Original Article

Impact of CYP3A4*1G Polymorphism on Fentanyl Analgesia Assessed by Analgesia Nociception Index in Chinese Patients Undergoing Hysteroscopy

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Abstract

Background: The clinical efficacy of fentanyl for pain control differs greatly across individuals. The purpose of this study was to investigate the impact of CYP3A4*1G polymorphism including wild-type homozygote (CYP3A4*1/*1, GG), mutant heterozygote (CYP3A4*1/*1G, GA), and mutant homozygote (CYP3A4*1G/*1G, AA) on fentanyl analgesia in Chinese patients undergoing hysteroscopy by the assessment of analgesia nociception index (ANI).

Methods: A total of 200 gynecologic patients scheduled for elective hysteroscopy under general anesthesia at Peking University People's Hospital from May to December in 2017 were enrolled in this study. Venous blood was withdrawn for genotyping of CYP3A4*1G before operation. Fentanyl 1 μg/kg was administered preoperatively followed by target-controlled infusion of propofol for induction and maintenance. Intraoperative analgesic efficacy of fentanyl was assessed by ANI monitoring at T0 (entering room), T1 (cervical dilation), T2 (start of cervical aspiration), and T3 (end of cervical aspiration) time points. The duration of propofol infusion and total dosage of propofol were recorded as well.

Results: The patients were divided into three groups according to CYP3A4*1G polymorphism, including 143 in GG group, 47 in GA group, and 10 in AA group. There was no significant difference in clinical demographics among three groups. The frequency of CYP3A4*1G variant alleles accounted for 16.8% and the distribution of variant alleles was consistent with Hardy–Weinberg equilibrium. Using a multilevel model, ANI values at T1 (63.81 ± 19.61), T2 (63.63 ± 17.82), and T3 (65.68 ± 17.79) were significantly lower than that at T0 (77.16 ± 12.93) in the study population ($F = 23.50$, $P < 0.001$), suggesting that higher levels of pain at T1, T2, and T3 than T0. Patients with GG genotype showed significantly lower ANI than those with GA or AA genotypes during hysteroscopy under the same dose of fentanyl.

Conclusion: CYP3A4*1G polymorphism associated with the analgesic efficacy of intraoperative fentanyl in the patients undergoing hysteroscopy under general anesthesia.

Key words: Analgesia; CYP3A4; Fentanyl; Genetic Polymorphism

Introduction

Analgesic response to a given opioid varies with each individual due to diverse factors such as gender, age, and genetic variation. Interindividual variability in the sensitivity to analgesic opioids has been explained mostly by different genetic factors. The genetic variation can influence pharmacokinetics by drug transporters and drug-metabolizing enzymes and/or pharmacodynamics by opioid receptor and catechol-O-methyl-transferase enzymes.[1] A recent meta-analysis showed that CYP3A4*1G carriers consumed less opioids than homozygous CYP3A4*1/*1 patients during the first 24 h of postoperative period whereas no significant differences were found in CYP3A5*3, ABCB1 C3435T, and

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G2477T/A genetic polymorphisms.[2] Fentanyl is an opioid widely used in clinical anesthesia, postoperative analgesia, and clinical pain management; however, its analgesic effects and side effects vary greatly in individuals.[3,4] Like all opioids, such individual difference is derived from the variability in the metabolism of fentanyl in the body.[5,6] Fentanyl is mainly metabolized by cytochrome P450 (CYP) 3A4 as the primary route of haptic biotransformation. Several studies have suggested that the amount of fentanyl metabolites correlates with CYP3A4 expression and catalytic activity.[7]

Genetic factors are known to make a great contribution to the variability in the CYP3A4 activity.[8-10] Among CYP3A4 alleles identified, CYP3A4*1G (CYP3A4 SNP, rs2242480 [G/A]) is a well-known single-nucleotide polymorphism site with a high mutation frequency in Chinese population.[11-14] A synonymous G-A transition in exon 10 has been confirmed to be associated with CYP3A4 enzyme activity, leading to change in drug metabolism and distinct response to treatment among different patients. CYP3A4*1G genetic polymorphism has been found to decrease fentanyl consumption and sufentanil consumption for postoperative pain control.[15] In addition, patients with CYP3A4*1G genetic polymorphism consumed significantly lower amount of sufentanil in general anesthesia during lung resection than the wild-type group. Nevertheless, it remains unclear whether patients carrying different CYP3A4*1G alleles have a distinct response to fentanyl at the same analgesic dose during operation.

