Cigarette Smoking Influences Montelukast Pharmacokinetics in Jordanian Population

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ABSTRACT

Background: Montelukast is one of the main therapeutic agents used for asthma management. Its therapeutic effectiveness is greatly influenced by the expression of metabolic enzymes and/or transporters involved in its disposition.

Objectives: To assess the effect of smoking on montelukast pharmacokinetics in four bioequivalence studies against the reference drug Singulair®.

Methodology: Data were extracted from bioequivalence studies to compare 10 mg generic Montelukast to Singulair® the originator. Primary pharmacokinetic parameters, maximum plasma concentration (C_{max}) and area under the curve ($AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$) were calculated using Kinetica®. Analysis of Variance was performed to compare montelukast pharmacokinetics between smokers and non-smokers. Statistical significance was set at $P \leq 0.05$.

Results: Mean± SD montelukast C_{max} (ng/mL) was 397.1 ± 125.7 in non-smokers compared to 352.8± 133.9 in smokers. Significant alterations in montelukast C_{max} (P= 0.0206), AUC $_{0\text{-}t}$ (ng. h/L) 2335 ± 111, P= 0.0016, and AUC $_{0\text{-}inf}$ (ng. h/L) 2509 ± 1163, P= 0.0015 were observed in the study participants who are smokers.

Conclusion: Despite the minimal fold-decrease in montelukast pharmacokinetic parameters in smokers compared to non-smokers, this might have a profound clinical impact on the therapeutic effectiveness of montelukast in patients.

Keywords: Montelukast Pharmacokinetics, smoking, bioequivalence, Singulair®, Montelukast bioequivalence, enzyme induction.

INTRODUCTION

Montelukast is a cysteinyl leukotriene subtype 1 receptor antagonist that has demonstrated high efficacy for allergic rhinitis and asthma treatment [1]. It was first licensed in 1998 under the brand name Singulair® and is available in three different forms; 4 mg oral granules, 4 and 5 mg chewable tablets and 10 mg film-coated tablets [2, 3]. In healthy adults, montelukast reaches the maximum plasma concentration (C_{max}) in 3–4 h following administration of 10 mg. *In vitro* analysis of montelukast metabolism showed major involvement of CYP3A4, CYP2C8, CYP2C9, and UGT1A3 enzymes [4]. Average elimination half-life ($t_{1/2}$) is 2.7 to 5.5 hours with no

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gender, age and body mass index (BMI) significant differences in Montelukast pharmacokinetics [5, 6].

Different studies comparing montelukast generics to Singulair® demonstrated bioequivalence under both fasted and fed states [7, 8]. However, adverse events have been reported when montelukast was administered under fasting conditions [7].

According to *Angelica Tiotiu et al*., 20% of patients with asthma are cigarette smokers [9]. The same study reported poor asthma control and higher exacerbation of symptoms in patients who were identified as current smokers [9]. Additionally, a poor response to corticosteroid treatment has been observed in this group of patients [10]. Unfortunately, the effect of smoking on treatment plans and outcomes is underestimated and has not received proper attention [11, 12]. For instance, smokers are excluded from pivotal clinical trials, which eventually leads to misinterpretation of the outcome in the general population, bearing in mind the high prevalence of smoking habits.

The objective of this study was to evaluate the effect of smoking habits on montelukast pharmacokinetics in four different bioequivalence studies.

METHODOLOGY

Materials:

Ethical approvals: The Institutional Review Board (IRBs) granted approval for this study on 07/06/2008, and the study was carried out under the protocol study number 32-16122-09-4223. The study precisely followed the ethical guidelines of the Declaration of ICH-GCP, Helsinki, and Jordan Food and Drug Administration, confirming that the participants were fully aware and consented before participation. The Investigator Good Clinical Practice (GCP) statement manages ethical conduct, stresses regulatory agreement, and protects participants.

Instrumentation and chromatographic conditions

The LC-MS/MS system used was an Agilent 1200 series (Agilent Technologies, India) equipped with a G1311A quaternary pump, which was attached to an API 4000 detector from SCIEX Applied Biosystems/MDS. Chromatograms were obtained using Analyst software (version 1.6). Chromatographic separation was carried out on a Thermo Hypersil GOLD™ Cyano HPLC column (50 × 4.6 mm; 5 µm) at 20 °C. Separation was achieved using an isocratic mobile phase consisting of 0.5 mM ammonium chloride and acetonitrile (20:80% v/v) at a flow rate of 0.5 mL/min. The total sample run time was 0.7 minutes (Figure 1). Detection of Montelukast and Montelukast-D6 (internal standard) was achieved using multiple reaction monitoring (MRM) in the positive ionization mode under optimized conditions, as summarized in Tables 1 and 2.

