Human Opioid Receptor A118G Polymorphism Affects Intravenous Patient-controlled Analgesia Morphine Consumption after Total Abdominal Hysterectomy

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Background: Animal and human studies indicate that genetics may contribute to the variability of morphine efficacy. A recent report suggested that cancer patients homozygous for the 118G allele caused by the single nucleotide polymorphism at nucleotide position 118 in the μ-opioid receptor gene require higher doses of morphine to relieve pain. The purpose of the current study was to investigate whether this polymorphism contributes to the variability of morphine efficacy in women who undergo abdominal total hysterectomy.

Methods: After informed consent was obtained, 80 female patients (American Society of Anesthesiologist physical status I or II) scheduled to undergo elective total hysterectomy surgery were enrolled in this study. All patients received general anesthesia and were screened for A118G polymorphism by blood sample. Intravenous morphine patient-controlled analgesia was provided postoperatively for satisfactory analgesia. The authors recorded the morphine consumption doses and demand times. Pain at rest and side effects were measured with rating scales.

Results: Forty-three women were A118 homozygous, 19 were heterozygous, and 18 were G118 homozygous. Patients homozygous for A118 required more morphine doses (33 ± 10 mg) to achieve adequate pain relief compared with patients homozygous for A118 (27 ± 10 mg) in the first 24 h (P = 0.02). However, there was no statistically significant difference for morphine consumption at 48 h.

Conclusion: Genetic variation of the μ-opioid receptor may contribute to interindividual differences in postoperative morphine consumption. In the future, identifying single nucleotide polymorphisms of patients may provide information to modulate the analgesic dosage of opioid for better pain control.

Materials and Methods

Subjects

With the approval of the Human Studies Committee at Chang Gung Memorial Hospital, Kaohsiung Hsien, Taiwan (No. 93-109), and written, informed consent, 80 adult female patients with American Society of Anesthesiologists physical status of I or II in whom intravenous morphine patient-controlled analgesia (PCA) was requested after abdominal total hysterectomy were included in this study. Patients with a history of significant cardiovascular disease, renal disease, diabetes, hepatic disease, or chronic pain and those taking pain medication were excluded from the study. 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. After induction of anesthesia, cisatracurium and the inhaled anesthetic desflurane at a low flow rate of 0.5 l/min were used for maintenance of anesthesia. One hour before completion of the operation, a 0.08-mg/kg loading dose...
of morphine was given intravenously. At the end of surgery, residual neuromuscular block was antagonized with 2.5 mg neostigmine and 1.0 mg atropine, and patients were extubated at the end of the surgical procedure. After tracheal extubation, patients were transferred to the postanesthesia care unit.

Patients were asked every 10–15 min after arrival at the postanesthesia care unit whether they needed pain medication until they became alert enough to use the PCA pump. The morphine solution provided in the PCA pump contained 250 ml normal saline and 100 mg morphine. The pump was set to deliver a 1-mg bolus of morphine solution with a lockout time of 5 min and a maximum dose of 15 mg within a 4-h period without a background infusion. Overdose was avoided by limiting the total dose administered within a given period of time. When the maximum-permitted dose of morphine was reached and the patient still reported postoperative pain, the authors prescribed another analgesic (1.5 mg/kg nalbuphine or 1.5 mg/kg meperidine) for rescue pain control.

The duration of effective analgesia was measured from time 0 to the next use of the PCA device and was recorded in minutes by the machine itself. Consumption of PCA-delivered morphine was recorded using an Abbott TRW printer model TP 40 (Abbott Life Care Infuser; Chicago, IL) at 3, 6, 12, 24, 36, and 48 h after the operation. The total amount of consumed morphine for 48 h after the operation was recorded by the PCA device. PCA was started immediately after patients were alert to control the PCA device in the postanesthesia care unit and was discontinued 48 h after the operation.

