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Original Article

Influences of CYP3A4*1G gene polymorphisms on anesthetic effect of propofol combined with remifentanil in cervical cancer

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Abstract: *Objective:* The aim of this study is to determine the influences of CYP3A4*1G gene polymorphisms on the anesthetic effect of propofol combined with remifentanil in the resection of cervical cancer. *Methods:* The allele distribution at the gene locus CYP3A4*1G in peripheral blood cells of 106 patients with cervical cancer was analyzed via reverse transcription-polymerase chain reaction (RT-PCR), the genetic equilibrium was detected using the TaqMan genotyping technique, and the multivariate analysis of variance was adopted for the genotype distribution and dosage of anesthetics. Moreover, the correlations of the influencing factors of gene polymorphisms (smoking and drinking) with the dosage of anesthetics were analyzed using the independent-sample *t* test. The visual analogue scale (VAS) score of patients with different genotypes and the time of anesthesia induction and recovery were measured and compared. The effects of gene polymorphisms on hemodynamics after extubation were detected using the analysis of variance. *Results:* The CYP3A4*1G gene polymorphisms were significantly associated with drinking and hypertension ($P < 0.05$), and the dosage of combined anesthetics in patients who smoked and suffered from hypertension showed significant differences compared with that in patients who did not smoke and had no hypertension ($P < 0.05$). According to the analysis of gene polymorphisms, the dosage of combined anesthetics, systolic pressure, diastolic pressure and heart rate of patients with mutant-type homozygotes present significant differences compared with those in patients with wild-type homozygotes ($P < 0.05$). *Conclusion:* CYP3A4*1G gene polymorphisms can affect the anesthetic effects of propofol combined with remifentanil in cervical cancer.

Keywords: CYP3A4*1G gene polymorphism, propofol, remifentanil, cervical cancer

Introduction

Cervical cancer is a common malignant tumor of the reproductive system in females worldwide, which is considered as a preventable sexually transmitted disease. The persistent infection of human papillomavirus (HPV) strains is related to the occurrence of about 99.9% of cervical cancer cases [1]. The preferred treatment of cervical cancer remains as early surgical resection, but the long operation time and strict requirement of anesthesia pose difficulties, along with the adverse reactions during the operation. Propofol is characterized by rapid metabolism, but the analgesic effect of propofol alone is unsatisfactory, and increased dosage will cause various unexpected symptoms. As a novel μ receptor agonist, remifentanil is characterized by rapid onset, short duration of side effects and easy control of intravenous infusion [2]. Fentanyl combined with propofol leads to adverse reactions, such as dizziness, nausea, vomiting, dysphoria and respiratory depression [3], but remifentanil combined with propofol significantly reduces drug dependence, respiratory depression and other adverse reactions, so they are widely-used as combined anesthetics. Due to gender, age and genetic variation, the analgesic response to anesthetics varies from individual to individual. Recent studies have demonstrated that genetic variation can affect the pharmacokinetics of drug transporters and drug-metabolizing enzymes, and the pharmacodynamics of opioid receptors and catechol-O-methyltransferase [4]. The biotransformation of anesthetics such as remifentanil is mainly realized by cytochrome P450 (CYP) 3A4 in the liver [5]. According to several studies, CYP3A4 gene polymorphisms, expression levels of related proteins and cata-

Table 1. Primer sequences in RT-PCR

Target gene	Forward primer (5'→3')	Reverse primer (5'→3')	Cycle	T
CYP3A4*1G	5'-AATAGAAAGCAGATGAACCAGAGCC-3'	5'-CACCCTGATGTCCAGCAGAAACT-3'	40	58
GAPDH	5'-TGAAGGTCGGAGTCAACGGATTTGGT-3'	5'-CATGTGGGCCATGAGGTCCACCAC-3'	40	58

lytic activity are apparently correlated with the metabolic rate of anesthetics, such as remifentanil [6, 7].

