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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 μ 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

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scores. Combinations of genetic variants within *OPRM1*, *COMT*, and *ESR1* better explain variability in morphine consumption than single genetic variants. Our results contribute to the development of genetic markers and statistical models for future diagnostic tools for opioid consumption/efficacy.

***Perspective:** This article presents the efforts dedicated to detect correlations between the genetic polymorphisms and the clinical morphine effect self-administered by patients using a patient-controlled analgesia pump after major surgery. The clinical effect is expressed in terms of morphine consumption and pain scores.*

Registered on ClinicalTrials.gov: NCT01233752.

***Key words:** Acute postoperative pain, genetic variability, postoperative opioid consumption, genetic variants combination, OPRM1 haplotype.*

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.[36] 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.[22] 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[11] and doses is attributable to genetic and environmental factors.[3,12,13,18,35] A multidisciplinary approach, including clinical and pharmacogenetic strategies, could be used to predict short-term postoperative outcomes in morphine consumption and pain intensity (PI).[6,12] 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.[15,21,28] The most compelling candidates are the genes coding the opioid receptor μ 1 (OPRM1), catechol-O-methyltransferase (COMT), and uridine diphosphate glucose-glucuronosyltransferase (UGT2B7) enzymes.[7,14,17,25,26,31] In addition, genetic variability at the estrogen receptor (*ESR1*) has been shown to influence chronic pain.[24,32] 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.[1]

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 .1 mg/kg and/or dexamethasone .1 mg/kg for postoperative nausea and vomiting prophylaxis. We administered a morphine bolus (.15 mg/kg ± 20%) 45 minutes before the end of the surgery, followed by intravenous morphine PCA (1 mg bolus, 5-minute