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Original Article

Pharmacogenetic study of pruritus induced by epidural morphine for post cesarean section analgesia

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ABSTRACT

Objective: The mechanism through which neuroaxial morphine causes pruritus has not been elucidated clearly and thoroughly.
Materials and methods: a study in 129 female parturients was conducted to investigate the effect of 14 single nucleotide polymorphisms (SNPs) on phenotype (pruritus) induced by neuroaxial (including intrathecal or epidural) morphine for cesarean section. 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.
Results: no significant association with the presence of phenotype (pruritus) versus genotype was observed (all p-values > 0.05). No significant association with severity of phenotype versus genotype of the 11 SNPs was observed except for unadjusted data for rs2737703. There was no significant difference between severity or incidence of IVPCA morphine-induced nausea and vomiting and genotype (11 SNPs).
Conclusion: our results showed no association between SNPs of any of the genes studied with neuroaxial morphine inducing pruritus.

Introduction

Epidural morphine injection twice per day is widely used for post-cesarean pain management due to its ability to provide slow onset and long-duration pain relief in our hospital [1]; however, the high incidence of associated side effects after neuroaxial analgesia may limit its clinical application [2,3]. The most common side effect of intrathecal and epidural opioids is pruritus [4], which can be accompanied by some other less common side effects such as nausea, vomiting, urinary retention and respiration depression [4,5]. The incidence of pruritus (3–7 h after morphine injection) varies from 62% to 92% [6,7]. The symptoms typically spread rostrally from the site of administration to the trunk, and subsequently are more likely to be localized to the face, neck or upper thorax [8]. Inter-parturient variability, including ethnicity, age, gender and other factors might be associated with the difference in the incidence and severity of those side effects, however, genetic factors are thought to have an influence as well.

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 [9–12]. However only very few studies have investigated how morphine-induced pruritus is affected by SNPs in these genes [10,12,13]. Previous studies from our laboratory and others investigating pruritus induced by neuroaxial morphine have been focused on the treatment and prevention of this condition [14–16]. Therefore, in this study, we examined, in a population of Taiwanese pregnant women receiving epidural morphine for post cesarean section analgesia, the 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

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in the post-receptor 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 neuraxial morphine-induced pruritus.

Materials & methods

Parturient profile and anesthetic procedure

This study was approved by the Ethic Institute Review Board of the National Taiwan University Hospital and after obtaining written informed consent from all participants and was in accordance with the most recent Declaration of Helsinki. This was a population-based, prospective observational study, with a blinded data analysis. A total of 217 American Society of Anesthesiologists physical status I and II, Taiwanese women who presented for elective cesarean delivery at 37 weeks of gestation and received epidural morphine for post cesarean pain control were recruited into this study in the 12-month period from 1 August 2007 to 31 July 2008. This sample size was chosen in order to achieve a power 480% so as to detect a 10% difference in genotype frequency among groups. All selected women could comprehend and describe the pain score, and the exclusion criteria were the following: contraindications for epidural morphine, complaint of pruritus before the cesarean section, coexisting skin disorder, any systemic disease associated with pruritus and the history of allergy to opioids. All of the study subjects, attending anesthesiologists and the well-trained investigator were unaware of the parturients' genotype at the time of surgery because genotyping was determined post hoc in the laboratory. All of the parturients received combined spinal with epidural anesthesia for the cesarean section. Under the right lateral vertebral body, spinal anesthesia was induced with a 27G Whitacre spinal needle at the L3–L4 level with 9–12 mg hyperbaric 0.5% bupivacaine (Marcaine; Astra Zeneca, Sodertalje, Sweden) to achieve an acceptable dermatome level of anesthesia for the cesarean section. The epidural was conducted with a 16G Tuohy needle and an epidural catheter was inserted simultaneously. In addition, a 3 ml test dose (2% xylocaine with 1: 200,000 epinephrine) was added to rule out a false-positive epidural space insertion. After the fetus was delivered, the first analgesic dose of morphine (2 mg in 10 ml sterile normal saline) was injected via an epidural catheter.

Post-C/S pain management, assessment and data collection

After cesarean section, the post-cesarean analgesic treatment regimen was a twice-a-day (08:00 and 20:00 h) bolus of morphine (2 mg in 10 ml sterile normal saline) through an epidural catheter. A trained investigator interviewed the parturient and all data were collected after three analgesic doses (6 mg) during the first 24 h post-operatively. If the parturients still felt wound pain (which was a score above 3 cm on a 10 cm VAS pain scale) even after 6 mg of epidural morphine, those cases were excluded from the study and received parturient-controlled analgesia with intravenous morphine as an alternative. Thus, all of the participants in this study had reduced pain scores after intrathecal morphine, and no other supplemental analgesics were administered. Data related to parturients' age, weight, height, history of previous cesarean section, ASA class as well as wound pain score were collected. Central type pruritus was defined as a sensation that induced a desire to scratch the skin over the trigeminal area. We recorded only typical episodes of central type pruritus; that is to say, itching sensations over the incision wound or abdominal area were not identified as central type pruritus. We used the Itching Severity Scale (ISS 0–4) to evaluate the intensity of the central type pruritus induced by neuroaxial morphine, which utilized the following scoring method: 0 = none; 1 = mild, not annoying or troublesome; 2 = moderate, annoying and troublesome, may interfere with normal daily activity and sleep; 3 = severe, very annoying and troublesome, substantially interfering with sleep and daily activities; 4 = very severe, warrants medication. Furthermore, we divided the incidence of pruritus into non-significant (ISS 0–1) and significant groups (ISS 2–4). The following side effects were also recorded by subjective complaint or objective observation: nausea on a severity scale of 0–3; vomiting on a severity scale of 0–3; and urinary retention. Women who had severe nausea or vomiting were treated with prochlorperazine (5 mg), and those with severe pruritus were treated with diphenhydramine HCL (4 mg).

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.

Statistical analysis

Phenotype was defined according to two symptoms, nausea and vomiting, which was divided into two groups (i.e., no symptoms and at least one symptom). The Hardy-Weinberg equilibrium test was performed by using SHEsis (17; *Shi YY, He L. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. Cell Res 2005;15:97-98*). One SNP was excluded from subsequent analysis because it contained only the CC genotype. And two SNPs with minor allele frequency less than 5% were also excluded from subsequent analysis. Age, height, weight, BMI were presented by mean and standard deviation, the independent t-test was performed to evaluate the differences between the two phenotype groups. Other categorical data were presented by number and percentage, Fisher's 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 95% confidence interval (95% CI). In order 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 two-tailed p-value less than 0.05 was considered statistically significant. Data were analyzed by using SPSS 15.0 statistics software (SPSS Inc, Chicago, Illinois, USA).

Table 1
SNPs investigated.

Gene Symbol	Name	Polymorphisms
Metabolism		
CYP3A4	cytochrome P450	rs2242480, rs28371759
CYP2D6	cytochrome P450	rs3892097, rs28365063
UGT2B7	UPD-glucourasyltransferase	rs7439366, rs7439152
Distribution		
ABCB1	ATP-binding cassette transporter	rs1045642
ABCC3	ATP-binding cassette transporter	rs2277624
Receptor		
OPRK1	κ-opioid receptor	rs1051660
OPRD1	δ-opioid receptor	rs1042114
Ion channel		
KCNJ6	G-protein activated K+ channel	rs2070995
KCNJ9	G-protein activated K+ channel	rs2737703