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Effects of *CYP2C9*1/*13* on the pharmacokinetics and pharmacodynamics of meloxicam

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Meloxicam is a substrate for the CYP2C9 and CYP3A4 enzymes.
- We have previously reported that the frequency of the *CYP2C9*1/*13* genotype in the Korean population is 1.1%.

WHAT THIS STUDY ADDS

- The *CYP2C9*1/*13* genotype is associated with decreased metabolism and increased pharmacodynamic effects of meloxicam.
- This is the first report that evaluates the *in vivo* effects of the *CYP2C9*13* allele on the pharmacokinetics and pharmacodynamics of CYP2C9 substrates with a sufficient sample size.

AIMS

To determine the effects of the *CYP2C9*1/*13* genotype on the pharmacokinetics and pharmacodynamics of meloxicam in Korean subjects.

METHODS

Meloxicam (15 mg) was orally administered to 21 healthy Korean volunteers with either the *CYP2C9*1/*1* or the *CYP2C9*1/*13* genotype. Plasma meloxicam concentrations were analysed by HPLC-UV for 72 h after drug administration. The pharmacodynamic effects of meloxicam were determined by measuring TXB_2 generated in blood.

RESULTS

The AUC(0,∞) and C_{max} of meloxicam were 2.43- and 1.46-fold higher in the *CYP2C9*1/*13* group than in the *CYP2C9*1/*1* group, respectively. The oral clearance of meloxicam was significantly lower in the *CYP2C9*1/*13* group (37.9% of wild type) than in the *CYP2C9*1/*1* group. The $t_{1/2}$ of meloxicam was 1.84-fold longer in the *CYP2C9*1/*13* group than in the *CYP2C9*1/*1* group. The rate of TXB_2 production was significantly lower in the *CYP2C9*1/*13* group than in the *CYP2C9*1/*1* group.

CONCLUSIONS

The *CYP2C9*1/*13* genotype is associated with decreased metabolism and increased pharmacodynamic effects of meloxicam.

Introduction

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) that inhibits the synthesis of prostaglandins through preferential cyclo-oxygenase-2 (COX-2) inhibition, imparting analgesic, antipyretic and anti-inflammatory properties [1] for the treatment of osteoarthritis and rheumatoid arthritis. Meloxicam is primarily metabolized to a 5′-hydroxymethyl metabolite by CYP2C9 (major) and CYP3A4 (minor) [2, 3]. In humans, the CYP2C subfamily is a drug metabolizing enzyme that accounts for approximately 18% of the CYP protein content in human liver microsomes and catalyzes approximately 20% of the CYP-mediated metabolic reactions of drugs currently on the market [4]. CYP2C9 is polymorphic and is involved in the oxidation of a wide range of drugs, including S-warfarin, phenytoin, losartan, tolbutamide and torsemide. Further, CYP2C9 also metabolizes NSAIDs including diclofenac, naproxen, piroxicam, tenoxicam and ibuprofen, as well as the selective COX-2 inhibitor celecoxib [5]. Thirty-four

allelic variants of the *CYP2C9* gene [6] show differences in enzyme expression and activity, leading to differences in dosing and the potential for unpredictable adverse effects [7]. Among these mutations, the *CYP2C9*2* (p.Arg144Cys) and *CYP2C9*3* (p.Ile359Leu) alleles show impaired activity towards a number of substrates both *in vivo* and *in vitro* [4, 5, 8]. *CYP2C9*13* was first described in a male Chinese individual, and a large decrease in enzyme activity is observed in individuals with the *CYP2C9*3/*13* genotype [9]. The *CYP2C9*13* allele involves a c.269T>C transition in exon 2, leading to a p.Leu90Pro substitution in the encoded protein [9]. The *CYP2C9*13* allele has been detected in Chinese, Japanese and Korean samples at low frequencies of 0.2% to 1.0% [9–11]. However, it is not detected in other populations including European, African-American, Hispanic and Ashkenazi Jewish [12]. Although the *CYP2C9*13* allele was reported to show decreased enzymatic activity towards some CYP2C9 substrates *in vivo* and/or *in vitro* [11, 13–17], the effects of the *CYP2C9*13* allele on the pharmacokinetics of CYP2C9 substrate drugs have not been sufficiently studied because of the low frequency with which the allele is found in the general population.

