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Original Article

Role of *OPRM1*, *ABCB1* and *CYP3A* genetic polymorphisms on sufentanil treatment of postoperative cancer patients in China

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Abstract: Sufentanil, a μ-opioid receptor agonist plays a key role in the analgesic action of opiate drugs. The aim of this study was to investigate the association between postoperative sufentanil therapy and genetic polymorphisms of *OPRM1*, *ABCB1* and *CYP3A* in cancer patients in China. Intravenous patient-controlled analgesia with sufentanil was provided postoperatively to 120 patients enrolled at the Affiliated Cancer Hospital of Xiangya Medical School, Central South University from 2012 to 2013. Cumulative sufentanil dosage was measured during the first 48 h postoperatively. The severity of pain at rest was assessed using the visual analogue scale. *OPRM1* 118A>G, *ABCB1* 2677G>A/T, *ABCB1* 3435C>T, *CYP3A4**1G and *CYP3A5**3 variant alleles were genotyped. The effects of genetic and non-genetic factors on sufentanil therapy were evaluated by multiple linear regression analysis. The 48-h cumulative sufentanil doses were significantly associated with pain score and age ($P < 0.05$). Genetic polymorphisms were not associated with sufentanil therapy. Old age was associated with decreased consumption of sufentanil during the first 24 h. Genetic variations play no significant role. In the Chinese patients, no association was found between genetic factors and postoperative sufentanil therapy.

Keywords: Pharmacogenetics, polymorphism, sufentanil, visual analogue scale (VAS), μ-opioid receptor gene (*OPRM1*)

Introduction

Sufentanil, *N*-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-*N*-phenyl propanamide, is a potent synthetic opioid. It is approximately five to ten times more potent than fentanyl, with a shorter duration of action. Sufentanil has high lipid solubility, with a rapid onset when administered intravenously [1, 2]. Sufentanil is metabolized in the liver and the small intestine by N-dealkylation and O-demethylation. The inactive metabolites are excreted in the urine and feces [3]. Sufentanil is used in surgical procedures and critical care where pain relief is required for a short period of time. It is also a sedative and therefore, used as an anesthetic. Sufentanil is the strongest opioid analgesic available for use in humans. The P450 CYP3A4/5 enzyme is responsible for N-dealkylation and metabolic transformation of this drug similar to fentanyl and alfentanil. Consequently, genetic variations of μ-opioid receptor gene (*OPRM1*) play a potent role in pain management of postoperative patients. The 118G allele reduces the analgesic potency and incidence of side effects of opioids, and results in higher pain scores. The *OPRM1* gene facilitates clinical management and analgesic use of opioids individually for improved outcomes. ATP-binding cassette B1 gene (*ABCB1* encoding P-glycoprotein) is mainly located in organs with excretory functions (e.g., liver, kidneys). It is also expressed in the blood-brain barrier as an outward transporter. Therefore, functional impairment of P-gp-mediated drug transport may result in increased bioavailability of orally administered drugs, reduced renal clearance, or increased substrate concentration in brain. The *ABCB1* 3435 C>T variant (rs1045642) is associated with decreased dos-

age requirements in opioids that are P-gp substrates and *CYP3A4/5* genes, responsible for activation of inactive opioid analgesics into active metabolite (CYP3A system). This enzyme is phenotypically highly variable, but only a minor part of this variability is attributed to genetics. Individuals with at least one *CYP3A5**1 allele possess a fully active CYP3A5 enzyme. It may contribute to individual variation in the effects of sufentanil [4].

OPRM1 118A>G, the most common variation of *OPRM1*, has been the focus of genetic studies associated with opioid responses as the μ-opioid receptor is the main target of opioid analgesics. An A-to-G substitution at position 118 (118A>G) in exon 1 leads to aspartate substitution for asparagine at position 40 of the extracellular receptor region that affects a putative glycosylation site of the receptor [5]. In an earlier *in vitro* study, the 118G variant receptor showed approximately 3-fold higher binding affinity and potency of β-endorphin compared with the wild type receptor [6]. However, this finding was not confirmed in follow-up studies [7, 8]. In another study, the *OPRM1* 118G variant led to reduced receptor expression [9] and was associated with increased intravenous morphine requirement for postoperative pain control [10-12]. Contradictory results were also observed with intrathecal fentanil [13]. Genetic variations including single nucleotide polymorphisms (SNPs) involved in the pharmacodynamics and pharmacokinetics of opioids may lead to individual differences in response to opioid treatment. These genes encode metabolic enzymes, drug transporters, receptors, or intracellular targets, such as transcription factors. *OPRM1* is involved in the pharmacodynamics of opioids. *OPRM1* codes for μ-opioid receptor, which is the main target of both endogenous and clinically relevant opioids, such as morphine, fentanyl and sufentanil. Sufentanil is a potent analgesic with very high receptor affinity and specificity, high lipid solubility, marked protein binding, and shorter elimination half-life than fentanyl. Due to the high hepatic extraction ratio, metabolic degradation and elimination depend on hepatic perfusion than on enzyme activity or renal clearance. Therefore, sufentanyl is the first drug of choice as an analgesic.

