Epidural Analgesia With Sufentanil in Relation to *OPRM1* and *ABCB1* Polymorphisms

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Summary

The aim of this study was to evaluate the association between *OPRM1* and *ABCB1* polymorphisms on pain relief with *epidural sufentanil* in 69 patients after rectosigma resection for cancer. The median number of injections (SD) 2.31 (1.36), IQR=1, required by *118AA* subjects was significantly lower in comparison with *118AG* group 5.25 (3.13), IQR=6.5, (χ^2=9.75, p=0.001); correspondingly median drug consumption of 1.16 (0.79), IQR=1.083, defined daily doses (DDD) was significantly less in the *118AA* group in comparison with 2.14 (1.17), IQR=2.23, DDD in *118AG* subjects, (χ^2=7.00, p=0.008). Opioid-induced adverse effects were observed in 15 % and 33 % of patients in *118AA* and *118AG* groups, respectively (χ^2=8.16, p=0.004). The median number of injections (SD) required by women and men was 3.30 (2.16), IQR=2, and 2.80 (1.59), IQR=1, respectively (χ^2=6.25, p=0.012). Opioid-induced adverse effects were observed in 26 % and 12 % of women and men, respectively (χ^2=5.49, p=0.011). Heterozygotes of *OPRM1* polymorphism and women were more difficult to treat subpopulations that required higher doses of *rescue analgesic medication* and suffered more adverse effects.

Key words

OPRM1 • *ABCB1* • Epidural sufentanil • Acute pain • Rescue analgesia

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Introduction

Opioids are generally considered as the first line therapy for patients with moderate to severe postoperative pain. Different responses to opioids and development of adverse effects are due to both genetic and non-genetic factors (Packiasabapathy and Sadhasivan 2018). Many studies describe that the polymorphism rs1799971in the *OPRM1* is associated with therapeutic opioid responses after morphine, fentanyl, remifentanil and sufentanil (Bakhouche *et al.* 2018, Hronová *et al.* 2016, Khalil *et al.* 2017). 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 (Mura *et al.* 2013, Ujčíková *et al.* 2014). The *118G* allele reduced analgesic potency and incidence of side effects of opioids, and resulted in higher pain scores (Manini *et al.* 2013). ATP-binding cassette B1 gene (*ABCB1* encoding P-glycoprotein) is mainly located in organs with excretory functions. It is also expressed in the blood-brain barrier as an outward transporter. Several studies reported that *ABCB1* genetic polymorphisms (rs1045642, rs2032582) were associated with the analgesic efficacy and consumption of opioids (Kim *et al.* 2013). However, the importance of *ABCB1* encoding P-glycoprotein is still unclear (Zhao *et al.* 2019).

Sufentanil is the one of strongest opioid analgesic available for the treatment of pain in humans in surgical procedures and critical care where pain relief is required for a short period of time. It is approximately

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five to ten times more potent than fentanyl, with a shorter duration of action (Wu and Raja 2011). The μ-opioid receptor, encoded by the human opioid receptor μ-1 gene *OPRM1*, is the primary site of action for sufentanil. The aim of this study was to test the association between *OPRM1* (rs1799971), *ABCB1* (rs1045642, rs2032582) polymorphisms, age and gender on postoperative pain relief with sufentanil in the acute postoperative period in patients who have undergone rectosigma resection for cancer.

Materials and Methods

Patients and surgical procedure

This was a prospective study in 69 patients after rectosigma resection for cancer at the 3rd Department of Surgery, First Faculty of Medicine, Charles University and University Hospital Motol. The study was approved by the local Ethics Committee Reference No.: 1452/13 and it was conducted in accordance with the Declaration of Helsinki. Main exclusion criteria included allergy to opioids, unwillingness to cooperate in the pain assessment, and administration of non-steroidal antiinflammatory analgesics and/or opioids one week before the surgery. Standard premedication protocol included diazepam *per os* in the evening before surgery. All patients underwent surgery under standardized general anesthesia, based on the combination of propofol (2 mg/kg) and sufentanil (2 μg/kg). Surgical procedures were conducted by an experienced surgeon, who followed rectosigma resection.