Analgesia nociception index (ANI) is a novel analgesic monitoring parameter to evaluate postoperative pain through analyzing heart rate (HR) variability of high frequency and calculating the power of reflex arc of parasympathetic nervous system.[16-18] The value of ANI, ranging from 0 (maximal nociception) to 100 (maximal analgesia), has a negative linear relationship with pain intensity assessed by a 0–10 numerical rating scale.[19] A low ANI indicates immediate postoperative pain and the need of optimizing acute pain management. It has been shown that ANI is a sensitive and specific tool to reflect the equilibrium between noxious stimulation and anti-nociceptive effect under general anesthesia and waking state.[20] In this study, the patients' analgesic level was monitored using ANI followed by analysis of the analgesic efficacy of fentanyl in patients carrying different CYP3A4*1G alleles. This study described the association between CYP3A4 gene polymorphism and intraoperative analgesic efficacy of fentanyl to provide clinical evidence for individualized treatment of fentanyl.

Methods

Ethical approval

This clinical trial was approved by Ethics Committee of Peking University People's Hospital (Approval No. 2013-13) and registered at Chinese Clinical Trial Registry (No. ChiCTR-ROC-17011159). It was conducted in accordance with the principles of the *Declaration of Helsinki*. All participants understood the implications of taking part in the study and gave an informed written consent.

Patients

Upon informed consent and sample size estimation, a total of 200 women scheduled for elective hysteroscopy under general anesthesia in the Department of Gynecology, Peking University People's Hospital from May to December in 2017 were enrolled in this study. Patient's characteristics were shown in Table 1. All patients were of Chinese Han ethnicity. Inclusion criteria were as follows: (1) aged 18–59 years; (2) body mass index (BMI) of 18–25 kg/m^2; and (3) having a physical status of I or II according to the American Society of Anesthesiologists classification. Exclusion criteria were as follows: (1) a history of psychiatric disease, significant cardiovascular disease, hepatic or renal dysfunction, or diabetes mellitus; (2) alcohol or drug abuse or chronic analgesic use; (3) opioid intolerance; (4) pregnant or lactating women; or (5) consuming drugs or foods known to inhibit or induce the expression of CYP3A enzymes in 2 weeks before surgery.

Anesthetic procedure

After the patient entered into the operating room, she was supplied with nasal catheter oxygen at a flow rate of 5 L/min followed by monitoring of electrocardiography, noninvasive blood pressure, pulse oxygen saturation (SPO_2), HR, end-tidal CO_2, and bispectral index (BIS). All patients received a standardized general anesthesia. Fentanyl 1 μg/kg was administered intravenously followed by infusion of propofol at a target plasma concentration of 5 μg/ml. When the patient's BIS reached 45–55, the dose of propofol was reduced to 3 μg/ml for maintenance, and vaginal disinfection was performed accordingly. During operation, the target control parameters of propofol were adjusted to maintain BIS within 45–55. Blood pressure was maintained in the range of 90/60–140/90 mmHg and ephedrine 6 mg was used as necessary. HR was maintained within 50–100 beats/min, and atropine 0.25 mg was used as necessary. If hypoxemia (SpO_2 <90%, lasted >10 s) was happened, assisted respiration would be given. To evaluate the perioperative analgesic efficacy of fentanyl, an ANI monitor (MetroDoloris®, Lille, France) was used to record immediate postoperative pain in patients undergoing general anesthesia. ANI was recorded at T0 (entering room), T1 (cervical dilation), T2 (start of cervical aspiration), and T3 (end of cervical aspiration) time points. Infusion time and total dosage of propofol were recorded postoperatively.

