Human Genetic Variability Contributes to Postoperative Morphine Consumption

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Abstract: High interindividual variability in postoperative opioid consumption is related to genetic and environmental factors. We tested the association between morphine consumption, postoperative pain, and single nucleotide polymorphisms (SNPs) within opioid receptor 1 (OPRM1), catechol-O-methyltransferase (COMT), uridine diphosphate glucose-glucuronosyltransferase-2B7, and estrogen receptor (ESR1) gene loci to elucidate genetic prediction of opioid consumption. We analyzed 20 SNPs in 201 unrelated Caucasian patients who underwent abdominal surgery and who were receiving postoperative patient-controlled analgesia-administered morphine. Morphine consumption and pain intensity were dependent variables; age and sex were covariates. A haplotype of 7 SNPs in OPRM1 showed significant additive effects on opioid consumption (P = .007); a linear regression model including age and 9 SNPs in ESR1, OPRM1, and COMT explained the highest proportion of variance of morphine consumption (10.7%; P = .001). The minimal model including 3 SNPs in ESR1, OPRM1, and COMT explained 5% of variance (P = .007). We found a significant interaction between rs4680 in COMT and rs4986936 in ESR1 (P = .007) on opioid consumption. SNPs rs677830 and rs540825 of OPRM1 and rs9340799 of ESR1 were nominally associated with pain Numeric Rating Scale...
Patient-controlled analgesia (PCA) was introduced more than 20 years ago, and has since become an accepted standard of acute postoperative pain management, with a well established record of efficacy, safety, and patient satisfaction. Morphine is the opioid of choice for PCA, because of the optimal kinetic and clinical profile (low volume of distribution, pure μ-receptor agonist, rapid onset of clinical analgesia). Morphine PCA provides better pain control and greater patient satisfaction than traditional intermittent intravenous opioid analgesia. However, because each patient often responds differently to specific opioids, providing adequate analgesia for individual patients without concomitant development of adverse effects is still a major challenge. The high interindividual variability in opioid responses and doses is attributable to genetic and environmental factors. A multidisciplinary approach, including clinical and pharmacogenetic strategies, could be used to predict short-term postoperative outcomes in morphine consumption and pain intensity (PI). A successful prediction of opioid response and required doses could help clinicians to develop interindividual, personalized pain therapies or identify patients in advance who may need high opioid doses.

Previous studies suggest that genetic variability may influence pain perception and responses to opioid therapy. The most compelling candidates are the genes coding the opioid receptor μ1 (OPRM1), catechol-O-methyltransferase (COMT), and uridine diphosphate glucose-glucuronosyltransferase (UGT2B7) enzymes. In addition, genetic variability at the estrogen receptor (ESR1) has been shown to influence chronic pain. However, the effect of genetic variability on opioid analgesia in the acute pain setting has not yet been fully elucidated. Overall, previous studies have attempted to find single-gene associations with opioid analgesia. However, the existence of a multigenic control in the response to opioids is more conceivable.

We analyzed 2 of the most studied nonsynonymous variations contributing to opioid response, OPRM1 rs1799971 (asparagine to aspartic acid substitution at amino acid 40) and COMT rs4860 (valine to methionine substitution at position 158), testing their correlation with postoperative outcome at 24 hours by monitoring PCA-administered morphine consumption and PI.

Furthermore, to elucidate potential genetic predictors for opioid response, we also evaluated the influence of other single nucleotide polymorphisms (SNPs) in OPRM1, COMT, UGT2B7, and ESR1 genes and the potential gene-to-gene interactions with morphine consumption and pain during the first 24 postoperative hours in adult Caucasian patients who underwent major abdominal surgery.

Methods

Setting and Study Design

We conducted this prospective study at the Fondazione IRCCS Policlinico San Matteo of Pavia and at the San Gerardo Hospital of Monza in Italy after institutional review board approval from both institutions (June 28, 2010, DS2943/2010; November 11, 2010, 611) and registration on ClinicalTrials.gov in November 2010 (NCT01233752). All study subjects provided informed consent.

