Prospective observational pharmacogenetic study of side effects induced by intravenous morphine for postoperative analgesia

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Abstract

Nausea and vomiting are probably the most unpleasant side effects that occur when morphine is used. A number of studies have investigated the effect on pain relief of single nucleotide polymorphisms (SNPs) in genes involved in morphine’s metabolism, distribution, binding, and cellular action. The mechanism through which morphine causes nausea and vomiting has not been elucidated clearly. We examined all the reported SNPs which are associated with the complications of morphine, including SNPs in genes for phase I and phase II metabolic enzymes, ABC binding cassette drug transporters, κ and δ opioid receptors, and ion channels implicated in the postreceptor action of morphine.

A prospective, observational study in 129 female patients was conducted to investigate the effect of 14 SNPs on nausea or vomiting induced by intravenous patient-controlled analgesia (IVPCA) with morphine after gynecology surgery. Clinical phenotype, subjective complaints, and objective observations were recorded. DNA from blood samples was used to record the SNPs. Eleven SNPs were then analyzed further.

No significant association with the presence of phenotype (nausea or vomiting) versus genotype was observed (all $P > 0.05$). No significant association with severity of phenotype versus genotype of the 11 SNPs was observed except for unadjusted data for rs2737709.

There was no significant difference between severity or incidence of IVPCA morphine-induced nausea and vomiting and genotype (11 SNPs). Further study should perhaps focus on mRNA and proteomics rather than SNPs.

Abbreviations: BMI = body mass index, CI = confidence interval, GI = gastrointestinal, IVPCA = intravenous patient-controlled analgesia, OR = odds ratio, SNPs = single nucleotide polymorphisms, VAS = visual analogue scale.

Keywords: morphine, nausea, postoperative analgesia, SNP, vomiting

1. Introduction

Nausea and vomiting are probably the most unpleasant side effects that occur when morphine, the drug commonly used as pain medication in cancer patients and after surgery, is given. There is a great deal of interpatient variability in the incidence and severity of these side effects.\cite{1,2} Ethnicity, type of surgery, type of cancer, and other factors influence the incidence of morphine-induced nausea and vomiting.\cite{1,2,5,10} But genetic factors are thought to have an influence as well.

A number of studies have investigated how morphine-induced nausea and vomiting are affected by SNPs in these genes.\cite{1,2,5,10} The results of the studies reported to date are contradictory, probably because each individual study encompasses a different type of patient and a different type of surgery or cancer, so the results cannot be accurately compared to each other. It would be helpful to have the effect of the various SNPs potentially affecting risk and severity of nausea and vomiting compared in a single population sample.

Therefore, in this study, we examined, in a population of Taiwanese women given patient-controlled postoperative morphine after total abdominal hysterectomy, all the reported SNPs which are associated with the complications of morphine, including SNPs in genes for phase I and phase II metabolic enzymes, ABC binding cassette drug transporters, κ and δ opioid receptors, and ion channels implicated in the postreceptor action of morphine. We hypothesized that examining, in a single defined population, SNPs from genes in the pathway from morphine’s metabolism and distribution to its later cellular action would
enable us to discover which step in this pathway had the biggest influence on morphine-induced nausea/vomiting.