P-gp, an efflux transporter, actively pumps the substrate out of the intracellular compartment. P-gp limits the entry of opioids across the blood-brain barrier and may reduce analgesic efficacy [14]. *ABCB1* 3435C>T, a common synonymous SNP that encodes P-gp, correlates significantly with P-gp expression levels and function [15]. *ABCB1* 3435C>T and 2677G>T/A have been associated with respiratory depression following fentanil administration [15]. Absence or blockade of this protein leads to increased response to substrate drugs.

Among genetic variations in the enzymes that metabolize sufentanil, CYP3A4*1G is notable. *CYP3A4/5* genes are responsible for metabolic activation of sufentanil. CYP3A4/5 enzyme induces oxidative metabolism of sufentanil. The enzyme is phenotypically highly variable, but only a minor part of this variability is attributed to genetics. *CYP3A4*1G* is the most frequent coding variant of *CYP3A4* in the Chinese population with an allele frequency of 22.1% and Japanese population with an allele frequency of 24.9% [16].

*CYP3A4*1G* is associated with reduced enzyme activity *in vitro* but not *in vivo* [16]. Among the SNPs, investigations suggested that *CYP3A5**3 mutant allele (6986ANG) in intron 3 of *CYP3A5* was the major defective allele among the known alleles. Kuehl et al [17] also demonstrated that *CYP3A5**3 induces alternative splicing and protein truncation, which deplete tissue CYP3A5 levels in some individuals. CYP3A5 may constitute up to 50% of total hepatic CYP3A protein in individuals carrying at least one *CYP3A5**1 allele. Thus, *CYP3A5**3 mutant allele may play an important role in inter-individual and inter-ethnic differences in drug metabolism [18]. The increased enzyme activity associated with CYP3A5*1 allele may cause accelerated elimination of CYP3A substrates such as sufentanil.

In this study, we identified the genetic and non-genetic factors affecting postoperative sufentanil therapy in Chinese cancer patients. Polymorphisms with functional consequences or with a relatively high incidence were selected as follows: *OPRM1* 118A>G, ABCB1 2677G>A/T, ABCB1 3435C>T, CYP3A4*1G and CYP3A5*3. We also analyzed the non-genetic factors, which affect postoperative sufentanil therapy. We found that pain scores were the only significant factors affecting sufentanil therapy, suggesting that pain sensitivity reflected the subjective analgesic response.

Table 1. Patient demographics (n=120)

Variables	
Age (y)	49.8±8.8
Gender (male/female)	30/90
Weight (kg)	56.53±9.91
BMI (kg/m^2)	22.71±3.48
Albumin (g/L)	39.91±5.51
Smoking history (%)	2.65±0.74
Types of cancer	
Lung cancer	4
Breast cancer	4
Carcinoma of uterine cervix	40
Colon cancer	6
Endometrial cancer	2
Gastric cancer	24
Ovarian cancer	8
Pancreatic cancer	2
Rectum cancer	8
Small intestinal cancer	2
VAS score at postoperative 2 h	2.50±0.83
VAS score at postoperative 6 h	2.36±1.00
VAS score at postoperative 12 h	2.19±1.08
VAS score at postoperative 24 h	1.69±0.99
VAS score at postoperative 48 h	0.90±0.70
Postoperative 2 h cumulative sufentanyl consumption (μg)	5.84±2.06
Postoperative 6 h cumulative sufentanyl consumption (μg)	15.92±4.01
Postoperative 12 h cumulative sufentanyl consumption (μg)	30.03±6.08
Postoperative 24 h cumulative sufentanyl consumption (μg)	55.46±7.76
Postoperative 48 h cumulative sufentanyl consumption (μg)	105.58±9.53

Materials and methods

Patients

This study was approved by the Institutional Ethics Committee of the Affiliated Cancer Hospital of Xiangya Medical School, Central South University, China. Written informed consents were obtained from all patients. Patients aged between 19 and 65 years, with an American Society, American Anesthesiologists physical status of I or II, and undergoing scheduled Cancer surgery under general anesthesia were enrolled (**Table 1**). Exclusion criteria were: patients with a history of significant cardiovascular disease, renal disease, hepatic disease, neurological disease, psychological disease, respiratory disease, sleep apnea, or chronic pain; those taking analgesic medications or other premedication; a recovery time of pain (VAS > 0) exceeding 3 h; or undergoing treatment with opioid receptor antagonists were excluded from the study. Patients with obesity (body mass index > 30 kg/m^2) were not included in this study. Smoking status was assessed preoperatively.