Here, we evaluated the effects of the *CYP2C9*13* allele on the pharmacokinetics and pharmacodynamics of meloxicam in a healthy Korean cohort.

Methods

Subjects

Among 1213 male Korean subjects tested for the *CYP2C9* genotype, 21 healthy subjects carrying either the *CYP2C9*1/*1* or *CYP2C9*1/*13* genotype were selected. All subjects were healthy according to medical history, physical examination and routine laboratory tests (blood chemistry, haematology and urine analysis). The subjects were asked to refrain from taking any medication, caffeine, grapefruit products, smoking and alcoholic beverages for at least 1 week before and throughout the study period. All subjects provided verbal and written informed consent. The study was performed according to the guidelines of the Declaration of Helsinki and was approved by the institutional ethics committee of the School of Pharmacy, Sungkyunkwan University, Suwon, Korea.

Study protocol

On the day of the study, each subject received a 15 mg oral dose of meloxicam (Mobic®, Boehringer Ingelheim Korea, Seoul, Korea) with 240 ml of water after an overnight fast. The subjects were maintained in the fasting state for 4 h after administering the drug. Venous blood samples (10 ml) were obtained before and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48 and 72 h after meloxicam administration. The blood samples were centrifuged immediately and plasma samples were stored at −70°C until needed.

CYP2C9 genotyping

Genomic DNA was isolated from peripheral blood leukocytes using the Wizard® Genomic DNA Purification Kit (Promega, Madison, WI, USA). *CYP2C9* genotyping for *CYP2C9*2*, **3*, **4*, **5*, **11* and **13* was performed using polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) and direct sequence analysis described in our previous study [10]. The *CYP2C9*1* allele was assigned in the absence of other detectable variant alleles. *CYP2C9* sequencing was performed for all subjects participating in this study in order to identify additional *CYP2C9* coding region changes. Direct sequencing of the *CYP2C9* gene for the amplification of all nine exons and exon/intron junctions were performed according to a previously reported method with slight modifications [10, 18]. PCR products were purified using a PCR purification kit (AxyPrep® PCR Clean-up Kit, Axygen Bioscience Inc., Union City, CA, USA) and were sequenced on an ABI3730 automatic sequencer (Applied Biosystems Inc., Foster City, CA, USA) using a BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems Inc.). There were no subjects carrying the *CYP2C9*2*, **4*, **5*, or **11* alleles in our study.

Assay of meloxicam plasma concentrations

The plasma concentrations of meloxicam were determined using a validated high-performance liquid chromatography (HPLC) assay with ultraviolet detection [19]. Briefly, 0.5 ml of plasma was spiked with 400 ng of an internal standard (piroxicam), acidified with 0.1 ml 5 M HCl, then extracted with 6 ml of diethyl ether. The organic phase was evaporated at 40°C under a constant flow of nitrogen gas. The residue was reconstituted with 500 µl of the mobile phase. A 65 µl aliquot was then injected into the analytical column (Sunfire, C18, 5 µm, 4.5 mm × 150 mm, Waters, MA, USA). The mobile phase consisted of a mixture of 20 mM phosphate buffer : acetonitrile (60 : 40, v : v, pH 3.5). The flow rate was 1.2 ml min^{-1} and the column oven temperature was 30°C. The effluents were detected with ultraviolet detection at 355 nm. The detection limit was 10 ng ml^{-1} for meloxicam. The linear ranges of the standard curves for meloxicam ranged from 10 to 2400 ng ml^{-1} in plasma (r^2 > 0.9998). The mean accuracy of meloxicam was 98–114% in plasma. The coefficients of the variation (within-day and between-day precision) of meloxicam were <8% in plasma.