Postoperative pain treatment, efficacy analysis and genotyping

After recovering from the anesthesia, all patients received *epidural sufentanil* (1.5 μg/kg/day) and bupivacain (0.50 mg/kg/day). The required number of following injections of analgetics was evaluated with Anatomical Therapeutic Chemical /Defined Daily Doses (ATC/DDD) methodology. Pain intensity was assessed using visual analogue scale (VAS 0-100 mm) at 1, 2, 3, 4, 5, 6, 12, 24, 36 and 48 h after the surgery. These values were used to calculate the sum of pain intensity differences (SPID). In addition, appearance of opioid-induced adverse effects was recorded. Postoperative nausea and vomiting (PONV) was considered as certain opioid-induced adverse effect, while headache, sedation, pruritus, vertigo, and hallucination represented possible opioid-induced adverse effects. To discriminate from nonspecific adverse reactions, only the appearance of either certain opioid-induced adverse effect in individual patient or at least two possible opioid-induced adverse effects resulted in classification as opioid-induced adverse effect. Pain intensity, required number of rescue analgesic medication and opioid-induced adverse effects were compared among the *OPRM1* (rs1799971), *ABCB1* (rs2032582, rs1045642*)* polymorphisms, gender and age. Genotyping was performed using our standard methods (Bartošová *et al.* 2015).

Statistical analysis

Hardy-Weinberg equilibrium was verified for observed genotype frequencies of the *OPRM1* (rs1799971) and *ABCB1* (rs2032582, rs1045642) polymorphisms and to detect deviation from the expected genotype distribution and to detect genotyping error. Kruskal-Wallis test for two dependent variables was used for statistical evaluation, categorical parameters were evaluated using χ^2 test ($p<0.05$).

Results

Totally 69 patients completed the study and all have been included into the evaluation. The demographic and surgical characteristics were similar among the genotype groups (Table 1) and genotype distribution complied with the Hardy-Weinberg equillibrium (Table 2). Table 3 summarizes analgesic efficacy of sufentanil and rescue analgesic medication use in *OPRM1* (rs1799971) and *ABCB1* (rs1045642, rs2032582) genotype groups. The median SPID for 0-48 h after surgery were not significantly affected by rs1799971, rs1045642, or rs2032582. There was a trend towards lower pain relief in patients carrying variant alleles in *OPRM1* and *ABCB1* in comparison with wild-type homozygous subjects. The median number of injections (SD) 2.31 (1.36), IQR=1, required by *118AA* subjects was significantly lower in comparison with *118AG* patients 5.25 (3.13), IQR=6.5, (χ^2=9.75, p=0.001); correspondingly median drug consumption of 1.16 (0.79), IQR=1.083, DDD was significantly less in the *118AA* group in comparison with *118AG* subjects requiring 2.14 (1.17), IQR=2.23, DDD, (χ^2=7.00, p=0.008). Opioid-induced adverse effects were observed in 15 % and 33 % of patients in *118AA* and *118AG* groups, respectively (χ^2=8.16, p=0.004). There was a trend towards higher required number of injections, higher number of DDD and higher opioid-induced adverse effects in patients

carrying variant in *ABCB1* in comparison with wild-type homozygous subjects (Table 4). The median number of injections (SD) required by women and men was 3.30 (2.16), IQR=2 and 2.80 (1.59), IQR=1, respectively (χ^2=6.25, p=0.012). Opioid-induced adverse effects were observed in 26 % and 12 % of patients in women and men, respectively (χ^2=5.49, p=0.011). Other clinical conditions did not differ between genders (Table 5). In addition, no significant impact was observed for age.

Table 1. Demographic and surgical data of patients.