CYP enzyme is a member of the monooxygenase superfamily [8]. Among all CYP subtypes, CYP3A4 is thought of as the most important enzyme involved in the metabolism of prescription drugs, and the effect of CYP3A4 single nucleotide polymorphisms (SNP) on its enzymatic activity has been fully confirmed [9]. CYP3A4*1G, as a form of SNP, has clear high mutations in the Chinese population [10], and it has been found in the analysis of CYP3A4*1G gene polymorphisms that CYP3A4*1G SNP includes the wild-type homozygote (CYP3A4*1/*1, GG), mutant-type heterozygote (CYP3A4*1/*1G, GA) and mutant-type homozygote (CYP3A4*1G/*1G, AA) [11]. It has been demonstrated that CYP3A4*1G gene polymorphisms can reduce the dosage of anesthetics, such as fentanyl, during postoperative pain control. Moreover, the dosage of fentanyl used in patients with the mutant-type CYP3A4*1G gene is observably lower than that in patients with wild-type gene [12]. However, whether CYP3A4*1G gene polymorphisms have influences on the anesthetic effects of propofol combined with remifentanil in cervical cancer has not been studied yet. In the present study, therefore, the influence of CYP3A4*1G gene polymorphisms on the anesthetic effects of propofol combined with remifentanil in cervical cancer was explored, so as to offer clinical evidence for the individualized treatment using combined anesthesia with propofol and remifentanil.

Materials and methods

Materials

A total of 106 female patients with cervical cancer who underwent cervical cancer surgery and combined anesthesia with propofol and remifentanil were selected as the objects of study, and they were aged from 33-59. Inclusion criteria: patients who were definitely diagnosed by pathology and completed follow-up data, those who were informed and voluntarily received postoperative analgesia, those who had no allergic history to any type of anesthetics, and those who had no surgical contraindications. This study was approved by the ethics committee in Jiangxi Maternal and Child Health Hospital, and all the enrolled subjects had signed informed consent.

*CYP3A4*1G genotyping*

In the morning, 3 mL of peripheral venous blood was drawn from the patients. Then the buffy coat was obtained using the Ficoll human peripheral blood lymphocyte separation medium. The mononuclear cells were lysed on ice using TRIzol for 30 min, centrifuged with chloroform and precipitated to extract the total RNA. The concentration of total RNA was determined using a spectrophotometer. The reverse transcription system (20 μL) was constructed according to the experimental instructions, and the total RNA was reversely transcribed into cDNA and stored at -80°C for later use. According to the instructions of the amplification kit, PCR amplification was performed under the total amplification system (25 μL) using the primer sequences (**Table 1**). After electrophoresis at 72°C and 120 V for 30 min, the images were analyzed using a gel imager (Bio-Rad). Based on the electrophoresis bands after amplification, CYP3A4*1G SNP was divided into the wild-type homozygote (CYP3A4*1/*1, GG), mutant-type heterozygote (CYP3A4*1/*1G, GA) and mutant-type homozygote (CYP3A4*1G/*1G, AA).

Anesthesia induction methods

The patients did not take preoperative drugs before anesthesia, and the electrocardiograph, systolic pressure, diastolic pressure, heart rate (HR) and arterial oxygen saturation were routinely monitored before operation. They underwent standardized induced anesthesia with remifentanil (Yichang Humanwell Pharmaceutical Co., Ltd., Sichuan, China. batch No.: 2014-0197, initial dose: 5 μg/L) and propofol (Sichuan Guorui Pharmaceutical Co., Ltd., Sichuan, China. batch No.: 20150824, initial dose: 3 mg/L). During the operation, the bispectral

Table 2. Clinical features

	CYP3A4*1G polymorphism			Total (n = 106)	F/χ^2	*P*
	GG	GA	AA			
Body weight	59.47 ± 8.31	6127 ± 9.63	59.75 ± 4.82	60.35 ± 6.87	2.03	0.163
Age	43.57 ± 6.35	44.21 ± 7.11	42.93 ± 5.46	43.39 ± 6.77	1.77	0.22
Drinking						
Yes	2	3	6	10	6.756	0.034
No	41	35	19	96		
Smoking						
Yes	4	5	6	15	2.859	0.235
No	39	33	19	91		
Hypertension						
Yes	8	8	13	30	6.370	0.041
No	35	30	17	76		
HPV infection						
Yes	39	35	22	96	0.299	0.861
No	4	3	3	10		
Enlargement of lymph nodes						
Yes	7	5	4	16	0.174	0.917
No	36	33	21	90		
Metastasis						
Yes	12	10	9	31	0.746	0.689
No	31	28	16	65		
Clinical stage						
I-II	21	19	11	51	0.233	0.890
III-IV	22	19	14	55		
Tumor diameter						
≤ 4 cm	17	12	10	39	0.694	0.707
> 4 cm	26	26	15	57		