Thromboxane B_2 (TXB_2) analysis

To assess the effects of meloxicam on platelet COX (cyclooxygenase), the level of TXA_2 generated during the clotting of whole blood was determined by measuring the concentration of its stable breakdown product, TXB_2, as described previously [20]. Briefly, blood samples without anticoagulant were obtained before and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48 and 72 h after meloxicam administration. Within 5 min

of blood collection, each sample was incubated for 1 h at 37°C to allow the blood to clot. The serum was then collected, immediately centrifuged, and stored at −70°C until assayed for TXB_2. Serum TXB_2 concentrations were determined using a commercially available TXB_2 enzyme immunoassay kit (Assay Designs, Ann Arbor, MI, USA).

Pharmacokinetic and pharmacodynamic analysis

The pharmacokinetic parameters of meloxicam were estimated using non-compartmental methods with the BA Calc 2002 analysis program (KFDA, Seoul, Korea); actual blood sampling times were used for analysis. The maximum plasma concentration (C_{max}) and time to reach C_{max} (t_{max}) were used as the observed values. The area under the plasma concentration–time curve (AUC) was calculated using the linear trapezoidal rule. The elimination rate constant (λ_z) was estimated from the least-squares regression slope of the terminal plasma concentration. The AUC from 0 to infinity [AUC(0,∞)] was calculated as $AUC(0,\infty) = AUC + C_t/\lambda_z$ (C_t is the last plasma concentration measured). The half-life ($t_{1/2}$) was calculated as $\ln 2/\lambda_z$, and the apparent oral clearance (CL/F) of meloxicam was calculated as $CL/F = Dose/AUC(0,\infty)$.

The inhibition of TXB_2 generation was calculated as the percent inhibition of TXB_2 generation in the serum relative to the baseline (pre-dose) values [TXB_2 inhibition % = (TXB_2 serum concentration at 0 h − TXB_2 serum concentration at *t* h)/(TXB_2 serum concentration at 0 h)]. The area under the effect (TXB_2 inhibition %)–time curve (AUEC) up to 72 h was calculated using the linear trapezoidal rule.

Statistical analysis

The number of subjects in each genotype group was estimated to be sufficient to detect a 50% difference in AUC(0,∞) of meloxicam between the two genotype groups with a statistical power of at least 80% (α level of 0.05). The power and sample size were calculated with the Power and Sample Size Program, PS (version 3.0.17) [21]. All pharmacokinetic data are expressed as the mean ± SD, except for t_{max}, which is presented as the median value and range. Differences in pharmacokinetic parameters between the genotype groups were assessed using Student's *t*-test or the Mann-Whitney rank sum test after normality and equal variance tests. Data were analysed using the statistical program Sigmastat for Windows (version 2.3; SPSS Inc., Chicago, IL, USA). *P* values of <0.05 were considered statistically significant.

Results

All subjects completed the study according to the protocol, and there were no clinically undesirable signs or symptoms attributed to the administration of meloxicam. In addition, there were no significant differences in the demographic parameters between the two genotyped groups (Table 1).

After a single 15 mg oral dose of meloxicam, heterozygous *CYP2C9*13* subjects showed a higher mean plasma meloxicam concentration curve than the wild-type *CYP2C9* subjects (Figure 1). Meloxicam pharmacokinetics were significantly different in subjects homozygous for the *CYP2C9*1* allele (Table 2). The mean AUC(0,∞) of meloxicam in the *CYP2C9*1/*13* subjects was 2.43-fold higher than in the *CYP2C9*1/*1* subjects ($P < 0.001$). Similarly, the $t_{1/2}$ of meloxicam was 1.84-fold longer in the *CYP2C9*1/*13* subjects than in the *CYP2C9*1/*1* subjects ($P < 0.001$). The mean CL/F value of meloxicam in the *CYP2C9*1/*13*