SNPs	Genotypes/ gender (n)	Ages (years)	Height (cm)	Weight (kg)	Gender (women/ men)	Length of operation (min)	Length of anesthesia (min)
OPRM1	AA (57)	64.38(11.06)	170.80(9.15)	79.09(14.39)	23/34	131.84(53.66)	172.31(58.87)
118A>G	AG (12)	65.25(17.97)	172.33(9.26)	76.50(7.13)	7/5	120.58(49.05)	159.91(58.85)
ABCB1	GG (27)	65.70(14.14)	173.85(7.47)	81.29(11.49)	13/14	117.81(54.04)	155.22(55.89)
2766G>T	GT (26)	62.96(11.15)	169.03(9.63)	73.53(13.59)	9/17	133.50(51.13)	174.26(59.44)
	TT (16)	65.12(11.51)	169.68(9.87)	82.43(13.72)	8/8	144.37(49.89)	188.68(57.27)
ABCB1	CC (15)	69.00(13.42)	170.66(8.79)	79.20(13.82)	8/7	107.26(57.73)	148.26(55.04)
3435C>T	CT (29)	64.48(10.46)	173.20(9.18)	79.20(13.82)	12/17	127.68(45.69)	166.34(53.12)
	TT (25)	61.92(13.44)	168.84(8.85)	78.17(13.82)	10/15	146.00(52.68)	187.72(62.63)
	Women (30)	67.93(14.30)	170.90(9.56)	78.53(14.90)	30/0	129.10(52.40)	171.56(53.52)
	Men (39)	61.92(10.27)	171.20(8.88)	78.71(12.20)	0/39	130.48(53.55)	169.07(62.97)

Data are presented as median (SD), SNP – single nucleotide polymorphism.

Table 2. Genotypes and allele frequencies of *OPRM1* (rs1799971) and *ABCB1*(rs2032582, rs1045642).

SNPs	Genotypes	Observed n (%)	Expected n (%)	Hardy-Weinberg test	
				χ^2	p-value
OPRM1	AA	57 (83)	57.52 (83)		
118A>G	AG	12 (17)	10.96 (16)		
	GG	0 (0)	0.52 (1)		
	Allele A	127 (92)	126 (91.3)		
	Allele G	11 (8)	12 (8.7)	1.03	0.905
ABCB1	GG	27 (39)	23.19 (34)		
2766G>T	GT	26 (37)	33.62 (49)		
	TT	16 (24)	12.19 (17)		
	Allele G	80 (58)	80 (57.97)		
	Allele T	58 (42)	58 (42.03)	3.21	0.523
ABCB1	CC	15 (21)	12.61 (18)		
3435C>T	CT	29 (42)	33.78 (49)		
	TT	25 (37)	22.61 (33)		
	Allele C	59 (43)	59 (42.75)		
	Allele T	79 (57)	79 (57.25)	1.00	0.910

SNP – single nucleotide polymorphism.

Table 3. SPID (cm) for *OPRM1* (rs1799971) and *ABCB1* (rs2032582, rs1045642) genotype groups.

SNPs	Genotypes (n)	$SPID_{0-6}$	$SPID_{0-12}$	$SPID_{0-24}$	$SPID_{0-36}$	$SPID_{0-48}$
OPRM1	AA (57)	16.22 (9.21)	19.52 (10.40)	22.69 (11.68)	26.19 (13.23)	28.53 (14.39)
118A>G	AG (12)	11.77 (4.93)	14.55 (5.29)	17.11 (5.87)	20.55 (5.90)	23.77 (6.64)
ABCB1	GG (27)	15.75 (8.67)	18.75 (9.31)	21.83 (9.69)	25.25 (9.95)	28.66 (11.22)
2766G>T	GT (26)	14.33 (5.58)	18.26 (5.81)	22.13 (6.08)	26.13 (6.86)	28.81 (8.46)
	TT (16)	13.95 (10.15)	16.71 (11.57)	19.38 (13.19)	22.80 (15.23)	25.19 (16.28)
ABCB1	CC (15)	14.27 (7.08)	17.94 (7.91)	21.77 (8.73)	26.00 (10.08)	29.55 (11.86)
3435C>T	CT (29)	16.22 (9.21)	19.31 (7.74)	22.73 (8.32)	26.21 (8.62)	29.73 (9.55)
	TT (25)	14.81 (12.22)	17.45 (14.05)	19.63 (16.08)	22.90 (18.69)	25.18 (19.77)

Data are presented as median (SD), SNP – single nucleotide polymorphism, SPID – sum of pain intensity differences.

Table 4. Number of injections, number of DDD and AEs for *OPRM1* (rs1799971) and *ABCB1* (rs2032582, rs1045642) genotype groups.

