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Correlations of analgesic dosage of morphine with SLC6A4 gene polymorphisms in patients with lung cancer

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Abstract. – OBJECTIVE: To investigate the correlations of analgesic dosage of morphine with solute carrier family 6 member 4 (SLC6A4) gene polymorphisms in patients with lung cancer.

PATIENTS AND METHODS: A total of 200 lung cancer patients without cancer pain were selected as painless group, and another 200 lung cancer patients with cancer pain as cancer pain group. Visual Analogue Scale (VAS) was applied to grade the pain, the patients in cancer pain group were treated with morphine, and the dosage of morphine within 24 h was recorded. Then, the genomic deoxyribonucleic acid (DNA) was extracted from the peripheral blood of the research subjects, and the polymorphisms rs1042173 and rs7224199 of SLC6A4 gene were detected.

RESULTS: There was a difference in the genotype distribution of SLC6A4 gene rs7224199 between painless group and cancer pain group (p=0.004), and the frequency of GG genotype was remarkably higher in cancer pain group [75 (0.375)]. The frequency of heterozygous model AC of rs1042173 and recessive model GT + TT of rs7224199 in cancer pain group was evidently lower than that in painless group (p=0.048, p=0.043). Besides, the lung cancer patients in cancer pain group had markedly lower frequency of AG haplotype (p=0.000), but notably higher frequency of AT (p=0.000) and CG (p=0.000) haplotypes of SLC6A4 gene rs1042173 and rs7224199 than those in painless group. No significant differences in genotypes of SLC6A4 gene rs1042173 (p=0.241) and rs7224199 (p=0.316) were detected among the degrees of cancer pain in cancer pain group. The analgesic dosage of morphine for the lung cancer patients was prominently correlated with the genotypes of SLC6A4 gene rs1042173 in cancer pain group. Moreover, in cancer pain group, there were significant differences in the dosage within 24 h (p=0.025), at 24 h after weight correction (p=0.001) and at 24 h after correction of weight and body surface area (p=0.000) among the genotypes, and the morphine dosage for the patients with CC genotype was significantly lower. Furthermore, the morphine dosage within 24 h (p=0.047), at 24 h after weight correction (p=0.042) and at 24 h after correction of weight and body surface area (p=0.031) were distinctly associated with the haplotypes of SLC6A4 gene in cancer pain group, of which the patients with CT haplotype were administered with a remarkably lower morphine dosage.

CONCLUSIONS: The morphine dosage for analgesia has significant correlations with SLC6A4 gene polymorphisms in patients with lung cancer.

Key Words:
Lung cancer, Morphine, SLC6A4, Polymorphisms.

Introduction

Lung cancer, one of the malignant tumors with the highest incidence rate in the world, threatens the lives of millions of patients[1,2]. The pathogeny of lung cancer is correlated with various factors[3], whose foundation is cell malignant transformation, hyperplasia of cancer tissues, and compression of normal tissues caused by external stimuli and *in vivo* factors. Meanwhile, dry cough, pain, and other symptoms may occur[4]. The cancer-induced pain of the lung cancer patients directly affects the normal functions in the body and their psychological reactions to disease, such as desire for survival. Clinically, the patients with malignant tumors intolerant of cancer pain are often treated with morphine as a symptomatic therapy, while the varying doses of the drug will directly result in differences in efficacy and adverse drug reactions[5,6]. Using morphine at a dose as low as possible can not only eliminate the pain of the lung cancer patients, but also reduce adverse reactions and drug dependence.

Gene polymorphisms influence the occurrence of many diseases, including chronic obstructive

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pulmonary disease[7], hypertension[8], and peptic ulcer[9], probably by changing their own gene expressions or affecting the expressions of other genes. Among them, the polymorphisms of some genes such as MDM2[10] and XPC[11] have effects on the susceptibility to lung cancer. It can be seen that the gene polymorphisms may play vital roles in the occurrence of lung cancer. Besides, the gene polymorphisms of solute carrier family 6 member 4 (SLC6A4), a 5-hydroxytryptamine (5-HT) transporter, are possibly associated with the occurrence of pain triggered by lung cancer and may influence the dosage of analgesic drugs.

Therefore, the polymorphisms rs1042173 and rs7224199 of SLC6A4 gene were compared between the lung cancer patients with pain and those without pain, the differences in haplotypes were analyzed, and the correlations of morphine dosage with polymorphisms rs1042173 and rs7224199 of SLC6A4 gene in the patients with cancer pain were observed in this paper, so as to explore the potential impacts of gene polymorphisms on the dosage of analgesics.

