# Pharmacokinetic behavior of montelukast in indigenous healthy male volunteers

**Amtul Fayyaz[1], Junaid Ali Khan[1], Muhammad Mudassar Ashraf[1,2]*, Naheed Akhter[3], Bilal Aslam[1], Muhammad Fiaz Khalid[1], Sidra Altaf[1], Rana Dawood Naseer[1], Muhammad Akram[2], Syed Muhammad Ali Shah[2], Muhammad Waqas Khadam[1] and Imtiaz Mahmood Tahir[3]**

[1]Institute of Pharmacy, Physiology and Pharmacology, University of Agriculture, Faisalabad, Pakistan
[2]Department of Eastern Medicine, Directorate of Medical Sciences, Government College University, Faisalabad, Pakistan
[3]College of Allied Health Professionals, Directorate of Medical Sciences, Government College University, Faisalabad, Pakistan

**Abstract**: Aim of present study was to investigate the pharmacokinetic behavior of Montelukast in the healthy male volunteers under indigenous conditions. One tablet of montelukast 10 mg was administered in each subject and blood at different time intervals. Concentration of montelukast in plasma samples was analyzed by high performance liquid chromatography method to calculate pharmacokinetic parameters. The plasma concentration of montelukast was in the range of 1.31-1.76µg/mL at 0.5-12 hours with $C_{max}$ value of 1.59±0.16µg/mL at 3.71±0.64 hours. These values of plasma drug concentrations were above the minimum effective concentration of montelukast during the entire study hours. Absorption and elimination half-lives of the montelukast were evaluated as 2.52±0.54 hours and 2.63±0.35 hours, respectively. The volume of distribution and total body clearance of montelukast were investigated as 0.34±0.01 L/kg and 0.01±0.00 L/hr/kg, respectively. The pharmacokinetic parameters i.e. $C_{max}$, AUC, $t_{1/2}$, $V_d$ and $Cl_B$ of montelukast calculated in present study were found different as compared to that of the previous literature values which was due to genetic and environmental variation.

**Keywords**: Kinetics, leukotriene, genetics, environmental, males.

## INTRODUCTION

Montelukast Sodium is a cysteinyl leukotriene receptor antagonist intended for the management of asthma. Chemically, montelukast is (S, E) -2-(1-((1-(3-(2-(7-chloroquinolin-2-yl) vinyl) phenyl) 3-(2-(2-hydroxypropan-2yl) phenyl) propylthio) methyl) cyclopropyl) acetic acid (Rana *et al*., 2013). It is well absorbed orally with bioavailability of 58-66%. Montelukast undergoes hepatic metabolism and is mainly excreted through the bile. It is metabolized through the CYP2C9 (liver enzyme) following methyl-hydroxylation and by CYP3A4 resulting in 21-hydroxylation and sulfoxidation. The resulting metabolites of montelukast are cleared off through the biliary excretion (Graff *et al.,* 2003).

Different states have varying environmental and topographical conditions in which mankind and animals are populated. The information of the drugs used for different disease conditions is usually obtained from the western country's literature where the genetic make-up and environmental conditions are different from the Asian countries. Pakistan is importing finished and raw drugs for the veterinary and human use. Drug development protocols supported by preclinical and clinical investigations are carried out in drug exporting countries where environmental conditions and genetic makeup of human and animals are different than in the drug importing countries (Naz *et al*., 2017; Sana et al., 2016; Aziz et al., 2016; Ashraf *et al*., 2015; Anwar *et al*., 2015).

Various studies have specified that pharmacokinetic, urinary excretion, renal clearance and optimal dosage are found to be diverse under indigenous circumstances after comparison with reported literature values or in the inserts within the products prepared by its manufacturers. These variations describe the environmental influences on the genetics and ultimately on the drug's pharmacokinetic behaviors. Hence it is necessary that an optimal dosage regimen should be based on pharmacokinetic parameters investigated in an environment and species in which a drug is to be clinically employed (Naz *et al*., 2017; Ashraf *et al*., 2015; Anwar *et al*., 2015; Marier *et al.,* 2004).

