IJPSR (2019), Volume 10, Issue 7 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 12 October 2018; received in revised form, 02 February 2019; accepted, 28 February 2019; published 01 July 2019

THE HEPATIC CYP3A4 UPREGULATED INCREASED METABOLISM IN RESPONSE TO PHYSICAL ACTIVITY AT HIGH ALTITUDE

Abhilash Thomas [*1], Malay K. Samanta [2], Raveen Chauhan [3], Sanesh P. Jose [2], Jeet B. Moktan [1] and N. B. Sridharamurthy [1]

Oxbridge College of Pharmacy [1], Bangalore - 560091, Karnataka, India.
J. S. S. University [2], Mysore - 570015, Karnataka, India.
Shoolini University [3], Solon - 173229, Himachal Pradesh, India.

Keywords:

Physical activity, IPAQ SF-7, CYP3A4, Pharmacokinetics, Alprazolam, Hypobaric hypoxia

Correspondence to Author:
Dr. Abhilash Thomas

Assistant Professor & Head, Department of Pharmacy Practice, Oxbridge College of Pharmacy, Bangalore - 560091, Karnataka, India.

E-mail: abhi0882@gmail.com

ABSTRACT: The present study was designed to assess the pharmacokinetics of drug metabolized by hepatic cytochrome 3A4 (CYP3A4) in human volunteers with physical activity at the high altitude hypobaric hypoxic environment. The International Physical Activity Questionnaire short form 7 (IPAQ SF-7) was used to measure the physical activity. The total of 24 healthy male volunteers participated in this study; for them, the intensity of physical activity was measured in terms of metabolic equivalence of tasks (METs). The pharmacokinetic study was conducted using an oral dose of Alprazolam. The blood samples were collected at fixed intervals up to 24 h. The pharmacokinetic variables were found to be changed with increased intensity of physical activity. The metabolism phase was significantly decreased in vigorous and walking physical activity groups. The area under the curve (AUC) and half-life were also decreased. The pharmacokinetics of drug was found to be decreased with increased intensity of vigorous and walking physical activity in humans working at high altitude hypobaric hypoxia environment. It was assumed that oxygenation of blood and blood flow to the liver was decreased in response to hypobaric hypoxia environment; thought to cause hepatic CYP3A4 dysregulation, resulting in increased metabolism and faster elimination of the drug.

INTRODUCTION: Physical activity was known to alter biotransformation by shunting blood away from splanchnic organs like liver, increase blood flow to skeletal muscles and increased maximal oxygen uptake on [1]. The hypobaric hypoxic (low atmospheric pressure oxygen) environment at high altitudes can also change cardiac output, blood flow to organs [2] and muscles and a decrease in cellular oxygen [3] and vasoconstrictor response [4]. These mechanisms will affect drug metabolism due to a change in the activity of CYP 450 enzymes [5].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(7).3359-63

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(7).3359-63

The intensity, duration, and timing of each type of physical activity shall matter behind these changes in pharmacokinetics [6, 7]. The present study was hypothesized that physical activity in hypobaric hypoxic conditions at high altitude was expected to affect hepatic drug metabolism by CYP3A4 enzyme dysregulation.

MATERIALS AND METHODS:

Study Design: This prospective interventional population pharmacokinetic (pop-PK) study was carried out in healthy male volunteers, non-smoker, non-alcoholic of age 20-60 years having normal body mass index (BMI) and waist-hip ratio (WHR). Subjects who had known medical conditions of metabolic disorders, cardiovascular disorders, hepatic or renal failure were excluded. The subjects who had taken over the counter (OTC) drugs and past histories of infection, inflammatory disorders

and dehydration from last 60 days were also excluded. Then the selected subjects were examined by a general physician and confirmed that they were healthy to participate in the study according to the criteria followed. Informed consent was obtained from all study subjects.

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of J. S. S. Academy of Higher Education and Research, India (Protocol id: JSSCP/DPP/IRB/008B/2013-14, Version 2) and this study was registered in the Clinical Trial Registry of India (Reg. no: CTRI/2016/11/ 007464), New Delhi, India.