2. Methods

2.1. Patient profile and anesthetic procedure

The present study was a prospective observational study, with a double blind designed in the data analysis. A total of 129 American Society of Anesthesiologists physical status I or II Taiwanese women who underwent total abdominal hysterectomy and received intravenous patient-controlled analgesia (IVPCA) with morphine for postoperative pain control were recruited into this study in the 12-month period from August 1, 2007 to July 31, 2008. The study was approved by the Ethics Institute Review Board of the National Taiwan University Hospital Research Ethics Committee (Approval number 201207049R1C). All patients gave written informed consent for participation. All recruited women could understand and describe the pain score. Women were excluded for any of the following reasons: contraindications for IVPCA (anesthesia, complaint of nausea or vomiting before the operation, a history of significant cardiovascular disease, renal disease, diabetes, hepatic disease, or chronic pain for which pain medication was being taken). All procedures related to the many drugs and conditions that might induce nausea or vomiting were standardized, including the anesthesia technique. A standardized, general anesthesia technique was used for all patients. For induction of anesthesia, 2 μg/kg fentanyl, 2 mg/kg propofol, and 0.15 mg/kg cisatracurium were used. For maintenance of anesthesia during the operation, cisatracurium and inhaled desflurane at a low flow rate of 0.5 L/min were used. Residual neuromuscular block was antagonized with 2.5 mg neostigmine and 1.0 mg atropine, and patients were extubated at the end of surgery. After extubation, patients were transferred to the postanesthesia care unit for observation for at least 1 h and then transferred back to the ward. The attending anesthesiologists involved in the anesthesia and analgesia, and the trained investigator conducting the postoperative interviews were blinded to the genotype at the time of surgery and follow-up because the genotyping was determined at a later time in the laboratory.

2.2. Postoperative pain management, assessment, and data collection

In the postanesthesia care unit, until they became alert enough to use the IVPCA pump, and terminated 72 hours after the operation, patients were asked every 15 minutes whether pain medication was needed to reduce their 10 cm visual analogue scale (VAS) pain score to <3. The morphine solution in the pump contained 250 mL normal saline and 100 mg pure morphine. The pump was set to deliver a 1-mg bolus of morphine solution with a lockout time of 5 minutes and a maximum dose of 15 mg within a 4-hour limit without a background. Overdose was prevented by limiting the total dose administered within a given period of time. The amount of morphine consumed during the 72 hours after the operation was recorded by the PCA device, using an Abbott TRW printer model TP 40 (Abbott Life Care Infuser; Chicago, IL.). A trained investigator interviewed the patient once a day during the first 72 hours postoperatively. The investigator who interviewed the patient would explain the possible side effects that could be induced by IVPCA morphine to patients and would record the side effects experienced (with a focus on nausea and vomiting) as mild or severe. If a patient still felt wound pain (10 cm VAS pain score >3) even after being given a loading dose of 3 mg of morphine and having the bolus dose doubled to 2 mg, that patient was excluded from the study. The reason that these patients were excluded due to the high morphine dose was the known risk factor for nausea and vomiting. For patients with severe side effects, the investigator would provide effective management immediately, following the anesthesiologist’s instructions. Side effects were also recorded and were defined as follows. Nausea was defined as the sensation of having an urge to vomit, and vomiting was defined by the number of episodes of retching with or without expulsion of fluids from the stomach. The side effects were scored on the following severity scale: severe = number of episodes >3 and medical treatment indicated; mild = number of episodes ≤3 and medical treatment not indicated; none = number of episodes = 0.[11] The incidence of the above effects was defined as the number of episodes taking place during the observation period. Patients who had severe nausea or vomiting were treated with prochlorperazine 5 mg.

2.3. Laboratory analysis of SNPs

Fourteen SNPs were investigated (Table 1). To analyze the different genotypes of the 14 SNPs, DNA was extracted from collected blood samples, amplified by the GeneAmp PCR System 9700, and sequenced with the ABI PRISM 7900 HT Sequence Detection System.

2.4. Statistical analysis

Phenotype was defined according to 2 symptoms, nausea and vomiting, which was divided into 2 groups (i.e., no symptoms and at least one symptom). The Hardy–Weinberg equilibrium test was performed by using SHEsis.[12] One SNP was excluded from subsequent analysis because it contained only the CC genotype. And 2 SNPs with minor allele frequency <5% were also excluded from subsequent analysis. Age, height, weight, and body mass index (BMI) were presented by mean and standard deviation; the independent t test was performed to evaluate the differences between the 2 phenotype groups. Other categorical data were presented by number and percentage. Fisher exact test was performed to evaluate the association between the phenotype and the categorical data (prescription, wound pain, dizziness, drowsiness, genotypes of SNPs). The magnitude of association between SNPs and phenotype was generated by logistic regression and was presented with odds ratio (OR) and its