Patients and Methods

Patients

A total of 400 lung cancer patients treated in our hospital from 2017 to date were selected as the research subjects. Those with cancer pain were enrolled into cancer pain group, and those without cancer pain were enrolled into painless group. The patients with non-cancer pain, such as pain responses caused by trauma, infection or other diseases, were excluded. Such clinical data as name, gender, hospital admission ID number, medical history, and history of drug allergy of all the subjects were collected. Among them, the average age was (56.12±5.12) years old in painless group and (58.29±6.37) years old in cancer pain group. The differences in age, body height, weight, body surface area, and other general data were not statistically significant. This investigation was approved by the Ethics Committee of First Affiliated Hospital of Jiamusi University. Signed written informed consents were obtained from all participants before the study.

Sample Collection and Processing

About 8 mL of peripheral blood was drawn from every patient in both painless group and cancer pain group by nurses. After that, the samples were put in a centrifuge within 2 h by experimental personnel for centrifugation at 3,000 rpm for 5 min. Subsequently, the nucleated cells in the middle layer were isolated and placed into new centrifuge tubes to extract the genomic deoxyribonucleic acids (DNAs).

Extraction of Genomic DNAs

The genomic DNAs in the peripheral blood of patients in painless group and cancer pain group were extracted using blood genomic DNA extraction kit (Tiangen, Beijing, China). All the steps were performed in strict accordance with the standards in the kit. Specifically, 200 μL of proteinase K solution was added into the centrifuge tubes according to the sample volume, and nucleated cells in the middle layer of the peripheral blood were added with 1-2 mL of buffer solution GE, mixed in a vortex oscillator for 1 min and placed at 65°C for 10 min. Then, the samples were mixed with 2 mL of absolute alcohol and transferred into an adsorption column, where 2 mL of buffer solution was added for centrifugation at 3,500 rpm for 1 min. Later, the buffer solution was added into the adsorption column and centrifuged. After 200 μL of elution buffer was added into the adsorption column, the solution obtained was the genomic DNA of the research subjects. The DNA samples would be favorable if the optical density (OD) $_{260}$/ OD_{280} value was 1.8-2.0.

Polymerase Chain Reaction (PCR) Amplification and Analysis of SLC6A4 Gene Polymorphisms

The regions of polymorphisms rs1042173 and rs7224199 of SLC6A4 gene were amplified using a PCR instrument with a total reaction system of 25 μL (1 μL of each primer, 0.5 μL of template DNA, 12.5 μL of Taq polymerase and 9.5 μL of dH_2O). PCR conditions: 95°C for 5 min, (95°C for 30 s and 58°C for 40 s) × 40 cycles, 72°C for 5 min and incubation at 4°C. The primers of polymorphisms are as follows: rs1042173: forward (5'→3'): TGCTCAAGTTTGGCAGGAAC (Tm value = 62.1) and reverse (5'→3'): GCTCCACGTAGCCGTTGTT (Tm value = 61.1), and rs7224199: forward (5'→3'): GACCTCTTCAGCAAGTCCGAC (Tm value = 59.8) and reverse (5'→3'): CACACCGGGTTCAGGTTGT (Tm value = 59.3). The PCR products were sent to Sangon Biotech (Shanghai, China) for sequencing, and the polymorphisms rs1042173 and rs7224199 of SLC6A4 gene in painless group and cancer pain group were analyzed.

Table I. Allele distribution of SLC6A4 gene rs1042173 and rs7224199 in painless group and cancer pain group.

Polymorphism	Allele	Painless group	Cancer pain group	OR	95% CI	χ^2	*p*-value
rs1042173	A	198 (0.495)	214 (0.535)	1.17	0.88-1.54	1.28	0.257
	C	202 (0.505)	186 (0.465)				
rs7224199	G	208 (0.520)	222 (0.555)	1.15	0.87-1.52	0.98	0.321
	T	192 (0.480)	178 (0.445)				

Morphine Doses and Visual Analogue Scale (VAS) Scores of Patients in Cancer Pain Group

The severity of pain was evaluated for all the patients in cancer pain group using the VAS scores, including mild pain (1-3 points), moderate pain (4-6 points), and severe pain (7-10 points). Morphine was administered as an analgesic drug to the patients with pain, supplemented with general treatment, and support therapy. The dosage of morphine was recorded within 24 h after the pain occurred.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 23.0 software (IBM, Armonk, NY, USA) was employed for statistical analysis. The *t*-test was used for analyzing measurement data. Differences between two groups were analyzed by using the Student's *t*-test. Comparisons among multiple groups were done using One-way ANOVA test followed by Post-Hoc Test (Least Significant Difference). Haplotypes were analyzed online using the SHEsis website, and $p<0.05$ suggested statistically significant differences.