CYP3A4*1G genotyping

Before the operation, 2 ml of venous blood was withdrawn for genotyping by using direct sequencing. CYP3A4*1G genotyping remain blinded for investigators during operation and examined after operation using a convenient kit designed specifically to CYP3A4*1G by Peking University Health

Table 1: Clinical characteristics of patients scheduled for elective hysteroscopy under general anesthesia in this study

Variables	Total (n = 200)	CYP3A4*1G polymorphism			F	P
		GG genotype (n = 143)	GA genotype (n = 47)	AA genotype (n = 10)		
Age (years)	42.6 ± 9.4	41.8 ± 9.0	44.4 ± 10.2	45.6 ± 9.2	1.88	0.155
Weight (kg)	60.0 ± 8.0	59.4 ± 8.3	61.7 ± 6.9	59.1 ± 8.0	1.49	0.228
Height (cm)	160.4 ± 11.5	160.2 ± 13.3	161.1 ± 4.7	160.9 ± 4.6	0.11	0.895
BMI (kg/m^2)	23.1 ± 2.8	23.0 ± 2.8	23.8 ± 2.6	22.8 ± 2.5	0.18	0.836

Data were shown as mean ± SD. BMI: Body mass index; SD: Standard deviation.

Science Center independently (Patent No. 201310054334.2; Patentee: Peking University). Genome DNA was isolated from 2 ml of peripheral venous blood with ethylenediaminetetraacetic acid as anticoagulant and analyzed for genotyping using TaqMan probe. CYP3A4*1G was amplified by polymerase chain reaction (PCR) with the primers: forward 5'-TGGTGAGGAGGCATTTTGC-3' and reverse 5'-TGCAGGAGGAAATTGATGCA-3'. PCR was carried out in a reaction mixture containing 0.4 μg of genomic DNA, 1.6 μmol/L of each primer, 0.25 μmol/L TaqMan probes (forward 5'-TCCTTCTCCATGTATCA-3' and reverse 5'-CTCCTTCTCCATGTACCA-3') and 1× PCR Mix (GeneCopoeia, Rockville, MD, USA). The PCR conditions included an initial denaturation at 95°C for 10 min, followed by 40 cycles of denaturation at 95°C for 10 s, annealing at 60°C for 30 s. During PCR amplification, the probe, which contains a fluorescence reporter gene and a fluorescence quenching gene at both ends, was digested and degraded by 5' nuclease of Taq enzyme to separate reporter gene and quenching gene. Because 5' nuclease of Taq enzyme can only degrade the same sequence with target sequence, genotyping was quantified by resulting fluorescence. The patients were classified by genotype including wild-type homozygote (CYP3A4*1/*1, GG), mutant heterozygote (CYP3A4*1/*1G, GA), and mutant homozygote (CYP3A4*1G/*1G, AA).

Statistical analysis

A prior study has shown that the distribution frequency of CYP3A4*1G alleles was GG: 46/79%, GA: 27/79%, and AA: 6/79% in female Chinese Han population.[21] In the other study conducted in patients, who underwent lower abdominal operation under general anesthesia and received fentanyl as patient-controlled intravenous analgesia in 24 h, the dose of fentanyl accounted for 247.1 ± 73.2 μg, 359.8 ± 120.2 μg, and 395.0 ± 138.5 μg in groups with AA, GA, and GG genotypes, respectively.[22] If it reasons that the patients enrolled in this study remain the same genotypes as previously reported, 15 patients with AA allele is required to observe the difference between AA group and GG group at a significance of 0.05 and a statistical power of 0.8. Taken into an account, the genotype distribution, 198 patients are needed. The 200 patients were eventually enrolled in this study considering potential drop-off.

