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ASSOCIATION OF SINGLE-NUCLEOTIDE POLYMORHISM C3435T IN THE ABCB1 GENE WITH OPIOID SENSITIVITY IN TREATMENT OF POSTOPERATIVE PAIN

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Abstract

Background: The minimal effective analgesic concentration of opioids required for satisfactory analgesia may differ significantly among the patients. Genetic factors may contribute to the variable response to opioids by affecting their pharmacokinetics or pharmacodynamics.

Methods: Ninety nine patients undergoing abdominal surgery with colorectal anastomosis because of colorectal carcinoma were enrolled in the present study. C34535T was genotyped in all subjects and the patients were divided into three groups according to their genotype: CC-wild type homozygous, CT-mutant heterozygous and TT-mutant homozygous. Intravenous fentanyl, patient controlled analgesia was provided postoperatively for pain control in the first 24 hour after surgery. Opioid consumption, pain scores and the adverse side effects were evaluated.

Results: Our main result is that the patients in the CC genotype group consumed significantly more fentanyl (375.0 μg ± 43.1) than the patients in the TT group (295.0 μg ± 49.1) and the CT (356.4 μg ± 41.8) group in the treatment of postoperative pain. The patients in the TT group had lower VAS scores at 6h, 12h, 18 h and 24h postoperatively. There were no significant differences in the side effects among the three groups regarding the vomiting and the sedation score. The patients in the TT group had more frequently nausea score 1, than the patients in the other two groups.

Conclusion: Our study indicates that the C3435T SNPs of the ABCB1 gene is associated with differences in the opioid sensitivity. The ABCB1 polymorphism may serve as an important genetic predictor to guide the acute pain therapy in postoperative patients.

Keywords: Fentanyl, ABCB1, Postoperative analgesia

Introduction

Opioids are generally considered as the first line therapy for patients with moderate to severe postoperative pain. The dose of opioids required to achieve sufficient postoperative pain relief is highly variable among patients. The inter-individual variations in response to opioids can partly be attributed to age, gender, weight (BMI), renal or liver functions. However, as each patient often responds differently to specific opioids, providing adequate analgesia for individual patients without concomitant development of adverse effects is still a major challenge.

Each patient may respond differently to specific different opioids. There still exists a need to sort out the multiple explanations for

some variability encountered with the human responses to opioids. The minimal effective analgesic concentration of opioids required for satisfactory analgesia may considerably vary among the patients [1]. Genetic factors may contribute to the variable response to opioids by affecting their pharmacokinetics (drug metabolizing enzymes and transporters) or pharmacodynamics (receptor and signal transduction).

Drug transporters are important structural proteins that can influence the absorption, distribution and elimination of opioids [2]. In the gastrointestinal tract and hepatocytes they have the ability to influence the bioavailability of the orally administrated opioids by restricting or facilitating the intestinal absorption and facilitating presystemic biliary elimination [3, 4]. In particular, the transporter expression at the blood–brain barrier has the potential to significantly influence the clinical efficacy and safety of opioids, whose major site of action lies within the central nervous system [2]. Both efflux and uptake carrier systems have been implicated in the transport of opioids (drugs and peptides), with multiple transporters often functionning in concert to facilitate the efficient transfer of substrates across biological membranes. The 2 major families of drug transporters of relevance to opioid pharmacokinetics are the ATP binding cassette (ABC) superfamily of efflux transporters, and the solute carrier (SLC) superfamily of influx transporters. The ABC superfamily of efflux transporter consist of nearly 50 known human members divided in 7 sub-families. The most characteristic of the ABC transporters is the ABCB1 MDR1, P – glycolprotein (P-gp) efflux transporter which functions at the capillary endothelial cells of the blood brain barrier (with the ABCC family being less well studied). Opioid induced analgesia is increased and prolonged in mice lacking P g-p. Morphine, methadone, loperamide, and fentanyl have all been confirmed as P-gp substrates [1].