Results

Allele Distribution of SLC6A4 Gene rs1042173 and rs7224199 In Painless Group and Cancer Pain Group

The allele distribution of SLC6A4 gene rs1042173 and rs7224199 in painless group and cancer pain group is shown in Table I. No significant differences in allele distribution of rs1042173 (p=0.257) and rs7224199 (p=0.321) of SLC6A4 gene were detected between painless group and cancer pain group.

Genotype Distribution of SLC6A4 Gene rs1042173 and rs7224199 in Painless Group and Cancer Pain Group

According to the genotype distribution of SLC6A4 gene rs1042173 and rs7224199 in painless group and cancer pain group (Table II), there were no significant differences in the genotypes of SLC6A4 gene rs1042173 (p=0.080), but difference in the genotypes of rs7224199 was observed between painless group and cancer pain group (p=0.004), and the frequency of GG genotype was remarkably higher in cancer pain group [75 (0.375)].

Analysis of Polymorphisms rs1042173 and rs7224199 of SLC6A4 Gene and Model Establishment in Painless Group and Cancer Pain Group

The analysis of polymorphisms rs1042173 and rs7224199 of SLC6A4 gene in painless group and cancer pain group indicated that the frequency of heterozygous model AC of rs1042173 and recessive model GT + TT of rs7224199 in cancer pain group was evidently lower than that in painless group (p=0.048, p=0.043) (Table III).

Analysis of Haplotypes of SLC6A4 Gene in Painless Group and Cancer Pain Group

As shown in Table IV, the analysis of haplotypes of SLC6A4 gene in painless group and can-

Table II. Genotype distribution of rs1042173 and rs7224199 of SLC6A4 gene in painless group and cancer pain group.

Polymorphism	Allele	Painless group	Cancer pain group	OR	95% CI	χ^2	*p*-value
rs1042173	AA	49 (0.245)	67 (0.335)	1.12	0.98-1.23	5.05	0.080
	AC	100 (0.500)	80 (0.400)				
	CC	51 (0.255)	53 (0.265)				
rs7224199	GG	52 (0.260)	75 (0.375)	1.43	1.04-1.65	10.81	0.004
	GT	104 (0.520)	72 (0.360)				
	TT	44 (0.220)	53 (0.265)				

Table III. Analysis of polymorphisms rs1042173 and rs7224199 of SLC6A4 gene and model establishment in painless group and cancer pain group.

	Polymorphism	Genotype	Painless group	Cancer pain group	χ^2	*p*-value
Dominant model	rs1042173	AA + AC	149 (0.745)	147 (0.735)	0.24	0.871
		CC	51 (0.255)	53 (0.265)		
	rs7224199	GG + GT	156 (0.780)	147 (0.735)	0.33	0.853
		TT	44 (0.220)	53 (0.265)		
Recessive model	rs1042173	AA	49 (0.245)	67 (0.335)	2.45	0.218
		AC + CC	151 (0.755)	133 (0.665)		
	rs7224199	GG	52 (0.260)	75 (0.375)	4.31	0.043
		GT + TT	148 (0.740)	125 (0.625)		
Heterozygous model	rs1042173	AA	49 (0.245)	67 (0.335)	4.22	0.048
		AC	100 (0.500)	80 (0.400)		
	rs7224199	GG	52 (0.260)	75 (0.375)	4.12	0.057
		GT	104 (0.520)	72 (0.360)		
Homozygous model	rs1042173	AA	49 (0.245)	67 (0.335)	3.25	0.136
		CC	51 (0.255)	53 (0.265)		
	rs7224199	GG	52 (0.260)	75 (0.375)	3.17	0.156
		TT	44 (0.220)	53 (0.265)		

cer pain group manifested that the lung cancer patients in cancer pain group had markedly lower frequency of AG haplotype (p=0.000) but notably higher frequency of AT (p=0.000) and CG (p=0.000) haplotypes of SLC6A4 gene rs1042173 and rs7224199 than those in painless group.

Correlations of Different Pain Degrees With Genotypes of SLC6A4 Gene rs1042173 and rs7224199 in Cancer Pain Group

The correlations of different pain degrees with genotypes of rs1042173 and rs7224199 of SLC6A4 gene in cancer pain group are shown in Table V. No significant differences in genotypes of SLC6A4 gene rs1042173 (p=0.241) and rs7224199 (p=0.316) were detected among the degrees of cancer pain in cancer pain group.