Treatment anesthetic methods

All patients underwent general anesthesia with 0.1 mg/kg midazolam, 0.5 mg/kg propofolum and 0.4 μg/kg sufentanil. End tidal CO_2 partial pressure was maintained between 35 and 40 mmHg by mechanical ventilation. Propofol and sufentanil were infused by micro-pumps and sevoflurane, which was inhaled to maintain anesthesia. Drug dosage was adjusted according to alterations in auditory-evoked potential and hemodynamics. An intermittent dose of 0.03-0.06 mg/kg vecuronium was administered to maintain adequate surgical muscle relaxation. During surgery, general anesthesia was maintained with sufentanil (0.1-0.2 μg/kg/min). Residual neuromuscular block was antagonized with 1 mg neostigmine and 0.5 mg atropine at the end of surgery. Blood samples (5 mL) were collected in heparinized tubes at the following times for pharmacokinetic measurement: immediately prior to induction with drugs (0 h), and at 15, 30 and 60 min after drug administration, and centrifuged at 3,000 rpm for 10 min to separate the plasma fractions. The collected plasma samples were stored at -40°C until analysis. The electrocardiogram, non-invasive blood pressure, pulse oximetry and arterial blood gas analysis were monitored.

Postoperative analgesia

Following operation, patients were sent to a post-anesthesia care unit (PACU). The trachea was extubated and the pain severity of patients was assessed. Patients were intravenously

Table 2. Allele frequencies of genetic variations of *OPRM1*, *ABCB1*, *CYP3A4* and *CYP3A5* in Chinese Han populations

Gene	SNPs	Position	Effect	Reference	Allele	Frequencies (%)
OPRM1	118A>G	Exon01	N40D	Rs1799971	A	63.3% (n=152)
					G	36.7% (n=88)
ABCB1	2677G>T/A	Exon21	A893ST	Rs2032582	G	58.3% (n=140)
					T	29.2% (n=70)
ABCB1	3435C>T	Exon26	I1145I	Rs10456420	A	12.5% (n=30)
					T	30% (n=72)
					C	70% (n=168)
CYP3A41*G	20070T>C	Exon10	L239P	Rs28371759	*1	76.7% (n=184)
					*1G	23.3% (n=56)
CYP3A5*3	6986A>G	Inton03	Splicing defect	Rs776746	*1	27.5% (n=52)
					*3	72.5% (n=137)

Table 3. Postoperative cumulative sufentanyl dosage in different genotypes

SNPs	Genotypes (n)	2 h cumulative sufentanyl dosage (μg)	6 h cumulative sufentanyl dosage (μg)	12 h cumulative sufentanyl dosage (μg)	24 h cumulative sufentanyl dosage (μg)	48 h cumulative sufentanyl dosage (μg)
OPRM1 118A>G	AA (46)	5.69±1.91	15.52±3.60	28.91±4.45	53.60±5.01	103.17±6.17
	AG (60)	6.05±2.32	16.11±4.43	30.40±6.92	56.20±9.14	107.28±7.59
	GG (14)	5.42±1.08	16.42±3.50	32.14±6.52	58.42±7.80	107.28±7.59
ABCB1 2766G>T/A	GG (48)	5.91±2.31	16.04±4.47	30.54±7.19	56.16±8.83	106.29±10.29
	GT (28)	6.14±2.06	16.07±3.70	29.85±4.12	55.21±5.67	105.57±8.32
	TT (14)	5.64±1.39	16.07±3.31	29.71±5.82	54.57±6.82	103.14±6.39
	GA (16)	5.50±1.93	15.75±4.05	30.12±6.72	55.75±9.60	105.37±13.00
	TA (14)	5.57±1.98	15.28±3.98	28.85±5.21	54.14±6.71	105.85±7.83
ABCB1 3435C>T	CC (60)	5.56±1.59	15.56±3.07	29.66±5.11	55.16±6.89	105.56±9.20
	CT (48)	6.16±2.64	16.31±5.17	30.50±7.39	55.83±9.15	105.79±10.76
	TT (12)	5.75±1.35	16.08±2.81	30.00±4.99	55.50±6.12	104.83±5.81
CYP3A41*G	*1/*1 (68)	5.80±2.37	15.98±4.49	30.47±7.05	56.35±9.25	106.80±11.29
	*1/*1G (46)	5.86±1.61	15.86±3.46	29.43±4.59	54.34±5.22	104.21±6.53
	*1G/*1G (6)	6.00±1.54	15.66±2.06	29.66±4.03	54.00±4.09	102.00±4.09
CYP3A5*3	*1/*1 (62)	5.64±2.12	15.77±4.24	30.33±7.05	56.33±9.39	106.90±11.44
	*1/*3 (50)	6.08±2.03	16.16±2.03	29.64±4.93	54.44±5.46	104.32±6.99
	*3/*3 (8)	6.00±1.69	15.75±3.15	30.00±4.84	54.75±5.82	102.75±5.82

