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Exploring joint effects of genes and the clinical efficacy of morphine for cancer pain:

OPRM1 and *COMT* gene

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Abstract

Pain is a complex human trait. It is likely that the interaction of multiple genes, each with a small individual effect, along with the effect of environmental factors, influences the clinical efficacy of opioids rather than a single gene alone. Polymorphisms in genes coding for the mu-opioid receptor (A118G) and catechol-O-methyl transferase (Val158Met) may be important modulators of opioid efficacy. We assessed joint effects of the OPRM1 and COMT genes in predicting morphine dose for cancer pain relief. We used genotype and clinical data from a pharmacokinetic study of morphine in 207 inpatients treated with stable morphine dose for at least 3 days by Palliative Medicine Specialists. Results showed significant variation in morphine dose requirement by genotype groups: carriers of COMT Val/Val and Val/Met genotype required 63% and 23%, respectively, higher morphine dose compared to carriers of Met/Met genotype (p=0.02). Carriers of OPRM1 GG genotype required 93% higher morphine dose compared to carriers of AA genotypes (p=0.012). When we explored for joint effects, we found that carriers of the OPRM1 AA and COMT Met/Met genotype required the lowest morphine dose to achieve pain relief (87mg/24h; 95% CI=57,116) and those with neither Met/Met nor AA genotype needed the highest morphine dose (147mg/24h; 95%CI=100;180). The significant joint effects for the Met/Met and AA genotypes (p<0.012) persisted, even after controlling for demographic and clinical variables in the multivariable analyses. Future studies are needed to further characterize the joint effects of multiple genes, along with demographic and clinical variables, in predicting opioid dose.

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INTRODUCTION

Cancer pain is one of the most persistent and incapacitating symptoms of cancer. While opioids remain the drug of choice for cancer pain therapy(World Health Organisation Geneva 1996) with morphine as the first line drug of choice, predicting the optimal morphine dose for patients remain a challenge. While traditionally, this inter-individual variability has been explained by differences in bioavailability, metabolism, differences in pain perception and other neurophysiological mechanisms, and socio cultural factors, evidence now suggests an important role of genetic variability in the clinical efficacy of opioids(Pasternak 2001;Lotsch, Skarke et al. 2004;Klepstad, Dale et al. 2005)

As the most important target for morphine, polymorphisms of the gene for the mu opiod receptor (*OPRM1*) located on human chromosome 6q24-q25(Wang, Johnson et al. 1994), are primary candidates for genetic influences on the efficacy of opioids(Uhl, Sora et al. 1999;LaForge, Shick et al. 2000;Hoehe, Kopke et al. 2000;Koch, Kroslak et al. 2000;Befort, Filliol et al. 2001;Wang, Quillan et al. 2001). Numerous single nucleotide polymorphisms (SNPs) in the *OPRM1* gene have been identified, but only a few have been explored for a possible relevance in opioid analgesia, including the A118G(Lotsch and Geisslinger 2006b).

The influence of the polymorphic catechol-O-methyltransferase (*COMT*) gene located on chromosome 22 (22q11.21) to pain has been an active area of investigation. The Val158Met polymorphism, a common genetic variant, has been shown to influence the activity of the *COMT* enzyme. The enzyme, which metabolizes the catecholamines dopamine, epinephrine and norepinephrine, is also key modulator of dopaminergic and adrenergic neurotransmission.

Polymorphisms in genes coding for the *OPRM1*(Bond, LaForge et al. 1998;Befort, Filliol, Decaillot, Gaveriaux-Ruff, Hoehe, and Kieffer 2001;Wang, Quillan, Winans, Lucas, and Sadee 2001;Lotsch, Zimmermann et al. 2002;Klepstad, Rakvag et al. 2004;Fillingim, Kaplan et al. 2005;Lotsch and Geisslinger 2006b) and *COMT*(Lachman, Papolos et al. 1996;Zubieta, Heitzeg et al. 2003;Shield, Thomae et al. 2004;Rakvag, Klepstad et al. 2005) may be important modulators of opioid efficacy. Pain is a complex human trait and it is likely that the interaction of multiple genes, each with a small individual effect, along with the effect of environmental factors, influences the clinical efficacy of opioids rather than a single gene alone.