Around 40 different types of CYP enzymes have been reported depending upon geographical location and genetic makeup. CYP enzymes play an important role in drug metabolism. Therefore, metabolism of same compound may differ in different regions (Hasler *et al.,* 1999). Genetics is the one reason for this variation. The genetic differences are responsible for different disposition properties of a drug administered in particular individual and hence exhibit different drug response. Different pharmacokinetic models are employed to investigate the pharmacokinetics of drug that help in drug development processes, desired therapeutic effects,

**Corresponding author* e-mail: mudassar_pharmacist@yahoo.com

investigate the drug-drug interactions and adjustment of the doses (Leahy, 2004). Inter individual variability is the major reason for different drug responses due to the genetic variation of enzymes related to the drugs metabolism. Certain enzymes have been studied regarding the ethnic and individual variation for the metabolism of drugs. The distribution of these enzymes may vary among different population; hence those drugs metabolized by CYP2C9 undergo varying disposition properties in different populations (Lewis and Lake, 1998; Zhou, 2003).

Although different researches have been carried out regarding efficacy and pharmacokinetics of montelukast in developing and developed countries. However, the data available for pharmacokinetics of montelukast in the local population is scanty and pharmacokinetics data may change in the local population. Therefore, it is needed to evaluate the pharmacokinetics of montelukast in healthy local population in Pakistan.

In view of the former outlines the present study was designed for the investigation of pharmacokinetic parameters of montelukast sodium in adult male subjects with good health under local environmental conditions.

## MATERIALS AND METHODS

Pharmacokinetics of montelukast in healthy male subjects was studied. These volunteers were selected from University of Agriculture after ethical approval. Written consent was taken and complete information regarding research was provided to all the volunteers. Disease free subjects with 60-75 kg weight and 23-30 years of age were selected on the basis of previous medical history and laboratory testing. Different eliminating factors like drug allergy or intolerance, donation of blood prior to the study initiation, history of drug abuse, alcoholism and smoking etc. were considered before selection of volunteers. The volunteers were asked to abstain from chocolate, grape fruit, caffeinated beverages and cruciferous vegetables during the entire study period as these products can interfere with cytochrome P450 which ultimately may affect drug metabolism. The volunteers were given same diet throughout the study period.

### *Design*

*Cannulation of brachial vein*

For the collection of blood one of the brachial veins was cannulated under strict aseptic conditions with plastic canola.

### *Montelukast*

Montelukast powder (98.6% pure) prepared by Zhejiang Better Pharmaceuticals Co., Ltd., China was a kind gift from NovaMed Pharmaceuticals, Ferozpur Road, Lahore, Pakistan. It was used to establish standard curve of montelukast through HPLC method using mefanamic acid as an internal standard which was prepared by the SynFine Research, Inc, Canada and was a kind gift from NovaMed Pharmaceuticals, Ferozpur Road, Lahore, Pakistan.

A commercial preparation of montelukast tablet (Whizix)®, 10mg (Merck Private Limited, Pakistan) was procured from market. It was administered as a single oral dose after overnight fasting with 100 ml of water.

### *Collection of blood sample*

Blank blood sample from every volunteer was taken before the administration of drug. Next blood samples (5 ml each) were taken at 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 hours post medication. These blood samples were collected in EDTA tubes and were centrifuged at 4000 rpm for 30 min. Collected plasma was preserved at -20ºC until its analysis.

### *Analysis*

*HPLC analysis of montelukast*

Montelukast in plasma was determined by using High Performance Liquid Chromatographic (HPLC) method (Sripalakit *et al.,* 2008). Liquid Chromatographic Pump Sykam S1122 with UV visible Detector Sykam S3210 and thermohypersil column C18 (250×4.6mn, 5µm) was used. Montelukast powder (98.6% pure) was used to establish standard curve of montelukast (fig. 1) through HPLC method using mefanamic acid as an internal standard. Mobile phase consisting of Acetonitrile and 0.05 M ammonium phosphate pH 3.5 (62:38) was used at flow rate of 1ml/min. Injection loop of 20µl was used for the purpose of sample injection. Wavelength, pressure and temperature were adjusted at 275nm, 36kg/cm$^{-2}$ and 25ºC, respectively. The output of detector was monitored by computer software (Peak Simple Chromatography Data System, Buck Scientific Inc., East Norwalk).