Data are expressed as mean ± SD. No significant differences were seen among genotype groups.

injected with a 20-μg bolus of sufentanil until a visual analog scale value < 3 (Scale label: 0-10. 0, no pain; 10, unbearable pain) was obtained. Patient-controlled intravenous analgesia (PCIA) commenced when patients perceived slight pain (VAS 1-3). Patients were administered sufentanil by PCIA when a slightly painful state (VAS 1-3) was reported. The electronic patient-controlled analgesia (PCA) pump was filled with 200 μg sufentanil with 0.9% normal saline diluted to 100 mL. The PCA was programmed to administer no background infusion with a 20-μg bolus of sufentanil solution, with a 10-min lockout time. PCA continued for 48 h following surgery. Postoperative pain was maintained at VAS < 3 at rest. When patients experienced VAS > 3, despite PCA, the dose of sufentanil was increased by pushing the bolus button. No other rescue drugs were used within the first 48 h following surgery. All patients were intravenously administered 8 mg ondansetron. Postoperative non-invasive blood pressure, heart rate, pulse oxygen saturation and VAS were documented at 2 h, 6 h, 12 h, 24 h and 48 h following surgery. The total amount of PCA sufentanil was recorded at 2 h, 6 h, 12 h, 24 h and 48 h. Patients and investigators involved in clinical data collection were blinded

Table 4. Linear regression analysis of factors affecting postoperative sufentanyl dosage (n=120)

Related factors	2 h cumulative sufentanyl dosage		6 h cumulative sufentanyl dosage		12 h cumulative sufentanyl dosage		24 h cumulative sufentanyl dosage		48 h cumulative sufentanyl dosage	
	r	*P*-value	r	*P*-value	r	*P*-value	r	*P*-value	r	*P*-value
Age	-0.134	0.145	-0.164	0.074	-0.173	0.058	-0.157	0.086	-0.129	0.159
Gender	-0.119	0.194	-0.088	0.340	-0.067	0.469	-0.05	0.589	-0.07	0.448
Weight	0.07	0.448	0.126	0.169	0.091	0.321	0.098	0.285	0.107	0.245
Types of surgery	0.002	0.979	0.028	0.761	0.000	1.000	0.006	0.948	0.010	0.918
BMI	0.045	0.628	0.073	0.430	0.061	0.509	0.085	0.356	0.094	0.305
Albumin	-0.097	0.293	-0.115	0.212	-0.088	0.336	-0.083	0.368	-0.044	0.634
CYP3A41*G	0.022	0.813	-0.02	0.829	-0.074	0.420	-0.126	0.171	-0.157	0.087
$ABCB_1$2677	0.119	0.197	0.058	0.532	0.049	0.595	0.029	0.754	0.026	0.778
$ABCB_1$3435	0.077	0.401	-0.003	0.971	-0.021	0.824	-0.01	0.911	0.052	0.574
OPRM1	-0.084	0.364	-0.067	0.466	-0.108	0.238	-0.150	0.103	-0.186*	0.042
CYP3A5*3	0.095	0.302	0.03	0.743	-0.045	0.625	-0.110	0.233	-0.154	0.093
VAS score	0.543**	0.000	0.567**	0.000	0.434**	0.000	0.560**	0.000	0.545**	0.000
Duration of surgery	0.136	0.140	0.195*	0.033	0.149	0.105	0.140	0.127	0.097	0.290
Smoking history	-0.102	0.270	-0.058	0.526	-0.059	0.523	-0.068	0.458	-0.106	0.250

**Significant correlation at 0.01 levels (double-sided). *Significant correlation at 0.05 levels (double-sided).

Table 5. Multiple linear stepwise regression analysis of factors affecting postoperative sufentanyl dosage (n=120)

Model	B	SE	t-value	*P*-value	95% CI
Postoperative 2-h cumulative sufentanyl dosage R=0.764 R^2=0.583					
Constant	12.433	1.224	10.158	0.000	10.009-14.858
VAS score at postoperative 2 hours	0.859	0.157	5.474	0.000	0.548-1.17
Postoperative 6-h cumulative sufentanyl dosage R=0.698 R^2=0.487					
Constant	19.983	1.682	11.880	0.000	16.652-23.314
VAS score at postoperative 6 h	1.506	0.293	5.146	0.000	0.927-2.086
Postoperative 12-h cumulative sufentanyl dosage R=0.743 R^2=0.551					
Constant	47.729	3.406	14.014	0.000	40.983-54.474
VAS score at postoperative 12 hours	0.910	0.453	2.009	0.047	0.013-1.808
Postoperative 24-h cumulative sufentanyl dosage R=0.827 R^2=0.683					
Constant	72.325	3.558	20.329	0.000	65.279-79.372
VAS score at postoperative 24 h	2.03	0.473	4.291	0.000	1.093-2.967
Postoperative 48 h cumulative sufentanyl dosage R=0.772 R^2=0.596					
Constant	138.975	4.934	28.165	0.000	129.2-148.75
VAS score at postoperative 48 h	5.615	0.850	6.608	0.000	3.932-7.298
Age	-0.229	-0.067	-3.348	0.001	-0.361-0.097

to patients' genotypes. The investigators involved in genotyping were blinded to clinical data.

