MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 5258-5262
DOI: 10.12659/MSM.914921

Received: 2019.01.02
Accepted: 2019.03.19
Published: 2019.07.15

Influence of (ATP)-Binding Cassette Transporter Subfamily B Member 1 (ABCB1) Gene Polymorphism on the Efficacy of Remifentanil

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Source of support: Departmental sources

Background: The aim of this study was to investigate the influence of adenosine triphosphate (ATP)-binding cassette transporter subfamily B member 1 (ABCB1) gene polymorphism on the efficacy of Remifentanil.

Material/Methods: A total of 276 patients undergoing elective surgeries were included to collect general clinical information and detect the polymorphism of ABCB1 rs1045642 using the TaqMan-MGB probe, and they were divided into 3 groups – a genotype AA group, a genotype AG group, and a genotype GG group – based on different genotypes of ABCB1 rs1045642.

Results: The comparisons showed that there were no differences in sex, age, body mass index (BMI), smoking, drinking status, or ASA class among the 3 groups ($P>0.05$). The genotype GG group had higher consumption of Remifentanil than the genotype AA group ($P<0.05$), but the genotype AG group was not different from the genotype AA and GG groups ($P>0.05$). Comparison of the surgery duration revealed no difference among the 3 groups ($P>0.05$). The analepsia time, autonomous respiratory recovery time, and orientation recovery time in the genotype GG group were longer than in the genotype AA group ($P<0.05$), but the genotype AG group was not different from the genotype AA and GG groups ($P>0.05$). There were no differences in adverse reactions among the 3 groups ($P>0.05$).

Conclusions: ABCB1 gene polymorphism can affect the clinical efficacy of Remifentanil.

MeSH Keywords: **Anesthesia and Analgesia • Polymorphism, Single Nucleotide • Treatment Outcome**

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/914921

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Background

Remifentanil is a new synthetic opioid μ receptor agonist that has the functions of sedation, analgesia, and respiratory depression. With unique ester linkages, Remifentanil can be easily hydrolyzed into inactive metabolites, and its metabolic process does not need to depend on liver and kidney functions. Additionally, this process features no release of histamine, a short acting time, rapid onset, and speedy elimination, so Remifentanil has been widely applied in clinical anesthesia. However, clinical results show that the anesthetic efficacy of Remifentanil varies among individuals, and studies have shown that this difference may be correlated with factors such as sex, age, type of surgery, and heredity [1–3]. Adenosine triphosphate (ATP)-binding cassette transporter subfamily B member 1 (ABCB1) gene, also known as multidrug resistance gene 1, and ABCB1-encoded P-glycoprotein (P-gp) can pump opioids out from cells, thus attenuating the analgesic and anesthetic effects of the opioid receptors on the central nervous system [4]. It was speculated that ABCB1 gene polymorphism is possibly correlated with the anesthetic efficacy of Remifentanil. Therefore, the present study focussed on the ABCB1 gene. We enrolled patients undergoing the elective surgeries in our department to detect the polymorphism of ABCB1 rs1045642 site using the TaqMan-MGB probe and explored the correlation of ABCB1 gene polymorphism with the analgesic and anesthetic efficacy of Remifentanil.

Material and Methods

Study subjects

We selected patients undergoing elective surgeries from January 2016 to January 2018 in the Anesthesia Surgery Department of the Affiliated Jining No. 1 People's Hospital of Jining Medical University. The study subjects were in grades I–II according to the classification of patients' physique and surgical risk before anesthesia by the American Society of Anesthesia. This study was approved by the Ethics Committee of the Affiliated Jining No. 1 People's Hospital of Jining Medical University.

Collection of general clinical information

We recorded the name, sex, age, body mass index (BMI), smoking history, and drinking history of the study subjects, as well as their surgery durations, consumption of Remifentanil, postoperative analepsia time (from cessation of anesthesia to analepsia), clinical efficacy (autonomous respiratory recovery time and orientation recovery time), and adverse reactions (dysphoria, nausea and vomiting, and respiratory depression). The criteria for recovery of autonomous respiration was that pulse oxygen saturation maintained above 95% for 15 min without supplemental oxygen in a quite state. The criteria for orientation recovery was being able to correctly state the time and place, as well as completing the specified action.

Extraction of DNA

After 3 mL of venous blood was taken from the elbows of the study subjects, deoxyribonucleic acid (DNA) was extracted using a whole-blood genomic DNA extraction kit (BioTeke Corporation, Beijing, China). The TaqMan® single-nucleotide polymorphism (SNP) genotyping assay (Thermo Fisher Scientific, Waltham, MA) was used to detect and analyze the genotype polymorphisms of the samples (Table 1).