Table 3. Hardy-Weinberg genetic equilibrium test in objects

Gene	Genotype	Actual frequency (%)	Theoretical frequency (%)	χ^2	*P*
CYP3A4*1G	GG	43 (40.57)	36 (33.96)		
	GA	38 (35.85)	51 (48.11)	3.654	0.161
	AA	25 (23.58)	19 (17.92)		

index was kept at 45-55, the concentration of propofol was adjusted at any time to maintain the mean arterial pressure at 60-90 mmHg and HR at 80-120 beats/min, and the concentration of remifentanil was also adjusted to maintain the stability of anesthesia. Remifentanil was infused until the end of the operation, and propofol was infused untill 5 min after operation. Ventilator-assisted ventilation was terminated when the patients began to breathe spontaneously, cough and swallow. The hemodynamics after anesthesia were observed, and the time of anesthesia induction, eye opening, respiratory recovery and tracheal extubation was recorded. Besides, the diastolic pressure, systolic pressure and HR of patients with different genotypes were recorded within 0-5 min after extubation. The visual analogue scale (VAS) score was recorded at 1, 2, 4 and 8 h after operation to observe the analgesia and adverse reactions.

Statistical processing

SPSS 22.0 software was used for the analysis of all data. In this paper, analysis of variance was performed for the measurement data of the patients' features, and χ^2 test was adopted for the enumeration data. The Hardy-Weinberg genetic equilibrium test was conducted for the genotypes of cervical cancer patients. Multivariate analysis of variance was used to

Table 4. Correlation analysis between CYP3A4*1G gene polymorphisms and dosage of anesthetics

Gene	Genotype	Propofol [μg (kg/min)]	F	*P*	Remifentanil [μg (kg/min)]	F	*P*	Combined dosage [μg (kg/min)]	F	*P*
CYP3A4*1G	GG	0.125 ± 0.0351	-	-	0.161 ± 0.0442			0.286 ± 0.0392		
	GA	0.115 ± 0.0363	5.43	0.032	0.142 ± 0.0393	7.89	0.012	0.257 ± 0.0371	6.33	0.026
	AA	0.109 ± 0.0297			0.124 ± 0.0417			0.233 ± 0.0359		

analyze the genotype distribution and dosage of anesthetics, and independent-sample *t* test was performed for the influencing factors for gene polymorphisms (smoking, drinking and dosage of anesthetics). The VAS score of patients with different genotypes and the time of anesthesia induction and recovery were compared, and the effects of gene polymorphisms on hemodynamics after extubation were detected using the analysis of variance. $P \leq 0.05$ suggested statistical differences.

Results

Clinical features of patients

A total of 106 patients with cervical cancer underwent combined anesthesia with propofol and remifentanil, and they were aged from 33-59. The patients with GG genotype were on average 43.57 ± 6.35 years old, those with GA genotype were 44.21 ± 7.11 years old and those with AA genotype were 42.93 ± 5.46 years old. All patients were pathologically diagnosed with cervical cancer for the first time, and none of them received chemoradiotherapy. There were 11 drinkers and 15 smokers, 29 cases of hypertension, 96 cases of HPV infection, 16 cases of enlargement of lymph nodes and 31 cases of metastasis. In terms of the clinical stage, there were 51 cases in stage I-II and 55 cases in stage III-IV. The tumor diameter was ≤ 4 cm in 39 cases and > 4 cm in 67 cases. The correlations between CYP3A4*1G polymorphisms at different loci and clinical features of patients were analyzed, and it was found that drinking and hypertension affected the distribution of CYP3A4*1G gene polymorphism ($P < 0.05$) (**Table 2**).

Hardy-Weinberg genetic equilibrium test in patients receiving combined anesthesia with propofol and remifentanil in cervical cancer surgery

To verify the CYP3A4*1G genetic equilibrium in subjects enrolled, χ^2 test was performed for the CYP3A4*1G genotype frequency. It was found that all the subjects met the CYP3A4*1G genetic equilibrium ($P > 0.05$) (**Table 3**).

