Taiwanese Journal of Obstetrics & Gynecology 57 (2018) 89–94

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Pharmacogenetic study of pruritus induced by epidural morphine for post cesarean section analgesia

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ARTICLE INFO

Article history:
Accepted 28 December 2016

Keywords:
Morphine
Neuroaxial
Phenotype
Pruritis
Single nucleotide polymorphisms (SNPs)

ABSTRACT

Objective: The mechanism through which neuroaxial morphine causes pruritus has not been elucidated clearly and thoroughly.
Materials and methods: a study in 129 female parturients was conducted to investigate the effect of 14 single nucleotide polymorphisms (SNPs) on phenotype (pruritus) induced by neuroaxial (including intrathecal or epidural) morphine for cesarean section. Clinical phenotype, subjective complaints and objective observations were recorded. DNA from blood samples was used to record the SNPs. Eleven SNPs were then analyzed further.
Results: no significant association with the presence of phenotype (pruritus) versus genotype was observed (all p-values > 0.05). No significant association with severity of phenotype versus genotype of the 11 SNPs was observed except for unadjusted data for rs2737703. There was no significant difference between severity or incidence of IVPCA morphine-induced nausea and vomiting and genotype (11 SNPs).
Conclusion: our results showed no association between SNPs of any of the genes studied with neuroaxial morphine inducing pruritus.
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Introduction

Epidural morphine injection twice per day is widely used for post-cesarean pain management due to its ability to provide slow onset and long-duration pain relief in our hospital [1]; however, the high incidence of associated side effects after neuroaxial analgesia may limit its clinical application [2,3]. The most common side effect of intrathecal and epidural opioids is pruritus [4], which can be accompanied by some other less common side effects such as nausea, vomiting, urinary retention and respiration depression [4,5]. The incidence of pruritus (3–7 h after morphine injection) varies from 62% to 92% [6,7]. The symptoms typically spread rostrally from the site of administration to the trunk, and subsequently are more likely to be localized to the face, neck or upper thorax [8]. Inter-parturient variability, including ethnicity, age, gender and other factors might be associated with the difference in the incidence and severity of those side effects, however, genetic factors are thought to have an influence as well.

A number of studies have investigated the effect on pain relief of single nucleotide polymorphisms (SNPs) in genes involved in morphine's metabolism, distribution, binding, and cellular action [9–12]. However only very few studies have investigated how morphine-induced pruritus is affected by SNPs in these genes [10,12,13]. Previous studies from our laboratory and others investigating pruritus induced by neuroaxial morphine have been focused on the treatment and prevention of this condition [14–16]. Therefore, in this study, we examined, in a population of Taiwanese pregnant women receiving epidural morphine for post cesarean section analgesia, the all the reported SNPs which are associated with the complications of morphine, including SNPs in genes for phase I and phase II metabolic enzymes, ABC binding cassette drug transporters, κ and δ opioid receptors, and ion channels implicated

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https://doi.org/10.1016/j.tjog.2017.12.015
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in the post-receptor action of morphine. We hypothesized that examining, in a single defined population, SNPs from genes in the pathway from morphine's metabolism and distribution to its later cellular action would enable us to discover which step in this pathway had the biggest influence on neuraxial morphine-induced pruritus.

Materials & methods

Parturient profile and anesthetic procedure

This study was approved by the Ethic Institute Review Board of the National Taiwan University Hospital and after obtaining written informed consent from all participants and was in accordance with the most recent Declaration of Helsinki. This was a population-based, prospective observational study, with a blinded data analysis. A total of 217 American Society of Anesthesiologists physical status I and II, Taiwanese women who presented for elective cesarean delivery at 37 weeks of gestation and received epidural morphine for post cesarean pain control were recruited into this study in the 12-month period from 1 August 2007 to 31 July 2008. This sample size was chosen in order to achieve a power 480% so as to detect a 10% difference in genotype frequency among groups. All selected women could comprehend and describe the pain score, and the exclusion criteria were the following: contraindications for epidural morphine, complaint of pruritus before the cesarean section, coexisting skin disorder, any systemic disease associated with pruritus and the history of allergy to opioids. All of the study subjects, attending anesthesiologists and the well-trained investigator were unaware of the parturients' genotype at the time of surgery because genotyping was determined post hoc in the laboratory. All of the parturients received combined spinal with epidural anesthesia for the cesarean section. Under the right lateral vertebral body, spinal anesthesia was induced with a 27G Whitacre spinal needle at the L3–L4 level with 9–12 mg hyperbaric 0.5% bupivacaine (Marcaine; Astra Zeneca, Sodertalje, Sweden) to achieve an acceptable dermatome level of anesthesia for the cesarean section. The epidural was conducted with a 16G Tuohy needle and an epidural catheter was inserted simultaneously. In addition, a 3 ml test dose (2% xylocaine with 1: 200,000 epinephrine) was added to rule out a false-positive epidural space insertion. After the fetus was delivered, the first analgesic dose of morphine (2 mg in 10 ml sterile normal saline) was injected via an epidural catheter.