Statistical analysis

Statistical Product and Service Solutions (SPSS) 20.0 software (IBM, Armonk, NY) was used for statistical analysis. The measurement data were expressed as ($\bar{\chi}\pm s$). The independent-samples *t* test was used for the comparisons of measurement data between 2 groups, and one-way analysis of variance (ANOVA) was used for comparisons among groups. The likelihood-ratio χ^2 test was performed to analyze whether the genotype distribution met the Hardy-Weinberg equilibrium criteria. $P<0.05$ suggested that the difference was statistically significant.

Results

General clinical data

The patients had not taken analgesics, sedatives, or cortisol drugs within the last year, had not received opioids within the last 5 years, had no evidence or family history of mental illness, and no heart, kidney, liver, or other major organic dysfunctions. According to the above criteria, this study included 276 patients undergoing elective surgeries. Among them, there were 129 males and 147 females, aged (44.30±6.50) years old

Table 1. Detection information of ABCB1 rs1045642 via TaqMan®-MGB probe assay.

SNP reference	rs1045642
Assay ID	C___7586657_20
SNP type	Silent mutation
Context sequence	TGTTGGCCTCCTTTGCTGCCCTCAC[A/G]ATCTCTTCCTGTGACACCACCCGGC

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Table 2. Distribution frequency of ABCB1 rs1045642 genotypes and alleles.

Genotype (%)			Gene (%)	
AA	AG	GG	A	G
164 (59.42)	88 (31.88)	24 (8.70)	416 (75.36)	136 (24.64)

Table 3. Genetic equilibrium test of ABCB1 rs1045642 genotypes.

AA		AG		GG		χ^2	P
Actual frequency	Theoretical frequency	Actual frequency	Theoretical frequency	Actual frequency	Theoretical frequency		
164	156.75	88	102.49	24	16.75	5.52	0.06

Table 4. Comparison of general information among different genotypes of ABCB1 rs1045642.

Item	AA	AG	GG
Sex (Male/Female)	76 (46.34)/88 (53.66)	42 (47.73)/46 (52.27)	11 (45.83)/13 (54.17)
Age (years old)	44.53±5.87	44.37±7.10	44.23±7.36
BMI (kg/m^2)	25.48±7.89	25.38±7.86	25.57±7.23
Smoking [(n)%]	65 (39.63)	33 (37.50)	10 (41.67)
Drinking [(n)%]	75 (45.73)	40 (45.45)	11 (45.83)
ASA class (I/II)	104 (63.4)/60 (36.6)	52 (59.1)/36 (40.9)	15 (62.5)/9 (37.5)

on average. All study subjects were unrelated Chinese Han individuals and signed the informed consent.

Distribution frequency of ABCB1 rs1045642 genotypes and alleles

The distribution frequencies of the 3 genotypes of ABCB1 rs1045642 (AA, AG, and GG) were 59.42%, 31.88%, and 8.70%, respectively, and that of the A and G alleles were 75.36% and 24.64%, respectively. Based on genotype, the 276 patients were divided into a genotype AA group, a genotype AG group, and a genotype GG group (Table 2).

Genetic equilibrium test

The likelihood-ratio χ^2 test was conducted to assess the actual and theoretical frequency of ABCB1 rs1045642 genotypes in the study subjects. The frequency distributions of ABCB1 rs1045642 genotypes were consistent with Hardy-Weinberg equilibrium (P>0.05) and were comparable (Table 3).

Comparison of general information among different genotypes of ABCB1 rs1045642

The comparisons showed that there were no differences in sex, age, body mass index (BMI), smoking, drinking status, or ASA class among the 3 different groups of genotypes (P>0.05) (Table 4).

Comparison of consumption of Remifentanil among different genotypes of ABCB1 rs1045642

The consumption of Remifentanil in the genotype GG group was higher than in the genotype AA group (P<0.05), but the genotype AG group was not different from the genotype AA group and genotype GG group (P>0.05). The comparisons revealed that there was no difference in surgery duration among the 3 groups of genotypes (P>0.05) (Table 5).

Comparison of clinical efficacy among different genotypes of ABCB1 rs1045642

The genotype GG group had longer analepsia time, autonomous respiratory recovery time, and orientation recovery time than the genotype AA group (P<0.05), while the genotype AG group was not different from the genotype AA group and the genotype GG group (P>0.05) (Table 6).

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Table 5. Comparison of consumption of Remifentanil among different genotypes of ABCB1 rs1045642.

Item	AA	AG	GG
Surgery duration	85.43±14.87	85.13±15.26	84.73±14.87
Consumption of Remifentanil (μg)	769.84±101.36	797.88±105.72	804.82±121.86**

** *P*<0.05 *vs.* genotype AA.

Table 6. Comparison of clinical efficacy among different genotypes of ABCB1 rs1045642.