Correlations of Analgesic Dosage of Morphine With Genotypes of SLC6A4 Gene rs1042173 and rs7224199 of Lung Cancer Patients in Cancer Pain Group

Based on the correlations of analgesic dosage of morphine with genotypes of SLC6A4 gene rs1042173 and rs7224199 of lung cancer patients in cancer pain group (Table VI), the analgesic dosage of morphine for the lung cancer patients was prominently correlated with the genotypes of SLC6A4 gene rs1042173 in cancer pain group. Herein, there were significant differences in the dosage within 24 h (p=0.025), at 24 h after weight correction (p=0.001) and at 24 h after correction of weight and body surface area (p=0.000) among the genotypes in cancer pain group, while the morphine dosage for the patients with CC genotype was significantly lower.

Correlations of Analgesic Dosage of Morphine With Haplotypes of SLC6A4 Gene rs1042173 and rs7224199 of Lung Cancer Patients in Cancer Pain Group

The correlations of analgesic dosage of morphine with genotypes of SLC6A4 gene rs1042173 and rs7224199 of lung cancer patients in cancer pain group are manifested in Table VII. It was revealed that the morphine dosage within 24 h (p=0.047), at 24 h after weight correction (p=0.042) and at 24 h after correction of weight and body surface area (p=0.031) were distinctly

Table IV. Analysis of haplotypes of SLC6A4 gene in painless group and cancer pain group.

Haplotype	Painless group	Cancer pain group	OR	95% CI	χ^2	*p*-value
AG	154 (0.387)	94 (0.237)	2.03	1.497-2.760	20.96	0.000
AT	59 (0.148)	104 (0.258)	0.51	0.350-0.713	14.947	0.000
CG	68 (0.168)	113 (0.283)	0.52	0.364-0.719	15.134	0.000
CT	119 (0.297)	89 (0.222)	1.48	1.076-2.036	3.852	0.086

Table V. Correlations of different pain degrees with genotypes of rs1042173 and rs7224199 of SLC6A4 gene in cancer pain group (n).

Polymorphism	Genotype	No.	Mild pain	Moderate pain	Severe pain	*p*-value
rs1042173	AA	67	21	23	23	0.241
	AC	80	31	28	21	
	CC	53	22	18	13	
rs7224199	GG	75	24	31	20	0.316
	GT	72	26	24	22	
	TT	53	24	14	15	

associated with the haplotypes of SLC6A4 gene of the lung cancer patients in cancer pain group, and the patients with CT haplotype had a remarkably lower morphine dosage.

Discussion

The occurrence of cancer pain in the case of lung cancer greatly affects the quality of life of tumor patients and causes patient's non-compliance with treatments[12,13]. This influence may be related to disordered expressions of molecules in cancer tissues, which leads to excessive intake or constant accumulation of pain-sensitive substances in cells and continuously aggravates the pain responses[14].

As a 5-HT transporter on the cell membrane, SLC6A4 mainly transports pain-sensitive substances into cells[15,16], whose polymorphisms have been proven to be associated with a variety of diseases, such as irritable bowel syndrome[17], obsessive-compulsive disorder[18], and polycystic ovary syndrome[19]. SLC6A4 primarily influences the perception level of organisms to pain, so as to produce varying pain senses and affect their mental status[20]. In this research it was found that the differences in allele distribution of rs1042173 (p=0.257) and rs7224199 (p=0.321) of SLC6A4 gene were not significant between painless group and cancer pain group. However, the genotype distribution of SLC6A4 gene rs7224199 had a difference between painless group and cancer pain group (p=0.004), and cancer pain group manifested remarkably increased frequency of GG genotype [75 (0.375)], suggesting that the patients with GG genotype of SLC6A4 gene rs7224199 are more vulnerable to cancer pain, which may bring the application of morphine forward.

The polymorphisms rs1042173 and rs7224199 of SLC6A4 gene were analyzed, and the models were established and integrated. It was discovered that the frequency of heterozygous model AC of rs1042173 and recessive model GT + TT of rs7224199 in cancer pain group declined evidently compared with that in painless group (p=0.048, p=0.043), implying that the polymorphisms rs1042173 and rs7224199 of SLC6A4 gene probably influence the occurrence of lung cancer pain together through genotype combinations of each polymorphism, and that the heterozygous model

Table VI. Correlations of analgesic dosage of morphine with genotypes of SLC6A4 gene rs1042173 and rs7224199 of lung cancer patients in cancer pain group.