Post-C/S pain management, assessment and data collection

After cesarean section, the post-cesarean analgesic treatment regimen was a twice-a-day (08:00 and 20:00 h) bolus of morphine (2 mg in 10 ml sterile normal saline) through an epidural catheter. A trained investigator interviewed the parturient and all data were collected after three analgesic doses (6 mg) during the first 24 h post-operatively. If the parturients still felt wound pain (which was a score above 3 cm on a 10 cm VAS pain scale) even after 6 mg of epidural morphine, those cases were excluded from the study and received parturient-controlled analgesia with intravenous morphine as an alternative. Thus, all of the participants in this study had reduced pain scores after intrathecal morphine, and no other supplemental analgesics were administered. Data related to parturients' age, weight, height, history of previous cesarean section, ASA class as well as wound pain score were collected. Central type pruritus was defined as a sensation that induced a desire to scratch the skin over the trigeminal area. We recorded only typical episodes of central type pruritus; that is to say, itching sensations over the incision wound or abdominal area were not identified as central type pruritus. We used the Itching Severity Scale (ISS 0–4) to evaluate the intensity of the central type pruritus induced by neuroaxial morphine, which utilized the following scoring method: 0 = none; 1 = mild, not annoying or troublesome; 2 = moderate, annoying and troublesome, may interfere with normal daily activity and sleep; 3 = severe, very annoying and troublesome, substantially interfering with sleep and daily activities; 4 = very severe, warrants medication. Furthermore, we divided the incidence of pruritus into non-significant (ISS 0–1) and significant groups (ISS 2–4). The following side effects were also recorded by subjective complaint or objective observation: nausea on a severity scale of 0–3; vomiting on a severity scale of 0–3; and urinary retention. Women who had severe nausea or vomiting were treated with prochlorperazine (5 mg), and those with severe pruritus were treated with diphenhydramine HCL (4 mg).

Laboratory analysis of SNPs

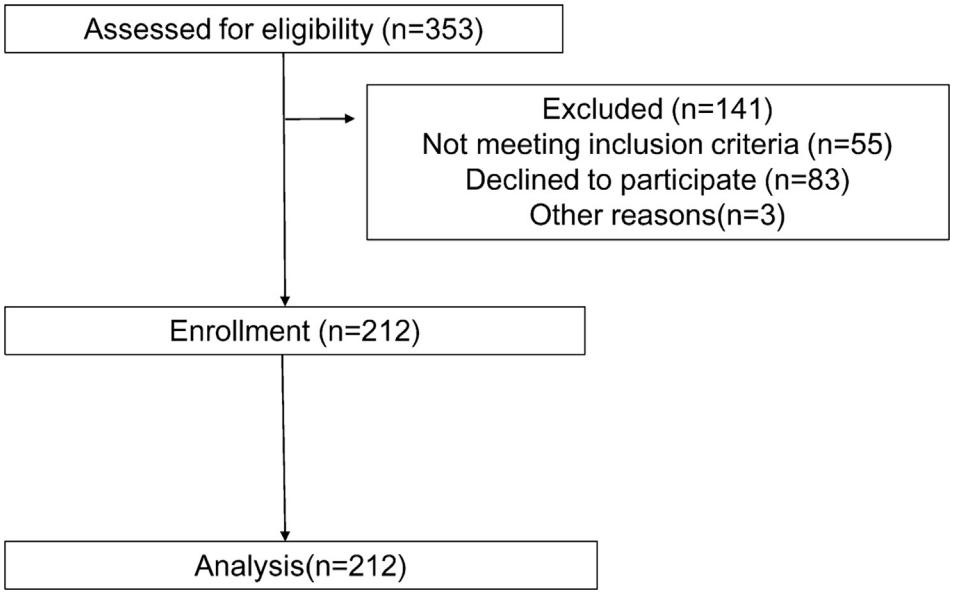
Fourteen SNPs were investigated (Table 1). To analyze the different genotypes of the 14 SNPs, DNA was extracted from collected blood samples; amplified by the GeneAmp ® PCR System 9700, and sequenced with the ABI PRISM ® 7900 HT Sequence Detection System.