Clinical efficacy	AA	AG	GG
Analepsia time	6.23±2.37	6.57±2.87	8.33±3.17*
Autonomous respiratory recovery time	4.84±1.37	5.37±1.70	6.73±2.36*
Orientation recovery time	12.28±5.49	14.75±5.86	19.42±6.23**

* *P*<0.05 and ** *P*<0.01 *vs.* genotype AA.

Table 7. Comparisons of adverse reactions among different genotypes of ABCB1 rs1045642.

Adverse reactions	AA		AG		GG	
Dysphoria [(n)%]	10	(6.10)	7	(7.95)	3	(12.50)
Nausea and vomiting [(n)%]	10	(6.10)	8	(9.09)	3	(12.50)
Respiratory depression [(n)%]	12	(7.32)	10	(11.36)	4	(16.67)

Comparisons of adverse reactions among different genotypes of ABCB1 rs1045642

The comparisons showed that there were no differences in adverse reactions among the 3 different groups of genotypes (*P*>0.05) (Table 7).

Discussion

Remifentanil is an ultrashort-acting anesthetic with high analgesic efficacy, and loses efficacy 5–10 min after drug withdrawal. The major mechanism of action of Remifentanil is that it is metabolized via non-specific esterase in organisms, and during this process, it neither produces biologically active metabolites nor causes release of histamine or central neurotoxicity. It can inhibit sympathetic excitement, maintain hemodynamic stability, and reduce surgery-induced body motion. Despite long-time transfusion, Remifentanil does not exhibit retention in the body or damage the liver, kidney, and other organs, and it can be administered to patients of all ages. Therefore, it has been widely applied in surgeries, such as trachea intubation, cesarean section, cardiac surgery, and craniocerebral surgery [5–9]. However, in clinical practice, it has been discovered that the anesthetic and analgesic efficacy of Remifentanil clearly varies among individuals [1–3]. A growing number of clinical pharmacogenomics studies have found that individual differences in dosage are significantly correlated with variations in polymorphisms of metabolic enzymes in different groups of patients. Individualized selection of anesthetic drugs and control of drug dose are of great significance for reducing anesthetic accidents and enhancing anesthetic efficacy.

ABCB1 gene, a member of the ATP-binding transport protein superfamily, encodes the P-gp on cytomembranes. P-gp, a glycosylated and phosphorylated transmembrane protein, possesses ATP-dependent drug efflux pumps with broad substrate specificity and can transfer drugs out of cells. In addition, it can interact with the captured drug molecules on the lipid bilayer of cell membranes. The hydrolysis of ATP offers P-gp the energy to transport substrates and enables the transported proteins to overcome concentration gradients, thus reducing the absorption of metabolites and drugs from the gastrointestinal tract, increasing the discharge of drugs from the bile duct and urine, and preventing parts of drugs from entering the central nervous system [10–14].

In the present study, ABCB1 rs1045642 was selected and the correlation of different ABCB1 genotypes with the analgesic and anesthetic efficacy of Remifentanil were explored in patients who underwent elective surgeries in our department. We found no differences in sex, age, BMI, smoking, or and drinking

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status among the 3 different groups of ABCB1 rs1045642 genotypes. This is similar to the results of studies conducted by other scholars, which also showed that patient sex, age, BMI, smoking, and drinking have no influence on the pharmacodynamics of Remifentanil [15,16]. Hence, it is believed that the sex, age, BMI, smoking, and drinking in this study did not affect the efficacy of Remifentanil, and its dose does not need to be adjusted in different ABCB1 rs1045642 genotype groups according to the sex age, BMI, smoking, and drinking status of the patients. Furthermore, we found that the genotype GG group had higher consumption of Remifentanil and longer analepsia time, autonomous respiratory recovery time, and orientation recovery time than in the genotype AA group, and there was no substantial difference in surgery duration. This indicates that the A→G mutation at ABCB1 rs1045642 site leads to higher consumption of Remifentanil, lower anesthetic efficacy, longer anesthetic duration, and poorer postoperative recovery. It is not clear whether the higher consumption of Remifentanil means the patients were less sensitive to Remifentanil. We speculated that G allele changes the expression and functions of P-gp, weakens its drug efflux function, and extends time of drug retention in the body, thereby further affecting the consumption and clinical efficacy of Remifentanil. However, the mechanism needs further investigation. We also compared adverse reactions among the 3 groups of genotypes, and found no differences, indicating that the adverse reactions during the application of Remifentanil have no correlation with different genotypes of ABCB1 rs1045642 site.

Conclusions

ABCB1 gene polymorphism can affect the clinical efficacy of Remifentanil.

Conflict of interest

None.

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