Assessment of Physical Activity: The physical activity was assessed by using the International Physical Activity Questionnaire-Short Form 7 (IPAQ SF-7) [8] which measures vigorous-intensity, moderate-intensity and walking physical activity in the period of last 7 days [9]. The intensity values were estimated by the Metabolic Equivalent of Tasks (METs) [8, 10].

The English version was obtained from websitewww.ipaq.ki.se with permission from the author Dr. Barbara E. Ainsworth. The original English version of IPAQ SF-7 was translated to Tamil version, back translated and cross-validated.

Pharmacokinetic Study: The pharmacokinetic study was carried out by using the conventional tablet of 1 mg Alprazolam. After overnight fasting of nine hours, in the morning, 1 mg of Alprazolam generic conventional tablet as the single oral dose was given orally to the subjects, in sitting posture with 300 ml of drinking water of ambient temperature.

The pre-dose blood sample was taken before the administration of study drug, and post-dose samples were collected at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 h. A total of 24 subjects had completed the study successfully in compliance with study conditions and preferred volume of blood samples at all time points. The plasma was separated from whole blood samples by centrifugation at 5000 rpm for 20 min and was stored at -70 °C till analysis. The pharmacokinetic variables AUC, C_{max}, T_{max}, Kel, $t_{½}$, Vd, Cl and MRT were measured by Liquid Chromatography-Mass Spectrometry (LCMS-MS).

Data Interpretation and Statistical Analysis: According to the METs values obtained from IPAQ SF-7, the subjects were grouped into 3; vigorous, moderate and walking physical activity groups; on to each, again subdivided in too low, moderate and high-intensity physical activity. Then, the pharmacokinetics values were compared by the average scores of each parameter of pharmacokinetics among low, moderate and high physical activities and statistical analysis was done by using one way ANOVA in SPSS 20 and significance was set at $P<0.05$.

RESULTS AND DISCUSSION: The present study results showed deviations in pharmacokinetics with an increase in the frequency of physical activity. It had been assumed that high intensities of physical activity at the hypobaric hypoxia environment resulted in reduced oxygenation. This was considered to be an indicator of exercise-induced arterial hypoxemia (EIAH) due to the inadequacies in ventilation and gas exchange [11] and alveolar hyperventilation during high physical exercise.

TABLE 1: THE PHARMACOKINETIC VARIABLES OF ALPRAZOLAM IN VIGOROUS PHYSICAL ACTIVITY GROUP

PK parameters	Intensity level	PK values [Average (SD)]
C_{max} (ng/ml)	Low	21.12 ± 1.48
	Moderate	20.84 ± 2.02
	High	20.55 ± 1.04
T_{max} (h)	Low	1.92 ± 0.18
	Moderate	2.0 ± 0
	High	1.95 ± 0.15
AUC 0-t (ng/ml*h) *	Low	184.73 ± 23.70
	Moderate	182.35 ± 45.11
	High	152.16 ± 13.16
AUC 0-Inf. (ng/ml*h)	Low	246.91±51.09
	Moderate	246.64 ± 78.06
	High	201.39 ± 21.31
$t_{½}$ (h)	Low	12.98 ± 1.14
	Moderate	12.20 ± 1.08
	High	11.07 ± 1.64
Cl (mg/ng/ml)/h	Low	0.00424 ± 0.008
	Moderate	0.00454 ± 0.002
	High	0.00501 ± 0.005
Kel (1/h)	Low	0.06099 ± 0.014
	Moderate	0.06541 ± 0.019
	High	0.06064 ± 0.012
Vd (mg/ng/ml)	Low	0.06962 ± 0.009
	Moderate	0.06893 ± 0.015
	High	0.08545 ± 0.017
MRT (h)	Low	17.33 ± 2.93
	Moderate	16.65 ± 4.51
	High	15.64 ± 2.15