Statistical analysis

Phenotype was defined according to two symptoms, nausea and vomiting, which was divided into two groups (i.e., no symptoms and at least one symptom). The Hardy-Weinberg equilibrium test was performed by using SHEsis (17; *Shi YY, He L. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. Cell Res 2005;15:97-98*). One SNP was excluded from subsequent analysis because it contained only the CC genotype. And two SNPs with minor allele frequency less than 5% were also excluded from subsequent analysis. Age, height, weight, BMI were presented by mean and standard deviation, the independent t-test was performed to evaluate the differences between the two phenotype groups. Other categorical data were presented by number and percentage, Fisher's exact test was performed to evaluate the association between the phenotype and the categorical data (prescription, wound pain, dizziness, drowsiness, genotypes of SNPs). The magnitude of association between SNPs and phenotype was generated by logistic regression and was presented with odds ratio (OR) and its 95% confidence interval (95% CI). In order to control for potential confounding effects, multiple logistic regression was performed with adjustment for age, body weight, prescription, type of surgery and dose of morphine. A two-tailed p-value less than 0.05 was considered statistically significant. Data were analyzed by using SPSS 15.0 statistics software (SPSS Inc, Chicago, Illinois, USA).

Table 1
SNPs investigated.

Gene Symbol	Name	Polymorphisms
Metabolism		
CYP3A4	cytochrome P450	rs2242480, rs28371759
CYP2D6	cytochrome P450	rs3892097, rs28365063
UGT2B7	UPD-glucourasyltransferase	rs7439366, rs7439152
Distribution		
ABCB1	ATP-binding cassette transporter	rs1045642
ABCC3	ATP-binding cassette transporter	rs2277624
Receptor		
OPRK1	κ-opioid receptor	rs1051660
OPRD1	δ-opioid receptor	rs1042114
Ion channel		
KCNJ6	G-protein activated K+ channel	rs2070995
KCNJ9	G-protein activated K+ channel	rs2737703



Results

Two hundred and twelve subjects were enrolled in the study and 14 SNPs investigated. Table 1 shows the genes containing each individual SNP and the function of the protein encoded by the gene. CYP3A4 and CYP2D6 encode phase I metabolic proteins; UGT2B7 encodes a phase II metabolic protein; ABC1 and ABC2 are membrane transport proteins; OPRK1 and OPRD1 are opioid receptors; KCNJ6, KCNJ9, and CACNA1E are ion channels involved in the downstream action of the receptor. Hardy-Weinberg equilibrium test has been completed for all the allele frequency and genotype distribution of the 14 SNPs, without any significant difference between 2 groups. No significant association of the presence of symptom pruritus versus genotypes of the 14 SNPs were observed (all p-values > 0.05, Table 2). Also no significant association of the severity of symptom pruritus versus genotypes of the 14 SNPs were observed (all p-values > 0.05, Table 3 and Table 4).

Table 2
Associations of the presence of symptom pruritus versus genotypes of the 14 SNPs.