In this study, statistical analyses were performed using SAS 9.4 statistical software (SAS Institute, Cary, NC, USA). Measurement data were presented as mean ± standard deviation (SD), comparison among groups was conducted by one-way analysis of variance, and categorical data were compared by Chi-square test. A mixed linear regression model was used to explore the association between ANI and CYP3A4*1G genotyping with adjustments of propofol dose and natural birth history. The outcome variable was ANI measured at T0 (entering room), T1 (cervical dilation), T2 (start of cervical aspiration), and T3 (end of cervical aspiration). The mixed model included a random intercept for each person and an unstructured (assumption free) covariate matrix structure. PASS 15.0 (NCSS Statistical Software, USA) was used to calculate the power. Statistical significance was considered at $P < 0.05$.

Results

In the present study, all the individuals were divided into three groups according to the results of CYP3A4*1G genotyping, including 143 (71.5%) with wild-type homozygote (GG), 47 (23.5%) with mutant heterozygote (GA), and 10 (5.0%) with mutant homozygote (AA). As shown in Table 1, no statistical significance was observed in clinical demographics including age, height, and weight among three groups ($P > 0.05$). Of 200 patients, the frequency of CYP3A4*1G alleles accounted for 16.8% (95% confidence interval [*CI*]: 0.13, 0.21). The allele frequency was consistent with Hardy–Weinberg equilibrium ($\chi^2 = 4.95$, $P > 0.05$), indicating that the genotype distribution of CYP3A4*1G in the study population was representative of the general population.

As shown in Table 2, there was no significant difference in ANI at different time points among patients with different genotypes (all $P > 0.05$). As other factors that might affect pain perception were not controlled, particularly the dose of propofol and the history of natural birth, the adjustment was applied in the following analyses. In Table 2, ANI values of AA group showed no significant difference at different time points ($P = 0.817$); however, ANI values of both GA group ($P = 0.016$) and GG group ($P < 0.001$) showed significant difference at different time points.

To further investigate the relationship between CYP3A4*1G genotype and ANI, we used a mixed linear regression model and adjusted the impact of propofol dosage and natural birth history. The power of test was 0.810 (95% *CI*: 0.72, 0.88) despite the relatively small sample size. As shown in Table 3, the Model 1 with random intercept (41.08 ± 13.36) indicated significantly different mean ANI values among patient

Table 2: Relationship between CYP3A4*1G polymorphism and analgesic efficacy of fentanyl in different groups

Variables	Total (n = 200)	CYP3A4*1G polymorphism			F/χ^2	P
		GG genotype (n = 143)	GA genotype (n = 47)	AA genotype (n = 10)		
Propofol infusion dose (mg·kg^{-1}·h^{-1})	17.12 ± 4.21	16.88 ± 4.19	17.67 ± 4.35	17.73 ± 3.92	0.72	0.487
Propofol infusion dose (mg)	275.69 ± 89.17	272.92 ± 83.43	291.79 ± 109.00	239.72 ± 48.40	1.66	0.193
Duration (min)	17.71 ± 8.54	18.04 ± 8.75	17.45 ± 8.55	14.40 ± 4.14	0.87	0.419
History of natural birth*	106/168 (63.1)	72/121 (59.5)	28/40 (70.0)	6/7 (85.7)	3.03†	0.220
ANI						
T0	77.16 ± 12.93	76.61 ± 13.04	78.37 ± 12.44	78.89 ± 14.71	0.36	0.696
T1	63.81 ± 19.61	61.96 ± 18.63	67.11 ± 22.49	73.78 ± 15.94	2.22	0.111
T2	63.63 ± 17.82	61.98 ± 15.90	66.56 ± 21.86	72.33 ± 19.82	2.17	0.117
T3	65.68 ± 17.79	64.81 ± 17.36	67.59 ± 18.35	70.50 ± 23.72	0.57	0.567
F	23.50	21.32	3.53	0.31	–	–
P	<0.001	<0.001	0.016	0.817	–	–

Data were expressed as mean ± SD or n/N (%). *The 32 cases that had missing data were excluded from this analysis. $^{\dagger}\chi^2$ value, otherwise F values. ANI: Analgesia nociception index; T0: Entering operating room; T1: Cervical dilation; T2: Start of cervical aspiration; T3: End of cervical aspiration; –: Not applicable; SD: Standard deviation.