The plasma concentration verses time data was plotted on a semilogarthmic graph and pharmacokinetic parameters were calculated with help of a by computer software MW-PHARM APO version 3.02 (Holland).

## STATISTICAL ANALYSIS

The mean value and its standard errors (mean ± SE) for each concentration and parameter was calculated (Steel *et al*., 1997).

## RESULTS

### *Plasma concentration of montelukast*

The values for plasma concentrations (table 1) of montelukast were determined at different time intervals following its oral administration 10 mg. The mean ± SD concentration of montelukast in plasma at 0.5 hour was calculated as 0.435±0.066µg/mL which reached with the passage of time to its maximum level (2.257±0.594

µg/mL) at 3.5 hours and then declined progressively to 0.513±0.211µg/mL at 12 hours.

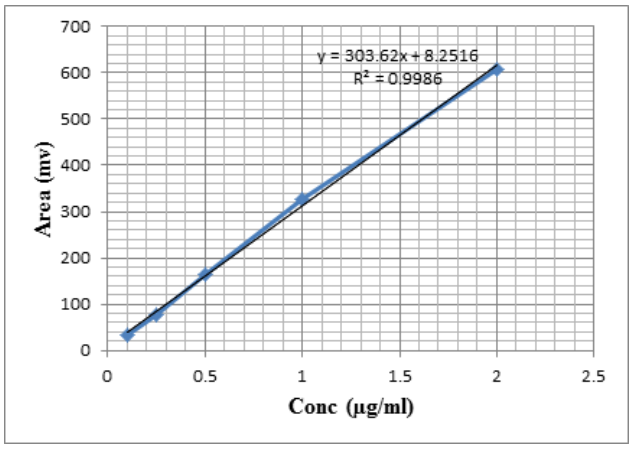


**Fig. 1**: Standard curve of Montelukast after Pharmacokinetic analysis

***Pharmacokinetics***

The concentration versus time data of montelukast 10 mg in healthy male volunteers was plotted on semilogrithmic graph and data was applied on a computer program MW/PHRAM version 3.02 by F. Rombout to determine different pharmacokinetic parameters. The mean ± SD values of various pharmacokinetic parameters have been given in the table 2.

***Peak Levels ($C_{max}$, $T_{max}$ and AUC)***

Mean ± S.D maximum concentration ($C_{max}$) of single oral 10 mg dose of montelukast in healthy male volunteers was 1.59±0.159µg/mL (ranging 1.31 - 1.76µg/mL) which was achieved at 3.71±0.639 hours ($T_{max}$) under the range of 2.66-4.32 hours. Whereas, area under plasma drug concentration versus time curve (AUC) of montelukast in present study ranged between 8.87-16.13 µg.h/ml with mean ± S.D value of 13.75±2.54 µg.h/ml.

***Rate constants ($K_{abs}$ and β)***

The absorption rate constant ($K_{abs}$) is representing the absorption curve slope and is ranged from 0.23-0.47 $hr^{-1}$ with mean ± S.D value of 0.29±0.08 $hr^{-1}$ in the present study. The overall elimination rate constant of montelukast 10 mg after oral administration in healthy volunteers was 0.27±0.04 $hr^{-1}$ within the range of 0.23-0.30 $hr^{-1}$.

***Half-lives ($t_{1/2abs}$ and $t_{1/2β}$)***

Mean ± S.D values of absorption and elimination half-life after single oral administration of montelukast 10mg in male volunteers was 2.52±0.54 (1.48-2.99) hr and 2.632± 0.353 (2.28-3.00) hr, respectively.

***Volume of distribution (Vd) and total body clearance ($Cl_B$)***

The apparent volume of distribution (mean ± S.D) of montelukast in present study was investigated as 0.03± 0.01 L/kg. The body clearance may also be the indicator of the body functions. The total body clearance (mean ± S.D) of montelukast in the present study was 0.01±0.00 L/hr/kg.