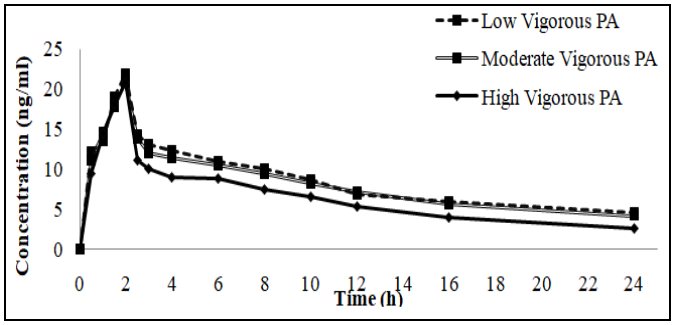
*P<0.05. Values are expressed in average ± SD and statistical significance by One-way ANOVA.

TABLE 2: THE PHARMACOKINETIC VARIABLES OF ALPRAZOLAM IN MODERATE PHYSICAL ACTIVITY GROUP

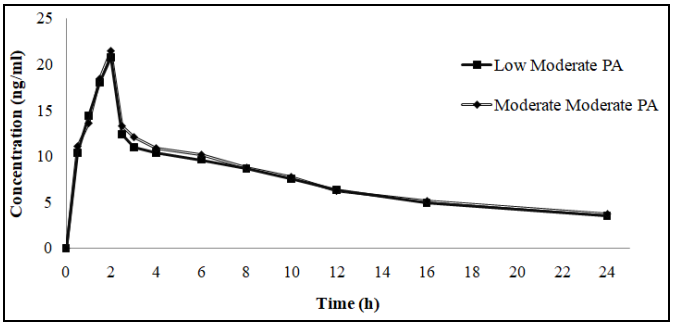
PK parameters	Intensity level	PK values [Average (SD)]
C_{max} (ng/ml)	Low	20.63 ± 1.56
	Mod	21.01 ± 1.37
T_{max} (h)	Low	1.96 ± 0.14
	Mod	1.95 ± 0.15
AUC 0-t	Low	170.34 ± 33.87
(ng/ml*h)	Mod	170.62 ± 30.23
AUC 0-Inf.	Low	228.79 ± 56.41
(ng/ml*h)	Mod	226.78 ± 54.89
$t_{½}$ (h)	Low	11.97 ± 2.17
	Mod	11.87 ± 2.15
Cl (mg/ng/ml)/h	Low	0.00461 ± 0.001
	Mod	0.00467 ± 0.001
Kel (1/h)	Low	0.06124 ± 0.011
	Mod	0.06317 ± 0.017
Vd (mg/ng/ml)	Low	0.07634 ± 0.016
	Mod	0.07564 ± 0.017
MRT (h)	Low	16.49 ± 3.19
	Mod	16.35 ± 3.24

*P<0.05. Values are expressed as average ± SD and statistical significance by One-way ANOVA.

Therefore, the high duration of physical activity found in subject's that underwent vigorous activity had increased risk of developing EIAH. The pharmacokinetic changes of Alprazolam in low, moderate and high intensities of vigorous physical activity were shown in **Table 1**. AUC was significantly lowered (P<0.05) in the high intensity vigorous physical activity group. **Plot 1** shows concentration *vs.* time of Alprazolam in low, moderate and high intensities of vigorous physical activity group in which the high-intensity group had shown a less concentration in the metabolism phase; the metabolic point of view, vigorous physical activity duration of approximately 20 sec demanded higher anaerobic energy of up to 90% [12] and exercise lasting for 20 sec to 1 min utilizes both aerobic and anaerobic energy, and exercises that exceed >1 min utilizes aerobic energy up to 50% [13]. The pharmacokinetic changes of Alprazolam in low and moderate intensities of moderate physical activity were shown in **Table 2**. The AUC in the high vigorous group was significantly reduced whereas in the moderate group; the variables were followed almost similar range. **Plot 2** shows concentration *vs.* time of Alprazolam in low and moderate intensities of moderate physical activity group in which both had shown similar concentration at each time point even after metabolism phase.