Table 3: Linear mixed model analysis for the relationship between ANI and CYP3A4*1G genotyping

Variables	Model 1		Model 2		Model 3	
	β (95% *CI*)	*P*	β (95% *CI*)	*P*	β (95% *CI*)	*P*
Fixed effects						
Intercept	67.65 (66.05, 69.25)	<0.001	81.87 (74.89, 88.85)	<0.001	82.83 (75.68, 89.98)	<0.001
Time (reference: T0)						
T1	–	–	−13.16 (−16.94, −9.39)	<0.001	−14.65 (−19.18, −10.12)	<0.001
T2	–	–	−13.13 (−16.83, −9.43)	<0.001	−14.87 (−19.33, −10.42)	<0.001
T3	–	–	−11.51 (−15.26, −7.76)	<0.001	−12.21 (−16.71, −7.71)	<0.001
CYP3A4*1G genotyping (reference: GG)						
GA	–	–	4.65 (1.03, 8.26)	0.012	1.84 (−4.48, 8.17)	0.568
AA	–	–	8.35 (0.66, 16.05)	0.034	2.79 (−10.78, 16.37)	0.689
Propofol infusion dose (mg·kg^{-1}·h^{-1})	–	–	−0.60 (−0.97, −0.24)	0.001	−0.60 (−0.97, −0.23)	0.001
History of natural birth (reference: no)						
Yes	–	–	7.75 (4.51, 10.99)	<0.001	7.73 (4.48, 10.97)	<0.001
CYP3A4*1G genotyping × time (reference: GG × T0)						
GA × T1	–	–	–	–	4.60 (−4.16, 13.36)	0.304
AA × T1	–	–	–	–	7.02 (−11.41, 25.46)	0.456
GA × T2	–	–	–	–	4.63 (−3.88, 13.14)	0.287
AA × T2	–	–	–	–	12.21 (−6.20, 30.63)	0.194
GA × T3	–	–	–	–	2.12 (−6.52, 10.77)	0.630
AA × T3	–	–	–	–	2.63 (−16.72, 21.98)	0.790
Random effects						
Intercept variance, mean ± SE	41.08 ± 13.36	0.001	24.93 ± 11.74	0.017	24.40 ± 11.79	0.019
Residual, mean ± SE	284.62 ± 18.38	<0.001	244.23 ± 17.48	<0.001	246.08 ± 17.75	<0.001

CI: Confidence interval; SE: Standard error; ANI: Analgesia nociception index; T0: Entering operating room; T1: Cervical dilation; T2: Start of cervical aspiration; T3: End of cervical aspiration; –: Not applicable.

groups. The Model 2 further involved in four influencing factors including time point, CYP3A4*1G genotype, propofol infusion dose, and natural birth history. First of all, the ANI values at T1 ($P < 0.001$), T2 ($P < 0.001$), and T3 ($P < 0.001$) were significantly lower than that at T0 with a negative β value. This phenomenon can be interpreted as a decline in analgesic efficacy during injurious operation. In addition, as compared with GG group, AA group, and GA group showed significantly higher ANI. As shown in Figure 1, patients of GG group showed the lowest ANI while superior analgesic effect was observed in patients carrying AA allele variant. In other words, CYP3A4*1G polymorphism associated with the analgesic efficacy of intraoperative fentanyl in the patients undergoing hysteroscopy under general anesthesia. In terms