| Gene symbol | Name | Polymorphisms |
|-------------|------|---------------|
| CYP3A4      | O coupled P450 | rs2242480, rs23871759 |
| CYP2D6      | O coupled P450 | rs3892097, rs28365063 |
| UGT2B7     | UDP-glucourasyltransferase | rs7430366, rs7439152 |
| ABCB1       | ATP-binding cassette transporter | rs1045642 |
| ABCB3       | ATP-binding cassette transporter | rs2277624 |
| OPRK1       | k-Opioid receptor | rs1051660 |
| OPRD1       | 8-Opioid receptor | rs1042114 |
| KCNJ6       | G-protein activated K+ channel | rs2070995 |
| KCNJ9       | G-protein activated K+ channel | rs2737703 |

SNPs, single nucleotide polymorphisms.
95% confidence interval (95% CI). To control for potential confounding effects, multiple logistic regression was performed with adjustment for age, body weight, prescription, type of surgery, and dose of morphine. A 2-tailed $P < .05$ was considered statistically significant. Data were analyzed by using SPSS 15.0 statistics software (SPSS Inc, Chicago, IL).

3. Results

One hundred twenty-nine subjects were enrolled in the study and 14 SNPs investigated. Table 1 shows the genes containing each individual SNP and the function of the protein encoded by the gene. CYP3A4 and CYP2D6 encode phase I metabolic proteins; UGT2B7 encodes a phase II metabolic protein; ABC1 and ABC2 are membrane transport proteins; OPRK1 and OPRD1 are opioid receptors; KCNJ6, KCNJ9, and CACNA1E are ion channels involved in the downstream action of the receptor. Table 2 shows the allele frequency and genotype distribution and the results of the Hardy–Weinberg equilibrium test for the 14 SNPs. All SNPs except for the rs2277624 SNP of the ABCC3 transmembrane transporter did not violate the Hardy–Weinberg equilibrium. The SNP for CYP2D6 (rs3892097) contained only the CC genotype, so this SNP was not studied further. In addition, 2 SNPs (i.e., rs28371759 and rs1042114) had minor allele frequency <5% and were thus excluded from further study, leaving 11 SNPs available for the final analyses.

Patient characteristics, except for dose of morphine, were comparable between 2 groups of phenotype (Table 3; all $P > .05$). A higher dose of morphine was found in patients with no symptoms than in those with at least one symptom of nausea or vomiting ($31.9 \pm 17.0$ vs $24.6 \pm 13.5$, $P = .014$).

In the univariate analysis, patients with TT genotype of rs2737703 had lower odds of nausea or vomiting compared to those with CC genotype (OR $= 0.09$, 95% CI $= 0.01$–0.83, $P = .033$). In addition, the likelihood of having at least one symptom of nausea and vomiting was lower in patients with