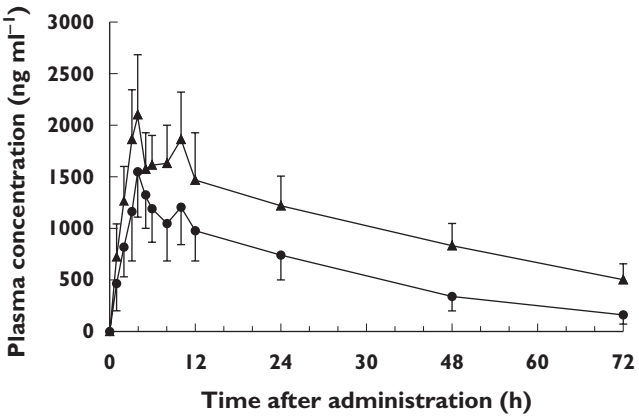

Figure 1

Plasma concentration–time profiles for meloxicam in *CYP2C9* genotype groups after a single 15 mg oral dose of meloxicam. Each value represents the mean ± SD. ●, *CYP2C9*1/*1* ($n = 12$); ▲, *CYP2C9*1/*13* ($n = 9$)

Table 1

Individual demographic characteristics (mean ± SD) according to *CYP2C9* genotype in 21 healthy Korean subjects

Genotype	Number of subjects	Age (years)	Height (cm)	Weight (kg)	Body mass index (kg m^{-2})
CYP2C9*1/*1	12	23.2 ± 2.6	176.0 ± 4.4	71.8 ± 8.1	23.1 ± 2.1
CYP2C9*1/*13	9	24.4 ± 2.5	174.1 ± 3.6	70.7 ± 7.3	23.3 ± 2.4

Table 2

Pharmacokinetic parameters of meloxicam determined after oral administration of 15 mg meloxicam according to *CYP2C9* genotype

Variable	*CYP2C9*1/*1* (*n* = 12)	*CYP2C9*1/*13* (*n* = 9)
C_{max} (ng ml^{-1})	1558 ± 394 (1308, 1808)	2270 ± 472** (1907, 2633)
t_{max} (h)	4.2 (4.0–5.0)	4.0 (3.0–5.0)
$t_{1/2}$ (h)	21.5 ± 4.6 (18.8, 24.4)	39.5 ± 5.5*** (35.3, 43.8)
CL/F (ml h^{-1})	367 ± 117 (292, 441)	139 ± 21*** (122, 155)
AUC(0,72 h) (μg ml^{-1} h)	40.3 ± 12.3 (32.5, 48.1)	78.6 ± 10.1*** (70.9, 86.3)
AUC(0,∞) (μg ml^{-1} h)	45.2 ± 15.2 (35.5, 54.8)	109.7 ± 15.8*** (97.6, 121.8)

Each value represents the mean ± SD apart from t_{max} which is given as a median (range). Values in parentheses represent 95% confidence intervals. C_{max} maximum plasma concentration; t_{max} time to reach the maximum plasma concentration; AUC(0,72 h) area under the plasma concentration–time curve from time 0 to 72 h; AUC(0,∞) area under the plasma concentration–time curve from time 0 to infinity; $t_{1/2}$ elimination half-life; CL/F apparent oral clearance. $^{**}P < 0.01$, $^{***}P < 0.001$ compared with the *CYP2C9*1/*1* group.