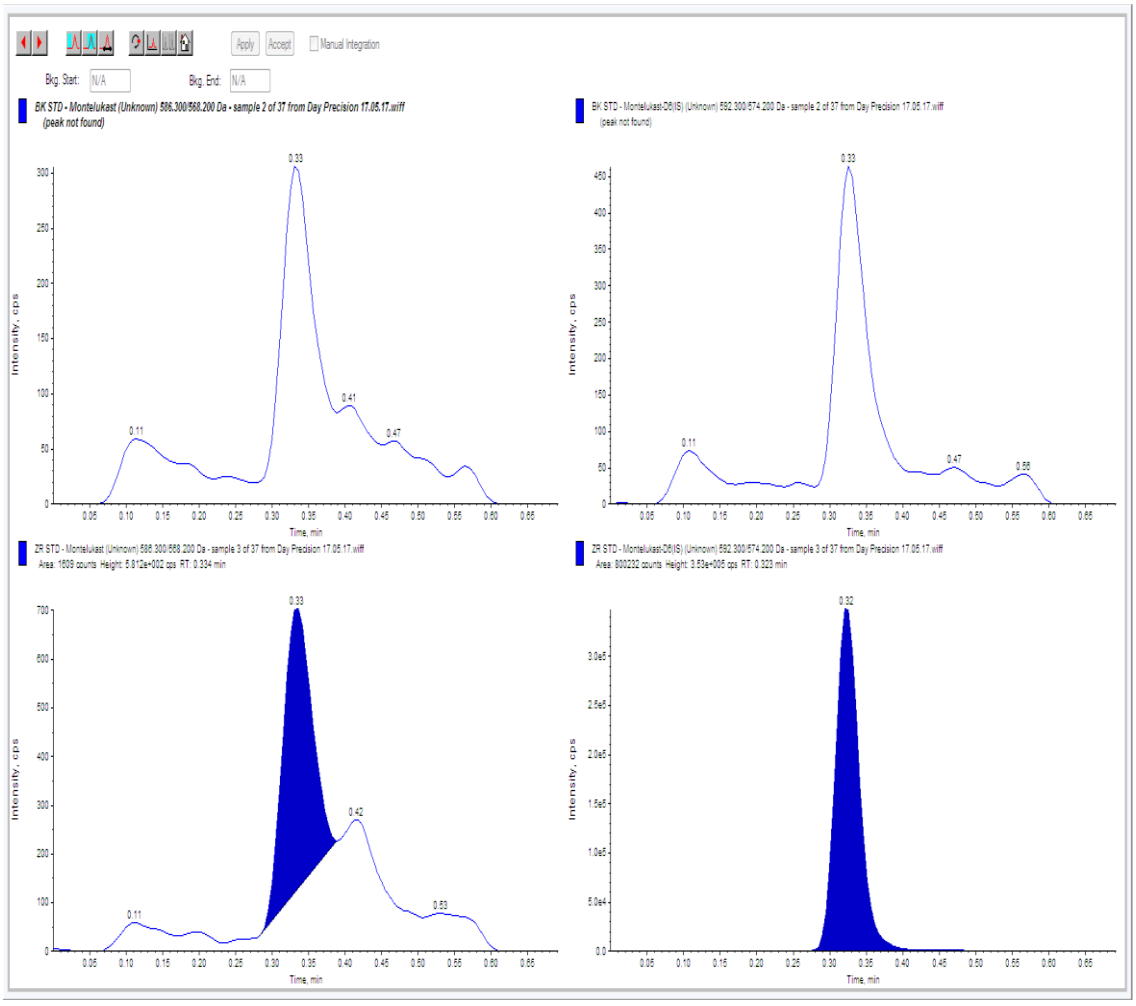
Table 1: Summary Table of Chromatographic Conditions and Mass Spectrometric Conditions

Flow Rate	**0.550 mL/min**
Column Temperature	20 °C
Autosampler Temperature	10 °C
Injection Volume	5 µl
Total Run Time	0.7 min
Column	Thermo Hypersil GOLD CN, (50×2.1) mm , 5 µm