SNPs	Genotypes (n)	No of injections	No of DDD	AEs yes/no (%)
OPRM1	AA (57)	2.31 (1.36)	1.16 (0.79)	15/85
118A>G	AG (12)	5.25 (3.13)**	2.14 (1.17) **	33/67 **
ABCB1	GG (27)	2.65 (1.85)	1.36 (1.02)	18/82
2766G>T	GT (26)	2.59 (0.91)	1.42 (0.57)	19/81
	TT (16)	4.12 (3.23)	1.73 (1.40)	25/75
ABCB1	CC (15)	2.80 (2.22)	1.48 (0.91)	20/80
3435C>T	CT (29)	2.44 (1.00)	1.29 (0.78)	17/83
	TT (25)	3.68 (2.70)	1.72 (1.04)	24/76

Data are presented as median (SD), SNP – single nucleotide polymorphism, DDD – defined daily dose, AE – adverse effect. *p<0.05, **p<0.01.

Table 5. Gender differences in clinical outcomes.

Gender (n)	$SPID_{0-48}$	No of injections	No of DDD	AEs yes/no (%)
Women (30)	24.66 (11.79)	3.30 (2.16)	1.69 (1.00)	26/74
Men (39)	28.48 (12.61)	2.80 (1.59)*	1.33 (0.89)	12/88*

Data are presented as median (SD), SPID – sum of pain intensity differences, DDD – defined daily dose, AE – adverse effect. *p<0.05, **p<0.01.

Discussion

In this study, we describe the association between *OPRM1* (rs1799971), *ABCB1* (rs1045642, rs2032582) polymorphisms, age and gender in postoperative pain relief with sufentanil efficacy in acute postoperative period in patients who underwent rectosigma resection for cancer. The clinical impact of *OPRM1* (rs1799971), and *ABCB1* (rs1045642, rs2032582) polymorphic variants was recently described in other studies (Owusu *et al.* 2017, Kaye *et al.* 2019, Viera *et al.* 2019). The *118G* allele reduces the analgesic potency, resulting in higher pain scores, and increased adverse effects of opioids. Our results indicate that heterozygotes for *OPRM1* (rs1799971) required significantly higher doses of analgesic rescue medication and suffered from more opioid-induced adverse effects.

The *ABCB1* gene polymorphisms have been

associated with altered P-gp expression and activity, which impacted opioid pharmacokinetics (Ren *et al.* 2015, Baber *et al.* 2016). P-gp in the blood-brain barrier blocks the entry of opioids into brain (Sanchez-Covarrubias *et al.* 2014). Our study describes only the trend towards higher doses of rescue analgesic medication and higher opioid-induced adverse effects in patients carrying *ABCB1* variants compared to wild-type homozygous subjects. However, the differences are not significant.

Various factors may contribute to individual differences in the analgesic effect of sufentanil, such as operation type, age, gender and psychological factors (Sarton *et al.* 2000, Cepeda and Carr 2003). In our study, women were more difficult to treat that required higher doses of rescue analgesic medication and suffered more opioid-induced adverse effects. In addition, no significant impact was observed for age in our results.

There are some limitations of the current study. First, the overall number of patients included in this trial is rather limited. Second, we have no variant homozygous genotype groups for *OPRM1* (rs1799971). However, the results describe a higher consumption of rescue medication in heterozygotes, suggesting a lower efficacy of sufentanil. Third, we did not monitor sufentanil plasma concentrations in order to determine the drug pharmacokinetics and possible pharmacokinetic factors that could influence its efficacy. Therefore, we conclude that the identification of *OPRM1* (rs1799971) polymorphism may provide valuable information on the individual analgesic doses of sufentanil required or help to decide on the need for combination analgesic treatment combining sufentanil with non-opioid medication to achieve satisfactory pain control.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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Abbreviations

ATC/DDD – anatomical therapeutic chemical/defined daily doses, DDD – defined daily doses, IQR – interquartile range, PONV – postoperative nausea and vomiting, SD – standard deviation, SNP – single nucleotide polymorphism, SPID – sum of pain intensity differences, VAS – visual analogue scale.

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