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ORIGINAL ARTICLE

Effect of μ-opioid receptor A118G polymorphism on the ED50 of epidural sufentanil for labor analgesia

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ABSTRACT
Background: A common polymorphism of the μ-opioid receptor gene (OPRM1, p.118A/G), which has been shown to effect the response to neuraxial opioids, occurs in 30% of Caucasian women. This double-blind up-down sequential allocation study was designed to examine the effect of p.118A/G on the ED50 of epidural sufentanil for labor analgesia.
Methods: Nulliparous women were recruited at 35 weeks of gestation ($n = 77$) and genotyped for p.118A/G. Those subsequently requesting epidural labor analgesia were enrolled. Each woman received epidural sufentanil diluted with 0.9% saline to a volume of 5 mL. The initial sufentanil dose was 21 μg, with subsequent doses determined by the response of the previous patient (testing interval 1 μg). Efficacy was accepted if the visual analogue score decreased to <10 mm on a 100-mm scale within 30 min of drug administration.
Results: Twenty patients were excluded, leaving 57 women from whom data were analyzed: 33 in Group A (wild-type A118 homozygotes) and 24 in Group G (heterozygotes and homozygotes G118). The ED50 for epidural sufentanil was 25.2 μg in Group A (95% CI 23.2–26.4) and 20.2 μg in Group G (95% CI 14.2–23.6) ($P = 0.03$). The potency ratio for epidural sufentanil in Group G compared to Group A was 1.25 (95% CI 1.00–1.64).
Conclusion: Women carrying the variant allele of p.118A/G of OPRM1 (G118) had a lower ED50 for epidural sufentanil given for early labor analgesia than women homozygous for the wild-type allele.

Keywords: Labor analgesia; Epidural; Sufentanil; Polymorphism; μ-opioid receptor

Introduction

The intensity of pain and analgesic requests during labor and delivery are variable and unpredictable. Some women need a minimal amount of analgesic drugs while others require intense analgesia in early labor. In addition to the nature of labor, individual sensitivity to endorphins and endogeneous opioids may explain why some women feel more intense pain during childbirth than others. Epidural and spinal opioids are commonly used in combination with local anesthetics for labor analgesia. However, a large inter-individual variability has been observed in analgesic efficacy, incidence and severity of side effects and tolerance profiles.

Recent developments in pharmacogenetic research have identified numerous genetic variations that may impact on the analgesic response to opioids, including potency, duration of effect and incidence and severity of adverse outcomes. In recent years, a number of genetic association studies have been performed in the context of labor and post-cesarean analgesia. However, since the nature of labor pain is multi-factorial, pain perception and responsiveness to analgesics is subjective and controversy exists about the impact of these findings on current practice. Therefore, the clinical relevance of these association studies warrants further investigation.

The μ-opioid receptor (μ-OR), encoded by the OPRM1 gene, has been the subject of several genetic studies in the context of obstetric analgesia because this receptor is the main site of action of many endogenous peptides including β-endorphin and encephalin.[1] OPRM1 is known to display several single nucleotide polymorphisms (SNPs).[2–4] There is great interest in one common polymorphism of OPRM1, p.118A/G, because the G118 allele has been shown to result in the substitution of amino acid asparagine with aspartate at position 40 which may increase the binding affinity and potency of β-endorphin.[5] Hypothetically, individu-

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als carrying the receptor gene variant may show differences in some μ-OR functions, including β-endorphin-mediated analgesia and pain threshold as suggested by an experimental human model.[6] Because of the relatively high prevalence of the G118 variant, if it does alter the clinical response to opioids, this may impact on the dose required to produce effective analgesia in 30% of women requesting an epidural for labor analgesia.[7] Previous work using the up-down sequential allocation method to investigate the effect of p.118A/G demonstrated that women carrying the G118 allele requested analgesia later in labor and had a lower ED50 for intrathecal fentanyl than women who were A118 homozygous, suggesting an increased potency of intrathecal fentanyl with this variant allele.[8] Another study, however, did not find an effect of this SNP on the duration of intrathecal fentanyl.[9]