Table 2: Compound's detection and retention times:

Compound Name	**Detection**			**Retention Time**	
Montelukast	Parent 586.30 and daughter 568.20			0.33 min	
Montelukast_D$_6$	Parent 592.30 and daughter 574.20			0.33 min	
MRM Parameters					
Compound Name		**DP**	**EP**	**CE**	**CXP**
Montelukast		81.0	10.0	19.0	22.0
Montelukast_D$_6$		81.0	10.0	19.0	22.0
Positive Mode					
CUR	**CAD**	**GS1**	**GS2**	**Temp.**	**IS Voltage**
25	8	35	50	550	5500

A



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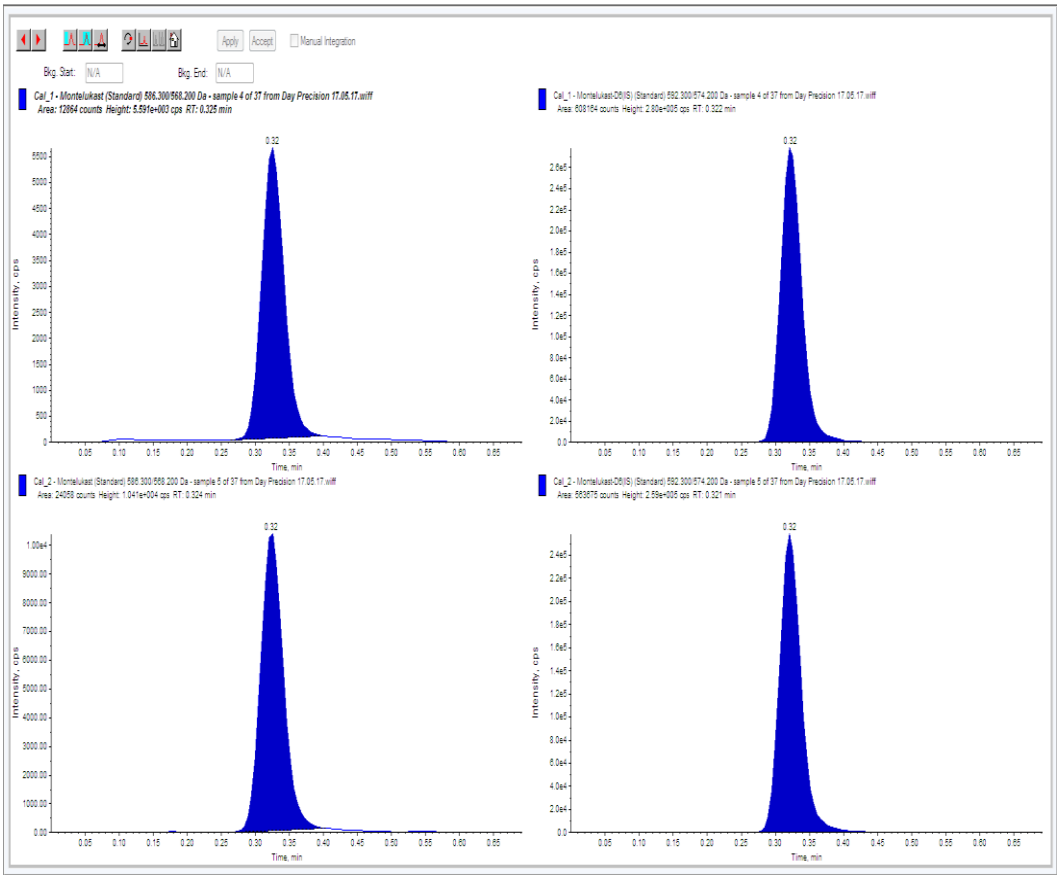

Figure 1: Representative MRM chromatograms of (A) Montelukast chromatograms for blank plasma free of Montelukast or IS and zero standard (Blank plasma with IS), (B) Montelukast HPLC chromatograms, LLOQ Blank plasma spiked with Montelukast (1st Calibrator 10.0 ng/ml,) and 2nd Calibrator 20.0 ng/mL.

