# Adverse events in analgesic treatment with tramadol associated with CYP2D6 extensive-metaboliser and OPRM1 high-expression variants

Tramadol, alone or in combination with paracetamol, is an effective analgesic that relieves the moderate to severe pain that accompanies various disorders (including osteoarthritis) and follows surgical operations. However, this synthetic atypical opioid frequently evokes various adverse events (AEs), and the most frequent are nausea and vomiting.[1] Although the mode of tramadol-induced nausea/vomiting is unclear, opioid receptors on the chemoreceptor trigger zone in the human brain can bind opioids to cause nausea/vomiting.[2] A major pathway of tramadol metabolism is demethylation to *O*-desmethyltramadol by cytochrome P450 enzyme 2D6 (CYP2D6),[3] and *O*-desmethyltramadol has an orders of magnitude higher affinity for the μ-opioid receptor (OPRM1) than tramadol and other metabolites.[4]

Because many genetic variations in *CYP2D6* confer large interindividual differences in enzyme activity,[5] and several variations in *OPRM1* substantially affect expression level,[6] this study examined genotype–phenotype associations between functional polymorphisms in *CYP2D6* and *OPRM1* and nausea/vomiting risk of tramadol treatment. In a previous clinical trial,[7] 250 unrelated Korean patients with knee osteoarthritis had taken a tablet of 37.5 mg tramadol/325 mg paracetamol (Ultracet) up to three times daily for 14 days or less. Of these, 54 patients having had nausea and/or vomiting were compared in this study with 106 who did not experience any AE.

*CYP2D6* was genotyped for 35 polymorphisms using the MassARRAY system (Sequenom, San Diego, California, USA), and for gene duplication and deletion using PCRs as previously described.[8] Of 160 participants genotyped, 154 (96.3%) were assigned *CYP2D6* alleles according to the nomenclature and an 'activity score' from 0 (no activity) to 2 based on predicted allele activities.[9] With respect to CYP2D6 activity levels, these participants were classified into two subgroups (table 1); extensive metabolisers (EM) having activity score 2.0 (two normal-activity alleles) or 1.5 (one normal-activity and one decreased-activity allele) and intermediate metabolisers (IM) having 1.0 (one normal-activity and one no-activity allele or two decreased-activity alleles) or 0.5 (one decreased-activity and one no-activity allele). IM participants had 3.4-fold lower odds of nausea/vomiting than EM participants (p=0.0051). Because plasma concentration of *O*-desmethyltramadol is correlated with CYP2D6 activity level,[10] the risk of nausea/vomiting could be attributed to *O*-desmethyltramadol.

All 160 participants were additionally genotyped for *OPRM1* A118G polymorphism (rs1799971). The minor-allele

**Table 1** Associations of *CYP2D6* and *OPRM1* genotypes with nausea/vomiting risk

| Genotype variant | Nausea/vomiting | AE free | Adjusted OR (95% CI)* | p Value* | Statistical power† |
|---|---|---|---|---|---|
| CYP2D6 activity | (n=53) | (n=101) | | | |
| EM (2.0 and 1.5) | 45 (85%) | 64 (63%) | 1.00 (reference) | – | – |
| IM (1.0 and 0.5) | 8 (15%) | 37 (37%) | 0.29 (0.12 to 0.69) | **0.0051** | 84% |
| *OPRM1* A118G | (n=54) | (n=106) | | | |
| *A/A* | 25 (46%) | 36 (34%) | 1.00 (reference) | – | – |
| *A/G* | 27 (50%) | 55 (52%) | 0.61 (0.30 to 1.27) | 0.20 | 25% |
| *G/G* | 2 (4%) | 15 (14%) | 0.16 (0.03 to 0.78) | **0.024** | 55% |

Values are n (%) of genotypes among the patients who had experienced nausea and/or vomiting and those who had not had any adverse events (AEs). All the *CYP2D6* alleles are described for enzyme activity levels in the *CYP2D6* allele nomenclature homepage (http://www.cypalleles.ki.se/cyp2d6.htm), except for **43* which was recently reported to have normal activity,[9] and their activity scores ranging from 0 to 1.0 were previously estimated,[9] except for decreased-activity alleles **39* and **49* given 0.5 here. Extensive metabolisers (EM) include participants of CYP2D6 activity score 2.0 with two normal-activity *CYP2D6* alleles (**1/*1*, **1/*2*, **1/*39*, **2/*2* and **2/*35*) and those of score 1.5 with one normal-activity and one decreased-activity allele (**1/*10*, **1/*41*, **2/*10*, **10/*39* and **43/*41*). Intermediate metabolisers (IM) include participants of score 1.0 with one normal-activity and one no-activity allele (**1/*5* and **2/*5*) or with two decreased-activity alleles (**10/*10*, **10/*41* and **10/*49*) and those of score 0.5 with one decreased-activity and one no-activity allele (**10/*4* and **10/*5*). Ultrarapid metabolisers having more than two normal-activity alleles or poor metabolisers having only no-activity alleles were not found in the participants of this study.
*ORs, 95% CIs and p values were calculated in logistic regression analyses using age, gender, CYP2D6 activity levels and *OPRM1* genotypes as covariants. Genotypic association p values lower than a significance level $\alpha=0.025$ for a Bonferroni correction of multiple testing are **italicised**.
†Statistical power was calculated using the program PS V.3.0 available online (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize).

homozygote *G/G* had 6.3-fold lower odds than the major-allele homozygote *A/A* (p=0.024), although association was not significant with the *A/G* heterozygote (p=0.20) possibly because of a low statistical power (25% vs 55%). Because the *A* to *G* substitution substantially reduces OPRM1 mRNA and protein levels in human brain,[6] high risk of nausea/vomiting is presumably associated with high levels of μ-opioid receptor.

Our results suggest that *O*-desmethyltramadol binding to μ-opioid receptor on the chemoreceptor trigger zone is responsible for inducing emetic response in tramadol treatment. This interpretation is supported by a previous finding that μ-opioid receptor has a higher affinity for *O*-desmethyltramadol than for tramadol or other metabolites.[4] Although our findings need to be confirmed in larger populations to be used as pharmacogenetic prediction of tramadol toxicity, high-activity genotypes of *CYP2D6* and a high-expression genotype of *OPRM1* appear to confer high risk of nausea/vomiting in tramadol treatment.

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## Notes