The purpose of this study was to explore the joint effects of genes previously shown to have influence on the clinical efficacy of morphine in a sample of cancer patients receiving morphine treatment for cancer pain. We specifically assessed joint effects of variation in the *OPRM1* and the *COMT* genes in predicting morphine dose for pain control.

PATIENTS AND METHODS

We used data from the study of Klepstad et al(2004) and Ravkag et al(Rakvag, Klepstad, Baar, Kvam, Dale, Kaasa, Krokan, and Skorpen 2005) that includes genotyping data and clinical variables for 207 patients admitted for cancer pain treatment. All patients were Caucasians and in-patients during the period June 1999 to February 2000 at St Olav University Hospital, a 900-bed tertiary hospital in Trondheim, Norway. Patients were treated with stable morphine dose for at least 3 days before inclusion in the pharmacokinetic study of morphine. Patients aged <

18, those not competent in the Norwegian language and those refusing consent to the study were not included in the study.

Patients' hospital records were reviewed for age, gender, cancer diagnosis, time since diagnosis, presence of metastases and time since start of morphine. Clinical and laboratory variables including serum albumin and creatinine levels, and morphine dose for the last 24 hours were abstracted from the patients' medical charts.

Pain Assessment

Pain was measured using the item of 'average pain' during the last 24 h in the Brief Pain Inventory (BPI). The patients rated pain on an 11-point numeric scale, where 0 represents 'no pain' and 10 represents 'pain as bad as you can imagine'. Recommended by the European Association of Palliative Care (Caraceni, Cherny et al. 2002)for use in clinical studies of pain, the BPI has been validated in Norwegian(Klepstad, Loge et al. 2002). The patients' functional status was assessed by the Karnofsky performance status(Yates, Chalmer et al. 1980;Mor, Laliberte et al. 1984).

Blood Sample, DNA Extraction and Genotyping

Collection of blood samples was described previously(Klepstad, Rakvag, Kaasa, Holthe, Dale, Borchgrevink, Baar, Vikan, Krokan, and Skorpen 2004). Briefly, genomic DNA was isolated from 50 to 200 ml EDTA blood on a MagNA Pure LC (Roche Diagnostics Scandinavia AB, Bromma, Sweden) using the MagNA Pure LC DNA Isolation Kit I applying the manufacturers high performance protocol. Purified genomic DNA was eluted in 100 ml elution buffer and stored at K20 8C.

The procedure for genotyping were described previously(Klepstad, Rakvag, Kaasa, Holthe, Dale, Borchgrevink, Baar, Vikan, Krokan, and Skorpen 2004;Rakvag, Klepstad, Baar, Kvam, Dale, Kaasa, Krokan, and Skorpen 2005).

Ethics

The study was conducted in accordance to the principles of the Helsinki Declaration and was approved by the Regional Committee for Medical Research Ethics, Health Region IV, Norway. Patients gave their oral and written informed consent before inclusion in the study.

Statistical Analyses—We performed univariate comparisons of genotype frequencies using the X^2 test. Comparisons across alleles for specific genotypes were performed using analysis of variance.

We conducted multivariable logistic regression analyses using morphine dose as the dependent variable. We used mean morphine dose (117mg/24h) to divide the groups (low=<117mg/24h; high>117mg/24h). Given the exploratory nature of this study, we did not assume gene-dose effect and instead created dummy variables for the different genotypes. The first model included all the variables found significant at $P < 0.20$ in the univariate level of analysis. (A *P*value of 0.20 was used as the cut-off since using a more traditional level [$P < 0.05$] often failed to identify variables known to be important(Bendel and Afifi 1977). Further variable selection in the model was conducted by using backward elimination. With the goal of having the most parsimonious model, only variables with $P < 0.05$ were included in the final model. Colinearity diagnostics were also performed. The Statistical Package for Social Sciences was used in all the analyses(SPSS 1998).