Participants

We recruited adult (18–80 years old) Caucasian patients scheduled for major abdominal surgery, after which PCA morphine use was planned for postoperative pain control, from January 2011 to July 2013. Patients were HIV-negative, pain-free before surgery, American Society of Anesthesiologists (ASA) physical status I to III, had no cognitive or mental impairments, had normal liver and renal functions (cholinesterase <3000 mU/mL, total bilirubin <2 mg/dL, and creatinine <1.2 mg/dL), and had no known intolerance to morphine. We excluded from the study patients needing postoperative sedation and/or mechanical ventilation in the intensive care unit or requiring reintervention. We induced anesthesia using propofol and/or midazolam and an opioid (remifentanil [29.15%], fentanyl [35.68%], or both [35.18%]) and we maintained with opioid and sevoflurane. We administered acetaminophen 1 g or ketorolac 30 mg approximately 45 minutes before the end of the surgery. Thirty minutes before the end of surgery, patients also received ondansetron 0.1 mg/kg and/or dexamethasone 0.1 mg/kg for postoperative nausea and vomiting prophylaxis. We administered a morphine bolus (0.15 mg/kg ± 20%) 45 minutes before the end of the surgery, followed by intravenous morphine PCA (1 mg bolus, 5-minute
lockout, 20 mg maximal dose every 4 hours) for at least 48 hours. We added acetaminophen 1 g or ketorolac 30 mg at regular intervals.

**Clinical Outcome Measures**

We evaluated morphine consumption and PI in the Post-Anesthesia Care Unit at the end of surgery (T0) and at 3, 6, 12, and 24 hours after surgery. We calculated morphine consumption using the PCA pump (Cadd; Smiths Medical, Dublin, OH) electronic registry. We evaluated PI using the Numeric Rating Scale (NRS; 0 [no pain] to 10 [worse pain] points) at rest and movement (eg, coughing, deep inspiration). We recorded blood pressure, heart and respiratory rate, and side effects at each evaluation interval during the study.

**Pharmacogenetic Analyses**

We collected approximately 5 mL of each peripheral blood sample into ethylenediaminetetraacetic acid-coated tubes. We extracted genomic DNA using a QI Amp DNA Blood Mini Kit (Qiagen, Monza, Italy) according to the manufacturer’s protocol and stored at −20°C.

We genotyped *OPRM1* (rs1799971, rs1319339, rs7776341, rs563649, rs2075572, rs540825, and rs677830), *COMT* (rs4680, rs6269, rs4633, rs4818, rs165774, and rs174696), and *UGT2B7* (rs743813S, rs7668258, rs73823859, and rs7668282) SNPs using Taqman SNP Genotyping Assays (Applied Biosystems, Foster City, CA) and a LightCycler 480 Real-Time PCR System (Roche Diagnostics Ltd, Lewes, United Kingdom) according to the manufacturer’s instructions in the Biochemistry and Genetics Laboratory, Division of Pneumology, Department of Molecular Medicine, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. We analyzed *ESR1* rs4986936, rs2234693 (also known as PvuII), and rs9340799 (also known as XbaI) SNPs using polymerase chain reaction amplicon direct sequencing, in the Department of Biology and Biotechnology, University of Pavia, Italy. We analyzed *COMT* rs4986936, rs2234693 (also known as PvuII), and rs9340799 (also known as XbaI) SNPs using polymerase chain reaction amplicon direct sequencing at the Department of Drug Sciences, Pharmacology Section, University of Pavia.

**Statistical Analysis**

Morphine consumption was not normally distributed, thus it was log-transformed (lnMDo) for the analyses. The primary end point was defined the association between postoperative analgesia (POA) and *OPRM1* rs1799971 for the first 24 postoperative hours. For sample size calculation, we used a method developed by Chou et al: we assumed an average morphine dose of 24 mg/d for the A/A homozygotes (group A) and 36 mg/d for the others (group B; a difference of 50%), with a common SD of 15 mg/d. Considering 160 subjects in group A and 40 subjects in group B, the power of the study would have been >95%. Assuming a 25% difference, the required sample size was 200.