PLOT 1: THE CONCENTRATION *vs.* TIME OF ALPRAZOLAM IN LOW, MODERATE AND HIGH INTENSITIES OF VIGOROUS PHYSICAL ACTIVITY GROUP



PLOT 2: THE CONCENTRATION *vs.* TIME OF ALPRAZOLAM IN LOW AND MODERATE INTENSITIES OF MODERATE PHYSICAL ACTIVITY GROUP

The pharmacokinetic changes of Alprazolam in low, moderate and high intensities of walking physical activity were shown in **Table 3**. The half-life was lowered (P<0.05) in moderate walking physical activity group than low intensity walking physical activity group. **Plot 3** shows concentration *vs.* time of Alprazolam in low and moderate intensities of walking physical activity in which the moderate intensity group had shown a less concentration in the metabolism phase.

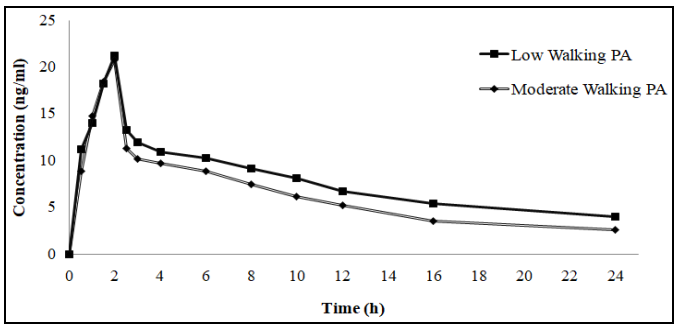
The vigorous physical activity with moderate walking in hypobaric environments might result in reduced arterial oxygenation thereby decreased oxygen saturation in blood for transportation; [14] due to this, hepatic blood flow was reduced. The faster elimination of drug might not support by Kel (elimination rate); found similar **Table 1**, **2**, **3** in vigorous, moderate and walking (P>0.05). The EIAH at high attitude usually tends to begin at moderate intensity physical activities and peaks from near the maximal intensities [14] of physical activity in the study subjects. At this point, their alveolar-arterial oxygen gradient (A-a G) would assume to reduced [15] or widen with hyper-

ventilation as a representation of hypoxemia. Hence, this systemic hypoxemia caused reduced oxygen supply might disrupt hepatic acinar III functions and caused CYP3A4 up-regulation thereby the drug underwent increased metabolism and faster elimination.

TABLE 3: THE PHARMACOKINETIC VARIABLES OF ALPRAZOLAM IN WALKING PHYSICAL ACTIVITY GROUP

PK Parameters	Intensity level	PK values [Average (SD)]
C_{max} (ng/ml)	Low	20.97 ± 1.54
	Mod	20.19 ± 1.02
T_{max} (h)	Low	1.97 ± 0.11
	Mod	1.90 ± 0.22
AUC 0-t (ng/ml*h)*	Low	176.13 ± 32.84
	Mod	148.93 ± 11.84
AUC 0-Inf.	Low	237.51 ± 57.11
(ng/ml*h) *	Mod	191.24 ± 16.84
$t_{½}$ (h) *	Low	12.40 ± 2.08
	Mod	10.14 ± 1.11
Cl (mg/ng/ml)/h	Low	0.00447 ± 0.001
	Mod	0.00526 ± 0.005
Kel (1/h)	Low	0.06098 ± 0.015
	Mod	0.06648 ± 0.019
Vd (mg/ng/ml)	Low	0.07467 ± 0.016
	Mod	0.08112 ± 0.015
MRT (h)	Low	16.97 ± 3.29
	Mod	14.35 ± 1.32

*P<0.05. Values are expressed as average ± SD and statistical significance by One-way ANOVA.