The following information and data were collected from the hospital and anesthetic records for each patient: age, weight, height, duration of anesthesia, and creatinine level.

**Assessments**

Postoperative assessments included PCA use (e.g., number of patient demands, total morphine administered) in each 24-h interval during the 48-h study period. Pain was measured using the resting pain score. A visual analog scale (VAS) was used for assessing the degree of pain at rest during PCA treatment (VAS: 0 = no pain to 10 = unbearable pain). The pain score was recorded at 30-min intervals in the postanesthesia care unit and at 6, 24, and 48 h postoperatively in the ward. The PCA dose was adjusted until pain scores at rest were less than 4. The VAS score and occurrence of any adverse effects (e.g., nausea, vomiting, sedation) were recorded by a nurse in the acute pain service, and the PCA dose administered was registered at the end of PCA. Patients rated their nausea using a four-point scale (0 = no nausea; 1 = mild; 2 = moderate; 3 = severe). Vomiting was assessed as events occurring in 24 h. Sedation was assessed using the Ramsay sedation score (0 = awake; 6 = unresponsive to strong, painful stimuli).

### Table 1. Genotypes and Allele Frequency Association

<table>
<thead>
<tr>
<th>A118G Genotypes</th>
<th>A118G Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA</td>
</tr>
<tr>
<td></td>
<td>43</td>
</tr>
</tbody>
</table>

This is not in Hardy-Weinberg equilibrium.

AA = wild homozygous; AG = mutant heterozygous; GG = mutant homozygous.

Patients were monitored closely to prevent morphine overdose. Respiratory rate (< 10 breaths/min), arterial carbon dioxide level (> 50 mmHg), and level of consciousness (progression to somnolence) were assessed at regular intervals. In the case of morphine overdose, an intravenous infusion of 100–200 µg/h naloxone was started. If a patient requested treatment for nausea and/or pruritus concomitant with a VAS score greater than 8, naloxone was also administered to reverse the effect of morphine. All patients treated with naloxone because of the above-mentioned causes were excluded from the study. The adverse effects of morphine were recorded by the authors.

#### Genotyping of the A118G SNP at the µ-Opioid Receptor

All patients were screened for A118G SNP at the µ-opioid receptor. Blood samples (10 ml) were collected from participants in the study and were separated by centrifugation (3,000 rpm, 15 min). Genomic DNA was isolated from buffy coat using the PureGene DNA Purification Kit (Gentra Systems, Minneapolis, MN). For polymerase chain reaction, two primers were used as forward and reverse primers, respectively, amplifying a 200-bp fragment of the human opioid receptor gene that includes the polymorphic site at nucleotide 118. Then polymorphisms were verified by DNA sequencing.

#### Statistical Analysis

Data for the morphine dose delivered via PCA were analyzed among the polymorphism group using one-way analysis of variance with a post hoc analysis. Between-group comparisons such as for the VAS pain score, nausea score, and sedation score were made using the Mann-Whitney test. The side effect of vomiting was analyzed using the Fisher exact test. The values are reported as mean ± SD. A probability value of P ≤ 0.05 was considered significant.

### Results

Eighty women (mean age, 46 ± 6 yr) were included in this study. Genotype and allelic frequencies for the A118G are shown in table 1, with overall G allelic frequencies of 34.4%. Of the 80 patients, 43 patients were A118 homozy-
Table 2. Demographic Data for 118A>G Genotype Groups

<table>
<thead>
<tr>
<th></th>
<th>AA (n = 43)</th>
<th>AG (n = 19)</th>
<th>GG (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>45 ± 5.8</td>
<td>46.4 ± 8.3</td>
<td>46.5 ± 6.8</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>63.4 ± 12.9</td>
<td>57.8 ± 5.9</td>
<td>63 ± 13.5</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165.9 ± 5.5</td>
<td>155.8 ± 5.1</td>
<td>156.7 ± 4.0</td>
</tr>
<tr>
<td>Duration of surgery, min</td>
<td>181 ± 63</td>
<td>188 ± 63</td>
<td>173 ± 28</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.72 ± 0.15</td>
<td>0.72 ± 0.17</td>
<td>0.69 ± 0.16</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.