		Non-pruritus (n = 100)	Pruritus (n = 112)	P-value
rs3892097	CC	100 (100.0)	110 (98.2)	0.499
	CT	0 (0.0)	2 (1.8)	
rs1065852	AA	41 (41.4)	36 (32.4)	0.337
	AG	34 (34.3)	48 (43.2)	
	GG	24 (24.2)	27 (24.3)	
rs2242480	CC	55 (55.0)	62 (55.4)	0.220
	CT	37 (37.0)	47 (42.0)	
	TT	8 (8.0)	3 (2.7)	
rs28371759	AA	98 (98.0)	108 (96.4)	0.686
	AG	2 (2.0)	4 (3.6)	
rs2277624	CC	60 (60.0)	63 (56.3)	0.568
	CT	35 (35.0)	39 (34.8)	
	TT	5 (5.0)	10 (8.9)	
rs1045642	AA	8 (8.0)	10 (8.9)	0.915
	AG	51 (51.0)	54 (48.2)	
	GG	41 (41.0)	48 (42.9)	
rs28365063	AA	53 (53.0)	70 (62.5)	0.356
	AG	43 (43.0)	38 (33.9)	
	GG	4 (4.0)	4 (3.6)	
rs7439152	GG	4 (4.0)	10 (8.9)	0.319
	GT	35 (35.0)	41 (36.6)	
	TT	61 (61.0)	61 (54.5)	
rs644796	CC	6 (6.0)	5 (4.5)	0.749
	CT	29 (29.0)	37 (33.0)	
	TT	65 (65.0)	70 (62.5)	
rs2737703	CC	55 (55.0)	58 (51.8)	0.580
	CT	35 (35.0)	46 (41.1)	
	TT	10 (10.0)	8 (7.1)	
rs2070995	CC	37 (37.0)	44 (39.3)	0.945
	CT	50 (50.0)	53 (47.3)	
	TT	13 (13.0)	15 (13.4)	
rs1042114	GT	0 (0.0)	1 (0.9)	1.000
	TT	100 (100.0)	111 (99.1)	
rs1051660	AA	5 (5.0)	1 (0.9)	0.239
	AC	28 (28.0)	32 (28.6)	
	CC	67 (67.0)	79 (70.5)	
rs7439366	CC	61 (61.0)	61 (54.5)	0.319
	CT	35 (35.0)	41 (36.6)	
	TT	4 (4.0)	10 (8.9)	

Data are presented by number and percentage.

Discussion

The most common side effect of intrathecal and epidural opioids is pruritus. It may be generalized but is more likely to be localized to the face, neck, or upper thorax. The localization of pruritus may vary with the opioid used. In one study, epidural fentanyl caused segmental pruritus, whereas epidural morphine was associated with generalized pruritus [17]. Pruritus usually occurs within a few hours of injection, may be more prevalent when the intrathecal route is used, and is less prevalent following subsequent doses [18]. The reported incidence of itching following intraspinal opioids is quite variable. Figures ranging from 0% to 100% have been published in the literature. The probable reason is that, if not asked specifically, most parturients do not complain about this complication because of its mild nature. In large series, the incidence of pruritus after epidural administration of up to 5 mg morphine is less than 10%, and the risk of severe, distressing itching is approximately 1% [19].

Pathophysiology

The mechanism by which opioids cause pruritus is unclear. Many substances induce pruritus by causing a release of histamine

Table 3
Associations of the severity of the symptom pruritus versus genotypes of the 14 SNPs.

		Non-pruritus (n = 100)	Non-significant pruritus (n = 97)	Significant pruritus (n = 15)	P-value
rs3892097	CC	100 (100.0)	95 (97.9)	15 (100.0)	0.345
	CT	0 (0.0)	2 (2.1)	0 (0.0)	
rs1065852	AA	41 (41.4)	33 (34.4)	3 (20.0)	0.480
	AG	34 (34.3)	40 (41.7)	8 (53.3)	
	GG	24 (24.2)	23 (24.0)	4 (26.7)	
rs2242480	CC	55 (55.0)	51 (52.6)	11 (73.3)	0.311
	CT	37 (37.0)	43 (44.3)	4 (26.7)	
	TT	8 (8.0)	3 (3.1)	0 (0.0)	
rs28371759	AA	98 (98.0)	94 (96.9)	14 (93.3)	0.399
	AG	2 (2.0)	3 (3.1)	1 (6.7)	
rs2277624	CC	60 (60.0)	54 (55.7)	9 (60.0)	0.593
	CT	35 (35.0)	33 (34.0)	6 (40.0)	
	TT	5 (5.0)	10 (10.3)	0 (0.0)	
rs1045642	AA	8 (8.0)	8 (8.2)	2 (13.3)	0.932
	AG	51 (51.0)	47 (48.5)	7 (46.7)	
	GG	41 (41.0)	42 (43.3)	6 (40.0)	
rs28365063	AA	53 (53.0)	61 (62.9)	9 (60.0)	0.649
	AG	43 (43.0)	32 (33.0)	6 (40.0)	
	GG	4 (4.0)	4 (4.1)	0 (0.0)	
rs7439152	GG	4 (4.0)	9 (9.3)	1 (6.7)	0.311
	GT	35 (35.0)	33 (34.0)	8 (53.3)	
	TT	61 (61.0)	55 (56.7)	6 (40.0)	
rs644796	CC	6 (6.0)	5 (5.2)	0 (0.0)	0.911
	CT	29 (29.0)	31 (32.0)	6 (40.0)	
	TT	65 (65.0)	61 (62.9)	9 (60.0)	
rs2737703	CC	55 (55.0)	50 (51.5)	8 (53.3)	0.637
	CT	35 (35.0)	41 (42.3)	5 (33.3)	
	TT	10 (10.0)	6 (6.2)	2 (13.3)	
rs2070995	CC	37 (37.0)	38 (39.2)	6 (40.0)	0.995
	CT	50 (50.0)	46 (47.4)	7 (46.7)	
	TT	13 (13.0)	13 (13.4)	2 (13.3)	
rs1042114	GT	0 (0.0)	1 (1.0)	0 (0.0)	0.528
	TT	100 (100.0)	96 (99.0)	15 (100.0)	
rs1051660	AA	5 (5.0)	1 (1.0)	0 (0.0)	0.524
	AC	28 (28.0)	29 (29.9)	3 (20.0)	
	CC	67 (67.0)	67 (69.1)	12 (80.0)	
rs7439366	CC	61 (61.0)	55 (56.7)	6 (40.0)	0.311
	CT	35 (35.0)	33 (34.0)	8 (53.3)	
	TT	4 (4.0)	9 (9.3)	1 (6.7)	