A secondary end point was the association of POA with *COMT* rs4680. We tested the interaction between rs1799971 and rs4680 using a univariate general linear model (GLM). We treated POA and PI as dependent variables with age and sex as covariates. We also evaluated the influence of the other selected SNPs and haplotypes on POA and PI. We tested Hardy–Weinberg equilibrium and inter-marker linkage disequilibrium using Haploview version 4.2. We performed multimarker haplotype and genotype association tests using UNPHASED version 3.1. We carried out genotype association tests using an additive genetic model. PHASE imputed individual haplotypes. For the primary and secondary end points, we considered statistically significant a 2-sided P-value of <.05.

We tested for a synergistic effect between rs1799971 and rs4680. The 2 SNPs showed an additive effect on Hardy–Weinberg equilibrium (see Supplemental Table 1, which shows all SNPs analyzed).

We did not find a significant association between *OPRM1* rs1799971, *COMT* rs4680, and POA. A linearity test showed a relationship between morphine dose increase and number of G alleles for the *OPRM1* rs1799971 SNP (A/A < A/G < G/G; P = .06; Fig 1) and *COMT* rs4680 SNPs (A/A < A/G < G/G; P = .12; Fig 2). Concerning rs4680, a test for interaction showed that age had a modifier effect on POA consumption. Indeed, among younger patients (23–63 years old; n = 103), G/G carriers consumed more morphine than the others (P = .005), but this was not true among older patients (P = .214; 64–79 years old; n = 98; see Supplemental Table 2, which illustrates test for interaction between age and rs4680 genotype in lnMDo).

We tested for a synergistic effect between rs1799971 and rs4680. The 2 SNPs showed an additive effect on POA (Fig 3). Besides rs1799971 and rs4680, we analyzed 18 other SNPs in the *OPRM1*, *COMT*, *UGT2B7*, and *ESR1* genes, but we did not find any statistically significant result regarding single SNP association with POA.
Next, we tested whether the combined effect of multiple SNP markers within the OPRM1 gene locus (See Supplemental Fig 1, showing the OPRM1 linkage disequilibrium blocks) could explain additional variability in morphine response. We first analyzed the association between OPRM1 haplotype and POA. OPRM1

Figure 1. Morphine consumption in patients according to OPRM1 rs1799971 genotype. Increase of lnMDo according to the number of G alleles: 136 patients are A/A, 56 are A/G, and 9 are G/G. The circle above the graph of A/A patients refers to the presence of 1 outlier.

Figure 2. Morphine consumption in patients according to COMT rs4680 genotype. Increase of lnMDo according to the number of G alleles: 51 patients are A/A, 89 are A/G, and 61 are G/G. The circle above the graph of A/A patients refers to the presence of 1 outlier.
haplotypes significantly affected POA consumption (global $P = .002$; Table 1).

In particular, haplotypes CAACTAA (H5) and TAGCCTG had a statistically significant effect on POA; carriers of the former required less POA than TAACCTG and carriers of the latter required more POA, suggesting allelic effects in the \textit{OPRM1} locus in addition to adenine to guanine transition at nucleotide position 118 (A118G). We also confirmed the effect of haplotype H5 using a GLM with sex and age as covariates and observed a significant linear additive effect ($P = .007$). Individuals with the H5/H5 diplotype consumed less POA, those with H5/non-H5 had an intermediate consumption, and those without H5 consumed the highest POA (Fig 4).