| Allele frequency | Allele n (%) | Genotype frequency | Genotype n (%) | Hardy–Weinberg equilibrium test |
|------------------|--------------|--------------------|----------------|-------------------------------|
| CYP2D6           | NA           | NA                 | CC             | 129 (100.0)                  |
| rs3892097        | G            | 145 (56.2)         | AA             | 42 (32.6)                    |
| rs1065622        | C            | 186 (72.1)         | GG             | 26 (20.2)                    |
| CYP3A4           | T            | 72 (27.9)          | TT             | 6 (4.7)                      |
| rs2242480        | A            | 145 (56.2)         | AA             | 120 (93.0)                   |
| CYP2D6           | C            | 184 (71.3)         | CC             | 61 (48.1)                    |
| rs28365063*      | G            | 58 (22.5)          | AG             | 48 (37.2)                    |
| rs7439152        | G            | 64 (24.8)          | GG             | 5 (3.9)                      |
| rs1051660        | T            | 194 (75.2)         | GT             | 50 (38.8)                    |
| rs847998         | C            | 51 (19.8)          | CC             | 3 (2.3)                      |
| CACNA1E          | T            | 207 (80.2)         | CT             | 45 (34.9)                    |
| rs2737703        | C            | 184 (71.3)         | CC             | 61 (47.3)                    |
| rs2070995        | T            | 74 (28.7)          | CT             | 62 (48.1)                    |
| rs1042114*       | G            | 2 (0.8)            | GT             | 2 (1.6)                      |
| OPR1             | T            | 254 (99.2)         | TT             | 126 (97.7)                   |
| rs1051660        | C            | 204 (79.1)         | AC             | 38 (29.5)                    |
| UGT2B7           | T            | 64 (24.8)          | CC             | 72 (55.8)                    |

The SNP with only the CC genotype and 2 SNPs with minor allele frequency <5% were excluded in subsequent analyses (i.e., rs3892097, rs28371759, and rs1042114*).

*Missing genotype in one observation.
4. Discussion

In the present study, we investigated the relationship between genetics and morphine-induced nausea/vomiting by studying SNPs involved in genes for enzymes involved in morphine metabolism and distribution, for opioid receptors, and for ion channels involved in postreceptor action. Our hypothesis that by studying, in a single defined population, SNPs from different steps in the pathway to morphine’s cellular action, we could determine which step was most important in causing nausea/vomiting was false. None of the 11 SNPs for which the final analyses were performed were related to the incidence of nausea/vomiting, and none were related to the severity of nausea/vomiting except for the rs27337703 SNP of the KCNJ6 potassium channel. However, the significance for this SNP seen in the raw data was lost when adjusted for multiple comparisons.

4.1. Opioid sites of action and metabolism

The sites where opioids may affect nausea/vomiting are the peripheral nerve, the chemoreceptor trigger zone, the vomiting center, the vestibular system, and gastrointestinal (GI) tract. However, most studies have reported no association between SNPs in these enzymes in clinical pain studies, and we saw no effect on nausea/vomiting of SNPs in either of the 2 phase I cytochrome P450 enzymes studied here. Another problem may be seen as a limitation of this study; there are many variants and subvariants of CYP2D6, but we did not evaluate in our samples.

The phase II metabolic enzyme studied here, UGTB7, glucuronidates morphine to a major, inactive metabolite, morphine-3-glucuronide, and a minor, active metabolite, morphine-6-glucuronide, said to be 50 times more potent than morphine itself. Previous studies have reported no effect on pain or adverse effects of SNPs in this enzyme, and we have reported no effects on nausea/vomiting of SNPs in this enzyme.

The ABCB1 drug efflux transporter (also called the multidrug resistance 1 gene) is a major component of the blood–brain barrier, and is involved in the transport of morphine into the brain. Studies of possible association of SNPs in this gene with pain control efficacy of morphine have yielded mixed results. For possible association of SNPs of this gene with nausea/vomiting, one study has reported a trend for lower nausea/vomiting with a combination of SNPs at 2 different sites. However, most studies have reported no association between SNPs in ABCB1 and nausea/vomiting. Our results showed no association between SNPs in either ABCB1 or ABCB3 and nausea/vomiting, results consistent with the majority of previous results and also with the fact that 2 of the sites for morphine’s nausea/vomiting action, the GI tract and the chemoreceptor trigger zone, are outside the blood–brain barrier and would not be affected by changes in these drug transporters.