Genotyping

Genomic DNA was isolated from whole blood using the Genomic DNA Purification Kit (PROMEGA, USA). All genotyping was performed with the validated genotyping technology platform established at the Institute of Clinical Pharmacology, Central South University, Changsha, China. Genomic DNA was extracted from peripheral blood cells and genotyped for SNPs identifying *OPRM1* 118A>G (rs1799971), *ABCB1* 2677G>A/T (rs2032582), *ABCB1* 3435C>T (rs1045642), *CYP3A4**1G (rs2837-1759) and *CYP3A5**3 (rs77674).

All genotypes were determined by single-base extension using a Qiagen PyroMark Q24 genetic analyzer and its mounted PyroMark Q24 (ver.2.06) software according to the manufacturer's protocol. There were no significant deviations from Hardy-Weinberg equilibrium for any of the SNPs tested.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Demographic and clinical data were presented as the mean ± SD, median (interquartile) and counts as appropriate. $P < 0.05$ was considered statistically significant. The Chi-square test was used to detect Hardy-Weinberg equilibrium. Depending on the data, Fisher's exact, Mann-Whitney U or t-tests were used to evaluate differences in clinical parameters (including age, gender, body weight, and VAS pain scores at 2 h, 6 h, 12 h, 24 h and 48 h between genotypes. In the present study, 24- and 48-h postoperative sufentanil dose was not normally distributed. Therefore, non-parametric analyses, including the Mann-Whitney U and Kruskal Wallis tests were performed to determine the effect of genotype on PCA sufentanil dose. The factors associated with postoperative cumulative sufentanil intake were determined using linear correlation analysis. The impact of genetic and non-genetic factors on sufentanil dosage was investigated using multiple linear stepwise regression analysis, with an inspection level for *a* equal to 0.05.

Results

A total of 120 patients were enrolled. Patients' mean age was 49.8±8.8 years. There were 30 males and 90 females. The mean weight (kg) was 56.53±9.91 and the mean BMI (kg/m^2) was 22.71±3.48 as presented in **Table 1**. In these patients, the PCA device was refilled with the same regimen and analgesic treatment was continued. Cumulative postoperative sufentanil doses administered at 2 h, 6 h, 12 h, 24 h and 48 h were 5.9±2.1 μg, 15.9±4.0 μg, 29.9±6.0 μg 55.3±7.7 μg and 105.4±9.5 μg (mean ± SD), respectively. Allele frequencies of genotypes are shown in **Table 2**. Postoperative cumulative sufentanil doses in the different genotype groups are displayed in **Table 3**. There were no differences in sufentanil dosage among the genotypes.

In univariate analysis, the factors associated with postoperative 2 h, 6 h, 12 h, 24 h and 48 h cumulative sufentanil consumption with $P < 0.05$ were evaluated as the VAS score. Additional postoperative 6 h cumulative sufentanil dose was associated with duration of surgery, postoperative score at 48 h was associated with *OPRM1* 118A>G (**Table 4**).

In multiple regression analysis using stepwise selection method, VAS score was associated with accumulation of sufentanyl at 2 h, 6 h, 12 h, 24 h and 48 h. The 48-h cumulative sufentanil intake was associated with age (**Table 5**). Old age was associated with decreased sufentanil dose levels during the first 24 h. None of the genotypes were significantly associated with sufentanil consumption. Genetic variations played no significant role in this group of patients, but the VAS value was significantly related to the postoperative sufentanil consumption.

There were no differences in postoperative VAS and sufentanil consumption among the different genders. Catalytic activity of CYP3A4 affected the metabolism of sufentanil. In CYP3A4*18, the most common SNP in Chinese population, G-to-A substitution occurred in intron 10, leading to altered pharmacokinetics of cyclosporine. CYP3A4*18 was responsible for the metabolism of fentanyl. However, we found no significant effects of CYP3A4*18 on sufentanil metabolism.