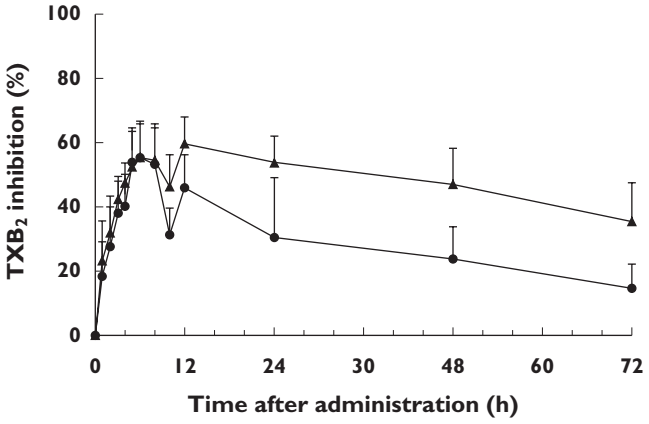

Figure 2

Percent inhibition of thromboxane B_2 (TXB_2) from baseline in the *CYP2C9* genotype groups after a single 15 mg oral dose of meloxicam. Each value represents the mean ± SD. ●, *CYP2C9*1/*1* (*n* = 12); ▲, *CYP2C9*1/*13* (*n* = 9)

subjects was decreased to 37.9% compared with that in the *CYP2C9*1/*1* subjects ($P < 0.001$). The C_{max} of meloxicam in the *CYP2C9*1/*13* subjects was 1.46 fold higher in the *CYP2C9*1/*1* subjects ($P < 0.01$).

The meloxicam-induced inhibition of TXB_2 generation was assessed from baseline after the oral administration of meloxicam. Subjects with *CYP2C9*1/*13* tended to show greater inhibition of TXB_2 generation relative to baseline than subjects with *CYP2C9*1/*1* (Figure 2). Likewise, *CYP2C9*1/*13* subjects tended to have significantly higher values for area under the effect curve from 0 to 72 h than the subjects with *CYP2C9*1/*1* (Table 3).

Table 3

Pharmacodynamic parameters (mean ± SD) of meloxicam according to *CYP2C9* genotype

Variable	*CYP2C9*1/*1* (*n* = 12)	*CYP2C9*1/*13* (*n* = 9)
Maximum observed TXB_2 inhibition (%)	60.3 ± 8.3 (55.0, 65.6)	63.5 ± 8.5 (56.9, 70.0)
AUEC (%·h)	2033 ± 631 (1633, 2435)	3337 ± 552*** (3013, 3862)

Values in parentheses represent 95% confidence intervals. AUEC, area under the effect (percent of inhibition of TXB_2 generation)–time curve. $^{***}P < 0.001$ compared with the *CYP2C9*1/*1* group.

Discussion

Genetic polymorphisms in drug-metabolizing enzymes cause significant inter-individual variability in dose–concentration relationships and drug response. In the present study, we examined the effect of the *CYP2C9*13* allele on the pharmacokinetics and pharmacodynamics of meloxicam. Here, the mean CL/F value of meloxicam was significantly lower in *CYP2C9*1/*13* subjects than in *CYP2C9*1/*1* subjects.

The *CYP2C9*13* allele was observed in 13 subjects from a population sample of 1213, and all 13 subjects with the *CYP2C9*13* allele were the heterozygous variant with *CYP2C9*1/*13* (data not shown). Among the 13 subjects with *CYP2C9*1/*13*, two had a liver health problem (abnormal aspartate transaminase and alanine transaminase concentrations) and two subjects did not consent to participate in the pharmacokinetic study of meloxicam. Thus, a total of nine subjects with *CYP2C9*1/*13* were enrolled in the clinical study of meloxicam. The frequency of the *CYP2C9*13* allele in Koreans (0.54%) is lower than in the Chinese population (1.02%) [9]. Interestingly, a Chinese subject who was a *CYP2C9*3/*13* heterozygote demonstrated a significantly longer elimination half-life for lornoxicam and tolbutamide compared with *CYP2C9*1/*1* [9]. In the three-dimensional structure models study, the *trans* configuration of the bond between p.Pro90 and p.Asp89 in *CYP2C9*13* was identified. In addition, the backbone of residues p.Ala106–p.Arg108 in *CYP2C9*13* turns over and their side chains block the entrance for accessing substrates so that the entrance of *CYP2C9*13* shrinks greatly compared with that in the wild-type, which is believed to be the dominant mechanism of the catalytic activity reduction [16]. Only two studies have previously evaluated whether the *CYP2C9*13* allele influences the pharmacokinetics of lornoxicam [13] or losartan [15]. However, small sample sizes were a limitation for both of these studies. Thus, our study is the first to evaluate the *in vivo* effects of the *CYP2C9*13* allele on the pharmacokinetics and pharmacodynamics of a CYP2C9 substrate with a sample size sufficient for a statistical power above 0.80. Here, the AUC