Montelukast working solutions: 10 mg of montelukast was dissolved in 7 mL of methanol (MeOH) in 10 mL of V.F, vortexed until dissolved, and completed to volume with MeOH, to obtain a concentration of (1.000 mg Montelukast/mL) stock solution. Five hundred microliters of montelukast stock solution (1.000 mg/mL) were diluted in 10 mL of (1:1 methanol: water). The final concentration was (50.000 µg Montelukast/mL). Montelukast_D_6 was dissolved in an equal volume of MeOH to obtain a concentration (1000 mg Montelukast_D_6 /mL). Montelukast_D_6 stock solution (25 µL, 1.000 mg/mL) was diluted to 10.0 ml of (1:1 methanol: water). The concentration obtained was (2.500 µg of Montelukast_D_6 /mL).

Method validation: The LC-MS/MS method was developed and validated according to the International Committee for Harmonization (ICH) guidelines. Interday accuracy, precision, linearity, recovery, stability, and robustness were assessed. The method linearity was investigated in the range of 10.00 -600.00 ng/mL. Method validation was previously published by *Said et al* [13].

Conduct of the bioequivalence study: Four separate

open, randomized, single-dose, two-way crossover bioequivalence studies were performed for four different test formulations to compare their bioavailability to that of the reference drug Singulair® 10 mg tablet. All studies were performed according to the GCP guidelines and were approved by the Jordan Food and Drug Administration. The main inclusion criteria were being healthy, male and aging 18-45 years. IRB approval and consent forms were obtained prior to study initiation and dosing. Participants were randomized to be offered either the reference drug, Singulair® 10 mg tablet or the test drug of the same strength. All participants received references and tests in either period 1 or period II. Participants fasted for 10 h prior to montelukast administration. The tablet contained 240 mL of ambient water. Blood samples were collected prior to dose administration and up to 24 h post-dose into K2EDTA tubes. The time points of samples collection were pre-dose, 0.33, 0.66, 1, 1.33, 1.66, 2, 2.33, 2.66, 3, 3.33, 3.50, 4, 5, 6, 8, 10, 12 and 24 hours. Blood samples were stored at -80 °C until the time of bioanalysis. Plasma samples were obtained *via* centrifugation for 10 minutes at 4000 RPM. The montelukast concentration was measured using the validated LC-MS/MS method. A total number of blood samples were collected and analyzed were 6912 samples and no withdrawal or dropouts were reported.

Pharmacokinetic and statistical analyses: The primary pharmacokinetic parameters, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} were calculated using non-compartmental analysis (Kinetica® 2000 version 4.1, Innaphase Corporation, France). A 90% confidence interval for the intra-individual ratios (test/reference) of the primary pharmacokinetic parameters was calculated, and an acceptance criterion for bioequivalence was set at (80%-125%). The significance level was set at $P < 0.05$. Unpaired Student's *t*-test was performed using GraphPad Prism version 6.01, released in 2012 (GraphPad Software, San Diego, USA), to compare the two formulations and investigate the period, subject, formulation, and sequence effects. Other covariates, such as demographic data (age, sex, height, weight, and smoking status), were also incorporated into the model. Univariate and multivariate regression analyses were used to assess the association between demographic data, lifestyle habits, and montelukast primary pharmacokinetic parameters. Data were summed from the four studies after ensuring that the same inclusion/exclusion criteria were maintained, IRB and consent forms were included, and sampling times were consistent.

RESULTS

Validation of the LC-MS/MS method

The analytical method was fully validated, including all critical parameters, such as accuracy, precision, specificity, linearity, stability, matrix effect, and robustness. Each parameter was fully evaluated to ensure the reliability and suitability of the method for the anticipated application [13]. The method was linear in the range 10.00 -600.00 ng/mL. The method proved to be precise and accurate; interday - intraday precision and accuracy were with CV% less than 8%, which is acceptable according to the ICH guidelines. The stability of the method was found to be consistent and reliable under various conditions, such as long term, short term, and room temperature. Short-term stability was assessed at different concentrations by comparing the analyzed quality control samples with their supposed concentrations, and the results showed that the samples remained stable for 18 h. Long-term stability was measured using QC samples kept at -70 ◦C for 31 days at different concentrations (LQC and HQC levels), and no significant concentration difference was observed, implying the stability of Montelukast and Montelukas_D6 at both -20 ± 5 ◦C and -70 ± 10 ◦C for a time interval of 31 days. No matrix effect was observed, and an acceptably high recovery was achieved [13].