Discussion

The *OPRM1* strongly modulates pain management in postoperative patients. The 118G allele reduces the analgesic potency and adverse effects of opioids, resulting in higher pain scores. The ATP-binding cassette B1 gene (*ABCB1* encoding P-glycoprotein) is located in different organs, and at the blood-brain barrier. Therefore, functional impairment of P-gp-mediated drug transport may increase the bioavailability of orally administered drugs, reduce the renal clearance, or increase the substrate concentration in brain. A few opioids are P-gp substrates. The *ABCB1* is associated with decreased dosage of opioids. *CYP3A4/5* genes activate inactive opioid analgesics to active metabolites (CYP3A system) resulting in individual variation in sufentanil pharmacological effects [4].

In this study, we discussed the association between *OPRM1* 118A>G, *ABCB1* 2677G>A/T, *ABCB1* 3435C>T, *CYP3A4*18*, *CYP3A5*3* and postoperative sufentanil dosage in patients undergoing cancer surgery. We found that none of the genetic polymorphisms showed significant relationship with sufentanil therapy for postoperative pain relief in Chinese population.

Clinical investigations suggest that inter-individual differences exist in the efficacy of fentanyl therapy for pain relief. It may be inferred that the individual differences in analgesic effect were partly influenced by gene polymorphisms. These individual differences may manifest as inadequate analgesic effect or increase in adverse reactions following similar drug doses. Various factors may contribute to individual differences in the analgesic effect of sufentanil, such as operation type, age, gender, psychological factors and genetic background [19, 20]. Genetic background may play a critical role in analgesia.

Diverse effects of the Al18G polymorphism of sufentanil on postoperative sufentanil therapy have been reported. Camorcia et al [21] designed a double-blind up-down sequential allocation study in 77 women undergoing labor epidural analgesia and found that women carrying the variant G allele had a lower ED50 for epidural sufentanil than women who were homozygous for the wild-type allele. The phenomenon was attributed to the higher receptor-binding affinity of μ-opioid receptor in response to epidural sufentanil in women carrying variant allele. Another report by Xu revealed that the analgesic requirements or pain scores of patients treated with sufentanil and ropivacaine via patient-controlled epidural analgesia (PCEA) after caesarean section were not associated with A118G polymorphism [22]. In our study, we failed to find any association between *OPRM1* 118A>G and postoperative sufentanil requirements, consistent with Xu's study. Individuals carrying G allele exhibited higher levels of sufentanil in our experiment, although the differences were not significant. Further studies are needed to reveal the internal biological mechanisms of *OPRM1* 118A>G. The discrepancies between these studies may be attributed to several factors, especially gender. Fillingim *et al* [23] indicated that a common *OPRM1* SNP may be associated with mechanical pain responses and heat pain perception in a sex-dependent manner in which men carrying the rare allele had higher pressure pain thresholds. Our study included both males and females, which may contribute to inconsistent findings.

Sufentanil metabolism is significantly correlated with the catalytic activity of *CYP3A4* [24]. *CYP3A4*18*, the most common SNP in Chinese population, involves G-to-A substitution in intron 10, leading to altered cyclosporine pharmacokinetics [25]. Yuan R et al reported that *CYP3A4*1G* affected the pharmacokinetics of fentanyl, and patients with variant A allele displayed a lower metabolic rate of fentanyl. *CYP3A4*1G* polymorphism was also related to fentanyl pharmacokinetics. Patients with *CYP3A4*1G* variant A allele showed a lower metabolic rate of fentanyl [26]. However, we did not observe any significant effects of *CYP3A4*18* on sufentanil, which was consistent with a previous report showing a decreasing trend in fentanyl consumption at 24 and 48 h in A allele carriers, compared with GG homozygotes in Chinese Han women with abdominal total hysterectomy, although the difference was not statistically significant [27].

CYP3A5 is another major component of CYP3A enzymes, which shares similar substrate and strong linkage with CYP3A4 [28]. A previous *in vitro* study showed that CYP3A5 was responsible for fentanyl oxidation [29] and fentanyl toxicity [30]. The frequency of CYP3A5*3 is 77.8% and approximate 62% of the Chinese are *CYP3A5*3/*3* genotype in the absence of CYP3A5 protein [18]. We found no significant relationship between CYP3A5*3 and sufentanil dosage.

P-gp in the blood-brain barrier blocks the entry of opioids into brain. It affects the bioavailability of many drugs [31]. The function of P-gp was impaired by 3435C>T and 2677G>T/A polymorphism in *ABCB1* [32]. Our study investigated the association between *ABCB1* polymorphism and dosage of postoperative sufentanil for the first time and found no significant differences.

In addition to the genetic factors, we analyzed the non-genetic factors that may affect postoperative sufentanil dose requirements. We found that only pain scores are significant factors

affecting the dose of sufentanil, suggesting that pain sensitivity reflected the need for analgesia and the response to analgesics was relatively subjective.

