D6) is superior to dolasetron for prophylaxis of PONV. In 150 patients receiving general anaesthesia with volatile agents and opioids given dexamethasone and either dolasetron 12.5 mg (\(n=75\)) or granisetron 1 mg (\(n=75\)), complete response was observed in 39% and 55%, respectively (\(P=0.049\)). All subjects were genotyped and classified as PM, IM, EM, or UM. The small number of PM, IM, and UM subjects did not allow for an accurate statistical analysis of differences in vomiting incidence between the groups. However, the six UM subjects in the dolasetron group had a total of six episodes of vomiting and the four UM subjects in the granisetron group only one episode. Although the study was underpowered, the results suggest that genotype may be associated with the individual efficacy of antiemetic treatment with 5-HT\(_3\) receptor antagonists.

Studies of 5-HT\(_3\) receptor antagonists used for prevention and treatment of nausea and vomiting induced by chemotherapy show similar results. A prospective non-interventional cohort study\(^ {18}\) demonstrated that genetically defined UM patients receiving chemotherapy had significantly higher frequency of vomiting when treated with tropisetron or ondansetron than other patients. In 270 patients receiving their first dose of chemotherapy, either tropisetron (\(n=96\)) or ondansetron (\(n=174\)) was given. Subjects with three active CYP2D6 alleles (i.e. UM phenotype) had a significantly higher mean number of vomiting episodes than other subjects within the first 4 h and from 5 to 24 h. The authors conclude that patients with a genotype associated with UM phenotype would benefit from a different antiemetic approach or significantly higher doses of the antiemetic than other patients.

Obviously, larger studies allowing stratification of risk factors and type of surgery and anaesthesia are warranted. Although the relationship between CYP2D6 genotype and the efficacy of 5-HT\(_3\) receptor antagonists observed thus far suggests that antiemetic treatment of PONV may be improved by individualizing the pharmacological approach on the basis of CYP2D6 genotyping, this should be tested in prospective, sufficiently powered gene-association studies in well-defined, highly phenotyped populations of patients. A patient with UM status for CYP2D6 could benefit from being recognized early, thereby allowing the clinician to either administer a larger dose of the drug to ensure the appropriate serum concentration or to use another antiemetic that is not metabolized by CYP2D6. As an alternative to preoperative genotype screening programmes, granisetron that is metabolized by CYP3A4 and independently of CYP2D6 could be used as standard treatment. Genetic polymorphisms in CYP3A4 have been identified, but these rarely affect drug metabolism.\(^ {10}\)

The prevalence of the different CYP2D6 genotypes and phenotypes varies markedly in different populations (Table 1). The results of the studies above\(^ {16–18}\) suggest that populations with high prevalence of individuals with UM phenotype would benefit the most from preoperative screening programmes for CYP2D6 and subsequent individualized treatment.

Variations in genotype and phenotype between different ethnic populations cannot only be explained by race as significant regional differences between populations of the same racial origin have been described.\(^ {13}\) The highest prevalence of UM individuals is described in an Ethiopian population, where 29% of the population investigated carried alleles with duplication or multiduplication of the CYP2D6 gene, indicative of ultrarapid metabolism.\(^ {19}\) The lowest prevalence of UM individuals is described in a Danish population, in which the frequency of CYP2D6 duplication is estimated to be 0.8%.\(^ {20}\) This is considerably lower than some Negroid or Asian populations. Thus,

<table>
<thead>
<tr>
<th>Population</th>
<th>PM phenotype</th>
<th>UM phenotype</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethiopia</td>
<td>1.8%</td>
<td>29%</td>
<td>19</td>
</tr>
<tr>
<td>Afro American</td>
<td>3.5–8%</td>
<td>4.9%</td>
<td>15, 21</td>
</tr>
<tr>
<td>Caucasians</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croatia</td>
<td>3%</td>
<td>4%</td>
<td>22</td>
</tr>
<tr>
<td>Poland</td>
<td>8.3%</td>
<td>0.8%</td>
<td>20</td>
</tr>
<tr>
<td>Denmark</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asians</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India (Kerala)</td>
<td>4.8%</td>
<td>21%</td>
<td>24</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>2%</td>
<td>0%</td>
<td>25</td>
</tr>
<tr>
<td>Hispanics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>10%</td>
<td>1.7%</td>
<td>26</td>
</tr>
<tr>
<td>Colombia</td>
<td>6.6%</td>
<td>1.7%</td>
<td>27</td>
</tr>
</tbody>
</table>

Table 1 Prevalence of PM and UM phenotype in selected populations
patients of Ethiopian or Saudi Arabian origin (Table 1) would be most likely to benefit from preoperative screening for CYP2D6 genotype and subsequent individualized antiemetic treatment because of the high prevalence of UM phenotype in these populations.

In conclusion, various studies have described significant inter-individual variation in the efficacy of antiemetic treatment with 5-HT3 receptor antagonists and genetic polymorphisms in the CYP system seem to be a part of the explanation. Dolasetron, tropisetron, and ondansetron are metabolized by the isoenzyme CYP2D6 that demonstrates extensive genetic polymorphism. Granisetron is metabolized independent of CYP2D6. Patients with a genotype associated with increased enzymatic activity of CYP2D6 metabolize dolasetron, tropisetron, and ondansetron faster than individuals with normal enzymatic activity. This leads to lower serum concentrations of the drugs, thereby increasing the risk of therapeutic failure. These patients may benefit from being identified early, thereby allowing the clinician to increase the dose of the drug or to use an antiemetic metabolized independent of CYP2D6. There is a variation in the prevalence of CYP2D6 phenotypes between different ethnic populations and some are more likely to benefit from preoperative screening for CYP2D6. The prevalence of individuals with increased CYP2D6 activity is important in predicting the response to treatment and allowing individualized treatment. However, further studies are necessary.

M. Nielsen* and N. V. Olsen

Department of Neuroanaesthesia
Copenhagen University Hospital
Rigshospitalet
Copenhagen
Denmark

*E-mail: memosu@stud.ku.dk

References

4 Gan TJ. Mechanisms underlying postoperative nausea and vomiting and neurotransmitter receptor antagonist-based pharmacotherapy. CNS Drugs 2007; 21: 813–33
5 Gan TJ. Selective serotonin 5-HT3 receptor antagonists for postoperative nausea and vomiting. CNS Drugs 2005; 19: 225–38
6 Ho KY, Gan TJ. Pharmacology, pharmacogenetics, and clinical efficacy of 5-hydroxytryptamine type 3 receptor antagonists for postoperative nausea and vomiting. Curr Opin Anaesthesiol 2006; 19: 606–11
8 Zanger UM, Raimundo S, Eichelbaum M. Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry. Naunyn-Schmiedebergs Arch Pharmacol 2004; 369: 23–37
11 McElroy S, Sachse C, Brockmoller J, et al. CYP2D6 genotyping as an alternative to phenotyping for determination of metabolic status in a clinical trial setting. AAPS Pharmsci 2000; 2: E33
14 Lavie R, Daly AK, Mestre GE, et al. Polymorphisms in CYP2D6 duplication-negative individuals with the ultrarapid metabolizer phenotype: a role for the CYP2D6*35 allele in ultrarapid metabolism? Pharmacogenetics 2001; 11: 45–55
23 Niewinski P, Orzechowska-Juzwenko K, Hurkacz M, et al. CYP2D6 extensive, intermediate, and poor phenotypes and