Montelukast pharmacokinetics

A total of 192 subjects were analyzed. The study participants were classified according to smoking status, and 56.25% were smokers. Mean± SD age and BMI were 29.86 ± 5.77 years and 26.02 ± 2.44 kg/m^2, respectively in non-smokers group. On the other hand, smokers had mean ± SD age and BMI of 29.26 ± 5.10 years and 25.34 ± 2.56

kg/m^2, respectively. Age and BMI were not predictors of montelukast pharmacokinetics according to smoking status (P= 0.4659 and P= 0.0643, respectively).

The plasma concentration vs. time profiles of both the test formulations and Singulair® were comparable (Figure 2). Mean± SD C_{max} and t_{max} of Montelukast for the test formula were 377.44± 124.06 ng/mL and 3.4± 1.36 hr while for the reference 369.29± 134.45 ng/mL and 3.21± 1.18 hr. The AUC_{0-t} was 2551.84± 1101.07 ng.hr/mL for the reference compared to 2580.19± 979.92 ng.hr/mL in the test group whereas AUC_{0-inf} was 2742.78± 1142.62 ng.hr/mL and 2767.48± 1073.95 ng.hr/mL in the reference and test groups, respectively. The study participants who were smokers had a significantly lower C_{max} than non-smokers by 11.16% (P= 0.0206) (Table 3). No significant difference in t_{max} was observed between smokers and non-smokers (P= 0.4065). In contrast, AUC $_{0-t}$ and AUC $_{0-inf}$ were significantly different between the two groups (P= 0.0016 and P= 0.0015, respectively). The fold-change in both AUC $_{0-t}$ and AUC $_{0-inf}$ was approximately 0.82-folds in smokers compared to that in non-smokers. Similarly, C_{max} in smokers group was 0.89 of that in non-smokers group (Table 3).

Table 3: Demographic and pharmacokinetic data of Montelukast presented as mean± SD

Variable	Non-smoker	Smoker	Difference (Smoker – Non)	95% CI	P-Value
N	84	108			
Age (Years)	29.86 ± 5.77	29.26 ± 5.10	-0.60 ± 0.82	-2.21 to 1.02	0.4659
BMI (kg/m^2)	26.02 ± 2.44	25.34 ± 2.56	-0.68 ± 0.36	-1.4 to 0.04	0.0643
C_{max} (ng/mL)	397.1± 125.7	352.8 ± 133.9*	-44.3 ± 18.9	-81.7 to -6.88	0.0206*
T_{max} (hours)	3.25 ± 1.42	3.41 ± 1.22	0.16 ± 0.19	-0.22 to 0.54	0.4065
AUC $_{0-t}$ (ng.hr/L)	2821 ± 953	2335 ± 111**	-486 ± 152	-785 to -186	0.0016**
AUC $_{0-inf}$ (ng.hr/L)	3020 ± 989	2509 ± 1163**	-511 ± 157	-823 to -198	0.0015**