Limitations

The study has several limitations as follows: First, in the absence of plasma concentrations of sufentanil and its metabolites, no pharmacokinetic index was available. Second, gender differences affect opioid-mediated behavior and analgesia. Our investigation included males and females but did not eliminate gender differences affecting postoperative analgesia. Further, patients were afflicted with various types of cancer that may be a confounding factor. Additional studies with large samples are needed to stratify the confounding factors. We did not evaluate the MMS value of the patient. Mental states and patients' attitude toward pain may be important factors dictating postoperative sufentanil therapy.

The polymorphisms of *OPRM1* 118A>G, *ABCB1* 2677G>A/T, *ABCB1* 3435C>T, *CYP3A4**1G and *CYP3A5**3 were not significantly associated with postoperative sufentanil dosage, suggesting that genetic factors may not play a major role in the analgesic effect of sufentanil. Due to the complex pharmacokinetic mechanisms of sufentanil, the role of gene polymorphism on sufentanil consumption should be elucidated in multi-center and larger controlled studies.

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Disclosure of conflict of interest

None.

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References

[1] Thomson IR, Harding G and Hudson RJ. A comparison of fentanyl and sufentanil in patients undergoing coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2000; 14: 652-656.

[2] Wu CL and Raja SN. Treatment of acute postoperative pain. Lancet 2011; 377: 2215-2225.

[3] Tateishi T, Krivoruk Y, Ueng YF, Wood AJ, Guengerich FP and Wood M. Identification of human liver cytochrome P-450 3A4 as the enzyme responsible for fentanyl and sufentanil N-dealkylation. Anesth Analg 1996; 82: 167-172.

[4] Kim KM, Kim HS, Lim SH, Cheong SH, Choi EJ, Kang H, Choi HR, Jeon JW, Yon JH, Oh M and Shin JG. Effects of genetic polymorphisms of OPRM1, ABCB1, CYP3A4/5 on postoperative fentanyl consumption in Korean gynecologic patients. Int J Clin Pharmacol Ther 2013; 51: 383-392.

[5] Mura E, Govoni S, Racchi M, Carossa V, Ranzani GN, Allegri M and van Schaik RH. Consequences of the 118A>G polymorphism in the OPRM1 gene: translation from bench to bedside? J Pain Res 2013; 6: 331-353.

[6] Bond C, LaForge KS, Tian M, Melia D, Zhang S, Borg L, Gong J, Schluger J, Strong JA, Leal SM, Tischfield JA, Kreek MJ and Yu L. Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: possible implications for opiate addiction. Proc Natl Acad Sci U S A 1998; 95: 9608-9613.

[7] Beyer A, Koch T, Schroder H, Schulz S and Holt V. Effect of the A118G polymorphism on binding affinity, potency and agonist-mediated endocytosis, desensitization, and resensitization of the human mu-opioid receptor. J Neurochem 2004; 89: 553-560.

[8] Befort K, Filliol D, Decaillot FM, Gaveriaux-Ruff C, Hoehe MR and Kieffer BL. A single nucleotide polymorphic mutation in the human mu-opioid receptor severely impairs receptor signaling. J Biol Chem 2001; 276: 3130-3137.

[9] Zhang Y, Wang D, Johnson AD, Papp AC and Sadee W. Allelic expression imbalance of human mu opioid receptor (OPRM1) caused by variant A118G. J Biol Chem 2005; 280: 32618-32624.

[10] Chou WY, Wang CH, Liu PH, Liu CC, Tseng CC and Jawan B. Human opioid receptor A118G polymorphism affects intravenous patient-controlled analgesia morphine consumption after total abdominal hysterectomy. Anesthesiology 2006; 105: 334-337.

[11] Manini AF, Jacobs MM, Vlahov D and Hurd YL. Opioid receptor polymorphism A118G associated with clinical severity in a drug overdose population. J Med Toxicol 2013; 9: 148-154.

[12] Sia AT, Lim Y, Lim EC, Goh RW, Law HY, Landau R, Teo YY and Tan EC. A118G single nucleotide polymorphism of human mu-opioid receptor