We analyzed haplotype effects in \textit{COMT}, \textit{UGT2B7}, and \textit{ESR1} without finding any statistically significant results with respect to POA. We next tested whether the combination of several SNPs within the selected genes could predict variability in responses to morphine. To find the best predictive model for POA, we applied a stepwise backward linear regression model using lnMDo as a dependent variable and SNP with age and sex as independent variables (Supplemental Table 3). The model explaining the highest variance of POA (10.7%; $P = .001$) included age and rs9340799, rs1799971, rs4986936, rs1319339, rs174696, rs677830, rs4680, rs4818, and rs540825 situated within the \textit{ESR1}, \textit{OPRM1}, and \textit{COMT} gene loci.

![Figure 3](image_url)

**Figure 3.** Evaluation of the synergic interaction between \textit{OPRM1} rs1799971 and \textit{COMT}rs4680. The 2 SNPs showed an additive effect on lnMDo, represented by the different angular coefficient of the 2 straight lines.

| HAPLOTYPE | rs1319339 | rs7776341 | rs1799971 | rs563649 | rs442075572 | rs540825 | rs4677830 | N (%) | AddVal | 95%LO | 95%HI | P  
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<td>71 (18.5)</td>
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<td>25 (6.4)</td>
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Abbreviations: AddVal, estimated additive genetic value; 95%LO, lower confidence limit for the additive value; 95%HI, upper confidence limit for the additive value.

**Table 1. \textit{OPRM1} Haplotype Association With POA**
Interestingly, the model including the lowest number of variables \((ESR1\ rs4986936,\ OPRM1\ rs1319339,\ COMT\ rs4680)\) explained 8.1% of POA variance \((P = .001)\). After excluding age, the same model explained 5% of POA variance \((P = .007)\). By using a GLM with lnMDo as a dependent variable, rs1319339, rs4680, and rs4986936 as independent variables, and age as a covariate, we found a significant gene-to-gene interaction between \(COMT\ rs4680\) and \(ESR1\ rs4986936\) \((P = .007;\ Fig\ 5)\). Next, we tested whether the SNPs and haplotypes associated with POA were also associated with PI. For each gene, we checked the association between all selected haplotypes and SNPs with PI, considering NRS as a dependent variable and age and sex as covariates. We measured PI at 5 time points: immediately after surgery, and at 3, 6, 12, and 24 hours after surgery. We analyzed patients with at least 3 evaluations, dichotomizing them between those who never reported PI with NRS >3 \((n = 105)\) and those who reported a higher score at 1 or more assessments \((n = 59)\). The SNPs rs677830 and rs540825 of \(OPRM1\) and rs9340799 of \(ESR1\) displayed only nominal associations with NRS \((P = .039\) for rs677830; \(P = .012\) for rs540825; \(P = .023\) for rs9340799).

**Discussion**

To investigate the role of genetics in modulating short-term postoperative outcome in terms of POA and PI, we focused on 2 main groups of polymorphisms associated with interindividual variability of opioid pharmacodynamics \((OPRM1)\) and pharmacokinetics \((UGT2B7)\). We also deepened the role of genetics in modulating differences in pain sensitivity, by analyzing several SNPs in \(COMT\) and \(ESR1\) genes. We analyzed the genotype/phenotype correlations between A118G and postoperative outcome at 24 hours in terms of PCA morphine consumption and PI. Age, sex, and surgery duration did not interact with A118G in influencing POA. This variant alone was not associated with postoperative NRS. We also analyzed the effect of rs4680, a nonsynonymous variation changing valine to methionine at codon 158 of the COMT enzyme, on POA, which has already been shown to correlate with postoperative morphine need.\(^8\)

We did not find a synergic effect between \(OPRM1\ rs1799971\) and \(COMT\ rs4680\); however, future studies on larger cohorts are needed to confirm our findings. Indeed, we found that none of the \(COMT\) variants analyzed, by themselves, were associated with morphine consumption, and these results did not reproduce our findings with postoperative pain and morphine.\(^12\) Our previous study,\(^12\) which analyzed the first 98 patients of this cohort, revealed a statistically significant effect of \(COMT\) variant rs4680 in modulating POA; nevertheless, this correlation was not confirmed in this larger cohort study. Our new results show, once again, how complex is the scenario of the genotype/phenotype correlations of complex traits such as POA and postoperative PI.