The use of lipid soluble synthetic opioids via epidural or combined spinal-epidural (CSE) techniques has become a standard of care for labor analgesia. In our practice, epidural sufentanil in combination with local anesthetic is the most commonly used analgesic technique for parturients requesting neuraxial analgesia early in labor.[10] To the best of our knowledge, the effect of p.118A/G of OPRM1 on the response to any opioid given epidurally or on the effect of neuraxial sufentanil for labor analgesia have not been reported previously. In the current study, we tested the hypothesis that the presence of the variant G118 allele of OPRM1 decreases the ED50 of epidural sufentanil for labor epidural analgesia, using the up-down sequential allocation method.

Methods

After Institutional Review Board approval and informed written consent, 77 nulliparous women with uncomplicated singleton vertex pregnancies scheduled to deliver at Città di Roma Hospital, who anticipated requesting epidural labor analgesia, were recruited at 33–35 weeks of gestation. Exclusion criteria were cardiovascular disease, history of drug abuse or use of chronic pain medication. Each woman was informed about the analgesic procedure and told that the decision to deliver with or without neuraxial analgesia, as well as the timing of analgesia, would be left to her discretion. Blood samples were obtained for genotyping within 72 h. Only women who subsequently requested neuraxial analgesia in labor were enrolled in the study; at that time, women were excluded if they were at gestational age <36 weeks, had preeclampsia or required cesarean delivery without a trial of labor. In addition, because epidural sufentanil alone does not provide sufficient analgesia during the second stage of labor, only women requesting analgesia in early labor (cervical dilatation <4 cm) were studied; of these, only women whose labor continued for at least 1 h were included in the final analysis.

Blood samples were sent for genotyping to the Department of Genetic and Laboratory Medicine, University Hospital of Geneva, Geneva, Switzerland. Genomic DNA was isolated from whole venous blood by a non-phenolic method using either Puregene Blood (Gentra, Minneapolis, MN, USA) or Nucleospin Blood (Macherey–Nagel, Düren, Germany) Extraction Kits, and tested for DNA integrity, purity/quality by gel electrophoresis and optical densitometry (260 nm/280 nm). Details of SNP genotyping are included in the Appendix.

After recruitment, a member of the team not involved in the study protocol, categorized women in one of two groups according to the genotype result. Group A consisted of wild-type homozygotes (A118) while Group G included heterozygotes and homozygotes carrying the G118 allele. When in spontaneous labor and requesting epidural analgesia, women were assigned to one of two up-down sequences, according to their genotype.

The patient, the anesthesiologist who performed the procedure and the anesthesiologist who performed the clinical assessments were blinded at all times to genotype and sufentanil dose. Sufentanil was prepared by the pharmacy of the Città di Roma Hospital in sterile pre-filled 5-mL syringes with a sufentanil concentration of 10 μg/mL. Syringes were placed in sealed envelopes and stored by a member of the team. In order to provide sufficient volume of the sufentanil solution in the epidural space, at the time of epidural placement, the study solutions were diluted to a total volume of 5 mL.

Immediately after maternal request for epidural analgesia, cervical dilatation was evaluated and epidural placement was performed with patients in the left lateral decubitus position. Using loss-of-resistance to saline, a 16-gauge Tuohy needle was inserted at the L3–4 or L4–5 interspace and a catheter threaded 3–5 cm into the epidural space. After negative aspiration, the catheter was secured before the patient was repositioned. For the purpose of the study, the volume of saline used was restricted to <2 mL in order to minimize dilution of sufentanil. No test dose was given.

Based on a previous study,[9] the initial starting dose of sufentanil for the first woman in each allocation arm was 21 μg. The dosing interval for the allocation sequence was fixed at 1 μg. The primary endpoint of the study was the analgesic efficacy of epidural sufentanil, assessed using a 100-mm visual analogue pain scale (VAPS) during the peak of a painful uterine contraction (0 mm = no pain, 100 mm = the worst possible pain) at 0, 10, 20, and 30 min after the injection of the study solution.

According to the woman's response to the analgesic dose, three possible outcomes were determined: