Research Article

Pamukkale Medical Journal
doi:https://dx.doi.org/10.31362/patd.1351539

The relationship of postoperative tramadol activity with the CYP2D6*17 genome in total knee artroplasty patients

*Total diz artroplastisi uygulanan hastalarda postoperatif tramadol etkinliğinin CYP2D6*17 genomu ile ilişkisi*

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Posted date:28.08.2023 Acceptance date:26.12.2023

Abstract

Purpose: In our study, we examined the effect of tramadol maintenance on the VAS score in geriatric patients. We observed them until the postoperative 60th minute. We investigated the incidence of pain in patients who underwent knee arthroplasty in the study. Our aim was to examine the effect of the *17 allele of the CYP2D6 genome on postoperative tramadol activity.

Materials and methods: In our study we examined 110 patients who underwent total knee arthroplasty in the Department of Orthopedics and Traumatology at our facility, along with 100 healthy individuals without complaints who served as the control group. Each patient received a 100 mg dose of intravenous tramadol (Contramal). The postoperative VAS scores of the patients were recorded at 0-15-30-45-60 minutes.

Results: The average age of the patients was 62.36 years. In our study, 86.4% of the patients were female, while this rate was 46% in the control group. We found that 3.65% of individuals (*17 carriers) possessed the *17 allele in both the patient group (n=7) and the control group (n=7). At the postoperative 0th minute, the VAS score for patients in the *1/*1 group was 91.07, while for the *1/*17 group, it measured 95.0. There was no statistically significant difference between the genomes (p>0.050). Likewise, no statistically significant difference was found between the genomes at the postoperative 15th, 30th, 45th, and 60th minutes (p>0.050). However, we observed a statistically significant decrease in the postoperative VAS score between 0-60 minutes in both groups, indicating time-dependent variation (p=0.000).

Conclusion: When examining diverse literature on tramadol classification as intermediate metabolizer (IM) or extensive metabolizer (EM) concerning the *17 allele, our study indicates that the *17 allele should be regarded as both extensive metabolizer (EM) and normal metabolizer (NM).

Keywords: Total knee arthroplasty CYP2D6, Tramadol, CYP2D6*1/*17, postoperartive pain.

Ok N, Gurbuz ME, Koseler A. The relationship of postoperartive tramadol activity with the CYP2D6*17 genome in total knee artroplasty patients. Pam Med J 2024;17:237-242.

Öz

Amaç: Geriatrik hastalarda tramadol idamesinin VAS skoruna etkisini incelediğimiz çalışmamızda ameliyat sonrası 60. dakikaya kadar gözlem yaptık. Çalışmada diz artroplastisi uygulanan hastalarda ağrı insidansını araştırdık. Ameliyat sonrası tramadol etkinliğine CYP2D6 genomunun *17 alelinin etkisini incelemeyi amaçladık.

Gereç ve yöntem: Bu çalışmaya Pamukkale Üniversitesi Tıp Fakültesi Ortopedi ve Travmatoloji Anabilim Dalı'nda servisimize total diz antroplastisi uygulanan 110 hasta ve kontrol grubu olarak şikâyeti olmayan sağlıklı 100 kişi dahil edildi. Her hastaya intravenöz yoldan 100 mg Tramadol (contramal) uygulandı. Hastaların post-op 0-15-30-45-60. dk VAS skorları kaydedildi.

Bulgular: Hastalar ortalama 62,36 yaşındaydı. Çalışmamızdaki hastaların %86,4'ü kadınken kontrol grubunda bu oran %46 olarak bulundu. *17 alelinin varlığı hasta (n=7) ve kontrol grubunda (n=7) toplamda %3,65 oranında (n=14) *17 taşıyıcısına rastladık. VAS postoperartive 0. dakikada *1/*1 grubundaki hastaların VAS skoru 91,07 ve *1/*17 genomunun VAS skoru 95,0 şeklindeydi ve genomlar arasında istatistiksel olarak anlamlı bir farklılık yoktu (p>0,050). Benzer şekilde ameliyat sonrası 15., 30., 45. ve 60. dakikada da genomlar arasında istatistiksel olarak anlamlı bir farklılık yoktu (p>0,050). Zamana bağlı değişimde her iki gruptada post-op VAS skorunun 0-60 dakika arasında istatistiksel olarak anlamlı şekilde düştüğünü gördük (p=0,000).

Sonuç: Tramadolun *17 aleli ile ilişkisinde IM veya EM olarak sınıflandırıldığı literatürdeki farklı sonuçlar alınmış çalışmaları incelediğimizde bizim çalışmamızın sonuçlarına göre: *17 aleli EM ile NM şeklinde değerlendirilmesi gerektiğini düşünüyoruz.

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Anahtar kelimeler: Total diz artroplastisi, CYP2D6, Tramadol, CYP2D6*1/*17, ameliyat sonrası ağrı.

Ök N, Gürbüz ME, Köseler A. Total diz artroplastisi uygulanan hastalarda postoperartive tramadol etkinliğinin CYP2D6*17 genomu ile ilişkisi. Pam Tıp Derg 2024;17:237-242.

Introduction

Tramadol is rapidly and nearly entirely absorbed after oral administration [1]. After a single oral dose, tramadol has an average bioavailability of around 68%, which escalates to over 90% following multiple doses [2, 3]. IV administration reports a single dose with 90% bioavailability [1]. Although CYP2D6 accounts for only about 2-4% of hepatic CYP enzymes, as one of the most extensively researched CYPs, it metabolizes approximately 25% of drugs processed in the human liver [4]. The liver metabolizes tramadol through O- and N-demethylation processes, alongside conjugation reactions that result in the production of glucuronides and sulfate metabolites. Cytochrome P450-2D6 mediates the (O-) demethylation of dexmethitramadol [5-7].

While tramadol is generally categorized as 'opioid-like,' previous studies have often included it indiscriminately with other opioids when describing the effects of opioids on postoperative outcomes [8-10]. It's commonly accepted that tramadol reaches peak effectiveness approximately 180 minutes after total knee arthroplasty (TKA) [10]. However, in some reports, this timeframe has been reported to decrease to 60 minutes, with patients experiencing a reduction in their VAS score to zero [11, 12]. In a study examining tramadol's efficacy after 60 minutes, the VAS score showed an average decrease of 70 units [12]. This study explores the effect of tramadol maintenance on the VAS score in geriatric patients, observed until the postoperative 60th minute. The aim of this study is to investigate the occurrence of pain in patients who underwent knee arthroplasty, examining the impact of the *17 allele of the CYP2D6 gene on postoperative tramadol efficacy.

Materials and methods

The study was conducted at Pamukkale University Faculty of Medicine, specifically within the orthopedics and traumatology service. The study group consisted of patients who had undergone total knee arthroplasty, a procedure recognized for its association with elevated levels of postoperative pain. For this study, we selected 110 patients who had undergone total knee arthroplasty, and the control group comprised 100 healthy individuals without pain. A total of 210 individuals participated in the study, and their CYP2D6 genes were analyzed through DNA isolation. Pain assessment was conducted using the Visual Analog Scale (VAS), which employed a scale ranging from 0 to 100 (no pain: 0, excruciating severe pain: 100).

We performed genomic DNA isolation from blood samples obtained from the study participants using the standard phenol-chloroform method. We utilized the Polymerase Chain Reaction method to amplify specific genomic regions from the isolated DNA genomes. We examined the presence of the *1/1 and *1/17 alleles within the isolated CYP2D6 genomes.

The drug doses administered were as follows: Tramadol (Contramal) 100 mg was diluted in 150 ml of saline and intravenously administered over 20 minutes at the onset of the postoperative period. We recorded pain scores during the initial 60 minutes and closely monitored patients for any potential side effects. Thankfully, no complications were noted, and the study concluded at the 60-minute postoperative interval. The patient group excluded individuals who had taken analgesics within the past 6 hours, those with kidney or liver diagnoses, individuals sensitive to Tramadol, and those who declined to participate.

Research Termination Criteria: No drug-related side effects were noted throughout the study. The study concluded upon reaching the specified number of participants.

Statistical analysis

IBM SPSS for Windows version 25 statistical package program was used for analysis. Number(n) and percentage (%) were used for categorical data, mean and standard deviation were used for numerical variables. Since the

ratio of the number of patients between alleles did not support the normal distribution, it was analyzed with the Mann Whitney U test. *P*<0.05 was considered significant.

Permission was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committee for the study 18/01/2022 date and 2022TIPF006 permission number.

Results

The average age of the patients was 62.36±13.62 years. In our study, 86.4% of the patients were women, while this percentage was 46% in the control group. Upon examining the presence of the *17 allele, we identified a total of 7% carriers of the *17 allele in both the patient and control groups (Table 1).

The comparison of the *17 allele with the normal metabolizer *1 allele in the CYP2D6 genome is given in the Table 2. At the 0th minute postoperative VAS assessment, patients with the *1/*1 genotype had a VAS score of 91.07, whereas those with the *1/*17 genotype scored 95.0. Notably, there was no statistically significant difference observed between the genomes (p>0.050). Likewise, no statistically significant difference was observed between the genomes at the 15th, 30th, 45th, and 60th minutes postoperatively (p>0.050). We observed a statistically significant decrease in the postoperative VAS score between 0 and 60 minutes in both groups, indicating a time-dependent variation (p=0.000).