gene influences pain perception and patient-controlled intravenous morphine consumption after intrathecal morphine for postcesarean analgesia. Anesthesiology 2008; 109: 520-526.
[13] Landau R, Kern C, Columb MO, Smiley RM and Blouin JL. Genetic variability of the mu-opioid receptor influences intrathecal fentanyl analgesia requirements in laboring women. Pain 2008; 139: 5-14.
[14] Thompson SJ, Koszdin K and Bernards CM. Opiate-induced analgesia is increased and prolonged in mice lacking P-glycoprotein. Anesthesiology 2000; 92: 1392-1399.
[15] Cascorbi I. P-glycoprotein: tissue distribution, substrates, and functional consequences of genetic variations. Handb Exp Pharmacol 2011; 261-283.
[16] Lee SJ, Lee SS, Jeong HE, Shon JH, Ryu JY, Sunwoo YE, Liu KH, Kang W, Park YJ, Shin CM and Shin JG. The CYP3A4*18 allele, the most frequent coding variant in asian populations, does not significantly affect the midazolam disposition in heterozygous individuals. Drug Metab Dispos 2007; 35: 2095-2101.
[17] Kuehl P, Zhang J, Lin Y, Lamba J, Assem M, Schuetz J, Watkins PB, Daly A, Wrighton SA, Hall SD, Maurel P, Relling M, Brimer C, Yasuda K, Venkataramanan R, Strom S, Thummel K, Boguski MS and Schuetz E. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. Nat Genet 2001; 27: 383-391.
[18] Hu YF, He J, Chen GL, Wang D, Liu ZQ, Zhang C, Duan LF and Zhou HH. CYP3A5*3 and CYP3A4*18 single nucleotide polymorphisms in a Chinese population. Clin Chim Acta 2005; 353: 187-192.
[19] Tan EC, Lim Y, Teo YY, Goh R, Law HY and Sia AT. Ethnic differences in pain perception and patient-controlled analgesia usage for postoperative pain. J Pain 2008; 9: 849-855.
[20] Cepeda MS and Carr DB. Women experience more pain and require more morphine than men to achieve a similar degree of analgesia. Anesth Analg 2003; 97: 1464-1468.
[21] Camorcia M, Capogna G, Stirparo S, Berritta C, Blouin JL and Landau R. Effect of mu-opioid receptor A118G polymorphism on the ED50 of epidural sufentanil for labor analgesia. Int J Obstet Anesth 2012; 21: 40-44.
[22] Xu GH, Gao M, Sheng QY, Liu XS and Gu EW. Opioid receptor A118G polymorphism does not affect the consumption of sufentanil and ropivacaine by patient-controlled epidural analgesia after cesarean section. Ther Drug Monit 2015; 37: 53-57.
[23] Fillingim RB, Kaplan L, Staud R, Ness TJ, Glover TL, Campbell CM, Mogil JS and Wallace MR. The A118G single nucleotide polymorphism of the mu-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in humans. J Pain 2005; 6: 159-167.
[24] Wang RW, Liu L and Cheng H. Identification of human liver cytochrome P450 isoforms involved in the in vitro metabolism of cyclobenzaprine. Drug Metab Dispos 1996; 24: 786-791.
[25] Hu YF, Qiu W, Liu ZQ, Zhu LJ, Liu ZQ, Tu JH, Wang D, Li Z, He J, Zhong GP, Zhou G and Zhou HH. Effects of genetic polymorphisms of CYP3A4, CYP3A5 and MDR1 on cyclosporine pharmacokinetics after renal transplantation. Clin Exp Pharmacol Physiol 2006; 33: 1093-1098.
[26] Yuan R, Zhang X, Deng Q, Wu Y and Xiang G. Impact of CYP3A4*1G polymorphism on metabolism of fentanyl in Chinese patients undergoing lower abdominal surgery. Clin Chim Acta 2011; 412: 755-760.
[27] Dong ZL, Li H, Chen QX, Hu Y, Wu SJ, Tang LY, Gong WY, Xie GH and Fang XM. Effect of CYP3A4*1G on the fentanyl consumption for intravenous patient-controlled analgesia after total abdominal hysterectomy in Chinese Han population. J Clin Pharm Ther 2012; 37: 153-156.
[28] Qiu XY, Jiao Z, Zhang M, Zhong LJ, Liang HQ, Ma CL, Zhang L and Zhong MK. Association of MDR1, CYP3A4*18B, and CYP3A5*3 polymorphisms with cyclosporine pharmacokinetics in Chinese renal transplant recipients. Eur J Clin Pharmacol 2008; 64: 1069-1084.
[29] Davis JJ, Swenson JD, Hall RH, Dillon JD, Johnson KB, Egan TD, Pace NL and Niu SY. Preoperative "fentanyl challenge" as a tool to estimate postoperative opioid dosing in chronic opioid-consuming patients. Anesth Analg 2005; 101: 389-395, table of contents.
[30] Jin M, Gock SB, Jannetto PJ, Jentzen JM and Wong SH. Pharmacogenomics as molecular autopsy for forensic toxicology: genotyping cytochrome P450 3A4*1B and 3A5*3 for 25 fentanyl cases. J Anal Toxicol 2005; 29: 590-598.
[31] Sanchez-Covarrubias L, Slosky LM, Thompson BJ, Zhang Y, Laracuente ML, DeMarco KM, Ronaldson PT and Davis TP. P-glycoprotein modulates morphine uptake into the CNS: a role for the non-steroidal anti-inflammatory drug diclofenac. PLoS One 2014; 9: e88516.
[32] Lotsch J, Geisslinger G and Tegeder I. Genetic modulation of the pharmacological treatment of pain. Pharmacol Ther 2009; 124: 168-184.