4.2. Opioid receptors

Morphine is a selective μ opioid agonist, and there have been a number of studies of the effect of SNPs in the μ opioid receptor (OPRM1), especially the G118A allele, and we also investigated this previously on both morphine-induced pain relief and morphine-induced nausea/vomiting. The results reported have been contradictory. Most, although not all, studies report the GG allele to provide less pain protection. One study found an effect on nausea/vomiting and one study a marginal effect, other studies found no effect of the G118A allele on

| Table 3 Summary for patient characteristics by phenotype groups (nausea or vomiting). |
|------------------------------------------|------------------------------------------|----------------|
| Neither symptoms (n = 47)             | At least one symptom (n = 82)           | P     |
| Age (y)†                                | 44.1 (9.4)                               | 43.1 (8.1) | .541 |
| Height (cm)‡                            | 159.7 (5.9)                               | 157.7 (5.8) | .058 |
| Weight (kg)§                            | 60.6 (11.1)                               | 57.2 (9.4) | .070 |
| BMI (kg/m²)§                            | 23.7 (3.7)                                | 23.0 (3.5) | .305 |
| Prescription†                           | M                                         | M+N | .191 |
|                                         | M+N                                      | M + P | .191 |
| Wound pain§                             | 27 (57.4%)                               | 57 (69.5%) | .191 |
| Dizziness§                             | 4 (8.5%)                                  | 9 (11.0%) | .191 |
| Drowsiness§                             | 16 (34.0%)                                | 16 (19.5%) | .191 |
| Dose of morphine†                       | 45 (95.7%)                                | 79 (96.3%) | .191 |
| Drowsiness§                             | 18 (38.3%)                                | 43 (52.4%) | .191 |
| BMI = body mass index.                  |                                           |       | .191 |
| † P < .05 indicates a significant difference among the 3 phenotype groups. |
| ‡ Data are presented by means and standard deviations; P values of the 2-sample independent t test are performed. |
| § Data are presented by counts and percentages; P values of the Fisher exact test are performed. |
| ‡ A total of 15 patients had missing dose of morphine. |

heterogeneous genotype than those with CC genotype of OPRK1 marker (rs1051660) (OR = 0.41, 95% CI = 0.19–0.90, P = .027). After considering potential confounders, the results of multiple logistic regression showed that the association between TT genotype of rs27337703 and phenotype disappeared (OR = 0.35, 95% CI = 0.13–0.92, P = .033) (Table 4).
**Table 4**

Summary for the associations of phenotype (nausea or vomiting) versus genotype.