Data are presented by number and percentage.

Table 4
Associations of the severity of the symptom pruritus by ISS score versus genotypes of the 14 SNPs.

		ISS 0-1 (n = 157)	ISS >1 (n = 55)	P-value
rs3892097	CC	155 (98.7)	55 (100.0)	1.000
	CT	2 (1.3)	0 (0.0)	
rs1065852	AA	59 (37.6)	18 (32.7)	0.732
	AG	61 (38.9)	21 (38.2)	
	GG	35 (22.3)	16 (29.1)	
		2 (1.3)	0 (0.0)	
rs2242480	CC	85 (54.1)	32 (58.2)	0.487
	CT	62 (39.5)	22 (40.0)	
	TT	10 (6.4)	1 (1.8)	
rs28371759	AA	154 (98.1)	52 (94.5)	0.182
	AG	3 (1.9)	3 (5.5)	
rs2277624	CC	94 (59.9)	29 (52.7)	0.478
	CT	51 (32.5)	23 (41.8)	
	TT	12 (7.6)	3 (5.5)	
rs1045642	AA	14 (8.9)	4 (7.3)	0.865
	AG	76 (48.4)	29 (52.7)	
	GG	67 (42.7)	22 (40.0)	
rs28365063	AA	91 (58.0)	32 (58.2)	0.664
	AG	61 (38.9)	20 (36.4)	
	GG	5 (3.2)	3 (5.5)	
rs7439152	GG	9 (5.7)	5 (9.1)	0.517
	GT	55 (35.0)	21 (38.2)	
	TT	93 (59.2)	29 (52.7)	
rs644796	CC	10 (6.4)	1 (1.8)	0.507
	CT	48 (30.6)	18 (32.7)	
	TT	99 (63.1)	36 (65.5)	
rs2737703	CC	85 (54.1)	28 (50.9)	0.890
	CT	59 (37.6)	22 (40.0)	
	TT	13 (8.3)	5 (9.1)	
rs2070995	CC	58 (36.9)	23 (41.8)	0.822
	CT	78 (49.7)	25 (45.5)	
	TT	21 (13.4)	7 (12.7)	
rs1042114	GT	1 (0.6)	0 (0.0)	1.000
	TT	156 (99.4)	55 (100.0)	
rs1051660	AA	6 (3.8)	0 (0.0)	0.151
	AC	48 (30.6)	12 (21.8)	
	CC	103 (65.6)	43 (78.2)	
rs7439366	CC	93 (59.2)	29 (52.7)	0.517
	CT	55 (35.0)	21 (38.2)	
	TT	9 (5.7)	5 (9.1)	

Data are presented by number and percentage.

from mast cells into the skin. Although opioids release histamine from mast cells systemically, this does not appear to be the underlying mechanism as the effect occurs about 3 h after spinal or epidural administration occurs. Pruritus also occurs with fentanyl, which does not cause histamine release. The most likely cause is via a direct central effect. Opioid receptors are found throughout the brain and spinal cord. High concentrations of opioid receptors are found in the substantia gelatinosa, an area within the spinal cord which is the primary site of action of intraspinal opioids. It is hypothesized that opioid-induced pruritus occurs secondary to direct opioid receptor binding in the spinal cord and brain or via neurotransmission stemming from opioid receptor binding [20,21]. This is supported by the fact that opioid antagonists eg naloxone, reverse this effect.