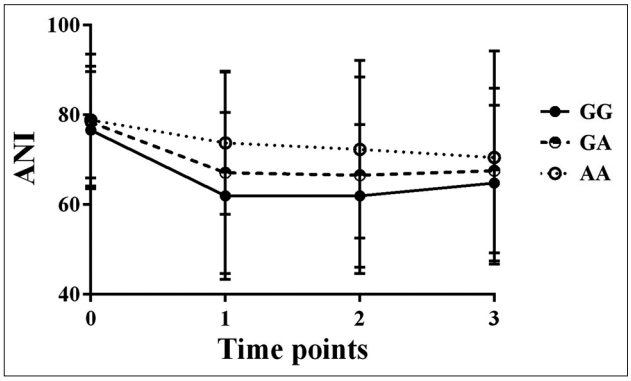

Figure 1: Effect of CYP3A4*1G genotyping on ANI. The mean ANI at different time points for CYP3A4*1G polymorphism groups. ANI: Analgesia nociception index; T0: Entering operating room; T1: Cervical dilation; T2: Start of cervical aspiration; T3: End of cervical aspiration.

of propofol infusion dose, a higher dose resulted in lower ANI with a negative β value, suggesting that patients who reacted to severe pain after noxious stimulation need a higher dose of propofol to enhance sedation. Finally, the β value of the history of natural birth accounted for 7.75 (95% *CI*: 4.51–10.99), suggesting that patients with a history of natural birth have a better analgesic effect than those without natural birth. In Model 3, we further considered the interaction between CYP3A4*1G genotypes and time points. As a result, no significance was observed by using the Model 3. Collectively, the interaction between CYP3A4*1G genotypes and time points has no statistical significance, and ANI values were not changed over time among different groups.

Discussion

This study investigated the effect of CYP3A4*1G polymorphism on analgesic efficacy of fentanyl during short-time hysteroscopy by using ANI for quantification of intraoperative analgesia. In the present study, individuals harboring mutant homozygote AA showed a more effective response to fentanyl than those with GG or GA. Genetic polymorphism of CYP3A4 is a susceptibility factor for drug biotransformation reaction.[23-25] The functional mutation of CYP3A4*1G gives rise to a difference in mRNA expression and resulting changes in drug metabolism rate. Studies showed that the patients with AA genotype had a less fentanyl consumption to achieve pain control than those carrying GG and AG genotypes during the first 24 h postoperatively in patients undergoing lower abdominal surgery or cesarean.[22,26] Moreover, *in vitro* study has shown reduced metabolism of fentanyl in liver microsomes of AA genotype.[5] Obviously, CYP3A4*1G polymorphism contributes to the variability in response to fentanyl.

Indeed, a majority of researches have focused on the relationship between CYP3A4*1G mutation and postoperative fentanyl dose. Nevertheless, intraoperative anesthesia is involved in divergent drug-drug interactions of sedatives and analgesics. So far, the effect of CYP3A4*1G polymorphism on perioperative efficacy of fentanyl remains unclear because different types of intraoperative anesthesia medication may have synergic interaction. Therefore, to investigate the relationship between CYP3A4*1G polymorphism and fentanyl analgesia, a persistent ANI monitoring was applied to identify the variability of fentanyl analgesia in the process of anesthesia. In this study, mutant homozygote AA group showed a higher ANI value than GG group and GA group, suggesting that analgesic efficacy of fentanyl was superior in AA group under the same analgesic dosage. We believed that a low CYP3A4 activity in AA group resulted in a high plasma concentration of fentanyl and strong suppression on stress in the body. This result was consistent with the finding of Zhang *et al*.[15] and further verified that low CYP3A4*1G activity induced by CYP3A4*1G mutation led to changes in fentanyl pharmacokinetics. This mutation not only caused low consumption of fentanyl in 24 h postoperation but also affected analgesic efficacy of fentanyl during the anesthesia process.

It is noteworthy that the plasma concentrations of fentanyl were not measured accordingly in this study. A previous report has shown that CYP3A4*1G variant increased fentanyl concentration at about 30 min after fentanyl administration in a dose-dependent manner.[22] However, the short hysteroscopy procedure appeared to be early for the full manifestation of the metabolic variability. Thus, the plasma concentration of fentanyl may not be changed greatly in short-term hysteroscopy among different individual groups. In light of lower ANI in GG group, the individualized difference in analgesic effect exists due to distinct affinity to opioid receptor or intense response to noxious stimulation in these populations. However, further investigations await measurement of fentanyl plasma concentration. Moreover, we also found that the patients with a history of natural birth showed higher ANI than those without natural birth, suggesting that the patients with a history of natural birth experienced less surgical pain during hysteroscopy. Therefore, a detailed medical history was critical for individualized analgesia in addition to pain threshold, operation type, and genotype.