| SNP         | Genotype | OR (95% CI) | P     | aOR (95% CI)* | P     |
|-------------|----------|-------------|-------|---------------|-------|
| DYPD       | AA       | 1.00        |       |               |       |
| rs1065652   | AG       | 0.89 (0.39–2.03) | .775  | 0.98 (0.34–2.85) | .969  |
|            | GG       | 0.68 (0.25–1.87) | .457  | 0.48 (0.14–1.69) | .254  |
| DYPD3A4     | CC       | 1.00        |       |               |       |
| rs2242480   | CT       | 1.41 (0.67–2.99) | .364  | 0.87 (0.35–2.14) | .759  |
|            | TT       | 3.51 (0.39–31.86) | .264  | 2.00 (0.20–20.32) | .558  |
| ABCC3       | CC       | 1.00        |       |               |       |
| rs2277624   | CT       | 0.72 (0.55–1.51) | .386  | 0.60 (0.25–1.46) | .260  |
|            | TT       | 0.98 (0.16–5.78) | .978  | 0.15 (0.01–1.87) | .140  |
| ABCB1       | GG       | 1.00        |       |               |       |
| rs1045642   | AG       | 0.06 (0.49–2.27) | .890  | 0.64 (0.25–1.66) | .357  |
|            | AA       | 1.90 (0.53–6.76) | .322  | 1.75 (0.36–8.53) | .492  |
| UGT2B7      | AA       | 1.00        |       |               |       |
| rs28365063  | AG       | 0.94 (0.44–1.99) | .866  | 0.64 (0.26–1.57) | .331  |
|            | GG       | 0.84 (0.13–5.37) | .657  | 0.59 (0.04–8.03) | .696  |
| UGT2B7      | TT       | 1.00        |       |               |       |
| rs7493152   | GT       | 0.80 (0.38–1.68) | .553  | 1.02 (0.40–2.57) | .969  |
|            | GG       | 1.33 (0.24–7.35) | .744  | 0.81 (0.13–5.32) | .830  |
| CACNA1E     | TT       | 1.00        |       |               |       |
| rs644706    | CT       | 0.79 (0.37–1.68) | .544  | 1.18 (0.46–3.02) | .724  |
|            | CC       | 1.06 (0.09–12.17) | .965  | 1.54 (0.12–20.36) | .743  |
| KCNJ6       | CC       | 1.00        |       |               |       |
| rs21730703  | CT       | 0.77 (0.36–1.62) | .487  | 0.90 (0.36–2.26) | .828  |
|            | TT       | 0.00 (0.01–0.83) | .033* | 0.07 (0.01–1.045) | .054  |
| KCNJ9       | CC       | 1.00        |       |               |       |
| rs2070995   | CT       | 1.31 (0.60–2.86) | .493  | 1.36 (0.52–3.53) | .533  |
|            | TT       | 2.37 (0.74–7.75) | .144  | 2.19 (0.55–8.73) | .269  |
| Oprk1       | CC       | 1.00        |       |               |       |
| rs1051660   | AC       | 0.41 (0.19–0.90) | .027* | 0.35 (0.13–0.92) | .033* |
|            | AA       | 3.19 (0.37–23.30) | .289  | 4.08 (0.42–39.90) | .227  |
| UGT7B7      | CC       | 1.00        |       |               |       |
| rs749366    | CT       | 0.80 (0.38–1.68) | .553  | 1.02 (0.40–2.57) | .969  |
|            | TT       | 1.33 (0.24–7.35) | .744  | 0.81 (0.13–5.32) | .830  |

*OR = odds ratio, aOR = adjusted odds ratio.
†P < 0.05.
*aOR adjusted for age, weight, prescription, and surgery.

**Table 4**

Summary for the associations of phenotype (nausea or vomiting) versus genotype.

Morphine, although a selective μ opioid agonist, also has effects on κ and δ opioid receptors, and κ receptors are found on peripheral nerve endings and in the vestibular zone (a site involved in nausea and vomiting responses). Therefore we investigated the effects of SNPs in genes for these receptors. No effects were seen. Another investigator, in a large multinational study, tried to determine the relationship between κ receptor gene SNPs and nausea/vomiting, but he was unable to do so because the frequency of the minor allele was too low.11

Several neurotransmitters have a general, not opioid-specific, influence on nausea/vomiting. We did not investigate SNPs in genes for these neurotransmitters, but Laugsand et al11 found SNPs in the serotonin receptor (HTR3B) and muscarinic acetylcholine receptor (CHRM3) genes to be associated with morphine-induced nausea/vomiting.

### 4.3. Ion channels

Morphine binding activates a G-protein whose downstream action is to activate an inwardly rectifying potassium channel and inactivate an R-type voltage-gated calcium channel, thus hyperpolarizing the cell membrane.46 Marker et al21 found that knockout mice for the 2 G protein-activated K+ genes studied here, KCNJ6 and KCNJ9, had reduced morphine-induced analgesic efficacy. In our study, the unadjusted, but not the adjusted, P values showed involvement of the KCNJ6 potassium channel in morphine-induced nausea/vomiting. Yokoyama et al24 showed that knock-out mice for the R-type voltage-gated calcium channel Cav2.3 also had altered morphine tolerance. Our results showed no influence on nausea/vomiting of the R-type voltage-gated calcium channel studied (CACNA1E). Further study of the influence of these channels on nausea/vomiting is indicated.

In conclusion, our results showed no association between SNPs of any of the genes studied with morphine-induced nausea/vomiting. Perhaps related studies of mRNA or proteonomics will give better information.

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