PLOT 3: THE CONCENTRATION *vs.* TIME OF ALPRAZOLAM IN LOW AND MODERATE INTENSITIES OF WALKING PHYSICAL ACTIVITY GROUP

CONCLUSION: The high intensities of vigorous and walking physical activity at high altitude hypobaric hypoxia environment had reduced the drug exposure and half-life in healthy human volunteers. The pharmacokinetics of drug was found to be decreased with increased intensity of vigorous and walking physical activity in humans working at high altitude hypobaric hypoxia environment.

It was assumed that oxygenation of blood and blood flow to the liver was decreased in response to hypobaric hypoxia environment; thought to cause hepatic CYP3A4 dysregulation, resulting in increased metabolism and faster elimination of the drug. This probably results in treatment hazard either a failure of treatment or drug toxicity which was the areas to be given more attention in future.

LIMITATIONS: The pharmacokinetic study could not be performed with the complete sample at time points 48 h and 72 h due to the failure of maintaining study conditions sampling procedure for more than 24 h.

The pharmacokinetic analysis of metabolites of Alprazolam could have been more authenticated to explain the activity of CYP3A4 with the drug to metabolite ratio.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: The authors declare that they have no conflict of interest.

REFERENCES:

1. Dossing M: Effect of acute and chronic exercise on hepatic drug metabolism. Clin Pharmacokinet 1985; 10: 426-31.
2. Heistad DR and Wheeler T: Reflex cardiovascular responses after 36 h of hypoxia. Am J Physiol 1971; 220: 1673-76.
3. Ritschel W and Paulos C: Pharmacokinetics of Acetazolamide in healthy volunteers after short- and long-term exposure to high altitude. J Clin Pharmacol 1998a; 36: 533-39.
4. Doyle JT and Wilson JS: The pulmonary vascular responses to short-term hypoxia in human subjects. Circulation 1952; 5: 263-70.
5. Fradette C and Du Souich P: Effect of hypoxia on cytochrome P450 ctivity and expression. Curr Drug Metab 2004; 5: 257-271.
6. Khazaeinia TA and Ramsey A: The effects of exercise on the pharmacokinetics of drugs. J Pharm Pharmaceut Sci 2000; 3: 292-02.
7. Lenz T L and Lenz NJ: Potential interactions between exercise and drug therapy. Sports Med 2004; 34: 293-06.
8. Ainsworth B, Bassett DR and Strath SJ: Comparison of three methods for measuring the time spent in physical activity. Med Sci Sports Exerc 2000; 32: S457-64.
9. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML and Ainsworth BE: International Physical Activity Questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003; 35(8): 1381-95.
10. Balady GJ: Survival of the fittest more evidence. N Engl J Med 2002; 346: 852-54.
11. Woorons XP, Mollard AP, Lamberto C and Duvallet A: Moderate exercise in hypoxia induces a greater arterial desaturation in trained than untrained men, Scand J Med Sci Sports 2007: 17: 431-36.

12. Peter BJ and Simon RG: Effect of altitude on the heart and the lungs. Circulation 2007; 116: 2191-02.
13. Palacios G, Pedrero-Chamizo R, Palacios N, Maroto-Sánchez B, Aznar S and González-Gross M: Biomarkers of physical activity and exercise. Nutr Hosp 2015; 31(3): 237-44.
14. Dempsey AJ and Wagner DP: Exercise-induced arterial hypoxemia. J Appl Physiol 1999; 87: 1997-06.
15. Gonzalez NC, Sokari A and Clancy RL: Maximum oxygen uptake and arterial blood oxygenation during hypoxic exercise in rats. J Appl Physiol 1991; 71: 1041-49.

How to cite this article:
Thomas A, Samanta MK, Chauhan R, Jose SP, Moktan JB and Sridharamurthy NB: The hepatic CYP3A4 upregulated increased metabolism in response to physical activity at high altitude. Int J Pharm Sci & Res 2019; 10(7): 3359-63. doi: 10.13040/IJPSR.0975-8232.10(7).3359-63.