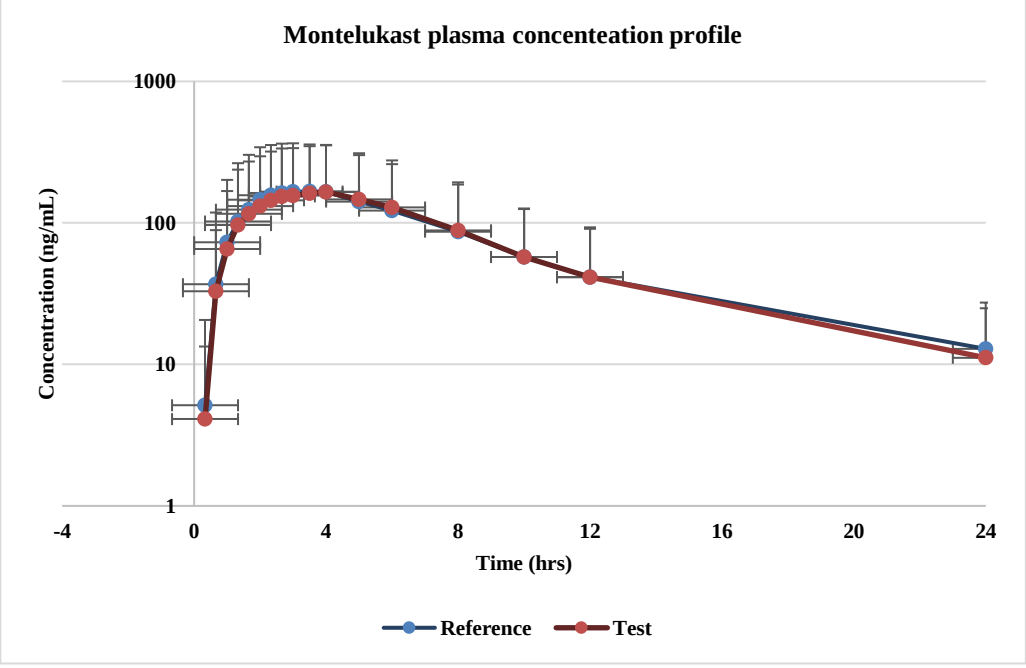

Figure 2 depicts the pharmacokinetic plasma concentration vs. time profile of both the test and reference (Singulair®) formulations of montelukast from four different bioequivalence studies (n=192).

DISCUSSION

Montelukast is one of the main therapeutic agents used for asthma treatment. Several formulations that are bioequivalent to the originator Singulair® are available in the market. However, therapeutic effectiveness can be influenced by several demographic factors, such as smoking status. Consequently, this study aimed to evaluate the effect of smoking status on montelukast pharmacokinetics in four different bioequivalence studies that compared generic formulations of Montelukast to Singulair®.

In the current study, smokers had a significantly reduced montelukast C_{max} compared to non-smokers (P= 0.0206). Similar findings were observed for amitriptyline, clozapine, and mirtazapine pharmacokinetics in smokers [14]. This could be explained by the demonstrated effects of cigarette smoking on the metabolism of different therapeutic agents. These effects are due to the induction of metabolic enzymes, whether phase I or Phase II enzymes [15]. For instance, clozapine and olanzapine pharmacokinetics significantly being influenced by cigarette smoking [16, 17]. Similar findings were reported for theophylline clearance, which increased in smokers (0.063 ±0.019 L/h/kg) compared with 0.040 ± 0.008 L/h/kg [18].

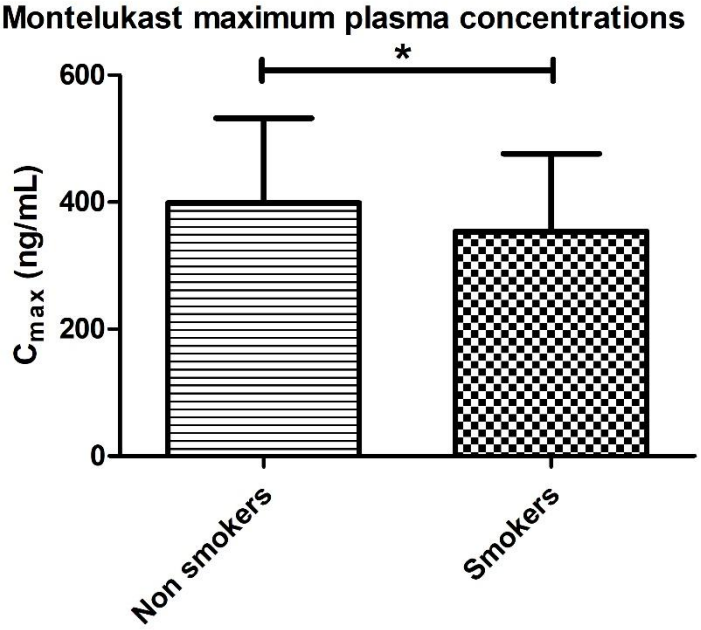

Figure 3 shows the differences in Montelukast C_{max} between smokers and nonsmokers. * Statistical significance.

Previous studies have reported the ability of cigarette smoking to induce the expression of CYP450 enzymes and drug transporters such as OATP1B1, OATP2B1, OAT2, NTCP, OCT1, and BSEP *via* aryl hydrocarbon receptor activation [19]. Montelukast hepatobiliary elimination is mediated through OATP1B1 transport, in which genetic polymorphisms in *SLCO2B1* gene coding for OATP2B1, such as rs12422149, are significantly associated with reduced plasma concentrations of montelukast [20, 21]. This could potentially influence the therapeutic efficacy of montelukast, especially in patients with asthma [20]. Thus, patients who are smokers and use montelukast to manage their asthma might need dosage adjustment and/or monitoring to achieve therapeutic effectiveness of their treatment. Nicotine, the

main ingredient in cigarettes, was found to induce the UGT1A3 enzyme which is one of the main enzymes involved in montelukast metabolism [14]. CYP2C9 polymorphisms may play a major role in altering montelukast pharmacokinetics [22]. Further pharmacogenetic studies are required to investigate the association between cigarette smoking, genetic polymorphisms, and montelukast pharmacokinetics.