RESULTS

Two hundred and seven patients, aged 29-89 years (mean age=63), receiving chronic morphine treatment for cancer pain were included in this study. There were more males than females (56% versus 44%). The most common type of cancer was urologic (28%), followed by breast (22%) and lung (19%). Ninety percent of the sample had metastatic disease. Mean duration of morphine use was 3.4 months (SD=6.9) and duration (time since cancer diagnosis) of cancer was from 0.4 to 50 months (mean=24 months;SD=48).

Patients received from 10 mg to 760mg/24h of morphine (mean=117 mg/24h;SD=116mg/24h). The median pain score for the whole sample was 4. There were no statistically significant differences in pain intensity scores.

Genotype Analyses

Allele frequencies and the results of the X^2 test for separation from Hardy-Weinberg equilibrium showed that there was no significant departure from Hardy-Weinberg equilibrium for *COMT* Val158Met(23) and *OPRM1* A118G (A=0.888;G=0.111;χ^2=0.29; p=0.91).

The total morphine dose, median and mean pain intensity by polymorphisms (Panel A) and genotype combination (Panel B) are shown in Table 1. There were no statistically significant differences in pain scores across genotypes and joint genotype combination. Panel A shows that carriers of Val/Val and Val/Met genotype required 63% and 23%, respectively, higher morphine dose compared to carriers of Met/Met genotype (p=0.02). For the OPRM1 gene, GG and AG genotype required 93% and 18%, respectively, higher morphine dose compared to carriers of AA genotypes [carriers of AA relative to GG (p=0.012)].

Panel B shows the total morphine dose, median and mean pain intensity by joint genotype combination. Since carriers of the *COMT* Met/Met and the *OPRM1* AA genotypes required the least morphine dose, we created the following 4 groups: 1) Met/Met and AA; 2) Met/Met but not AA; 3) AA but not Met/Met; and 4) neither Met/Met nor AA. We observed statistical significance for the joint effects of Met/Met and AA genotypes (p<0.017). We did not observe statistically significant differences for the other groups, which could be explained by the large variation in morphine dose for those groups.

Multivariable Regression Analyses

We assessed if the joint effects of *COMT* and *OPRM1* genotype on morphine dose will persist, controlling for variables known to potentially confound the relationship. Demographic variables such as age and gender and clinical variables such as Karnofsky status, time since cancer diagnosis and months using morphine and creatinine and albumin levels were included in the model. Variables found in the univariate analysis to be significantly associated with morphine dose at a level of p<0.20(Bendel and Afifi 1977), were next entered into a multivariate logistic regression analysis with the purpose of building a model to determine the predictive value of genotype on morphine dose. Results showed that joint Val158Met and A118G genotypes, months using morphine and time since cancer diagnosis as significant variables in predicting morphine dose. Table 2 shows that even after controlling for clinical variables, we observed statistical significance for the joint effects of *COMT* Met/Met and *OPRM1* AA (p<0.012) on morphine dose. We also conducted multivariable linear regression analyses, with morphine dose as a continuous variable (analyses not shown). We observed statistical significance for the joint effects of *COMT* Met/Met and *OPRM1* AA (p<0.012) on morphine dose.

DISCUSSION

This study examined the potential joint effect of genes in predicting the clinical efficacy of morphine for cancer pain treatment and control. A number of studies have looked at the joint effects of genes in diseases like asthma(Hong, Lee et al. 2005), diabetes(Maier, Chapman et al. 2005;Bergholdt, Taxvig et al. 2005), prostate(Xu, Lowey et al. 2005) and lung cancer (Zhang, Miao et al. 2006), alzheimers disease(Infante, Sanz et al. 2004), heart disease(Ye, Dhillon et al. 2003). The joint effects of genes can be expected to enhance, suppress or have no effect on the phenotypic outcome of interest.

Our findings provide empirical support for the importance of joint effects of the *OPRM1* and *COMT* gene in the clinical efficacy of morphine. We have shown that carriers of Met/Met and AA genotype in the *COMT* and *OPRM1* gene, respectively, needed less morphine dose for pain relief, thus providing preliminary support for the potential use of genetic data in predicting morphine dose for adequate control of pain in cancer patients. To our knowledge this is the first study to have looked at the joint effects of genes in opioid analgesia.