## DISCUSSION

The plasma concentration of montelukast calculated at 0.5 hour after drug administration was 0.44±0.07µg/mL at which increased with the passage of time and became maximum (2.26±0.59µg/mL) at 3.5 hours then progressively declined to 0.51±0.21µg/mL at 12 hours. Plasma concentration versus time data was applied on a pharmacokinetic software MW-PHARM APO version 3.02 to determine different kinetic parameters. The maximum plasma concentration ($C_{max}$) of montelukast in present study was recorded as 1.59±0.16µg/mL after 10 mg single oral dose in healthy male volunteers which was found lesser than 2.35µg/mL (Abbas *et al.,* 2013), 2.47± 0.051µg/mL (Kim *et al.,* 2012) and 3.85µg /ml±0.06 (Cheng *et al.,* 1996) following single oral administration of montelukast 10 mg in healthy volunteers. Mean ± S.D $T_{max}$ value of montelukast in the present study was 3.71± 0.64 hr which was found similar to 3.61±1.25 hr in Thai males (Sripalakit *et al.,* 2008) and 3.7 hr in both males and females in USA (Cheng *et al.,* 1996).

Area under the curve (13.74±2.53 µg.h/ml) of single oral administration of 10mg montelukast in healthy male subjects of present study was investigated lesser than AUC value of 37.12±10.20 µg.h/ml in healthy male volunteers of Thailand (Sripalakit *et al.,* 2008), 22.70 µg.h/ml and 19.37 µg.h/ml in females and males, respectively (Cheng *et al.,* 1996) and 1 8.35 µg.h/ml and 1 9.30µg.h/ml for test and reference, respectively, formulations of montelukast (Kim *et al.*, 2012).

The mean ± S.D half-life (2.52±0.54 hours) of single oral dose of montelukast 10 mg in the present study was shorter than half-life values, 5.25hr and 5.30 hr, of two different formulations of montelukast in healthy subjects in Korea (Kim *et al.,* 2012). Similarly, the present half-life value was shorter than half life values, 6.7 hr and 6.3 hr, observed after administration of montelukast in young and elderly individuals of USA (Zhao *et al.,* 1997) and half-life of 3.86±0.58 hours in Thai healthy subjects (Sripalakit *et al.,* 2008). Whereas in a study conducted in healthy Indian subjects, the values of half life were determined as 2.76 hours in poor metabolizers and 1.65 hours for extensive metabolizers of montelukast (Rani and Padh, 2006) which were corresponding to that of half life value of present study.

The apparent volume of distribution is not the actual volume while it serves as proportionally constant that relates the plasma drug concentration to total amount of drug after distribution equilibrium has been attained

**Table 1**: Mean ± SD values of plasma concentration (µg/mL) of montelukast 10 mg after single oral administration in healthy male volunteers.

| Time (hours) | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | 3.0 | 3.5 | 4.0 | 6.0 | 8.0 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Drug Concentration (µg/mL) | 0.44 ±0.07 | 0.77 ±0.08 | 0.99 ±0.05 | 1.26 ±0.27 | 1.55 ±0.39 | 1.93 ±0.19 | 2.26 ±0.59 | 2.02 ±0.45 | 1.27 ±0.35 | 1.02 ±0.36 | 0.51 ±0.21 |

**Table 2**: Mean ± SD values of pharmacokinetic parameters of montelukast 10 mg following single oral administration in healthy male volunteers.

| Parameters | $C_{max}$ (µg/mL) | $T_{max}$ (hr) | AUC (µg.hr$^2$/ml) | $K_{abs}$ (hr$^{-1}$) | β (hr$^{-1}$) | B (µg/mL) | $t_{1/2abs}$ (hr) | $t_{1/2\beta}$ (hr) | MRT (hr) | $V_d$ (L/kg) | $Cl_B$ (L/hr/kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mean ± S.D | 1.59 ±0.16 | 3.71 ±0.64 | 13.75 ±2.54 | 0.29 ±0.08 | 0.27 ±0.04 | 4.24 ±0.63 | 2.52 ±0.54 | 2.63 ±0.35 | 7.44 ±1.24 | 0.03 ±0.01 | 0.01 ±0.00 |

