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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 G118 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.**

IT has been known for a long time that the effects of morphine as an agent for pain control vary in different individuals. Morphine produces its clinical effects mainly through μ-opioid receptors. Polymorphisms in the μ-opioid receptor gene may be associated with the clinical effects of opioid analgesics,[1–3] which encourages research into human genetic polymorphisms and their clinical consequences.

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Several single nucleotide polymorphisms (SNPs) have been identified in the human μ-opioid receptor gene. The A118G mutation is the most common one leading to a change in the gene product in the human μ-opioid receptors, which is an A to G substitution in exon 1 and results in an amino acid exchange at position 40 from asparagine to aspartate (N40D).[4] Functional effects of the A118G polymorphism have been demonstrated both *in vitro* and *in vivo*. *In vitro*, β-endorphin has been shown to bind three times more tightly at the receptor of homozygous G allele than at that of homozygous A allele.[4] A recent report also suggested that cancer patients who were homozygous for the G118 variant required higher doses of oral morphine for long-term treatment of their pain.[2] Romberg *et al.*[5,6] studied the pharmacokinetics and pharmacodynamics of morphine-6-glucuronide (M6G), a μ-opioid agonist, and also found that A118G mutation of the human μ-opioid receptor gene reduced analgesic responses to M6G. The effect of μ-opioid receptor genotype on acute postoperative morphine requirements has not been reported; therefore, we decided to determine morphine consumption with intravenous patient-controlled analgesia in women undergoing total abdominal hysterectomy according to A118G polymorphism.

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

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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.[7] 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 Ramsey sedation score (0 = awake; 6 = unresponsive to strong, painful stimuli).

Table 1. Genotypes and Allele Frequency Association

A118G Genotypes				A118G Alleles		
AA	AG	GG	Total	A	G	Total
43 (53.7%)	19 (23.8%)	18 (22.5%)	80	105 (65.6%)	55 (34.4%)	160

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 $P \leq 0.05$ 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-

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Table 2. Demographic Data for 118A>G Genotype Groups

	AA (n = 43)	AG (n = 19)	GG (n = 18)
Age, yr	45 ± 5.8	46.4 ± 8.3	46.5 ± 6.8
Weight, kg	63.4 ± 12.9	57.8 ± 5.9	63 ± 13.5
Height, cm	156.9 ± 5.5	155.8 ± 5.1	156.7 ± 4.0
Duration of surgery, min	181 ± 63	168 ± 63	173 ± 28
Creatinine, mg/dl	0.72 ± 0.15	0.72 ± 0.17	0.69 ± 0.16

Data are expressed as mean ± SD.

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

gous (AA), 19 patients were heterozygous (AG), and 18 patients were homozygous for the 118G allele (GG). Table 2 compares the patients' demographic data in the different genotype groups. There were no significant differences in the key variables such as age, body weight, height, duration of surgery, and serum creatinine concentration between the various genotypes.

One hour before completion of the operation, the loading dose of morphine 0.08 mg/kg was given intravenously. The mean VAS pain scores at rest and every 30 min are presented in table 3, and there was no significant difference across genotypes. PCA morphine consumption (table 4) was 27 ± 10 mg in the AA group, 29 ± 9 mg in the AG group, and 33 ± 10 mg in the GG group, respectively, in the first 24 h. There was significant difference in first 24-h morphine consumption between the GG and AA groups ($P = 0.02$). Morphine demands were also more frequent in the GG group when compared with other groups: 59 ± 45 mg (AA), 66 ± 42 mg (AG), 70 ± 44 mg (GG) in the first 24 h and 12 ± 9 mg (AA), 16 ± 14 mg (AG), 18 ± 14 mg (GG) in second 24 h. However, the difference was not statistically significant. No one needed rescue management for inadequate pain control.

Assessment of nausea scores, sedation scores, and number of patients with vomiting is summarized in table 5. Side effects were mild and did not necessitate aggressive treatment. No patient requested termination of PCA because of side effects. There was no significant difference in frequency of vomiting, nausea scores, and sedation scores between groups.

Table 3. VAS Pain Scores at Rest

	Group		
Postoperative Time, h	AA	AG	GG
0.5	5.8 ± 2.8	6.5 ± 2.1	6.2 ± 2.5
1	5.3 ± 2.4	4.9 ± 1.8	5.2 ± 2.1
1.5	4.3 ± 2.2	3.9 ± 1.7	4.4 ± 2.0
6	3.8 ± 1.8	3.6 ± 1.5	3.8 ± 1.4
24	2.8 ± 1.2	2.8 ± 0.7	2.9 ± 1.0
48	2.1 ± 0.9	2.3 ± 1.0	1.9 ± 0.8

Data are expressed as mean ± SD. No significant differences were observed within groups (one-way analysis of variance).

AA = wild homozygous; AG = mutant heterozygous; GG = mutant homozygous; VAS = visual analog scale.

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

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

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

	AA (n = 43)	AG (n = 19)	GG (n = 18)
Nausea score*	0.8 ± 0.3	1.0 ± 0.5	0.8 ± 0.2
Vomiting†	7 (16%)	4 (22%)	1 (6%)
Sedation score*	0.6 ± 0.2	0.3 ± 0.1	0.4 ± 0.2

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.

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homozygous for the wild-type A118 allele (33 ± 10 *vs.* 27 ± 10 mg; $P = 0.02$; table 4). Because women were all treated in the same manner and with similar VAS pain scores during the first 24 h (table 3), this probably reflects a true difference in postoperative morphine requirement in 24 h after total abdominal hysterectomy. The current study found that patients homozygous for the 118G allele need more morphine doses to achieve adequate pain control. The finding may suggest that opioid effects can be clinically relevant to 118A>G SNP.

In humans, the major production of morphine metabolism is M6G. The role of M6G in mediating these differences was not explored here. M6G might contribute to analgesia when morphine is administered orally.[14] However, several studies found that M6G does not contribute to a significant extent in the presence of morphine at an analgesic dose or if used for a short duration.[15–17] The authors believe that M6G does not contribute to pain reduction within the specified time frame in the study, and the lack of plasma concentration measurements for M6G can be ignored.

Postoperative nausea and vomiting (PONV) are common side effect of general anesthesia, and patients undergoing hysterectomy are especially prone to PONV. The incidence of PONV within 24 h in our study was 17.5%. It is relatively low when compared with the incidence of 26–75% for moderate to severe nausea in previous studies.[7,18] The incidence of vomiting was more frequent in patients of the AA group and AG group than in patients of the GG group (table 5). Someone may criticize that the greater morphine consumption in the GG group might be due to the lower incidence of vomiting; however, there was no statistical difference in the incidence of PONV per genotype.

We could not rule out many factors such as mood and anxiety that might alter opioid requirements. Emotional states and attitudes of patients toward pain before surgery may be important factors in determining postoperative demand for analgesics.[19] However, in the current study, Taiwanese women undergoing total abdominal hysterectomy needed more morphine consumption doses to achieve adequate postoperative pain relief during the first 24 h in the group homozygous for the variant G allele, compared with individuals homozygous for the A allele involving nucleotide 118 at *OPRM1*. The genetic variation of the μ-opioid receptor was associated with the different response to intravenous PCA morphine therapy for surgical pain. It might be warranted to 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.

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