of meloxicam was increased 2.43-fold and its oral clearance was decreased by 62.1% in two *CYP2C9*1/*13* subjects compared with *CYP2C9*1/*1*, indicating a significant decrease in meloxicam metabolism and suggesting potential toxicity with other CYP2C9 substrates that have a narrow therapeutic index.

CYP2C9 sequencing was performed in order to identify additional changes of the *CYP2C9* coding region in all subjects participating in this clinical study of meloxicam. The genotype results obtained by PCR-RFLP fully corresponded to the sequencing results. Further, no additional changes in the *CYP2C9* coding region were identified in any of the subjects.

Most plasma concentration–time curves exhibited two peaks after oral administration of meloxicam, with a small second peak occurring 10 to 12 h after administration. This result has also been reported previously for the disposition of piroxicam [22, 23] and meloxicam [24–27]. The AUC and the elimination half-life of intravenous meloxicam are reduced by cholestyramine, indicating involvement of the entero-hepatic or entero-enteric circulation [28], which may explain the observed double peaks and prolonged absorption of meloxicam.

The enolic acid of meloxicam preferentially inhibits COX-2 over COX-1 [29–31], and the inhibition of COX-1 by meloxicam was determined by measuring TXB_2 concentrations in clotted whole blood *ex vivo*. The pharmacodynamic data from our study suggested that a single 15 mg dose of meloxicam was sufficient to significantly inhibit TXB_2 generation, which is consistent with a previous report [32]. The *CYP2C9*1/*13* genotype significantly increased the inhibition of TXB_2 generation (AUEC) in this study. Taken together with the pharmacokinetic and pharmacodynamic results of this study, the *CYP2C9*13* allele may increase the potential for unpredictable adverse effects of meloxicam.

The oral clearance of meloxicam in subjects with *CYP2C9*1/*13* was significantly decreased by 62% compared with subjects with *CYP2C9*1/*1*. Although different from the results of *in vitro* studies on CYP2C9 substrates, the *CYP2C9*13* allele appeared to have lower activity than the *CYP2C9*1* allele, which has been extensively studied in humans. In addition to meloxicam, CYP2C9 is involved in the metabolism of hypoglycaemic, anticonvulsant, anticoagulants and antihypertensive drugs. Interestingly, the *CYP2C9*1/*13* genotype was recently found to be associated with a lower warfarin dose following mechanical heart valve replacement in a Korean patient [17]. In addition, phenytoin clearance is impaired by *CYP2C9*2*, **3*, **5*, **6* and **11* variants [33–35]. Based on these results, the *CYP2C9*13* allele is expected to have lower activity than the *CYP2C9*1* allele, and may be at risk for narrow therapeutic indices, e.g. warfarin and phenytoin. Although the frequency of the *CYP2C9*13* allele is low, it should nevertheless be considered for warfarin and phenytoin dosing predictions in East Asian populations.

In conclusion, the *CYP2C9*1/*13* genotype is associated with decreased metabolism and increased pharmacodynamic effects of meloxicam.

Competing Interests

All of the authors declare that there are no financial or personal relationships connected with the research described herein that would lead to a conflict of interest.

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