(Ashraf *et al*., 2015). The apparent volume of distribution (mean ± S.D) of montelukast in the present study was investigated as 0.03±0.01 L/kg which was much lesser than the values of the $V_d$, 9.76 L/kg and 9.66 L/kg, in young and elderly individuals, respectively, following the oral administration of montelukast 10mg (Zhao *et al.,* 1997) showing that montelukast was not distributed widely in the body. This difference in the volume of the distribution of montelukast in the present study and that of the value in literature may be due to any change in flow of the blood to the tissues, any change in extent of protein binding, any diseased conditions or any change in the genetics and environment.

Total body clearance is the sum of the all processes contributing to drug elimination from body. It is total volume of blood cleared of the drug in a unit time by various elimination processes (Ashraf *et al*., 2015). The total body clearance of montelukast (0.01±0.00 L/hr/kg) in this study was reported much lesser than the $Cl_B$ values in literature *i.e.* 0.42 L/hr/kg in diseased children (Faure *et al*., 2001) and 0.62±0.27 L/hr/kg and 0.51±0.34 L/hr/kg in healthy adults and children suffering from GERD, respectively (Marier *et al.,* 2004) after oral administration of montelukast. These differences in pharmacokinetic parameters may be attributed to the genetic or environmental variations (Ashraf *et al*., 2015).

## CONCLUSION

It was concluded from present study that the values of pharmacokinetic parameters such as $C_{max}$, AUC, $t_{1/2}$, $V_d$ and $Cl_B$ of montelukast were lesser than the respective values in literature. However, no difference was observed in the values of $T_{max}$ of the present study and that of the literature. These differences between pharmacokinetic parameters of montelukast in local subjects and their foreign counterparts are attributed to the various factors like changes in genetic morphology, dietary habits and local environmental conditions.

## REFERENCES


Abbas M, Khan AM, Amin S, S Riffat, Ashraf M and Waheed N (2013). Bioequivalence study of montelukast tablets in healthy Pakistani volunteers. *Pak. J. Pharm. Sci.*, **26**: 255-259.

Anwar M, Bilal A, Muhammad MA and Ahmed R (2015). Renal clearance and urinary excretion of cefspan® in healthy male volunteers. *Scholar's Adv. Anim. Vet. Res.*, **2**: 117-122.

Ashraf MM, Ijaz J, Bilal A and Tanweer K (2015). Disposition kinetics and bioavailability comparison of two formulations of cefixime in healthy adult male subjects. *Professional Med. J.,* **22**: 959-965.

Aziz A, Aslam B, Ashraf MM, Naz U, Ashraf N, Raza A, Sarwar A and Sarwar F (2016). Pharmacokinetic study of glimepiride alone and in combination with atorvastatin in healthy male volunteers. *Lat. Am. J. Pharm.,* **35** (10): 2331-2336.

Berube D, Djandji M, Sampalis JS and Becker A (2014). Effectiveness of montelukast administered as monotherapy or in combination with inhaled corticosteroid in pediatric patients with uncontrolled asthma: A prospective cohort study. *Allergy Asthma Clin. Immunol*., **10** (1): 21.

Cheng H, Leff JA, Amin R, Gertz BJ, De-Smet M, Noonan N, Rogers JD, Malbecq W, Meisner D and Somers G (1996). Pharmacokinetics, bioavailability, and safety of montelukast sodium (MK-0476) in healthy males and females. *Pharm. Res.,* **13**: 445-448.

Faure C, Michaud L, Shaghaghi EK, Popon M, Laurence M, Mougenot JF, Hankard R, Navarro J and Jacoz-Aigrain E (2001). Lansoprazole in children: pharmacokinetics and efficacy in reflux oesophagitis. *Aliment. Pharmacol. Ther*., **15**: 1397-1402.