Recent debates on the assessment of candidate genes for pain and painrelated traits have focused on the need for a polygenic model for these complex phenotypes. Ideally, many genes with functional significance should be assessed. We selected the *OPRM1* and the *COMT* variants in this study because of the strength of previously published associations of these genes with pain and pain-related phenotypes and the minor allele frequencies(Hoehe, Kopke, Wendel, Rohde, Flachmeier, Kidd, Berrettini, and Church 2000;Mayer and Hollt 2001).

Human studies showed the importance of the A118G polymorphism in pain and pain-related phenotypes. Fillingim and colleagues showed that the A118G polymorphism was associated with pressure pain sensitivity(Fillingim, Kaplan, Staud, Ness, Glover, Campbell, Mogil, and Wallace 2005) and a recent study by Lotsch and Geisslinger(Lotsch and Geisslinger 2006b) also showed that the A118G polymorphism is an important target for understanding variability in opioid efficacy as observed in human experimental pain models. We extended these findings by providing preliminary evidence of the effects of A118G polymorphism in the clinical efficacy of opioids and its joint effects with Val158Met.

That pain and pain-related phenotypes may also be modulated by the function of several endogenous substances such as adrenergic and noradrenergic neurotransmitters has also been shown in previous studies. Steiner and Gerfen (1998) found that the neuronal content of enkephalins is reduced by chronic activation of dopaminergic neurotransmission, which is followed by an up-regulation of mu-opioid receptor density in various regions of the brain (Chen, Aloyo et al. 1993;Steiner and Gerfen 1998). Variable *COMT* enzyme activity may therefore alter dopaminergic activity and could, through an altered action of dopaminergic substances, have an influence on the enkephalin content and opioid receptor density.

Diatchenko and colleagues (*2005*) found haplotypes of the gene encoding *COMT* and found significant associations between the *COMT* haplotypes and pain sensitivity. Zubieta and colleagues found that Val158Met polymorphisms were associated with several pain phenotypes such as mu opioid system responses and higher sensory and affective ratings of pain(Zubieta, Heitzeg, Smith, Bueller, Xu, Xu, Koeppe, Stohler, and Goldman 2003). Homozygosity for the Met158 allele was associated with diminished regional mu-opioid system responses to pain and increases in μ-opioid receptor binding potential(Zubieta, Heitzeg, Smith, Bueller, Xu, Xu, Koeppe, Stohler, and Goldman 2003). The increase in the density of opioid receptors in those with Met/Met allele may therefore result to an improved efficacy of morphine. Rakvag et al(Rakvag, Klepstad, Baar, Kvam, Dale, Kaasa, Krokan, and Skorpen 2005) found that Val158Met polymorphism in the *COMT* gene is a significant predictor of

morphine dose requirements for treatment of cancer pain. In this study, we found that *COMT* Val158Met had joint effects with the A118G polymorphisms in the *OPRM1* gene.

Klepstad et al (Klepstad, Rakvag, Kaasa, Holthe, Dale, Borchgrevink, Baar, Vikan, Krokan, and Skorpen 2004) and Ravkag et al (Rakvag, Klepstad, Baar, Kvam, Dale, Kaasa, Krokan, and Skorpen 2005) assumed a gene-dose effect on univariate analyses, with carriers of *OPRM1* GG allele and *COMT* Val/Val allele associated with a higher morphine dose. However, we did not assume a gene-dose effect in the multivariate model, given the exploratory nature of this study. Future studies are needed to assess if there are gene-dose effects in the relationship between *OPRM1* and *COMT* genotypes and opioid efficacy.

We found that the duration of morphine treatment was an important predictor for morphine dose. It is possible that this time interval is reflective of the progression of disease, i.e., as patients progressed in their disease, they required higher morphine dose. Another explanation is that repeated administration of morphine leads to the need for higher dose or the need for opioid rotation. A known mechanism for this phenomenon is the reduction in the responsiveness of the G-protein coupled opioid receptors(Nestler 1992) leading to either desensitization or downregulation. More recently the concept of paradoxical pain leading to analgesic tolerance has also been proposed(King, Ossipov et al. 2005).

There are limitations to this study. Arguably the design of our study may be associated with several biases, such as the heterogeneity of our study population. Another limitation is that the data were already previously analyzed for the individual effects of the OPRM1 and the COMT variant. Nonetheless the present analyses point to the importance of assessing the joint effects of genes on pain and pain-related phenotypes.