Pruritus can be evoked by physical stimuli, such as a thin wire, electrical stimuli, and thermal heat, and chemical stimuli, such as histamine, serotonin, and substance P. Prostaglandins and dry skin, although not stimuli by themselves, both lower the threshold for evoking itch. Itch receptors are free unmyelinated penicillate nociceptors in the epidermis [22]. Unmyelinated C fibers carry the sensation of itch along the afferent pathway. These enter the dorsal horn of the spinal cord, synapse, cross the midline, and ascend in the spinothalamic tracts closely associated with pain fibers to the thalamus. Tertiary neurons ascend from the thalamus to higher centers that regulate the conscious perception of itch. Central nervous system (CNS) factors can modulate our perception of itch by either amplifying or inhibiting the sensation. An example of inhibition is the effect of scratching an itch. Scratching demonstrates the concept of gating of sensory afferent activity. In this system, simultaneous firing of large-diameter myelinated fibers can presynaptically inhibit firing of smaller afferent fibers so that the sensations they usually evoke would be diminished in intensity or not perceived. Scratching stimulates firing of large-diameter myelinated A fibers that can presynaptically inhibit the firing of smaller afferent C fibers carrying itch. Psychologic factors, such as emotion and past experience, may also act on the gate-control system and modify the perception of itch. An additional central influence on itch involves the enkephalins and opioid receptors in the CNS. When enkephalins bind to opioid receptors, they relieve pain and may cause itch [23]. A pharmacologic example is the itching seen in more than 50% of parturients who receive intraspinal or epidural morphine. When the opioid receptors are blocked by administration of a competitive antagonist, such as naloxone, itching is diminished or disappears. Parenteral naloxone has been used successfully in treating itching in cholestasis [23]. Histamine is the classic mediator of pruritus. Derived from mast cells, histamine acts on H_1 receptors to cause itch. But how histamine mediates itch in many dermatologic and general diseases is a paradox. Experimentally induced itching is always associated with wheal and flare, yet most clinical itch is not. Also, repeat injections

of histamine at the same site results in tachyphylaxis. Antihistamines are often ineffective in relieving itch. An unknown cytokine has been proposed as mediator of itch in diseases such as atopic dermatitis [23]. Supporting this is the antipruritic effect of cyclosporin A (a cytokine inhibitor) in atopic dermatitis, lichen planus, and mycosis fungoides. Substance P and serotonin also mediate itch. Peptides, such as bradykinin, vasoactive intestinal polypeptide (VIP), neurotensin, secretin, and substance P, are potent histamine releasers rather than primary mediators of itch. Prostaglandins modulate rather than cause itch. Prostaglandin E lowers the threshold for histamine-induced itch [23].

Pruritus is likely caused by cephalad migration of the drug in the CSF and its subsequent interaction with the trigeminal nucleus, located superficially in the medulla. Opioid receptors are present in the trigeminal nucleus and trigeminal nerve roots. Animal studies support the concept of an "itch center" located in the lower medulla and indicate that the trigeminal nucleus is involved in the itch reflex. The altered CNS perception of pain may also play a role in pruritus induced by intrathecal and epidural opioids. A link exists between the use of epidural morphine in obstetric parturients and the reactivation of herpes simplex labialis virus (HSV). The reactivation of HSV typically occurs 2–5 days after epidural administration of an opioid. As many as 84% of previously HSV-infected pregnant women have peripartum recurrences whether or not intraspinal opioids are used [24].

One of the postulated mechanisms of intrathecal opioid-induced pruritus is a direct excitatory effect of the opioid on the dorsal horn. High concentrations of 5-HT3 receptors have been located in the dorsal part of the spinal cord, especially in the superficial layers of the dorsal horn, and in the nucleus of the spinal tract of the trigeminal nucleus, in animal studies [25]. This indicates that opioids might cause pruritus by activating central 5-HT3. There are few studies on the effectiveness of 5-HT3 antagonists reported, and these have provided conflicting results. A study by Iatrou and colleagues [26] showed a decreased incidence and severity of pruritus with the use of ondansetron and dolasetron in parturient undergoing urological, orthopaedic or vascular surgery using intrathecal morphine. A similar result was obtained by Charuluxananan and colleagues [27].