The most investigated of the common ABCB1 genetic polymorphisms is the non-synonymous exon 26 SNP, C3434T, which is observed with a frequency of 50–60% in Caucasians, 40–50% in Asians, and 10–30% in Africans. [5–8]. There was a significant relationship between 3435 genotype and the extent of loperamide miotic effects following p-gp inhibition by quinidine [1].

The ABCB1 gene is composed of 28 exons ranging in size from 49 to 299 base pairs, encoding an mRNA of 4.5 kb. The most common polymorphisms found in ABCB1 are 1236C > T, 2677 G > T/A/C, and 3435C > T. It has been suggested that the genetic variations in ABCB1 could be a cause of inter-individual differences in drug response [9]. In this study we investigated the C3435T Single Nucleotide Polymorphisms – SNPs of ABCB1 where C > T. Thus, the major allele is CC, the heterozygous minor allele is CT and homozygous minor allele is TT.

The aim of the study is to evaluate the association between C3435T and the opioid consumption in the acute postoperative period in patients who have undergone abdominal surgery with colorectal anastomosis. Additionally, we explored the association between C3435T and the opioid side effects in the acute postoperative period in the same population.

Methods

Study subjects and analgesia

This was a prospective study approved by the institutional Ethics Committee (No 03-6608/2). A signed informed consent was obtained from all patients. Between July 2013 and February 2016, 100 patients with the American Society of Anesthesiologist physical status of I-III aged 35–75 years, and undergoing abdominal surgery with colorectal anastomosis because of colorectal carcinoma, were enrolled in the present study. The main exclusion criteria included liver and renal disease, history of chronic pain, severe cardiovascular disease, diabetes mellitus, psychiatric disorders, pregnancy, lactation, allergy to opioids, unwillingness to cooperate in the pain assessment, and administration of non-steroidal anti-inflammatory analgetics and/or opioids one week before surgery. All patients underwent surgery under combined general/epidural anesthesia.

After recovering from anesthesia, all patients received fentanyl by intravenous patient-controlled analgesia (PCA) using a PCA pump containing 100 ml saline 0.9%, 1 mg fentanyl. The PCA pump was programmed to give a 20 μg bolus (2 ml) of solution with 5-min lockout time, 5 $\mu g.h^{-1}$ fentanyl background infusion and maximum 145 $\mu g.h^{-1}$ [10]. The delivered fentanyl dose was automatically recorded by the pump. Nausea and vomiting following abdominal surgery are common, therefore all patients were intravenously administered 30 mg metoclopramide divided into three doses. The pati-

ents were monitored closely to prevent fentanyl overdose (pulse oxygen saturation, heart rate and noninvasive blood pressure).

Pain at rest was assessed using 10 cm VAS with a range 0–10, with no pain as zero and the worst possible pain as ten. Successful analgesia was defined as a postoperative VAS pain score ≤ 3. The side effects were recorded every 6 h after completion of the operation, i.e. at 6, 12, 18 and 24 h. Patients rated their nausea on a four-point scale (0-no nausea; 1-mild nausea, 2-moderate nausea; 3-severe nausea). Vomiting was assessed as events occurring in the first 24 h. Sedation was assessed using Ramsay sedation score (0 awake, 6 unresponsive to a strong, painful stimuli). [11–13].

Statistical analysis

The statistical data processing was done in the statistical program SPSS 17 for Windows. The testing of normality in the distribution of the data was used Kolmogorov-Smirnov and Shapiro-Wilk's W test. Categorical traits displayed by absolute and relative representation with quantitative traits mean, SD. For comparison of the three genotypes in relation to the variables analyzed were used the Chi-square test, Fisher exact test, Student's t test, One-way analysis of variance (post hoc Bonferroni test). The correlation between the consumption of fentanyl with age and duration of operative intervention was analyzed with the Pearson's coefficient of linear regression. Concerning the level of significance or importance, the value of $p < 0.05$ was taken, a significant higher value than $p < 0.01$.