Management of asthma primarily depends on the therapeutic concentrations achieved following administration as well as adherence to medication. Considering that one-fifth of asthmatic patients are smokers and montelukast is a major therapeutic agent in their regimen, patients should be monitored for asthma management if they are smokers. A rigorous judgment on the need to adjust the montelukast dose in smokers cannot be made without performing a clinical trial on patients with asthma who are smokers. Previous studies were performed on the montelukast and fluticasone combination compared to placebo. The results showed improved asthma management in asthmatic smokers. However, the smoking effect was not investigated in this trial as a covariate; thus, no concrete conclusions can be drawn [23].

A limitation of this study is that the data were taken collectively from four different bioequivalence studies despite having the same inclusion/exclusion criteria and being from the same ethnic background. Additionally, the pharmacokinetics of these four formulations might be different owing to differences in formulation. However, this limitation was found in both the reference and test groups, which could limit bias.

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Conflict of interest

The authors have no conflict of interest to declare

Funding

The authors did not receive funding to conduct this study.

Authors' contribution

Dr. Rana Said was the primary investigator who designed and conceptualized the study. Rana Abutaima interpreted the data and drafted the manuscript. Dr. Lidia K. Al-Halaseh and Dr. Khaldun have reviewed the manuscript. Dr. Basel Arafat and Prof. Tawfiq Arafat supervised the bioequivalent studies.

Data availability

All data generated in this study is available within the manuscript or supporting material.

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تأثير تدخين السجائر على الحرائك الدوائية لمونتلوكاست في السكان الأردنيين

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ملخص

المقدمة: يُعد مونتلوكاست أحد الخيارات العلاجية الرئيسية المستخدمة في علاج الربو. تتأثر فعاليته العلاجية بشكل كبير بتعبير الإنزيمات الأيضية و/أو النواقل المشاركة في توزيعه.

الأهداف: تقييم الاختلافات في الحرائك الدوائية لمونتلوكاست في أربع دراسات تكافؤ حيوي مقارنةً بالدواء المرجعي سينجولير®.

المنهجية: تم جمع البيانات بشكل رجعي من دراسات التكافؤ الحيوي لمقارنة تحضيرات مونتلوكاست الجنيسة بجرعة 10 مجم مع دواء سينجولير® الأصلي. تم حساب المعلومات الدوائية الأساسية؛ تركيز البلازما الأقصى، المساحة تحت المنحنى AUC_{0-inf} و AUC_{0-t} باستخدام برنامج Kinetica®. تم إجراء تحليل التباين (ANOVA) لمقارنة الحرائك الدوائية لمونتلوكاست بين المدخنين وغير المدخنين. تم اعتبار قيمة $P \leq 0.05$ دلالة إحصائية.

النتائج: كان متوسط ± الانحراف المعياري للعمر ومؤشر كتلة الجسم 5.10 ± 29.26 سنة و25.34 ± 2.56 كجم/م^2 في مجموعة المدخنين. كان تركيز مونتلوكاست الأقصى 125.7 ± 397.1 (ng/mL) في غير المدخنين مقارنةً بـ 352.8 ± 133.9عند المدخنين. تم ملاحظة تغيير كبير في تركيز مونتلوكاست الأقصى(P= 0.0206) ، و AUC_{0-t} (ng.hr/L) (P= 0.0016), 2335 ± 111و AUC_{0-inf} (ng.hr/L) (P= 0.0015), 2509 ± 1163 في المشاركين.

الاستنتاج: بالرغم من الانخفاض الطفيف في معلمات الحرائك الدوائية لمونتلوكاست لدى المدخنين مقارنةً بغير المدخنين، إلا أن ذلك قد يكون له تأثير سريري كبير على الفعالية العلاجية لمونتلوكاست لدى المرضى الذين يستخدمونه.

الكلمات الدالة: الحرائك الدوائية لمونتلوكاست، التدخين، التكافؤ الحيوي، سينجولير®، التكافؤ الحيوي لمونتلوكاست، تحفيز الإنزيمات.

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