Analysis of dosage of anesthetics in patients receiving combined anesthesia with propofol and remifentanil in cervical cancer surgery

The gene polymorphism and protein activity of CYP3A4*1G, a member of the monooxygenase superfamily, are significantly correlated with drug metabolism. It was found in the multivariate analysis of variance of dosage of propofol and remifentanil during operation that the dosage of the single and combined application of these two drugs had obvious differences due to the CYP3A4*1G gene polymorphisms ($P < 0.05$), indicating that the CYP3A4*1G gene polymorphisms affect the dosage of combined anesthetics of propofol and remifentanil in cervical cancer surgery (**Table 4**). As shown in **Table 1**, drinking and hypertension were important factors affecting the CYP3A4*1G gene polymorphisms. Therefore, the correlations of the risk factors (drinking and hypertension) with the dosage of anesthetics were analyzed using the independent-sample *t* test, and it was found that both drinking and hypertension could significantly affect the dosage of propofol combined with remifentanil ($P < 0.05$) (**Table 5**).

Comparison of VAS score of patients with different genotypes undergoing combined anesthesia with propofol and remifentanil in cervical cancer surgery

To observe whether the analgesic effect of propofol combined with remifentanil on cervical cancer patients at different time points is related to the CYP3A4*1G gene polymorphisms, the VSA score (0-10 points) was given for the analgesic effect on patients with different genotypes at 1, 2, 4 and 8 h. The results revealed that in patients with the same genotype, the pain was clearly relieved at 2, 4 and 8 h compared with that at 1 h ($P < 0.05$). At the same time point, compared with that in patients with GG genotype, the pain was clearly relieved in patients with AA genotype at 1, 2, 4 and 8 h ($P < 0.05$), and it was also noticeably relieved in

Table 5. Correlation analysis between drinking and hypertension and dosage of anesthetics

Index	n	Propofol [μg (kg.min)]	*t*	*P*	Remifentanil [μg (kg.min)]	*t*	*P*	Combined dosage [μg (kg min)]	*t*	*P*
Drinking										
Yes	11	0.131 ± 0.0463	7.387	0.012	0.166 ± 0.0329	6.243	0.048	0.297 ± 0.0387	6.33	0.026
No	95	0.112 ± 0.0382			0.138 ± 0.0316			0.25 ± 0.0341		
Hypertension										
Yes	29	0.129 ± 0.0462	8.992	0.0023	0.163 ± 0.0294	10.763	< 0.001	0.292 ± 0.0378	9.118	< 0.001
No	77	0.109 ± 0.0381			0.129 ± 0.0273			0.238 ± 0.0319		

Table 6. Comparison of VAS score of patients with different genotypes

Gene	Genotype	n	1 h	2 h	4 h	8 h
CYP3A4*1G	GG	43	4.75 ± 1.23	3.67 ± 1.11$^{\Delta}$	2.35 ± 0.69$^{\Delta}$	2.14 ± 0.41$^{\Delta}$
	GA	38	4.63 ± 1.03$^{\cdot}$	3.41 ± 0.98$^{\Delta,\cdot}$	2.26 ± 0.77$^{\Delta}$	2.09 ± 0.43$^{\Delta}$
	AA	25	4.51 ± 1.31$^{\cdot}$	3.35 ± 1.04$^{\Delta,\cdot}$	2.19 ± 0.81$^{\Delta,\cdot}$	1.97 ± 0.52$^{\Delta,\cdot}$

$^{\Delta}P < 0.05$ vs. 1 h in the same genotype. $^{\cdot}P < 0.05$ vs. GA, AA and GG at the same time point.

Table 7. Comparison of time of anesthesia induction and recovery of patients with different genotypes

Gene	Genotype	n	Time of anesthesia induction (min)	Time of respiratory recovery (min)	Time of eye opening (min)	Time of extubation (min)
CYP3A4*1G	GG	43	3.77 ± 0.33	5.77 ± 0.21	8.75 ± 0.69	8.65 ± 0.31
	GA	38	3.66 ± 0.29$^{\cdot}$	5.84 ± 0.28	8.72 ± 0.77	8.64 ± 0.26
	AA	25	3.61 ± 0.31$^{\cdot}$	5.65 ± 0.24$^{\cdot}$	8.67 ± 0.81$^{\cdot}$	8.57 ± 0.22$^{\cdot}$

$^{\cdot}$The time of anesthesia induction and recovery has statistically significant differences compared with GG genotype ($P < 0.05$).

patients with GA genotype at 1 and 2 h ($P < 0.05$), while no significant differences were found at other time points ($P > 0.05$) (**Table 6**).