Most opioid drugs are metabolized to some extent by the two cytochrome P450 enzymes, CYP2D6 and CYP3A4 [10–12,28,29]. Although SNPs in these enzymes have been studied extensively for their effect on pain control by opioid drugs, these studies were not usually carried out on morphine, but on other opioid drugs, mostly those that are metabolized to active metabolites by these enzymes, However there is little or no evidence of any effect of SNPs in these enzymes in clinical pain studies [10], and we saw no effect on neuroaxial morphine inducing pruritus of SNPs in either of the two Phase I cytochrome P450 enzymes studied here. Another problem may be seen as a limitation of this study; there are many variants and subvariants of CYP2D6 but we did not evaluated in our samples. The phase II metabolic enzyme studied here, UGTB7, glucuronidates morphine to a major inactive metabolite, morphine-3-glucuronide, and a minor, active metabolite, morphine-6-glucuronide, said to be 50 times more potent than morphine itself [9,30]. Previous studies have reported no effect on pain or adverse effects of SNPs in this enzyme [31,32], and we have reported no effects on neuroaxial morphine inducing pruritus of SNPs in this enzyme.

The ABCB1 drug efflux transporter (also called the multidrug resistance 1 gene) is a major component of the blood–brain barrier [32], and is involved in the transport of morphine into the brain [9]. Studies of possible association of SNPs in this gene with pain control efficacy of morphine have yielded mixed results [10,28,29,31,32]. However, most studies have reported no association between SNPs in ABCB1 and neuroaxial morphine inducing pruritus [31,33,34]. Our results showed no association between SNPs in either ABCB1 or ABCB3 and neuroaxial morphine inducing pruritus, results consistent with the majority of previous results and also with the fact that two of the sites for neuroaxial morphine inducing pruritus action.

Opioid receptors

Morphine is a selective μ opioid agonist, and there have been a number of studies of the effect of SNPs in the μ opioid receptor (OPRM1, especially the G118A allele) on both morphine-induced pain relief and neuroaxial morphine inducing pruritus. The results reported have been contradictory. Most, although not all, studies report the GG allele to provide less pain protection [11,28]. One study found an effect on nausea/vomiting [11], one study a marginal effect [32], and other studies found no effect of the G118A allele on neuroaxial morphine inducing pruritus [31,33,34]. In our previous study, we have investigated SNPs in the μ opioid receptor gene. Morphine although a selective μ opioid agonist, also has effects on κ and δ opioid receptors and κ receptors are found on peripheral nerve endings and in the vestibular zone (maybe the site involved in neuroaxial morphine inducing pruritus). Therefore we investigated the effects of SNPs in genes for these receptors. No effects were seen.

Ion channels

Morphine binding activates a G-protein whose downstream action is to activate an inwardly-rectifying potassium channel and inactivate an R-type voltage-gated calcium channel, thus hyperpolarizing the cell membrane [9]. Marker et al. found that knockout mice for the two G protein-activated K+ genes studied here, KCNJ6 and KCNJ9, had reduced morphine-induced analgesic efficacy [35]. In our study, the unadjusted, but not the adjusted, p values showed involvement of the KCNJ6 potassium channel in neuroaxial morphine inducing pruritus. Yokoyama et al. showed that knockout mice for the R-type voltage-gated calcium channel Cav2.3 also had altered morphine tolerance [36]. Our results showed no influence on neuroaxial morphine inducing pruritus of the R-type voltage-gated calcium channel studied (CACNA1E).

In conclusion, our results showed no association between SNPs of any of the genes studied with neuroaxial morphine inducing pruritus. Perhaps related studies of mRNA or proteonomics will give better information.

Funding

None.

Conflicts of interest

The authors declare that they have no competing interests.

Author's contributions

Study conception and design: LKC, CCK, SCC, and HJY. Analysis and interpretation of data: LKC, CCK, SCC, and HJY. Drafting of manuscript: LKC, CCK, SCC, CJL, and HJY. All Authors read and approved the final manuscript.

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