We also recognize that the complexity of morphine pharmacology suggests that the variability in opioid pain treatment is associated with genetic variation in several genes(Mogil 1999;Thompson, Koszdin et al. 2000;Mogil, Yu et al. 2000;Flores and Mogil 2001;Duguay, Baar et al. 2004;Max 2004;Belfer, Wu et al. 2004;Kim, Neubert et al. 2004;Diatchenko, Slade et al. 2005;Stamer, Bayerer et al. 2005;Lee, Kim et al. 2006;Lotsch and Geisslinger 2006a).

Despite major improvement in pain control over the last 15 years, cancer-related pain continues to be a significant public health concern. Morphine is recommended as a first line strong opioid (World Health Organisation Geneva 1996). The appropriate use and the ability to predict the optimal dose of opioids for cancer patients are crucial aspects for the effective treatment and management of cancer pain. Previous studies have focused on disease-related variables, clinical health status and sociodemographic characteristics in understanding adequate treatment and control of pain. Advances in molecular technology have now made it possible to assess the contribution of genes in pain treatment and control. Our observation that genetic differences influence clinical efficacy of morphine may prove useful in managing patients who receive these drugs, and importantly, preventing negative responses due to inappropriate dosing. Because pain is prevalent not just in cancer patients but in other diseases, the *COMT* and *OPRM1* genotypes may be relevant information to consider when implementing pain therapy.

In conclusion, our preliminary findings suggest the importance of assessing joint effects of genes in studies of clinical efficacy of morphine. Future studies with larger cohorts are needed to further characterize the joint effects of multiple genes, along with demographic and clinical variables, in predicting opioid dose.

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Table 1

Total morphine dose (mg/24h) and pain outcomes by genotype (Panel A) and joint genotype combination (Panel B)

Genotype	Morphine Dose mg/24 Mean	95% CI	Pain Scores***	
			Pain Intensity Median	Pain Intensity Mean (SD)
Panel A*				
COMT				
Val/val (n=44)	155	106; 203	4	3.94(2.2)
Val/met (n=96)	117	97; 137	3	3.66(2.6)
Met/met (n=67)	95	71; 119	3.5	3.46(2.3)
OPRM1				
AA (n=166)	112	96; 128	3	3.60(2.6)
AG (n=36)	132	76; 187	4	4.10(1.8)
GG (n=5)	216	60; 371	2	2.0(1.2)
Panel B**				
Met/Met & AA (n=58)	87	57; 116	3	3.18 (2.3)
AA but not Met/Met (n=108)	126	104; 147	4	4.89 (1.8)
Met/Met but not AA (n=9)	140	72; 224	5	3.83 (2.6)
Neither Met/Met nor AA (32)	147	100; 180	3	3.48 (1.8)

OPRM1= Mu Opioid Receptor 1; COMT=Cathechol-O-MethylTransferase

* Panel A: Statistically significant difference for mean morphine dose for carriers of val/val relative met/met (p=0.023) Statistically significant difference for mean morphine dose for carriers of AA relative to GG (p=0.012)

** Panel B: Statistically significant difference (p=0.017) for mean morphine dose for carriers of Met/met and AA relative to Neither Met/Met nor AA

*** No statistically significant differences for pain intensity scores by genotype groups

Table 2

Logistic regression model for morphine dose

Parameter	p-value	Odds Ratio	95% Lower Bound	95% Upper Bound
Joint genotype groups	0.05			
a. Met/Met & AA	0.012	0.278	0.102	0.756
b. AA but not Met/Met	0.280	0.625	0.266	1.467
c. Met/Met but not AA	0.191	0.240	0.028	2.039
Months using morphine	0.005	1.106	1.031	1.186
Time since cancer diagnosis (in months)	0.006	0.988	0.980	0.987

Morphine dose (low=≤ 117mg/24H; high>117mg/24h)

Reference variable is Neither Met/Met nor AA

Candidate variables included months using morphine, time since cancer diagnosis, age, sex, Karnofsky performance status, serum albumin, serum creatinine