Comparison of time of anesthesia induction and recovery of patients with different genotypes who received combined anesthesia with propofol and remifentanil in cervical cancer surgery

In the comparison of anesthesia induction and recovery time among patients with different genotypes, It was found that the patients with AA genotype are profiled with significantly shorter time of anesthesia induction, respiratory recovery, eye opening and tracheal extubation than patients with GG genotype ($P < 0.05$). However, significantly shorter time of anesthesia induction in the patients with GA genotype was observed over that in patients with GG genotype ($P < 0.05$), while no significant differences were found in other time periods ($P > 0.05$) (**Table 7**).

Effects of gene polymorphisms on hemodynamics after extubation

Hemodynamics was compared at different time points after extubation in patients with different genotypes. The diastolic pressure was remarkably lower in patients with AA genotype than that in patients with GG genotype at 0 and 2 min ($P < 0.05$), while it had no statistical differences in patients with GA genotype at each time point ($P > 0.05$). The systolic pressure was also remarkably lower in patients with AA genotype than that in patients with GG genotype at 0-4 min ($P < 0.05$), while there were differences between patients with GA genotype and patients with GG genotype only at 0 and 1 min ($P < 0.05$). Besides, HR was remarkably lower in patients with AA genotype than that in patients with GG genotype at 0-5 min ($P < 0.05$), while significant differences were also observed between patients with GA genotype and patients with GG genotype only at 1-3 min ($P < 0.05$) (**Table 8**).

Discussion

CYP3A4 is a subtype of cytochrome oxidase in hepatocytes and it is involved in the process of drug metabolism in hepatocytes, SNPs can usually be detected in different ethnic groups. The incidence of gene polymorphism of CYP3A4*1G, an important subtype, in Asian popu-

Table 8. Hemodynamic changes after extubation

	Genotype	0 min	1 min	2 min	3 min	4 min	5 min
Diastolic pressure	GG	97.21 ± 6.78	90.33 ± 5.78	89.99 ± 6.33	87.21 ± 6.77	85.46 ± 7.21	82.33 ± 8.31
	GA	97.57 ± 6.97	90.21 ± 7.21	89.78 ± 6.77	87.18 ± 7.14	85.21 ± 6.98	82.17 ± 6.19
	AA	96.18 ± 7.56*	90.07 ± 6.51	87.81 ± 7.12*	87.04 ± 7.27	84.93 ± 7.33	82.09 ± 6.22
Systolic pressure	GG	167.12 ± 15.33	162.78 ± 17.57	156.43 ± 14.57	148.67 ± 13.25	142.57 ± 12.96	138.14 ± 12.26
	GA	166.78 ± 15.67*	161.33 ± 18.47*	155.79 ± 15.89	148.32 ± 11.87	141.12 ± 12.08	136.91 ± 10.98
	AA	166.65 ± 14.98*	160.86 ± 20.31*	154.65 ± 13.77*	146.12 ± 12.32*	140.88 ± 15.84*	137.55 ± 11.79
HR	GG	96.78 ± 9.12	82.42 ± 9.57	81.05 ± 7.51	78.54 ± 7.46	73.45 ± 7.52	78.35 ± 6.22
	GA	96.45 ± 9.14	79.56 ± 8.12*	79.86 ± 7.45*	76.56 ± 6.57*	73.42 ± 6.58	75.87 ± 6.42*
	AA	94.37 ± 10.86*	79.35 ± 7.85*	77.58 ± 8.97*	76.2 ± 7.34*	72.34 ± 7.37*	76.2 ± 7.12*

*The hemodynamics has statistically significant differences compared with GG genotype ($P < 0.05$).