Some limitations of our study should be noted. ANI offers a promising measurement of postoperative pain reflecting the analgesia/nociception balance, however, the calculation of this parameter is based on the respiratory sinus arrhythmia, which could be the result of pulmonary stretch receptors. Long-term apnea may induce deviation of ANI values. In this study, assisted respiration would be given by holding up the jaw of the patient without manually controlled ventilation when breathlessness lasted more than 10 s. Thus, autonomous respiration was present during data acquisition, and ANI values obtained from this study were reliable. In addition, ANI had a negative linear relationship with visual analogue pain score, and a substantial declined in ANI occurs during uterine contraction. Nevertheless, despite irregular breathing, uterine contraction did not affect ANI measurement.[27] In the other study which evaluated the relationship between ANI and objective measurements of pain intensity in young or cognitively impaired children, after surgical or imaging procedures under general anesthesia, ANI provided an

objective measurement of acute postoperative pain, which was correlated with that measured on a FLACC pain scale even though the young or cognitively impaired children experienced erratic breathing due to crying and screaming.[28] Collectively, ANI was an ideal monitoring parameter which reflected analgesic level under anesthesia; however, ANI should be interpreted with caution.

Taken together, this study highlighted the fact that CYP3A4*1G polymorphism affected the analgesic efficacy of fentanyl. The estimation of fentanyl dose could not depend solely on body weight and age. CYP3A4*1G genotyping would predict the individual variation in the patient's response to analgesia with fentanyl, to facilitate individualized treatment of fentanyl and optimize anesthesia management.

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Conflicts of interest

There are no conflicts of interest.

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通过镇痛-伤害性刺激指数 (ANI) 评估CYP3A4*1G基因多态性对子宫镜检查患者芬太尼镇痛效应的影响

摘要

背景：芬太尼的临床镇痛疗效具有很大的个体差异。本研究的目的是采用镇痛-伤害性刺激指数（ANI），探讨CYP3A4*1G基因多态性（即野生型纯合子（CYP3A4*1/*1, GG）、突变型杂合子（CYP3A4*1/*1G, GA）和突变型纯合子（CYP3A4*1G/*1G, AA）对宫腔镜检查患者芬太尼镇痛效应的影响。

方法：本研究招募了200名2017年5月至12月期间在北京大学人民医院进行择期全身麻醉子宫镜检查的妇科患者。术前采集2 ml静脉血，用于CYP3A4*1G的基因分型。术前给与芬太尼1 μg/kg，以及异丙酚靶控输注作为诱导与维持。在T0（进入手术室）、T1（扩宫颈）、T2（清宫吸引开始）和T3（清宫吸引结束）时间点，通过ANI监测，评估芬太尼的术中镇痛效应。同时记录异丙酚输注的持续时间与总剂量。

结果：根据CYP3A4*1G的基因多态性，将200例手术患者随机分成3组：GG组143例、GA组47例、AA组10例。各组人口学资料无差异。CYP3A4*1G等位基因频率为16.8%，等位基因分布符合Hardy-Weinberg平衡（P> 0.05）。本研究采用了多水平模型，结果发现研究人群在T1(63.81 ± 19.61)、T2(63.63 ± 17.82)和 T3(65.68 ± 17.79)的ANI显著低于T0(77.16 ± 12.93, F=23.50, P <0.001)。在使用相同剂量的芬太尼时，子宫镜检查时GG组患者的ANI显著低于GA或AA组。

结论：CYP3A4*1G基因多态性与全身麻醉宫腔镜检查患者的术中芬太尼镇痛效果有关。