Genotyping

Venous blood samples (2 ml) were collected from all patients in the study. Genomic DNA was extracted from whole blood using SaMag Blood DNA Extraction Kit (Sacace Biotechnologies, Como, Italy) on an automatic DNA extractor (SaMag – 12 System, Sacace Biotechnologies, Como, Italy) according to the manufacturer's provided protocol. The quantity and quality of the extracted genomic DNA was determined using NanoDrop 2000 spectrophotometer (Thermo Scientific, USA) with measurements performed at 260 and 280 nm. The ABCB1 C3435T (rs1045642) polymorphism was genotyped using a TaqMan® Drug metabolism genotyping assay (ID C 7586657 20, Applied biosystems, Life Technologies, USA). Amplification reactions were performed in a total volume of 25 µL containing 20 ng genomic DNA, 12.5 µL 2 × Taqman Universal PCR Master Mix and 1.25 µL 20 × Drug Metabolism Genotyping Assay Mix. Thermal cycling was performed according to the manufacturer's recommended protocols using a Stratagene MX3005P real-time PCR system (Agilent Technologies). Both positive and negative controls were included in every genotyping assay.

Results

Out of 100 patients, one did not complete the procedure and was excluded due to problems with DNA isolation. Patients were divided into CC, CT and TT groups after genotyping. Among the remaining 99 subjects, there were 28 wild type homozygotes (CC), 45 heterozygotes (CT), and 26 mutant homozygotes (TT). (Table 1). There were no significant differences in the demographic characteristics among the three genotype groups with regard to sex, age, weight, height, duration of surgery and ASA score (Table 2). In the remaining 99 patients, there were no PCA device failures and no intolerable opioid side effects. There was significant differences in VAS scores between CC and TT groups, and CT and TT. VAS scores 6 h after surgery were CC 4.39 ± 13; CT 3.64 ± 1.3 and 2.1 ± 92.0 for TT genotype group. VAS scores 12h after surgery were 3.18 ± 0.18 in group CC, 3.0 ± 0.7 CT, and 1.73 ± 1.2 for group TT. After 18 h VAS scores for three groups were 2.61 ± 0.6 CC; 2.2 ± 0.7 in group CT and 1.54 ± 0.9 in group TT. VAS scores 24 h postoperatively for three groups were 1.82 ± 0.9 for CC group; 1.56 ± 0.7 among the patients in CT group, and 1.08 ± 0.8 for TT group (Table 3). There were no significant differences in side effects among the three groups regarding vomiting and sedation score. The patients in the TT group had more frequently nausea score 1 than the patients in the other two groups (Table 4). The patients in the CC group consumed significantly more fentanyl (375.0 µg ± 43.1) than the patients in the TT group (295.0 µg ± 49.1) and CT (356.4 µg ± 41.8) group (Table 5).

Table 1

*Genotype distribution of ABCB1 (C3435) in 99 patient*s

ABCB1	**N (%)**
CC	28 (28.28)
CT	45 (45.45)
TT	26 (26.26)
All	99 (100)

CC, wild type homozygous; CT, mutant heterozygous; TT mutant homozygous

Table 2

Demographic and clinical characteristics of ABCB1 genotype groups

Characteristics	ABCB1 CC (n = 28)	ABCB1 CT (n = 45)	ABCB1 TT (n = 26)	p value
Sex n(%)				
Male n = 59	17 (60.71)	26 (57.78)	16 (61.54)	[a]p = 09
Female n = 40	11 (39.29)	19 (42.22)	10 (38.46)	
Age, years				
(mean ± SD)	60.18 ± 9.9	60.2 ± 9.7	56.12 ± 8.7	[b]p = 018
Height (cm)				
(mean ± SD)	170.36 ± 8.4	171.09 ± 8.6	171.19 ± 6.0	[b]p = 091
Weight (kg)				
(mean ± SD)	71.36 ± 12.7	74.84 ± 12.6	77.58 ± 10.6	[b]p = 017
ASA n(%)				
1	6 (21.43)	6 (13.33)	4 (15.38)	
2	20 (71.43)	39 (86.67)	19 (73.08)	[c]0.14
3	2 (7.14)	0	3 (11.54)	
Duration of surgery (min)				
(mean ± SD)	186.25 ± 34.2	198.56 ± 38.6	191.15 ± 35.5	[b]p = 036