Besides rs1799971 and rs4680, we investigated the role of 18 SNPs in \(OPRM1,\ COMT,\ UGT2B7,\) and \(ESR1\) gene loci, along with their corresponding haplotypes, which have already been correlated with interindividual
variability of opioid response or postoperative pain in predicting short-term postoperative outcome.\textsuperscript{10,27,30,33}

We found that the \textit{OPRM1} CAACTAA haplotype, constituted by markers rs1319339, rs7776341, rs1799971, rs563649, rs2075572, rs540825, and rs677830, predicted decreased POA, with a significant additive effect. On the contrary, the TAGCCTG haplotype, the only one including the G allele of rs1799971, predicted increased POA. This result confirms the literature data: in a very recent meta-analysis, Hwang et al showed that G-allele carriers of rs1799971 required a higher mean opioid dose than A/A homozygotes in the postoperative period.\textsuperscript{23} Next, we hypothesized that a combination of multiple allelic variants situated within the multiple genes related to the opioid pain pathway, each one with a mild effect size, if combined, can predict better response to morphine. We found 2 significant models: 1 (model 11) included 9 SNPs (2 in \textit{ESR1}, 4 in \textit{OPRM1}, 3 in \textit{COMT}) and age and explained the highest lnMDo variance (10.7%); the other involved the least number of predictors (3 SNPs in \textit{ESR1}, \textit{COMT}, and \textit{OPRM1}), and therefore could be proposed as a potential biomarker in clinical practice to tailor morphine postoperative treatment (variance explained 5%; \textit{P} = .007).

The contribution of \textit{ESR1} to both models of the variability of POA at 24 postoperative hours strongly suggests that \textit{ESR1} may play a substantial role in the modulation of perception of acute postoperative pain. Available literature reports are inconsistent, although most painful conditions such as migraine and temporomandibular joint disorders are more prevalent in women than in men.\textsuperscript{32} Notably, Govindan et al found a significant association between the \textit{PvuII} C allele and endometriosis and uterine fibroids.\textsuperscript{19} Also, Roh et al recently reported that the \textit{ESR1} XbaI polymorphism was associated with Visual Analogue Scale back pain scores in 192 Korean patients with degenerative spondylolisthesis.\textsuperscript{32} Contrary to the importance of genetic variability in morphine pharmacodynamics, we did not find any correlation between genotype/phenotype and morphine pharmacokinetics: no \textit{UGT2B7} SNPs were significantly associated with POA, consistent with previous findings on \textit{UGT2B7} variants and morphine glucuronidation in cancer patients.\textsuperscript{20}

Our study highlights the relevance of testing the gene–gene interactions between apparently unrelated genes in complex traits such as POA. The present findings, if confirmed in larger and ethnically different cohorts may pave the path toward a personalized clinical approach in POA dosing.

However, it is important to acknowledge the limitations of the present study. We analyzed common
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functional SNPs in the candidate genes; additional potentially functional variants should be assessed in future studies; we used intraoperative remifentanil, fen-
tanyl, or both, and we used midazolam only in part of the studied subjects. We did not analyze preoperative mental status and anxiety, which may have influenced postoperative outcome.\textsuperscript{4,5,11,29} The study included a number of patients that provided a sufficient statistical power to detect significant associations. However, the actual number of 9 G/G subjects advise for some caution in the interpretation of the results. To overcome these limitations we now are replicating these analyses in 2 larger cohorts of patients suffering from acute and chronic pain.

Conclusions

In summary, our study highlights the important contribution of genetic variability to short-term POA. We found that combinations of genetic allelic variants within the \textit{OPRM1}, \textit{COMT}, and \textit{ESR1} genes substantially influence opioid consumption, but not PI. Our findings could contribute to the further development of personalized approaches to opioid use, maximizing the therapeutic benefits of postoperative management on the basis of genetic makeup of an individual patient.

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Supplementary Data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jpain.2016.02.003.

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