lations is significantly higher than that in other ethnic groups. For example, Miura et al, confirmed that the mutation rate of CYP3A4*1G was significantly higher in patients with kidney disease in Japan than that in other ethnic groups [13]. Gao et al, found through the genotyping of 217 patients with hyperlipidemia that the frequency of CYP3A4*1G was 0.276 [14]. According to other related reports, the mutation frequency of CYP3A4*1G in the Chinese Han populations is between 0.188 and 0.227, which is significantly higher than that in other ethnic groups [7, 11, 13, 15]. Related studies have also confirmed that the gene polymorphism of CYP3A4*1G, as a drug metabolism-related gene, also played an important role in promoting drug metabolism. Moreover, the occurrence of CYP3A4*1G locus mutations and polymorphisms have an important influence on the activity of CYP3A in the liver, thereby reducing the consumption of the anesthetic fentanyl [16, 17]. Whether the metabolism of commonly-used anesthetics propofol and remifentanil in the liver is affected by the CYP3A4*1G polymorphism has not been reported yet. In this paper, therefore, the correlation between gene polymorphisms and anesthetics was studied in patients receiving combined anesthesia with propofol and remifentanil in cervical cancer surgery. Through the RT-PCR amplification, enzyme digestion and gel electrophoresis for the CYP3A4*1G locus in cervical cancer patients, it was found that CYP3A4*1G gene polymorphisms were significantly associated with drinking and hypertension ($P < 0.05$). In addition, the correlation analysis between CYP3A4*1G gene polymorphisms and dosage of propofol combined with remifentanil in cervical cancer surgery showed that the dosage of combined anesthetics in patients with gene mutations was significantly lower than that in patients without gene mutations ($P < 0.05$), indicating that the CYP3A4*1G gene polymorphisms have significant influences on the dosage of combined anesthetics in cervical cancer surgery. The changes in gene polymorphisms of CYP3A4, a drug and toxin degradation-related gene, is related to not only genetic factors and other congenital factors [18], but also acquired environment, such as drinking and hypertension [14, 19]. Drinking and hypertension may, through increasing the gene mutations and recombination at the locus in hepatocytes, promotes the changes in CYP3A4*1G gene polymorphisms, and enhances or weakens the metabolism of toxins and anesthetics in hepatocytes. Although it has been confirmed that the CYP3A4*1G gene polymorphisms in cervical cancer patients may reduce the dosage of combined anesthetics, the specific mechanism at the protein level has not been studied. Therefore, in subsequent studies, the correlation between CYP3A4*1G gene polymorphisms and changes in proteins related to metabolism of toxins and anesthetics can be analyzed, so as to provide an individualized program of anesthesia for patients.

It has been demonstrated that the changes in gene polymorphisms can greatly influence drug metabolism. For example, in tonsillectomy in children, the MDR1 gene polymorphism can significantly affect the anesthetic effects of propofol combined with remifentanil [20]. In this paper, the correlation between CYP3A4*1G gene polymorphism and dosage of propofol combined with remifentanil was analyzed, and it was found that the genetic changes had obvious influences on the time of anesthesia induction and recovery and hemodynamics after extubation ($P < 0.05$). The changes in gene polymorphism in mutant-type homozygote AA

had more significant influences on the time of anesthesia induction and recovery, as well as hemodynamics than mutant-type heterozygote GA. Moreover, the analysis of patients' clinical features showed that drinking and hypertension were associated with gene polymorphisms. Considering the clear influences of gene polymorphisms on the dosage of combined anesthetics, the effects of drinking and hypertension on the dosage of combined anesthetics were also analyzed. The results revealed that the dosage of combined anesthetics in drinkers and hypertension patients present significant differences compared with that in non-drinkers and non-hypertension patients ($P < 0.05$), suggesting that such factors as drinking and hypertension that alter the gene polymorphisms can also affect the dosage of anesthetics.

Conclusion

In conclusion, this study demonstrated that CYP3A4*1G gene polymorphisms have significant influences on the dosage of combined anesthetics of propofol and remifentanil in cervical cancer patients. Therefore, the correlations of CYP3A4*1G gene function and protein expression with the metabolism of combined anesthetics based on the differences in genotype and gene frequency can provide a new direction for clinical research on individualized anesthesia in patients with cervical cancer.

Disclosure of conflict of interest

None.

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