- Continuous variables expressed as mean ± standard deviation.
- [a](Chi-square test) [b](Analysis of Variance) [c](Fisher exact test)
- ASA – American Society of Anesthesiologists

Table 3

ABCB1 C3435T polymorphism and postoperative pain in 6h, 12 h, 18h and 24 h postoperatively

Characteristics	ABCB1 CC (n = 28)	ABCB1 CT (n = 45)	ABCB1 TT (n = 26)	p value
VAS (6h)				
(mean ± SD)	4.39 ± 1.3	3.64 ± 1.3	2.19 ± 2.0	[b]p = 0000003**
VAS (12h)				
(mean ± SD)	3.18 ± 0.8	3.0 ± 0.7	1.73 ± 1.2	[b]p < 0001
VAS (18h)				
(mean ± SD)	2.61 ± 0.6	2.2 ± 0.7	1.54 ± 0.9	[b]p = 0000001**
VAS (24h)				
(mean ± SD)	1.82 ± 0.9	1.56 ± 0.7	1.08 ± 0.8	[b]p = 00023**

- Post hoc analysis Bonferroni. VAS (6h) 1вcs3 p = 0.00011** 2vs3 p = 0.0006** VAS (12h) 1вc3 p = 0.0001**
- 2vs3 p = 0.0001** VAS (18h) 1вc3 p = 0.0001** 2vs3 p = 0.0007** VAS (24h) 1вc3 p = 0.0018**
- 2vs3 p = 0.035 **p < 0.05 **p < 0.01
- VAS – visual analogue scale

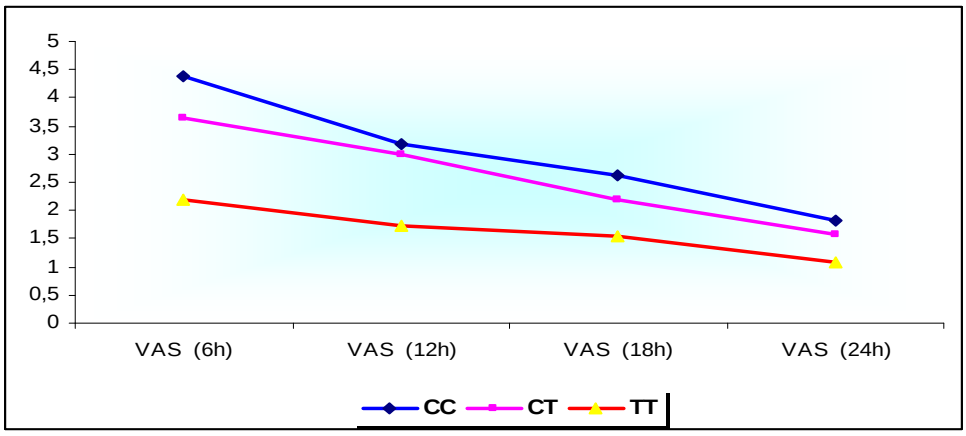

Fig. 1 – Pain assessment by visual analogue scale (VAS). VAS (mean± standard deviation) was recorded at 6h, 12 h, 18h and 24 h after the completion of the operation in three genotype groups CC, CT and TT. CC, wild type homozygous; CT, mutant heterozygous; TT mutant homozygous

Table 4

Side-effects of fentanyl delivered via patient-controlled analgesia (PCA) for patients receiving PCA, in three genotype groups

Characteristics	ABCB1 CC (n = 28)	ABCB1 CT (n = 45)	ABCB1 TT (n = 26)	p value
Nausea – n (%)				
0	24 (85.71)	43 (95.56)	18 (69.23)	[c] 0.014
1	3 (10.71)	2 (4.44)	4 (15.38)	
2	1 (3.57)	0	4 (15.38)	
Vomiting – n (%)				
0	27 (96.43)	44 (97.78)	25 (96.15)	[c] 1 0
1	1 (3.57)	1 (2.22)	1 (3.85)	
Sedation – n (%)				
0	28 (100)	43 (95.56)	23 (88.46)	[c] 0.12
1	0	2 (4.44)	3 (11.54)	

[c] (Fisher exact test)
CC, wild type homozygous; CT, mutant heterozygous; TT mutant homozygous.
Patients rated their nausea using a four –point scale (0, no nausea; 1, mild nausea; 2, moderate nausea; 3 severe nausea). Vomiting was assessed as events occurring in 24 h. Sedation was assessed using the Ramsey sedation score (0, awake; 6 unresponsive to strong painful stimuli).