					Dosage at 24 h after weight correction (mg/24 h)		Dosage at 24 h after correction of weight and body surface area (mg/24 h)	
			Dosage within 24					
Polymorphism	Genotype	No.	Mean	*p*-value	Mean	*p*-value	Mean	*p*-value
rs1042173	AA	67	82.34	0.025	1.51	0.001	0.84	0.000
	AC	80	85.15		1.44		0.82	
	CC	53	62.15		1.21		0.72	
rs7224199	GG	75	73.51	0.125	1.32	0.106	0.82	0.115
	GT	72	81.38		1.42		0.84	
	TT	53	78.34		1.35		0.79	

Table VII. Correlations of analgesic dosage of morphine with haplotypes of SLC6A4 gene rs1042173 and rs7224199 of lung cancer patients in cancer pain group.

Haplotype	No.	Dosage at 24 h after weight correction (mg/24 h)	Dosage at 24 h after weight correction (mg/24 h)	Dosage at 24 h after correction of weight and body surface area (mg/24 h)
AG	94	86.13	1.64	0.86
AT	104	81.36	1.42	0.75
CG	113	78.37	1.38	0.63
CT	89	75.87	1.27	0.57
p-value		0.047	0.042	0.031

of rs1042173 and recessive model of rs7224199 can prominently reduce the probability of pain in the lung cancer patients. Meanwhile, the haplotypes in the two groups of patients were analyzed by combining SLC6A4 gene rs1042173 with rs7224199. It was manifested that the frequency of AG haplotype was markedly decreased (p=0.000), but that of AT (p=0.000) and CG (p=0.000) haplotypes of SLC6A4 gene rs1042173 and rs7224199 was increased notably in the lung cancer patients in cancer pain group in comparison with those in painless group, illustrating that diversified haplotypes of SLC6A4 gene may have evident impacts on the occurrence of pain in lung cancer patients. All those results jointly elaborate that the influences of SLC6A4 gene polymorphisms on the pain in lung cancer patients may be attributed to the combined actions of multiple genotypes at the same locus or of two polymorphisms, instead of merely differences in a single genotype at one locus.

The pain of the patients in cancer pain group was graded by means of VAS scores, and the results showed that there were no significant differences in the genotypes of SLC6A4 gene rs1042173 (p=0.241) and rs7224199 (p=0.316) among the degrees of cancer pain in cancer pain group, thereby guaranteeing the validity for subsequent comparisons of morphine dosage among different genotypes and serving as a premise of subsequent statistical analyses. Based on 24-h analysis of the patients with cancer pain, the analgesic dosage of morphine for the lung cancer patients had remarkable correlations with the genotypes of SLC6A4 gene rs1042173 in cancer pain group. In cancer pain group, the differences in the dosage within 24 h (p=0.025), at 24 h after weight correction (p=0.001) and at 24 h after correction of weight and body surface area (p=0.000) were significant among the genotypes, while the morphine dosage for the patients with CC genotype was significantly lower, elucidating that the patients with cancer pain who have CC genotype of SLC6A4 gene rs1042173 are more sensitive to morphine, and that a relatively low analgesic dosage can produce preferable analgesic effects. In the meantime, the morphine dosage within 24 h (p=0.047), at 24 h after weight correction (p=0.042) and at 24 h after correction of weight and body surface area (p=0.031) exhibited distinct associations with the haplotypes of SLC6A4 gene of the lung cancer patients in cancer pain group, of which the morphine dosage was markedly lower for the patients with CT haplotype. The aforementioned findings demonstrate that the polymorphisms (rs1042173 and rs7224199) and haplotypes of SLC6A4 gene indeed have influences on the sensitivity of lung cancer patients to morphine. In clinical work, the morphine dosage can be appropriately adjusted according to the polymorphisms rs1042173 and rs7224199 of SLC6A4 gene in the lung cancer patients, so as to obtain the best efficacy *via* the lowest dose and reduce adverse drug reactions and addiction to morphine as much as possible. Limitations still exist in our study. In the current study, we only analyzed the difference of SLC6A4 gene polymorphism between painless group and pain group among lung cancer patients. We did not perform the sub-group analysis among the pain group patients. In our future research, we plan to adopt the questionnaire to divide pain group patients into several groups according to different grades of pain and then perform the subgroup analysis. Based on these results, we can analyze the relationship between different pain grades and SLC6A4 gene polymorphism in lung cancer patients.

Conclusions

In short, the morphine dosage for analgesia is markedly associated with SLC6A4 gene polymorphisms in patients with lung cancer.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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