Graff GR, Weber A, Starman DW and Smith AL (2003). Montelukast pharmacokinetics in cystic fibrosis. *J. Pediatr.,* **142**: 53-56.

Hasler JA, Estabrook R, Murray M, Pikuleva I, Waterman M, Capdevila J, Holla V, Helvig C, Falck JR, Farrell G, Kaminsky LS, Spivack SD, Boitier E and Beaune P

(1999). Human cytochromes P450. *Molecular aspects of medicine*, **20**: 1-137.

Kim HT, Song YK, Lee SD and Kim CK (2012). Relative Bioavailability of Two 5-mg Montelukast Sodium Chewable tablets: A Single Dose Randomized, Open-Label, 2-Period Crossover Comparison in Healthy Korean Adult Male Volunteers. *Arzneimittel-Forschung* **62**: 123-127.

Leahy DE (2004). Drug discovery information integration: Virtual humans for pharmacokinetics. Drug discovery today. *Biosilico*., **2**: 78-84.

Lewis DFV and Lake BG (1998). Molecular modelling and quantitative structure-activity relationship studies on the interaction of omeprazole with cytochrome P450 isozymes. *Toxicol.*, **125**: 31-44.

Marier JF, Dubuc MC, Drouin E, Alvarez F, Ducharme MP and Brazier JL (2004). Pharmacokinetics of omeprazole in healthy adults and in children with gastroesophageal reflux disease. *Therapeutic drug monitoring*, **26**: 3-8.

Martinez FD (2007). Genes, environments, development and asthma: a reappraisal. *European Resp. J.*, **29**: 179-184.

Matsuse H, Tsuchida T, Fukahori S, Kawano T, Tomari S, Matsuo N, Nishino T, Fukushima C and Shigeru K (2013). Retrospective cohort study of leukotriene receptor antagonist therapy for preventing upper respiratory infection-induced acute asthma exacerbations. *Allergy Rhinol. (Providence)*, **4**: e127-e131.

Naz U, Ashraf MM, Javed I, Aslam B, Khan JA, Muhammad F, Khaliq T, Rahman ZU, Anwar H, Ashraf N, Raza A and Naeem MA (2017). Comparative pharmacokinetics of cefspan and ceforal-3 in adult human healthy female subjects. *Lat. Am. J. Pharm.*, **36**: 776-782.

Rana NS, KSRajesh, Nikita NP, Patel PR, Limbachiya U, and Pasha TY (2013). Development and validation of RP-HPLC method for the simultaneous estimation of montelukast sodium and ebastine in tablet dosage form. *Ind. J. Pharm. Sci.*, **75**: 599-602.

Rani S and Padh H (2006). Inter-individual variation in pharmacokinetics of proton pump inhibitors in healthy Indian males. *Ind. J. Pharm. Sci.*, **68**: 754-759.

Sana T, Aslam B, Aslam N, Ashraf MM, Ashraf A, Malik TA, Niazi SG, Tahir IM, Rehman MR and Ahmed (2017). Therapeutic effect of atorvastatin on kidney functions and urinary excretion of glimepiride in healthy adult human male subjects. *Pak. J. Pharm. Sci.*, **29**: 1885-1891.

Sripalakit P, Bungon K and Aurasorn S (2008). A simple bioanalytical assay for determination of montelukast in human plasma: Application to a pharmacokinetic study. *J. Chromatogr. B.*, **869**: 38-44.

Steel RGD, Dickey DA and Torrie JH (1997). Linear regression. *In*: Principles and Procedures of Statistics: A biometrical approach. 3rd Ed. McGraw-Hill series in probability and statistics. London. pp.253-285.

Zhao JJ, Rogers JD, Holland SD, Larson P, Amin RD, Haesen R, Freeman A, Seiberling M, Merz M and Cheng H (1997). Pharmacokinetics and bioavailability of montelukast sodium (MK-0476) in healthy young and elderly volunteers. *Biopharm. Drug Dispos.* **18**: 769-777.

Zhou H (2003). Pharmacokinetic strategies in deciphering atypical drug absorption profiles. *J. Clin. Pharmacol.*, **43**: 211-227.