Table 5

Postoperative consumption of fentanyl (μg) in three genotype groups

Characteristics	ABCB1 CC (n = 28)	ABCB1 CT (n = 45)	ABCB1 TT (n = 26)	p value
Postoperative consumption of fentanyl (μg)				
(mean ± SD)	375,0 ± 43.1	356,4 ± 41.8	295,0 ± 49.1	[b]p < 0.0001

Post hoc analysis Bonferroni **p < 0.01

Discussion

Our main result is that, in Macedonian patients who underwent abdominal surgery with colorectal anastomosis due to colorectal carcinoma, subjects with ABCB1 3435T allele (TT mutant type homozygous) received less fentanyl in the early postoperative period and had lower VAS scores. According to our results subjects in this group are "good respondent" to fentanyl, while patients in the CC group (wild type homozygous) are "bad respondent". The subjects in the CT group (mutant heterozygous) are "moderate respondents". This provides support for potential use of genetic data in predicting the fentanyl doses for adequate postoperative pain control. Some evidence suggests that other variables (e.g., age, sex and type of surgery) may also influence the postoperative pain [14–15]. There are conflicting results in literature regarding the influence of SNPs in ABCB1 gene on both, effects and side effects of opioids. It has been suggested that the TT carriers of C3435T were good respondents to morphine while those with CC or CT were moderate respondents. It has been speculated that the absorption of morphine is reduced in the CC carriers due to the effective efflux by P-gp in gut and/or through the blood brain barrier and consequently reducing the bioavailability of morphine for the receptors in brain. Conversely the TT carriers with abnormal function of P-gp should have a higher concentration of morphine [16]. The C3435T ABCB1 SNP has recently been associated with a different need for morphine in humans. Meineke et al. showed that patients carrying the TT genotype of the C3435T ABCB1 SNP, associated in other tissues with lower P-gp expression, had higher morphine cerebrospinal fluid concentrations than patients carrying the wild type C allele, associated with higher P-gp expression. These pharmacogenetics data obtained in humans are consistent with the involvement of P-gp in morphine brain disposition [17]. Age and prior use of psychotro-

pic agents are associated with postoperative morphine dose requirements. Whether ABCB1 polymorphisms might predict morphine side effects remains to be determined [18]. Previous investigations have observed that opioids are the substrates for P-gp involved in drugs cellular membrane permeability, disposition, and therefore analgesia effect in CNS [19]. In the study of Gong et al., they failed to reveal any significant difference in 24 h opioids doses among the subjects carrying various ABCB1 C3435T phenotypes in patients with cancer pain. However, when they measured using weight-surface area-adjusted-24h-opioids doses instead, TT homozygotes tended to require significantly lower opioids intake dosage than CC/CT carriers. [20]. In the study of Candiotti et al. where C3435T was genotyped in 152 patients undergoing a nephrectomy, authors found an association between the ABCB1 polymorphism (C3435T) and inter individual variations in opioid consumption in the acute postoperative period after nephrectomy. Analyzing the pain scores from 24-hour postoperative period, they observed that the CC genotype demonstrated the highest numerical pain score, the CT group an intermediate score, and the TT genotype the lowest. The same trend was observed in the 6 and 12 hour postoperative pain scores [21]. It has been reported that variants in ABCB1 are associated with the central side effects of opioids such as sedation, confusion, and hallucination in chronic cancer patients [2]. In our study we didn't find association between genetic polymorphisms of ABCB1 C3435T SNP and opioids side effects: vomiting and sedation. Patients in the TT genotype group had more frequently nausea score 2 than CC and CT group. Coulbault et al. suggested that ABCB1 polymorphisms could predict the side effects of morphine remains to be determined [18]. In the study of Candiotti et al. the authors also investigated a possible correlation between morphine related side effects (symptomatic nausea/vomiting) and the ABCB1 gene SNP. Their data showed that the CC genotype demonstrated the numerically lowest usage of emesis medication, the CT genotype demonstrated intermediate usage levels, and the TT genotypes showed the highest usage, but there were no statistically significant differences among the three genotype groups for emesis medications usage at 24 hours after surgery [21]. Wallden et al. also considered that the genetic polymerphism does not explain the nausea and vomiting caused by fentanyl. However, they found that the incidence of nausea and vomiting was higher in patients with inhibit gastric motility. This finding provides another explanation for postoperative nausea and vomiting, namely this may be associated with the opioid-induced changes in gastric motility [22].