AA = wild homozygous; AG = mutant heterozygous; GG = mutant homozygous.

Table 4. Morphine Consumption in the First and Second 24 Hours

<table>
<thead>
<tr>
<th></th>
<th>AA (n = 43)</th>
<th>AG (n = 19)</th>
<th>GG (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 morphine dose, mg/24 h</td>
<td>27.11 ± 9.57</td>
<td>29.46 ± 8.79</td>
<td>33.32 ± 10.49</td>
</tr>
<tr>
<td>Day 2 morphine dose, mg/24 h</td>
<td>9.59 ± 6.70</td>
<td>11.09 ± 10.60</td>
<td>10.51 ± 6.23</td>
</tr>
<tr>
<td>Total morphine dose, mg</td>
<td>37.75 ± 12.32</td>
<td>41.58 ± 17.79</td>
<td>43.97 ± 13.92</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.

\( P \) value for one-way analysis of variance with post hoc tests (\( P < 0.05 \) shows statistically significant difference). * \( P = 0.024 \) for differences in morphine doses between AA and GG.

AA = wild homozygous; AG = mutant heterozygous; GG = mutant homozygous.

Discussion

Our study used a group of patients undergoing abdominal hysterectomy, a moderately painful procedure, chosen because the surgical technique is fairly standardized. Pain after abdominal hysterectomy can be multifactorial. Incision pain, pain from visceral structure, and, particularly, dynamic pain can be severe.\(^8\) Previous animal and human studies demonstrated the existence of sex-related differences in opioid-mediated behavior and analgesia.\(^9\)–\(^11\) In our study, all patients were female, and sex-related differences in morphine analgesia can be ignored.

Ethnic differences in the frequency of the A118G variant have been noted. In Asian populations, a G118 frequency ranging between 35% (Chinese) and 47% (Indian)\(^12\) has been reported, regardless of sex. In females, Landau et al.\(^13\) reported that the frequencies of homozygous G118 and heterozygous subjects in the obstetric population are 4% and 29%, respectively, with an 18.8% G118 allelic frequency. A higher frequency of A118G variant was shown in our study. The frequencies of homozygous G118 and heterozygous groups in our study were 22.5% and 23.8%, respectively. Our overall G118 allelic frequency was 34% (table 1).

Our data demonstrate that the first 24-h morphine consumption was different according to genotype, with women homozygous for the G118 allele requiring statistically significantly higher doses compared with women.

Table 5. Complications of PCA in First 24 Hours

<table>
<thead>
<tr>
<th></th>
<th>AA (n = 43)</th>
<th>AG (n = 19)</th>
<th>GG (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea score*</td>
<td>0.8 ± 0.3</td>
<td>1.0 ± 0.5</td>
<td>0.8 ± 0.2</td>
</tr>
<tr>
<td>Vomiting†</td>
<td>7 (16%)</td>
<td>4 (22%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Sedation score*</td>
<td>0.6 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.2</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or number (percentage).

* No significant difference (Mann–Whitney U test). † No significant difference (Fisher exact test).

AA = wild homozygous; AG = mutant heterozygous; GG = mutant homozygous; PCA = patient-controlled analgesia.
extend these results to other ethnic groups. We also need more investigation to determine which factors affect the opioid dose for postoperative analgesic. In the future, identifying SNPs might give us information to modulate the analgesic dosage of opioid individually for better pain control.

References

17. Lutsch J, Skarke C, Schmidt H, Grosch S, Geisslinger G: The transfer half-life of morphine-6-glucuronide from plasma to effect site assessed by pupil size measurement in healthy volunteers. Anesthesiology 2001; 95:1329–38