Table 1. Demographic and clinical data

		Patient (n=110)	Control (n=100)
Gender	Female	95 (86.4%)	46 (46%)
	Male	15 (13.6%)	54 (54%)
CYP2D6	*1/*1	103 (93.6%)	93 (93%)
	*1/*17	7 (6.4%)	7 (7%)

Table 2. VAS score variation of CYP2D6 *1/*1 and *1/*17 alleles

VAS score	*1/*1 (n=103)	*1/*17 (n=7)	*p*
Postoperative 0. min	91.07±9.31	95.0±5.0	0.306
Postoperative 15. min	70.92±16.87	78.57±8.99	0.144
Postoperative 30. min	52.04±23.47	42.86±17.04	0.198
Postoperative 45. min	37.33±20.81	27.14±18.00	0.207
Postoperative 60. min	29.47±19.28	22.86±14.96	0.369
p*	0.000	0.000	

*Change between 0-60 minutes, VAS: Visual Analog Scala

Discussion

In our study, 86.4% of the patients who underwent knee osteoarthritis prosthesis were predominantly women. The average age of these patients, 67.19, aligns with the geriatric patient population. While investigating the influence of the CYP2D6 genome on the population, including healthy individuals, the average age of the healthy participants was 57.05, notably lower than that of the patients. Given the stability of the CYP2D6 genome in patient genetics and its independence from age-related changes, we excluded the age difference between the groups from the statistical analysis.

The IM phenotype is characterized by a combination of a null allele and an allele with reduced function (*10, *14, *17, *18, *36, *41, *47, *49, *50, *51, *54, 55, and 57). Reduced enzymatic activity can stem from factors such as diminished protein stability, alterations in

substrate recognition, or reduced substrate affinity [4]. A multicenter study demonstrated a 93.1% reduction in tramadol clearance among individuals with CYP2D610, whereas those with CYP2D617 exhibited a 64% reduction in tramadol sensitivity [13]. Remarkably, the diminished substrate-enzyme affinity observed with other CYP2D6 substrates interacting with the *10 and *17 variants was absent in this case [13].

Dagostino et al. [14] compiled the association between CYP2D6 alleles and metabolizer classification, categorizing the *1/*17 and *2/*17 alleles as extensive metabolizers (EM), while *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *29, *35, and *41 haplotypes were considered intermediate metabolizers (IM). In their meta-analysis, Magarbeh et al. [15] designated the *17 allele as an extensive metabolizer and compared it to other studies. These studies encompassed two investigations examining the *17 allele's involvement in codeine toxicity and tramadol activity, suggesting that the *17 allele might exhibit greater efficacy compared to the *1/*1 genotype in these scenarios [15-17]. Nevertheless, due to the relatively lower frequency of studies focusing on CYP2D6 compared to other alleles in its group, it is frequently compared in the literature. It's important to note that it doesn't enjoy the same level of prominence as other alleles such as *2, *3, *4, *6, *10, and *41, for which extensive data on the mechanism of action is available.

According to a study conducted by Aynacioglu et al. [18] in Türkiye with 404 participants, the incidence rate of the *17 allele in the Turkish population is 1.11%. Even in the Indian population, where the *17 allele is most prevalent globally, it has been reported to occur in 3.3% of the population [19]. Its prevalence was reported to be 0.8% in the African population [20]. In our study, we identified a higher occurrence of the *17 allele, present in 14 patients (3.65%) out of a total of 210 participants, which contrasts with the frequencies commonly reported in the literature.

The activation and metabolism of tramadol's primary active metabolite are largely mediated by CYP2D6 [21, 22]. Therefore, CYP2D6 plays a crucial role in tramadol pharmacokinetics [5]. Previous studies have investigated the influence of the CYP2D6 genotype on plasma levels of tramadol and its metabolites, as well as on the efficacy and adverse reactions associated with tramadol (such as nausea, vomiting, sweating, pruritus, constipation, and headache) [21, 23, 24]. Oscarson et al. [19] observed that the *17 allele alone did not exhibit any effect on enzyme activity. However, their findings indicated that the CYP2D6*17 allele had a distinct impact, as it represents a polymorphic variant of cytochrome P450. This variant requires a combination of substitutions to modify the catalytic properties of the enzyme.

In conclusion, our study revealed that patients possessing the *17 allele reported less pain compared to those without it. However, all patients who received tramadol after total knee arthroplasty had pain scores below 50, considered the pain threshold at 60 minutes. We hypothesize that the absence of a statistically significant difference could be attributed to the limited number of patients carrying the *17 allele in our study. Nonetheless, our observed carrier rate of 3.65% was notably higher than the rates commonly reported in the literature.

At the 30th minute, patients with the *17 allele exhibited a VAS score below 50, while patients with the *1/*1 genotype maintained a VAS score above 50.

Upon reviewing literature studies categorizing tramadol as IM or EM concerning the *17 allele, our study's findings suggest that the *17 allele should be regarded as both EM and NM.

Conflict of interest: No conflict of interest was declared by the authors.

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Ethics committee approval: Permission was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committee for the study 18/01/2022 date and 2022TIPF006 permission number.

Authors' contributions to the article

M.E.G. and N.O. constructed the main idea and hypothesis of the study. M.E.G. and A.K. developed the theory and arranged the material and method section. N.O. and A.K. have done the evaluation of the data in the results section. Discussion section of the article written by N.O. and M.E.G.

A.K. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.