Our study has some limitations. This was strictly a gene association study trial and as such opioid levels were not measured in the CNS or blood. Additionally, the study only enrolled patients undergoing abdominal surgery which is very painful. Secondly, the mixed gender study population may have increased variability in postoperative fentanyl requirements, although no statistically significant differences in gender were found between the different genotypes. In addition, only one gene polymorphism was analyzed, leaving a number of gens with functional significance to be assessed in future studies.

Conclusion

Our study indicates that the C3435T single nucleotide polymorphism of the ABCB1 gene is associated with differences in postoperative opioid consumption in patients who underwent abdominal surgery with colorectal anastomosis. The ABCB1 polymorphism may serve as a genetic predictor to guide acute pain therapy in postoperative patients.

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Резиме

ПОВРЗАНОСТ НА ЕДИНЕЧНИОТ НУКЛЕОТИДЕН ПОЛИМОРФИЗАМ НА C3435T ОД ABCB1 ГЕНОТ СО ОПИОИДНАТА ОСЕТЛИВОСТ ВО ТРЕТМАНОТ НА ПОСТОПЕРАТИВНАТА БОЛКА

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Вовед: Минималната ефективна концентрација на опиоиден аналгетик може значително да се разликува помеѓу пациентите. Генетските фактори кои влијаат врз фармакокинетиката и фармакодинамиката на опиоидните аналгетици може да придонесат за различната осетливост на опиоидните аналгетици.

Пациенти и методи: Во студијата беа вклучени 99 пациенти оперирани од колоректален карцином. Кај сите пациенти беше земена

венска крв за ДНК-изолација и генотипизација на C3435T од ABCB1 генот. Според генотипот, пациентите беа поделени во три групи: CC-хомозиготи со див тип алели, CT-хетерозиготи со мутантни алели и TT-хомозиготи со мутантни алели. Кај сите пациенти постоперативно беше даден фентанил на PCA-пумпа (patient controlled analgesia). Степенот на болка, потрошувачката на фентанил и несаканите ефекти беа корелирани со резултатите од генетска анализа.

Резултати: Пациентите со генотип CC консумирале значително повеќе фентанил (375,0 μg ± 43,1), од пациентите во TT генотипската група (295,0 μg ± 49,1) и CT-групата (356,4 μg ± 41,8) во третманот на постоперативна болка. Пациентите во TT-групата имаа понизок степен на болка според VAS-скалата по 6 часа, 12 часа, 18 часа и 24 часа по операција. Нема значајни разлики во несакани ефекти кај трите генотипски групи во однос на инциденца на постоперативно повраќање и седација. Пациентите во групата TT имале почесто гадење степен 1, за разлика од пациентите во другите две групи.

Заклучок: Нашата студија покажува дека полиморфизмите на C3435T од генот ABCB1 се поврзани со разликите во степенот на болка и потрошувачката на фентанил кај пациенти кои биле оперирани од колоректален карцином. Генетскиот полиморфизам на C3435T може да послужи како важен генетски предиктор при третман на постоперативна болка.

Клучни зборови: фентанил, ABCB1, постоперативна аналгезија